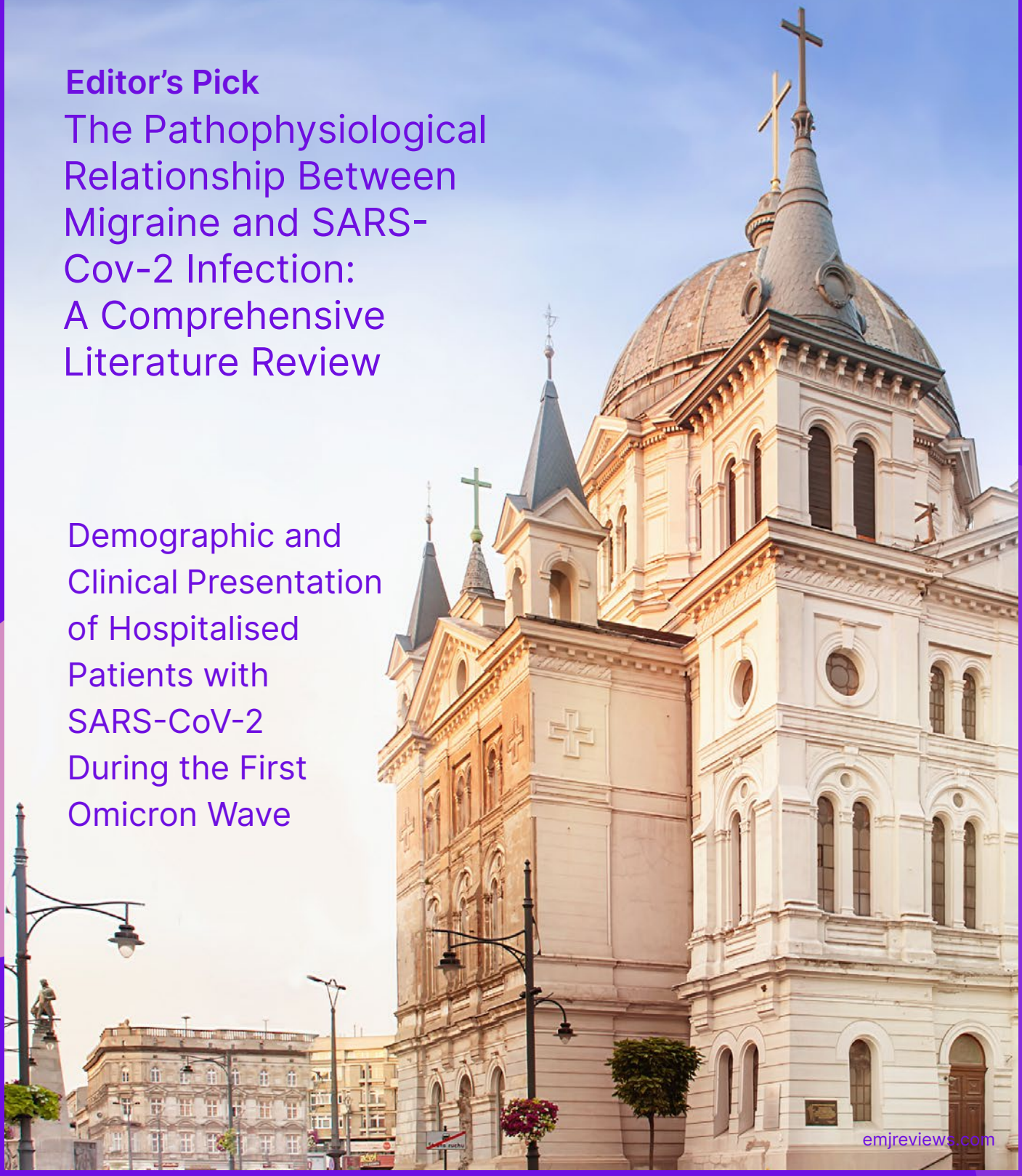
Volume 7.4 December 2022

EMJ

Editor's Pick

The Pathophysiological Relationship Between Migraine and SARS-Cov-2 Infection: A Comprehensive Literature Review

Demographic and Clinical Presentation of Hospitalised Patients with SARS-CoV-2 During the First Omicron Wave



emjreviews.com

Contents

Articles

Editorial Board

Aims and Scope

EMJ is an online only, peer-reviewed, open access general journal, targeted towards readers in the medical sciences. We aim to make all our articles accessible to readers from any medical discipline.

EMJ allows healthcare professionals to stay abreast of key advances and opinions across Europe.

EMJ aims to support healthcare professionals in continuously developing their knowledge, effectiveness, and productivity. The editorial policy is designed to encourage discussion among this peer group.

EMJ is published quarterly and comprises review articles, case reports, practice guides, theoretical discussions, and original research.

EMJ also publishes 18 therapeutic area journals, which provide concise coverage of salient developments at the leading European congresses. These are published annually, approximately 6 weeks after the relevant congress. Further details can be found on our website: www.emjreviews.com

Editorial Expertise

EMJ is supported by various levels of expertise:

- Guidance from an Editorial Board consisting of leading authorities from a wide variety of disciplines.
- Invited contributors are recognised authorities from their respective fields.
- Peer review, which is conducted by EMJ's Peer Review Panel as well as other experts appointed due to their knowledge of a specific topic.
- An experienced team of editors and technical editors.

Peer Review

On submission, all articles are assessed by the editorial team to determine their suitability for the journal and appropriateness for peer review.

Editorial staff, following consultation with either a member of the Editorial Board or the author(s) if necessary, identify three appropriate reviewers, who are selected based on their specialist knowledge in the relevant area.

All peer review is double blind.
Following review, papers are either accepted without modification, returned to the author(s) to incorporate required changes, or rejected.

Editorial staff have final discretion over any proposed amendments.

Submissions

We welcome contributions from professionals, consultants, academics, and industry leaders on relevant and topical subjects.

We seek papers with the most current, interesting, and relevant information in each therapeutic area and accept original research, review articles, case reports, and features.

We are always keen to hear from healthcare professionals wishing to discuss potential submissions, please email: editorial.assistant@emjreviews.com

To submit a paper, use our online submission site: www.editorialmanager.com/e-m-j

Submission details can be found through our website: www.emjreviews.com/contributors/authors

Reprints

All articles included in EMJ are available as reprints (minimum order 1,000). Please contact hello@emjreviews.com if you would like to order reprints.

Distribution and Readership

EMJ is distributed through controlled circulation to healthcare professionals in the relevant fields across Europe.

Indexing and Availability

EMJ is indexed on DOAJ, the Royal Society of Medicine, and Google Scholar®; selected articles are indexed in PubMed Central®.

EMJ is available through the websites of our leading partners and collaborating societies.

EMJ journals are all available via our website: www.emjreviews.com

Open Access

Congress Notice

Staff members attend medical congresses as reporters when required.

This Publication

ISSN **2397-6764**

EMJ is published **four times** a year. For subscription details please visit: www.emjreviews.com

Front cover and contents photograph: Lodz, Poland,
© **agephotography** / stock.adobe.com

Welcome letter

Koutsouki

Evgenia Koutsouki
Editor

Dear Readers,

Welcome to the final issue of *EMJ* for 2022! This has been an eventful year that has seen great progress in clinical medicine across different disciplines, but was also marked by the breakout of a war in Europe. Throughout this year, we chose to explore themes in our flagships ranging from climate change to rare diseases, spotlighting areas that are of considerable impact in healthcare.

Of course, COVID-19 remains a theme encountered throughout healthcare, with patients and clinicians still being affected by the virus and its aftermath. Having focused our first *EMJ* issue of 2022 on COVID-19, it is good to see that at the end of 2022 we seem to be experiencing the tail-end of the pandemic.

Our Editor's Pick for this issue is a review article examining the relationship between migraine and COVID-19, and how COVID-19 infection affects people who suffer from migraine. Also included in this issue is an article analysing demographic aspects of people hospitalised with COVID-19 during the first Omicron wave in a hospital in London, UK. Of course, among our other articles are a number of case reports and reviews across different disciplines in the field.

On behalf of the whole EMJ team, I would like to thank our authors for sharing their research insights in our journal, our peer reviewers and Editorial Board for ensuring the high quality of the content, and the EMJ team for working tirelessly to produce this journal. I wish you a peaceful and happy 2023, and I look forward to welcoming you to our first *EMJ* issue for 2023 in March.

Contact us

Editorial enquiries: editor@emjreviews.com
Sales opportunities: salesadmin@emjreviews.com
Permissions and copyright: accountsreceivable@emjreviews.com
Reprints: info@emjreviews.com
Media enquiries: marketing@emjreviews.com

Foreword

Dear Colleagues,

It is a pleasure to share the latest issue of *EMJ*, which is filled with insightful research articles, case studies, and reviews from across medical disciplines. Of course, this issue still features articles detailing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with focuses on respiratory and microbiology and infectious diseases.

My Editor's Pick for this issue, which continues in this vein, is an engaging article by Elkurwi and Elkurwi. The authors delve into how SARS-CoV-2 has affected individuals with migraine. In this literature review, they detail the differences in migraine frequency and severity in those who have been infected with SARS-CoV-2 and those who have not.

This issue also features a number of fascinating articles from other fields such as reproductive health, with Vuong and Nguyen's case study and literature review on umbilical cord haematoma and uterine torsion in pregnancy. While umbilical cord haematoma is rare, it has not been recorded in the literature, making this a particularly noteworthy article.

Metabolic syndrome is a serious public health problem, related to an increased risk of cancer, Type 2 diabetes, and cardiovascular disease. As blood adiponectin levels have been linked to cardiovascular mortality in patients with diabetes, Singhal et al. investigated to see if there was a link between metabolic syndrome and blood adiponectin levels in this enthralling observational, cross-sectional, hospital-based study.

Finally, I would like to thank everyone who was involved in bringing this issue together, from the authors and interviewees to the reviewers and Editorial Board. To all the readers, I hope that you enjoy this issue of *EMJ*, and find it insightful.

Markus Peck-Radosavlijevic

Professor of Medicine, Chairman of the Department of Gastroenterology and Hepatology, Klinikum Klagenfurt am Wörthersee, Klagenfurt, Austria

According to international guidelines:

IMPROVE.* **PROTECT.†** **PREVENT.‡**

T2D requires a holistic approach to reduce short-term and long-term risks*

For your patients with T2D and CVD

Add JARDIANCE early on to help reduce cardio-renal risk[1-3]

35% RRR IN HOSPITALISATION FOR HEART FAILURE[1,2§]

39% RRR IN INCIDENT OR WORSENING NEPHROPATHY[3¶]

38% RRR IN CV DEATH[1,2#]

*According to the ADA 2022 Standards of Care in Diabetes: 'Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control. Ongoing diabetes

JARDIANCE also helped slow the decline in kidney function.[3]
JARDIANCE is not indicated for the treatment of chronic kidney disease.

For your patients with T2D and CVD

THE POWER TO ACCOMPLISH MORE

MULTIPLE BENEFITS** PROVEN PROTECTION††

JARDIANCE has an established safety profile.[1,2]

According to the JARDIANCE Summary of Product Characteristics, the overall incidence of AEs in patients treated with empagliflozin was similar to placebo. The most frequently reported adverse reaction was hypoglycaemia when used with sulphonylurea or insulin. The overall safety profile of empagliflozin was generally consistent across the studied indications. For detailed adverse reactions information, please consult the JARDIANCE Summary of Product Characteristics, section 4.8.[1]

JARDIANCE IS APPROVED‖ For use down to an eGFR of

30 mL/min/1.73 m²

For initiation and dosing details for T2D patients with and without CVD, please see the full label.‖

Boehringer Ingelheim

Lilly

FOOTNOTES

'According to the 2020 KDIGO® Diabetes Management in CKD Guideline: '...SGLT2i demonstrated substantial reductions in both composite cardiovascular outcomes and composite kidney outcomes. The cardiovascular and kidney benefits appear independent of glucose-lowering, suggesting other mechanisms for organ protection, such as reduction in intraglomerular pressure and single-nephron hyperfiltration leading to preservation of kidney function.'[2]

‡According to the 2022 AHA/ACC/HFSA Clinical Practice Guideline: 'In patients with T2D and either established CVD or at high cardiovascular risk, SGLT2i should be used to prevent hospitalisations for HF.'[3]

§Hospitalisation for heart failure was a secondary CV outcome in the EMPA-REG OUTCOME® trial. The primary composite endpoint in the EMPA-REG OUTCOME® trial was 3-point MACE.[2]

¶Incident or worsening nephropathy is defined as progression to macroalbuminuria, doubling of serum creatinine, eGFR of ≤45 mL/min/1.73 m²; initiation of renal replacement therapy; death from renal disease. Incident or worsening nephropathy was a prespecified component of the secondary microvascular outcome in the EMPA-REG OUTCOME® trial.[3]

The primary composite endpoint in the EMPA-REG OUTCOME® trial was 3-point MACE, composed of death from CV causes, nonfatal MI, or nonfatal stroke, as analysed in the pooled JARDIANCE group versus the placebo group. The 14% RRR in 3-point MACE (HR: 0.86; 95% CI: 0.74–0.99) was driven by a reduction in the risk of CV death (HR: 0.62; 95% CI: 0.49, 0.77); there was no change in risk of nonfatal MI (HR: 0.87; 95% CI: 0.70–1.09) or nonfatal stroke (HR: 1.24; 95% CI: 0.92–1.67).[1,2]

‖ See Summary of Product Characteristics for dosing details.

**Reductions in HbA1c, weight, and blood pressure. In a 24-week, double-blind, placebo-controlled study of 637 patients with T2D, the efficacy and safety of JARDIANCE 10 mg (n=217) and JARDIANCE 25 mg (n=213) as add-on therapy to metformin ≥1,500 mg were evaluated versus placebo added to metformin (n=207). The primary endpoint was adjusted SE from baseline in HbA1c (%); weight loss and blood pressure reduction were key secondary and exploratory endpoints, respectively.[1,4]

††Reduced risk of CV death and HHF in adults with insufficiently controlled T2D and CV disease (CAD, PAD, or a history of MI or stroke). The primary composite outcome in the EMPA-REG OUTCOME® trial was 3-point MACE, composed of death from CV causes, nonfatal MI, or nonfatal stroke, as analysed in the pooled JARDIANCE group versus the placebo group. The 14% RRR in 3-point MACE (HR: 0.86; 95% CI: 0.74–0.99) was driven by a reduction in the risk of CV death (HR: 0.62; 95% CI: 0.49–0.77); there was no change in risk of nonfatal MI (HR: 0.87; 95% CI: 0.70–1.09) or nonfatal stroke (HR: 1.24; 95% CI: 0.92–1.67). The primary outcome occurred in 490 of 4,687 patients in the pooled JARDIANCE group and in 282 of 2,333 patients in the placebo group. Hospitalisation for heart failure was a secondary CV outcome in the EMPA-REG OUTCOME® trial (HR: 0.65; 95% CI: 0.50–0.85).[1,2]

REFERENCES

1. JARDIANCE [Summary of Product Characteristics]. Ingelheim am Rhein, Germany: Boehringer Ingelheim International GmbH; June 2022.
2. Zinman B et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117-28.
3. Wanner C et al.; EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med. 2016;375(4):323-34.
4. Häring et al.; EMPA-REG Met Trial Investigators. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care. 2014;37(6):1650-9.

ABBREVIATION KEY:

AE: adverse event; CAD: coronary artery disease; CF: cardiovascular; CI: confidence interval; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; HHF: hypertensive heart failure; HR: hazard ratio; MI: myocardial infarction; PAD: peripheral arterial disease; RRR: relative resk reduction; SE: standard error; T2D: type 2 diabetes.

Jardiance® (empagliflozin)

Management of Children with Swallowing Problems: New Advances in Paediatric Thickeners

This satellite symposium took place on 14th September 2022, at the European Society for Swallowing Disorders (ESSD) 12th Annual Congress held in Leuven, Belgium

Chairperson:	Karen van Hulst[1]
Speakers:	Karen van Hulst,[1] Ben Hanson,[2] Analou Sugar[3] 1. Radboud University Medical Center, Amalia's Children's Hospital, the Netherlands 2. Department of Engineering, University College London, UK 3. Chelsea and Westminster Hospital Foundation Trust, London, UK
Disclosure:	Van Hulst is a speaker for NHSc and her employer, the Radboudumc, has received consultancy fees from NHSc. Hanson has received honoraria, consultancy/speaker fees, and/or educational grants from Abbott, Aymes, Fresenius-Kabi, Nestlé Health Science, Nomad Foods, Nutricia, Stable Micro Systems, Thixo-D, and Viscgo. Sugar declares that the study presented was sponsored by Nestlé Health Science.
Acknowledgements:	Writing assistance was provided by Eleanor Roberts, Beeline Science Communications, Ltd, London, UK, and funded by EMJ.
Support:	This article was funded by an educational grant from Nestlé Health Science, Vevey, Switzerland.
Disclaimer:	The opinions expressed in this article belong solely to the named speakers.

Citation: EMJ. 2022:7[4]:10-18. DOI/10.33590/emj/10047359. https://doi.org/10.33590/emj/10047359.

Meeting Summary

A satellite symposium on the evaluation and management of dysphagia in children was held during the 12th Annual Congress of the European Society for Swallowing Disorders (ESSD) in Leuven, Belgium, on 14th September 2022. Dysphagia is the impairment or difficulty in swallowing and may have an oropharyngeal or oesophageal cause. This can result in delayed transit of liquids or solid food from the mouth to the stomach. Food thickening agents can reduce regurgitation and improve swallowing mechanics, particularly in infants and young children. At this symposium, Karen van Hulst, Speech and Language Therapist and Clinical Epidemiologist at Radboud University Medical Center, Amalia's Children's Hospital, the Netherlands, introduced the topic of dysphagia and its complications, and the evaluation of dysphagia. She then discussed the use of thickening agents in children with dysphagia. Ben Hanson from the Department of Engineering, University College London, UK, introduced the International Dysphagia Diet Standardization Initiative (IDDSI). The IDDSI has developed a standardised and practical method of measuring the thickness of liquid and food that can be used when preparing foods

at home or in the hospital, and may be applied commercially. Analou Sugar, Clinical Lead in Paediatric Speech and Language Therapy at Chelsea and Westminster Hospital Foundation Trust, London, UK, ended the symposium with a presentation of her recent clinical experience using a new thickener (ThickenUp® Junior, Nestlé Health Science, Vevey, Switzerland) in paediatric patients.

Introduction

Dysphagia is defined as "any disruption to the swallow sequence that results in compromise to the safety, efficiency, or adequacy of nutritional intake."[1] Dysphagia may have an oropharyngeal or oesophageal cause, resulting in delayed transit of liquids or solid food from the mouth to the stomach.[1] Approximately one in 100 children experience swallowing difficulties; therefore, the clinical evaluation and management of abnormalities in swallowing are important for adequate nutrition and the health of children.[2] Three symposium speakers at the 12th Annual ESSD Congress, Karen van Hulst, Ben Hanson, and Analou Sugar, introduced the topic of paediatric dysphagia, its assessment, and management using dietary thickeners.

Introduction to Paediatric Dysphagia and the Importance of Thickeners

Karen van Hulst

Problems Arising from Dysphagia

To enable safe and efficient feeding, a child should be able to swallow effectively. "Appropriate nutritional input is essential for development and growth during infancy and childhood," said van Hulst, and "feeding should be pleasant, tasty, social, joyful, and provide opportunities for social interaction."

The complex swallowing process starts with two voluntary phases: oral bolus preparation and oral bolus propulsion. These phases are followed by the involuntary pharyngeal phase, where food is irreversibly directed into the oesophagus and the airway is automatically protected from aspiration; and the oesophageal phase, where food is moved down to the stomach.[1]

Paediatric dysphagia can occur due to a disorder in one or more of these phases, and can manifest as an inability to swallow food, drinks, or medication; or regurgitation of reflux material or saliva, also called posterior drooling. Dysphagia can result in direct or indirect aspiration before, during, or after swallowing. Aspiration prior to swallowing is most common when drinking liquids as the bolus may go from the mouth to the pharynx before airway closure occurs. Aspiration during swallowing is most often due to co-ordination problems. Aspiration after swallowing is usually caused by a pharyngeal bolus residue, most likely due to a problem with swallow strength.[1]

Dysphagia can arise at different levels, all with their own swallow patterns, and can be due to central neurological problems, such as spasticity or central hypotonia syndromes; bulbar motor problems; muscle disorders; or anatomical problems.[1] While an estimate of approximately 1.0% of the general paediatric population may have swallowing difficulties,[2] incidence is much higher in at-risk populations.[3] For example, 90.0% of children with neurological impairments have oropharyngeal dysfunction, 80.0% of children with developmental delays and 24.5% of premature infants have feeding problems, and 22.0–50.0% of children with cardiopulmonary disease have dysphagia.[4]

In neuromuscular disorders, muscle weakness can result in pharyngeal residue following swallowing. Children with central nervous system disorders such as cerebral palsy can develop dysphagia in one or more phases of swallowing.[5] The findings from a study of 130 preschool children with cerebral palsy showed that common observed signs during mealtimes included coughing (44.7%), multiple swallows (25.2%), a gurgly voice (20.3%), wet breathing (18.7%), and gagging (11.4%).[6]

Dysphagia can not only prolong mealtimes, lead to an inability to consume foods and fluids safely and in adequate quantities, and cause respiratory problems; it can also have longer

term consequences such as impaired growth due to inadequate nutrition, and lowered health outcomes and quality of life, with increased stress for the child and their caregivers.[7,8]

Assessment of Dysphagia

The 'Algorithm for Evaluation and Management of Paediatric Dysphagia' provides a stepwise approach for clinical assessment. Evaluation first involves distinguishing between feeding difficulties due to dysphagia or oral aversion, specific food aversion, or other symptoms. If dysphagia is suspected, the next stage is to evaluate whether there is an oropharyngeal or oesophageal cause.[1] This is most often carried out using a video fluoroscopic swallow test, which should be personalised through discussion with the child's caregiver(s), clinical team, and the radiology department.[1,4] Diagnosis in children with complex feeding problems may also involve endoscopic evaluation of swallowing. Here, a flexible scope is passed through the nose so that the area above the vocal folds can be viewed and swallowing visualised.[1]

Management of Dysphagia

Treatment for paediatric dysphagia depends on the underlying cause. For example, a child with oral dysphagia may require feeding therapy, e.g., changing feeding position, pacing feeds, and/or conditioning exercises; and/or changing a feeding bottle nipple to one that best suits the condition. A child with pharyngeal dysphagia associated with aspiration of food and drink may require surgical management (gastrostomy) as well as medical management, including using thickening agents (thickeners) combined with feeding therapy and/or formula changes. Treatment for oesophageal dysphasia may require either medical or surgical management, depending on the cause of the condition.[4,9,10]

Children with central and peripheral neurologic disorders have distinctive patterns of dysphagia when they undergo a videofluoroscopic swallowing examination. For instance, children with cerebral palsy tend to have more problems with thin liquids, whereas children with spinal muscular atrophy tend to have more problems with puréed foods.[5] This means, advised van Hulst, that while thickeners should be used for children with cerebral palsy if co-ordination is a problem, for children with neuromuscular disorders, thickeners should preferably not be used if swallow strength is a problem.

Food and thickeners are commonly used for children with dysphagia. They have been shown to enable better oral co-ordination, improve pacing, change swallow mechanics, and allow the bolus to move more slowly from the oropharynx to the oesophagus. The use of thickeners for feeds has also been shown to reduce the number of regurgitation episodes in several studies, and is supported by gastroesophageal reflux disease (GERD) guidelines from the North American Society For Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), and the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN).[11,12]

There is a range of different thickeners available for the paediatric population, and van Hulst recommended using a thickener that does not change the nutritional value or composition of the food it is added to. Food purées, for example, often contain fructose, and infant cereals can be high in iron and carbohydrates. Starch-based thickeners can change viscosity over time when they come in contact with saliva, as well as being broken down by amylase. Locust bean and xanthan gum-based thickeners have an advantage by not having any of these issues.[11]

Van Hulst noted that while thickened liquids reduce the risks of laryngeal penetration and aspiration, they can increase the risk of post-swallow residue in the pharynx. Thickened food and liquids also require greater strength in terms of tongue propulsive forces used to drive a bolus to the oropharynx. If these propulsive mechanisms are reduced, and there is also reduced pharyngeal strength, there is a risk for residues to remain in the pharynx after swallowing, increasing the risk of post-swallow aspiration.[9,11] Therefore, she advised, thickeners should not be used in children with reduced pharyngeal muscle strength.

Van Hulst concluded by discussing that thickeners are usually well-tolerated with few side effects. However, close follow-up is required to ensure that children tolerate thickeners, and that there is an adequate improvement in the symptoms of dysphagia.

Optimal Food and Beverage Thickening: Introduction to the International Dysphagia Diet Standardization Initiative (IDDSI) Standards

Ben Hanson

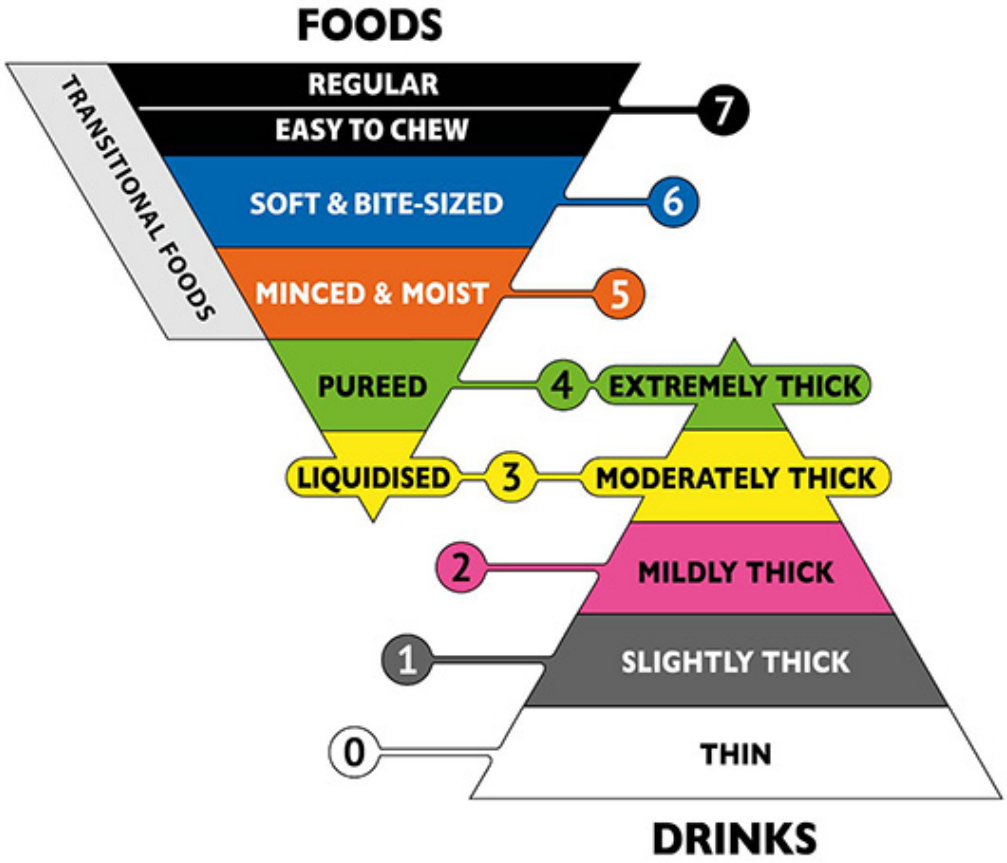
Assessing the Texture of Foods and Drinks

The IDDSI framework is a continuum that can be used to rate consistency levels of food or drink.[13] Figure 1 shows that drinks can be rated from 0 to 4 (thin to extremely thick) and foods from 3 to 7 (moderately thick to regular/easy to chew).[13]

These IDDSI ratings consider the food breakdown process, from taking a bite to producing a smooth, lump-free, moist bolus capable of being swallowed, as well as physiological information regarding tracheal size, particle size, and bolus smoothness.[13]

In the paediatric population, increasing food texture is fundamental to the normal developmental process of weaning a child onto solid foods. Texture, said Hanson, can include particles, crunchiness, slipperiness, and thickness. The latter is a quality that can be used to modify the swallowing process. Echoing the study presented by van Hulst, Hanson commented on a study related to intra-oral pressures with IDDSI-standardised textures in healthy adults. This study showed that increasing the thickness of a liquid enhanced the pressure used by the tongue to swallow boluses. This pressure increase reduced the volume of sip size

Figure 1: The International Dysphagia Diet Standardization Initiative (IDDSI) framework. Food and drinks classification and testing.



The International Dysphagia Diet Standardisation Initiative 2019 at https://iddsi.org/framework/ Licensed under the CreativeCommons Attribution Sharealike 4.0 License https://creativecommons.org/licenses/by-sa/4.0/legalcode. Derivative works extending beyond language translation are NOT PERMITTED.[15]

participants took, which, said Hanson, illustrates how changes in thickness can have a variety of influences on the swallowing process.[14]

Hanson also discussed how, as infants expend a lot of energy in the process of eating, drinking, and digesting, there is a need to make sure this process is not impeded in children with dysphagia, as increasing the fluid thickness increases the amount of energy needed to extract liquids through a nozzle due to the above discussed pressure increase.[14] However, while increasing feeding bottle teat hole size may be seen as a solution, this could actually increase the risk of aspiration.[11]

Ensuring the Optimal Use of Thickeners

There is a long history in food science of controlling texture using a range of ingredients. Thickeners are predominantly composed of powdered carbohydrate grains. When added to a liquid, these swell up and partially dissolve, forming a gel network that holds the liquid together, thus increasing thickness.[16] Hanson mentioned, in the question and answer session, that thickener can be added to hot or cold drinks, and that for powdered drinks it is best to mix them up first, then add a thickener.

The thickening process can be influenced by a variety of factors. For instance, when trying to thicken milk, the presence of fats, proteins, and sugars can inhibit the absorption of water and with some thickeners it can take at least 30 minutes, and up to 24 hours, for a stable thickness to be reached.[17] Additionally, the method used to mix up liquids, be it stirring or shaking, can also have a large effect on the end result when using a thickener.[18] In the question and answer session, Hanson said: "The best way we found to produce a stable consistency quickly was to shake it in a bottle." He explained that attention also needs to be paid to small changes in the thickness of a liquid that can arise when a measuring scoop is not levelled off properly, or the volume of the liquid to be thickened is not accurately measured each time.

Viscosity can be difficult to measure. Although some liquids may be Newtonian, such as honey or oils, most foods and drinks are non-Newtonian fluids. Yoghurt, for example, has properties of both a liquid and a solid. This makes it difficult to classify thick liquids consumed by children with dysphagia. In Hanson's laboratory, a rheometer is used to measure samples under controlled conditions, but this is not a practical tool for a domestic or hospital/care home kitchen.[16] Therefore, a flow test for liquids, based on IDDSI standards, has been developed, whereby thickness can be measured by assessing flow rate through a 10 mL syringe or a standardised IDDSI funnel.

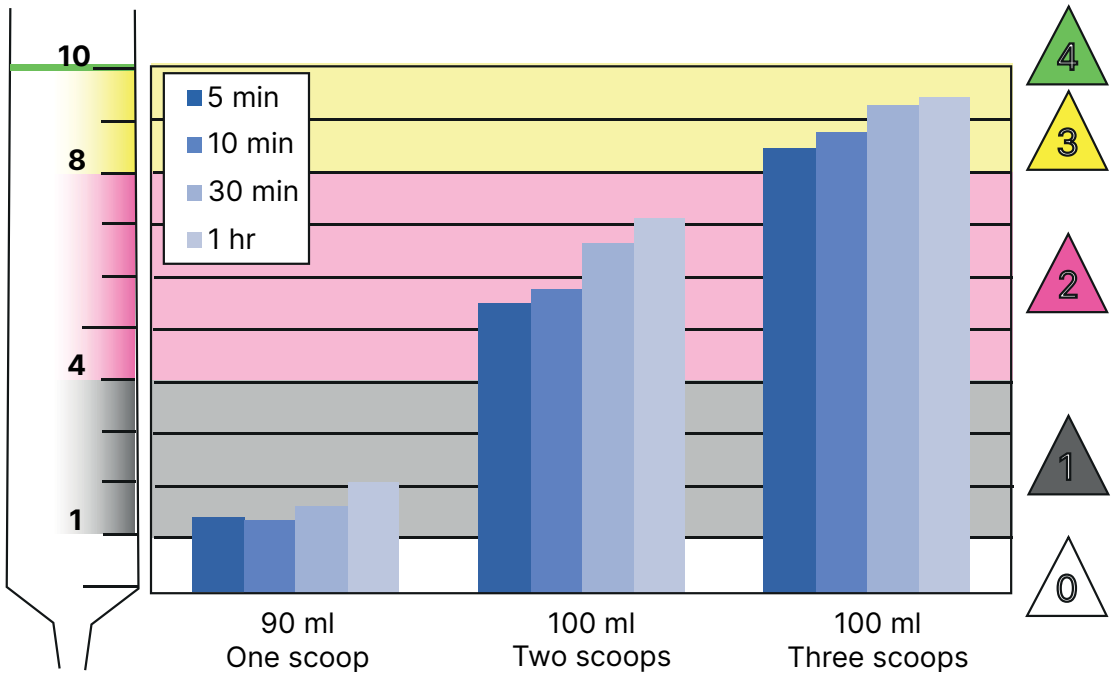
For foods and thicker liquids at IDDSI Level 3 and above, the qualities of a thickened liquid can be assessed by ascertaining whether or not it drips off of a fork or slides off a spoon as a cohesive lump.[13] To ascertain the softness of a food, Hanson's team developed tests based on the pressure used to squash a food sample with a thumb on a fork where the nail blanched. This was found in laboratories to be roughly equivalent to the pressure the tongue uses to generate the swallow reflex. According to Hanson, these practical, easily reproducible tests can help ensure that a person with dysphagia is consuming foods and liquids that are easy to control on the tongue without spilling, and are moist and easy to swallow.

As an example, Hanson discussed the use of ThickenUp Junior, a thickener composed of 10:1 locust bean gum and xanthan gum.[19] Unpublished results he presented showed that when added to a commercial ready-to-use baby milk formula (SMA Pro Follow-On Milk 2®, Nestlé Health Science, Vevey, Switzerland) this can reach a stable consistency very quickly when thoroughly mixed, and remain stable over 24 hours, which is important when feeds are interrupted (Figure 2).

Hanson also reported that similar results had been found using a wide range of milks and soft drinks, such as orange juice or chamomile tea, and even high energy powdered formula (for example, SMA Pro Follow-On Milk 2). He showed that small changes to formula/water mixing ratios, for instance using 90 mL rather than 100 mL of water, can allow for fine-tuning of a liquid's consistencies to meet specific needs (Figure 3).

Hanson also added that he had noted how adding a small amount of saliva can change the consistency of a food such as porridge made

Figure 2: Thickness over time when adding a defined amount of ThickenUp® Junior to defined volumes of a commercial infant formula (SMA® [SMA Nutrition, Nestlé, Vevey, Switzerland] Pro Follow-On Milk 2; scoops).



with milk, decreasing its IDDSI level. He found that adding an amylase resistant thickener (such as ThickenUp Junior) could prevent changes due to saliva.

Using the IDDSI tests, peer-reviewed, scientific studies are now building a consensus as to how dysphagia can be managed with texture modification. These include investigations of transitional food samples, and studies of how modification techniques impact the rheological properties of foods and liquids used for people with dysphagia.[20,21] Together these mean, that in domestic and hospital or care home settings, a standard thickness of a particular food or liquid can be produced every time it is needed.

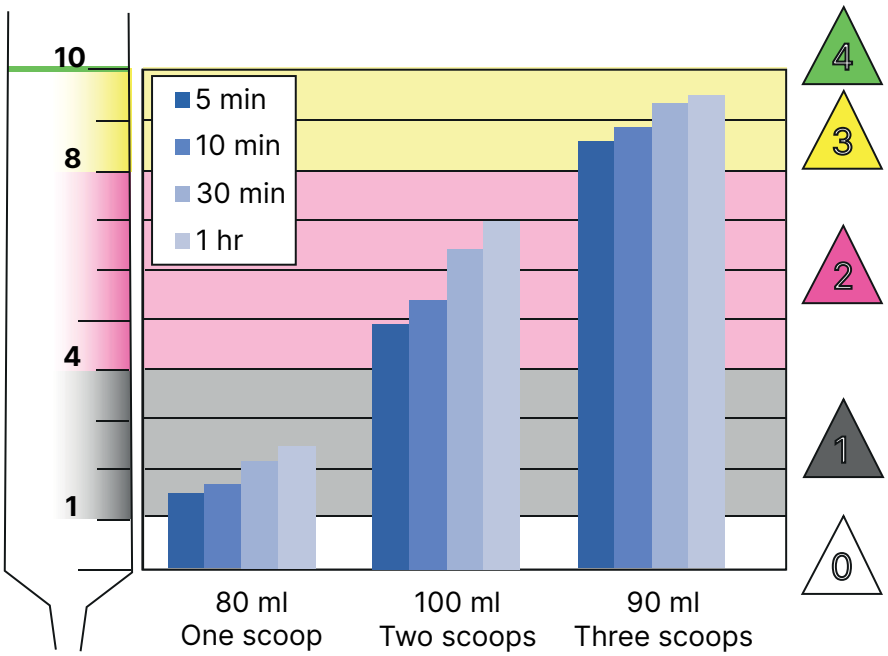
In conclusion, Hanson discussed the need to consider how food and drink texture affects an individual's swallowing, as this can impact the comfort of the child, their quality of life, and their safety.[11] The IDDSI standards can be used to help select products and diets, monitor consumption progress, and aid research in dysphagia.

Tolerance and Effectiveness of a New Paediatric Thickener: Clinical Experience

Analou Sugar

Sugar began her presentation by stating: "The impact of dysphagia on a parent and family should never be underestimated." She continued: "It's very disempowering if you can't feed your child or if you have to be socially excluded, be different, struggle with feeds, etc." In support of these statements is a recently published cross-sectional study that included 50 children aged 2–5 years with a diagnosis of feeding disorder. The findings showed that paediatric feeding impairments can impact areas such as social, physical, emotional, and school functioning of the child; and daily activities, feeding, and worry for the caregiver. Importantly, the impact of poorly managed dysphagia on the wellbeing of children and their families was more significant than for several other paediatric conditions, including kidney transplantation and acute liver failure. The authors concluded that improved diagnosis and treatment individualised to each child's needs

Figure 3: Thickness over time of defined ratios of a commercial infant formula (SMA Pro Follow-On Milk 2®, Nestlé Health Science, Vevey, Switzerland) and water when mixed with a defined amount of ThickenUp® Junior (scoops).



could improve the overall wellbeing of children and their families.[7]

To illustrate the utility of thickeners, Sugar reported the results of a trial of ThickenUp Junior that aimed to evaluate its acceptability, gastrointestinal (GI) tolerance and compliance, in children aged 6 months and above for the management of reflux, GERD, and dysphagia. The trial ran from August 2021 to May 2022 and recruited UK National Health Service (NHS) patients in both inpatient and outpatient settings with a diagnosis of dysphagia and under the care of a multidisciplinary team. Parents completed a 28-day diary reporting the amount of thickener used, amount of liquid consumed, and tolerance to the feeds.

GI tolerance was determined by recording several GI markers. These included symptoms such as diarrhoea, constipation, bloating/distension, nausea, vomiting, burping, flatulence, and regurgitation; and those that may be associated with GI symptoms, such as indices of abdominal discomfort and pain, back arching, and crying. The Bristol Stool Chart[22] was used to describe stool consistency.

Inclusion criteria were infants and children who were already using a thickener or required such for management of GERD and/or dysphagia, and who were able to comply with the study protocol. Exclusion criteria were contraindications to any of the ingredients used in ThickenUp Junior or milk, as some milk products may be present during processing of the thickener. During the trial, no new weaning or introduction of new foods could take place. Parents were trained on how to use ThickenUp Junior to prepare liquids and provided with written information regarding preparation of liquids at home.[19]

Of the 15 children included in the study, eight were female, seven were male, and the age range was 9 months–8 years, with 10 participants under the age of 32 months. Participants presented with a range of diagnoses, including asthma, bulbar palsy, congenital heart disease, prematurity, trisomy 21, GERD, and tracheoesophageal fistula. Six participants withdrew from the study, three due to refusing the new thickener, and three to becoming unwell for reasons unrelated to thickener use.

Drinks were prepared to a range of IDDSI levels from 1 to 3, with IDDSI 3 used more in the older children and IDDSI 1 and 2 in younger participants.

The results showed that all hydration requirements and targets were met or improved. The use of this new thickener was generally well-tolerated, with any reported GI symptoms being limited and transient. Three recruits became unwell and discontinued the study; this was not deemed to be study-related.

Sugar also discussed the study participants' experiences, as reported by their caregivers. One said: "We have noticed that she is not vomiting or coughing when drinking, which is fab!" Another reported that the thickener "has made nursery staff and them [the caregivers] more confident, and they are 'less scared' due to no coughing or vomiting." A third caregiver described how their child was "going to the drink station at nursery to grab her sippy cup, the one with a straw, and drink by herself."

The limitations of the study were acknowledged during the question and answer session. These included the small number of study participants, and the lack of a control group. Sugar commented that this is a first promising trial and more assessment is needed. She suggested that further studies could utilise standardised measures of feeding and caregiver responses, and these could be monitored both pre-intervention and post-intervention to give a better idea of the effectiveness and experience using ThickenUp Junior.

In conclusion, Sugar discussed how using ThickenUp Junior meant that drinks can be prepared to a consistent IDDSI level, which is a safer practice, can aid compliance, and enhance the patient experience. She reported that her findings show that the use of ThickenUp Junior can enhance the patient's experience, and she suggested that, even-though not firmly investigated yet, its use may reduce the need for hospital appointments and interventions, such as enteral feeding and management of GI complications in children with dysphagia.

References

1. Dodrill P, Gosa MM. Pediatric dysphagia: physiology, assessment, and management. Ann Nutr Metab. 2015;66 Suppl 5:24-31.
2. Bhattacharyya N. The prevalence of pediatric voice and swallowing problems in the United States. Laryngoscope. 2015;125(3):746-50.
3. Lefton-Greif MA, Arvedson JC. Pediatric feeding and swallowing disorders: state of health, population trends, and application of the international classification of functioning, disability, and health. Semin Speech Lang. 2007;28(3):161-5.
4. Lawlor CM, Choi S. Diagnosis and management of pediatric dysphagia: a review. JAMA Otolaryngol Head Neck Surg. 2020;146(2):183-91.
5. van den Engel-Hoek L et al. Children with central and peripheral neurologic disorders have distinguishable patterns of dysphagia on videofluoroscopic swallow study. J Child Neurol. 2014;29(5):646-53.
6. Benfer KA et al. Clinical signs suggestive of pharyngeal dysphagia in preschool children with cerebral palsy. Res Dev Disabil. 2015;38:192-201.
7. Simione M et al. Examining health conditions, impairments, and quality of life for pediatric feeding disorders. Dysphagia. 2022;DOI:10.1007/s00455-022-10455-z.
8. Lefton-Greif MA et al. Impact of children's feeding/swallowing problems: validation of a new caregiver instrument. Dysphagia. 2014;29(6):671-7.
9. Tutor JD, Gosa MM. Dysphagia and aspiration in children. Pediatr Pulmonol. 2012;47(4):321-37.
10. Prasse JE, Kikano GE. An overview of pediatric dysphagia. Clin Pediatr (Phila). 2009;48(3):247-51.
11. Duncan DR et al. Clinical aspects of thickeners for pediatric gastroesophageal reflux and oropharyngeal dysphagia. Curr Gastroenterol Rep. 2019;21(7):30.
12. Rosen R et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2018;66(3):516-54.
13. International Dysphagia Diet Standardisation Initiative (IDDSI). Food and drinks classification and testing. 2020. Available at: https://iddsi.org/IDDSI/media/images/Posters/IDDSI_Whole_Framework_A3_Poster_INT_VERSION_May_16_2020_no_bleed.pdf. Last accessed: 28 October 2022.
14. Steele CM et al. Modulation of tongue pressure according to liquid flow properties in healthy swallowing. J Speech Lang Hear Res. 2019;62(1):22-33.
15. The International Dysphagia Diet Standardisation Initiative (IDDSI). The IDDSI framework. 2019. Available at: https://iddsi.org/framework. Last accessed: 28 October 2022.
16. O'Leary M et al. Viscosity and non-Newtonian features of thickened fluids used for dysphagia therapy. J Food Sci. 2010;75(6):E330-8.

17. Ng V et al. Thickened formulas used for infants with dysphagia: influence of time and temperature. Dysphagia. 2022;37(4):923-32.
18. Rush OM et al. Effect of mixing method on resulting thickness of infant formula. J Texture Stud. 2021;52(1):57-70.
19. Nestlé Health Science. ThickenUp Junior. Scientifically designed to help children with dysphagia or reflux drink safely. Available at: https://www.nestlehealthscience.com/brands/resource/thicken-up/thicken-up-junior. 2022. Last accessed: 28 October 2022.
20. Barewal R et al. A comparison of behavior of transitional-state foods under varying oral conditions. Dysphagia. 2021;36(2):316-24.
21. de Villiers M et al. The impact of modification techniques on the rheological properties of dysphagia foods and liquids. J Texture Stud. 2020;51(1):154-68.
22. Heaton KW et al. How bad are the symptoms and bowel dysfunction of patients with the irritable bowel syndrome? A prospective, controlled study with emphasis on stool form. Gut. 1991;32:73-79.

EMJ Podcasts

The EMJ Podcast aims to provoke conversations around the latest trends and innovations in healthcare, provide engaging and educational content for healthcare professionals, and hosts conversations with physician entrepreneur, Jonathan Sackier.

Listen today

www.emjreviews.com

EMJ

Tailoring Motor Fluctuation Treatment: Beyond Levodopa Dose Adjustment

A review of the Bial satellite symposium at the 8th Congress of the European Academy of Neurology (EAN), which took place on 26th June 2022 in Vienna, Austria

Chairperson: Susan Fox[1,2,3]

Speakers: Susan Fox,[1,2,3] Angelo Antonini,[4,5] Joaquim Ferreira[6,7]

1. Division of Neurology, University of Toronto, Canada
2. Division of Neurology, University Health Network/Sinai Health System Hospitals, Toronto, Canada
3. Edmond J. Safra Program in Parkinson's Disease, Krembil Brain Institute, Toronto Western Hospital, Canada
4. Department of Neuroscience, University of Padua, Italy
5. Parkinson and Movement Disorders, University Hospital Padua, Italy
6. Laboratory of Clinical Pharmacology and Therapeutics, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal
7. Campus Neurológico (CNS), Torres Vedras, Portugal

Disclosure: Fox has received clinic support from the Edmond J. Safra Foundation for Parkinson Research, Parkinson Foundation, and UHN Foundation; consultancy/speaker fees from Alexion, Bial, Paladin, Pharma Two B, and Sunovion; honoraria from the International Parkinson and Movement Disorder Society; research funding from Michael J. Fox Foundation for Parkinson Research, NIH (Dystonia Coalition), and Parkinson Canada; royalties from Oxford University Press; and is site principal investigator for clinical trials for Alexion, Biotie Therapies, Eisai, Pharma Two B, and Revance. Antonini has received compensation for consultancy and speaker-related activities from AbbVie, Bial, Boehringer Ingelheim, Britannia, Ever Pharma, General Electric, Jazz Pharmaceuticals, Kyowa Kirin, Medscape, Roche, Theravance Biopharma, UCB, and Zambon Pharma; research support from Angelini Pharmaceuticals, Bial, CaRiPaRo Foundation, Horizon 2020 (Grant 825785), Horizon 2020 (Grant 101016902), Lundbeck, Ministry of Education University and Research (MIUR [Grant ARS01_01081]), Movement Disorders Society for Non Motor Symptoms Scale validation, and Roche; and serves as a consultant for Boehringer Ingelheim for legal cases on pathological gambling. Ferreira has received payments for advisory boards, consultancy, and grants from Abbott, AbbVie, Affiris, Allergan, Angelini, Bial, Biogen, Fundação MSD (Portugal), GlaxoSmithKline, Grunenthal, Ipsen, Lundbeck, Medtronic, Merck-Serono, Merz, MSD, Novartis, Teva Pharmaceuticals, Solvay, Sunovion Pharmaceuticals, and Zambon Pharma.

Acknowledgements: Writing assistance was provided by Najeeb Ashraf, SciVoc™ Consulting Inc., Toronto, Canada. Opicapone prescribing information and adverse event reporting information can be found at the end of the article.

Support:	The publication of this article including medical writing assistance was funded by Bial. Bial also organised and fully sponsored this satellite symposium.
Citation:	EMJ. 2022;7[4]:20-27. DOI/10.33590/emj/10022165. https://doi.org/10.33590/emj/10022165.

Meeting Summary

Susan Fox opened this satellite symposium at the 8th European Academy of Neurology (EAN) Congress with an overview of the concept of motor fluctuations (MF) in Parkinson's disease (PD). She emphasised that levodopa remains the gold standard therapy for PD. However, MFs are one of the critical complications of levodopa therapy that affect many patients with advancing PD and, when diagnosed, represent a challenge in patient management. Alternative options are, therefore, needed to provide continuous dopaminergic stimulation while maximising the levodopa benefit. Despite different options, Angelo Antonini showed that neurologists often prefer to adjust levodopa dose rather than add an adjunctive agent. Market research confirms that, in patients with PD, the levodopa dose is adjusted in around 80% of patients, while only 20% have adjunct therapy as a first-line option. Adjusting the levodopa dose, either by increasing or fractionating the dose, or both, remains a valid, tried-and-tested option, although it has limitations. Joaquim Ferreira presented emerging evidence from a Phase II clinical trial, suggesting a potential benefit of adding opicapone 50 mg compared with 100 mg levodopa to treat patients with PD and end-of-dose fluctuations. This symposium aimed to present the effect of opicapone with relatively low total daily doses of levodopa; an option that may not have been traditionally considered by neurologists who are used to adjusting levodopa as a first-line response.

Motor Fluctuations in Parkinson's Disease

Susan Fox

Fox emphasised that PD is one of the fastest-growing neurological disorders. Disability and deaths related to it have more than doubled from 1990–2015. Its prevalence is expected to grow exponentially by 2040, affecting approximately 12.9 million individuals worldwide.[1]

Since its introduction in 1967, levodopa has been the gold standard therapy for PD.[2] However, long-term usage of high doses of levodopa may lead to complications, which are usually associated with advanced stages of PD, as the risk of developing MF and dyskinesia also increases with longer disease duration, but not with levodopa treatment duration.[3,4] Yet, research shows that motor complications can also occur in the early phases of PD.

In a cross-sectional, questionnaire-based study in Europe, responses were collected from 817 patients with PD with an average disease duration of 3.3 years (mean Hoehn and Yahr score of 2.1).[5] Results from this study indicated the presence of motor complications in 33% of patients, peak-dose dyskinesia in 15% of patients, and 'OFF' dystonia in 6% of patients.[5] Presence of ON–OFF fluctuations were associated with poorer quality of life as measured by the EuroQoL 5-dimension (EQ-5D) questionnaire and Parkinson's Disease Questionnaire-39 (PDQ-39).[5] In another prospective longitudinal study in the UK, 734 patients with PD were followed for 10 years from diagnosis. Findings indicated the presence of motor complications in early PD and showed that higher levodopa dose, younger age, and baseline non-motor symptoms were associated with increased risk of such complications.[6] Fox emphasised that a possible strategy to delay the development of MF in early PD and the

progression of MF into the advanced disease stage would be to keep low doses of levodopa while adding adjunctive therapies, with the aim of achieving an extended duration of action and increased levodopa exposure through a continuous dopaminergic stimulation strategy.[2]

Dose Response to Levodopa Changes Over Time

Fox mentioned that the pharmacodynamic response to levodopa treatment changes over time. In early PD, administration of levodopa results in a linear dose–response (i.e., increased response with increased dose).[7] However, as the disease progresses, higher doses of levodopa might be used to achieve a clinical response, which may result in peak-dose dyskinesia. Patients with advanced PD commonly experience the 'ON–OFF' phenomenon and increasing the dose further may extend the duration of peak-dose dyskinesia.[7] Fox highlighted that overcoming this issue remains a challenge for healthcare professionals treating patients with PD and that it might be avoided using the lowest possible levodopa doses.

Pathophysiology of Levodopa-Induced Complications

Fox believes the answer to why patients develop such levodopa-induced motor and non-motor complications remains complex. Decades of research indicate that the short duration of action of levodopa results in intermittent pulsatile stimulation of dopamine D1 receptors and multiple changes within the secondary messenger system, which ultimately leads to MF.[8,9] Published evidence suggests that abnormal plasticity drives levodopa-associated motor complications at both pre- and post-synaptic levels.[8,10] Firstly, as the disease progresses, there is a loss of pre-synaptic dopamine terminals in the nigrostriatal pathway and altered synaptic structure.[10] The exogenously derived striatal dopamine is not stored well or cleared, resulting in large fluctuations in extracellular dopamine levels.[8] Secondly, the peripheral metabolism of levodopa results in a short half-life due to various gastrointestinal factors, including dietary competition with protein in the gastrointestinal tract and across the blood–brain barrier; slowed gastric emptying due to disease, constipation, anticholinergics; and potentially *Helicobacter pylori* infection.[11-13] Lastly, and most importantly, post-synaptic mechanisms within the striatum affect dopamine and non-dopaminergic neurotransmission. This is due to abnormal pulsatile stimulation of postsynaptic dopamine D1 receptors, leading to changes in the second messenger signalling pathways and altered neuron firing patterns.[10] "Our research is focused on trying to prevent this intermittent pulsatile stimulation," Fox emphasised, intending to prevent the development of MF.

In concluding her talk, Fox highlighted the need for alternative therapeutic options to provide continuous dopaminergic stimulation while maximising the benefit of levodopa and presented a clinical case of a patient with recently diagnosed MF. Fox asked the audience how they would manage the patient's symptoms among different options, such as adding a catechol-O-methyl transferase (COMT) inhibitor, reducing the time interval between levodopa doses, starting a monoamine oxidase-B inhibitor, stopping the dopamine agonist they were receiving, and increasing the levodopa dose. Fox then presented a rationale for choosing or not choosing each of the options above.

Newly Emergent Motor Fluctuations: What We Think We Know

Angelo Antonini

Antonini's lecture explored and discussed the validity of the most common approaches routinely used to treat MF. An online market research survey (unpublished data, sponsored by Bial) of healthcare professionals (n=409) with extensive experience in treating patients recently diagnosed with MF (n=1,636) was conducted across six European countries. In 81% of patients (n=656), immediate change in levodopa dose was the preferred approach for managing MF versus adding an adjunct therapy (21% of patients [n=173]). However, more than twice as many movement disorder specialists (31%) versus general neurologists (15%) preferred an adjunctive treatment as the first-line option, suggesting that clinical experience in PD management is important (unpublished data, Bial).

The Goal of Optimising Levodopa Pharmacokinetics

As a prodrug, levodopa is converted to dopamine. When it crosses the blood–brain barrier, levodopa is decarboxylated to dopamine, released from the synaptic cleft, and stimulates the dopaminergic receptors, compensating for the depleted supply of endogenous dopamine in PD. Antonini briefly reviewed the concept of continuous dopamine delivery, which would mimic the normal physiological state of the brain. In this state, dopaminergic neurons fire tonically, providing an almost steady dopamine flow to the dopamine receptors. In PD, dopamine release becomes phasic and spaced out due to the gradual loss of dopaminergic neurons.[9,14] Disease progression with 70%–80% of neuron loss affects the pre-synaptic storage capacity, resulting in phasic firing, leading to peak and trough fluctuations in striatal dopamine levels. This is primarily due to a progressive decrease in the ability of the nigrostriatal neurons to synthesise and store dopamine formed from exogenous levodopa, causing a reduction in the long duration and an increase in the magnitude of the short duration response.[14,15] Eventually, patients are deemed 'fluctuators' when the benefit of levodopa is dependent on the magnitude of the short duration of levodopa response, explained Antonini.[15]

Levodopa treatment in the early stages of PD may restore normal striatal dynamics and tonic release of dopamine from presynaptic terminals; however, the short half-life of levodopa also leads to its pulsatile delivery to the brain and the development of motor complications.[11] Continuous dopaminergic stimulation more closely resembles the regular physiological phasic dopamine release and may better facilitate movement control.[9,14]

Understanding levodopa pharmacokinetics could explain the reasons behind optimal and effective treatment options. An increase in levodopa exposure (via increases of the area under the curve) increases the relative bioavailability of levodopa to be converted into dopamine.[16] Through a continuous delivery approach, one can increase levodopa troughs (i.e., increase minimum observed plasma concentration), which may lead to a decrease in OFF-time and time-to-ON (Figure 1).[16,17] By controlling the levodopa plasma peaks (control maximum observed plasma concentration), one can reduce the risks of developing dopaminergic adverse events (AE).[16,17] Therefore, pharmacokinetic optimisation of levodopa can increase its bioavailability while minimising motor complications and AEs.[16,17]

Levodopa Dose Increase Versus Dose Fractionation

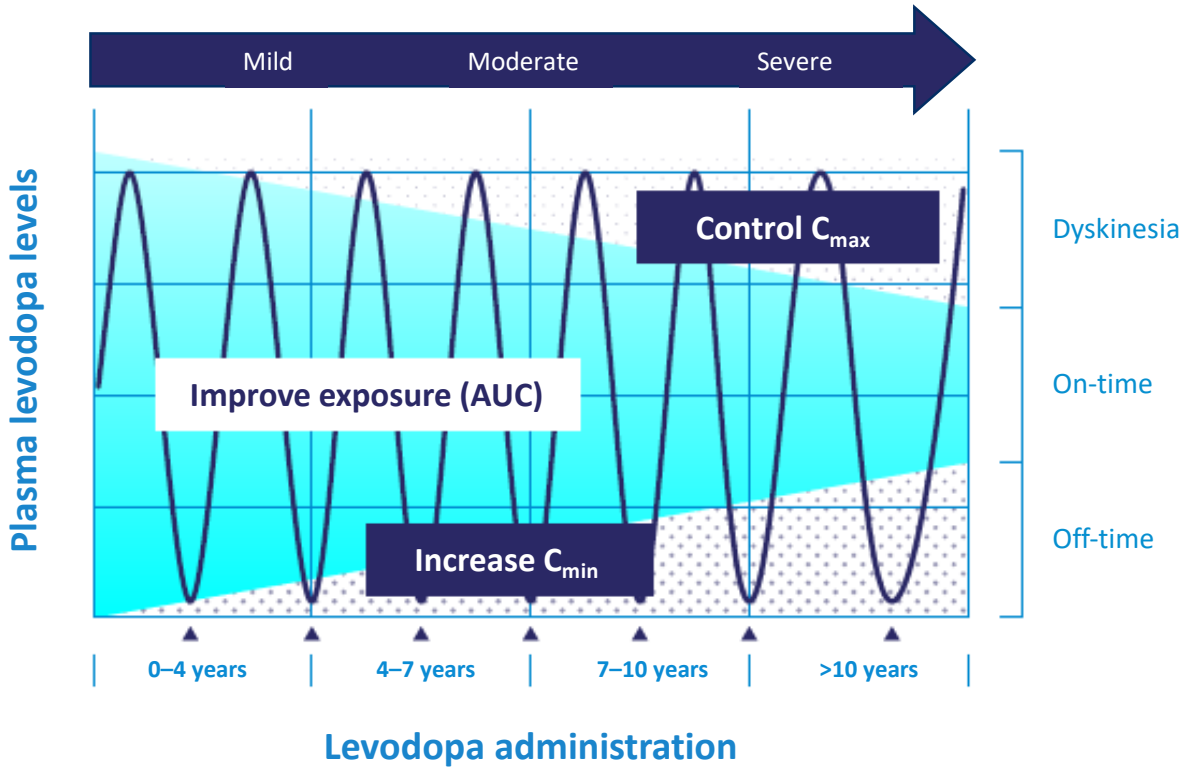
Levodopa dose adjustment (dose increase or fractionation) is still the most common approach for patients with early MF (unpublished data, Bial). However, Antonini scrutinised this approach and highlighted that increasing the amount of each dose of levodopa does not eliminate plasma level troughs, and it may lead to increased pulsatility and a greater incidence of dyskinesia.[18] Similarly, levodopa dose fractionation is ineffective at reducing troughs in plasma levels and is often associated with intermittent re-emergence of symptoms due to suboptimal levodopa exposure.[18] Results from the ELLDOPA trial[19] suggested that levodopa is the most effective drug to manage PD. Patients taking levodopa 150 mg/day (n=92) had a significantly lower risk of dyskinesia versus those taking levodopa 600 mg/day (n=91; 3.3% versus 16.5% at 42 weeks; $p<0.001$).[19] Similarly, a sub-analysis of the STRIDE-PD study[20] demonstrated a significant levodopa dose-dependent increase in wearing-off and dyskinesia risk ($p<0.001$ for both) and supported Cilia et al.'s[3] observations that motor complications and dyskinesia are not associated with the duration of levodopa therapy but rather with longer disease duration and higher levodopa dose.[3,21] Antonini concluded the session by stating that levodopa remains the gold standard treatment.[2] Adjustment of its dose remains a common approach to treating recently diagnosed MF, but therapeutic strategies to limit the increases of levodopa doses should be preferred to optimise its pharmacokinetics.[21]

Newly Emergent Motor Fluctuations: What We Thought We Knew

Joaquim Ferreira

Ferreira opened his presentation by discussing that one alternative approach to optimise levodopa pharmacokinetics would be using enzyme inhibitors such as dopa-decarboxylase inhibitors (carbidopa and benserazide), COMT inhibitors (tolcapone, entacapone, and opicapone), and monoamine oxidase-B inhibitors

Figure 1: Pattern of motor response towards levodopa changes during Parkinson's disease progression.



Mild refers to early onset of PD for 0–4 years, moderate refers to 4–10 years, and severe refers to more than 10 years of PD.

Adapted from Cenci.[17]

AUC: area under the curve; C_{max}: maximum observed plasma concentration; C_{min}: minimum observed plasma concentration; PD: Parkinson's disease.

(selegiline, rasagiline, and safinamide).[22] Research indicates that dual inhibition of dopa-decarboxylase and COMT may cause a 30–50% reduction in plasma variability of levodopa.[22,23]

Opicapone as a Levodopa Optimising Agent

Ferreira emphasised that peripheral levodopa would need to be optimised to compensate for the drop in dopamine levels in the brain in patients with PD.[22] Ferreira discussed the utilisation of opicapone (50 mg) as an adjuvant to optimise levodopa levels in the brain as an alternative option to directly adjusting the levodopa dose.[24,25]

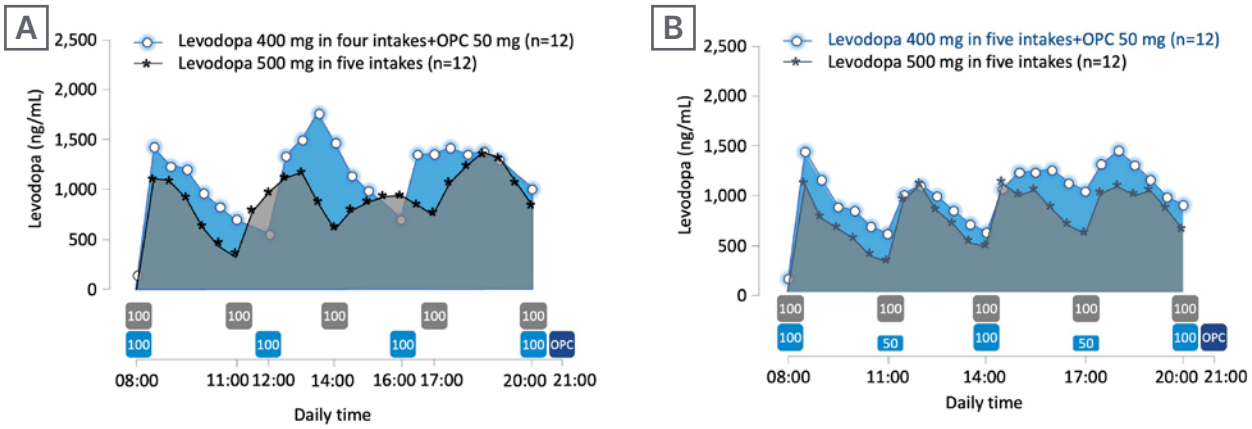
Ferreira asked the audience about their expected range of change in levodopa exposure after adding opicapone 50 mg and decreasing the daily levodopa dose by 100 mg (from 500 mg). Overall, 44% of responding attendees believed that levodopa exposure would increase by 10–20%. To explore this question further, Ferreira described results from a Phase II, open-label, modified crossover, exploratory trial (EudraCT number: 2020-003139-12) to study the effect of opicapone 50 mg on levodopa pharmacokinetics with different levodopa/carbidopa regimens in patients experiencing end-of-dose MF.[25] The effect of opicapone 50 mg on levodopa pharmacokinetics (total levodopa daily dose 400 mg) compared with baseline (total of 500 mg levodopa [without opicapone]) was the primary endpoint. Secondary endpoints included tolerability, ON- and OFF-time (measured using 12-hours ON/OFF diaries), and Patient Global Impression of Change (PGI-C).[25] Patients received levodopa/carbidopa

400/100 mg, either in four intakes (levodopa 100 mg at 4 hour intervals) plus opicapone 50 mg once daily (n=12), or in five intakes (levodopa 100/50/100/50/100 mg at 3 hour intervals) plus opicapone 50 mg once daily (n=12), for up to 14±2 days, and were compared with baseline levodopa/carbidopa 500/125 mg in a five-intake regimen (at 3 hour intervals).[25] Results indicated improvements in the pharmacokinetic profile of levodopa upon adding opicapone 50 mg despite a decrease of 100 mg levodopa in patients with PD and end-of-dose MF (Figure 2), with subsequent benefits in the motor response (Figure 3).[25]

Furthermore, patients experienced an improvement in the PGI-C upon adding opicapone to levodopa treatment in both treatment arms.[25] In the four-intake levodopa/carbidopa 400/100 mg plus opicapone 50 mg regimen, 66.7% of patients (n=12) reported an improvement on the PGI-C (very much/much/minimal improvement) with 33.4% experiencing 'much/very much improvement'.[25] Similarly, with the five-intake levodopa/carbidopa 400/100 mg plus opicapone 50 mg regimen, 91.7% reported improvement on the PGI-C (very much/much/minimal improvement), with 41.7% experiencing 'much improvement'. 'Much' and 'very much' worsening was not reported in either of the treatment arms and 'minimally worse' was reported in 8.3% patients in the four-intake arm only. Overall, addition of opicapone 50 mg to levodopa/carbidopa treatment regimen was well-tolerated.[25] Only two AEs were reported during the study (blood glucose and gamma-glutamyl transferase increased), both in the four-intakes arm. Despite the increased levodopa exposure with opicapone versus baseline, no patients reported dyskinesia as an AE.[25]

To further clarify the role of opicapone in the optimisation of levodopa, the ADOPTION trial[26] is an ongoing Phase IV, randomised, open-label, exploratory trial being conducted in 25 European sites. It aims to explore the potential of opicapone 50 mg to optimise levodopa/dopa-decarboxylase inhibitors as a first-line approach to treat wearing-off (stable treatment plus the addition of opicapone 50 mg versus an additional 100 mg levodopa/carbidopa) in approximately 100 patients with signs of wearing-off for less than 2 years, and treated with 3–4 daily oral levodopa doses (up to 600 mg) in a 4-week

Figure 2: Response to levodopa therapy in relation to levodopa pharmacokinetics.

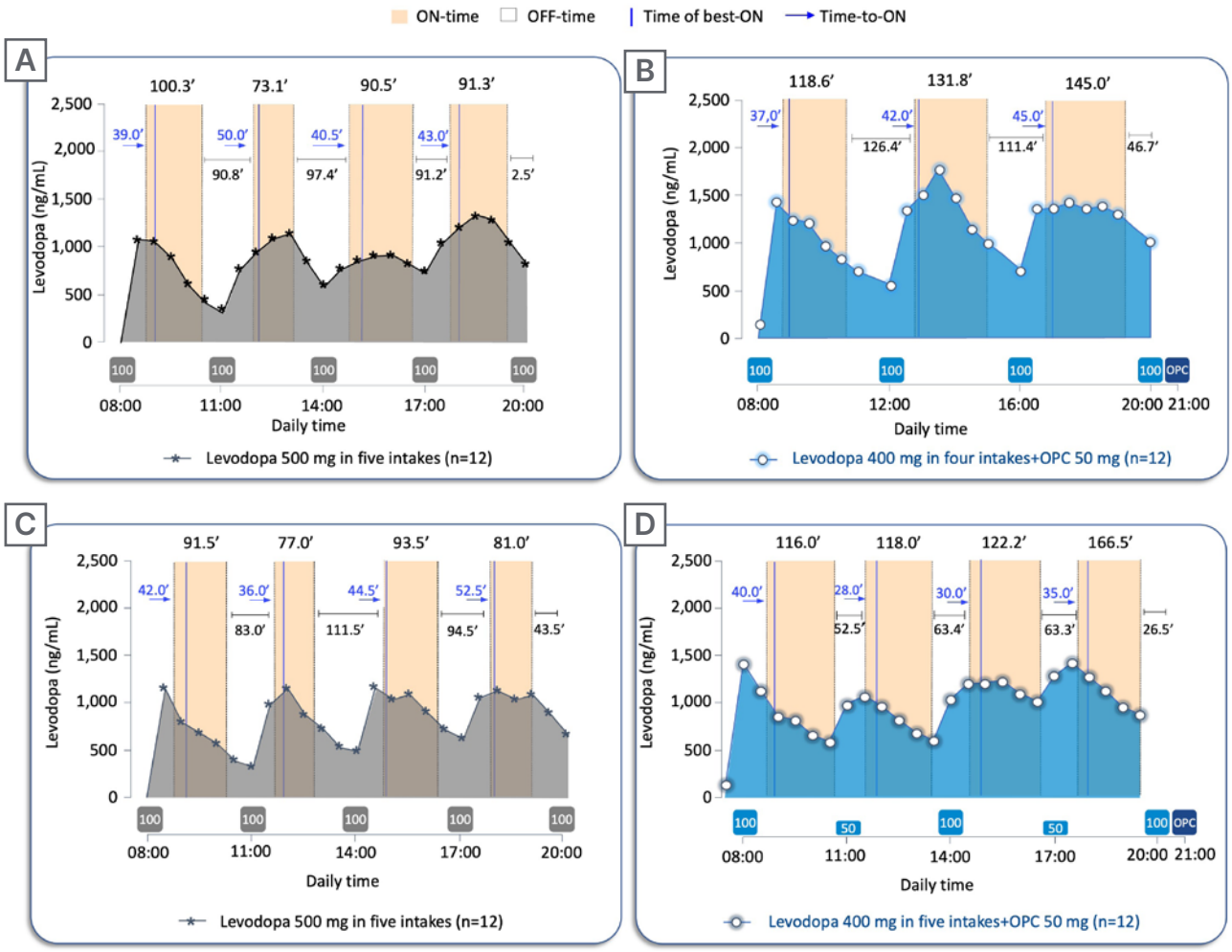


Mean levodopa plasma profile versus time following 2-week five-intake (every 3 hours) daily oral administrations of levodopa/carbidopa 500/125 mg, compared with 2-week four-intake (every 4 hours) daily oral administrations of levodopa/carbidopa 400/100 mg plus once-daily opicapone 50 mg **(A)**, or compared with 2-week, five-intake (every 3 hours) daily oral administrations of levodopa/carbidopa 400/100 mg plus once-daily opicapone 50 mg **(B)**. The boxes under the graphs indicate when levodopa (grey box for baseline regimen and light blue for test regimens; dose in mg) and opicapone (dark blue) were taken.

Adapted from Ferreira et al.[25]

OPC: opicapone.

Figure 3: Twelve-hour ON-/OFF-time data on pharmacokinetic assessment days.



Twelve-hour ON-/OFF-time data reported on pharmacokinetic assessment days superimposed to the mean levodopa plasma profile versus time following: **A)** 2-week five-intake (every 3 hours) daily oral administrations of levodopa/carbidopa 500/125 mg without opicapone, compared with **B)** 2-week four-intake (every 4 hours) daily oral administrations of levodopa/carbidopa 400/100 mg plus once-daily opicapone 50 mg; and **C)** 2-week five-intake (every 3 hours) daily oral administrations of levodopa/carbidopa 500/125 mg without opicapone, compared with **D)** 2-week five-intake (every 3 hours) daily oral administrations of levodopa/carbidopa 400/100 mg plus once-daily opicapone 50 mg. The boxes under the graphs indicate when levodopa (grey box for baseline regimen and light blue for test regimens; dose in mg) and opicapone (dark blue) were taken. Time of best-ON and Time-to-ON are reported in minutes.

OPC: opicapone.

period.[26] These inclusion criteria are a crucial aspect of the ADOPTION trial, as patients have less severe motor fluctuations (total daily OFF-time ≤5 hours) than those observed in Phase III trials, which led to the current indication of opicapone. The primary endpoint is the change from baseline in 'OFF' time at week 4. Secondary endpoints include tolerability, functional motor, and non-motor assessments through questionnaires, Hauser's home diary, and PGI-C.[26] Ferreira closed the session by describing that the ongoing studies and specifically the ADOPTION study, will help assess the effect of opicapone across the whole spectrum of MF,[26] and not only in mid-to-late stages of PD, as traditionally accepted for COMT inhibitors so far.

References

1. Dorsey ER, Bloem BR. The Parkinson pandemic - a call to action. JAMA Neurol. 2018;75(1):9-10.
2. Fahn S. A new look at levodopa based on the ELLDOPA study. J Neural Transm Suppl. 2006;(70):419-26.
3. Cilia R et al. The modern pre-levodopa era of Parkinson's disease: insights into motor complications from sub-Saharan Africa. Brain. 2014;137(10):2731-42.
4. Olanow CW, Stocchi F. Levodopa: a new look at an old friend. Mov Disord. 2018;33(6):859-66.
5. Hechtner MC et al. Quality of life in Parkinson's disease patients with motor fluctuations and dyskinesias in five European countries. Parkinsonism Relat Disord. 2014;20(9):969-74.
6. Kelly MJ et al. Predictors of motor complications in early Parkinson's disease: a prospective cohort study. Mov Disord. 2019;34(8):1174-83.
7. Stocchi F et al. Strategies for treating patients with advanced Parkinson's disease with disastrous fluctuations and dyskinesias. Clin Neuropharmacol. 1997;20(2):95-115.
8. Calabresi P et al. Levodopa-induced dyskinesias in patients with Parkinson's disease: filling the bench-to-bedside gap. Lancet Neurol. 2010;9(11):1106-17.
9. Olanow CW et al. Continuous dopaminergic stimulation as a treatment for Parkinson's disease: current status and future opportunities. Mov Disord. 2020;35(10):1731-44.
10. Matarazzo M et al. Dyskinesias and levodopa therapy: why wait? J Neural Transm (Vienna). 2018;125(8):1119-30.
11. Poewe W et al. Levodopa in the treatment of Parkinson's disease: an old drug still going strong. Clin Interv Aging. 2010;5:229-38.
12. Tan AH et al. Helicobacter pylori eradication in Parkinson's disease: a randomized placebo-controlled trial. Mov Disord. 2020;35(12):2250-60.
13. Chaná P et al. Delayed early morning turn "ON" in response to a single dose of levodopa in advanced Parkinson's disease: pharmacokinetics should be considered. J Neurol Neurosurg Psychiatry. 2004;75(12):1782-3.
14. Jenner P. Wearing off, dyskinesia, and the use of continuous drug delivery in Parkinson's disease. Neurol Clin. 2013;31(Suppl 3):S17-35.
15. Stocchi F et al. When do levodopa motor fluctuations first appear in Parkinson's disease? Eur Neurol. 2010;63(5):257-66.
16. Olanow CW et al. Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications. Lancet Neurol. 2006;5(8):677-87.
17. Cenci MA. Presynaptic mechanisms of l-DOPA-induced dyskinesia: the findings, the debate, and the therapeutic implications. Front Neurol. 2014;5:242.
18. Stocchi F. The levodopa wearing-off phenomenon in Parkinson's disease: pharmacokinetic considerations. Expert Opin Pharmacother. 2006;7(10):1399-407.
19. Fahn S et al.; Parkinson Study Group. Levodopa and the progression of Parkinson's disease. N Engl J Med. 2004;351(24):2498-508.
20. Stocchi F et al. Initiating levodopa/carbidopa therapy with and without entacapone in early Parkinson disease: the STRIDE-PD study. Ann Neurol. 2010;68(1):18-27.
21. Olanow CW et al. Factors predictive of the development of levodopa-induced dyskinesia and wearing-off in Parkinson's disease. Mov Disord. 2013;28(8):1064-71.
22. Jenner P et al. Redefining the strategy for the use of COMT inhibitors in Parkinson's disease: the role of opicapone. Expert Rev Neurother. 2021;21(9):1019-33.
23. Tuite P et al. "New treatment modalities in Parkinson's disease," Gálvez-Jiménez N (ed.), Scientific Basis for the Treatment of Parkinson's Disease (2013), London, Taylor & Francis, pp. 223-45.
24. Ferreira JJ et al. Effect of opicapone on levodopa pharmacokinetics, catechol-O-methyltransferase activity and motor fluctuations in patients with Parkinson's disease. Eur J Neurol. 2015;22(5):815-25.
25. Ferreira JJ et al. Effect of opicapone on levodopa pharmacokinetics in patients with fluctuating Parkinson's disease. Mov Disord. 2022;DOI: 10.1002/mds.29193.
26. Ferreira J et al. Opicapone ADOPTION study in Parkinson's: design of a randomized prospective, open-label exploratory trial. Eur J Neurol. 2021;28(Suppl 1):720.

Opicapone prescribing information can be found here.
For UK HCPs only, opicapone prescribing information and adverse event reporting can be found here.

ON/NOV22/G/202
Date of preparation: November 2022

Current Evidence on Tobacco Harm Reduction in Pneumology: Interviews with Two Key Opinion Leaders

Interviewees:	Wolfgang Popp,[1] Klara Szondy[2] 1. Döbling Doctor's Center, Privatklinik Döbling, Vienna, Austria 2. Semmelweis University, Budapest, Hungary

Disclosure:	Popp and Szondy have declared no relevant conflicts of interest.
Acknowledgements:	Medical writing assistance provided by Amanda Barrell, Brighton, UK.
Disclaimer:	The opinions expressed in this article belong solely to the named interviewees.
Support:	The publication of this article was supported by Philip Morris International.
Citation:	EMJ. 2022;7[4]:28-34. DOI/10.33590/emj/10044289. https://doi.org/10.33590/emj/10044289.

Interview Summary

The negative impact of smoking on the lung is well documented. Cigarette smoke is the cause of 90% of cases of chronic obstructive pulmonary disease (COPD), which includes chronic bronchitis and emphysema. COPD is a progressive and debilitating condition with morbidity and mortality rates similar to myocardial infarction (MI) and stroke. Despite the widely recognised risks, millions of people continue to smoke, in some cases even after receiving a diagnosis of COPD and despite knowing that the habit will accelerate disease progression. While there is no doubt that smoking cessation is the most important health intervention for all cigarette smokers, it can be challenging. Nicotine addiction, social norms and culture, and the length of time it can take smokers to feel the adverse consequences of the habit all contribute to the high cessation failure rate. However, increasing clinical and epidemiological evidence indicates that for those who are unwilling or cannot stop smoking, harm reduction strategies can help reduce exposure to the harmful chemicals and carcinogens released during tobacco combustion. Electronic devices heat processed tobacco without combusting it to deliver an aerosol containing fewer toxic products or harmful and potentially harmful constituents (HPHC) than cigarette smoke. Clinical evidence to support their use is growing. In Japan, for example, a decrease in hospitalisations due to COPD exacerbation after the introduction of such heat-not-burn (HNB), or tobacco heating systems (THS), has been reported.

In this article, Wolfgang Popp, Döbling Doctor's Center, Privatklinik Döbling, Vienna, Austria, and Klara Szondy, Semmelweis University, Budapest, Hungary, discuss the impact of cigarette smoke on the lung, and how to support smoking cessation in those willing and able to quit smoking. They also explain when strategies that reduce the harmful effects of smoking may be useful, and outline the latest evidence supporting the use of HNB systems.

SMOKING AND PULMONARY HEALTH

The harmful effects of cigarette smoke on human health are well documented and supported by evidence from preclinical, clinical, and epidemiological studies. Cigarette smoking damages multiple organs and leads to 8 million global deaths per year from direct use and passive exposure of cigarette smoke to non-smokers.[1] Smoking is associated with the development of at least 15 types of cancer,[2] including 80% of all cases of lung cancer,[3] and also laryngeal, oral, oesophageal, kidney, and bladder cancer.[2] Explaining that the habit reduced an individual's lifespan by an average of 10 years,[4] Popp said: "A heavy smoker has a one in eight chance of developing lung cancer, and smoking is an important risk factor for cardiovascular diseases. The risk of infections (bacterial infection and viral disease) is increased in smokers. We see so many problems with smoking."

Outlining its impact on pulmonary health, Szondy stated that cigarette smoke, which is generated when tobacco is ignited to temperatures of up to 900 °C in the burning tip,[5] contains many toxic substances that are harmful to the human body. "Since the majority of them enter the lung, they understandably damage the lung's mucous membrane, which leads to emphysema and damage to flagella, resulting in worse lung clearance," Szondy said, explaining that emphysema and poor lung clearage were characteristic of COPD.[6] "When entering the alveolar space, these materials are absorbed and damage other organs as well via oxidative stress and an incidental inflammatory pathomechanism," they added.

Smoking-related structural lung changes are responsible for an estimated 90% of all cases of COPD,[7] a chronic and progressive lung disease that includes chronic bronchitis and emphysema.[8] Long-term exposure to the toxic substances released during tobacco combustion, or HPHCs, contributes to chronic inflammation that causes airway narrowing and reduced lung expansion. COPD is characterised by progressive airflow limitation and lung tissue destruction, which results in dyspnoea, chronic cough, and expectoration.[9] Popp described COPD as "a hard disease to live with." Popp also stated that COPD "is something that really decreases health-related quality of life (HRQoL)."

Popp also stated that "people will have these problems for the rest of their life. They have the sputum production, the shortness of breath, the difficulties breathing in the morning. Then there are the social problems; people do not go out because they will be out of breath for the rest of the day. They have to use inhalers and other medicines and experience the side effects." The chronic course of COPD includes exacerbations, which can significantly impact HRQoL and health outcomes. Exacerbations of COPD are defined as acute episodes of clinical instability characterised by worsening respiratory symptoms, which often require hospitalisation.[10] Exacerbations of COPD tend to become more common in the moderate and severe stages of disease (Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stages II–IV) and are associated with increased morbidity and mortality.[10] Explaining that hospitalisation for COPD exacerbation has a lower survival rate than MI, Popp stated that "COPD is more dangerous than MI."[11]

The economic burden of the healthcare costs and social consequences of lung disease associated with smoking, including COPD, are also significant. Szondy stated that "the illnesses represent a great burden on healthcare, not only because the treatment is costly, but also due to their impact on hospital wards and the healthcare system." According to a 2017 report from the British Lung Foundation (BLF), the annual economic burden of COPD in direct healthcare and indirect societal costs to the UK economy alone is 1.9 billion GBP.[12] In Europe, the annual costs of healthcare and lost productivity due to COPD are estimated at 48.4 billion EUR.[13] "In addition to the financial implications for family members, emotional stress is also a huge factor, partly due to their concern for a loved one and partly because they must carry the burden of the illness together," Szondy added.

Despite the well-documented consequences of tobacco use and the clear medical and economic incentives to cease smoking, an estimated 1.3 billion people worldwide still smoke, which includes many smokers with a diagnosis of COPD.[1,14] For people living with the condition, smoking cessation is the most

effective intervention for halting progression, increasing survival, and reducing morbidity. However, approximately 54–77% of patients with mild COPD (Stage I) and 38–51% of patients with severe COPD (Stages III and IV) continue to smoke.[14] Popp stated that "many very severe patients, those with Stage III and IV disease stop because they cannot breathe anymore. They have to use oxygen, and that makes it hard to smoke. Unfortunately, many patients with COPD Stage II, who could modify the course of their disease, continue to smoke."

SUPPORTING SMOKING CESSATION

Physiological, psychological, and societal factors are all barriers to smoking cessation. "Smoking brings some people together; when we smoke together, it is a social situation," said Popp, adding that it was simply part of the culture in some places. "It has a psychotropic effect that amplifies the current situation," Popp said. However, many smokers want to stop. "I believe that more than one-half want to give up, and about 80% have already tried. The real problem is the addiction itself. Nicotine reaches the brain, activating dopamine neurons in just a few seconds, making it highly addictive,"[15] said Popp. Unsuccessful cessation attempts are often attributable to the "well-known and barely tolerable symptoms of nicotine withdrawal," added Szondy. "Irritability, unease, poor concentration, headaches, fatigue, excessive perspiration, weight gain due to slow metabolism, anxiety, and cravings are all among the symptoms of nicotine withdrawal," Szondy said.

"Supporting cessation can be challenging," said Popp, adding that the first step is a willing patient. "You have to have a motivated patient, that is the most important thing. As a doctor, you cannot give motivation, you can only take it away," Popp said. They also stated that "education and awareness are the keys to building this motivation. Doctors have to help the patient to understand that they are addicted, that this addiction is doing them harm, and that they do not need the addiction to be happy."

Popp highlighted the European Society of Cardiology (ESC) 'Five As' stepwise approach to supporting patients who are trying to stop smoking:[16]

1. Ask: systematically inquire about smoking status at every opportunity
2. Advise: unequivocally urge all smokers to quit
3. Assess: determine the person's degree of addiction and readiness to quit
4. Assist: agree on a smoking cessation strategy, including setting a quit date, behavioural counselling, and pharmacological support
5. Arrange: schedule a follow-up appointment to discuss progress, and offer any additional support that might be necessary

Szondy made clear that ongoing education programmes, one-to-one counselling, and raising awareness of health and social issues are the most effective means of smoking cessation support. However, this approach may not work for everyone. "Despite our best efforts, a mere 5–8% of smokers are able to quit,[17] even with all the help provided," Szondy said.

HARM REDUCTION

Smoking cessation remains the first-line intervention, but harm reduction strategies provide a practical second-line intervention for people unwilling or unable to stop completely. The concept is well established in substance and alcohol misuse fields, and has shown to be effective in reducing morbidity and mortality where abstinence is not feasible.[18] When applied to smoking, harm reduction strategies can include encouraging those unwilling or unable to quit to switch to smoke-free products, such as e-cigarettes or HNB systems.[19] "Thanks to advances in science and technology, nowadays there are alternative tobacco products, which provide an opportunity for nicotine intake without combustion and smoke alongside the mental pleasure of smoking for those who are unable or unwilling to quit smoking," said Szondy.[20]

HNB systems heat tobacco to create an aerosol that contains nicotine and a tobacco flavour, but with significantly fewer HPHCs and toxic agents than cigarette smoke.[21] Studies suggest these systems have the potential to reduce the risk to health when compared with

traditional, combustible cigarettes.[22-25] "For example, participants in a 6-month clinical study who predominantly used Philip Morris International's (PMI [New York City, New York, USA]) HNB product (≥70% HNB) had biomarker levels indicating substantially reduced exposure to a broad range of HPHCs,"[22] said Szondy. "Significantly less HPHCs associated with smoking are released when such products are used, meaning less harmful substances enter the bodies of adult smokers who cannot quit and the people around them," Szondy said.

With the growing evidence to support smoking harm reduction strategies, regulators and policy leaders are increasingly backing them. For example, the authors of the ESC smoking cessation guidelines[26] identified evidence that e-cigarettes were "probably less harmful than tobacco"[27] and more effective than nicotine replacement therapy.[28] The guidelines also noted that HNBs are lower in toxic agents when compared with regular cigarettes, although a warning was given that these systems do still contain tobacco.[26] In the USA, the U.S. Food and Drug Administration (FDA) has authorised the marketing of PMI's HNB product IQOS™ (Philip Morris International) as a modified-risk tobacco product.[29,30] Heating rather than burning tobacco significantly reduces the production of HPHCs, and scientific studies showed that completely switching from conventional cigarettes to the IQOS system reduced exposure to toxic agents.[29,30]

Of course, it is important to note that such approaches are not risk-free. Most of the new products contain nicotine, which is addictive. The long-term effects are not yet known, but potential side effects of e-cigarettes include cough, trouble breathing or chest pain, nausea, vomiting, diarrhoea, fatigue, fever, or weight loss.[31] There is also evidence to suggest that HNB systems can lead to oxidative stress, atrial stiffness, elevated heart rate and blood pressure, and vascular endothelial dysfunction.[32]

However, Popp and Szondy said they had seen how smokers were impacted by switching to HNB products. "In our experience," said Szondy, "those suffering from smoking-related respiratory diseases stop coughing soon after switching to heated tobacco products, with a rapid improvement in lung clearance."

Popp said that this effect helped them to use harm reduction strategies as a tool to aid complete smoking cessation. "Heated tobacco products reduce risk by producing a lower level of harmful substances. Carcinogenic substances and carbon monoxide are reduced immediately," they said. Popp confirmed that using these supportive products allows people to feel the benefits of cessation, whether they be increasing fitness levels or improvements in taste, and helps people better appreciate the reasons to stop completely.

CLINICAL EVIDENCE BASE

A growing number of clinical studies on the effects of HNB systems on pulmonary health have been published in recent years, further supporting their use. Szondy stated that "while previously the only results available for the impact assessment of tobacco heating system technologies essentially came from *in vitro* research and *in vivo* animal model studies, the most recent publications contain the results of follow-up studies at the population level."

For example, HNB technologies were first introduced to the Japanese market in 2014, allowing for a real-world study of hospitalisations for COPD before and after their use.[33] Analyses of real-word evidence provided the first evidence that HNB technologies could considerably reduce the consumption of conventional cigarettes among active smokers ($p<0.01$), and may also significantly reduce hospitalisations due to acute exacerbations of COPD.[33]

A 5-year follow-up cohort study from Kazakhstan evaluating exacerbations, symptoms, and lung function in people who used IQOS (n=400) compared with cigarette smokers (n=801) has published preliminary data from the 2-year follow-up.[34] Szondy said: "Persons aged between 40 and 59 years who had been smoking for at least 10 years and had switched to using mainly HNB products (>70%) were recruited as subjects, while the control group consisted of persons in the same age groups who smoked conventional cigarettes."[34] Szondy also explained that "according to the study results, tests of pulmonary function, such as the forced expiratory volume in the first second and forced vital capacity measured before and

after bronchodilation, showed improved results for THS users compared to people smoking conventional cigarettes (both p<0.05 [Table 1]). There were some positive effects among people who used THS in terms of conditions associated with metabolic syndrome, with the most significant improvement being related to blood pressure."[34]

In Italy, a retrospective study by Polosa et al.[35] looked at the effects of HNB product use on changes in COPD status between 2017 and 2020. Daily cigarette consumption, yearly exacerbation events, pulmonary function, patient-reported health outcomes, and the results of a 6-minute walk test (6MWT) test were measured in 19 adult smokers with COPD who reduced conventional smoking (dual users) or achieved abstinence by switching to heated tobacco products at months 0, 12, 24, and 36.[35] The age- and sex-matched control group comprised of 19 patients with COPD who used conventional cigarettes. Over the course of the study, dual users reduced daily conventional cigarette smoking by at least 70%.[35] "All in all, the number of acute exacerbations dropped by more than 40% while using THS,"[35] said Szondy. No significant pulmonary function changes were observed in either group. However, in many cases, the THS users moved from GOLD Stages IV and III to GOLD Stages II and I, while disease classification remained essentially the same in the control group.[35]

When recording the COPD Assessment Test (CAT) score, which measures patient-reported disease burden on parameters including cough frequency, chest tightness, and restrictions to daily living, patients with COPD using THS reported significant improvements at all follow-up assessments. However, no changes were seen in the control group (Table 2).[35] Popp said the "most important medical results" from the study were those that had the most impact on patients' wellbeing (i.e., the reduction in exacerbations and CAT score improvements).

In terms of physical endurance, an improvement was observed in the THS cohort, as recorded by the 6MWT (p=0.005). Those in the control group recorded a median distance of 250 m at baseline and 270 m at 3 years. In comparison, a median distance of 281 m was recorded among THS users at baseline, and this had increased to 350 m at a 3-year follow-up. The average improvement among the THS users was 69 m.[35] Szondy said: "According to the results of the trial, smokers who were patients with COPD and stopped consuming or at least significantly reduced their consumption of conventional cigarettes while using THS reported long-term improvement of numerous objective and subjective parameters during the 3-year follow-up period. All of this seems to demonstrate how smokeless technologies achieve harm reduction. The reduction in disease burden is most likely

Table 1: Forced expiratory air volume and forced vital capacity among conventional cigarette and heat-not-burn users at baseline, 12- and 24-month follow-ups.[34]

	Baseline	12-month follow-up	24-month follow-up	p
Conventional cigarette users	n=800	n=738	n=683	N/A
FEV1 (mean, SD)	3.11 (0.74)	3.02 (0.73)	3 (0.72)	0.0128
FVC (mean, SD)	3.74 (0.88)	3.64 (0.86)	3.52 (0.84)	<0.0001
THS users	n=400	n=362	n=329	N/A
FEV1 (mean, SD)	3.17 (0.71)	3.12 (0.67)	3.13 (0.68)	0.5187
FVC (mean, SD)	3.70 (0.83)	3.74 (0.80)	3.55 (0.80)	0.4126

P values were calculated with one-way analysis of variance for comparison of conventional cigarette and THS users at baseline and the two follow-up visits.

No post hoc tests were performed. FEV1: forced expiratory air volume; FVC: forced vital capacity ratio; N/A: not applicable; SD: standard deviation; THS: tobacco heating system.

Table 2: Comparison of chronic obstructive pulmonary disease assessment test (CAT) score between controls and heat-processed tobacco users at baseline, 12-, 24-, and 36-month follow-up visits.[35]

	Baseline	Month 12	Month 24	Month 36
Controls (n=19)	19 (17.5; 24.0)	20 (18.0; 22.0; p=0.284)	20 (15.5; 24.5; p=0.520)	20 (18.0; 23.0; p=0.709)
HNB (n=19)	20 (17.0; 24.5)	16 (14.5; 19.0; p<0.001)	17 (14.5; 19.0; p=0.001)	15 (13.0; 21.0; p=0.006)

P values were calculated through within-group comparisons vs baseline.

HNB: heat-not-burn.

attributable to the lack of chronic exposure to combustion products." No long-term harmful effects caused by THS were identified during the trial.[35] Szondy added: "The first impact assessment involving patients with COPD and other results accumulated in recent years seem to indicate that switching to smoke-free HNB technologies offers significant improvement in terms of HRQoL and physical activity among patients who are unable or unwilling to quit smoking for some reason."[35]

However, it should be noted that the study conducted by Polosa et al.[35] indicated that while harm reduction can slow down disease progression, the deterioration of pulmonary function caused by COPD is an irreversible effect of smoking. In addition, despite the overall reduction of the harmful effects of consuming tobacco products for those who do not quit smoking, THS "definitely cannot be regarded as risk-free," emphasised Szondy. "Additional studies are required in order for us to draw valid conclusions," they said, explaining that the long-term effects of glycerine, a compound present in heated tobacco products, on the bronchial mucous membrane are not yet known.

CONCLUSION

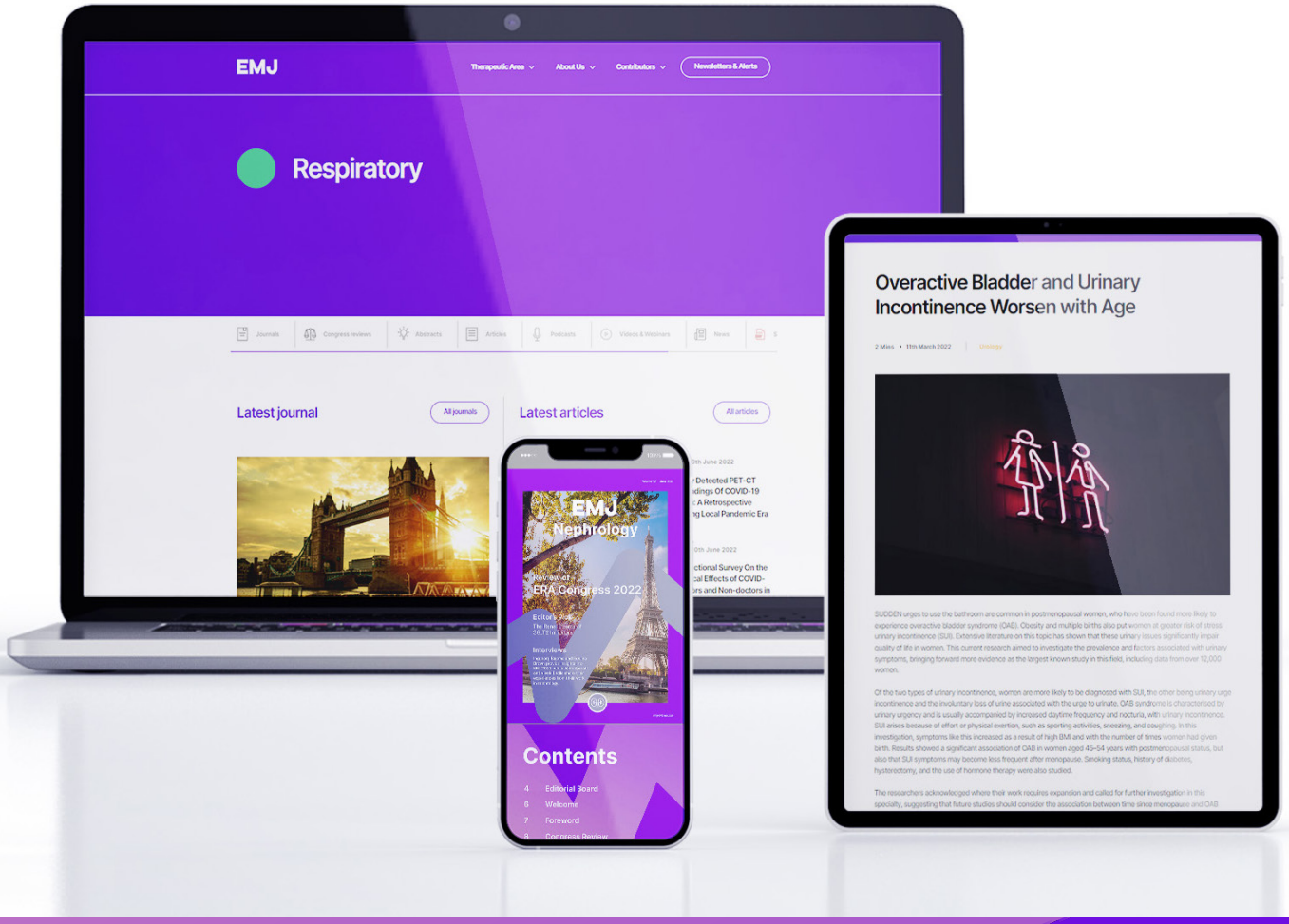
The fact that smoking kills has been proven. Studies published over the last six decades have built an indisputable evidence base demonstrating that cigarette smoke leads to multiple conditions including cancers and pulmonary diseases such as COPD. "Fully refraining from using nicotine and tobacco products continues to be the most effective way of reducing the harm caused by smoking," said Szondy.

However, harm reduction strategies, including using HNB products, provide another option to help people. "I believe this is a much better way to save people than to say: 'quit or die'. Harm reduction in cigarette smoking, just the same as in alcohol or drugs, is a more holistic, more humanistic approach," said Popp.

References

1. World Health Organization (WHO). Tobacco. 2022. Available at: https://www.who.int/news-room/fact-sheets/detail/tobacco#. Last accessed: 25 October 2022.
2. Cancer Research UK (CRUK). How does smoking cause cancer? 2021. Available at: https://www.cancerresearchuk.org/about-cancer/causes-of-cancer/smoking-and-cancer/how-does-smoking-cause-cancer#. Last accessed: 25 October 2022.
3. American Cancer Society (ACS). Lung cancer risk factors. 2019. Available at: https://www.cancer.org/cancer/lung-cancer/causes-risks-prevention/risk-factors.html. Last accessed: 25 October 2022.
4. Centers for Disease Control and Prevention (CDC). Smoking & tobacco use. Tobacco-related mortality. 2020. Available at: https://www.cdc.gov/tobacco/data_statistics/fact_sheets/health_effects/tobacco_related_mortality/index.htm#. Last accessed: 25 October 2022.
5. World Health Organization (WHO). Heated tobacco products: a brief. 2020. Available at: https://www.euro.who.int/__data/assets/pdf_file/0008/443663/Heated-tobacco-products-brief-eng.pdf. Last accessed: 25 October 2022.
6. National Health Service (NHS). Causes: chronic obstructive pulmonary disease (COPD). 2019. Available at: https://www.nhs.uk/conditions/chronic-obstructive-pulmonary-disease-copd/causes/#. Last accessed: 25 October 2022.

7. American Lung Foundation. COPD causes and risk factors. 2021. Available at: https://www.lung.org/lung-health-diseases/lung-disease-lookup/copd/what-causes-copd. Last accessed: 25 October 2022.
8. National Health Service (NHS). Chronic obstructive pulmonary disease (COPD). 2019. Available at: https://www.nhs.uk/conditions/chronic-obstructive-pulmonary-disease-copd/causes/#. Last accessed: 25 October 2022.
9. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease USA: Global Initiative for Chronic Obstructive Lung Disease. 2020. Available at: https://goldcopd.org/gold-reports/. Last accessed: 25 October 2022.
10. Gutiérrez Villegas C et al. Cost analysis of chronic obstructive pulmonary disease (COPD): a systematic review. Health Econ Rev. 2021;11(1):1-12.
11. Hillas G et al. Acute exacerbation of COPD: is it the "stroke of the lungs"? Int J Chron Obstruct Pulmon Dis. 2016;11:1579-86.
12. British Lung Foundation (BLF). The battle for breath: the economic burden of lung disease. 2016. Available at: https://www.blf.org.uk/policy/economic-burden. Last accessed: 25 October 2022.
13. European Respiratory Society (ERS). The economic burden of lung disease. 2012. Available at: https://www.erswhitebook.org/chapters/the-economic-burden-of-lung-disease/#. Last accessed: 25 October 2022.
14. Tønnesen P. Smoking cessation and COPD. Eur Respir Rev. 2013;22(127):37-43.
15. Wei C et al. Response dynamics of midbrain dopamine neurons and serotonin neurons to heroin, nicotine, cocaine, and MDMA. Cell Discov. 2018;4(1):1-16.
16. Visseren FLJ et al.; ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227-37.
17. Creamer MR et al. Tobacco product use and cessation indicators among adults—United States, 2018. MMWR Morb Mortal Wkly. 2019;68(45):1013-9.
18. Tatarsky A, Marlatt GA. State of the art in harm reduction psychotherapy: an emerging treatment for substance misuse. J Clin Psychol. 2010;66(2):117-22.
19. National Institute for Health and Care Excellence (NICE). Tobacco: preventing uptake, promoting quitting and treating dependence. 2022. Available at: https://www.nice.org.uk/guidance/ng209. Last accessed: 25 October 2022.
20. Znyk M et al. Exposure to heated tobacco products and adverse health effects, a systematic review. Int J Environ Res Public Health. 2021;18(12):6651.
21. Simonavicius E et al. Heat-not-burn tobacco products: a systematic literature review. Tob Control. 2019;28(5):582-94.
22. Haziza C et al. Assessment of the reduction in levels of exposure to harmful and potentially harmful constituents in Japanese subjects using a novel tobacco heating system compared with conventional cigarettes and smoking abstinence: a randomized controlled study in confinement. Regul Toxicol Pharmacol. 2016;81:489-99.
23. Haziza C et al. Evaluation of the tobacco heating system 2.2. Part 8: 5-Day randomized reduced exposure clinical study in Poland. Regul Toxicol Pharmacol. 2016;81(Suppl 2):S139-50.
24. Lüdicke F et al. Effects of switching to the tobacco heating system 2.2 menthol, smoking abstinence, or continued cigarette smoking on biomarkers of exposure: a randomized, controlled, open-label, multicenter study in sequential confinement and ambulatory settings (part 1). Nicotine Tob Res. 2018;20(2):161-72.
25. Lüdicke F et al. Effects of switching to a heat-not-burn tobacco product on biologically relevant biomarkers to assess a candidate modified risk tobacco product: a randomized trial. Cancer Epidemiol Biomarkers Prev. 2019;28(11):1934-43.
26. European Society of Cardiology (ESC). 2021 ESC guidelines on cardiovascular disease prevention in clinical practice: ESC Clinical Practice Guidelines. 2021. Available at: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/2021-ESC-Guidelines-on-cardiovascular-disease-prevention-in-clinical-practice. Last accessed: 25 October 2022.
27. Public Health England (PHE). E-cigarettes: an evidence update. 2015. Available at: https://www.gov.uk/government/publications/e-cigarettes-an-evidence-update. Last accessed: 25 October 2022.
28. Myers Smith K et al. E-cigarettes versus nicotine replacement treatment as harm reduction interventions for smokers who find quitting difficult: randomized controlled trial. Addiction. 2022;117(1):224-33
29. U.S. Food and Drug Administration (FDA). 2020. FDA authorizes marketing of IQOS tobacco heating system with 'reduced exposure' information. Available at https://www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-iqos-tobacco-heating-system-reduced-exposure-information. Last accessed: 25 October 2022.
30. U.S. Food and Drug Administration (FDA). Scientific review of modified risk tobacco product application (MRTPA) under section 911(d) of the FD&C Act -technical project lead. 2016. Available at: https://www.fda.gov/media/139796/download. Last accessed: 25 October 2022.
31. American Cancer Society (ACS). Health risks of e-cigarettes. 2020. Available at: https://www.cancer.org/healthy/stay-away-from-tobacco/health-risks-of-tobacco/health-risks-of-e-cigarettes.html. Last accessed: 25 October 2022
32. Fried ND et al. Heat-not-burn tobacco products: an emerging threat to cardiovascular health. Am J Physiol Heart Circ. 2020;319(6):H1234-9.
33. van der Plas A et al. Ischemic heart disease and chronic obstructive pulmonary disease hospitalizations in Japan before and after the introduction of a heated tobacco product. Front Public Health. 2022;10:909459.
34. Sharman A et al. Respiratory function and physical capacity in combustible cigarettes and heated tobacco products users: a two-year follow-up cohort study. Glob J Respir Care. 2021;7:27-34.
35. Polosa R et al. Health outcomes in COPD smokers using heated tobacco products: a 3-year follow-up. Intern Emerg Med. 2021;16(3):687-96.



Stay up to date with new advancements across European healthcare

Visit EMJ for our comprehensive collection of peer-reviewed research articles, latest interviews, and features across a range of therapeutic disciplines.

Visit EMJ

www.emjreviews.com

EMJ

Mexiletine in the Treatment of Non-dystrophic Myotonia: Interviews with Six Medical Experts

Interviewees:	Dipa Jayaseelan,[1] Valeria Ada Sansone,[2] Christiane Schneider-Gold,[3] Savine Vicart,[4] Jordi Díaz Manera,[5-7] Karim Wahbi[8] 1. University College London Institute of Neurology, UK 2. The NeMO Clinical Center, Neurorehabilitation Unit, University of Milan, Italy 3. Department of Neurology, St. Josef Hospital, Ruhr-University Bochum, Germany 4. Reference Center for Muscle Channelopathies, Service of Neuromyology, Pitié-Salpêtrière Hospital, Paris, France 5. John Walton Muscular Dystrophy Research Center, Newcastle University Translational and Clinical Research Institute, UK 6. Laboratori de Malalties Neuromusculars, Insittut de Recerca de l'Hospital de la Santa Creu i Sant Pau, Barcelona, Spain 7. Centro de Investigación Biomédica en Red en Enfermedades Raras (CIBERER), Barcelona, Spain 8. Cardiology Department, Cochin Hospital, Paris, France

Disclosure:	Sansone provides intellectual and scientific advice and receives honoraria to participate in advisory boards for Biogen, Roche, Novartis, Dyne Therapeutics, Lupin, and PTC Therapeutics. The other interviewees have declared no conflicts of interest. There was no financial support to participate in this study and provide expert opinion for this survey.
Acknowledgements:	Writing assistance was provided by Helen Boreham, HB Medical (UK) Ltd, Wetherby, UK.
Disclaimer:	The opinions expressed in this article belong solely to the named interviewees.
Support:	The publication of this interview feature was supported and reviewed by Lupin Neurosciences, a Specialty Division of Lupin Atlantis Holdings SA, Zug, Switzerland.
Citation:	EMJ. 2022;7[4]:36-43. DOI/10.33590/emj/10197860. https://doi.org/10.33590/emj/10197860.

Interview Summary

Evidence from randomised controlled clinical trials demonstrates that mexiletine effectively controls myotonic symptoms with a well-described safety profile. Despite this, there are still a limited number of patients on this treatment, and physicians from expert neuromuscular centres may not be fully aware of the potential benefits of mexiletine treatment, including improvements in patients' quality of life (QoL), the impact on activities of daily living, and the favourable safety profile, even in younger patients.

During this 'Meet the Experts' interview series, five neurologists experienced in the management of non-dystrophic myotonias (NDM), and one specialist cardiologist offered their expert insights on the clinical data and real-world evidence supporting the use of mexiletine in NDM.

Addressing patient concerns and encouraging treatment acceptance were highlighted as key steps to optimise outcomes from mexiletine therapy. The medical experts emphasised the importance of contextualising the favourable benefit-to-risk profile of mexiletine, particularly regarding cardiac safety concerns and drug monitoring requirements. The expert cardiologist further explained that, in their experience, the cardiac safety profile of mexiletine was no different in patients with NDM when compared to healthy controls used in clinical studies when used as directed.

When considering anti-myotonia treatment in patients with NDM, medical experts stressed that decision-making should be driven by the overall degree of myotonia. Healthcare professionals (HCP), therefore, need to look beyond basic clinical assessment to understand the true impact of myotonia on patients' everyday lives.

Overall, these interviews highlighted the critical role that HCPs can play in leveraging the clinical data and managing patient expectations to ensure maximum treatment success when recommending mexiletine to patients with NDM.

INTRODUCTION

NDM includes a group of rare hereditary neuromuscular disorders caused by mutations in the genes that encode sodium or chloride muscle channels.[1] Myotonia is the hallmark symptom of NDM and presents as muscle stiffness, often associated with pain, fatigue, and weakness, which can limit function.[2] Mexiletine is a Class IB antiarrhythmic medication, which has been shown to reduce muscle fibre excitability caused by common NDM mutations in preclinical models.[2] Mexiletine (NaMuscla® [Lupin Healthcare (UK) Ltd, Slough, UK]) is currently authorised by the European Medicines Agency (EMA) and Medicines and Healthcare products Regulatory Agency (MHRA) for the treatment of myotonia in adult patients with non-dystrophic myotonia disorders.[3]

This article captures the views of six medical experts who were posed questions on key topics relevant to the use of mexiletine in NDM as a part of a 'Meet the Experts' interview series conducted by Lupin Neurosciences (Zug, Switzerland). Five neurologists with a wealth of experience in the field were interviewed, as well as one expert cardiologist, who was questioned specifically on the cardiac safety profile and cardiac monitoring requirements with mexiletine.

THE RELEVANCE OF TREATMENT FOR MYOTONIA IN PATIENTS WITH NON-DYSTROPHIC MYOTONIAS AND PATIENT QUALITY OF LIFE

In the first part of this interview series, the NDM experts considered the relevance of the treatment of myotonia in patients with NDM, particularly the impact on QoL. QoL is an important issue for clinical consideration as evidence indicates that, although transient, symptoms such as myotonia exert a high impact on QoL in patients with NDM. In a study where QoL was assessed using the individualised QoL (INQoL) and Short Form 36 (SF-36) questionnaires, patients with skeletal muscle channelopathies showed similar scores and negative perceptions of QoL to those of patients with myotonic dystrophies.[4]

The five experts in neuromuscular disorders highlighted how symptoms of myotonia in patients with NDM could vary in frequency and severity, which may influence the clinical decision to treat. In particular, they noted the key factors that can trigger symptoms (e.g., cold weather or changes in outside temperature) and suggested how the timing and duration of treatment may be tailored accordingly. "I'll often suggest a short trial of treatment, if patients have significant symptoms; symptoms that are affecting their life, even if it's not every day, because often,

they won't realise some of the myotonia that's there in the background that they've been compensating for all their life," said Dipa Jayaseelan, University College London Institute of Neurology, UK. Jayaseelan also stated that "trying the treatment can really reveal to them how good they could be." Jordi Díaz Manera's, John Walton Muscular Dystrophy Research Center, Newcastle University, UK, clinical experience confirms that "patients [...] always have days that are better and days that are worse, although they always have like a certain degree of myotonia." Díaz Manera emphasised that "it's a question of discussing with them what can improve [...] and then in most of the cases, they will like to be treated."

The experts were unanimous on the importance of looking beyond the clinical assessment of myotonia in NDM and considering the broader impact on the daily lives of patients with NDM when making a decision about treatment. In particular, they highlighted the difference between how patients present in a clinical consultation in a warm indoor setting versus the challenges they may face when dealing with the symptoms of myotonia on a daily basis. Jayaseelan stated that "it's a hugely important part of the assessment, seeing how they are outside of the consultation and discussing what those symptoms are that they struggle with, and how treatment might help with those, and target it." Christiane Schneider-Gold, Department of Neurology, St. Josef Hospital, Ruhr-University Bochum, Germany, supported this point: "I think the impression you have from patient you see in your outpatient department or in your private practice may give you an impression of the severity of myotonia in general, but it may not reflect special situations in daily life. You have to listen carefully to the patient to get an overall impression of the disease and severity of disease in this particular patient." Valeria Ada Sansone, The NeMO Clinical Center, Neurorehabilitation Unit, University of Milan, Italy, further emphasised that it was important to "listen to the patients and see and hear what they tell you about how they're doing." Savine Vicart, Reference Center for Muscle Channelopathies, Service of Neuromyology, Pitié-Salpêtrière Hospital, Paris, France, cautioned that "clinical assessment of myotonia performed during a visit or consultation and the impact of the myotonic symptoms on the patient's daily life are not always correlated."

Alongside clinical and functional assessment tools, the experts highlighted the key questions that can help HCPs to better understand the burden of myotonia experienced by patients with NDM. This includes asking patients about their pain and fatigue, as well as probing the impact of myotonia symptoms on school or work life; sports; travel; and activities of daily life such as feeding and talking. As Jayaseelan elaborated: "For a patient, it's often very individual, the things that cause the myotonia to get worse and the things, the elements of their life, that the myotonia affects, and so we like to delve into those aspects to really understand how the myotonia is affecting them." Díaz Manera recommended asking patients to provide examples of how activities are influenced by the symptoms as it is "really useful to understand what's going on in the patient."

The experts stressed that understanding the true burden of myotonia symptoms and the associated impact on QoL was pivotal in determining which patients would benefit from anti-myotonia treatments such as mexiletine. "The decision to treat the patient with an anti-myotonia treatment is based on the individual type of myotonia and individual degree of the severity of myotonia and the individual challenges in the patient's life," noted Schneider-Gold. Although mexiletine is not a curative option for NDM, the experts agreed that it can have a significant positive effect in relieving disease burden, even in those patients who may not appreciate the true impact of the condition on their everyday lives. As Sansone explained: "I recommend mexiletine as the first line of choice to all patients with myotonia. I don't base myself on their channel pathology. If I see myotonia I suggest mexiletine, and I talk them into the action and why I'm giving it to them, and the safety profile and I try to make them think that they may feel better."

This point was reiterated by Vicart: "I consider that patients with NDM who will benefit in the first place from anti-myotonia treatment are the ones who present clinical severe myotonia, because I assume they might have an important impact of their symptoms in their daily life." In Díaz Manera's experience, "if they have symptoms that are impacting the way how they do things in their daily life, then they will benefit."

EXPERT DISCUSSION ON MEXILETINE DATA

In the second part of this interview series, the experts discussed the key clinical studies that provided the evidence to support the use of mexiletine in treating myotonia symptoms in patients with NDM.

Clinical data have shown that the symptoms of myotonia are reduced significantly following treatment with mexiletine, and the experts agreed that this has important implications for patients with NDM in terms of improvement in their QoL.[2,5,6] "There is actually very good evidence that treating patients who have NDM with mexiletine improves their symptoms," remarked Jayaseelan, "and this is really reflected in their QoL measures in the study and when you speak to the patients." Schneider-Gold agreed: "Patients with NDM can expect that mexiletine contributes to their QoL and their ability to move and to do all the things in daily life during the time they take mexiletine, and it has been clearly shown in short-term as well as in long-term studies there was no decline of efficacy of mexiletine during the treatment period."

Supporting the positive impact of mexiletine on both clinical symptoms and patient QoL, the experts referred to the randomised, placebo-controlled trial conducted in seven clinical centres in four countries[7] and also reported by Statland et al.[2] in 2012, as well as the more recent MYOMEX study[5] from France, which was reported in 2021. "Statland et al. showed significant improvements not only in the stiffness, but also in pain and fatigue scores for those patients who got mexiletine over placebo," stated Jayaseelan. "The MYOMEX study as well also showed significant improvement of QoL scores across the board for all domains." As Vicart elaborated: "According to the French MYOMEX study, in addition to the stiffness improvement, an improvement in QoL assessed by the INQoL scale was observed in patients with myotonia congenita and paramyotonia congenita, and this improvement under mexiletine was significant for the total population with the treatment effect on each domain of the INQoL questionnaires." Díaz Manera described several examples of mexiletine's clear (positive) impact on daily activities of patients, corroborating the findings in clinical trials that "patients explain that there is a clear change in the daily activities, thanks to the medication." Jayaseelan concluded: "So, I do think there's good evidence that mexiletine improves quality of life in patients."

When asked about long-term safety data supporting the prolonged use of mexiletine in patients with NDM, the medical experts highlighted the favourable safety profile and good tolerability of mexiletine. "There are short-term and long-term studies showing that there is no severe increase of side effects during treatment [...] mexiletine seems to be rather safe and well tolerated in most patients," commented Schneider-Gold. Vicart further explained that the long-term safety of mexiletine in NDM has been evaluated in two retrospective studies, which found that "no patient developed a cardiac arrhythmia or other serious side effects requiring drug discontinuation," and in which "mexiletine was considered as a well-tolerated drug in most of the patients."[8,9] Jayaseelan added that "in our clinical practice, we've not seen any severe cardiac adverse events [...] generally, the feeling is the long-term safety data does support prolonged use of mexiletine and that it's safe." This point was reiterated by Sansone: "There's real-world evidence and personal experience with years and years of mexiletine, meaning decades of use, with safety monitoring of both the symptoms and the ECG, with basically very few patients having to stop because of cardiac side effects."

All five experts in the neuromuscular field acknowledged that it would be helpful to continue to gather longer-term clinical safety data on the use of mexiletine in NDM, including in paediatric patients, as this will add to the existing clinical evidence base. "There is quite good safety data available on mexiletine in the short term, there's less long-term safety data," conceded Jayaseelan. "Long-term data would really be helpful, especially for the cardiac side and for gastrointestinal issues," added Sansone. Díaz Manera added that "although [mexiletine] is an anti-arrhythmia drug, there are no data suggesting that [it] has any cardiac toxic effects, which I think it's very important that patients do not develop arrhythmias because of the treatment."

All the experts were aligned on the view that mexiletine shows similar efficacy in patients with NDM, irrespective of the underlying channelopathy. "Based on the data and clinical studies, there's no major difference in the response to mexiletine in sodium and chloride channelopathies," commented Schneider-Gold. Vicart concurred: "None of the clinical trials published can conclude clearly to a significant difference of mexiletine efficacy between patients with chloride or sodium channel mutations." However, the medical experts explained that some adjustments may be required to the mexiletine dose in sodium channelopathy patients in the clinical practice setting, depending on the improvement in key symptoms such as pain. Jayaseelan pointed out that recessive patients can be more treatment resistant and may require higher doses of mexiletine to optimise clinical outcomes.

General consensus among the medical experts was that mexiletine data obtained from clinical trials showed good concordance and correlation with their real-life experiences of using the drug to treat patients with NDM. "Data from clinical studies really fit very well with real-life data, showing that mexiletine improves pain, myotonia, and, in some aspects, also weakness and fatigue, in patients with NDM," noted Schneider-Gold. "In both groups, sodium channelopathies and chloride channelopathies, there's no major difference and the effects are comparable in those types of NDM." This point was echoed by Jayaseelan: "We do see in clinical practice that patients notice quite striking differences in their stiffness when they start mexiletine [...] the real-life data very much reflects what we've seen in the trials," and further supported by Vicart, who stated: "In my opinion, the data from all the clinical trials, published for 10 years, now position mexiletine as the first treatment, [and] have such a strong evidence based on efficacy and safety." While Sansone agreed that "there's sufficient data to say that myotonia is taken care of by mexiletine," they added the caveat is "the extent of what symptoms really respond and for how long and for which patients specifically, I don't think there's sufficient information to be so clear on this." Sansone also noted that, in their experience, improvement in symptoms tended to be more marked in chloride versus sodium channel patients. Díaz Manera described their experience, and that "what patient say in the trial is what we see when we treat a patient in normal clinic, so patients improve their QoL [and] the daily life activities actually improve."

HOW EXPERTS ADDRESS PATIENT CONCERNS AND EXPECTATIONS ABOUT TREATMENT

For the third segment of the interview, the medical experts considered how to address patient concerns and expectations around treatment with mexiletine, particularly regarding safety, including cardiac assessments and follow-up.

The experts acknowledged that patient expectations before receiving mexiletine could have a significant influence on their treatment satisfaction. Vicart explained that "if a patient expects to be totally cured by mexiletine," then this patient has "a huge risk to be disappointed and then to stop the medication." Managing patients' expectations of potential improvements in their NDM symptoms was, therefore, seen as crucial when recommending mexiletine. "We go through quite a careful process

when we're prescribing mexiletine, or suggesting the treatment with mexiletine," elaborated Jayaseelan. "We do spend a lot of time explaining what we think will benefit from the mexiletine, so we talk about how it's going to most likely to benefit their stiffness, and possibly some of their pain and tiredness, but much more the stiffness, so we manage the expectations of what exactly the treatment is going to do for their non-dystrophic myotonia." Schneider-Gold agreed: "Depending on the severity of NDM, I explain that the patient will have benefit from mexiletine, but in some cases, it cannot be expected that the patient will be completely free of symptoms." Sansone mentioned that some patients may feel that myotonia is not really important to them "because of the warm-up phenomenon." Sansone shared their pragmatic approach to prompting those patients to think what their life would be like if they didn't have that problem, which usually results in them agreeing that it would be much better without myotonia. "Once they have the drug and they see it's really doing something, they rather would stay on the drug because they see it's working."

The experts in the neuromuscular field agreed on the importance of accurately positioning the benefits and risks of mexiletine when discussing treatment with patients with NDM. Jayaseelan said that they would begin by outlining the efficacy benefits of mexiletine to patients and then move on to an open discussion about the potential side effects and how these will be monitored, thus making it "much more likely that they get good benefit without having significant disadvantages from it."

Regarding potential side effects with mexiletine, Sansone noted: "My experience is that it's quite a well-tolerated drug." Sansone added that taking the drug with meals can help reduce the likelihood of gastrointestinal disturbances. Schneider-Gold concurred: "I tell the patient that no drug is really without outside effects and that he or she can't expect there will be no sensation of anything, but in normal situations, there will be no major side effects." Vicart reiterated that the benefit-to-risk balance for mexiletine is mainly favourable as "all the studies published showed that mexiletine significantly improved stiffness and, when it was assessed, the QoL, and that treatment was well tolerated, confirming a positive safety profile." In Díaz Manera's experience, patients with whom they discussed mexiletine "are not really worried about the adverse effects," and "when you do describe to them that they can improve, they are more interested in the positive part of the treatment than any potential harm."

Mexiletine requires mandatory cardiac assessments before initiation and during titration. The neuromuscular experts underscored the importance of good patient education to mitigate any potential impact of this on willingness to accept treatment. As Vicart advised: "It's our role to explain to the patient that there is no cardiac involvement in NDM and that in the literature data, older literature data showed the absence of any significant change in cardiac monitoring and assessment, or showed the absence of serious cardiac adverse events during short-term and long-term follow-up." However, Vicart acknowledged that "it's important to identify the patients who can have a potential underlying cardiac problem due to another origin and which can be aggravated by the mexiletine." Jayaseelan also pointed out that "most patients are very keen to have those initial tests done to make sure their heart is safe to have the medication [...] and most patients continue with them throughout and without significant problems." Díaz Manera explained that it is normal for patients to initially feel anxious about starting a treatment that "can be somewhat dangerous." Díaz Manera's recommendation to address these concerns was to discuss the long-term safety data, and to show patients that there is a clear plan to minimise risk, including the tests that will be performed. Sansone noted: "For all patients with myotonia, I think that a cardiac check to start with, with an ECG and a cardiologist saying okay you can start, makes everybody happy. And I don't see that as a limitation."

WHAT CAN BE LEARNT FROM THE CLINICAL DATA IN RELATION TO THE CARDIAC SAFETY OF MEXILETINE?

To further understand the experts' experience related to the cardiac safety profile of mexiletine, this topic was the focus of the final interview segment, with additional expert insights provided by Consultant Cardiologist Karim Wahbi, Cochin Hospital, Cardiology department, Paris, France.

"Mexiletine treatment [...] has a direct effect on the cardiac electrical system, and inappropriate use of the treatment can result in an increased risk for cardiac complications, mainly cardiac arrhythmias," clarified Wahbi. The other experts agreed that the paradoxical potential of mexiletine to cause or exacerbate arrhythmias was the main cardiac safety concern associated with the drug. However, Sansone pointed out that "patients with channelopathies usually do not have a cardiac rhythm abnormality as part of their disease." Sansone added that ECG monitoring is preferred, especially for patients with sodium channelopathies.

When asked about the long-term cardiac safety data supporting the use of mexiletine in patients with NDM, Wahbi responded: "Well, we have several studies showing that the safety of mexiletine in patients with NDM is extremely good. In those studies, which have been published to date, the incidence of major complication was extremely low." Wahbi concluded that "we have currently a body of evidence suggesting that the treatment can be used extremely safely in this population." Other experts and clinical studies support this view that the long-term data from clinical trials of mexiletine in NDM have not revealed any evidence of arrhythmia or increased risk of cardiac events during treatment.[8,9]

Key measures are already in place and outlined in the summary of product characteristic, to minimise the risk of potential cardiac side effects due to mexiletine in patients with NDM. The experts flagged the importance of implementing these precautionary steps, particularly in patients with pre-existing cardiac abnormalities. "It is extremely important to offer patients very careful cardiac assessments before the initiation of the treatment, just to make sure that there is no contraindication to the treatment and during follow up [...] as long as patients are treated," explained Wahbi. Wahbi continued: "Before the initiation of the treatment, it's important to have an ECG and an echocardiogram to make sure that patients do not have conduction defects, or repolarisation abnormalities, or left ventricular dysfunction that may present a contraindication to the treatment [...] Later, patients treated with mexiletine should have cardiac investigations [...] at least every 2 years, if all previous assessments were normal, and those assessments should be repeated more frequently, every 6 months or on a yearly basis, if mild abnormalities have been identified, that do not present contraindications to use the treatment. Those assessments should include an ECG [at each follow-up visit and less frequently], an echocardiogram and a Holter ECG." These recommendations were supported by Vicart: "Patients who can have another pre-existing cardiac abnormality, those patients will need cautious cardiac monitoring with ECG performed after each dose increases and a periodic cardiac evaluation at least annually, and for the other patient without pre-existing cardiac abnormalities, which fortunately represent the majority of the patients with NDM, a periodic ECG is recommended annually or at least every 2 or 3 years."

Wahbi advised that "one other important point is that patients who complain of cardiac symptoms during follow-up systematically referred to a cardiologist in order to estimate the potential role played by mexiletine in the development of those symptoms, and to make sure that patients did not develop significant cardiac abnormalities during follow-up."

The experts then discussed the potential benefits of the mandatory cardiac assessments required before initiation and during titration of mexiletine in patients with NDM, noting how these steps can

help both patients and clinicians feel 'safer' in prescribing mexiletine by ensuring any cardiac risks are effectively mitigated. As Wahbi emphasised: "The purpose of cardiac investigations is to avoid major cardiac complications in patients treated with mexiletine. If mexiletine is used properly, then the cardiac risk is close to that of an individual in the general population. So, it's very important to arrange cardiac investigations, just to make sure that patients do not have abnormalities that may confer a specific risk for them to develop cardiac complications [...] if you do those assessments properly, then patients have very reasonable risk to develop complications and the treatment can be used really safely." Overall, the experts concurred that the cardiac safety profile of mexiletine in patients with NDM is equivalent to that in a healthy, or control, population when the drug is used as directed.

In summary, the NDM experts agreed that there was a strong link between how physicians present treatment options, such as mexiletine, and how patients perceive the benefits of treatment. For patients with chronic diseases, such as NDM, an improved understanding of the burden of disease and benefits of treatment can improve drug treatment compliance and treatment outcomes, leading to greater success in controlling symptoms such as myotonia.

References

1. Vereb N et al. Non-dystrophic myotonias: clinical and mutation spectrum of 70 German patients. J Neurol. 2021;268(5):1708-20.
2. Statland JM et al. Mexiletine for symptoms and signs of myotonia in non-dystrophic myotonia: a randomized controlled trial. JAMA. 2012;308(13):1357-65.
3. European Medicines Agency (EMA). Mexiletine (NaMuscla®): summary of product characteristics. 2018. Available at: https://www.ema.europa.eu/en/documents/product-information/namuscla-epar-product-information_en.pdf. Last accessed: 5 August 2022.
4. Sansone VA et al. Measuring quality of life impairment in skeletal muscle channelopathies. Eur J Neurol. 2012;19(11):1470-6.
5. Vicart S et al. Efficacy and safety of mexiletine in non-dystrophic myotonias: a randomised, double-blind, placebo-controlled, cross-over study. Neuromuscul Disord. 2021;31(11):1124-35.
6. Kwieciński H et al. Treatment of myotonia with antiarrhythmic drugs. Acta Neurol Scand. 1992;86(4):371-5.
7. Richard Barohn, MD. Effectiveness of mexiletine for treating people with non-dystrophic myotonia. NCT00832000. https://www.clinicaltrials.gov/ct2/show/NCT00832000.
8. Suetterlin KJ et al. Long-term safety and efficacy of mexiletine for patients with skeletal muscle channelopathies. JAMA Neurol. 2015;72(12):1531-3.
9. Modoni A et al. Long-term safety and usefulness of mexiletine in a large cohort of patients affected by non-dystrophic myotonias. Front Neurol. 2020;11:300.

TAKING CARE OF PATIENTS WITH PCA: A FOCUS ON THE TIMELINESS OF ADT

The publication of this infographic is supported by an unrestricted educational grant from Recordati.

EPIDEMIOLOGY

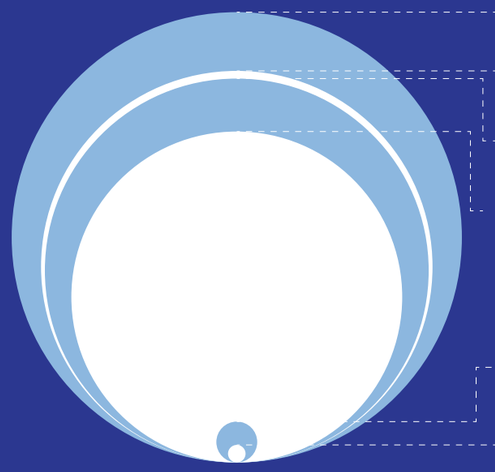
PCa is the 2nd **most commonly diagnosed cancer in males**[1]

In 2020[2]

335,514 new cases

69,945 deaths

Geographic epidemiology of PCa incidence (ASR per 100,000)[1]



GUIDANCE ON THE USE OF ANDROGEN DEPRIVATION THERAPY

ADT is the current standard of care for advanced PCa[1]

LHRH agonists and antagonists are used to suppress serum T levels to those seen following surgical castration[1]

Dosage available at 1-, 3-, and 6-month delivery intervals via subcutaneous or intramuscular injection[1]

Current EAU guidelines state a **castration T level as <50 ng/dL**, but a more appropriate level should be defined as <20 ng/dL (1 nmol/L) as current testing shows a level of **15 ng/dL** in surgically castrated patients[1]

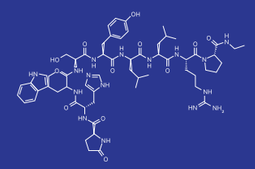
Better results shown from maintaining lower T levels **(<20 ng/dL)**[1]

Approximately **13–38%** of patients treated with an LHRH analogue fail to achieve T levels <20 ng/dL[1]

Advantages to treatment maintaining T levels at <20 ng/dL

- **Improved** biochemical relapse-free survival[3]
- **Extends** tumour-specific survival rates[4]
- **Prolonged** time to progression in metastatic disease[5]
- **Improvement** in duration of response and time to CRPC[7]
- **Lower** rate of biochemical recurrence[6]

DRUG POSITIONING OF LEUPRORELIN ACETATE AS A SOLUTION FOR PCa



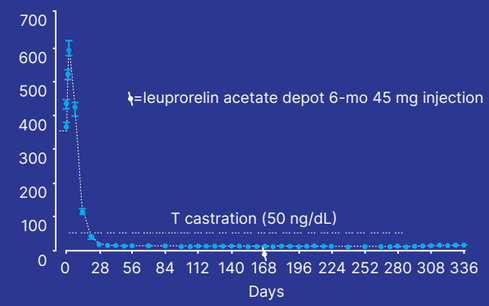
Introduced for medical use in 1985, **leuprorelin acetate** was the **first LHRH agonist** synthesised and used for PCa treatment for >30 years[8]

Successful in **delaying tumour progression** and alleviating symptoms e.g., bone pain[8]

88%

Leuprorelin acetate depot **suppresses T to <20 ng/dL in 88% of patients** (n=111) (EAU Guideline revised recommendation)[1,9]

Graph presenting the mean serum T ±SE during treatment:[9]



Average T level (±SE)=12.3 (±2.1) ng/dL at 12 months[9]

Maintained through ongoing treatment

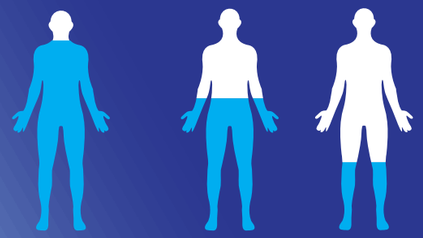
- Hot flashes
- Injection site burning
- Gynecomastia

Adverse effects noted were known physiological changes **as a result of testosterone suppression**[9]

IMPORTANCE OF DOSING TIMELINES

Retrospective analysis of records of patients with PCa in USA (n=22,860)[4]

Late Dosing Prevalence (over a 28-day month period)[4]



Overall **84%** ADT injections late

60% >1 week late

29% >2 weeks late

Late Dosing Prevalence (over the 'extended' month period)[4]

Overall **27%** ADT injections late

13% >1 week late

9% >2 weeks late

Impact[4]

4% of **early/on-time** ADT injections associated with T >50 ng/dL

15% of **late** 28-day month and **27%** **late** extended month ADT injections associated with T >50 ng/dL

Impact on the goal of reducing T <20 ng/dL (on-time dosing vs. late dosing)[4]

28-day month

22% vs **31%**

associated with T >20 ng/dL

28-day month

21% vs **43%**

associated with T >20 ng/dL

Key effects on treatment outcomes[4]

Failure in maintaining T <20 ng/dL may lead to treatment failure → decreased survival → increased costs for further healthcare

Increased potential for restoration of hypothalamic pituitary–gonadal axis function with rise in T

Increased likelihood of acute-on-chronic T surges with further doses

Abbreviations

ADT: androgen deprivation therapy; ASR: age-standardised rates; CRPC: castration-resistant prostate cancer; EAU: European Association of Urology;GnRH: gonadotropin-releasing hormone; LHRH: lutenising hormone-releasing hormone; PCa: prostate cancer; SE: standard error; T: testosterone.

References

1. Mottet N et al. EAU - EANM - ESTRO - ESUR – SIOG guidelines on prostate cancer. 2020. Available at: https://uroweb.org/guidelines/prostate-cancer. Last accessed: 14 October 2022.
2. ECIS - European Cancer Information System. Estimates of cancer incidence and mortality in 2020, for all countries. 2020. Available at: https://ecis.jrc.ec.europa.eu/explorer. Last accessed: 10 April 2021.
3. Ozyigit G et al. Prognostic significance of castrate testosterone levels for patients with intermediate and high risk prostate cancer. World J Clin Oncol. 2019;10(8):283-92.
4. Crawford ED et al. The impact of late luteinizing hormone-releasing hormone agonist dosing on testosterone suppression in patients with prostate cancer: an analysis of United States clinical data. J Urol. 2020;203:743-50.
5. Tamada S et al. Time to progression to castration-resistant prostate cancer after commencing combined androgen blockade for advanced hormone-sensitive prostate cancer. Oncotarget. 2018;9(97):36966-74.
6. Gomella LG. Effective testosterone suppression for prostate cancer: is there a best castration therapy? Rev Urol. 2009;11(2):52-60.
7. Klotz L et al. Nadir testosterone within first year of androgen-deprivation therapy (ADT) predicts for time to castration-resistant progression: a secondary analysis of the PR-7 trial of intermittent versus continuous ADT. J Clin Oncol. 2015;33(10):1151-6.
8. Merseburger AS, Roesch MC. Advanced delivery of leuprorelin acetate for the treatment of prostatic cancer. Expert Rev Anticancer Ther. 2022;22(7):703-15.
9. Crawford ED et al. A 12-month clinical study of LA-2585 (45.0 mg): a new 6-month subcutaneous delivery system for leuprolide acetate for the treatment of prostate cancer. J Urol. 2006;175:533-6.

The Pathophysiological Relationship Between Migraine and SARS-CoV-2 Infection: A Comprehensive Literature Review

Editor's Pick

Severe acute respiratory syndrome coronavirus 2 has brought new challenges for healthcare professionals around the world. While a large focus has been on respiratory conditions, neurologists such as Elkurwi and Elkurwi have investigated how COVID-19 has affected patients with migraine. The authors of this literature review took a deep dive into those who had been infected with severe acute respiratory syndrome coronavirus 2 and those who had not, and how COVID-19 has impacted their condition.

Markus Peck-Radosavljevic
Professor of Medicine, Chairman, Department of Gastroenterology and Hepatology, Endocrinology, Rheumatology and Nephrology, Klinikum Klagenfurt am Wörthersee, Klagenfurt, Austria

Authors:	*Noor Elkurwi, Qabas Elkurwi Department of Neurology, Stroke and Neurorehabilitation, Barlicki Hospital, Medical University of Łódź, Poland *Correspondence to nrthja@gmail.com
Disclosure:	The authors have declared no conflicts of interest. The work was equally divided between the authors. Both authors read and approved the final manuscript.
Acknowledgements:	The authors would like to acknowledge and thank their supervisor, Jacek Rożniecki, for their expert advice and support throughout this project. Rożniecki's guidance carried the authors through all stages of writing this research article.
Received:	04.05.22
Accepted:	02.11.22
Keywords:	Calcitonin gene-related peptide (CGRP), COVID-19, cytokines, mechanism of action, migraine, nod-like receptor protein 3 (NLRP3) inflammasomes, pathophysiology, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
Citation:	EMJ. 2022;7[4]:46-55. DOI/10.33590/emj/10054250. https://doi.org/10.33590/emj/10054250.

Abstract

People with migraine, and individuals with other neurological conditions, have suffered in multiple aspects during the COVID-19 pandemic. This paper will discuss the factors that impacted the neurology department. The emergence of severe acute respiratory syndrome coronavirus 2 in late 2019 has generated

new challenges in healthcare systems across the globe. Similar to the fields of pulmonology and cardiology that saw an increase in research, the neurology department was in search of possible relationships between COVID-19 and other medical conditions. Research on the possible common pathophysiological mechanism between COVID-19 and migraine is currently being studied. The most recent hypothesis suggests the following: migraine is caused by an increased release of calcitonin gene-related peptide from the trigeminal ganglion, which will cause an increase in nitric oxide and IL-1β, resulting in vasodilation and inducing hyperalgesia. COVID-19 causes an increase in nod-like receptor protein 3, which causes the production of IL-1β and again induces an inflammatory response. This review article looks at the mechanisms of migraine and COVID-19, and tries to link a common pathophysiological pathway between the two. This report also serves as a gateway for further research regarding possible management that could potentially target both of these mechanisms.

Key Points

1. The authors examine existing literature to investigate possible pathologies between migraine and COVID-19 infection, endeavouring to establish whether there is a common physiological pathway between the two.

2. The authors discuss the differences between COVID-19-associated headaches, which are holocranial and pressing, and the classical presentation of migraine.

3. This article also examines the impact upon the treatment of migraine during the height of the COVID-19 pandemic, and the effects of external stressors on patients.

INTRODUCTION

Migraine is a complex, neurovascular, inflammatory condition defined as "an intense pulsing or throbbing pain in one area of the head" that could be chronic or episodic, according to the definition of the National Institute of Neurological Disorders and Stroke (NINDS).[1]

The emergence of COVID-19 has raised the worries of physicians across all specialties, including neurologists, with the main concern being the protection of vulnerable patients and tracking of possible neurological changes caused by the disease.[2] COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. SARS-CoV-2 belongs to the family of coronaviruses, the same viral family as acute respiratory distress syndrome and Middle East respiratory syndrome.[3] Coronavirus is an enveloped, single-stranded RNA virus composed of several proteins: spike (S), membrane, envelope (E), and nucleocapsid proteins.[4,5] The protein S is responsible for viral entry into the host cell;[5] the membrane protein is essential for the formation of the viral shape;[6] the protein E is responsible for several processes in the host cell such as inhibition of host cell stress response, ion channels activity, and mature virion secretion from the host cell;[4,7] and, finally, the nucleocapsid protein assists in the packaging of genomic RNA.[8]

Although migraine and COVID-19 do not share risk factors, they have multiple comorbid diseases such as hypertension and cardiovascular and allergic diseases.[2,9,10] Contrary to migraine, which is more prevalent in younger females, there appears to be a higher risk of more severe SARS-CoV-2 infection in older males.[2,9] This paper focuses on the correlation of migraine and COVID-19 in regard to their mechanism of action and pathophysiology. It also provides a summary of possible preventative measures to migraine and COVID-19 that may serve as a path for clinicians and doctors to conduct more research testing the credibility of those inferences.

Migraine in the Era of COVID-19

The phenotype of COVID-19 headache in people with migraine was described as holocranial and pressing, and may be associated with phonophobia, or less often photophobia, nausea, and vomiting. These features are different from the classical presentation of migraine.[2,11,12] Moreover, these headaches do not respond to abortive migraine drugs such as fremanezumab and sumatriptan.[13,14] Headache manifestations in patients with COVID-19 may present as secondary, or exacerbations of primary headache, and it is vital for neurologists to identify the correct diagnosis for proper treatment.[13]

Several studies done during the COVID-19 pandemic on people with migraine have shown that the overall condition of the pain was improved in the majority of the participants.[15-18] Research was conducted to study the impact of the COVID-19 pandemic on people with migraine based on the headache frequency, intensity, and medication consumption during quarantine. The results showed that almost half of the participants had a decrease in migraine frequency, nearly one-quarter did not experience any change in their condition, while less than one-third reported worsening of their migraine.[15] Factors that were associated with the improvement of migraine during quarantine ranged from social and familial support, owning outdoor living space, a full-time job, maintaining a positive mindset during quarantine, an increase in leisure activity time, and many more that reduced the surrounding stressors.[15]

As a matter of fact, according to a study conducted in a paediatric migraine centre in Italy, there was an evident reduction in intensity and frequency of migraine attacks in children and adolescents during the pandemic, mainly due to the psychosomatic nature of the disease in this age group.[18] However, the opposite serves true regarding factors that worsened migraine during the pandemic. Examples include stressors related to loss of job or increase in workload (especially for healthcare providers), being single, social isolation, anxiety and depression, and lack of physical activity.[15,17] People with migraine who were infected with SARS-CoV-2 reported worsening of their conditions, either by an increase in migraine frequency or an increase in the intensity of the pain.[15,19] The increase in migraine frequency was postulated to be due to fever, sleep disturbances, and dehydration that was accompanied by acute COVID-19 infection.[2] However, is the worsening of migraine headache attributed only to the stressors that are associated with the disease, or due to a potential common pathway that is shared between the two diseases? In this article, the authors will try to understand the pathophysiology of migraine and COVID-19 and correlate as to why people with migraine saw worsening of their attacks.

METHODS

The authors utilised PubMed as the main database to gather the most accurate and updated journal articles. They searched for the following keywords: "COVID-19," "SARS-CoV-2," "headache," "migraines," "mechanism of action," "NLRP3," "CGRP," "pathophysiology," and "management." The results were an astonishing number of more than 10,000 research articles and journals in total, many of which had little to do with what the authors were looking for. Therefore, they attempted to narrow down the results by combining certain keywords to attain a desired and specific result. The results were placed in order of most relevant search according to PubMed's display options. The authors only considered articles that were published in English and were open access.

Following this, the authors went through all the articles, removed the duplicates, and excluded the ones that they deemed irrelevant to their report. As the authors were reviewing the articles, they included those that had information relevant to the main purpose of their article. When reading many of the articles regarding the mechanism of migraine, the authors noticed a trend in almost all of them, mainly that the majority referenced two old research articles that described one of the original postulated pathophysiologies of migraine. These articles go back as far as 1961 and 1972. Therefore, the authors used these two journals as a credible reference for the exact pathophysiology of migraine. Furthermore, when the authors were looking through the journals that described the mechanism of COVID-19, they ran into a similar situation where some articles were referencing older journal articles that describe the pathophysiology of coronaviruses in general.

Thus, the authors checked these articles, read them, and included them as credible references to their review.

DISCUSSION

Correlation Between the Mechanisms of Migraine and COVID-19 Headaches

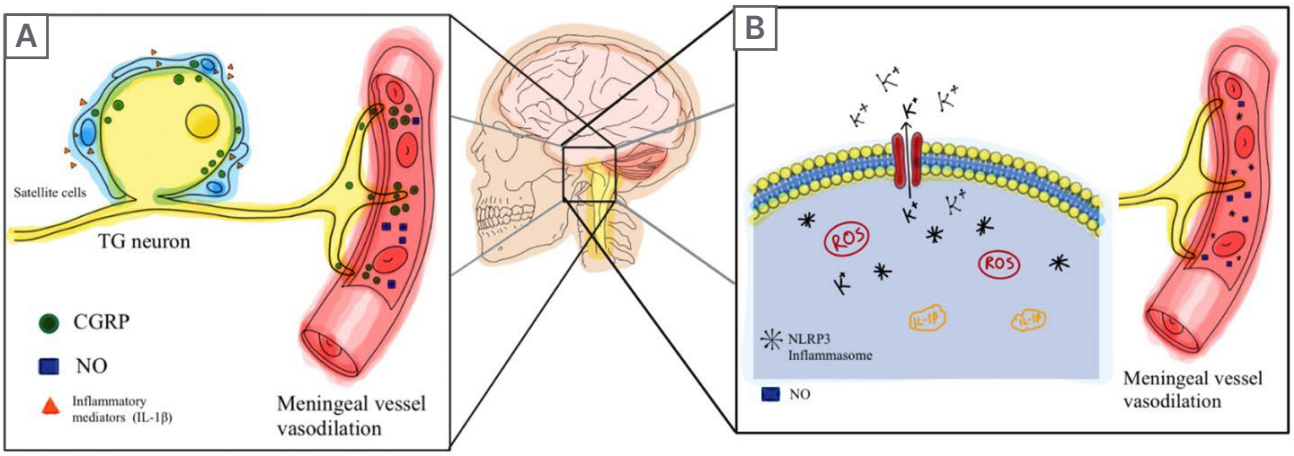
In addition to all the environmental factors, the physiological mechanism of COVID-19 infection is hypothesised to play a major role in the exacerbation of migraine attacks. To understand the correlation between COVID-19 and migraine, it is imperative to first understand the pathogenesis of migraine and COVID-19 independently.

The mechanism behind a migraine attack mainly revolves around cortical spreading depression. This is defined as a slowly transmitting wave of neuronal and glial depolarisation that lasts for a few minutes.[20] During this propagating wave, ions, protons, and inflammatory agents are fluxed through the neurons in the cortex, leading to the activation of meningeal nociceptors.[20-22] This mechanism is responsible for the aura that precedes migraine and triggers the attack.[20] An early reported pathophysiology of migraine is dependent on serotonin, also known as 5-hydroxytryptamine (5-HT).[23] A central deficiency of serotonin neurotransmission accompanied by central super sensitivity to 5-HT receptors was one of the first postulated theories for the genesis of migraine.[24] Evidently, males tend to synthesise 5-HT at a faster rate compared with females, while females utilise serotonin at a faster rate, hence the higher incidence of migraine in females compared with males.[25] Serotonin receptors are highly expressed in the trigeminal vascular system.[26] The low level of serotonin induces vasodilation and, for the duration of the attack, an increase in serotonin metabolites levels will be observed in the urine.[27,28] In addition, 5-HT reduces calcitonin gene-related peptide (CGRP) levels, which are also thought to be an essential part of migraine pathogenesis.[28]

CGRP and nitric oxide (NO) are involved in the second possible mechanism of migraine (Figure 1A).[9,26] CGRP is a 37 amino acid neuropeptide with two main isoforms: α-CGRP and β-CGRP.[29] Both of these isoforms are widely distributed in the peripheral and the central nervous systems (CNS). α-CGRP is predominantly expressed in the somatosensory peripheral nervous system and CNS, while β-CGRP is highly expressed in motor neurons and the enteric nervous system.[30] α-CGRPs are thought to play an essential role in migraine pathogenesis as they are overexpressed in the trigeminal ganglion (TG) neurons.[31] Inflammatory mediators such as TNF and IL-1β, are responsible for the increase of CGRP in the meningeal vasculature, causing the release of NO, eventually leading to vasodilation.[32] One study has shown that the administration of glyceryl trinitrate to healthy individuals will cause an increase in NO, causing migraine-like symptoms.[33] Interestingly enough, NO also induces further secretion of CGRP from TG neurons.[34] CGRP that is released from the neuronal cell body within the TG leads to the release of more inflammatory mediators, namely IL-1β, which is responsible for the neurogenic inflammation, causing a vicious cycle of CGRP release and inflammatory loop.[32] The accumulation of CGRP in the trigeminal nucleus caudalis excites secondary neurons leading to central sensitisation, and the manifestation of hyperalgesia and allodynia that are seen in people with migraine.[32]

The third proposed mechanism of migraine pathophysiology is associated with the nod-like receptor protein 3 (NLRP3) inflammasome complex (Figure 1B). Inflammasomes are cytosolic protein complexes that activate caspase-1 to secrete proinflammatory cytokines, namely IL-1β and IL-18.[35,36] NLRP3 inflammasomes are found in TG neurons, microglia, oligodendrocytes, astrocytes, and neurons.[10] One study conducted on mice suggested that glyceryl trinitrate increased the formation of NLRP3, thus further promoting the release of IL-1β.[37] To further understand the association between NLRP3 and migraine, the researchers gave the affected mice NLRP3 or IL-1β inhibitors. The results were surprising, as NLRP3 and IL-1β inhibitors reduced CGRP levels, and migraines resolved in the mice.[37] In addition, the increase of NO results in the overexpression of NLRP3 inflammasomes, leading to the production of proinflammatory cytokines such as ILs, prostaglandins, leukotrienes, and TNF, which all amplify the inflammation.[9,32] In fact, new research is proposing another perspective

Figure 1: Calcitonin gene-related peptide and nod-like receptor protein 3 inflammasome-related migraine pathways.



A) An initial inflammatory reaction occurs that activates the TG. This induces the release of CGRP into the meningeal vasculature, leading to the release of NO in the vessels, promoting vasodilation. Additionally, CGRP is released from the TG neuron cell, stimulating the surrounding satellite glial cells. Consequently, more inflammatory mediators such as IL-1β and IL-6 are released and activate the TG (causing an inflammatory vicious cycle).

B) Triggers of migraines (sleep deprivation, hunger, etc.) or genetic factors induce CSD. K^+ ions are effluxed outside of the cell due to CSD, inducing cellular stress. ROS are formed either via the mitochondria, or other pathways, in response to stress. The imbalance of ions along with the newly formed ROS causes the assembly of NLRP3. Once NLRP3 is formed, caspase-1 is activated and pro-IL-1β and pro-IL-8 are turned into their active forms. These mediators induce a signalling-neurogenic inflammation in the neighboring cells. Then, the trigeminovascular system is activated and the CGRP pathway is initiated.

CGRP: calcitonin gene-related peptide; CSD: cortical spreading depression; K^+: potassium; NLRP3: nod-like receptor protein 3; NO: nitric oxide; ROS: reactive O_2 species; TG: trigeminal ganglion.

of migraine pathophysiology that depicts the involvement of NLRP3 inflammasomes.[10] Triggers of migraines overexcite the brain, resulting in cortical spreading depression. As mentioned previously, this induces potassium efflux out of the neuronal cell, which causes additional stress to the cell.[10] This cellular stress promotes the formation of reactive O_2 species (ROS). Following a complex inflammatory process, NLRP3 is formed and activates IL-1β. This cascade continues until it reaches the trigeminovascular system and aggravates it, triggering the CGRP pathway.[10]

Another concept that sheds light on NLRP3 involvement in migraine is the fact that a mutation in the NLRP3 gene causes the autosomal dominant disease known as cryopyrin-associated periodic fever syndrome.[36,38] Mutation in this gene instigates high production of IL-1β and systemic inflammation, leading to migraine-like attacks.[10,38] Hence, NLRP3 indirectly induces migraine attacks via the production of IL-1β.

Although the pathophysiology of COVID-19 is not yet clearly understood, there are some theories about what might cause the disease. It is believed that the binding of SARS-CoV-2 to angiotensin-converting enzyme 2 (ACE-2) receptors in the upper respiratory tract provides viral entry access to the cytosol.[9,39] In fact, SARS-CoV-2 has multiple entry access points into the CNS: either retrogradely via ACE-2 receptors in the trigeminal nerve terminals of the nasal cavity, through the cribriform plate of the ethmoid, or the circulatory system leading to cerebral circulation in the late stages of the disease.[40,41] Several studies suggest that the pathophysiology behind COVID-19 is related to a cytokine storm.[5,10,42-44] SARS-CoV-2 induces a hyperinflammatory state through the recruitment of IL-6, which dysregulates other inflammatory

and coagulation factors.[45] Therefore, it is hypothesised that during COVID-19 infection, there is a meningeal peripheral sensitisation that activates the TG, causing a headache that resembles migraine.[43] The cytokine storm may also incite blood–brain barrier instability, which activates the trigeminovascular system, causing headaches.[45]

Another suggested pathophysiology of COVID-19 is related to NLRP3 inflammasomes.[10] The most important protein that might be responsible for the host cell inflammatory cascade is the protein E. Hence, the hypothesised inflammation pathogenesis of COVID-19 is as follows: S glycoprotein attaches to the ACE-2 receptors in the upper respiratory tract.[46,47] As ACE activities are disturbed, angiotensin (Ang) II will not be converted to Ang I, resulting in an accumulation of Ang II. Elevated levels of Ang II lead to the activation of NLRP3, as well as the release of CGRP into the meningeal vessels, causing vasodilation and migraine-like headache symptoms.[9,48] Moreover, once the virus enters the host cell, a cascade of inflammatory reactions is triggered, which involves the release of NLRP3 inflammasome and nuclear factor-κB (Figure 2A).[9,39] NLRP3 inflammasomes then initiate the cytokine storm.[49]

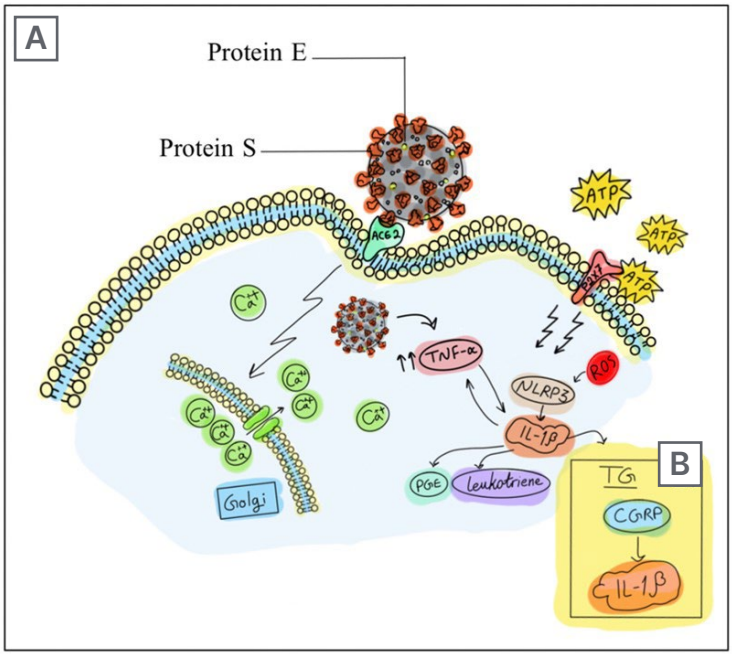
The inflammatory reaction is believed to be mediated by the E viroporin. Studies have shown that the E viroporin of SARS-CoV-2, which causes acute respiratory distress syndrome, activates NLRP3 inflammasomes in the host.[3,5] NLRP3 inflammasome is activated through an imbalance of calcium (Ca^{2+}) cations within the cell due to the formation of Ca^{2+} channels by the protein E of SARS-CoV-2.[5] This imbalance causes cellular stress and the formation of mitochondrial ROS that induce the assembly of NLRP3.[10] Although it is not yet confirmed whether a similar viroporin is present in SARS-CoV-2, it is suspected that such a mechanism is the cause of the inflammatory reaction of COVID-19; however, further studies need to be done.[5,10] Another possible factor that might activate NLRP3 inflammasomes during COVID-19 infection is the hyperactivation of P2X7 receptors due to the elevated levels of extracellular adenosine triphosphate.[44] P2X7 receptors are cation channels that are highly expressed in multiple parts of the CNS and are activated by adenosine triphosphate.[42] Once NLRP3 inflammasomes are activated, the same mechanism as migraine follows, in which caspase-1 is activated and cleaves the inactive pro-IL-1β into its active form IL-1β.[5] Eventually, IL-1β triggers a cascade of subsequent mediator activation such as IL-6, TNF, leukotrienes, and prostaglandins.[5]

The third mechanism of SARS-CoV-2 infection involves the CGRP pathway and it is currently under study.[11] As the virus gains entry via ACE-2 receptors, an inflammatory reaction is initiated in the nasal mucosa, which involves an extreme increase in TNF-α.[50] TNF-α further promotes a nociceptive process that increases the expression of IL-1β in the nasal mucosa.[51] Both of these mediators, TNF-α and IL-1β, stimulate the release of CGRP from the TG neurons (Figure 2B).[11] Simultaneously, CGRP promotes the release of cytokines such as IL-1β from the TG satellite glial cells.[11] IL-6 and Ang II are also thought to induce a systemic increase in CGRP, not only from the TG.[48] In fact, the presence of CGRP in small- and medium-sized sensory neurons as well as in the TG activates the trigeminal nerve endings, inducing a similar mechanism as migraine.[52]

A tangential mechanism for COVID-19 headache may be due to hypoxaemia, in which the alveolar damage and lung oedema reduce O_2 levels in the CNS. An acidic environment is established following hypoxia-induced anaerobic metabolism, leading to cerebral vasodilation and cerebral oedema, hence the headache.[53]

Considering all the mechanisms mentioned above, the authors can correlate the common pathophysiology of COVID-19 and migraine. COVID-19 increases the release of NLRP3, which causes the release of inflammatory mediators (especially IL-1β and NO). Migraine attacks are provoked by CGRP, which causes an inflammatory mediator release cascade (including IL-1β and NO). In both migraine and COVID-19, mitochondrial ROS are formed in a similar manner, eventually creating an almost identical further molecular inflammatory pathway that involves NLRP3 inflammasome.[10] Not only is CGRP released in the nasal mucosa following the increase in TNF-α during COVID-19 infection, but it is also released from the dura mater, thus increasing the meningeal blood flow.[11,54] Therefore, the cytokines will induce a secondary activation of meningeal nociceptors, causing headache.[11]

Figure 2: Severe acute respiratory syndrome coronavirus 2 spike protein provides access into the cell through angiotensin-converting enzyme 2 receptors.



A) Viroporin E is believed to start an inflammatory cascade by forming Ca2+ channels on the Golgi apparatus membrane.. The imbalance of intracellular Ca^{2+} causes the formation of mitochondrial ROS. In addition, the cellular inflammatory state leads to elevated levels of ATP, which activates P2X7 receptors. The ion imbalance that is caused by E protein Ca^{2+} channels and the activation of P2X7 receptors promote the formation of NLRP3 inflammasome complex, which provokes COVID-19 headache.

B) The other mechanism suggests that the recruitment of TNF-α, in response to viroporin E entry, increases the expression of IL-1β. This will cause the release of CGRP in the TG, which triggers a similar mechanism to a migraine attack. The released CGRP stimulates the surrounding satellite glial cells to release more inflammatory cytokines.

ACE-2: angiotensin-converting enzyme 2; ATP: adenosine triphosphate; Ca^{2+}: calcium; CGRP: calcitonin gene-related peptide; E: envelope; NLRP3: nod-like receptor protein 3; PGE: prostaglandin; ROS: reactive O_2 species; S: spike; TG: trigeminal ganglion.

A CGRP-induced headache caused by COVID-19 may resemble migraine due to the common pathophysiology of CGRP. In fact, it was found that patients with COVID-19 who had an early diagnosis of migraine had longer and more intense COVID-19-associated headaches.[55] This phenomenon is explained by the increased nociceptive processing in the trigeminal cervical complex after COVID-19 infection.[55] The peripheral sensitisation during COVID-19, in patients with sustained migraine attacks, may induce central sensitisation and reduced pain threshold, leading to prolonged and exaggerated response.[55] Though the results are remarkable, more research needs to be done to confirm the hypothesis that COVID-19 may cause a more severe headache in people with migraine.

Management of Migraine During COVID-19

According to various sources, the recommended treatment for migraine ranges from nonsteroidal anti-inflammatory drugs (NSAID) to renin-angiotensin system (RAS) inhibitors. It all depends on the severity and whether the attacks are chronic or acute. Deciding on which migraine medication to use during COVID-19 is crucial in determining whether the course of the headache will improve or worsen, according to the previously discussed mechanisms. This section

will focus on the management of migraines and the implemented changes that took place due to the pandemic. According to the American Headache Society (AHS), NSAIDs and triptans are the first-line treatments for acute migraine attacks, and this was backed up by strong evidence from research.[56] Other preventative medications include onabotulinumtoxinA injections, CGRP monoclonal antibodies, β-blockers, and angiotensin receptor blockers.[44,56]

With the pandemic and lockdown, research was conducted to study the possible link and interaction between COVID-19 and these medications. One initial fear of the use of NSAIDs and RAS inhibitors was due to the belief that they may result in worse COVID-19 clinical symptoms, due to proven studies that RAS blockers up-regulate ACE-2 expression.[56,57] Since the evidence is lacking and no proper link has been established between COVID-19 and these medications, the choice to use them remains a patient-to-doctor discussion.

CGRP monoclonal antibodies are commonly used as a prophylactic for migraine attacks. As of now, neurologists are recommended to keep prescribing anti-CGRP monoclonal antibodies since there is no evidence suggesting increased susceptibility to SARS-CoV-2 infection.[29] Since CGRP plays a significant role in the pathogenesis of COVID-19, clinical trials, namely BHV3500, are being conducted to evaluate the efficacy of CGRP-antagonists in the treatment of SARS-CoV-2 infection.[58] The trial raises suspicion that monoclonal antibodies against CGRP would be the preferred choice of treatment for people with migraine who are infected with COVID-19. Other possible medical interventions for COVID-19 headache and migraines are blockade of IL-6, as it is linked to increased severity of the infection.

Furthermore, drugs targeting the NLRP3 inflammasome pathway are a potential treatment for migraine and COVID-19, some of which are currently under clinical development.[5,10,59,60]

CONCLUSION

To sum it up, people with migraine who were not infected with SARS-CoV-2 had an overall improvement in their condition during quarantine due to a decrease in the surrounding stressors, whereas people with migraine infected with COVID-19 reported a worsening of their condition. Multiple environmental and pathophysiological factors were considered to reach this conclusion. Up to this point, research has attributed this trend to be caused by the life stressors that surfaced during the pandemic, or to the accompanying COVID-19 symptoms. However, the authors believe that pathophysiological factors, including neuropeptide CGRP and NLRP3, are the cause of the increased severity of migraine attacks in patients with COVID-19.

The overall conclusion of all these studies is summarised by the fact that migraine attacks are caused by an increase in CGRP, NO, and IL-1β. COVID-19 also seems to affect these factors by increasing the stimulation of NLRP3 and possibly CGRP, thus IL-1β and NO are overproduced. This raises the question of whether people with migraine will have an increased risk of frequent and intense attacks when infected with SARS-CoV-2. It also provides a linking point, which makes it easier to conduct further research for a possible drug that targets the potential common pathway. More research needs to be done to fully understand the concept and the correlation between NLRP3 release as a result of COVID-19 and levels of CGRP.

References

1. National Institute of Neurological Disorders and Stroke (NINDS). Migraine. 2019. Available at: https://www.ninds.nih.gov/Disorders/All-Disorders/Migraine-Information-Page. Last accessed: 22 August 2021.
2. Angus-Leppan H et al. Navigating migraine care through the COVID-19 pandemic: an update. J Neurol. 2021;268:4388-95.
3. Nieto-Torres J et al. Severe acute respiratory syndrome coronavirus E protein transports calcium ions and activates the NLRP3 inflammasome. Virology. 2015;485:330-9.
4. Kirtipal N et al. From SARS to SARS-CoV-2, insights on structure, pathogenicity and immunity aspects of pandemic human coronaviruses. Infect Genet Evol. 2020;85:104502.
5. Shah A. Novel coronavirus-induced NLRP3 inflammasome activation: a potential drug target in the treatment of COVID-19. Front Immunol. 2020;11:1021.
6. Siu YL et al. The M, E, and N structural proteins of the severe acute respiratory syndrome coronavirus are required for

efficient assembly, trafficking, and release of virus-like particles. J Virol. 2008;82(22):11318-30.

7. Ruch TR, Machamer CE. The coronavirus E protein: assembly and beyond. Viruses. 2012;4(3):363-82.
8. Chang CK et al. Modular organization of SARS coronavirus nucleocapsid protein. J Biomed Sci. 2006;13(1):59-72.
9. Bolay H et al. Are migraine patients at increased risk for symptomatic coronavirus disease 2019 due to shared comorbidities? Headache. 2020;60(10):2508-21.
10. Kursun O et al. Migraine and neuroinflammation: the inflammasome perspective. J Headache Pain. 2021;22(1):55.
11. Messlinger K et al. Activation of the trigeminal system as a likely target of SARS-CoV-2 may contribute to anosmia in COVID-19. Cephalalgia. 2022;42(2):176-80.
12. Porta-Etessam J et al. Spectrum of headaches associated with SARS-CoV-2 infection: study of healthcare professionals. Headache. 2020;60(8):1697-1704.
13. Arca KN, Starling AJ. Treatment-refractory headache in the setting of COVID-19 pneumonia: migraine or meningoencephalitis? Case report. SN Compr Clin Med. 2020;2(8):1200-3.
14. Singh J, Ali A. Headache as the presenting symptom in 2 patients with COVID-19 and a history of migraine: 2 case reports. Headache. 2020;60(8):1773-6.
15. Schiano di Cola F et al. Migraine monitoring in the time of COVID-19: triggers and protectors during a pandemic. Pain Medicine. 2021;22(11):2728-38.
16. Delussi M et al. Investigating the effects of COVID-19 quarantine in migraine: an observational cross-sectional study from the Italian National Headache Registry (RICe). Front Neurol. 2020;11:597881.
17. Parodi I et al. Impact of quarantine due to COVID infection on migraine: a survey in Genova, Italy. Neurological Sciences. 2020;41(8):2025-7.
18. Dallavalle G et al. Migraine symptoms improvement during the COVID-19 lockdown in a cohort of children and adolescents. Front Neurol. 2020;11:579047.
19. Smith M et al. Early impact of the COVID-19 pandemic on outpatient migraine care in Hawaii: results of a quality improvement survey. Headache. 2020;61(1):149-56.
20. Chen L et al. Chemical stimulation of the intracranial dura activates NALP3 inflammasome in trigeminal ganglia neurons. Brain Res. 2014;1566:1-11.
21. Costa C et al. Cortical spreading depression as a target for anti-migraine agents. J Headache Pain. 2013;14(1):62.
22. Zhang X et al. Activation of meningeal nociceptors by cortical spreading depression: implications for migraine with aura. J Neurosci. 2010;30(26):8807-14. Erratum in: J Neurosci. 2010;30(30):10259.
23. Sicuteri F et al. Biochemical investigations in headache: increase in the hydroxyindoleacetic acid excretion during migraine attacks. Int Arch Allergy Immunol. 1961;19:55-8.
24. Sicuteri F. Headache as possible expression of deficiency of brain 5-hydroxytryptamine (central denervation supersensitivity). Headache. 1972;12:69-72.
25. Panconesi A. Serotonin and migraine: a reconsideration of the central theory. J Headache Pain. 2008;9(5):267–76.
26. Gupta S et al. Chemical mediators of migraine: preclinical and clinical observations. Headache. 2011;51(6):1029-45.
27. Robertson W. Migraine in children. 2019. Available at: https://emedicine.medscape.com/article/1179268-overview#a5. Last accessed: 7 February 2022.
28. Aggarwal M et al. Serotonin and CGRP in migraine. Ann Neurosci. 2012;19(2):88-94.
29. Caronna E et al. Safety of anti-CGRP monoclonal antibodies in patients with migraine during the COVID-19 pandemic: present and future implications. Neurologia (Engl Ed). 2021;36(8):611-617.
30. Villalón C, Olesen J. The role of CGRP in the pathophysiology of migraine and efficacy of CGRP receptor antagonists as acute antimigraine drugs. Pharmacology Ther. 2009;124(3):309-23.
31. Iyengar S et al. CGRP and the trigeminal system in migraine. Headache. 2019;59(5):659-81.
32. Iyengar S et al. The role of calcitonin gene–related peptide in peripheral and central pain mechanisms including migraine. Pain. 2017;158(4):543-59.
33. Vanmolkot F, de Hoon J. Comments on 'Calcitonin gene-related peptide (CGRP) levels during glyceryl trinitrate (GTN)-induced headache in healthy volunteers'. Cephalalgia. 2010;31(3):380.
34. Bellamy J et al. Nitric oxide regulation of calcitonin gene-related peptide gene expression in rat trigeminal ganglia neurons. Eur J Neurosci. 2006;23(8):2057-66.
35. Lamkanfi M, Dixit VM. Mechanisms and functions of inflammasomes. Cell. 2014;157(5):1013-22.
36. Cordero M et al. Gain of function mutation and inflammasome driven diseases in human and mouse models. J Autoimmun. 2018;91:13-22.
37. He W et al. Microglial NLRP3 inflammasome activation mediates IL-1β release and contributes to central sensitization in a recurrent nitroglycerin-induced migraine model. J Neuroinflammation. 2019;16(1):78.
38. Keddie S et al. Cryopyrin-associated periodic fever syndrome and the nervous system. Curr Treat Options Neurol. 2018;20(10):43.
39. Samavati L, Uhal B. ACE2, much more than just a receptor for SARS-COV-2. Front Cell Infect Microbiol. 2020;10:317.
40. Baig A et al. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci. 2020;11(7):995-8.
41. Molina-Gil J et al. Trigeminal neuralgia as the sole neurological manifestation of COVID-19: a case report. Headache. 2021;61(3):560-2.
42. Ribeiro DE et al. Hyperactivation of P2X7 receptors as a culprit of COVID-19 neuropathology. Mol Psychiatry. 2021;26(4):1044-59.
43. Caronna E et al. Headache: a striking prodromal and persistent symptom, predictive of COVID-19 clinical evolution. Cephalalgia. 2020;40(13):1410-21.
44. Bobker SM, Robbins MS. COVID-19 and headache: a primer for trainees. Headache. 2020;60(8):1806-11.
45. Caronna E, Pozo-Rosich P. Headache as a symptom of COVID-19: narrative review of 1-year research. Curr Pain Headache Rep. 2021;25(11):73.
46. Yang J et al. Molecular interaction and inhibition of SARS-CoV-2 binding to the ACE2 receptor. Nat

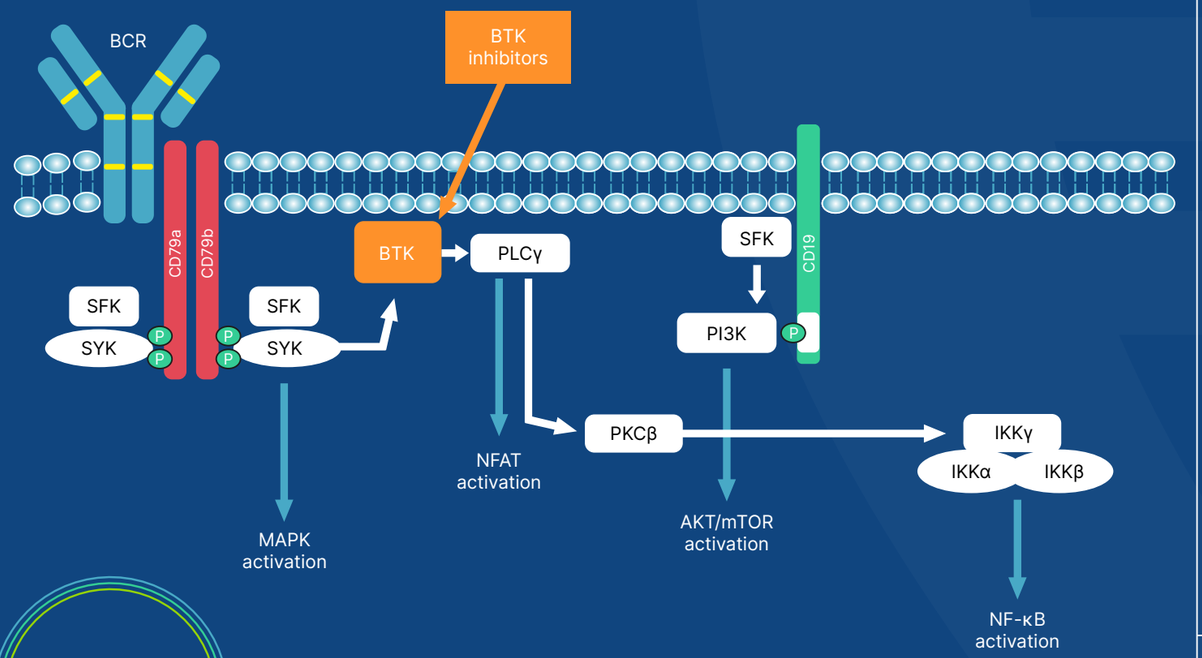
Commun. 2020;11(1):4541.

47. Gonzalez-Martinez A et al. Headache during SARS-CoV-2 infection as an early symptom associated with a more benign course of disease: a case–control study. Eur J Neurol. 2021;28(10):3426-36.
48. Uygun Ö et al. Headache characteristics in COVID-19 pandemic-a survey study. J Headache Pain. 2020;21(1):121.
49. Andrejew R et al. The P2X7 receptor: central hub of brain diseases. Front Mol Neurosci. 2020;13:124.
50. Torabi A et al. Proinflammatory cytokines in the olfactory mucosa result in COVID-19 induced anosmia. ACS Chem Neurosci. 2020;11(13):1909-13.
51. Durham ZL et al. Tumor necrosis factor-α stimulates cytokine expression and transient sensitization of trigeminal nociceptive neurons. Arch Oral Biol. 2017;75:100-6.
52. Toptan T et al. Case series of headache characteristics in COVID-19: headache can be an isolated symptom. Headache. 2020;60(8):1788-92.
53. Tolebeyan AS et al. Headache in patients with severe acute respiratory syndrome coronavirus 2 infection: a narrative review. Headache. 2020;60(10):2131-38.
54. Skaria T et al. CGRP receptor antagonism in COVID-19: potential cardiopulmonary adverse effects. Trends Mol Med. 2021;27(1):7-10.
55. Membrilla JA et al. Headache as a cardinal symptom of coronavirus disease 2019: a cross-sectional study. Headache. 2020;60(10):2176-91.
56. Szperka CL et al. Migraine care in the era of COVID-19: clinical pearls and plea to insurers. Headache. 2020;60(5):833-42.
57. MaassenVanDenBrink A et al. Headache medication and the COVID-19 pandemic. J Headache Pain. 2020;21(1):38.
58. Bioaven Pharmaceuticals, Inc. Safety and efficacy trial of Zavegepant* intranasal for hospitalized patients with COVID-19 requiring supplemental O2. NCT04346615. https://clinicaltrials.gov/ct2/show/NCT04346615.
59. Robertson CE. Could CGRP antagonists be helpful in the fight against COVID-19? Headache. 2020;60(7):1450-2.
60. Starobova H et al. The NLRP3 inflammasome: role and therapeutic potential in pain treatment. 2020;11:1016.

DIFFERENCES IN MECHANISM OF ACTION AND SELECTIVITY OF COVALENT AND NON-COVALENT BTK INHIBITORS

Provided by Clinical Care Options, LLC. Supported by an educational grant from Lilly.

The BCR Pathway and BTK's Role in B-Cell Malignancies[1]



BCR & BTK

The BCR pathway plays a role in the growth, proliferation, and survival of normal and malignant B-cells

BTK is an essential enzyme in the BCR signalling pathway

Inhibition of BTK leads to downstream mitigation of cell growth, proliferation, adhesion, migration, and survival of malignant B-cells

Three covalent BTK inhibitors are approved in multiple lymphoma settings including CLL, MCL and MZL, and Waldenström macroglobulinaemia.

These inhibitors form irreversible covalent bonds with a cysteine (C481) in the BTK kinase domain.

Kinase Selectivity of Covalent and Non-Covalent BTK Inhibitors in Vitro[2]

Covalent

Kinase	IC_{50} (nM) Ibrutinib	Acalabrutinib	Zanubrutinib
BTK	1.5	5.1	0.3
TEC	10	126	2
ITK	4.9	≥1000	56
BMX ETK	0.8	46	0.62
EGFR	5.3	≥1000	2.6
HER2	6.4	~1000	530
HER4	3.4	16	1.58
JAK3	32	≥1000	580
BLK	0.1	≥1000	1.13
RLK TXK	2.0	368	2.5

Non-covalent

Kinase	IC_{50} (nM) Pirtobruinib	Nemtabrutinib	Fenebrutinib
BTK	3.15	0.85	2.3
TEC	1234	5.8	1000
ITK	>5000	>10000	1000
BMX ETK	1155	5.2	351
EGFR	>1000	--	1000
HER2	--	--	1000
HER4	13.3	--	1000
JAK3	--	--	1000
BLK	4100	9.7	1000
RLK TXK	209	36	1000

Select Adverse Events of Special Interest of Covalent Versus Non-Covalent BTKis

Ibrutinib[4]
- Arthralgia/myalgia: **11%**
- Bleeding: **23%**
- Hypertension: up to **19%**
- Incidence of atrial fibrillation: **11% in MCL**

Acalabrutinib[5]
- Arthralgia/myalgia: **up to 29%**
- Bleeding: **22%**
- Hypertension: **up to 5%**
- Incidence of atrial fibrillation: **None in MCL (8% other cardiac dysfunction)**

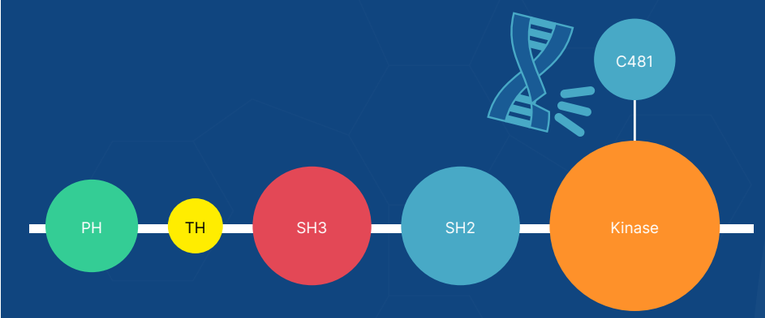
Zanubrutinib[6]
- Arthralgia/myalgia: **up to 14%**
- Bleeding: **50%**
- Hypertension: **12%**
- Incidence of atrial fibrillation/flutter: **2% in MCL**

Pirtobrutinib[7]
- Arthralgia/myalgia: **up to 11%**
- Bleeding: **8%**
- Hypertension: **7%**
- Incidence of atrial fibrillation: **2% across different hematologic cancers including MCL**

Nemtabrutinib[8]
- Arthralgia/myalgia: **20%**
- Bleeding: **none reported**
- Hypertension: **23%**
- Incidence of atrial fibrillation: **None reported across different B-cell malignancies**

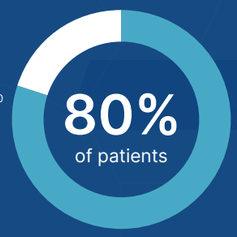
Acquired Resistance to Covalent BTK Inhibitors[9]

Acquired resistance to covalent BTK inhibitors is generally driven by mutations in *BTK* at the C481 site



BTK C481 mutations, most of which are C481S mutations, have been found in patients with CLL and MCL after treatment with a covalent BTK inhibitor

For example, in one study[10]



with CLL who experienced relapse after ibrutinib harboured a C481 mutation

Acquired resistance to covalent BTK inhibitors contributes to disease progression. Noncovalent reversible BTK inhibitors do not require C481 for binding.

Relative Binding Affinities of BTK Inhibitors to Different *BTK* Mutations[3]

Non-covalent Covalent

	Pirtobrutinib	Nemtabrutinib	Vecabrutinib	Fenebrutinib	Ibrutinib	Acalabrutinib	Zanubrutinib
Wild type	Normal	Normal	Normal	Normal	Normal	Normal	Normal
A428D	None	Decreased	None	None	None	None	None
M437R	Decreased	Normal	Decreased	Decreased	Normal	Decreased	Normal
T474I	Decreased	Decreased	Decreased	Normal	Normal	Decreased	Decreased
L528W	None	None	Decreased	Normal	None	Decreased	None
C481S	Normal	Normal	Normal	Normal	Decreased	Decreased	Decreased

BCR: B-cell receptor; BTK: Bruton's tyrosine kinase; CLL: chronic lymphocytic leukaemia; IC_{50}: half-maximal inhibitory concentration; MCL: mantle-cell lymphoma; MZL: marginal zone lymphoma

References 1. Young RM, Staudt LM. Targeting pathological B cell receptor signalling in lymphoid malignancies. Nat Rev Drug Discov. 2013;12(3):229-43. 2. Estupiñán HY, Berglöf A. Comparative analysis of BTK inhibitors and mechanisms underlying adverse effects. Front Cell Dev Biol. 2021;9:630942. 3. Wang E et al. Mechanisms of resistance to noncovalent Bruton's tyrosine kinase inhibitors. N Engl J Med. 2022;386:735-43. 4. Imbruvica. Highlights of prescribing information. 2022. Available at: https://www.imbruvica.com/files/prescribing-information.pdf. Last accessed: 19 October 2022. 5. Calquence. Highlights of prescribing information. 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/210259s000lbl.pdf. Last accessed: 19 October 2022. 6. Brukinsa. Highlights of prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213217s000lbl.pdf. Last accessed: 19 October 2022. 7. Wang M et al. Pirtobrutinib, a next generation, highly selective, non-covalent BTK inhibitor in previously treated mantle cell lymphoma: updated results from the phase 1/2 BRUIN study. Blood. 2021;DOI:10.1182/blood-2021-149138. 8. Woyach J et al. Nemtabrutinib (MK-1026), a non-covalent inhibitor of wild-type and C481S mutated bruton tyrosine kinase for B-cell malignancies: efficacy and safety of the phase 2 dose-expansion BELLWAVE-001 study. Hemasphere. 2022;6:578-9. 9. Gu. J, Tang H. Targeting Bruton tyrosine kinase using non-covalent inhibitors in B cell malignancies. J Hematol Oncol. 2021;14(1):40. 10. Woyach JA, Ruppert AS. BTKC481S-mediated resistance to ibrutinib in chronic lymphocytic leukemia. J Clin Oncol. 2017;35(13):1437-1443.

Demographic and Clinical Presentation of Hospitalised Patients with SARS-CoV-2 During the First Omicron Wave

Authors:	*Mehool Patel, Elizabeth Aitken Lewisham and Greenwich NHS Trust, London, UK *Correspondence to Mehool.patel@nhs.net

Disclosure:	The authors have declared no conflicts of interest.
Received:	14.05.22
Accepted:	17.10.22
Keywords:	Clinical presentation, COVID-19, demographic differences, Omicron variant.
Citation:	EMJ. 2022; DOI/10.33590/emj/10174872. https://doi.org/10.33590/emj/10174872.

Abstract

Introduction: The objectives of this retrospective study were to describe clinical presentations and mortality outcomes of hospitalised patients with the COVID-19 Omicron variant within two acute district general hospitals, and to evaluate demographic factors associated with these presentations and mortality.

Methods: Data was obtained over a month in 2021–2022 from multi-ethnic patients who were hospitalised and detected to have severe acute respiratory syndrome coronavirus 2 Omicron infection. Details included socio-demographic characteristics, vaccination, and mortality. Patients were subdivided into three groups: Group 1 were admitted with true COVID-19 pneumonitis, Group 2 had incidental COVID-19 on admission screening, and Group 3 were negative on admission but developed COVID-19 over 7 days post-admission.

Results: Of 553 patients, only 24.1% (133/553) were in Group 1, 58.2% (322/553) in Group 2, and 17.7% (98/553) in Group 3. Patients in Group 1 and Group 3 were significantly older than those in Group 2 ($p<0.001$). Thirty percent of patients from Black, Asian, and minority ethnic backgrounds had COVID-19 pneumonitis compared with 19% of those with White ethnicity ($p=0.002$). Twenty percent of patients were admitted within nonmedical specialties, i.e., surgical specialties, paediatrics, and obstetrics. Of 36 requiring critical care, 21 were in Group 1. Of those patients, 20/21 (95%) were unvaccinated and seven of the 21 who died were all unvaccinated (100%). Common COVID-19 presentations included delirium, falls, seizures, chronic obstructive pulmonary disease, and antenatal problems. Overall, 13.7% (76/553) patients died and 4.7% (26/553) were directly attributable to COVID-19.

Conclusions: This large, multi-ethnic study has described clinical presentations and mortality of hospitalised patients with Omicron. It has determined socio-demographic factors associated with these presentations, including ethnicity and vaccination rates. The study provides useful information for future COVID-19 studies examining outcomes and presentations of Omicron and future COVID-19 variants.

Key Points

1. This is one of the first large, multi-ethnic, hospital-based studies that has described the clinical presentation of hospitalised patients with Omicron COVID-19 infections. Unlike previous surges in the UK, there were significantly fewer patients admitted with true COVID pneumonitis (24%). While 58% were admitted for other reasons and had COVID-19 detected on routine admission screening, 18% patients had probable hospital-associated COVID-19 infections.

2. Patients with COVID-19 from Black, Asian, and minority ethnic backgrounds had significantly higher rates of COVID-19 pneumonitis (30%) compared with those from White ethnicity (19%).

3. The authors' findings are consistent with other recent studies, which also found that Omicron infections caused less severe illness and death, and that many deaths that may be classified as COVID-19-related were actually not directly attributable to COVID-19 pneumonitis.

INTRODUCTION

Since the detection of the first cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variant causing COVID-19 infections in South Africa in November 2021, there have been a few population-based reports to suggest that the clinical severity and presentation of this variant is different to previous COVID-19 surges.[1-4] This variant is known to have several mutations to previous variants of this virus; hence, it was predicted to be much more infectious due to possible immune evasion.[5]

Population-based reports have evaluated clinical severity of Omicron COVID-19 in the general population.[4] There are few studies that have examined the demographic and clinical presentation of hospitalised patients with Omicron COVID-19 infections.[6,7] A recent South African study described the clinical presentation of hospitalised patients with the Omicron variant, but that study did not differentiate between those patients admitted with symptoms of COVID-19 infection from those who were admitted for other reasons, or were already in hospital and were found to have an incidental positive COVID-19 test result.[7] A recent study showed that the outcomes of the presumed Omicron variant were substantially better than previous variants, but the study did not describe the clinical presentations and socio-demographic associations of these patients.[8]

The objectives of this retrospective, observational study were to describe the clinical presentations and mortality outcomes of hospitalised patients with the COVID-19 Omicron variant within a busy acute district general hospital trust, and to evaluate demographic factors associated with these presentations and mortality.

METHODS

Data was obtained from a retrospective survey of all patients hospitalised in an acute London, UK, hospital trust who were detected to have SARS-CoV-2 Omicron variant infection over a month from 15th December 2021 to 15th January 2022. The trust provides healthcare to a diverse, multi-ethnic, inner-city population from two extremely busy acute district general hospital legacy sites. Whilst information on precise genotype of the COVID-19 variant was not available, national data had shown that 87.5% of COVID-19 infections within London were due to the Omicron variant by 15th December 2021.[9]

Since mid-2020, the hospital trust has a policy of screening every hospital admission for COVID-19; therefore, on admission, all patients undergo an urgent routine PCR test to screen for COVID-19 infection. Panther® Fusion SARS-CoV-2 assays (Hologic, Marlborough, Massachusetts, USA) were employed for this test.[10] This is a real-time, reverse transcription PCR, *in vitro* diagnostic test intended for the qualitative detection of SARS-CoV-2 RNA, isolated and purified from nasopharyngeal and oropharyngeal swab specimens.[10]

For this study, data was obtained from the hospital electronics patient record system. Data

included socio-demographic details such as age, sex, and ethnicity. Clinical data included presenting complaints (reasons for admission), COVID-19 vaccination status, whether critical care support was required, admitting specialty, and mortality outcome.

These patients were divided into three groups for analyses. Group 1 included those patients who were admitted with COVID-19 pneumonitis (true COVID-19). For the purpose of this study, the pragmatic definition of this diagnosis was based on the presenting clinical signs and symptoms of the patient, as stated by the admitted medical team and confirmed by the admitting consultant. Group 2 included patients who were admitted for a different reason to COVID-19 pneumonitis, but their routine PCR COVID-19 screening test on admission was positive (incidental COVID-19). Group 3 included those patients who were negative for COVID-19 on admission but developed the infection more than 7 days after admission i.e., probable hospital-associated COVID-19 (HAC) infection.

Simple descriptive statistical methods were used to examine the prevalence rates of the antibodies within various socio-demographic groups. Simple statistical χ^2 tests of distribution were performed using Stata statistical package (StataCorp, College Station, Texas, USA). Multivariable analyses, using stepwise backward logistic regression, were also conducted to identify any independent differences between the three designated groups. It was not appropriate or possible to involve patients or the public in the design, conduct, reporting, or dissemination plans of the research.

RESULTS

There were 553 patients hospitalised in the trust that were detected as having COVID-19 infection between 15th December 2021 and 15th January 2022. Unlike the previous two surges in the UK, there were significantly fewer patients admitted with true COVID-19 pneumonitis; therefore, Group 1 only included 24.1% (133/553) of patients. Group 2, which included patients who were admitted for other reasons and had COVID-19 detected on routine admission screening, included 58.2% (322/553) of participants. Finally, Group 3, which was made up of patients who had probable HAC, included 17.7% (98/553) of participants.

The data was analysed for all patients in the survey, as well as the three groups individually, according to various socio-demographic factors (Table 1). As might be expected, patients with COVID-19 pneumonitis (Group 1) and HAC (Group 3) were significantly older than those in Group 2. However, there were no significant differences across the three groups in terms of sex.

The distribution of clinical presentation in terms of ethnicity showed that there was a significantly greater proportion of White patients in Group 3. A greater proportion of older, frail patients who are in hospital for a longer period were more likely to be of White ethnicity. While the distribution of other ethnic groups appeared similar across Groups 1 and 2, it is interesting to note that 30% (36/120) of Black Caribbean, 25% (17/67) of Black African, and 36% (14/39) of South Asian patients had COVID-19 pneumonitis compared with 19% (62/319) of patients from White ethnicity. Thus, 30% (71/234) of patients from Black, Asian, and minority ethnic (BAME) backgrounds had COVID-19 pneumonitis, which was significantly higher than patients of White ethnicity (19% [62/319]; p=0.002).

Multivariable analyses, using stepwise, backward, logistic regression and controlling for age, sex, and ethnicity, showed that older age >70 years (odds ratio [OR]: 2.4; 95% confidence interval [CI]: 1.2–4.5) and being South Asian (OR: 2.1; 95% CI: 1.1–4.3) were independently associated with COVID-19 pneumonitis.

Unlike the previous two surges, 20.7% of patients with COVID-19 were admitted within nonmedical specialties, i.e., surgical specialties, paediatric medicine, and obstetrics. Fewer patients required critical care support compared with previous surges. Of 36 patients requiring this support, only 21 were admitted due to COVID-19 pneumonitis. Ninety-five percent (20/21) of these patients were unvaccinated; seven of the 21 who died were all unvaccinated.

Of those admitted with COVID-19 pneumonitis, 52.0% (69/133) were unvaccinated, and a further 22.5% had had only one or two vaccinations. Thus, only 25.0% of those admitted with COVID-19 had triple vaccinations.

Similar rates were observed in Group 2 as well. In Group 3, 75% of patients had between two and three vaccinations.

Table 2 describes the top presentations of those patients in Group 2. Unlike the previous surges when the presenting complaint for hospitalised patients was almost exclusively COVID-19 pneumonitis, this study showed that common presentations, including delirium, falls (some leading to significant fractures), seizures, and acute exacerbations of chronic obstructive airways disease or asthma, were associated with co-existing COVID-19 infection. COVID-19 was detected in patients admitted for antenatal problems.

Table 1: Hospitalised patients with COVID-19 (Omicron) at Lewisham and Greenwich Trust, London, UK, from 15th December 2021 to 15th January 2022.

	Total number with COVID-19	Admitted with COVID-19 pneumonitis	COVID-19 detected on admission screening	Probable hospital-associated COVID-19	p
Number of subjects	553	133 (24.1%)	322 (58.2%)	98 (17.7%)	N/A
Sex					
Male	268 (48.5%)	68 (51.1%)	149 (46.3%)	51 (52.0%)	p=NS
Female	285 (51.5%)	65 (48.9%)	173 (53.7%)	47 (48.0%)	
Age (years), mean (SD), median, range	62.2 (24.3), 68, 0–100	63.9 (18.4), 65, 17–98	56.7 (26.7), 61, 0–98	78.1 (13.8), 82, 29–100	p<0.001
Age group, n (%)					
0–40	117 (21.2%)	13 (9.8%)	102 (31.7%)	2 (2.0%)	p<0.001
40–50	38 (6.9%)	16 (12.0%)	21 (6.5%)	1 (1.0%)	
50–60	65 (11.8%)	25 (18.8%)	33 (10.3%)	7 (7.1%)	
60–70	65 (11.8%)	20 (15.0%)	33 (10.3%)	12 (12.2%)	
70–max	268 (48.5%)	59 (44.4%)	133 (41.3%)	76 (77.6%)	
Ethnicity					
White	319 (57.7%)	62 (46.6%)	188 (58.4%)	69 (70.4%)	p=0.002
Black Caribbean	120 (21.7%)	36 (27.1%)	62 (19.3%)	22 (22.5%)	
Black African	67 (12.1%)	17 (12.8%)	47 (14.6%)	3 (3.1%)	
South Asian	39 (7.1%)	14 (10.5%)	21 (6.5%)	4 (4.1%)	
East Asian	8 (1.5%)	4 (3.0%)	4 (1.2%)	0 (0.0%)	
BAME	234 (42.3%)	71 (53.4%)	134 (41.6%)	29 (29.6%)	

	Total number with COVID-19	Admitted with COVID-19 pneumonitis	COVID-19 detected on admission screening	Probable hospital-associated COVID-19	p
Vaccination status					
Unvaccinated	190 (34.4%)	69 (51.9%)	105 (32.6%)	16 (16.3%)	p<0.001
1	42 (7.6%)	5 (3.8%)	28 (8.7%)	9 (9.2%)	
2	153 (27.7%)	25 (18.8%)	92 (28.6%)	36 (36.7%)	
3	139 (25.1%)	34 (25.6%)	72 (22.4%)	33 (33.7%)	
N/A (children)	23 (4.3%)	0 (0.0%)	23 (7.4%)	0 (0.0%)	
Unknown	5 (0.9%)	0 (0.0%)	1 (0.3%)	4 (4.1%)	
Site					
UHL	240 (43.4%)	62 (46.6%)	146 (45.3%)	32 (32.7%)	p=NS
QEH	313 (56.6%)	71 (53.4%)	176 (54.7%)	66 (67.3%)	
Critical care required					
General wards	517 (93.5%)	112 (84.2%)	315 (97.8%)	90 (91.8%)	N/A
Critical care	36 (6.5%)	21 (15.8%)	7 (2.2%)	8 (8.2%)	
Outcome					
Discharged	450 (81.4%)	107 (80.5%)	282 (87.6%)	61 (62.2%)	p<0.001
Inpatient	27 (4.9%)	5 (3.8%)	12 (3.7%)	10 (10.2%)	
Death	76 (13.7%)	21 (15.8%)	28 (8.7%)	27 (27.6%)	
Admitting discipline					
Acute and elderly medicine	439 (79.4%)	132 (99.2%)	223 (69.3%)	84 (85.7%)	N/A
Surgical specialties	55 (10.0%)	0 (0.0%)	42 (13.0%)	13 (13.3%)	
Obstetrics and gynaecology	36 (6.5%)	1 (0.8%)	34 (10.6%)	1 (1.0%)	
Paediatrics	23 (4.2%)	0 (0.0%)	23 (7.1%)	0 (0.0%)	

BAME: Black, Asian, and minority ethnic; N/A: not applicable; NS: not significant; QEH: Queen Elizabeth Hospital; SD: standard deviation; UHL: University Hospital Lewisham.

This study also described the mortality rates post-COVID-19 (Tables 1 and 3). In total, 13.7% of patients with COVID-19 died. For those with true COVID-19 (Group 1), the rate was 15.8%. Of the 76 deaths, only 21 were admitted with COVID-19 pneumonitis (27.6%).

Further analyses of patients who died in this study showed that of those who were not admitted with COVID-19 pneumonitis (Group 2), only 7/322 (2.2%) went on to develop COVID-19 pneumonitis and of these, only one died due to COVID-19. Similarly, in Group 3, 6/98 (6.1%) developed COVID-19, of whom four (4.1%) died. All five patients who died in Groups 2 and 3 had multiple comorbidities. Of the 55 deaths in Groups 2 and 3, only five had developed COVID-19 pneumonitis before their death. There were, therefore, 26 deaths directly attributable to COVID-19 pneumonitis. This represents only 4.7% (26/553) of all patients admitted with COVID-19. Of these 26 deaths, only six patients had had triple vaccinations, 11 patients were unvaccinated, and nine had between one and two vaccinations. Admittedly, the numbers are small for any meaningful comparisons.

Multivariable analyses, using stepwise, backward, logistic regression, showed that people from a Black Caribbean background (OR: 0.27; 95% CI: 0.07–0.98) were independently associated with lesser mortality, controlling for age, sex, and ethnicity.

DISCUSSION

This is one of the first large, multi-ethnic, hospital-based studies that has described the clinical presentation of patients hospitalised with Omicron COVID-19 infections and showed that these presentations are very different to those who presented to hospital in the previous surges in the UK. There have been very few studies that have described the clinical characteristics of patients hospitalised with the Omicron variant of COVID-19.[7,8] A recent South African study showed that patients admitted due to the Omicron variant had significantly lower odds of severe disease compared with the Delta variant (OR: 0.3; 95% CI: 0.2–0.5), but that study did not describe the actual clinical presentations.[7]

The strengths of this study include the large number of patients managed within a very short period of time, thereby giving a good indication of proportion of the disease within the three designated groups of this study; multi-ethnic diversity of the cohort, which implies the rates could be generalisable to other healthcare populations; the study's ability to examine various socio-demographic factors associated with the prevalence of the infection, which would enable healthcare institutions in terms of future healthcare planning; detailed information on the presenting clinical features of these patients confirming that Omicron COVID-19 is significantly different in its presentation and pattern compared to previous COVID-19 variants; and the novel socio-demographic and outcome comparison between the three groups identified in this study.

This study showed that a significant proportion of patients presented to hospital with other symptoms and conditions, and that they had an incidental positive COVID-19 test result on admission screening for COVID-19. Common presentations included delirium, falls and fractures, and non-COVID-19 respiratory illnesses (Table 2). These are recognised common presentations in hospitalised older adult patients; therefore this observation is reflective of the fact that most COVID-19 admissions to hospitals are amongst older, frailer patients with existing comorbidities. Furthermore, this study showed that COVID-19 was also incidentally detected in the maternity units among females presenting with antenatal problems, in a variety of surgical specialties, and in children. Seizures were the most common presenting feature in children. These observations are valuable for clinicians managing patients in various hospital specialties and would have implications in infection prevention and control, and in-hospital clinical pathways in terms of COVID-19 and non-COVID-19 pathways.

The authors also examined socio-demographic associations of hospitalised patients with COVID-19. They found that patients with COVID-19 pneumonitis (Group 1) and HAC (Group 3) were significantly older than those in Group 2. These differences could be explained to a certain extent by the fact that Group 2 had patients who were children or who had antenatal problems. Both of these cohorts included younger

Table 2: Top 12 presentations of patients admitted with incidental Omicron COVID-19.

Order	Medical presentation	Frequency
1	Falls and fractures	37
2	Antenatal problems	35
3	Delirium	34
4	COPD/asthma	14
5	Solid and metastatic cancer	14
6	Urosepsis	14
7	Pneumonia (non-COVID-19)	11
8	Diabetic emergencies	11
9	Seizures	11
10	Musculoskeletal conditions	10
11	Sickle cell crises	10
12	Congestive heart failure	8

COPD: chronic obstructive pulmonary disease.

patients than those with other presentations. In accordance with previous studies, 30% of BAME patients had COVID-19 pneumonitis, which was significantly higher than 19% of patients from White ethnicity. There are possible speculative hypotheses that may explain these differences, including ethnic genetic variability in terms of innate immune response to viral infections, though yet unproven in COVID-19 infection specifically;[11,12] higher prevalence of underlying health diseases such as diabetes, which may lend them to be more susceptible to developing infections;[13-16] and worse deprivation rates and higher household density amongst BAME population.[13,15-17] While there was no data available for the authors' study on whether the Delta variant was more prevalent in patients from BAME backgrounds compared with White patients, they do not believe that there were any ethnic variations in the prevalence of Omicron or Delta during the study period. As described earlier, national data had shown that 87.5% of COVID-19 infections within London were due to the Omicron variant by 15th December 2021. Hence, the authors believe that the majority of infections in BAME patients were also Omicron. Other studies did not show any ethnic variation between Delta and Omicron infections either.[18]

This study demonstrates important differences in terms of mortality due to the Omicron variant as compared to previous studies examining COVID-19 mortality. Compared with previous studies from the same hospitals trust, this study showed that mortality rate post-COVID-19 was significantly lower than the previous two surges within this trust.[19,20] Compared with 29.5% and 18.5% during the first two surges, respectively,

only 13.7% of patients with COVID-19 died.[20] For those with true COVID-19 (Group 1), the rate of 15.8% was still lower than previous reports. This study found only 26 deaths that were directly attributable to COVID-19 pneumonitis. This represents only 4.7% of all patients admitted with COVID-19. These are important observations as most mortality data from COVID-19 would include patients in all the three groups combined (13.7%) rather than those who truly died from COVID-19. The authors' findings are consistent with other recent studies, which also found that Omicron infections caused less severe illness, with similar reductions in hospitalisations and death associated with Omicron infection.[18,21,22] Moreover, this study showed that many deaths that may be classified as COVID-19-related were actually not directly attributable to COVID-19 pneumonitis.

Table 3: Mortality in patients with COVID-19 (Omicron) at Lewisham and Greenwich Trust, London, UK from 15th December 2021 to 15th January 2022.

	Total deaths in patients with COVID-19 detected	Admitted with COVID-19 pneumonitis	COVID-19 detected on admission screening	Probable hospital-associated COVID-19	p
Number of subjects	76	21 (27.6%)	28 (36.8%)	27 (35.5%)	N/A
Sex					
Male	43 (56.6%)	11 (52.4%)	17 (60.7%)	15 (55.6%)	p=NS
Female	33 (43.4%)	10 (47.6%)	11 (39.3%)	12 (44.4%)	
Age (years), mean (SD), median, range	79.1 (13.7), 82, 12–97	75.3 (12.5), 80, 49–95	79.9 (17.3), 84, 12–97	81.2 (9.5), 85, 57–93	p<0.001
Age group, n (%)					
0–40	1 (1.3%)	0 (0.0%)	1 (3.6%)	0 (0.0%)	p<0.001
40–50	1 (1.3%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	
50–60	5 (6.6%)	2 (9.5%)	1 (3.6%)	2 (7.4%)	
60–70	9 (11.8%)	4 (19.1%)	3 (10.7%)	2 (7.4%)	
70–max	60 (79.0%)	14 (66.7%)	23 (82.1%)	23 (85.2%)	
Ethnicity					
White	54 (71.1%)	10 (47.6%)	21 (75.0%)	23 (85.2%)	p=NS
Black Caribbean	14 (18.4%)	7 (33.3%)	4 (14.3%)	3 (11.1%)	
Black African	4 (5.3%)	2 (9.5%)	2 (7.1%)	0 (0.0%)	
South Asian	3 (4.0%)	1 (4.8%)	1 (3.6%)	1 (3.7%)	
East Asian	1 (1.3%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	
BAME	22 (28.9%)	11 (52.4%)	7 (25.0%)	4 (14.8%)	

	Total deaths in patients with COVID-19 detected	Admitted with COVID-19 pneumonitis	COVID-19 detected on admission screening	Probable hospital-associated COVID-19	p
Vaccination status					
Unvaccinated	20 (26.3%)	9 (42.9%)	5 (17.9%)	6 (22.2%)	p<NS
1	8 (10.5%)	0 (0.0%)	4 (14.3%)	4 (14.8%)	
2	27 (35.5%)	6 (28.6%)	11 (39.3%)	10 (37.0%)	
3	17 (22.4%)	6 (28.6%)	7 (25.0%)	4 (14.8%)	
N/A (children)	1 (1.3%)	0 (0.0%)	1 (3.6%)	0 (0.0%)	
Unknown	3 (4.0%)	0 (0.0%)	0 (0.0%)	3 (11.1%)	
Critical care required					
General wards	69 (90.8%)	14 (66.7%)	28 (100.0%)	27 (100.0%)	N/A
Critical care	7 (9.2%)	7 (33.3%)	0 (0.0%)	0 (0.0%)	
Admitting discipline					
Acute and elderly medicine	70 (92.1%)	21 (100.0%)	24 (85.7%)	25 (92.6%)	N/A
Surgical specialties	5 (6.6%)	0 (0.0%)	3 (10.7%)	2 (7.4%)	
Obstetrics and gynaecology	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Paediatrics	1 (1.3%)	0 (0.0%)	1 (3.6%)	0 (0.0%)	

BAME: Black, Asian, and minority ethnic; N/A: not applicable; NS: not significant; SD: standard deviation.

Speculative reasons for improved outcomes in this study include the fact that the Omicron variant may be less virulent and aggressive in its effects compared to previous variants, including less endothilialitis;[21] higher vaccination rates, which would reduce the impact of COVID-19 infections on the body; availability of better medical treatments, including steroids, antiviral therapy, and neutralising monoclonal antibodies; and more structured and faster processes for infection prevention and isolation, which meant fewer vulnerable patients may have been exposed to the risk. These results are in accordance with recent results published by the Office for National Statistics (ONS), which showed that the risk of death due to Omicron variant was 67% lower compared to the Delta variant in December 2021.[23]

This study showed that 52.0% of those admitted with COVID-19 pneumonitis were unvaccinated, and a further 22.5% had only had one or two

vaccinations. While it may appear that only 52.0% of those admitted with COVID-19 pneumonitis were unvaccinated, implying that 48.0% had had at least one vaccination, it is important to compare these figures with the vaccination rates within the region at that time. As of 13th December 2021, there were 10.0–16.0% patients over 60 years who were unvaccinated (16.0% being 60–64 years and 10.0% being >80 years).[24] These figures are important as the majority of the patients admitted were older than 60 years. Thus, this small proportion of patients in the local population contributed to over half of all admissions directly related to COVID-19. The vaccination status in Group 3 (75.0% had had between two and three vaccinations) is reflective of this cohort being predominantly an older, frailer cohort with multiple comorbidities, thus likely to have higher vaccination rates.

Limitations

There are some limitations to this study. The authors did not have information on the precise genotype of SARS-CoV-2 in these patients. Instead, they assumed it to be Omicron on the basis of prevalence data available for the population in the catchment area of the hospitals, which is in accordance with recent studies.[7,8] The authors did not have any information on existing comorbidities of patients, which would have been useful in evaluating outcomes further. Whilst there were only three types of vaccines administered in the area served by the hospital prior to the period of the study (Pfizer–BioNTech COVID-19 vaccine, Oxford–AstraZeneca COVID-19 vaccine, and a very small proportion were administered the Moderna COVID-19 vaccine), there was no data available regarding the precise type of vaccine taken by the individual patients in this study. Therefore, the authors were unable to assess whether there were any differences in patient outcomes due to the type of vaccine administered. Finally, the authors do not have outcome data for the study for approximately 4.9% of patients who were still in hospital; however, it is unlikely that this missing data would have made any significant difference to the mortality rates identified in the study.

CONCLUSION

This large, multi-ethnic, hospital-based study has described the clinical presentations and mortality outcomes of hospitalised patients with the COVID-19 Omicron variant. It has determined socio-demographic factors associated with these presentations, including ethnicity and vaccination rates. The study provides information that may be useful in future COVID-19 studies examining outcomes and presentations of Omicron and future COVID-19 variants.

References

1. World Health Organization (WHO). Classification of omicron (B.1.1.529): SARS-CoV-2 variant of concern. 2021. Available at: https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern. Last accessed: 15 December 2021.
2. Viana R et al. Rapid epidemic expansion of the SARS-CoV-2 omicron variant in southern Africa. Nature. 2022;DOI:10.1038/d41586-021-03832-5.
3. National Institute for Communicable Diseases (NICD). COVID-19 weekly epidemiology brief. South Africa. Week 48 2021. 2021. Available at: https://www.nicd.ac.za/wp-content/uploads/2021/12/COVID-19-Weekly-Epidemiology-Brief-week-48-2021.pdf. Last accessed: 3 November 2022.
4. Ferguson N et al. Report 50: hospitalisation risk for omicron cases in England. 2021. Available at: https://www.imperial.ac.uk/media/imperial-college/medicine/mrc-gida/2021-12-22-COVID19-Report-50.pdf. Last accessed: 10 January 2022.
5. Scheepers C et al. Emergence and phenotypic characterization of the global SARS-CoV-2 C.1.2 lineage. Nat Commun. 2022;DOI:10.1038/s41467-022-29579-9.
6. Wolter N et al. Early assessment of the clinical severity of the SARS-CoV-2 omicron variant in South Africa: a data linkage study. Lancet. 2022;399(10323):437-46.
7. Maslo C et al. Characteristics and outcomes of hospitalized patients in South Africa during the COVID-19 omicron wave compared with previous waves. JAMA. 2022;327(6):583-4.
8. Lewnard JA et al. Clinical outcomes associated with SARS-CoV-2 omicron (B.1.1.529) variant and BA.1/BA.1.1 or BA.2 subvariant infection in Southern California. Nat Med. 2022;DOI:10.1038/s41591-022-01887-z.
9. UK Government. Change in new cases by specimen date. 2022. Available at: https://coronavirus.data.gov.uk/metrics/doc/changeInNewCasesBySpecimenDate. Last accessed: 15 February 2022.
10. Hologic. SARS-COV-2 assay (Panther Fusion® system). 2020. Available at: https://www.hologic.com/sites/default/files/2020-03/AW-21159-001_002_01.pdf. Last accessed: 3 November 2022.
11. Kenney AD et al. Human genetic determinants of viral diseases. Annu Rev Genet. 2017;51:241-63.
12. Sambaturu N et al. Role of genetic heterogeneity in determining the epidemiological severity of H1N1 influenza. PLoS Comput Biol.

2018;14(3):e1006069.

13. Williamson E et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;DOI:10.1038/s41586-020-2521-4.
14. Lassale C et al. Ethnic disparities in hospitalisation for COVID-19 in England: the role of socioeconomic factors, mental health, and inflammatory and pro-inflammatory factors in a community-based cohort study. Brain Behav Immun. 2020;88:44-9.
15. The Institute for Fiscal Studies (IFS). Are some ethnic groups more vulnerable to COVID-19 than others? 2020. Available at: https://ifs.org.uk/inequality/chapter/are-some-ethnic-groups-more-vulnerable-to-covid-19-than-others/. Last accessed: 3 November 2022.
16. Mude W et al. Racial disparities in COVID-19 pandemic cases, hospitalisations, and deaths: a systematic review and meta-analysis. J Glob Health. 2021;11:05015.
17. Aldridge RW et al. Black, Asian and minority ethnic groups in England are at increased risk of death from COVID-19: indirect standardisation of NHS mortality data. Wellcome Open Res. 2020;5:88.
18. Wrenn JO et al. COVID-19 severity from omicron and delta SARS-CoV-2 variants. Influenza Other Respir Viruses. 2022;16(5):832-6.
19. Omotade I et al. Factors associated with mortality in multi-ethnic hospitalised COVID patients. Abstract 670. BSG Autumn Meeting, 24-26 November, 2021.
20. Patel M et al. Demographic variability in mortality from COVID during the two surges. Abstract 671. BSG Autumn Meeting, 24-26 November, 2021.
21. Corriero A et al. COVID-19 variants in critically ill patients: a comparison of the delta and omicron variant profiles. Infect Dis Rep. 2022;14(3):492-500.
22. Ulloa AC et al. Estimates of SARS-CoV-2 omicron variant severity in Ontario, Canada. JAMA. 2022;327(13):1286-8.
23. Office for National Statistics (ONS). Coronavirus (COVID-19) latest insights: deaths. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/articles/coronaviruscovid19latestinsights/deaths. Last accessed: 20 February 2022.
24. National Health Service (NHS). COVID-19 vaccinations archive. 2022. Available at: https://www.england.nhs.uk/statistics/statistical-work-areas/covid-19-vaccinations/covid-19-vaccinations-archive/. Last accessed: 20 February 2022.

Adult-Onset Idiopathic Cervical Dystonia

Authors:	*Shameer Rafee, Mahmood Al-Hinai, Michael Hutchinson Department of Neurology, St Vincent's University Hospital, Dublin, Republic of Ireland *Correspondence to srafee@tcd.ie

Disclosure:	Rafee has received payment or honoraria for lectures from Merz and Ipsen and meeting attendance support from AbbVie. Al-Hinai has declared no conflicts of interest. Hutchinson has received support from Merrion Neuroscience Research Foundation and grants from Dystonia Ireland and Health Research Board Ireland.
Received:	14.05.22
Accepted:	04.11.22
Keywords:	Cervical dystonia, focal dystonia, management, non-motor symptoms, pathophysiology, superior colliculus.
Citation:	EMJ. 2022;7[4]:69-76. DOI/10.33590/emj/10005730. https://doi.org/10.33590/emj/10005730.

Abstract

Adult-onset idiopathic focal dystonia is the most common type of primary dystonia, and adult-onset idiopathic cervical dystonia (AOICD) is its most prevalent phenotype. AOICD is an autosomal-dominant disorder with markedly reduced penetrance; clinical expression is dependent on age, sex, and environmental exposure. Motor symptoms at presentation are poorly recognised by non-specialists, leading to long delays in diagnosis. Certain features of history and examination can help diagnose cervical dystonia. There is a relatively high prevalence of anxiety and/or depression, which adversely affects health-related quality of life. Recent studies indicate that patients with AOICD also have disordered social cognition, particularly affecting emotional sensory processing. AOICD can be treated reasonably effectively with botulinum toxin injections, given at 3-month intervals. Oral antidystonic medications are often trialled initially, but are largely ineffective. Comprehensive modern management of patients with AOICD requires recognition of presence of mood disorders, and actively treating the endogenous mood disorder with antidepressant therapy. Botulinum toxin injections alone, no matter how expertly given, will not provide optimal therapy and improved health-related quality of life without an holistic approach to patient management. Increasing evidence indicates that AOICD is a neurophysiological network disorder of GABAergic inhibition, causing a syndrome of dystonia, mood disturbance, and social cognitive dysfunction, with the superior colliculus playing a central role.

Key Points

1. Cervical dystonia typically presents to neurologists as a motor disorder but has a spectrum of non-motor symptoms, including psychiatric, sensory, and cognitive function. The non-motor symptoms can have a significant impact on quality of life.

2. Botulinum toxin is an effective treatment but a good knowledge of anatomy and careful muscle selection is needed for effective outcomes.

3. Although classically considered a basal ganglia disorder, it is likely that superior colliculus dysfunction underlies the motor and non-motor symptoms.

INTRODUCTION

Dystonias are a group of hyperkinetic movement disorders characterised by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous.[1] They can be classified into primary (idiopathic or genetic) or secondary. Anatomical distribution of the dystonia can be focal, multifocal, segmental, or generalised.[2]

Adult-onset idiopathic focal dystonia (AOIFD) is the most frequent presentation of dystonia with a number of phenotypes; their typical manifestations are shown in Table 1. Sex is probably the single most important biological variable in relation to disease penetrance and expression. In AOIFD, the female to male sex ratio increases with increasing age of onset, which accounts for 60% of the variation in sex ratios.[3,4]

AOIFD presenting as musician's dystonia mostly affects males with age of onset under 40 years. After 45 years, AOIFD phenotypes predominantly affect females and, with increasing age at onset, there is a steady decrease in the proportion of males affected.

This review of the total spectrum of the syndrome aims to holistically explain the pathophysiology of the diverse symptomatology as being caused by dysfunction within the collicular–pulvinar–amygdala network.

ADULT-ONSET IDIOPATHIC CERVICAL DYSTONIA/CERVICAL DYSTONIA

Cervical dystonia (CD) is the most common expression of AOIFD, characterised by sustained, involuntary contractions of the cervical neck muscles.[5] Originally, cervical dystonia was considered a psychogenic disorder. The first

Table 1: The spectrum of presentations with adult-onset idiopathic focal dystonia.

AOIFD phenotypes	Mean age at presentation (years)
Focal hand dystonia	38.9
Cervical dystonia	45.4
Laryngeal dystonia	47.0
Blepharospasm	56.1

The only phenotype with a male predominance is focal hand dystonia.

AOIFD: adult-onset idiopathic focal dystonia.

book on movement disorders by Henri Meige (1901)[6] described "le torticollis mental" (cervical dystonia) as a tic disorder. The peculiar "geste antagoniste" was used as evidence for its psychogenic nature. This belief persisted until the late 1900s, when a conceptual change occurred in how these conditions were viewed.

CERVICAL DYSTONIA: CLINICAL CHARACTERISTICS

Demographics

CD affects females more than males (with a ratio of 1.5 females to every 1.0 male). The mean age of onset for females is 45.9 years, and the mean age of onset for males is 5.0–6.0 years earlier, at 40.0 years.[3,5,7] Delays in diagnosis complicate research into cervical dystonia, and accurate assessment of age of onset can be difficult. This disorder is poorly recognised. One Australian study found a mean delay to diagnosis of 6.8 years.[8] Referral by primary care physicians to non-neurologists is also common due to symptomatic overlap with musculoskeletal disorders. Many patients are initially told their symptoms are secondary to anxiety or depression.[8]

Risk Factors

AOIFD is an autosomal dominant disorder with poor penetrance.[9] It is likely that environmental influences trigger both penetrance and expression of these genes and development of CD, or another AOIFD phenotype. Studies have suggested various risk factors associated with the development of the different types of AOIFD.[10] Neck and trunk injuries were associated with cervical dystonia in a large Italian registry.[11] Surgical procedures and car accidents requiring hospital attendance have also been linked with CD.[12] Although car accidents are associated with whiplash and secondary cervical dystonia, and there is a lot of overlap between the disorders, certain features can be used to distinguish this from idiopathic cervical dystonia.[12,13]

Motor Features

Patients with CD frequently show an irregular, arrhythmic, 'spasmodic' jerking movement of the head with slower recovery phases towards the neutral position. Slow rhythmic deviations, sustained tonic movements, and permanent fixed deformities can also be seen.[14] Specific symptoms, pain, and social anxiety associated with these should be probed in patients for targeted treatments.[15] Head tremor in cervical dystonia can be a troublesome symptom, and is often the most debilitating. It can be seen in up to 80% of CD cases and has an association with positive family history.[16] Tremor associated with dystonia is a separate entity and is defined as the presence of tremor in a body part not affected by dystonia, e.g., limb tremor in patients with CD.[16] Clinically, limb tremor in CD can be indistinguishable from essential tremor. Tremor amplitudes are subclinically larger in patients with essential tremor, and limb tremor in CD is often more irregular, although it can be difficult to identify this on examination.[17] A list of differential diagnoses is given in Table 2.

Sensory Features

Numerous sensory changes have been associated with focal dystonias, and will not be discussed here.[18] One feature, however, is an important diagnostic clue: the "geste antagoniste," a term first introduced in Meige's book on movement disorders.[6,19] This 'sensory

Table 2: Cervical dystonia: differential diagnoses.[14]

Orthopaedic: atlanto-axial subluxation, ligamentous injury, herniated cervical disc
Neurological: posterior fossa mass, Arnold–Chiari malformation, syringomyelia, focal seizures, tic disorders
Other: congenital muscle lesions, labyrinthitis, acute infectious torticollis

trick' can be used by patients to attenuate the symptoms of CD. In one study of 50 patients, all had at least one geste involving arm movement towards the face or head. Over half of patients have more than one geste. The cheek and chin are areas most commonly involved.[20] Tactile stimuli are thought to modulate sensorimotor feedback and diminish motor output, although specific mechanisms remain elusive. This unique sign may be lost with disease progression.[21]

Pain is a prominent symptom and can affect the majority of patients with CD. It has been described as "continuous," "radiating," and "tiring" and is often unilateral.[22] It can be the presenting symptom prior to onset of motor features.[23] The high prevalence is unique to CD among the various focal dystonias. The presence of pain may be related to muscle hypertrophy from forced contractions or due to higher density of pain receptors in affected muscles.[24] Pain is not always related to dystonia severity, and contributes significantly to reduced quality of life (QoL) in CD.[25]

Psychiatric Symptoms

Anxiety and/or depression are important features of AOIFD. Anxiety and depression can affect up to 40% of patients with CD, depending on the assessment method used.[26] These symptoms often have a bigger impact on QoL in CD than the motor dystonic features.[27] Although the gold standard assessment method would be psychiatrist-led clinical review, this is impractical in a neurologist-led botulinum toxin service. The Beck Anxiety Index (BAI)[28] and Beck Depression Inventory (BDI)[29] are frequently used, but are not disease-specific. These brief screening tools are easily applied, short, and self-administered. High scores, indicating excess symptoms of anxiety or depression, should prompt neurologists to further probe these symptoms.

Cognitive Symptoms

A detailed account of cognitive changes is beyond the scope of this manuscript. Clinicians treating patients with AOIFD should be cognisant that dystonia is more than a motor disorder. Various cognitive changes have been noted in the AOIFD literature, e.g., using basic screening tools to cognitive impairment,[30] executive function and working memory,[31] deficits in cognitive flexibility,[32] and sustained attention.[33] The authors' research group has found changes in social cognition,[34] although this is contested and warrants further probing.[35] Research into cognitive symptoms can be difficult due to variations in AOIFD, variations within AOIFD, disease rarity, and consistency across measurement tools.

Treatment

Oral medication options for CD are limited. Generally, anticholinergic medications are most effective. A majority of patients with dystonia trialled on high dose trihexyphenidyl showed a benefit, with over one-third of patients showing a dramatic benefit over long-term use. However, this study involved younger patients with mixed dystonia aetiologies.[36] Long-term outcomes may differ for AOIFD. A limiting factor in anticholinergic use are the side effects, which can be significant in older patients. Important unwanted impacts include memory loss, confusion, and insomnia in adults, and chorea or exacerbation of pre-existing tic disorders in children.[37] Peripheral anticholinergic symptoms, e.g., urinary retention, can be difficult to manage. Oral pyridostigmine can mitigate some side effects. Anticholinergic drugs can also be abused, trihexyphenidyl in particular, as it can cause a perceived sense of relaxation or euphoria, and is of particular concern in patients with psychiatric comorbidities.[38]

Benzodiazepines, particularly clonazepam, are commonly used in focal dystonias. They may be especially effective in treating CD with head tremor. An initial dose of 0.5 mg clonazepam in the evenings can be trialled.[37] Clonazepam may be more useful in patients with milder disease, and in blepharospasm.[39]

Botulinum toxin (BoNT) is the most effective treatment for focal dystonias. It began to be used for therapeutic purposes in the 1980s. This toxic compound is produced by *Clostridium botulinum* and has seven different forms (A–G); Types A and B are used for clinical treatment purposes. The toxin works presynaptically by blocking the binding of acetylcholine-containing vesicles with the cell membrane, preventing acetylcholine exocytosis. It results in muscle paresis and can cause muscle atrophy.[40] In cervical dystonia, BoNT can be given

without using ultrasound or electromyographic guidance; this is routine practice at the authors' centre. Careful visual inspection and palpation is usually sufficient for a good outcome. Even though clinical improvement is seen, palpation has been shown to inferior to ultrasound in terms of accuracy of injection, in particular for splenius capitis and deeper muscles.[41,42] In the authors' experience, ultrasound can provide confidence to neurologists starting BoNT injections in avoiding vasculature and in patients with obesity. However, as with any medical device, there is a learning curve. BoNT improves dystonic posturing, pain, and QoL in patients with CD. Guidance is available for recommended BoNT dosage following muscle identification.[42] It can take up to 2 weeks for the therapeutic effect to be seen, and repeat treatment is advised at 12 weeks, although flexible dosing schedules should be considered for appropriate patients.[42] The most common adverse effects are muscle weakness, dysphagia, dry mouth, pain, and influenza-like symptoms. These symptoms are typically transient, and severe events are rare.[43] A combination of botulinum toxin treatment and physiotherapy can be more effective than BoNT alone. One study suggested that a combined approach results in lower toxin dosing and longer duration of benefit of treatment; patients also reported lower pain and improved QoL.[44] Neurologists should consider physiotherapy as a useful adjunct, particularly in patients who are relatively refractory to treatment with BoNT therapy alone.

Targeting of muscles is the most important aspect of BoNT therapy, and a strong knowledge of functional anatomy of neck muscles is required. Cervical muscles are arranged in redundant layers, and often, several muscles need to be injected to achieve satisfactory outcomes. Examination of a patient with CD should focus on defining the posturing and dystonic muscles. The collum-caput method allows for identification of specific dystonic muscles according to neck posturing. When injecting, clinicians should be cognisant that injecting non-dystonic muscles can accentuate abnormal posturing and make identification of abnormal muscles more difficult.[45]

Other targeted options for refractory CD include surgical options like deep brain stimulation (DBS) and neuro-ablative procedures. DBS targets for CD include the globus pallidus interna (GPi) and the subthalamic nucleus (STN). Typically, patients are selected for DBS treatment based on lack of response to BoNT, absence of cognitive/psychiatric issues, and significant impact of CD on QoL. Bilateral GPi DBS has been shown to improve symptoms by more than 50% over long-term follow-up.[46] Improvement in pain and disability accompany the amelioration in motor symptoms.[47] However, pallidal treatment is not without complications. There are reports of development of bradykinesia in non-dystonic limbs that can affect daily functioning. This phenomenon appears to impact patients that report the greatest benefit from pallidal DBS and can be mitigated, but not eliminated, with alterations to stimulation.[48] Other serious adverse events include subcutaneous infection, lead dislodgement/breakage, and dysarthria, and worsening of dystonia responsive to reprogramming.[49] One meta-analysis has shown similar efficacy in STN DBS and GPi DBS, with a lower rate of complications in STN DBS.[50]

Historically, thalamotomies and pallidotomies were standard surgical treatments for CD.[51,52] Although ablative therapies can be effective, the reversibility and adaptability of DBS, which can be turned on and off, has led to it being the main surgical treatment method. Currently, pallidotomies are reserved for some patients when DBS fails.[53] Peripheral denervation is no longer performed.

RATING SCALES AND MEASURING DYSTONIA SEVERITY

Tracking disease changes and benefit of treatment in CD can be difficult in clinic settings, especially in the first few months after starting treatment. A validated method for assessing changes in muscle posturing, pain, and functional disability is important for treatment titration. The utility of a rating scale depends on its reliability, validity, and easy application in busy services.[14] There are a number of such scales available for use in patients with CD. The Cervical Dystonia Impact Scale 58 (CDIP-58) and the revised Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS-R) are instruments that are

used both clinically and in research. The latter is probably too complex for routine use.[54] The Tsui score is another objective method for rating dystonia severity, and is also well validated for use in CD. It evaluates amplitude and duration of sustained postures as well as abnormal shoulder posturing.[55] However, clinicians should be cognisant that for all AOIFD, variabilities in disease severity due to stress, fatigue, and activity can confound assessments at any single time point.

ANATOMY OF CERVICAL DYSTONIA

Basal Ganglia

Traditionally, secondary dystonias have been associated with insults causing dysfunction within the basal ganglia. Lesions to the ventral anterior and ventrolateral nucleus of the thalamus, putamen, and globus pallidus can cause dystonia. Onset of dystonic symptoms is often delayed by months after the initial injury.[56] More evidence for basal ganglia involvement comes from the co-existence of dystonia with other disorders classically associated with the basal ganglia, e.g., Parkinson's disease and Huntington's disease. However, many patients with dystonia show no evidence of structural basal ganglia abnormalities. Moreover, many patients with basal ganglia lesions do not manifest dystonia. Animal studies have also indicated that other regions functionally connected to the basal ganglia may be implicated.[57]

MRI evidence suggest that AOIFD is a 'network disorder' affecting multiple distinct regions in the brain.[58] Functionally, the superior colliculus (SC) likely plays a central role in disease mechanism, and this has been corroborated, particularly through utilisation of temporal discrimination.[59] The SC is a laminated, multi-layered structure that sits at the rostral most aspect of the brainstem. Functionally, it has been divided into two layers: a superficial layer, mainly visual and sensory receptive, and a deep layer, which projects motor outputs. At its deepest, the SC blends with the reticular formation. Ventromedially lies the periaqueductal grey matter.[60]

AOIFDs could be considered a disorder due to disinhibition at the level of the SC.

Animal studies have confirmed that SC disinhibition evokes dystonic posturing. Inhibition of the SNpr, resulting in loss of inhibition (disinhibition or excitation) affecting the SC, evokes a dystonic head tilt in macaques.[61] A number of downstream motor (reticulospinal) pathways exit from the SC that can affect cervical neck muscles to explain the dystonic features. Stimulation of the SC in monkeys results in evoked EMG responses in obliquus capitis, rectus capitis, and splenius capitis.[62]

The temporal discrimination threshold (TDT) is the shortest time interval at which two sequential stimuli are perceived as asynchronous. It has been demonstrated previously that an abnormal TDT is an important state-independent endophenotype in CD.[63,64] Abnormal TDTs are easily assessed clinically and are a sensitive measure of defective processing within the SC.[65] The SC detects salient environmental change and neurons enter an 'on' state. SC cells exhibit an 'on', 'pause', and 'off' state in response to detection, persistence, and removal of stimuli, respectively. GABAergic gating shapes the generation of the pause and on phases and inhibition, e.g., with gabazine, leads to prolongation of both the on and off states, resulting in prolonged TDT.[66] Patients and unaffected relatives with abnormal TDTs show reduced SC activity compared to controls, supporting the hypothesis that disrupted SC processing (loss of inhibition at the level of the SC) mediates abnormal temporal discrimination.[59]

Finally, it is important for any anatomical and functional model explaining AOIFD mechanisms to accommodate the non-motor symptoms as well as motor features. The authors have previously described the importance of the collicular–pulvinar–amygdala network as a potential explanation for the spectrum of changes in AOIFD and CD.[67] Tractography has confirmed the existence of anatomical connections between the three regions.[68] The collicular–pulvinar–amygdala network has a role in encoding emotion towards emotional/aversive stimuli,[69] perceptual decision making,[70] social cognition,[71] depression, and anxiety.[72,73] An understanding of anatomical functional networks underpinning CD can help lead to an holistic

approach to patient care beyond focus on BoNT therapy alone.

CONCLUSION

Cervical dystonia is a rare, poorly recognised disorder that can have a big impact on patient QoL. A clear understanding of the presentation of CD and differential diagnoses are required to identify patients appropriate for BoNT therapy. Treatment with BoNT also takes practice, and knowledge of neck anatomy is important for positive outcomes. Clinicians should also familiarise themselves with ultrasound and electromyography guidance for patients that do not respond well to unguided injections. With careful muscle selection and accurate injections, CD can be treated very effectively. A holistic approach, with multidisciplinary input, including physiotherapists, occupational therapists, and psychologists, would be most effective in improving QoL.

References

1. Albanese A et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord. 2013;28(7):863-73.
2. Tarsy D, Simon DK. Dystonia. N Engl J Med. 2006;355(8):818-29.
3. Butler JS et al. Age-related sexual dimorphism in temporal discrimination and in adult-onset dystonia suggests GABAergic mechanisms. Front Neurol. 2015;6:258.
4. Williams L et al. Epidemiological, clinical and genetic aspects of adult onset isolated focal dystonia in Ireland. Eur J Neurol. 2017;24(1):73-81.
5. Jankovic J et al. Cervical dystonia: clinical findings and associated movement disorders. Neurology. 1991;41(7):1088-91.
6. Meige H, Feindel E. Les tics et leur traitement. Available at: https://gallica.bnf.fr/ark:/12148/bpt6k9761496r/f9.item. Last accessed: 15 November 2022.
7. LeDoux MS et al. Clinical and genetic features of cervical dystonia in a large multicenter cohort. Neurol Genet. 2016;2(3):e69.
8. Bertram KL, Williams DR. Delays to the diagnosis of cervical dystonia. J Clin Neurosci. 2016;25:62-4.
9. Waddy HM et al. A genetic study of idiopathic focal dystonias. Ann Neurol. 1991;29(3):320-4.
10. Defazio G et al. Do primary adult-onset focal dystonias share aetiological factors? Brain. 2007;130(5):1183-93.
11. Defazio G et al. Possible risk factors for primary adult onset dystonia: a case-control investigation by the Italian Movement Disorders Study Group. J Neurol Neurosurg Psychiatry. 1998;64(1):25-32.
12. Molloy A et al. An evaluation of the role of environmental factors in the disease penetrance of cervical dystonia. J Neurol Neurosurg Psychiatry. 2015;86(3):331-5.
13. Samii A et al. Post-traumatic cervical dystonia: a distinct entity? Can J Neurol Sci. 2000;27(1):55-9.
14. Jankovic J, Hallett M (eds.), Therapy with Botulinum Toxin (1994) 1st edition, London; Taylor & Francis.
15. Moriarty A et al. Longitudinal follow-up of mood in cervical dystonia and influence on age at onset. Mov Disord Clin Pract. 2022;9(5):614-8.
16. Hvizdošová L et al. The prevalence of dystonic tremor and tremor associated with dystonia in patients with cervical dystonia. Sci Rep. 2020;10(1):1436.
17. Shaikh AG et al. Irregularity distinguishes limb tremor in cervical dystonia from essential tremor. J Neurol Neurosurg Psychiatry. 2008;79(2):187-9.
18. Conte A et al. The role of sensory information in the pathophysiology of focal dystonias. Nat Rev Neurol. 2019;15(4):224-33.
19. Broussolle E et al. Early illustrations of geste antagoniste in cervical and generalized dystonia. Tremor Other Hyperkinet Mov (N Y). 2015;5:332.
20. Müller J et al. Clinical characteristics of the geste antagoniste in cervical dystonia. J Neurol. 2001;248(6):478-82.
21. Martino D et al. The phenomenology of the geste antagoniste in primary blepharospasm and cervical dystonia. Mov Disord. 2010;25(4):407-12.
22. Kutvonen O et al. Pain in spasmodic torticollis. Pain. 1997;69(3):279-86.
23. Sheehy MP, Marsden CD. Trauma and pain in spasmodic torticollis. Lancet. 1980;315(8171):777-8.
24. Chan J et al. Idiopathic cervical dystonia: clinical characteristics. Mov Disord. 1991;6(2):119-26.
25. Dauer WT et al. Current concepts on the clinical features, aetiology and management of idiopathic cervical dystonia. Brain. 1998;121(4):547-60.
26. Berman BD et al. Psychiatric associations of adult-onset focal dystonia phenotypes. J Neurol Neurosurg Psychiatry. 2017;88(7):595-602.
27. Ndukwe I et al. Trust the patient not the doctor: the determinants of quality of life in cervical dystonia. Front Neurol. 2020;11:991.
28. Beck AT et al. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol. 1988;56(6):893-7.
29. Beck AT et al. Comparison of Beck depression inventories -IA and -II in psychiatric outpatients. J Pers Assess. 1996;67(3):588-97.
30. Yang J et al. Screening for cognitive impairments in primary blepharospasm. PLoS One. 2016;11(8):e0160867.
31. Niccolai L et al. An examination of the neurocognitive profile and base rate of performance impairment in primary dystonia. J Clin Neurosci. 2020;74:1-5.
32. Lencer R et al. Primary focal dystonia: evidence for distinct neuropsychiatric and personality profiles. J Neurol Neurosurg Psychiatry. 2009;80(10):1176-9.
33. Allam N et al. Sustained attention in cranial dystonia patients treated

with botulinum toxin. Acta Neurol Scand. 2007;116(3):196-200.

34. Monaghan R et al. Non-motor features of cervical dystonia: cognition, social cognition, psychological distress and quality of life. Clin Park Relat Disord. 2020;4:100084.
35. Ellement B et al. Social cognition in cervical dystonia: phenotype and relationship to anxiety and depression. Eur J Neurol. 2021;28(1):98-107.
36. Burke RE et al. Torsion dystonia: a double-blind, prospective trial of highldosage trihexyphenidyl. Neurology. 1986;36(2):160-4.
37. Cloud LJ, Jinnah HA. Treatment strategies for dystonia. Expert Opin Pharmacother. 2010;11(1):5-15.
38. Chiappini S et al. Misuse of anticholinergic medications: a systematic review. Biomedicines. 2022;10(2):355.
39. Greene P et al. Analysis of open-label trials in torsion dystonia using high dosages of anticholinergics and other drugs. Mov Disord. 1988;3(1):46-60.
40. Dressler D, Saberi FA. Botulinum toxin: mechanisms of action. Eur Neurol. 2005;53(1):3-9.
41. Kreisler A et al. Anatomy-guided injections of botulinum neurotoxin in neck muscles: how accurate is needle placement? Eur J Neurol. 2020;27(11):2142-6.
42. Albanese A et al. Practical guidance for CD management involving treatment of botulinum toxin: a consensus statement. J Neurol. 2015;262(10):2201-13.
43. Truong D. Botulinum toxins in the treatment of primary focal dystonias. J Neurol Sci. 2012;316(1-2):9-14.
44. Tassorelli C et al. Botulinum toxin and neuromotor rehabilitation: an integrated approach to idiopathic cervical dystonia. Mov Disord. 2006;21(12):2240-3.
45. Reichel G. Cervical dystonia: a new phenomenological classification for botulinum toxin therapy. Basal Ganglia. 2011;1(1):5-12.
46. Hung SW et al. Long-term outcome of bilateral pallidal deep brain stimulation for primary cervical dystonia. Neurology. 2007;68(6):457-9.
47. Kiss ZHT et al. The Canadian multicentre study of deep brain stimulation for cervical dystonia. Brain. 2007;130(11):2879-86.
48. Berman BD et al. Induction of bradykinesia with pallidal deep brain stimulation in patients with cranial-cervical dystonia. Stereotact Funct Neurosurg. 2009;87(1):37-44.
49. Volkmann J et al.; DBS Study Group for Dystonia. Pallidal deep brain stimulation in patients with primary generalised or segmental dystonia: 5-year follow-up of a randomised trial. Lancet Neurol. 2012;11(12):1029-38.
50. Tsuboi T et al. A pooled meta-analysis of GPi and STN deep brain stimulation outcomes for cervical dystonia. J Neurol. 2020;267(5):1278-90.
51. Bertrand C et al. Combined stereotactic and peripheral surgical approach for spasmodic torticollis. Appl Neurophysiol. 1978;41(1-4):22-133.
52. Hassler R, Dieckmann G. Stereotactic treatment of different kinds of spasmodic torticollis. Confin Neurol. 1970;32(2):135-43.
53. Cif L, Hariz M. Seventy years of pallidotomy for movement disorders. Mov Disord. 2017;32(7):972-2.
54. Albanese A et al. Dystonia rating scales: critique and recommendations. Mov Disord. 2013;28(7):874-83.
55. Jost WH et al. Rating scales for cervical dystonia: a critical evaluation of tools for outcome assessment of botulinum toxin therapy. J Neural Transm (Vienna). 2013;120(3):487-96.
56. Park J. Movement disorders following cerebrovascular lesion in the basal ganglia circuit. J Mov Disord. 2016;9(2):71-9.
57. Kim JE et al. Cerebellar 5HT-2A receptor mediates stress-induced onset of dystonia. Sci Adv. 2021;7(10):eabb5735.
58. Valeriani D, Simonyan K. A microstructural neural network biomarker for dystonia diagnosis identified by a DystoniaNet deep learning platform. Proc Natl Acad Sci U S A. 2020;117(42):26398-405.
59. Mc Govern E et al. Disrupted superior collicular activity may reveal cervical dystonia disease pathomechanisms. Sci Rep. 2017;7(1):16753.
60. May PJ. The mammalian superior colliculus: laminar structure and connections. Prog Brain Res. 2006;151:321-78.
61. Holmes AL et al. Superior colliculus mediates cervical dystonia evoked by inhibition of the substantia nigra pars reticulata. J Neurosci. 2012;32(38):13326-32.
62. Corneil BD et al. Neck muscle responses to stimulation of monkey superior colliculus. II. Gaze shift initiation and volitional head movements. J Neurophysiol. 2002;88(4):2000-18.
63. Kimmich O et al. Temporal discrimination, a cervical dystonia endophenotype: penetrance and functional correlates. Mov Disord. 2014;29(6):804-11.
64. Bradley D et al. Temporal discrimination threshold: VBM evidence for an endophenotype in adult onset primary torsion dystonia. Brain. 2009;132(9):2327-35.
65. Conte A et al. Temporal discrimination: mechanisms and relevance to adult-onset dystonia. Front Neurol. 2017;8:625.
66. Kaneda K, Isa T. GABAergic mechanisms for shaping transient visual responses in the mouse superior colliculus. Neuroscience. 2013;235:129-40.
67. Rafee S et al. Adult onset dystonia: a disorder of the collicular-pulvinar-amygdala network. Cortex. 2021;143:282-9.
68. Rafal RD et al. Connectivity between the superior colliculus and the amygdala in humans and macaque monkeys: virtual dissection with probabilistic DTI tractography. J Neurophysiol. 2015;114(3):1947-62.
69. Kragel PA et al. A human colliculus-pulvinar-amygdala pathway encodes negative emotion. Neuron. 2021;109(15):2404-12.
70. Jun EJ et al. Causal role for the primate superior colliculus in the computation of evidence for perceptual decisions. Nat Neurosci. 2021;24(8):1121-31.
71. Frith CD, Frith U. Mechanisms of social cognition. Annu Rev Psychol. 2012;63:287-313.
72. MacMaster FP et al. Amygdala and hippocampal volumes in familial early onset major depressive disorder. Biol Psychiatry. 2008;63(4):385-90.
73. Tadayonnejad R et al. Aberrant pulvinar effective connectivity in generalized social anxiety disorder. Medicine (Baltimore). 2016;95(45):e5358.

Umbilical Cord Haematoma and Uterine Torsion: Rare Pregnancy Complications at Tu Du Hospital in Vietnam and a Review of Literature

Authors: Anh Dinh Bao Vuong, *Phuc Nhon Nguyen

Department of High-Risk Pregnancy, Tu Du Hospital, Ho Chi Minh City, Vietnam
*Correspondence to docternhon@gmail.com

Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: The authors would like to thank the patient, who allowed them to publish the clinical data. The authors are also grateful for all colleagues working at Department of High-Risk Pregnancy at Tu Du Hospital, Ho Chi Minh City, Vietnam. All of them attributed to provide the authors with the pictures, take care of the patient, and perform the operation.

Received: 07.03.22

Accepted: 27.04.22

Keywords: Caesarean delivery, computerised cardiotocography (cCTG), fetal death, fetal heart rate monitoring (FHRm), maternal-fetal medicine, obstetric complications, pregnancy, short-term variability (STV), umbilical cord haematoma (UCH), uterine torsion.

Citation: EMJ. 2022; DOI/10.33590/emj/10009645. https://doi.org/10.33590/emj/10009645.

Abstract

Umbilical cord haematoma (UCH) and uterine torsion are extremely rare complications in pregnancy. These abnormalities may present in acute and spontaneous conditions, however, they should not be neglected in clinical practice when monitoring an abnormal fetal heart without other suspects. The authors hereby report a rare case of UCH and uterine torsion as well as a review of the literature. A female, aged 35 years old (gravida 1, para 0), was admitted to the Emergency Department of Tu Du Hospital, Ho Chi Minh City, Vietnam, due to term gestation without complaints. They had an uncomplicated pregnancy, except a large uterine fibroid and cervical pessary which prevented pre-term birth from 28 weeks of gestational age. A very rare complication of UCH was revealed accidentally following emergency caesarean section associated with abnormal fetal heart rate tracing. Asymptomatic uterine torsion was noticed at the same time as this dramatic event. Pre-operative diagnosis of two rare complications was missed; hence, the authors timely delivered the baby based on another modality of management, computerised cardiotocography. In conclusion, UCH along with uterine torsion is difficult to diagnosis due to its rarity; it is usually an incidental finding. Moreover, no available imaging modality could investigate UCH prior to delivery. Surveillance on fetal heart rate monitoring may be helpful in this fatal situation.

Key Points

1. Uterine torsion can occur in pregnancy with large fibroid, which can lead to an umbilical cord haematoma.

2. Umbilical cord haematoma may be carefully considered in cases of neonatal acidosis at term if other aetiologies are not found, since this pathology suddenly causes abnormal fetal heart rate.

3. Strict surveillance on cardiotocography is necessary for all suspected cases, and caesarean section is needed in an emergency due to the high rate of fetal mortality.

INTRODUCTION

Abnormalities of the umbilical cord are very common in pregnancy. These include marginal insertion, velamentous cord insertion, umbilical cord true knot, umbilical torsion, and many more.[1-3] Nevertheless, term umbilical cord haematoma (UCH) is an extremely rare complication; it is almost unheard of. An average obstetrician may face it once in their lifetime. The rate of this accident occurs in around 1/5,500–1/11,000 births.[4-6]

To the authors' knowledge, the first case was reported in 1981 by Benirschke K et al.[7] At the time of writing this article, the authors found about 10 cases published in the last 10 years from around the world (Table 1).

The umbilical cord is the vital line between placenta and fetus; it is the attachment of fetoplacental circulation. The structure of a normal umbilical cord includes two arteries and one vein. It is surrounded by Wharton's jelly, which is 40–60 cm in length and the mean cord thickness is 1.21 (±0.39) cm.[16,17] At term, maternal blood flow through the placenta is nearly 600–700 mL/min.[18] Certainly, if there is an interruption in the maternal blood supply, a lethal event of the fetus *in utero* is unpreventable. UCH is defined as the incomplete extravasation of blood due to an unpreventable rupture of the umbilical vasculature, which mechanically compresses the vessels, resulting in the interruption of the blood supply to the fetus and leading to severe acute fetal hypoxia. The elastic fibres and reduction in stromal myfibroblasts are abnormally shaped and blunted instead of stellate.[9]

Regardless of pathogenesis, UCH is sequelae of the accumulation of blood into the Wharton's jelly due to partial laceration of the umbilical vein. In almost all cases, it occurs spontaneously and without clear aetiology, or it may be secondary from trauma during labour. A certain diagnosis is usually determined at delivery. Meanwhile, other risk factors include anatomic abnormalities, invasive fetal procedures such as amniocentesis, oligohydramnios, shortness of structure, traction of cord, post-maturity, chorioamnionitis, long-lasting fetal infection, or in association with disorder of coagulation factors. Degeneration of the umbilical cord caused by a meconium-stained liquor or funisitis may worsen the factors described.[2,4,8,9,19]

Generally, diagnosis of UCH is very difficult in clinical practice because of its rarity. Almost all cases were determined postnatally. Moreover, it is usually missed on sonography unless it is accompanied by an abnormal Doppler flow, or other structural anomalies such as an umbilical cord cyst, haemagioma, or a cord that is swollen more than the normal size.[5,20,21]

Umbilical abnormalities are not strictly related to life-threatening gestational accidental deaths. In late first and second trimesters, these abnormalities can cause sudden and unexplained fetal death. Later, this complication is responsible for severe fetal distress and causes approximately 50% of perinatal deaths in this situation. Evolution is associated with hypoxic encephalopathy, which increases mortality rate if a diagnosis is missed. Therefore, careful examination of placenta and cord is considered in such cases.[3,9,22]

Table 1: Review of the literature of umbilical cord haematomas that have been reported in last decade.

Report	Gestational age and time discovered	Antenatal sign	Risk factor	Mode of intervention	Fetal outcome	Histopathological result	Structural anomalies accompanied	Macroscopic description
Jouannelle et al. (2011)[8]	Full-term; at delivery	Decreased fetal movement and fetal heart deceleration	Congenital factor VII deficiency	CS	APGAR score of 0/1 min, 3/5 min, 7/10 min; multiorgan failure on Day 6 at NICU; and spontaneous intracranial haemorrhage	Not given	None	UCH at skin junction; compressed the cord; meconium-stained
Toni et al. (2015)[9]	Full term; at birth	Loss of fetal heart lasting for 90 sec	None	VB	APGAR score of 3/1 min, 5 min, and 10 min; acidosis; hypothermia; severe HIE	Disruption in the wall of the umbilical vein with discontinuity in the layers of the subintimal and internal elastic lamina. One umbilical artery presented with peripheral dissection, subintimal myxoid degeneration, and widespread disruption of the elastic fibres	Amniotic band at UC insertion into the chorionic plate, markedly congested chorionic vessels with dispersed distribution	Not given
McAdams et al. (2016)[10]	Not informed; after birth	None	Macrosomia; 4,500 g, shoulder dystocia	VB	Asymptomatic except for a slight decrease in haematocrit and bleeding from UC stump	N/A	Adrenal haemorrhage	A darkish bulge of UC
Hooper et al. (2016)[11]	At term; after birth	None	None	VB with IOL	None	Not given	None	Dark red discolouration and markedly increased thickness, measuring 4.5 cm in diameter at the widest part
Koukoura et al. (2016)[12]	39 weeks	Decreased fetal movement for 12 hours; repeatedly severe decelerations; absence of variability; and meconium stained	None	CS	APGAR score of 8/1 min and 9/5 min	The cord had three vessels and histological examination of the UC revealed disruption of the vein wall and haematoma involving the Wharton's jelly; the umbilical arteries were normal	None	A large cord haematoma was evident, originating from the fetal insertion and measuring approximately 5 cm in length
Koukoura et al. (2016)[12]	39 weeks; at labour	None	None	Spontaneous VB	Respiratory distress soon after birth; followed for 4 days at NICU	Not given	None	A huge haematoma measuring 8 cm in length was discovered close to the fetal insertion of the cord

Table 1 continued.

Report	Gestational age and time discovered	Antenatal sign	Risk factor	Mode of intervention	Fetal outcome	Histopathological result	Structural anomalies accompanied	Macroscopic description
Arora et al. (2017)[13]	39 weeks; after birth	None	None	Spontaneous VB	Baby in good condition	Not given	None	A 4 cm long and 2 cm wide reddish-purple non-tender swelling was noted in the cord, proximal to the level of the skin
Scutiero et al. (2018)[5]	41 weeks and 3 days	None	None	VB with elective IOL by process	Hypotonic; no cardiac activity at birth	Highlighted oedema in the Wharton's jelly; circumscribed haematic infiltrates; marked venous ectasia with delamination; haematic infiltration of the venous walls; extensive haemorrhage of the Wharton's jelly within the whole portion of UC; the lumen of the vein was completely occluded by coagulated haematic material	None	Blackish-reddish material in the proximity of the placental insertion measuring approximately 3 cm. A hematoma of the cord was noted at 34 cm from the placental insertion
Skowronek et al. (2018)[14]	41 weeks and 3 days	Bradycardia up to 80 beats/min	None	IOL by Foley catheter; CS	APGAR score of 1/1 min	Extravascular hematoma of UC cross-section	None	A dark-violet 15 cm section of UC near the fetus
Mota et al. (2019)[6]	39 weeks	None	None	VB	Follow-up without any intervention	Not given	None	Small swelling of UC stump
Khatiwada et al. (2021)[15]	Full-term	Two episode of fetal heart rate tracing of the category II variety	None	IOL by oxytocin, amniotomy, VB	Routine newborn care	Not given	The placenta had clots measuring 4×5 cm	The oedematous UC was found to be stained black and red, measuring 4×3 cm at the point of insertion into the fetal side.

APGAR: Appearance, Pulse, Grimace, Activity, and Respiration score; CS: Caesarean section; HIE: hypoxic ischaemic encephalopathy; IOL: induction of labour; NICU: neonatal intensive care unit; UC: umbilical cord; UCH: umbilical cord haematoma; VB: vaginal birth.

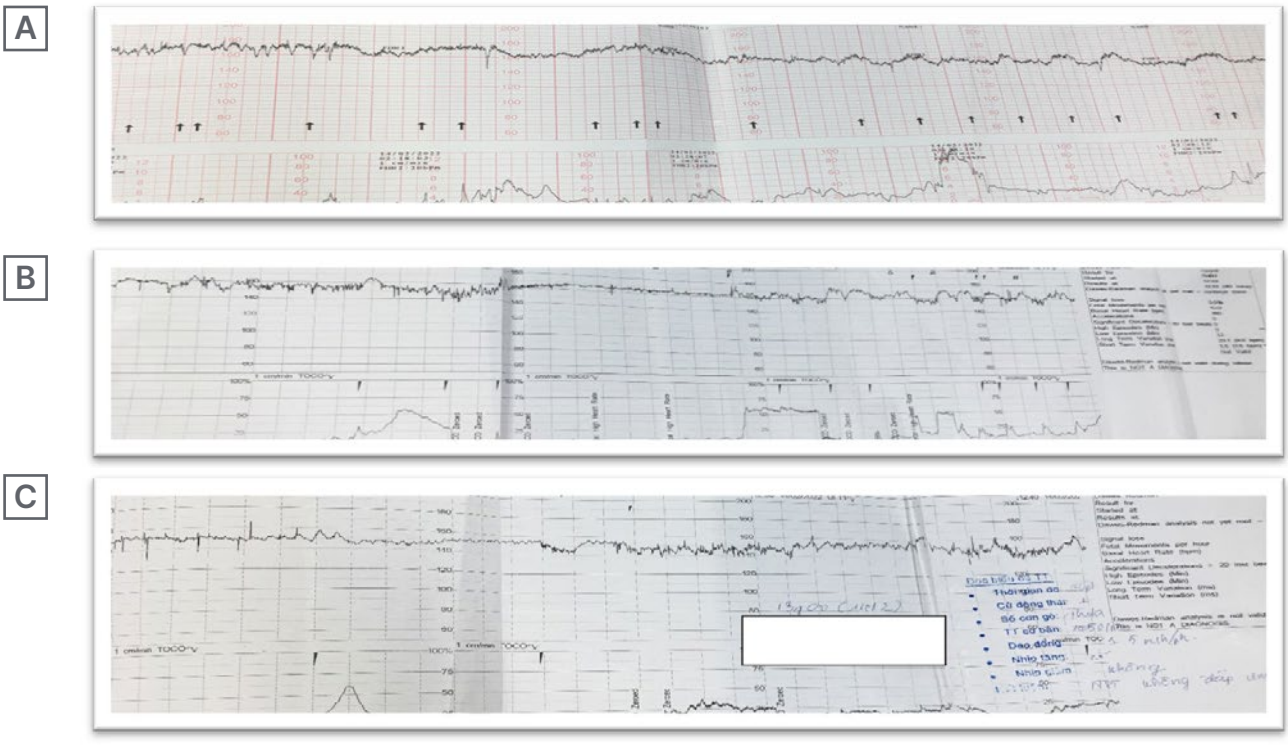
PRESENTATION

A 35-year-old female who was primigravida was admitted to a tertiary hospital due to term gestation at 39 weeks and 2 days without complaints. Their medical history recorded hyperthyroidism well-controlled by medical treatment. They had a large fibroid, which was accidentally discovered before pregnancy. They got pregnant after 7 years of primary infertility. The results of their Group B streptococcal test was positive. The patient underwent cervical support by pessary from Week 28 for the prevention of preterm risk factors. They had already received two 12 mg doses of betamethasone for fetal lung maturity. Prior to admission, the patient had also not received cordocentesis during antenatal care.

At hospitalisation, the patient had normal vital signs, without remarkable signs of labour. Digital examination showed that an Arabin® pessary (Dr. Arabin, Witten, Germany) was in place without cervical dilation, and no uterine contraction appeared on cardiotocography (CTG). Routine laboratory tests were within in normal limits.

An ultrasound examination showed a vital fetus with appropriate development for gestational age and a normal Doppler flow in the middle cerebral artery, as well as in the umbilical artery. Furthermore, the structure of the placenta, umbilical cord, and fetal morphology were also normal. The fibroid was approximately 8×10 cm in size and located at the posterior, lower segment of the uterus. However, during routine management, the fetal heart rate monitoring (FHRm) on CTG and computerised CTG was abnormal, showing recurrent variable decelerations accompanied by minimal baseline variability (Figure 1A and 1B). Consequently, CTG was classified as Group 2, following classification from the American College of Obstetricians and Gynecologists (ACOG). The lowest short-term variability (STV) was 1.5 msec (the normal value on the monitor was >3.5 msec [Figure 1C]). The fetus's health was not good; although, the

Figure 1: Image showing cardiotocography and computerised cardiotocography at admission (A), surveillance (B), and prior to Caesarean section (C), respectively. All were classified followed Group 2 by the 2009 American College of Obstetricians and Gynecologists (ACOG) classification due to low variability.



fetus was reanimated by changing the mother's lying position to the left lateral side. Intravenous infusion with lactated Ringer's solution and supplemental oxygen was given to the mother at 6 L/min during 30 min. Therefore, the authors immediately decided to perform an emergency Caesarean section (C-section) to deliver the baby, which the patient allowed.

Interestingly, at laparotomy, the uterus was rotated at 90 ° right axis. After an incision in the lower segmental uterus, the authors promptly saved a healthy male infant, who weighed 3,200 g. The Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score of the baby was 7 and 8 at 1 and 5 minutes, respectively. At the same time, the authors noticed that the umbilical cord was reddish, even though amniotic fluid was a normal colour. No mass was found on the umbilical cord, but a haemorrhage was discovered that followed a 'flat' form along the length of the placental cord insertion to fetal cord insertion (Figure 2A). The fetal surface placenta was also haemorrhagic in macroscopic appearance.

After de-torsing the uterus, haemostasis of the bleeding surface at the placental site was performed. In addition, the authors performed a ligation of bilateral uterine arteries to prevent late postpartum haemorrhage due to uterine torsion. Due to a large intramuscular fibroid located at posterior lower uterine segment, the authors promptly decided not to carry out a myomectomy in this situation. Following all these procedures, the uterus contracted effectively.

Post-operatively, the baby's umbilical cord was normally dry in 48 hours and there was no additional haematoma. Due to neonatal jaundice, blood samples for serum bilirubin were taken from the baby, as well as screening the congenital diseases as a matter of routine. Results were within normal limits.

Both mother and baby were discharged home on Day 5 post-partum. The patient was scheduled for a routine 1 month follow-up and their health was still stable.

DISCUSSION

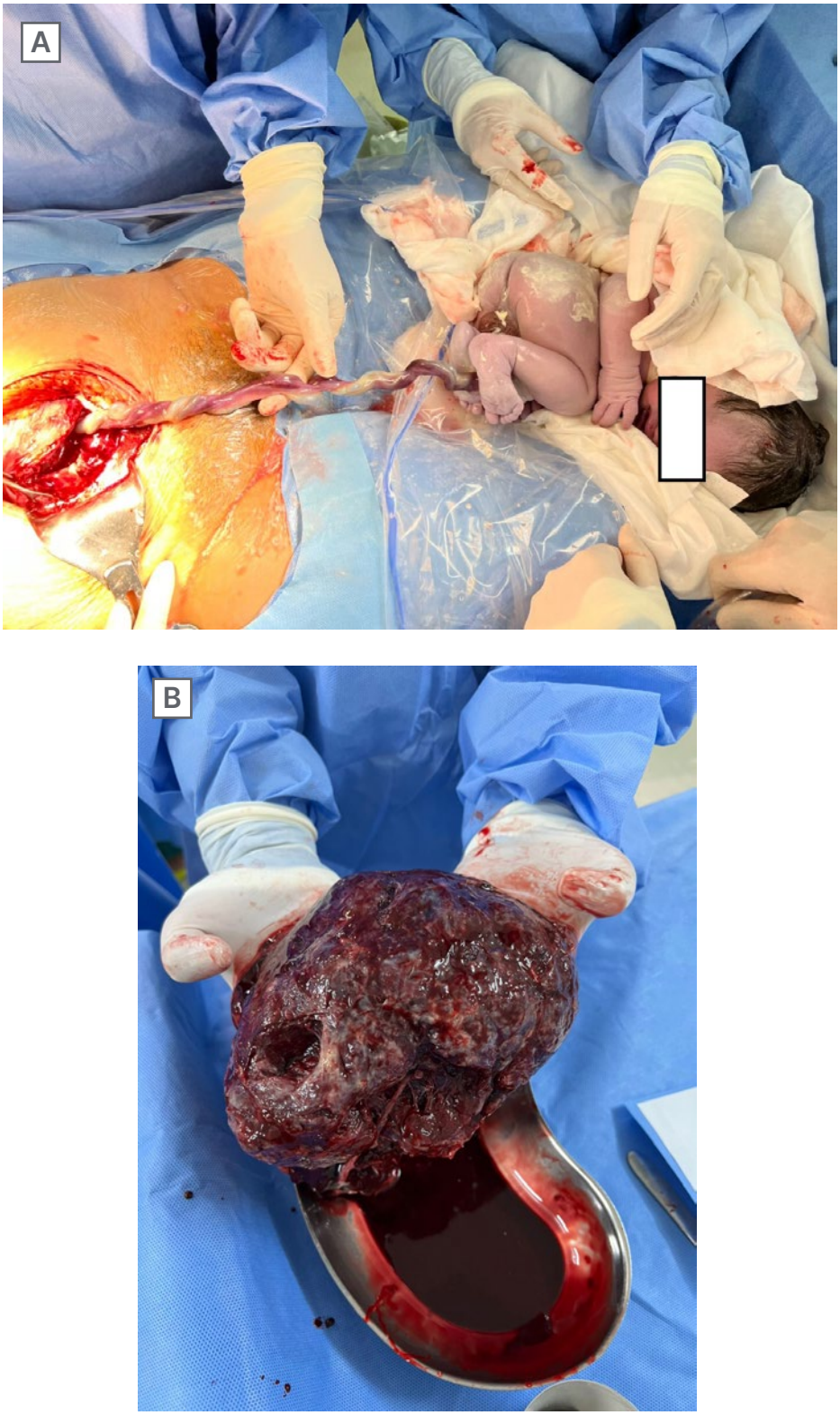
In the presented case, UCH was accidentally found during the C-section and could have been caused by uterine torsion. The haemorrhage appeared in placenta and umbilical cord; however, the authors did not find any haematoma in the placenta.

However, the patient had no symptoms for clinical diagnosis of uterine torsion prior to C-section. This is probably because the malposition was in an acute condition, so vascular damage did not have enough time to develop. Moreover, the uterus was not necrotic because of lack of blood supply. Necrosis is commonly mentioned as a complication of gradual uterine torsion, not only during pregnancy, but also in patients who are pregnant. Additionally, urgent complications such as haemorrhages, coagulopathy disorders, and sepsis are also described.[23]

In fact, uterine torsion, which leads to mortality for both mother and fetus, is extremely rare. Some articles that discuss this condition show that it is diagnosed in the second or third trimesters, or even at term gestation, similar to the case presented by the authors.[23] This fatal condition typically has acute symptoms such as vomiting, vaginal bleeding, excruciating abdominal pain, and even uterine necrosis due to irreducible torsion. It rarely presents without symptoms or signs.[24-26]

Rotation ranges between 45 ° and 72 ° compared with its longitudinal axis.[27] Interestingly, rotation along with horizontal axis or transversal axis has also been reported. Risk factors of malposition include morphologic anomalies, pelvic tumours, pelvic adhesion, asymmetry in the transverse diameter of the uterus because of transverse presentation, lateral fibroids, bicornuate uterus, and multiple pregnancies.[26] In the authors' case, the patient had no abnormality of anatomic structure, which caused axial torsion, and they found an enlarged fibroid of approximately 8×10 cm. Some reports revealed that a huge fibroma could be attributed to uterine torsion because of asymmetric weight distribution, which is commonly found in non-gravid uteruses and in postmenopausal periods due to atrophy of uterus. Diagnosis by imaging technology such as MRI can be helpful in this complication.[23,28,29] At the time of

Figure 2: Macroscopic images of umbilical cord and placenta at Caesarean section.



A) The UCH discovered at the time of the C-section. B) The placenta without detachment at maternal surface.

C-section: Caesarean section; UCH: umbilical cord haematoma.

writing, the authors were not able to find any case reports related to uterine torsion in combination with a cervical pessary. Therefore, they could not conclude that a cervical pessary is a risk factor for uterine fibroid in this case. The authors are waiting for further investigations about this mechanism.

Similar to all cases reported, no clinical sign or image scan contributed to detect antepartum UCH in the author's case. However, reduced fetal movements were reported in most cases.[5] With this patient, the authors accidently discovered this intraoperative complication due to other indications. To be precise, the authors performed a C-section following abnormal FHRm (Figure 1A–C). Accordingly, STV was in association with hypoxia and increased acidaemia in the umbilical cord blood sampling, which has been described by several authors.[30,31] The cut-off point of STV is still unclear, but some reports have agreed that a low STV means that there is a poor prognosis for the fetus and needs further investigation.[31]

Fortunately, in the authors' case, they were promptly informed of this due to FHRm, and thus, they could intervene rapidly and save the baby's life. In this case, UCH was discovered that followed a flat feature form and the mass was not palpated on umbilical cord. According to literature, UCH located in the proximal portion of the fetal cord insertion causes severe obstruction of blood flow (Table 1). In 2009, Towers et al.[32] and Barbati et al.[33] also reported similar cases, which were discovered spontaneously by a fetal heart monitor in the USA and Italy. Recently, Koukoura et al.[12] and Khatiwada et al.[15] also reported on two cases that were similar to this event, with the precious experience on continuous FHRm in surveillance of labour.

Similar to some cases reported in literature, uterine torsion in relation to large fibroids was found at upon laparotomy in the full-term pregnancy.[34] Spontaneous UCH was diagnosed following a C-section as in the author's case. Unfortunately, they did not have histopathological results compared with other reports as well as legal evidence in situation of fetal death.[9,14]

The newborn was in good condition after birth and the neonatal course was uneventful. No anomalies were observed on examination. Both the mother and baby were in a healthy condition after a one-month follow-up.

CONCLUSION

UCH is an extremely rare entity in obstetric practice. Particularly UCH, in the context of uterine torsion, is an unheard phenomenon in the literature. In reality, antenatal diagnosis of two rare complications is not commonly recognised. Furthermore, fetal prognosis is poor if urgent extraction of fetus is delayed. At the time of writing, none of tool can approach in determination of this consequence. However, obstetricians should take extra care in evaluating pregnancies with large uterine fibroids, as well the accident of UCH to rule out cases of unexplained hypoxia. Following fetal heart monitoring managed by computerised CTG was strictly useful for a timely interpretation. Further data is required to elucidate this tissue.

References

1. Bohîlțea RE et al. Clinically relevant prenatal ultrasound diagnosis of umbilical cord pathology. Diagnostics (Basel). 2022;12(2):236.
2. Mantakas X et al. Placenta and umbilical cord cause in antepartum deaths. Cureus. 2018;10(11):e3556.
3. Antolin E et al. Umbilical cord torsion; a rare cause of intra-uterine fetal death. J Obstet Gynaecol. 1994;14(5):324-5.
4. Sizun J et al. [Spontaneous umbilical cord hematoma, a rare cause of acute fetal distress]. Arch Pediatr. 1995;2(12):1182-3. (In French).
5. Scutiero G et al. Umbilical cord hematoma: a case report and review of the literature. Obstet Gynecol Int. 2018;2018:1-6.
6. Mota F et al. Spontaneous umbilical cord haematoma. BMJ Case Rep. 2019;12(6):e229952.
7. Benirschke K et al., "Anatomy and pathology of the umbilical cord," Benirschke K et al. (eds.), Pathology of the Human Placenta (2012), Berlin: Springer International, pp.309-75.
8. Jouannelle C et al. Spontaneous umbilical cord haematoma and congenital factor VII deficiency. Haemophilia. 2012;18(1):e24-5.
9. Tonni G et al. Histopathological findings in spontaneous hematoma of the umbilical cord: severe hypoxic-ischemic encephalopathy in a term survived newborn. Am J Forensic Med Pathol. 2015;36(4):254-6.
10. McAdams RM, Chabra S. Umbilical cord haematoma and adrenal haemorrhage in a macrosomic neonate with anaemia. BMJ Case Rep. 2016;2016:bcr2015214140.

11. Hooper K, Sebire P. Spontaneous umbilical cord haematoma. Arch Dis Child Fetal Neonatal Ed. 2016;101(4):F332.
12. Koukoura O et al. Spontaneous cord hematoma: report of two cases. CRPM. 2016;5(2):97-9.
13. Arora PK et al. Spontaneous umbilical cord hematoma. J Pediatr. 2017;184:233-233.e1.
14. Skowronek R et al. Spontaneous umbilical cord hematoma as a clinical and forensic medical problem in case of suspected obstetrician's medical malpractice. Ginekol Pol. 2018;89(11):642-3.
15. Khatiwada P et al. Spontaneous umbilical cord hematoma. Cureus. 2021;13(2):e13048.
16. Basta M, Lipsett BJ. Anatomy, Abdomen and Pelvis, Umbilical Cord (2022), Florida: StatPearls Publishing. [Internet].
17. Sharma S, Soliriya V. Study of length of umbilical cord at term and its correlation with fetal outcome: a study of 500 deliveries. Journal of SAFOG. 2016;8(3):207-11.
18. Wang Y, Zhao S. Vascular Biology of the Placenta (2010), San Rafael: Morgan & Claypool Life Sciences. [Internet].
19. Clermont-Hama Y et al. Risk factors for spontaneous hematoma of the umbilical cord: a case-control study. Placenta. 2020;99:152-6.
20. Sepulveda W et al. Fetal death due to umbilical cord hematoma: a rare complication of umbilical cord cyst. J Matern Fetal Neonatal Med. 2005;18(6):387-90.
21. Brown R, Nicolaides K. Umbilical cord hematoma associated with an umbilical cord cyst and fetal death at 28 weeks of gestation. J Ultrasound Med. 2000;19(3):223-5.
22. Gualandri G et al. Spontaneous umbilical cord hematoma: an unusual cause of fetal mortality: a report of 3 cases and review of the literature. Am J Forensic Med Pathol. 2008;29(2):185-90.
23. Chua KJ et al. Uterine torsion with necrosis of bilateral adnexa in a postmenopausal woman. BMJ Case Rep. 2019;12(6):e229311.
24. Rood K, Markham KB. Torsion of a term gravid uterus: a possible cause of intrauterine growth restriction and abnormal umbilical artery doppler findings. J Ultrasound Med. 2014;33(10):1873-5.
25. Chau KT et al. Uterine torsion in a 25-week pregnant female with congenital uterine didelphys and intraoperative complication of uterine atony: a report of a rare clinical case. CEOG. 2021;48:185-8.
26. Liang R et al. Uterine torsion: a review with critical considerations for the obstetrician and gynecologist. Transl. Res. Anat. 2020;21:100084.
27. Kilicci C et al. Uterine torsion of 720 degrees in the third trimester of pregnancy and accompanying bladder torsion: a case report. Pan Afr Med J. 2018;29:175.
28. Ferrari F et al. Uterine torsion and intrauterine growth restriction: case report and systematic literature review. J Obstet Gynaecol Res. 2021;47(12):4224-31.
29. Kocher M, Hirsig L. A case of uterine incarceration with unrecognized uterine torsion. Radiol Case Rep. 2020;15(10):1943-7.
30. Serra V et al. The value of the short-term fetal heart rate variation for timing the delivery of growth-retarded fetuses. BJOG. 2008;115(9):1101-7.
31. Wretler S et al. Fetal heart rate monitoring of short term variation (STV): a methodological observational study. BMC Pregnancy Childbirth. 2016;16(1):55.
32. Towers CV et al. The fetal heart monitor tracing in pregnancies complicated by a spontaneous umbilical cord hematoma. J Perinatol. 2009;29(7):517-20.
33. Barbati A et al. Umbilical cord haematoma with altered fetal heart rate. J Obstet Gynaecol. 2009;29(2):150-1.

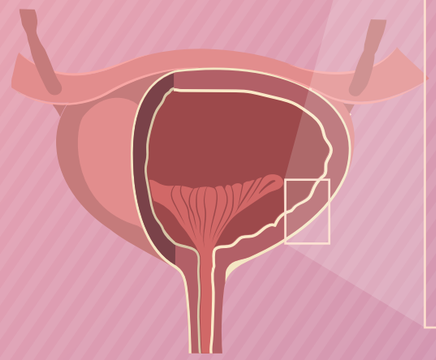
MIUC Treatment Landscape 2022

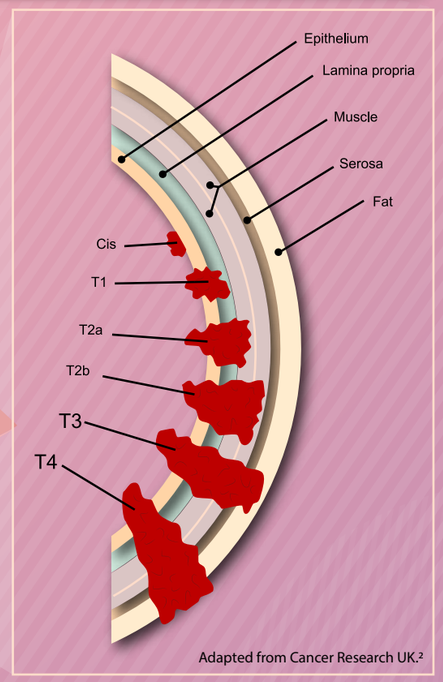
Treatment Modalities for High-Risk Resectable MIUC

Goals of treatment[1]

Improve survival and prevent death from MIUC

Prevent tumour metastasis





Adapted from Cancer Research UK.[2]

Treatment modalities[1,3-7]

	Surgery	Neoadjuvant chemotherapy	Adjuvant chemotherapy	Radiotherapy
Tumour location: **Bladder**	RC, partial cystectomy, and TURBT RC is primary treatment for MIUC (cT2, cT3, cT4a)	Improved OS compared with surgery alone	May delay recurrence and improve survival for patients with no NAC Benefits not established	Curative intent in bladder-sparing treatments May be used as AC after RC for T2b patients Used as a palliative treatment
Tumour location: **Upper tract (renal pelvis and ureter)**	Nephroureterectomy or ureterectomy ± regional lymphadenectomy ± perioperative intravesical chemotherapy Endoscopic resection	Promising retrospective studies	Recommended for pT2 Decline in renal function post-surgery may preclude AC with full-dose cisplatin	Data remain controversial and insufficient for conclusions

Unmet Needs in High-Risk MIUC

40–67% of patients with pT3-T4a or lymph node-positive disease relapse after RC alone, with a poor 5-year OS (25-30%)[8,9]

Only **10–21%** of patients with MIUC undergoing RC receive NAC, despite current guidelines[10]

66% of patients with T2 disease receiving NAC prior to RC may not respond and are at risk of progression to ≥ pT2 disease; 5-year DFS may be as low as 40%[11]

Up to **83%** and **52%** of patients may be ineligible for neoadjuvant and adjuvant cisplatin-based therapy, respectively; there is no SOC for these patients[12]

Disease States in High-Risk MIUC[13]

	T2	T3	T4
ypT2+	✓	✓	✓
OR			
pT3-4a	–	✓	✓
OR			
N+*	✓	✓	✓

View the full symposium ***Navigating the Integration of Immuno-oncology Into the Perioperative Muscle-Invasive Urothelial Carcinoma Treatment Landscape*** now for further insights!

Symposium Agenda

Faculty	Title	Time
Andrea Necchi	Welcome and Introduction	18:30-18:35
Morgan Rouprêt	The MIUC Treatment Landscape in 2022	18:35-18:50
Margitta Retz	Opportunities for I-O Use in the Perioperative Setting	18:50-19:05
Andrea Necchi	Optimizing Patient Treatment: Perspectives on the Future Treatment Landscape	19:05-19:20
All Faculty	Interactive Multidisciplinary Team Meeting	19:20-19:40
All Faculty	Q&A	19:40-19:55
Andrea Necchi	Summary and Close	19:55-20:00

Programme Faculty

Meeting Chair
Andrea Necchi, MD
IRCCS San Raffaele Hospital and Scientific Institute
Milan, Italy

Faculty
Morgan Rouprêt, MD, PhD
Sorbonne University, AP-HP, Urology
Pitie-Salpetriere Hospital
Paris, France

Faculty
Margitta Retz, MD, PhD
Rechts der Isar Medical Center
Department of Urology
Technical University
Munich, Germany

Abbreviations: AC: adjuvant chemotherapy; cT: clinical stageDFS: disease-free survival; I-O: immune-oncology; MIBC: muscle invasive bladder cancer; MIUC: muscle-invasive urothelial carcinoma; N+: cancer has spread to one or more lymph nodes in the pelvis, near the bladder;NAC: neo-adjuvant chemotherapy; OS: overall survival; RC: radial cystectomy; SOC: standard of care; TURBT: transurethral resection of bladder tumour; ypT2: residual muscle-invasive disease.

References

1. National Comprehensive Cancer Network®. NCCN clinical practice guidelines in oncology (NCCN Guidelines®) for bladder cancer. 2021. Available at: Last accessed on July 2022
2. Cancer Research UK. Stages of bladder cancer. 2022. Available at: https://www.cancerresearchuk.org/about-cancer/bladder-cancer/-types-stages-grades/stages. Last accessed: Last accessed on July 2022
3. Witjes JA et al. EAU guidelines on muscle-invasive and metastatic bladder cancer. 2021. Available at: https://uroweb.org/guide-lines/muscle-invasive-and-metastatic-bladder-cancer. Last accessed on July 2022
4. Bellmunt J et al. Bladder cancer: ESMO practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25(Suppl 3):40-8.
5. Japanese Urological Association. Evidence-based clinical practice guidelines for bladder cancer (summary - JUA 2009 edition). Int J Urol. 2010;17(2):102-24.
6. Rouprêt M et al. European association of urology guidelines on upper urinary tract urothelial carcinoma: 2020 update. 2021;79(1):62-79.
7. Gartrell BA, Sonpavde G. Emerging drugs for urothelial carcinoma. 2013;18(4):477-94.
8. Dahm P, Gschwend JE. Malignant non-urothelial neoplasms of the urinary bladder: a review. Eur Urol. 2003;44(6):672-81.
9. Shariat SF et al. Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: a contemporary series from the Bladder Cancer Research Consortium. J Urol. 2006;176:2414-22.
10. Reardon ZD et al. Trends in the use of perioperative chemotherapy for localized and locally advanced muscle-invasive bladder cancer: a sign of changing tides. Eur Urol. 2015;67(1):165-70.
11. Manoharan M et al. Outcome after radical cystectomy in patients with clinical T2 bladder cancer in whom neoadjuvant chemotherapy has failed. BJU International. 2009;104(11):1646-9.
12. Dash A et al. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. Cancer. 2006;107(3):506-13.
13. Miura Y et al. Prognostic impact of eligibility for adjuvant immunotherapy in locally advanced urothelial cancer. BJUI Compass. 2022;3(2):146-53.

The publication of this infographic was funded by Bristol Myers Squibb

The Treatment Algorithm in Diabetic Foot: An Alternative Against Amputation?

Authors:	*Tacettin Güçer Professor and Chief, Kafkas University Faculty of Medicine, Plastic and Reconstructive Surgery Department, Kars, Türkiye *Correspondence to tgucer@hotmail.com

Disclosure:	The author has declared no conflicts of interest.
Received:	09.05.22
Accepted:	02.11.22
Keywords:	Diabetic foot, rheologic agents, vacuum therapy, wound healing.
Citation:	EMJ. 2022;7[4]:88-94. DOI/10.33590/emj/10100084. https://doi.org/10.33590/emj/10100084.

Abstract

This clinical treatment modality was applied to 62 diabetic ulcers on lower extremities for which surgeons had been advised amputation. Total healing was achieved in 53 of them and was achieved through this treatment in a 3-month period. The remaining nine cases also showed improvement in healing at different levels, but they were not accepted as a 'satisfactory result'. This treatment modality contains a synthetic prostacyclin analogue, two different phosphodiesterase inhibitors, a peripheral revascularisation agent, another agent increasing peripheral resistance to ischaemia, and a polysaccharide with positive rheologic properties on capillary circulation. Therefore, this treatment was found to be effective on circulation of the extremities, with radiologically-proven insufficient blood supply. The treatment also had a positive effect on recirculation and effects on collateral revascularisation through mechanical vacuum application, modified from standard vacuum treatments. With this combination, this technique was found extremely effective by application, according to the algorithm explained below, and should be an alternative to the current therapy applications in diabetic ulcers.

Key Points

1. Diabetic foot wounds are usually a result of diabetes-related vascular disease and neuropathy, and present with various symptoms such as inflammation, foot lesions, and a purulent discharge.

2. This article explores how diabetic foot wound develop and provides case studies on treated patients, including insight into the challenge of treating heavy smokers.

3. The author discusses the possibility of preventing diabetic foot wound through patient education and supportive treatments.

INTRODUCTION

Although there are many reasons for the development of diabetic foot wound, the main reason is the combined effect of diabetes-related vascular disease and neuropathy. Aerobic Gram-positive cocci are mostly responsible for superficial diabetic foot infections (DFI), which develop in patients with cellulitis who have not used antibiotics before. *Pseudomonas aeruginosa* is one of the common causes when the patient's toes remain wet.[1] After excluding other causes, DFI should be considered when at least two of the classic signs of inflammation are present, including redness, warmth, swelling, tenderness, pain in the foot lesion, or presence of purulent discharge.[2]

Patients diagnosed with DFIs are primarily classified as mild, moderate, or severe in terms of severity of infection, based on criteria such as the depth and width of the wound, and whether there are systemic signs of infection.[1-3] The perfusion, extent, depth, infection, and sensation system should be the preferred classification system as it has a high predictive value for diabetes-related foot complications.[3]

A culture sample from a diabetic foot wound should be obtained only when clinical infection is suspected and before starting antibiotic therapy if possible. Biomarkers such as leukocyte count, C-reactive protein (CRP), erythrocyte sedimentation rate, and procalcitonine, which are indicators of inflammation, may be useful in distinguishing between infection and colonisation.[4,5] MRI is a sensitive and specific method for patients who cannot be mobilised, and who are thought to have osteomyelitis or deep soft tissue abscess, to assess the response to treatment. The gold standard in the diagnosis of osteomyelitis is histopathological examination. Requirements to ensure wound healing and to save the leg are the removal of dead and infected tissues with urgent and aggressive debridements, appropriate antibiotic therapy, metabolic control, relieving the foot from weight and pressure, diagnosis and appropriate treatment of peripheral arterial disease, and regaining the function of the foot. The fact that the factors playing a role in its ethiopathogenesis are very different, complicates the developing lesions and requires a team understanding in the approaches to such patients.[6,7]

Diabetic foot problems are the only complications of diabetes that can be prevented through education.[6]

Major Mechanisms Involved in Diabetic Wound Development

The major mechanisms involved in diabetic wound development are nerve hypoxia/ischaemia; collagen molecules disorders (elastin, proteoglycan); auto-oxidative stress; endothelial dysfunction; increased activity in the polyol pathway; mitochondrial dysfunction; increased advanced glycation products; lack of growth factors; γ-linolenic acid deficiency; changes in the immune mechanism; increase in protein kinase C, especially B isoform; increase in protease secretion; dysfunction of cytokines; and others. All of these factors should be interpreted separately and in combination, to achieve a satisfactory result in DFIs.[8-14]

Local and Systemic Treatment of Diabetic Foot Ulcer

Wound care is one of the local and systemic treatments of diabetic foot ulcer. In wounds with risky circulation and sensory protection, this care should feature aggressive debridement of necrotic tissues; local chemical (antiseptic) and antimicrobial (antibiotic) treatment for infected tissues (systemic antibiotic in wound culture positive with single pathogen cases only); vacuum-combined dressing (different from standart vacuuming, where the negative pressure is applied continuously and up to -600 mmHg, and wound coverage is obtained through a mixture of nitrofurazone ointment and rifamycine applied gauze with its specific colour, sensitive to pH changes and covered with transparent film dressings; the colour changes from orange to white and indicates the wound dressing change periods); balancing dressing techniques according to secretion status (wet to dry, dry to wet); observing the wound with transparent covering material without changing the dressing; obtaining data from the distal part of the lesion by pulse oximetry if possible; and measurement of extremity temperature at room temperature from the distal of the lesion, which is another parameter for wound healing.

Further treatment should include the treatment of circulatory failure and neuropathic component,

with rheological agents such as low molecular weight (LMW) dextran (MW:40), pentoxifylline, trimetazidine, cilostazole, synthetic prostacyclin, and tadalafil.[1-5]

Low Molecular Weight Dextran

Investigations in this new field received great impetus from the discovery and commercial availability of dextrans. These polysaccharides have the ability to alter blood-flow properties. The alterations vary with the molecular weight of the dextran. LMW dextran has demonstrated its ability to decrease blood viscosity and reverse cell aggregation, producing an increase in blood flow and tissue perfusion. It has been suggested that the value of LMW dextran will best be determined by observations on its effectiveness in relieving symptoms and diminishing complications, in conditions known to cause stasis in blood vessels.[15]

Pentoxifylline

Effect Mechanism

As a phosphodiesterase inhibitor, it prevents cyclic adenosine monophosphate degradation, and increases glycolysis and endogenous adenosine triphosphate production. It also increases erythrocyte flexibility and has an antiaggregant effect (with a dextran-like mechanism).

Therapeutic indications

Therapeutic indications include occlusive diseases of peripheral arteries and arteriovenous circulation disorders caused by arteriosclerotic or diabetic causes (such as intermittent claudication, rest pain); trophic disorders (such as leg ulcers and gangrene); cerebral circulation disorders; and circulatory disorders of the eye and ear with a degenerative vascular process.[16]

Trimetazidine

Effect Mechanism

Trimetazidine prevents the decrease in intracellular adenosine triphosphate by preserving energy metabolism in cells exposed to hypoxia or ischaemia. In this way, it ensures the proper functioning of the ion pumps and the transmembranal sodium-potassium flow. Trimetazidine increases glucose oxidation by blocking long chain 3-ketoacyl-CoA thiolase and inhibiting β-oxidation of fatty acids. In an ischaemic cell, the energy obtained during glucose oxidation requires less oxygen consumption than the β-oxidation process. Enhancement of glucose oxidation optimises cellular energy processes, and thus maintains proper energy metabolism during ischaemia.[17]

Cilostazole

This the first choice drug, as 3–6 months of evidence shows an increase in both treadmill exercise performance and quality of life. It is an effective drug to improve symptoms and increase walking distance in patients with lower extremity peripheral artery disease and intermittent claudication. It is recommended in all patients with life-limiting claudication.[18]

Synthetic Prostacyclin

Iloprost (ZK36374) has a cytoprotective effect, as it kept the kidney tissue alive for 7 days *in vitro*. It also increases tolerance to ischaemia in the heart muscle and striated muscle. It is a peripheral potent vasodilator and antiaggregant, and is the major component of the treatment.[19]

Tadalafil

This medication is added to the treatment later for the expected rheologic improvements, following the publications explaining positive effects on microcirculation by vasodilation. It was applied on the last 23 cases and was well tolerated, especially by male patients, according to the rest of the treatment components.[20]

METHODOLOGY

The treatment begins with pentoxyfilline 900 mg solutions applied with LMW dextrane 500 mL daily and 50 mL on an hourly basis. Synthetic prostacycline is also applied (20 µg) on an hourly basis via a different intraveinous route, following hospitalisation and monitoring of cardiac functions and vital signs. This intraveinous treatment is limited to 12 hours a day, and for rest of the day only the additional fluid requirements are provided if necessary. At the same time trimetazidine 80 mg and cilostazole

100 mg per day (on the seventh day cilostazole dose increased to 200 mg daily) are administered orally. Finally, tadalafil 5 mg daily is added to this polipharmacy group.

The side effects mainly belong to pentoxfilline and syntetic prostacycline, and include nausea, vomiting (which is easily controlled by antiemetics), flushing on face and body, hypotension, and slight tachycardia transiently in the first 5 days of treatment. Blood sugar alterations were frequent due to rheologic agents (mainly LMW dextrane), and close monitoring and proper treatments were applied to regulate blood sugar levels. In most of the cases, management was effective, and this has been checked by lowering HbA1c levels in the 6-week period following the treatment. Treatment continues for 10 days as a combination, mainly in the hospital. Following the first treatment period, the patient is discharged from the hospital with oral pentoxyfilline, trimetazidine, cilostazole, and tadalafil in the same doses. The follow-up is continued for 12 weeks on an outpatient basis, unless a surgical step to cover the wound (such as a skin grafting or local flap procedures) is necessary.

White blood cell and procalcitonine levels were not accepted as important statistically (with student T-test) because of the results' stability independently from the clinical status of the patients. CRP and erythrocyte sedimentation rate (ESR) levels seemed important as the initial period (15–30 days) of treatment eliminated the infectious agents from the wound, reflecting the parameters with the absence of a serious finding and circulation restoration. The parameters of the extremity circulation improvement were; temperature, colour, capillary filling (if present, the refilling time following application of finger pressure over the skin), and measurable oxygen saturation at the distal part of the extremities. Blood sugar levels and HbA1c levels were also important because of the effectivity of the treatments' indirect effects on blood sugar variations.

Patients in this study had HbA1c levels of minimum 8.5 and maximum 10.9 (mean: 9.7) and were aged between 48–84 years. There were 39 males and 24 females. Nine of 62 patients were accepted as 'unsatisfactory results'. Of those patients, eight had a limiting factor such as heavy smoking (more than a package per day), and six of them were male. The last patient was a female who smoked and had systemic lupus disease. These cases were all subject to amputation, and four amputations were performed. The other five refused the amputation and follow-ups are still continuing, without a significant improvement in the treatment of their ulcers.

RESULTS AND DISCUSSION

Complete recovery was achieved with this method in 53 out of 62 cases with indication for amputation, and this state of well-being continued for at least 2 years.

The longest follow-up of cases was 11 years; however, in six cases (four of whom were smokers), patients required additional treatment sessions starting from the second year, and these sessions yielded successful results in all of them. None of them required another session of treatment although their risk factors were still present. The theoretical explanation could be the neovascularisation on a capillary level (Figures 1–3). There was no control group except for six patients who refused the treatment. All of them underwent an amputation in the following 2 years. Some parameters for diabetes and wound healing were observed and checked by laboratory findings, during and following the treatment. Most of them showed statistically important improvements and indicated the effectiveness of this treatment.

In the diabetic foot, it is possible to prevent complications with supportive treatment and patient education. For the foot ulcers with poor control of blood sugar, this modality is effective not only for wound healing, but also for the control of the blood sugar levels in the post-healing period.[6] The HbA1c levels showed an approximately 15% decrease in the first 6 weeks and up to 30% in a 12-week period with this treatment in 52 cases. This decrease is also accepted as an indicator for the effectiveness of this modality. As a control group, the rest of the 62 patients (nine cases) also showed some improvement on their wounds and blood sugar levels, but 12 weeks of treatment did not result in ulcer healing. In 52 of the cases, the CRP levels were higher than normal (approximately 25%) for the whole population. Following the

Figure 1: Pre-treatment of four cases (A) and appearance of the cases following treatment (B) in a 3-month period.

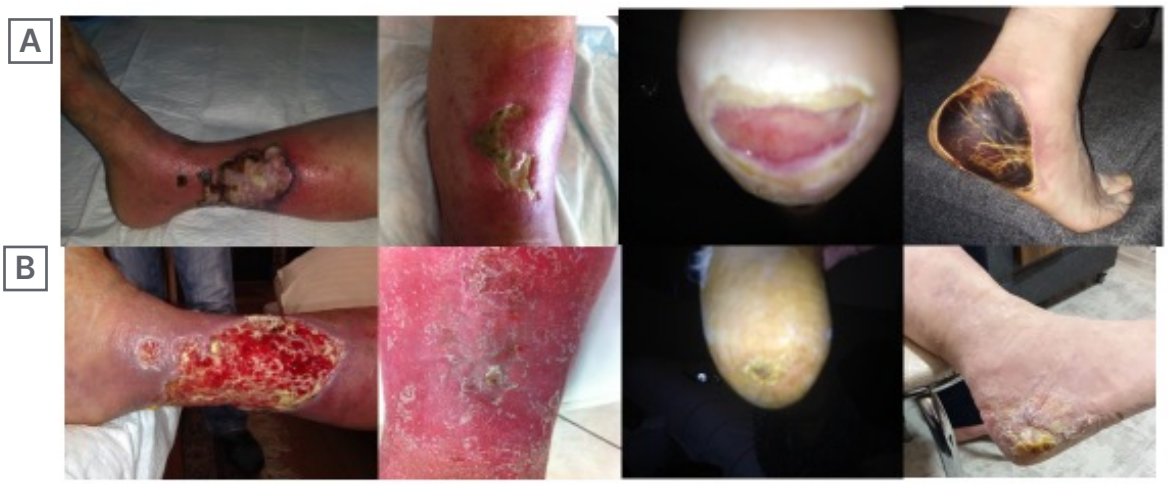
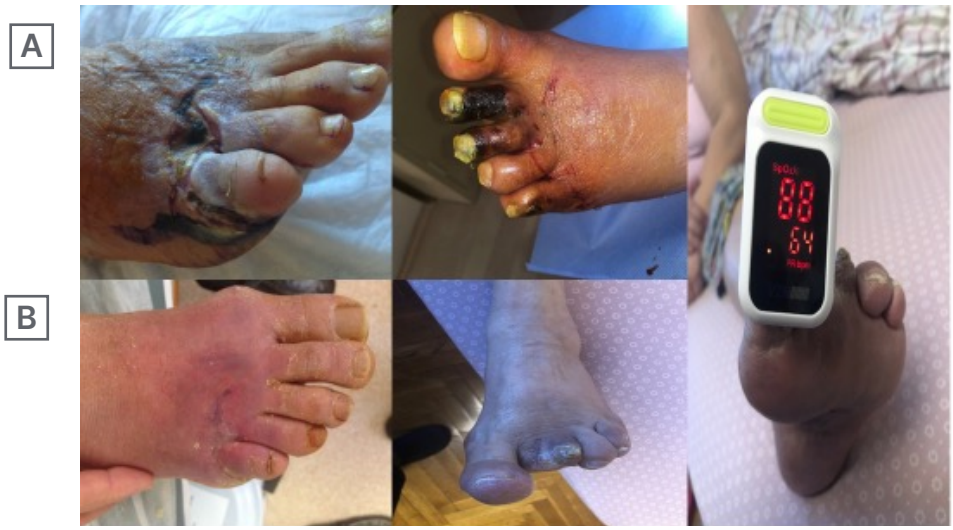


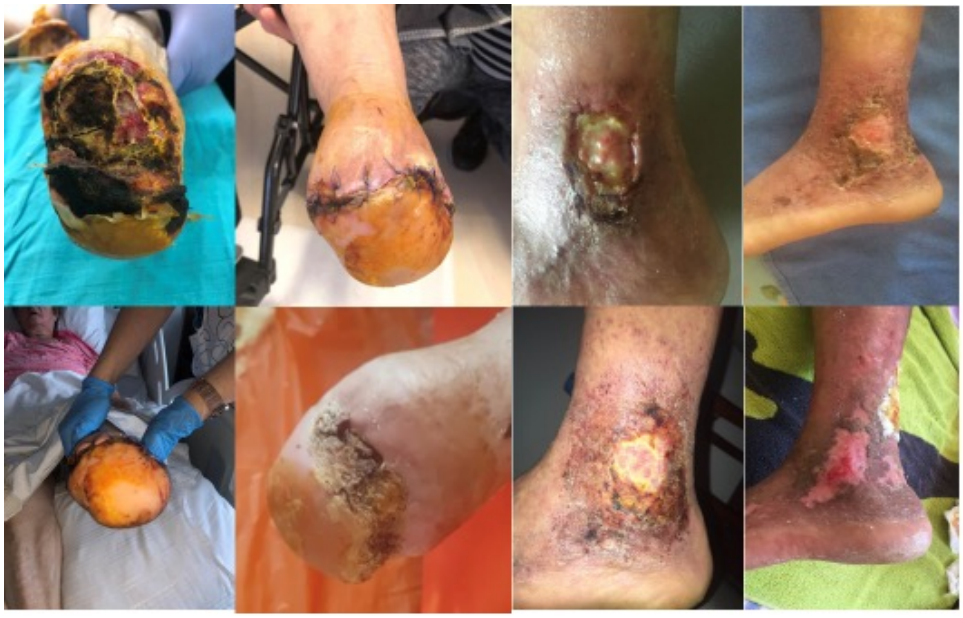
Figure 2: These cases had very high levels of HbA1c (such as 10.9) and after only 15 days of treatment (including amputation of necrotic parts), the ulcers were completely ephitelialised and survived against high levels of HbA1c for 4 years.



A) Pre-treatment and **B)** post-treatment with measurable oxygen saturation (which was impossible at the beginning).

ephitelisation, in a 3-week period, 46 patients showed a return to normal levels of CRP and the rest of the cases remained above the normal levels of CRP. In these cases, Hba1c levels did not alter more than 10% and autologous wound coverages were not more than 20% of the wound surfaces (Table 1). The dimensions of the wounds were calculated by milimetric paper measurement as a classic parameter in wound healing research. Finally, four of the cases were amputated below knee level, and five of patients did not allow amputation and continued with wound dressing changes, without further complications. Therefore, even for the failure of the treatment cases, there is still effectiveness in the later periods, and up to 2 years there was no progression on wounds, or further complications such as gangrene or osteomyelitis.

Figure 3: These two cases were resistant to treatment in the first 8 weeks because of pre-existing smoking, and continuing another 4 weeks resulted in healing.



Cessation of smoking gives better results following reduction of blood nicotine levels to normal.

Table 1: Clinical and laboratory parameters for follow-up of the patients.

Parameter	Day 0	Day 15	Day 30	Day 45	Day 60	Day 90
WBC (4–11.000)	6400–9800	6200–9200	5800–7800	5400–7200	5600–7400	4400–8400
CRP (up to 1 mg/L; N)	4.0–36.0	4.0–12.0	3.0–8.0	3.0–5.0	1.0–3.0	0.4–1.5
ESR (up to 30 mm/hour; N)	20–44	14–30	12–30	8–20	6–18	6–18
HbA1c (up to 5.6%; N)	8.2–10.4	8.1–9.8	7.2–8.4	6.8–8.2	6.2–7.4	5.4–6.4
Fasting Blood Sugar level (up to 125 mg/dL)	240–380	180–240	120–180	104–148	98–136	100–132
Peripheral O_2 saturation (if present)	N/A	N/A	N/A	N/A	60–72%	74–82%
Procalcitonine (up to 0.05; N)	0.04	0.04	0.04	0.03	0.04	0.03

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; N/A; not applicable; WBC: white blood cell.

In addition to the treatment, new pharmaceuticals (glucagon-like peptide, glifozine, and their variations) have been put forward for the regulation of blood sugar, which have positive effects on the continuity of the treatment (Figures 1–3). It can be said that there is now a serious treatment alternative for the diabetic foot ulcers with this method, even when there is an indication for amputation.[21]

CONCLUSION

In conclusion, this treatment modality seems extremely effective in an area with too many ineffective methods described in literature; however, it is not a solution for the treatment of all types of diabetic ulcers. There are some restrictions and limitations of the treatment such as a history of myocardial infarction in last 6 months, presence of heavy smoking or another pre-existing vascular disease, and inability to control the blood sugar levels. Therefore, the number of 53 out of 62 cases with complete healing and without recurrence in at least 2 years on diabetic ulcers proves a treatment alternative on this unsolved problem. As a result, it can be said that, with a careful verification of the limiting and restricting factors, this method should be a first alternative in the therapeutic arsenal of the treatment of diabetic ulcers.

References

1. Mendes JJ, Neves J. Diabetic foot infections: current diagnosis and treatment. J Diabet Foot Complicat. 2012;4(2):26-45.
2. Caputo GM et al. Foot infections in patients with diabetes. Am Fam Physician. 1997;56(1):195-202.
3. Slovenkai MP. Foot problems in diabetes. Med Clin North Am. 1998;82(4):949-71.
4. Armstrong DG, Lipsky BA. Diabetic foot infections: stepwise medical and surgical management. Int Wound J. 2004;1(2):123-32.
5. Sacks DB et al. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Diabetes Care. 2011;34(6):61-99.
6. Markuson M et al. The relationship between hemoglobin A(1c) values and healing time for lower extremity ulcers in individuals with diabetes. Adv Skin Wound Care. 2009;22(8):365-72.
7. Wu SC et al. Foot ulcers in the diabetic patient, prevention and treatment. Vasc Health Risk Manag. 2007;3(1):65-76.
8. Halperin JL. Evaluation of patients with peripheral vascular disease. Thromb Res. 2002;106(6):303-11.
9. Maeda TM et al. Increase in skin perfusion pressure after maggot debridement therapy for critical limb ischaemia. Clin Exp Dermatol. 2014;39(8):911-4.
10. Venturi ML et al. Mechanisms and clinical applications of the vacuum-assisted closure (VAC) device: a review. Am J Clin Dermatol. 2005;6(3):185-94.
11. Dinh TL et al. A review of the mechanisms implicated in the pathogenesis of the diabetic foot. Int J Low Extrem Wounds. 2005;4(3):154-9.
12. Boykin JV et al. Treatment of elevated homocysteine to restore normal wound healing: a possible relationship between homocysteine, nitric oxide, and wound repair. Adv Skin Wound Care. 2005;18(6):297-300.
13. Aguilar Rebolledo F et al. "The pathogenesis of the diabetic foot ulcer: prevention and management," Dinh T (ed.), Global Perspective on Diabetic Foot Ulcerations (2011) London: IntechOpen, pp.155-82.
14. Grunfeld C. Diabetic foot ulcers: etiology, treatment and prevention. Adv Intern Med. 1992;37:103-32.
15. Low molecular weight dextran and ıschemia. JAMA. 1965;193(9):734.
16. Wang P et al. Pentoxifylline restores cardiac output and tissue perfusion after trauma-hemorrhage and decreases susceptibility to sepsis. Surgery. 1993;114(2):352-9.
17. Dézsi CA. Trimetazidine in practice: review of the clinical and experimental evidence. Am J Ther. 2016;23(3):e871-9.
18. Morikawa T et al. The effects of cilostazol on tissue oxygenation upon an ischemic-reperfusion injury in the mouse cerebrum. Adv Exp Med Biol. 2010;662:89-94.
19. Türker RK et al. Iloprost preserves kidney function against anoxia. Prostaglandins Leukot Essent Fatty Acids. 1988;31(1):45-52.
20. Matin T et al. Tadalafil to improve cutaneous flap perfusion in smokers: a case series and literature review. JAAD Case Rep. 2021;15:126-8.
21. Guyton J et al. Glucagon-like peptide 1 receptor agonists in type 1 diabetes mellitus. Am J Health Syst Pharm. 2019;76(21):1739-48.

Aetiology and Outcomes of Thrombocytopenia in Pregnancy: A Cross-Sectional Study in a University Hospital, India

Authors:	Sudha V. Hooli, *Neelima Shah, Prashant Shah, Shrradha Suresh, Bali Sukeshani Sunil Department of Obstetrics and Gynecology, Dr. D. Y. Patil Hospital, Kolhapur, India *Correspondence to neelimapshah@gmail.com

Disclosure:	The authors have declared no conflicts of interest.
Received:	02.05.22
Accepted:	25.10.22
Keywords:	Aetiologies, maternal outcomes, thrombocytopenia (TCP).
Citation:	EMJ. 2022; DOI/10.33590/emj/10015267. https://doi.org/10.33590/emj/10015267.

Abstract

Background: Thrombocytopenia (TCP) is the second most common haematological finding in pregnancy next to anaemia. It carries a risk for both the mother and the fetus, associated with substantial maternal or neonatal morbidity and mortality. However, a specific therapy, if instituted promptly, improves the outcome for affected patients and their offspring. In patients in India, TCP during pregnancy is an underexplored condition.

Objectives: To assess the aetiology of TCP in pregnancy and to assess the maternal outcomes of TCP in pregnancy.

Methodology: The authors included a total of 133 patients in their third trimester (>32 weeks), with a platelet count <149,000 /mm^3, admitted to the authors' institution from 1st January 2021 to 31st December 2021. Patient-related data such as menstrual and obstetric history, presenting complaints, obstetric examination, and basic investigations were collected in a pre-designed, pre-tested proforma. All cases were followed until delivery to record any maternal complications, or any other morbidities. The data were analysed using SPSS (International Business Machines Corporation, Armonk, New York, USA) software. $\chi 2$ test was used to compare the proportions between the groups. $p<0.05$ was considered significant.

Results: Overall, 64.7% of patients were in the 18–25 years age group and 49.6% of patients were primigravida. Furthermore, 60.9% of patients were diagnosed to have mild TCP, 32.3% had moderate TCP, and only 6.8% patients had severe TCP. The majority (75.2%) of cases were of gestational TCP. In total, 15.8% of cases had pregnancy-induced hypertension (PIH); 3.0% had dengue; 2.3% were COVID-19 positive; 1.5% were diagnosed with haemolysis, elevated liver enzymes, and low platelets syndrome; 1.5% had immune TCP; and only one patient had leptospirosis. Four percent of cases had gestational TCP, 9.5% had PIH, one patient (25.0%) had dengue, and both cases of immune TCP had severe TCP. Twenty-eight percent of gestational TCP cases; 47.6% of PIH cases, both cases of haemolysis, elevated liver enzymes, and low platelets syndrome; 50.0% of dengue cases; and one COVID-19

positive case (33.0%) had moderate TCP. Finally, 6.25% of patients who underwent lower segment caesarean section had severe TCP, 6.00% of patients who underwent vaginal delivery had severe TCP, and out of two patients who had a spontaneous abortion, one (50.00%) had severe TCP at the time of admission. The association was significant ($p<0.05$).

Conclusion: TCP is a crucial condition among pregnant patients. Mild TCP is a common type. Correct aetiological diagnosis, and promptly administered adequate and specific therapy are, therefore, essential to significantly improve the outcomes of pregnant patients and their offspring.

Key Points

1. During pregnancy, the second most common haematological complication after anaemia is thrombocytopenia (TCP). This coagulation disorder causes an abnormally low level of platelets.
2. The authors' studied cohort of patients in their third trimester with a platelet count <149,000 /mm^3 had predominantly mild cases of TCP, with the majority of cases due to gestational TCP.
3. TCP is associated with heightened maternal or neonatal morbidity and mortality, but the implementation of specific treatments, tailored to aetiology, can significantly improve outcomes.

INTRODUCTION

Thrombocytopenia (TCP) is a common condition that occurs in pregnancy. It is the second most common haematological finding in pregnancy next to anaemia. In pregnancy, physiological and pathological changes occur in platelet number and their functions, which can be of clinical concern. Inherited qualitative and quantitative platelet disorders may also manifest during pregnancy with the risk of bleeding.[1]

TCP affects 7–10% of all pregnancies.[1] Most studies report a reduction in platelet count approximately 10% lower than pre-pregnant values. The normal range of platelets in non-pregnant patients is 150–400×10^9 /L.[1] TCP is defined as a drop in platelet count below 150×10^9 /L. It may result from a variety of causes, from a spectrum of benign conditions such as gestational TCP, to life-threatening syndromes such as haemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome. Gestational TCP is the most common aetiology, which accounts for almost three-quarters of all cases. TCP complicating hypertensive disorders of pregnancy are responsible for approximately 20% of all cases of TCP during pregnancy. Gestational or incidental TCP, the most common cause of TCP during pregnancy, accounts for 75% of pregnancy-associated TCPs. The incidence of immune thrombocytopenia (ITP) is one case of TCP per 1,000 pregnancies, and it accounts for 5% of cases of pregnancy-associated TCP.[2] The authors found significant TCP most commonly in the first trimester. Pre-eclampsia is present in 21% of cases of maternal TCP.[3] TCP occurs in 50% of patients with pre-eclampsia, and occasionally precedes other manifestations of the disease.

TCP is very risky for the mother and the fetus, and it is associated with maternal or neonatal morbidity, as well as mortality. If a specific therapy is applied, it will improve the outcome for affected patients and their offspring.[4] There is limited research that investigates platelet count during pregnancy in India. This study was conducted to assess causative aetiology and outcome of TCP in pregnancy in India.

MATERIAL AND METHODS

The study was conducted in the department of Obstetrics and Gynaecology, Dr. D. Y. Patil

Medical College Hospital and Research Institute, Kolhapur, India. This study was a hospital-based, prospective, observational study. A total of 133 patients who were admitted in their third trimester (>32 weeks) took part in the study. The sample was calculated on the basis of the Cochran formula (4 pq/L^2) on the basis that TCP affects 7–10% of pregnancies.[1] Patients were selected by the universal sampling method. The study was conducted from 1st January 2021 to 31st December 2021.

Inclusion criteria to enrol in the study were antenatal patients with platelet count lower than 150×10^9 /L, in the third trimester, and who were willing to participate in the study. Exclusion criteria were patients who refused participation; patients with known haematological disorders; patients with a history of diabetes, collagen disorders, tuberculosis, and epilepsy; and patients who had had a previous caesarean section.

Approval from the Institutional Ethics Committee (IEC) was received. Informed consent from the patients and patient-related data were collected, including detailed menstrual and obstetric history; presenting complaints; and findings of general, systemic, and obstetric examination, including pelvic examination. Investigations were performed, including urine tests for albumin/sugar, complete blood count, liver function test, renal function test, peripheral blood smear, coagulation profile, detection of malaria, and collection of dengue IgG and IgM antibodies, in a pre-designed, pre-tested proforma. Gestational age was established by menstrual history and clinical examination, confirmed by ultrasonography. Platelet count of 100,000–149,999 /mm^3 was classified as mild TCP; 50,000–100,000 /mm^3 as moderate TCP; and <50,000 /mm^3 as severe TCP.

All the cases were followed until delivery to record any complications such as pre-term labour, abruption, pre-eclampsia, postpartum haemorrhage, or any other morbidities. Duration of pregnancy at the time of delivery, indication of induction, and method (if required) and mode of delivery, including indication for instrumental delivery or caesarean section, were recorded. The data were coded and entered in Microsoft Office Excel 2020 (Microsoft, Redmond, Washington, USA). The data were then analysed using SPSS software version 21 (International Business Machines Corporation [IBM], Armonk, New York, USA). The categorical data were represented as a number (percentage) and numerical data as mean with standard deviation. An χ^2 test was used to compare the proportions between the groups for samples larger than 30. Mann–Whitney U test was used to compare the means of quantitative data with the non-normal distribution. $P<0.05$ was considered statistically significant.

RESULTS

In the present study, 133 pregnant patients with confirmed cases of TCP were enrolled. Demographic characteristics of the cohort are displayed in Table 1. Most of the patients (86 [64.7%]) were in the 18–25 year age group, followed by 34 patients (25.6%) from 26–30 years. The majority (107 [80.5%]) were homemakers, followed by eight teachers, seven nursing staff, and six laboratory technicians. Furthermore, 130 (97.8%) were Hindu, 64 (48.1%) were from the lower-middle class, and only one patient was illiterate. Parity shows that 66 (49.6%) patients were primigravida and the remaining 67 (50.4%) were multipara (Table 1).

Based on platelet counts on admission, patients were categorised into three groups: mild, moderate, and severe TCP. Figure 1 illustrates the distribution of TCP by severity. In total, 81 (60.9%) patients were diagnosed to have mild TCP (1 Lakh–1.5 Lakh), 43 (32.3%) moderate (50,000–1 Lakh), and only nine (6.8%) patients were found to have severe TCP (≤50,000 [Figure 1]).

Figure 2 demonstrates the prevalence of each underlying aetiology of TCP. The majority (100 cases [75.2%]) were of gestational TCP. Further, 21 (15.8%) cases had PIH; four (3.0%) had dengue; three (2.3%) were COVID-19 positive; two (1.5%) were diagnosed with HELLP syndrome; two (1.5%) had ITP; and only one patient had leptospirosis.

Table 2 shows an association between various aetiologies and maternal outcomes with grades of TCP. Among aetiologies, four (4.0%) cases of gestational TCP, two (9.5%) cases of PIH, one case (25.0%) of dengue, and two cases of

Table 1: Demographic characteristics of the patients.

Demographic characteristics		Frequency	%
Age group (years)	18–25	86	64.7
	26–30	34	25.6
	≥31	13	9.8
Occupation	Homemaker	107	80.5
	Teacher	8	7.1
	Nursing staff	7	5.3
	Laboratory technician	6	4.5
	Student	3	2.3
	Farmer	2	1.5
Religion	Hindu	130	97.8
	Muslim	3	2.2
Socio-economic status	Middle class	50	37.6
	Lower-middle class	64	48.1
	Lower class	19	14.3
Education status	Postgraduate	4	3.0
	Graduate	10	7.5
	HSC	41	30.8
	SSC and below	77	57.9
	Illiterate	1	0.8
Parity	Primigravida	66	49.6
	Multipara	67	50.4
Total		133	100.0

HSC: higher secondary certificate; SSC: secondary school certificate.

ITP had severe TCP. Furthermore, 28 (28.0%) cases of gestational TCP, 10 (47.6%) cases of PIH, two cases of HELLP syndrome, two (50.0%) dengue cases, and one COVID-19 positive case (33.0%) had moderate TCP. The remaining cases had mild TCP. The association was found to be significant ($p<0.05$).

Three (30%) patients with bleeding tendency had severe TCP, but only six (5%) of the patients without bleeding tendency had severe TCP. The association was significant ($p<0.05$). Sixty-one full-term patients had mild TCP versus only 20 pre-term patients. The bleeding tendency was higher in patients with severe TCP but the difference was not significant ($p=0.73$).

Five (6.25%) patients who had undergone lower segment caesarean section (LSCS) had severe TCP, three (6.00%) patients who undergone vaginal delivery had severe TCP; and out of two patients who had a spontaneous abortion, one (50.00%) had severe TCP at the time of admission. There were more complications in patients with severe TCP and the association was significant ($p<0.05$). After admission, every patient was managed and platelet counts were achieved. Later the patients delivered as per the indications.

Figure 1: Grades of thrombocytopenia.

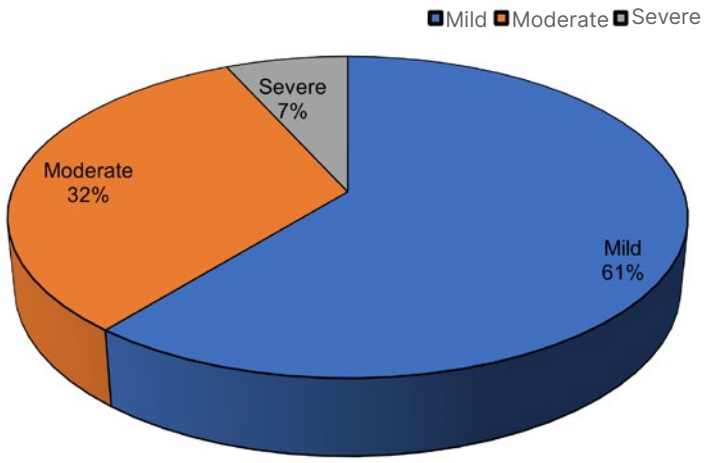
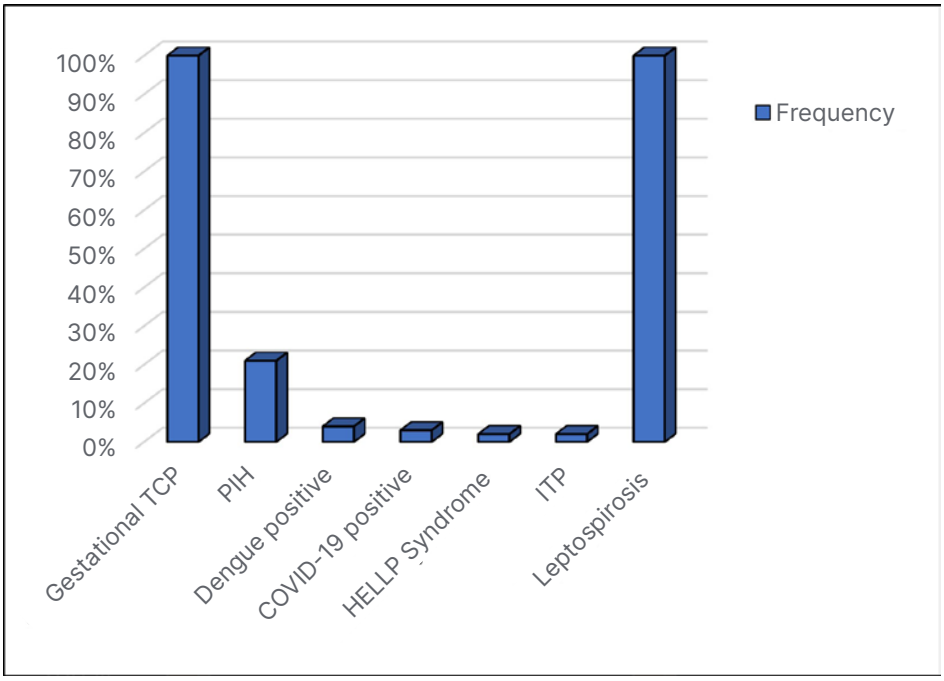


Figure 2: Aetiology of thrombocytopenia.



HELLP: haemolysis, elevated liver enzymes, and low platelets; ITP: immune thrombocytopenia; PIH: pregnancy-induced hypertension; TCP: thrombocytopenia.

DISCUSSION

In the authors' study, of the total 133 cases studied, the majority (75.2%) were found to have gestational TCP; 15.8% cases had PIH; 3.0% had dengue, 2.3% were COVID-19 positive; 1.5% were diagnosed to have HELLP syndrome; 1.5% had ITP; and only one patient had leptospirosis. In a

Table 2: Association of aetiologies and maternal outcomes with grades of thrombocytopenia.

Aetiology and outcomes		Grades of TCP			Total	p
		Mild	Moderate	Severe		
Aetiology	Gestational TCP	68	28	4	100	0.00070
	PIH	9	10	2	21	
	Dengue positive	1	2	1	4	
	COVID-19 Positive	2	1	0	3	
	HELLP syndrome	0	2	0	2	
	ITP	0	0	2	2	
	Leptospirosis	1	0	0	1	
Bleeding Tendency	Yes	2	5	3	10	0.00040
	No	79	38	6	123	
Term	Full-term	61	30	6	97	0.73000
	Pre-term	20	13	3	36	
Mode of delivery	LSCS	51	24	5	80	0.00002
	Vaginal delivery	29	18	3	50	
	Spontaneous abortion	1	0	1	2	
	VBAC	0	1	0	1	
Total		81	43	9	133	

ITP: idiopathic thrombocytopenic purpura; HELLP: haemolysis, elevated liver enzymes and low platelet; LSCS: lower segment caesarean section; PIH: pregnancy-induced hypertension; TCP: thrombocytopenia; VBAC: vaginal delivery after caesarean.

study conducted by Wang et al.,[5] the incidence of gestational TCP was 60.0%, while the incidence of hypertensive disorders was 28.2%, and other causes, including ITP, made up 11.8%. The results in the authors' study are comparable with this study.

In a study conducted by Sainio et al.,[6] the incidence of gestational TCP was 81%, while that of pre-eclampsia was 16%, and ITP was 3%. This study included only term patients, and this may be the reason for a slightly higher incidence of pre-eclampsia in the authors' study.

A study conducted by Parnas et al.[7] found that the main causes of TCP were gestational TCP (59.30%), immune thrombocytopenic purpura (11.05%), pre-eclampsia (10.05%), and HELLP syndrome (12.06%). In study conducted by Anita et al.,[8] gestational TCP included 64%, with hypertensive disorders making up 21%, and other disorders 13%. Ajzenberg et al.[9] assumed that gestational TCP occurs due to increased platelet consumption within the placental circulation and/or normal inhibition of megakaryocytopoiesis.

During pregnancy, haemodilution caused by the relative increase in plasma volume, coupled with increased platelet turnover, leads to the development of so-called gestational or incidental TCP, which accounts for three-quarters of cases of TCP detected during pregnancy.[10]

Immune-mediated TCP is an autoimmune disorder caused by the development of IgG auto-antibodies that are directed against a number of platelet glycoproteins. Antibody-bound platelets are rapidly cleared from the maternal circulation once they bind specific antibody receptors on macrophages, which might cause TCP.[10]

There is endothelial cell activation or dysfunction in pre-eclampsia. Cytokines such as TNF-α and ILs may contribute to the systemic oxidative stress associated with pre-eclampsia. This is characterised by reactive oxygen species and free radicals, which lead to the formation of self-propagating lipid peroxides. These peroxides in turn generate highly toxic radicals that injure systemic vascular endothelial cells, modify nitric oxide production by these cells, and interfere with prostaglandin balance. Other consequences of oxidative stress include the production of the lipid-laden macrophage foam cells seen in placental atherosis, and the activation of systemic microvascular coagulation manifested by TCP.[11] Burrows and Kelton[12] proposed that, in addition to an increased vascular tone during pregnancy, inducing platelet destruction, coagulation defects also occur. Some patients who are pregnant and have hypertension have an increased platelet-related IgG serum level; however, the increase in Ig is not specific, and does not necessarily indicate an immunologic-mediated TCP.[13] All patients with HELLP syndrome may have an underlying coagulopathy, which is usually undetectable. TCP has been attributed to increased consumption and/or destruction of platelets.[14]

In dengue infection, the dengue virus could directly or indirectly affect bone marrow progenitor cells by inhibiting their function to reduce the proliferative capacity of haematopoietic cells.[15] Increased platelet clearance may occur in dengue infection as a consequence of platelet activation. The platelets from patients with dengue display classic signs of apoptosis that include increased phosphatidylserine exposure, mitochondrial depolarisation, and activation of caspase-9 and 3. Moreover, TCP in patients with dengue strongly associates with enhanced platelet activation and apoptosis.[16] COVID-19 may increase levels of auto-antibodies and immune complexes, resulting in specific destruction of platelets by the immune system.[17]

In the present study, most of the females were between 18–25 years. Of those patients, 49.6% were primigravida and 50.4% were multigravida. Asrie et al.[4] conducted a study in Ethiopia in 2014, which reported that 35% of the study group were primigravida and 65% were multigravida. There were more primigravida patients in the authors' study compared with this study.

In the authors' study, among those with gestational TCP, 68% had mild TCP, 28% had moderate TCP, and 4% reported severe TCP. This shows that gestational TCP is usually of mild severity. This is comparable with Olayemi et al.'s[18] study in Ghana, where 65% had mild TCP. Boehlen et al.[19] also reported that gestational TCP is usually mild.

The present study shows that two (9.5%) cases of PIH had severe TCP; and 10 (47.6%) cases of PIH and both cases of HELLP syndrome had moderate TCP. The results are comparable with the study conducted by Rupakala et al.[20] on TCP in hypertensive disorders in pregnancy, in which severe TCP is seen in 5.8%, moderate TCP in 35.5%, and mild TCP in 58.7% of cases. Incidence of HELLP in this study was 6.60%, which is also comparable to the authors' study. Özdemir et al.[21] showed that the incidence of TCP in patients with hypertension was 24.2% and severe TCP was seen in 8.1% of cases. Magann et al.[22] reported that severe TCP is seen in 12% of patients with HELLP syndrome, 30% of eclampsia cases, and 18% of severe pre-eclampsia cases.

In the authors' study 60.0% of patients underwent a LSCS, 38.0% delivered vaginally, two patients (1.5%) had a spontaneous abortion, and one case delivered vaginally after a caesarean section. Further, 6.25% of patients who underwent a LSCS had severe TCP, 6.00% of patients who underwent a vaginal delivery had severe TCP, and out of two patients who had a spontaneous abortion, one (50.00%) had severe TCP at the time of admission. In a study at Safdarjung Hospital, New Delhi, India, it has been found that around 94.00% patients delivered vaginally and, among these, nine patients had instrumental delivery.[23] In the authors' study 38.00% of patients delivered vaginally, which is lower when compared with this study. The American College of Obstetricians and Gynecologists (ACOG) recommends that

the definitive treatment of maternal TCP in the setting of PIH with HELLP syndrome is the termination of pregnancy.

Activation of the coagulation and fibrinolytic systems cause the development of life-threatening TCP and disseminated intravascular coagulation, which occurs in some patients having symptoms of pre-eclampsia, and plays a role in stimulating platelet activation and accelerated clearance.[24] The authors came to the conclusion that HELLP syndrome causes haemolysis, liver function disturbance, lower count of platelets, and severe hypertension in patients, and that they are associated with high maternal and fetal morbidity, as well as mortality.

CONCLUSION

The most common cause of TCP in pregnancy is gestational. TCP is a crucial problem among patients who are pregnant, with mild TCP being the most common type. Correct aetiological diagnosis, and promptly administered adequate and specific therapy are therefore essential to significantly improve the outcomes of pregnant patients and their offspring; therefore, specific attention should be given to patients with severe TCP due to pre-eclampsia and HELLP syndrome to establish the best moment for therapeutical intervention.

References

1. Valera M-C et al. Physiologic and pathologic changes of platelets in pregnancy. Platelets. 2010;21(8):587-95.
2. Matthews JH et al. Pregnancy-associated thrombocytopenia: definition, incidence and natural history. Acta Haematol. 1990;84(1):24-9.
3. Bujold E et al. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. Obstet Gynecol. 2010;116(2 Pt 1):402-14.
4. Asrie F et al. Prevalence of thrombocytopenia among pregnant women attending antenatal care service at Gondar University Teaching Hospital in 2014, northwest Ethiopia. J Blood Med. 2017;8:61-6.
5. Wang X et al. Thrombocytopenia in pregnancy with different diagnoses: differential clinical features, treatments, and outcomes. Medicine (Baltimore). 2017;96(29):e7561.
6. Sainio S et al. Maternal thrombocytopenia at term: a population-based study. Acta Obstet Gynecol Scand. 2000;79(9):744-9.
7. Parnas M et al. Moderate to severe thrombocytopenia during pregnancy. Eur J Obstet Gynecol Reprod Biol. 2006;128(1-2):163-8.
8. Anita H et al Thrombocytopenia in pregnancy. Indian J Obstet Gynecol Res. 2016;3(1):7-12.
9. Ajzenberg N et al. Pregnancy-associated thrombocytopenia revisited: assessment and follow-up of 50 cases. Blood. 1998;92(12):4573-80.
10. McLintock C et al., "Hematologic Disease in Pregnancy," Powrie RO et al. (eds.), de Swiet's Medical Disorders in Obstetric Practice (2010) 5th edition, West Sussex: Wiley Blackwell, pp. 61-63.
11. Cunningham FG et al. (eds.), "Hypertensive Disorders," Williams Obstetrics (2018), 25th edition, New York: McGraw Hill Medical, pp.715.
12. Burrows RF, Kelton JG. Pregnancy in patients with idiopathic thrombocytopenic purpura: assessing the risks for the infant at delivery. Obstet Gynecol Surv. 1993;48(12):781-8.
13. Habas E et al. Thrombocytopenia in hypertensive disease of pregnancy. J Obstet Gynaecol India. 2013;63(2):96-100.
14. Padden MO. HELLP syndrome: recognition and perinatal management. Am Fam Physician. 1999;60(3):829-36.
15. de Azeredo EL et al. Thrombocytopenia in dengue: interrelationship between virus and the imbalance between coagulation and fibrinolysis and inflammatory mediators. Mediators Inflamm. 2015;2015:313842.
16. Hottz ED et al. Dengue induces platelet activation, mitochondrial dysfunction and cell death through mechanisms that involve DC-SIGN and caspases. J Thromb Haemost. 2013;11(5):951-62.
17. Xu P et al. Mechanism of thrombocytopenia in COVID-19 patients. Ann Hematol. 2020;99(6):1205-8.
18. Olayemi E, Akuffo FW. Gestational thrombocytopenia among pregnant Ghanaian women. Pan Afr Med J. 2012;12:34.
19. Boehlen F. Thrombocytopenia during pregnancy. Importance, diagnosis and management. Hamostaseologie. 2006;26(1):72-8.
20. Rupakala BM et al. Thrombocytopenia in hypertensive disorders of pregnancy. Int J Reprod Contracept Gynecol. 2018;7(3):848-54.
21. Özdemir S et al. A comparison of maternal and fetal outcomes of pregnancies complicated by moderate to severe thrombocytopenia caused by gestational thrombocytopenia preeclampsia / HELLP syndrome and immune thrombocytopenic purpura. GORM. 2008;14(3):154-8.
22. Magann EF et al. Antepartum corticosteroids: disease stabilization in patients with the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP). Am J Obstet Gynecol. 1994;171(4):1148-53.
23. Zutshi V et al. Prevalence of gestational thrombocytopenia and its effect on maternal and fetal outcome. Iraqi J Hematol. 2019;8(1):21-4.
24. López-Llera M et al. Abnormal coagulation and fibrinolysis in eclampsia. Am J Obstet Gynecol. 1976;124970:681-7.

A Study of Correlation of Adiponectin Levels in Metabolic Syndrome

Authors:	Apurv Singhal,[1] Vedpal Singh Punia,[1] *Akash Bharti,[1] Shaavi Mittal,[1] Praveen Raman Mishra,[2] Prem Kumar[1] 1. Department of General Medicine, School of Medical Sciences and Research, Sharda Hospital, Greater Noida, Uttar Pradesh, India 2. Department of General Medicine, All India Institute of Medical Sciences Gorakhpur, Uttar Pradesh, India *Correspondence to akash.bharti@sharda.ac.in

Disclosure:	The authors have declared no conflicts of interest.
Received:	16.03.2022
Accepted:	07.10.2022
Keywords:	Adiponectin, cardiovascular disease (CVD), insulin resistance syndrome, metabolic syndrome (MetS).
Citation:	EMJ. 2022; DOI/10.33590/emj/10146572. https://doi.org/10.33590/emj/10146572.

Abstract

Introduction: Metabolic syndrome (MetS), also known as insulin resistance syndrome, is described as a cluster of cardiometabolic symptoms such as high blood pressure, elevated fasting glucose, or insulin resistance. MetS is one of the most serious public health problems being faced globally. The purpose of the current investigation was to determine its prevalence, as well as the relationship between blood adiponectin levels and the development of MetS.

Materials and Methods: This observational cross-sectional hospital-based study was performed in the Department of General Medicine, School of Medical Sciences and Research, Sharda Hospital, Greater Noida, Uttar Pradesh, India, from January 2019–June 2020. Sixty patients attending the medicine out- or inpatient department, who confirmed consent, and fit into the International Diabetes Federation (IDF) inclusion criteria for MetS, were recruited for this study. The final sample size for this study was found to be 60, with a prevalence of 10%. This is the reason the study's precision decreased to ±7.6%, implying that the precision of the end result may vary by ±7.6%.

Results: Subjects without MetS were on average younger, had a lower BMI, and had a smaller waist circumference than those who had MetS, according to the findings. They also had lower blood pressure, pulse rate, and fasting plasma glucose levels than the people with MetS, and there were statistically significant variations in lipid profiles between those with and without MetS. In people who did not have MetS, the mean serum adiponectin concentration was 15.79±2.90 mg/mL, whereas the mean serum adiponectin concentration in people who did have MetS was 11.02±2.63 mg/mL ($p<0.001$). The levels of adiponectin were compared with the different components of MetS as defined by the IDF. The mean adiponectin concentrations in connection to the clinical characteristics of MetS are shown in Table 1 . The authors discovered that lower adiponectin levels were statistically significantly linked with the majority of the characteristics. In a multivariate analysis,

the serum adiponectin content was found to be significantly inversely associated to systolic blood pressure (r=-0.262; p<0.050), BMI (r=-0.288; p<0.050), total cholesterol (r=-0.515; p<0.001), and low-density lipoprotein (r=-0.305; p<0.050) in the study participants.

Conclusion: In conclusion, the present results suggest that circulating levels of adiponectin are reduced in the presence of MetS.

Key Points

1. Metabolic syndrome (MetS) is an insulin resistance syndrome with cardiometabolic symptoms, including high blood pressure, elevated fasting glucose, or insulin resistance, and is one of the most serious public health problems being faced worldwide.

2. This observational cross-sectional hospital-based study carried out in India investigates the relationship between adiponectin levels in MetS and other MetS components.

3. The association between adiponectin and high-density lipoprotein cholesterol, triglycerides, fasting blood sugar, BMI, and waist circumference could explain the reason why people with MetS have lower levels of adiponectin compared to the general population.

INTRODUCTION

Metabolic syndrome (MetS), also known as an insulin resistance syndrome, has been related to higher blood pressure outside of the normal range, insulin resistance, and increased fasting glucose levels.[1] It is one of the world's most important public health issues due to its growing prevalence in society and its impact on a large number of people.[2] In today's scenario, it is an alarming healthcare issue; however, if detected early enough, further complications can be avoided and quality of life improved. According to the World Health Organization (WHO), both developed and developing countries are seeing a growth in the number of cases of MetS. It affects anywhere from 15–40% of the population, with a higher prevalence rate in impoverished nations than in more developed ones.[3] MetS is related to an increased risk of cancer, in addition to coronary heart disease, Type 2 diabetes (T2D), and other cardiometabolic disorders.[4] MetS is a collection of risk factors for cardiovascular disease (CVD) that includes insulin resistance, obesity, hypertension, elevated triglycerides, and low levels of high-density lipoprotein (HDL).[5]

MetS is a powerful predictor of T2D, as people affected by the disease have a five to seven-fold greater chance of getting T2D. Those with MetS are also twice as likely to have CVD.[6] The heterogeneous condition is caused by obesity, particularly visceral adiposity, and insulin resistance. It is a group of common clinical diseases that includes obesity, hypertension, insulin resistance, glucose intolerance, and dyslipidaemia.[7] It has been suggested that visceral fat deposits are more implicated in the advancement of obesity-related disorders such MetS, T2D, and coronary artery disease, since they have a higher metabolic activity than subcutaneous fat deposits.[8] Adiponectin is an adipocytokine, which means it regulates blood sugar and cholesterol levels, as well as the cardiovascular system.

The amount of adiponectin in people with obesity was shown to be lower, despite the fact that it is mostly generated by adipose tissue, and higher levels were related to a drop in overall body weight in patients with obesity, implying an inverse relationship between adiponectin and body weight. This could be explained by the fact that subjects who are overweight receive negative feedback.[9]

Adiponectin contributes to the pathogenesis of cardiac MetS through various mechanisms. It has a detrimental influence on blood glucose and free fatty acid levels, among other factors.[10] To the authors' delight, it appears that the connection between insulin resistance and adiponectin

secretion runs both ways. Adiponectin improves insulin receptor sensitivity in peripheral tissues, affecting food intake, metabolic rate, and body weight.[11] Insulin resistance was shown to be worsened, and increasing insulin resistance was linked to lower levels of the bioactive adiponectin in those with high insulin levels. Inflammation and oxidative stress, both of which are related to insulin resistance, decrease adiponectin levels.[12]

It has been proven that the hormone serum adiponectin has an inverse connection with insulin resistance and body fat mass in adults. People with T2D and those with coronary artery disease have abnormally low levels in their blood. As a result of this, adiponectin is commonly believed to promote insulin sensitivity and to contribute to cardiovascular protection.[13] Lower than normal levels of the high molecular weight component of adiponectin in plasma, in particular, is a significant risk factor for the onset of MetS.[14] Fatigue, excess weight, and abdominal obesity were the most common anomalies among people with MetS, especially in the abdominal area. Because of its connection to insulin resistance and low-grade chronic inflammation in the body, abdominal obesity is usually considered as the most significant underlying cause of MetS.[15] The waist-to-hip ratio, commonly known as the waist-to-height ratio, is a better predictor of MetS than the BMI.[16]

IL-6 and other pro-inflammatory cytokines have been related to poor metabolic health in both people with and without obesity. Adipokines like adiponectin, on the other hand, have been linked to improved metabolic health in both groups.[17] Increased IL-6 levels and reduced adiponectin have been related to MetS and related processes in the absence of disease.[18] Because the MetS pandemic has been detected in a wide range of populations, it is urgently necessary to investigate the mechanism underlying the disease, as well as to search for robust and sensitive biomarkers that can be used as a diagnostic tool for the early detection and diagnosis of MetS, both in humans and in animals. Adiponectin and MetS are related in a range of ethnic groups, including White, Korean, and Japanese people. In the Indian population, the relationship between adiponectin levels and MetS criteria is yet unknown, as a limited number of Indian studies are available, including within the south of the country. To the authors' knowledge, this is one of the first studies to be conducted in their region, evaluating the relationship between adiponectin levels in MetS and other MetS components. This is a huge oversight, given the high prevalence of MetS, diabetes, and CVD in this part of India. Adiponectin levels have been associated with an increased risk of cardiovascular mortality in patients with diabetes; however, this is assumed to be a response to microvascular issues rather than a separate risk factor. The authors wanted to see whether there was a connection between MetS and blood adiponectin levels in healthy people.

MATERIALS AND METHODS

This observational cross-sectional hospital-based study was performed in the Department of General Medicine, School of Medical Sciences and Research, Sharda Hospital, Greater Noida, Uttar Pradesh, India, between January 2019–June 2020. Sixty patients attending the medicine out- or inpatient department and fitting into the International Diabetes Federation (IDF) inclusion criteria for MetS were recruited for this study. The study's final sample size was determined to be 60 individuals, with a 10% prevalence rate. This is the reason the study's precision decreased to ±7.6%, implying that the precision of the end result may vary by ±7.6%. The study was conducted after taking approval from the institutional ethical committee and written informed consent from the participants.

IDF inclusion criteria are visceral obesity, defined as waist circumference ≥102 cm in males and ≥88 cm in females; fasting plasma glucose ≥100 mg/dL; systolic blood pressure (SBP) ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg, or patient on antihypertensive treatment; and serum triglycerides ≥150 mg/dL or patient on lipid lowering treatment, and HDL-cholesterol (HDL-C) <40 mg/dL in males and <50 mg/dL in females.

After a written informed consent form had been obtained, detailed history of the presenting symptoms and their onset was recorded. Detailed histories of all the patients were obtained, including demographic details and age of the patient; and clinical details such as blood

pressure, heart rate, lipid profile, BMI, and blood sugar level (fasting and prandial) were noted on patients' proforma.

Analysers used enzyme digestion to measure blood glucose, total cholesterol (TC), HDL-C, and triglycerides in the fasting stage of the bloodstream. Dextran sulphate and magnesium chloride were used to precipitate non-HDL-C, and HDL-C was tested afterwards. Low-density lipoprotein (LDL)-cholesterol was estimated using Friedewald's equation in blood samples with triglycerides below 400 mg/dL. The levels of adiponectin in 180 randomly selected sera were measured using an ELISA (Immuno Concept Pharmacueticals, Sacramento, California, USA) in this sub-study. The intra- and inter-assay coefficients of variation of adiponectin were 10% and 13%, respectively. The second sample was treated with ethylenediaminetetraacetic acid and centrifuged at 3,000 xg for 15 minutes before the adiponectin level was determined at -20 °C. Fasting blood glucose, serum uric acid, and lipid profile were all tested using ViTROS® FS 5.1 (Ortho Clinical Diagnostics, Raritan, New Jersey, USA). Colorimetric techniques were used to measure the results. In order to determine postprandial blood glucose levels on the VITROS 5.1 analyser, the authors collected samples 2 hours after the meal.

For the data analysis, SPSS Statistics version 23.0 (International Business Machines Corporation [IBM], Armonk, New York, USA) on Windows (Microsoft, Redmond, Washington, USA) was utilised, and Excel (Microsoft) was used to construct the database, as well as generate the graphs. To describe quantitative data with a normal distribution, the mean and standard deviation were utilised. Statistical difference between two groups was analysed using the student t-test. Data were used to assess adiponectin levels in patients with MetS. When p values of <0.05 were attained, statistical significance was considered to be achieved.

RESULTS

Subjects without MetS in this study were younger, had lower BMIs, and had smaller waist circumferences in comparison to individuals with MetS; however, there were significant differences in overall lipid profiles between those with and without MetS as well. Those without MetS also had lower blood pressure, pulse rates, and fasting plasma glucose levels than subjects with MetS. Subjects without MetS had a higher mean serum adiponectin concentration (15.79±2.90 mg/mL) than those with MetS (11.02±2.63 mg/mL), with statistical significant difference as p<0.050.

The levels of adiponectin were compared with the IDF MetS components. To better understand how adiponectin levels correlate with MetS signs, see the data in Table 1. The majority of the features examined showed that low adiponectin levels were statistically significant.

As the number of MetS components rises, adiponectin levels decrease (p<0.001; Table 2).

According to multivariate analysis, the serum adiponectin concentration was significantly negative correlated with the SBP (r=-0.262; p<0.050), BMI (r=-0.288; p<0.050), TC (r=-0.515; p<0.001), and LDL (r=-0.305; p<0.050), respectively.

In Figure 1, the receiver operating curve (ROC) shows that an adiponectin level with a cut-off <12.45 µg/mL revealed a sensitivity of 90.0%, specificity of 63.3%, and accuracy of 87.6% to predict the incidence of MetS in individuals.

DISCUSSION

The current research was a 1-year cross-sectional study. It was used to investigate the relationship between adiponectin levels in MetS and other MetS components. Researchers Shashank et al.,[19] Isa et al.,[20] Chen et al.,[21] Ntzouvani et al.,[22] and Singh et al. [23] all used a similar methodology in their respective studies.

Isa et al.,[20] Singh et al.,[23] Chen et al.,[21] and Shashank et al.[19] utilised comparable approaches in their perspective studies. Results indicate that those without MetS were younger, had lower BMIs, and had smaller waist circumference measurements than those with MetS. They also had lower blood pressure, pulse rate, and fasting plasma glucose levels than the people with MetS, and there were statistically

Table 1: Correlation between adiponectin levels and metabolic syndrome components.

Adiponectin	Pearson correlation	p
Age	-0.106	0.422
SBP	-0.262*	0.043
DBP	-0.231	0.076
BMI	-0.288*	0.026
Waist circumference	-0.185	0.158
FBS	-0.223	0.086
Triglyceride	-0.220	0.962
HDL	-0.006	0.475
TC	-0.515†	<0.001
LDL	-0.305*	0.018

*Correlation is significant at the 0.05 level (2-tailed).

†Correlation is significant at the 0.01 level (2-tailed).

DBP: diastolic blood pressure; FBS: fasting blood sugar; HDL: high-density lipoprotein; LDL: low-density lipoprotein SBP: systolic blood pressure; TC: total cholesterol.

significant variations in lipid profiles between them and the patients with MetS, according to the findings. People without MetS had a greater mean serum adiponectin concentration (15.79±2.90 µg/mL) than those with MetS, who had a lower mean serum adiponectin concentration (11.02±2.63 µg/mL). The authors discovered that decreased adiponectin levels were statistically significantly linked with the majority of the characteristics of MetS. An increase in MetS components was observed to decrease adiponectin levels, which is statistically significant compared to previous studies.

SBP (r=-0.262; p<0.050), BMI (r=-0.288; p<0.050), TC (r=-0.515; p<0.001), and LDL cholesterol (r=-0.305; p<0.050) were all linked to blood adiponectin levels in this study. Patient adiponectin levels <12.45 ng/mL may be used as a cut-off to predict the occurrence of MetS in patients, according to the ROC, with a sensitivity of 90.0%, specificity of 63.3%, and an accuracy of 87.6%.

The mean baseline adiponectin level in participants with diabetes was lower than the mean baseline adiponectin level in subjects without diabetes (11.19±3.09 g/mL versus 15.21±3.06 mg/mL; p<0.001), according to this study. In a study performed by Chamukuttan et al.,[24] adiponectin levels were shown to be lower in patients with diabetes (10 individuals) than participants without diabetes (23 individuals [11.3±5.5 versus 16.7±7.6 µg/mL; p=0.0017]). According to research by Singh et al.,[23] adiponectin levels in patients with diabetes are lower than in participants without diabetes (6.07±1.02 versus 7.48±1.91 µg/mL; p=0.003). As reported by the study's results, low levels of adiponectin in the blood are connected to T2D and to MetS.

Table 2: Adiponectin levels decrease as metabolic syndrome components rise.

			Frequency (N=60)	Adiponectin (µg/ml) (mean±SD)	p
BMI (kg/m^2)	≤25		19	15.63±2.90	0.001
	>25		41	12.37±3.53	
SBP (mmHg)	≤130		39	14.09±3.55	0.045
	>130		21	12.12±3.57	
DBP (mmHg)	≤ 85		38	14.18±3.69	0.030
	>85		22	12.07±2.24	
FBS (mg/dL)	≤100		33	15.21±3.06	<0.001
	>100		27	11.19±3.09	
Triglyceride (mg/dL)	≤150		33	14.76±3.69	0.001
	<150		27	11.74±2.87	
HDL-C (mg/dL)	Male	≤40	9	12.16±3.72	0.479
		>40	21	13.08±3.22	
	Female	≤50	18	13.76±3.92	0.682
		>50	12	14.37±4.02	
Waist circumferences (cm)	Male	<90	19	13.74±3.34	0.034
		≥90	11	11.18±2.38	
	Female	<80	17	12.96±3.73	0.094
		≥80	13	15.37±3.83	

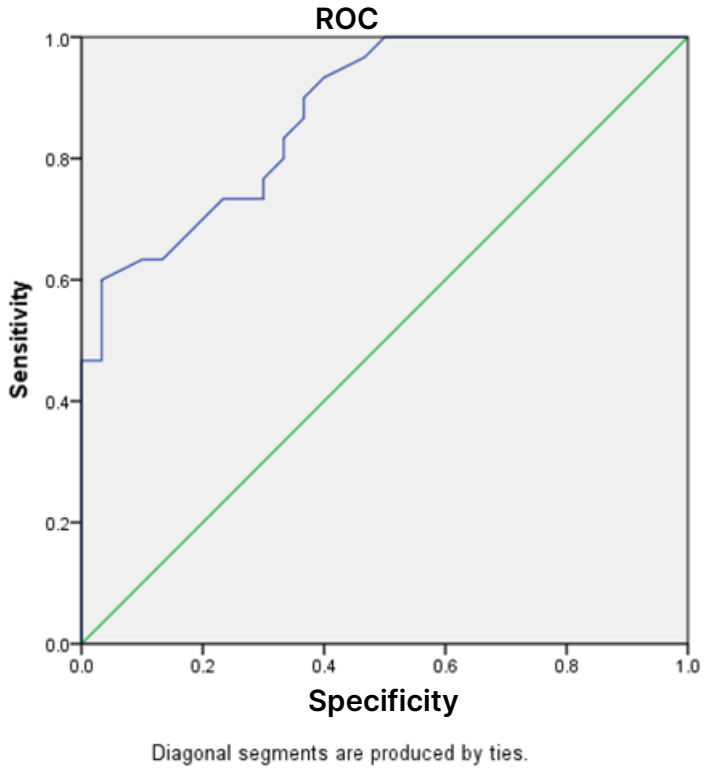
DBP: diastolic blood pressure; FBS: fasting blood sugar; HDL-C: high-density lipoprotein cholesterol; SBP: systolic blood pressure; SD: standard deviation.

Low adiponectin levels have been revealed to be a powerful predictor of future diabetes development, as well as a positive indication of that development. According to studies by Isa et al.,[20] study participants who were hypoglycaemic exhibited no statistically significant variations in adiponectin levels compared to patients with normal glucose levels. The researchers hope to fill in the gaps by increasing the sample size and transitioning from a cross-sectional study to a cohort study with a longer follow-up period.

The adiponectin concentration observed in patients with hypertension (12.12±3.57 µg/mL) was lower than the concentration obtained in those without hypertension (14.09±3.55 µg/mL), and the link between the two was statistically significant. Furuhashi et al.[25] reported that adiponectin concentrations were decreased in patients who are insulin-resistant and with essential hypertension, but not in patients who are normotensives or have hypertension but are non-insulin-resistant, indicating that hypoadiponectinemia in patients with essential hypertension is associated with insulin resistance. Both hypoadiponectinemia and insulin resistance are linked to the development of MetS, according to Renaldi et al.[26]

Males had adiponectin levels that were significantly higher than females (90 cm-13.74±3.34 µg/mL versus 90 cm-11.18±2.38 µg/mL; p=0.034), but females had lower levels (80 cm-12.96±3.73 g/mL versus 80 cm-15.37±3.83 µg/mL; p=0.094) and the association was insignificant. Males have more visceral fat and secrete more of the same hormones than females. Singh et al.[23] found a significant association between waist circumference and circulating adiponectin, which was stronger

Figure 1: Predicting the prevalence of metabolic syndrome through the receiving operating curve.



Cut-off value	12.45 (µg/mL)
Sensitivity	90.0%
Specificity	63.3%
Accuracy	87.6%

ROC: receiving operating curve.

than the connection between circulating adiponectin and BMI. This shows that visceral obesity (central fat distribution) rather than total fat mass is a better predictor of circulating adiponectin. P<0.001 was found for waist circumference in females more than 80 cm (5.98±1.18 mg/mL) compared with 9.90±2.70 mg/mL in females. In males greater than 90 cm (5.81±4.10 mg/mL) versus (7.90±0.05 mg/mL) was significant (p<0.001).

SBP (r=-0.262; p<0.050), BMI (r=-0.288; p<0.050), TC (r=-0.515; p<0.001), and LDL (r=-0.305; p<0.050) were all found to be inversely associated to serum adiponectin levels. According to Blaslov et al.,[27] patients with higher adiponectin levels (n=39) had a significantly lower waist circumference (p=0.002), fasting venous glucose levels (p=0.001), higher HDL3-cholesterol (p=0.011), and estimated glomerular filtration rate (p=0.003) when compared to the group with lower adiponectin levels, which had a higher prevalence of MetS (p=0.045). Estimated glomerular filtration rate increased by 1.09mg/kg-1 min-1 for every 1 µg/mL rise in total fasting plasma adiponectin (p=0.003), with each additional gramme of adiponectin (p=0.003). In the logistic regression model, the presence of MetS was found to be inversely linked with the level of adiponectin (p=0.014). According to Taniguchi et al.,[28] serum adiponectin levels were found to be negatively correlated with BMI (r=-0.308; p=0.002), diastolic blood pressure (r=-0.269; p=0.0012), and triglycerides (r=-0.338; p=0.001); and positively correlated with HDL-C (r=0.300; p=0.003). Similarly to this study's findings, Chen et al.[29] found that serum adiponectin was inversely linked with MetS.

Subjects without MetS had a higher mean serum adiponectin concentration (15.79±2.90 mg/mL) than those with MetS (11.02±2.63 mg/mL) with statistical significant difference as p<0.050 in this study. Adiponectin levels have previously been shown to vary by ethnicity, with African Americans having lower values.[30,31] Asian Indians were shown to have lower adiponectin values

than White people in a recent study by Abate et al.[32] This study's findings are noteworthy in this regard since they point to a strong correlation between adiponectin and MetS in Asian Indians. These data allow them to formulate a hypothesis that reduced adiponectin levels may be a contributing factor to the unexplained high level of insulin resistance seen among Asian Indians. This hypothesis might then be tested in prospective global research.

In the pre-set study, ROC showed that an adiponectin level with cut-off <12.450 µg/mL revealed a sensitivity of 90.0%, specificity of 63.3%, and accuracy of 87.6% to predict the incidence of MetS in individuals. In the prediction of MetS, adiponectin concentrations <7.425 µg/mL were shown to have high sensitivity (69.8%) and specificity (91.9%), as revealed by Singh et al.[23] in their study. In the context of diabetes, plasma adiponectin levels may also be used to predict MetS; however, lower cut-off values are also recommended.

Plasma adiponectin may be a potential marker for MetS in the future, as each component of MetS was found to be strongly linked to the plasma concentration of adiponectin. The study's most remarkable conclusion was that people in the lowest quartiles had a significantly greater risk of MetS than people in the highest quartiles when their mean adiponectin levels were compared. This study's findings were supported by Singh et al.,[23] Isa et al.,[20] Taniguchi et al.,[28] and Shashank et al.,[19] in addition to other researchers.

The limitation of the study was the small size of the study group: 60 individuals. The participants in this study were middle-aged adults who did not have a history of CVD. Extrapolating the findings to other populations, such as those who are younger, of a different race, or who have CVD, should be done with caution.

The biochemical indices were evaluated by a single accredited laboratory throughout the whole process. When it came to evaluating the existence of MetS, the authors used IDF definitions. Currently, there are two definitions used to define MetS that are closely linked but differ mainly in the criteria for abdominal obesity. Finally, a study that gives a convincing explanation for the correlation between adiponectin and MetS has been released.

CONCLUSION

Current studies reveal that MetS lowers adiponectin levels in the circulatory system, and that these levels continue to fall as the number of MetS components in the population rises. The connection between adiponectin and HDL-C, triglycerides, fasting blood sugar, BMI, and waist circumference might explain why people with MetS have lower levels of adiponectin than the general population. To confirm the mechanisms that support this relationship, further prospective study is required.

References

1. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486-97.
2. Eckel RH et al. The metabolic syndrome. Lancet. 2005;365(9468):1415-28.
3. Gronner M et al. Prevalence of metabolic syndrome and its association with educational inequalities among Brazilian adults: a population-based study. Braz J Med Biol Res. 2011;44(7):713-9.
4. Gami AS et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol. 2007;49(4):403-14.
5. Kassi E et al. Metabolic syndrome: definitions and controversies. BMC Med. 2011;9:48.
6. Grundy SM. Metabolic syndrome pandemic. Arterioscler Thromb Vasc Biol. 2008;28(4):629-36.
7. Moller DM, Kaufman KD. Metabolic syndrome: a clinical and molecular perspective. Annu Rev Med. 2005;56:45-62.
8. Hamdy O et al. Metabolic obesity: the paradox between visceral and subcutaneous fat. Curr Diabetes Rev. 2006;2(4):367-73.
9. Lamiaa A et al. Cut off value of serum adiponectin levels in Egyptian patients with metabolic syndrome. AJRIMPS. 2017;1(4):1-8.
10. Shehzad A et al. Adiponectin: regulation of its production and its role in human diseases. Hormones (Athens). 2012;11(1):18-20.
11. Kubota N et al. Adiponectin stimulates AMP-activated protein kinase in the hypothalamus and increases food intake. Cell Metab. 2007(1);6:55-68.
12. Deng Y, Scherer PE. Adipokines as novel biomarkers and regulators of the metabolic syndrome. Ann N Y Acad Sci. 2010;1211:E1-19.

13. Lima Marcos M et al. Adiponectinay susefectospleiotrópicos en el sistema cardiovascular. Rev Venez Endocrinol Metab. 2009;7:3-9.
14. Yamauchi T, Kadowaki T. Physiological and pathophysiological roles of adiponectin and adiponectin receptors in the integrated regulation of metabolic and cardiovascular diseases. Int J Obes (Lond). 2008;32(Suppl 7):S13-8.
15. Silva TE et al. Adiponectin: a multitasking player in the field of liver diseases. Diabetes Metab. 2014;40(2):95-107.
16. Kadowaki T et al. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest. 2006; 116(7):1784-92.
17. Kaser S et al. Effect of obesity and insulin sensitivity on adiponectin isoform distribution. Eur J Clin Invest. 2008;38(11):827-34.
18. Grundy SM et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005;112(17):2735-52.
19. Shashank R et al. A comparative study of serum adiponectin levels in patients of acute coronary syndrome with and without central obesity. Int J Adv Med. 2019;6(1):66-70.
20. Isa FI et al. Association of serum adiponectin levels with metabolic syndrome risk factors in Malay adults. World Nutrition Journal. 2017; 1(1):17-22.
21. Chen MC et al. Low serum adiponectin level is associated with metabolic syndrome and is an independent marker of peripheral arterial stiffness in hypertensive patients. Diabetol Metab Syndr. 2017;9:49.
22. Ntzouvani A et al. Reduced circulating adiponectin levels are associated with the metabolic syndrome independently of obesity, lipid indices and serum insulin levels: a cross-sectional study. Lipids Health Dis. 2016;15(1):140.
23. Singh YP et al. Plasma adiponectin is an independent predictor of metabolic syndrome. JDMS. 2012;2(4):34-43.
24. Chamukuttan S et al. Plasma adiponectin is an independent predictor of type 2 diabetes in Asian Indians. Diabetes Care. 2003;26(12):3226-9.
25. Furuhashi M et al. Blockade of the renin-angiotensin system increases adiponectin concentrations in patients with essential hypertension. Hypertension. 2003;42(1):76-81.
26. Renaldi O et al. Hypoadiponectinemia: a risk factor for metabolic syndrome. Acta Med Indones. 2009;41(1):20-4.
27. Blaslov K et al. Relationship between adiponectin level, insulin sensitivity, and metabolic syndrome in type 1 diabetic patients. Int J Endocrinol. 2013;2013:535906.
28. Taniguchi A et al. Adiponectin, leptin, and insulin resistance in nonobese Japanese type 2 diabetic patients. Metabolism. 2006;55(2):258-62.
29. Chen MC et al. Low serum adiponectin level is associated with metabolic syndrome and is an independent marker of peripheral arterial stiffness in hypertensive patients. Diabetol Metab Syndr. 2017;9:49.
30. Hulver MW et al. Ethnic differences in adiponectin levels. Metabolism. 2004;53(1):1-3.
31. Retnakaran R et al. Hypoadiponectinaemia in South Asian women during pregnancy: evidence of ethnic variation in adiponectin concentration. Diabet Med. 2004;21(4):388-92.
32. Abate N et al. Adipose tissue metabolites and insulin resistance in nondiabetic Asian Indian men. J Clin Endocrinol Metab. 2004;89(6):2750-5.

EGFR-Mutant Non-small Cell Lung Cancer: State-of-the-Art and Future Perspectives

Authors: Antonio Rossi,[1] Ettore Mari[2]

1. Oncology Centre of Excellence, Therapeutic Science & Strategy Unit, IQVIA, Milan, Italy
2. Medical Science and Strategy Hematology/Oncology, IQVIA, Milan, Italy

*Correspondence to arossi_it@yahoo.it

Disclosure: The authors have declared no conflicts of interest.

Received: 06.06.22

Accepted: 11.11.22

Keywords: Epidermal growth factor receptor (EGFR), mutations, non-small cell lung cancer (NSCLC), tyrosine kinase inhibitors (TKI).

Citation: EMJ. 2022;7[4]:112-122. DOI/10.33590/emj/10136032. https://doi.org/10.33590/emj/10136032.

Abstract

EGFR mutations are the first identified targetable driver alterations in advanced non-small cell lung cancer (NSCLC), for which specific epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKI) have been developed. These small molecules, administered orally, changed the natural history of patients with *EGFR*-mutated NSCLC, reporting impressive response and survival data.

Osimertinib, a third-generation EGFR-TKI, can be considered the standard first-line therapy for the 'common' *EGFR* mutations, which include the exon 19 deletion and Leu858Arg point mutation in exon 21, accounting for 90% of cases. The 'uncommon' *EGFR* mutations, highly heterogeneous and with a low frequency, seem to be more sensitive to afatinib and osimertinib, a second-generation EGFR-TKI, excluding the *EGFR* exon 20 insertions mutations, for which a platinum-based regimen should be recommended while waiting for specific targeted inhibitors to reach the market.

However, after an initial activity to first-line EGFR-TKI treatment, a disease progression is reported due to the presence of an intrinsic resistance or the onset of an acquired resistance. The latter can be broadly grouped into *EGFR*-dependent or *EGFR*-independent mechanisms of resistance, for which several new drugs and strategic approaches are under investigation.

This review focuses on the state-of-the-art EGFR-TKIs in the treatment of metastatic NSCLC harbouring *EGFR* mutations, and also discusses potential future perspectives.

Key Points

1. The landscape treatment of NSCLC has dramatically changed in the last years starting from the discovery of EGFR mutations as key drivers of a subgroup of lung cancer and their inhibitors development. This led to the start of "Precision Medicine" era for this disease, an approach in continuous evolution in needs of frequent updates.

2. The standard of care of EGFR-TKIs in the treatment of metastatic NSCLC harbouring EGFR mutations, the management of mechanisms of resistance, and the potential future perspectives in this setting are discussed in this article.

3. The "Precision Medicine" is a reality for the NSCLC management. The histotype and biomarkers profile of NSCLC are essential to apply the more appropriate therapeutic approach, especially in the presence of driver alterations, such as EGFR mutations, for which inhibitors are clinically available and able to change the natural history of these NSCLC subgroups.

INTRODUCTION

Epidermal growth factor receptors (EGFR), the first of four members of the ErbB family, play essential roles in both normal physiological and cancerous conditions. EGFR is characterised by an extracellular ligand-binding domain, which when activated by the ligand leads to the receptor dimerisation; a transmembrane domain, responsible for the dimerisation; and an intracellular tyrosine kinase domain that activates the intracellular kinase domain and the autophosphorylation of tyrosine residues within the cytoplasmic domain of the receptor. Through the association with intracellular signalling molecules, an EGFR is able to activate a variety of signalling pathways responsible for cell proliferation, survival, and differentiation. The function of the EGFR can be dysregulated in various types of malignancy due to gene amplification, mutations, or overexpression, becoming a promising therapeutic target.[1]

EGFR mutations are reported in approximately 17% and 50% of metastatic lung adenocarcinomas in people of White and Asian background, respectively.[2,3] The 'common' mutations, that account for approximately 90% of all *EGFR* mutations, include the in-frame deletions around the LeuArgGluAla motif (residues 746–750) of exon 19, and the Leu858Arg (L858R) point mutation in exon 21.[4] These common *EGFR* mutations are detected with a higher frequency in metastatic tumours in females, people from an Asian background, never-smokers, and those with lung adenocarcinoma.[5] Huge radiographic and clinical responses are reported with the corresponding monotherapy tyrosine kinase inhibitors (TKI), oral small molecules that block the activation of downstream signalling induced by EGFR, by binding to the adenosine triphosphate-binding sites.[4]

After an initial first-line EGFR-TKI treatment activity, lasting around 10–14 months, a disease progression is reported in the majority of patients with metastatic non-small cell lung cancer (NSCLC), with mechanisms of resistance that may vary.

The 'uncommon' *EGFR* mutations account for approximately 10% of all cases, most of which are *EGFR* exon 20 insertion (ex20ins) mutations, and are associated with poor responses to EGFR-TKI therapy.[6,7]

In this article, the authors review the state of the art of EGFR-TKIs in the treatment of metastatic NSCLC harbouring *EGFR* mutations, and also discuss the potential future perspectives.

STATE-OF-THE-ART

EGFR mutations, especially exon 19 deletions and the L858R mutation, are associated with sensitivity to EGFR-TKIs, predicting a favourable clinical outcome for patients with NSCLC receiving this therapy.[8] In fact, several EGFR-TKI generations have been developed and investigated in clinical trials, reporting results able

to modify the natural history of this subgroup of patients.

First-Generation EGFR-TKIs

Gefitinib, erlotinib, and icotinib belong to the first-generation EGFR-TKIs. These small molecules are reversible inhibitors of EGFR, administered orally at the dose of 250 mg/day for gefitinib, 150 mg/day for erlotinib, and 125 mg three times per day for icotinib. First-generation EGFR-TKIs improved, with a statistical and clinical significance, the first-line outcomes of advanced NSCLC harbouring *EGFR* mutations when compared to platinum-based chemotherapy. The objective response rates (ORR) were 58–83% with first-generation EGFR-TKIs versus 15–45% with platinum-based regimens, with a progression-free survival (PFS) of 8.4–13.7 months versus 4.6–7.9 months, respectively. Although overall survival (OS) seemed not to improve with these small molecules, the high crossover rates mitigated the potential advantages that were reflected in both arms of each trial, reporting a range of 18.0 months to 35.5 months for EGFR-TKIs and 20.8 months to 38.8 months for chemotherapy. These survival results had never been observed in metastatic NSCLC before the introduction of EGFR-TKIs in the experimental and standard therapy of NSCLC positive for *EGFR* mutations (Table 1). [9-15]

A meta-analysis of randomised trials that compared EGFR-TKIs to chemotherapy showed that toxic deaths were reported in 1.7% of cases, with pneumonitis being the most frequent cause, without significant differences between EGFR-TKIs. Grade ≥3 adverse events were reported in approximately 40% of patients receiving EGFR-TKIs, with diarrhoea and skin rash, typical adverse events related to this drug class, being the most frequent. In particular, the risk for increased liver enzyme levels was higher with gefitinib than with the other EGFR-TKIs. Discontinuation of treatment due to toxicity occurred in 7.7% of patients, with no significant differences between EGFR-TKIs.[21] Table 2 summarises the main Grade ≥3 adverse events reported by first- or second-generation EGFR-TKIs when compared, in first-line treatment, to chemotherapy in advanced NSCLC harbouring *EGFR* mutations.

Second-generation EGFR-TKIs

This subgroup of EGFR-TKIs includes mainly the irreversible small molecules afatinib and dacomitinib. Afatinib is administered orally at the dose of 50 mg/day, while dacomitinib is administered at the oral dose of 45 mg/day.

Afatinib was compared with platinum-based regimens in the first-line treatment of advanced NSCLC harbouring *EGFR* mutations, reporting statistical and clinical improvements of all outcomes. In fact, ORR was 56.0–66.9% with afatinib and 23.0% with platinum-based chemotherapy, PFS was 11.0 months versus 5.6–6.9 months and OS was 23.1–28.2 months versus 23.5–28.2 months, respectively. Furthermore, in these trials, a high crossover was reported (Table 1).[16,17] The rate of Grade ≥3 adverse events for afatinib was 42.1%, with a higher risk of rash and diarrhoea for afatinib than with first-generation EGFR-TKIs (Table 2).[21]

LUX-Lung 7, a Phase IIb, randomised trial, compared afatinib with gefitinib in the first-line treatment of advanced NSCLC harbouring *EGFR* mutations. There were three co-primary endpoints: PFS, time-to-treatment failure, and OS. Despite afatinib showing a slightly better OS compared to gefitinib, these data should be interpreted with caution since they are coming from a Phase IIb study. The trial confirmed the safety profile of each drug.[18]

No studies compared dacomitinib to chemotherapy. Conversely, a Phase III study, ARCHER-1050, evaluated the head-to-head comparison of dacomitinib and gefitinib in first-line therapy of advanced NSCLC selected for *EGFR* mutations. PFS, the primary endpoint, and OS were significantly improved by dacomitinib compared to gefitinib, with adverse events typical of second- and first-generation EGFR-TKIs.[19]

Overall, the results of these head-to-head trials showed a superior control of disease by second-generation, irreversible EGFR-TKIs, compared to first-generation, reversible, EGFR-TKIs (Tables 1 and 3).

Third-generation EGFR-TKIs

In nearly 50% of cases, the acquired mechanisms of resistance to first- and second-generation EGFR-TKIs is due to the onset of a new *EGFR*

Table 1: Results of the first-line Phase III trials comparing both first- and second-generation epidermal growth factor receptors-tyrosine kinase inhibitors versus platinum-based chemotherapy, or head-to-head epidermal growth factor receptors-tyrosine kinase inhibitors, in advanced non-small cell lung cancer harbouring *EGFR* mutations.

Trial	Region	ADK/no-ADK (%)	Male/female (%)	Smoker/non-smoker (%)	Common/uncommon (%)	Therapy	No. pts	ORR (%)	PFS (mos)	OS (mos)
WJTOG3405[9]	Japan	96.5/4.5	31.4/68.6	29.0/71.0	100.0/0.0	Gefitinib versus CDDP+TXT	86 86	62.1 p<0.0010 32.2	9.2 HR=0.49 6,3	35.5 HR=1.18 38.8
NEJ002[10]	Japan	90.4/9.6	36.8/63.2	34.2/65.8	93.9/6.1	Gefitinib versus CBDCA+PAC	114 110	73.7 p<0.0010 30.7	10.8 HR=0.32 5.4	27.7 HR=0.88 26.6
Patil VM[11]	India	100.0/0.0	46.2/53.8	22.1/77.9	97.2/2.8	Gefitinib versus CBDCA+PEM	145 145	63.5 p=0.0030 45.3	8.4 HR=0.66 5.6	18.0 HR=0.78 22.6
EURTAC[12]	Europe	95.0/5.0	33.0/67.0	34.0/66.0	100.0/0.0	Erlotinib versus DDP+TXT or GEM	86 87	58.0 p<0.0001 15.0	9.7 HR=0.37 5.2	22.9 p=0.97 22.1
OPTIMAL[13]	China	88.0/12.0	41.0/59.0	28.0/72.0	100.0/0.0	Erlotinib versus CBDCA+GEM	82 72	82.0 p<0.0001 36.0	13.1 HR=0.16 4.6	22.8 HR=1.19 27.2
ENSURE[14]	China, Malaysia, Philippines	94.5/5.5	38.2/61.8	28.2/71.8	100.0/0.0	Erlotinib versus CDDP+GEM	110 107	62.7 NR 33.6	11.0 HR=0.34 5.5	26.3 HR=0.91 25.5
CONVINCE[15]	China	100.0/0.0	29.1/70.9	21.6/78.4	100.0/0.0	Icotinib versus CDDP+PEM	148 137	NR	11.2 HR=0.61 7.9	30.5 HR=0.88 32.1
LUX-Lung 3[16]	Asia, Europe, North America, South America, Australia	100.0/0.0	36.1/63.9	32.6/67.4	88.7/11.3	Afatinib versus CDDP+PEM	230 115	56.0 p=0.0010 23.0	11.1 HR=0.58 6.9	28.2 HR=0.88 28.2
LUX-Lung 6[17]	China, Thailand, South Korea	100.0/0.0	36.0/64.0	25.2/74.8	89.3/10.7	Afatinib versus CDDP+GEM	242 122	66.9 p<0.0001 23.0	11.0 HR=0.28 5.6	23.1 HR=0.93 23.5
LUX-Lung 7[18]	Australia, Canada, China, Hong Kong, Japan, South Korea, Singapore, Spain, Sweden, Taiwan, UK	99.0/1.0 99.0/1.0	43.0/57.0 33.0/67.0	34.0/66.0 33.0/67.0	100.0/0.0 100.0/0.0	Afatinib versus gefitinib	160 159	72.5 p=0.0018 56.0	11.0 HR=0.74 10.9	27.9 HR=0.86 24.5
ARCHER-1050[19]	China, Hong Kong, Japan, South Korea, Poland, Italy, Spain	100.0/0.0 100.0/0.0	36.0/64.0 44.9/56.0	35.0/65.0 44.0/56.0	100.0/0.0 100.0/0.0	Dacomitinib versus gefitinib	227 225	75.0 p=0.4200 72.0	14.7 HR=0.59 9.2	34.1 HR=0.76 26.8

Table 1: Continued.

Trial	Region	ADK/no-ADK (%)	Male/female (%)	Smoker/non-smoker (%)	Common/uncommon (%)	Therapy	No. pts	ORR (%)	PFS (mos)	OS (mos)
FLAURA[20]	Australia, Asia, Canada, Europe, Japan, North America, South Korea, UK	99.0/1.0 98.0/2.0	36.0/64.0 38.0/62.0	35.0/65.0 37.0/63.0	100.0/0.0 100.0/0.0	Osimertinib versus gefitinib or erlotinib	279 277	80.0 p=0.2400 76.0	18.9 HR=0.46 10.2	38.6 HR=0.80 31.8

ADK: lung adenocarcinoma; CBDCA: carboplatin; CDDP: cisplatin; DDP: platinum; EGFR-TKI: epidermal growth factor receptor-tyrosine kinase inhibitor: HR: hazard ratio; GEM: gemcitabine; mos: months; NSCLC: non-small cell lung cancer; No. pts: number of patients; NR: not reported; ORR: objective response rate; OS: overall survival; PAC: paclitaxel; PEM: pemetrexed; PFS: progression-free survival; TXT: docetaxel.

mutation, the T790M, in exon 20, which causes impaired binding of the TKI.[22] In order to overcome this resistance, osimertinib, a third-generation irreversible EGFR-TKI given at the daily dose of 80 mg, was developed, in view of its ability to cross the brain barrier to control central nervous system (CNS) metastases. The AURA3 Phase III, randomised trial demonstrated the superiority of osimertinib versus pemetrexed plus carboplatin or cisplatin in patients with NSCLC harbouring *EGFR* exon 20 p.T790M as mechanism of resistance to EGFR-TKIs.[23] The AURA3 trial showed a median PFS of 10.1 months in the osimertinib arm versus 4.4 months in the chemotherapy arm (hazard ratio: 0.30; 95% confidence interval: 0.23–0.41; p<0.001) in patients without CNS metastasis. In patients with CNS involvement, the median PFS was 8.5 versus 4.2 months (hazard ratio: 0.32; 95% confidence interval 0.21–0.49), respectively.[23]

The FLAURA Phase III trial compared osimertinib versus gefitinib or erlotinib in first-line treatment of advanced NSCLC harbouring common *EGFR* mutations. Osimertinib was shown to significantly improve the survival outcomes both statistically and clinically, with a favourable safety profile (Tables 1 and 3).[20] The interesting results reported in metastatic disease led to investigate osimertinib in early stages of NSCLC. The ADAURA Phase III, randomised trial enrolled Stages IB–IIIA, completely resected, *EGFR* mutation-positive NSCLCs to receive osimertinib versus placebo.[24] The primary endpoint was disease-free survival in Stages II–IIIA, which was not reached in the osimertinib group and was 19.6 months in the placebo arm. In the overall population, the median disease-free survival was not reached in the osimertinib group, versus 27.5 months in the placebo group.[24] Other third-generation EGFR-TKIs are under investigation, with imminent results.[25]

Uncommon *EGFR* Mutations

Despite the fact that common *EGFR* mutations are particularly sensitive to EGFR-TKIs, which represent the standard of care first-line therapy, a meta-analysis showed that exon 19 deletion is associated with longer PFS compared to exon 21 L858R mutation. This confirms that exon 19 deletions and L858R point mutations are two different disease entities in regards to outcomes of EGFR-TKIs and prognosis.[26] Furthermore, this issue is also reported for osimertinib, which showed lower efficacy against *EGFR* L858R, with no overall benefit in the FLAURA trial.[23] These considerations do not affect the standard of care first-line approach for common *EGFR* mutations due to the clear improved outcomes with EGFR-TKIs.

This different sensitivity is particularly true for the uncommon *EGFR* mutations, which are highly heterogeneous and often have very low frequencies. The most prevalent uncommon *EGFR* mutations include G719X, S768I, and

Table 2: Phase III trials main Grade ≥3 adverse events reported by first- and second-generation epidermal growth factor receptors-tyrosine kinase inhibitors when compared with chemotherapy in advanced non-small cell lung cancer harbouring *EGFR* mutations.

	Gefitinib			Erlotinib			Icotinib	Afatinib	
Trial	WJTOG3405[9]	NEJ002[10]	Patil VM[11]	EURTAC[12]	OPTIMAL[13]	ENSURE[14]	CONVINCE[15]	LUX-Lung 3[16]	LUX-Lung 6[17]
No. pts	86	114	145	86	82	110	148	230	242
Toxicity	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**
Rash	2 (2.3)	6 (5.3)	40 (28.4)	11 (13.0)	2 (2.0)	7 (6.4)	22 (14.9)	37 (16.2)	35 (14.6)
Diarrhoea	1 (1.2)	1 (0.9)	NR	4 (5.0)	1 (1.0)	2 (1.8)	11 (7.4)	33 (14.4)	13 (5.4)
Fatigue	2 (2.3)	3 (2.6)	NR	5 (6.0)	0 (0.0)	NR	5 (3.4)	3 (1.3)	1 (0.4)
Stomatitis	0 (0.0)	0 (0.0)	NR	NR	1 (1.0)	NR	NR	20 (8.7)	13 (5.4)
Paronychia	1 (1.2)	3 (2.6)	NR	NR	0 (0.0)	NR	NR	26 (11.4)	0 (0.0)
AST	14 (16.3)	30 (26.3)	57 (40.4)	2 (2.0)	0 (0.0)	NR	4 (2.7)	NR	1 (0.4)
ALT	24 (28.0)		72 (51.1)		3 (4.0)	NR	3 (2.0)	NR	4 (1.7)
Pneumonitis/ ILD	2 (2.3)	3 (2.6)	NR	1 (1.0)	0 (0.0)	0 (0.0)	NR	3 (1.0)	1 (0.4)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; EGFR-TKI: epidermal growth factor receptor-tyrosine kinase inhibitor; ILD: interstitial lung disease; No.: number; No. pts: number of patients; NR: not reported; NSCLC: non-small cell lung cancer.

L861Q, in exons 18, 20, and 21, respectively. These *EGFR* mutations are generally excluded from randomised trials and very little prospective data are available. Mainly afatinib and osimertinib, which showed a similar activity between uncommon and common *EGFR* mutations,might be considered for the treatment of this subgroup.[27]

A different group of the uncommon *EGFR* mutations includes the ex20ins mutations that are relatively frequent, representing approximately 4% of all *EGFR*-mutated NSCLCs. These mutations confer intrinsic resistance to available EGFR-TKIs, as they result in steric hindrance of the drug-binding pocket, and are usually associated with an immediate inefficacy of EGFR-TKIs.[27] The first-line standard approach is a platinum-based regimen; thus, a different approach was investigated for this specific group of patients. Among the drugs under development, amivantamab is an anti-EGFR and anti-mesenchymal epithelial transition factor (MET) bispecific antibody with immune cell-directing activity, which binds to each receptor's extracellular domain, bypassing resistance at the TKI binding site. In a total of 81 previously treated patients, amivantamab, given intravenously at the dose of 1,050 mg if the patient's weight was <80 kg or 1,400 mg with a weight ≥80 kg, showed an ORR of 40%, with a median duration of response of 11.1 months. The median PFS was 8.3 months, with the most common Grade ≥3 adverse events being hypokalaemia in six patients (5%), and rash, pulmonary embolism, diarrhoea, and neutropenia in four (4%) each.[28] These results led amivantamab to become the first treatment to be approved by the U.S. Food and Drug Administration (FDA) for patients with advanced NSCLC harbouring *EGFR* ex20ins mutations whose disease has progressed on or after platinum-based chemotherapy. Mobocertinib, a first-in-class EGFR-TKI being developed for the treatment of EGFR ex20ins-positive NSCLC, also granted accelerated approval by FDA, in the same setting of amivantamab, at the daily oral dose of 16o mg.[29]

Table 3: Phase III trials main Grade ≥3 adverse events reported by Phase III trials comparing the different generation pidermal growth factor receptors-tyrosine kinase inhibitors in advanced non-small cell lung cancer harbouring *EGFR* mutations.

Trial	LUX-Lung 7[18]		ARCHER-1050[19]		FLAURA[20]	
	Afatinib	Gefitinib	Dacomitinib	Gefitinib	Osimertinib	Gefitinib or erlotinib
No. pts	160	159	227	225	279	277
Toxicity	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**
Rash	15 (9.4)	5 (2.1)	10 (4.0)	0 (0.0)	3 (1.0)	20 (7.0)
Diarrhoea	21 (13.1)	2 (1.3)	19 (8.0)	2 (1.0)	7 (3.0)	7 (3.0)
Fatigue	9 (5.6)	0 (0.0)	5 (2.0)	3 (1.0)	2 (1.0)	2 (1.0)
Stomatitis	7 (4.4)	0 (0.0)	8 (4.0)	1 (<1.0)	1 (<1.0)	1 (<1.0)
Paronychia	3 (1.9)	1 (0.6)	17 (7.0)	3 (1.0)	2 (1.0)	2 (1.0)
AST	0 (0.0)	4 (2.5)	0 (0.0)	9 (4.0)	2 (1.0)	12 (4.0)
ALT	0 (0.0)	13 (8.2)	2 (1.0)	19 (8.0)	2 (1.0)	25 (9.0)
Pneumonitis/ ILD	0 (0.0)	3 (1.9)	3 (1.0)	3 (1.0)	3 (1.0)	3 (1.0)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; EGFR-TKI: epidermal growth factor receptor-tyrosine kinase inhibitor; ILD: interstitial lung disease; No.: number; No. pts: number of patients; NSCLC: non-small cell lung cancer.

EGFR MECHANISMS OF RESISTANCE

The immediate inefficacy of first-line EGFR-TKIs leads to consideration of an intrinsic resistance that is often due to the presence of non-sensitive *EGFR* mutations, such as *EGFR* ex20ins mutations.[27] The presence of concurrent molecular or genetic alterations, which could potentially decrease the sensitivity of patients with sensitising *EGFR* mutations to EGFR-TKI treatment, may be considered as other agents responsible of intrinsic resistance.[30]

EGFR mutation-positive NSCLCs, after a variable period of response to EGFR-TKIs, develop acquired mechanisms of resistance with progression of the disease. To define the acquired resistance to first-line EGFR-TKIs, a clinical definition was proposed to benefit both practising oncologists and researchers.[31]

Moreover, according to the progression disease, a clinical subtyping of acquired resistance was also proposed, namely CNS only, oligo-progression, and systemic progression.[32] These classifications can help physicians to define the most appropriate therapeutic approach to this group of patients according to progression patterns.[33]

The most frequent *EGFR*-dependent mechanism of resistance, for the first- and second-generation EGFR-TKIs, is the onset of a new *EGFR* mutation, the T790M, which is sensitive to third-generation EGFR-TKIs.[25]

The histological transformation from adenocarcinoma to small cell lung cancer (SCLC) was observed by rebiopsies performed during the natural history of patients with *EGFR*-mutated NSCLC. This phenomenon is considered

another mechanism of acquired resistance to EGFR-TKIs, probably due to the origination of SCLC cells from minor pre-existent cells under the selection pressure of EGFR-TKIs, or transdifferentiated from the adenocarcinoma cells, or arisen from the multipotent stem cells.[34] Once the tumour transformation in SCLC is diagnosed, the standard chemotherapy for this histotype leads to a response and survival to treatment comparable to that of classic SCLC.[35,36]

At progression from EGFR-TKIs, in the view of a strategy of biomarker-driven approaches, the amplification of the *MET* oncogene, the most frequent *EGFR*-independent mechanisms of resistance, accounts for 5–20% of EGFR-TKIs acquired resistance causes, regardless of the EGFR-TKI generation or line of treatment. MET, a transmembrane tyrosine kinase receptor, is activated by the hepatocyte growth factor, promoting the activation of the downstream AKT pathway, leading to cell proliferation, survival, and antiapoptosis. The most widely-adopted definition for *MET* amplification is the presence of the *MET* gene with a copy number of ≥5 or a MET/CEP7 ratio of ≥2.[37] Tepotinib, capmatinib, and savolitinib are daily orally-administered potent MET inhibitors that demonstrated activity in *MET* exon 14 skipping mutations that occur in 3–4% of NSCLC.[38-40] These MET inhibitors have also demonstrated preclinical activity in *EGFR*-mutant/*MET*-amplified models of acquired EGFR-TKI resistance when combined with the same EGFR-TKI. A Phase Ib/II study showed that the combination of capmatinib, at the dose of 400 mg twice daily, plus gefitinib at the standard dose, is a promising treatment for patients with *EGFR*-mutated, *MET*-amplified NSCLC, who experienced disease progression while receiving EGFR-TKI treatment.[41] In a Phase Ib trial, the combination of osimertinib at the standard dose, and savolitinib at the weight-based dosing of 300 mg or 600 mg, showed encouraging antitumour activity in patients with *MET*-amplified, *EGFR* mutation-positive, advanced NSCLC, who had disease progression on a previous EGFR-TKI.[42] Based on these results, the SAVANNAH Phase II trial of osimertinib plus savolitinib for patients with *EGFR*-mutant, *MET*-amplified NSCLC, following disease progression on osimertinib, is ongoing.[43] INSIGHT 2, an international, open-label, multicentre, Phase II trial, is an ongoing study assessing the combination of tepotinib at the dose of 500 mg/day, plus osimertinib at the standard dose, in patients with *EGFR*-mutant NSCLC and acquired resistance to first-line osimertinib due to the onset of *MET*-amplification.[44]

The second most frequent mechanism, behind *MET*-amplification, of acquired resistance to first-line osimertinib is the onset of the tertiary *EGFR* C797S mutation, which occurs in exon 20 with a frequency of 7%.[45] Several further mechanisms of acquired resistance to EGFR-TKIs have been described, with the future perspectives of defining the best strategy to overcome them.[46]

At progression from third-generation EGFR-TKIs, in the presence of a nontargetable biomarker or in the absence of an identified molecular target, chemotherapy with platinum-based regimens is the appropriate strategic approach.[47,48]

FUTURE PERSPECTIVES

Several efforts are ongoing to improve the outcomes of this subgroup of patients with NSCLC, both in overcoming the acquired resistances and in defining strategies to delay and prevent the emergence of these resistances.

In this regard, a meta-analysis pooled the results of randomised trials comparing first-generation EGFR-TKI monotherapy versus the combination of the same EGFR-TKI plus chemotherapy. The results showed that the combination therapy significantly improved ORR, and prolonged PFS and OS of first-line treatment in patients with advanced NSCLC harbouring activating *EGFR* mutations, especially when chemotherapy included platinum-based doublets in concurrent administration with EGFR-TKI. No differences were observed between *EGFR* 19 deletion and L858R, probably related to the addition of chemotherapy to the EGFR-TKI. Even though an increasing incidence of adverse events was registered in the combination arm, the treatment was tolerable and clinically manageable.[49] Based on these interesting results, and the availability of third-generation osimertinib, the FLAURA-2 trial of osimertinib with or without platinum–pemetrexed regimen as first-line treatment in patients with mutated EGFR NSCLC is ongoing, with PFS as the primary endpoint.[23]

Fourth-generation allosteric EGFR-TKIs, such as EAI045, JBJ-04-125-02, BLU-945, CH7233163, TQB3804, and BBT-176, designed to target drug-resistant *EGFR* C797S and T790M mutations, are in development with *in vitro* and *in vivo* activity. These drugs are able to target contemporary common *EGFR* mutations, with T790M and C797S also appealing for an upfront approach. To date, several preclinical studies showed promising results, but no clinical data are available yet.[33]

CONCLUSION

The detection of the *EGFR* mutation status for metastatic lung adenocarcinoma and/or never-smokers is mandatory before defining the most appropriate therapy for each patient. Osimertinib remains the standard of care for the first-line treatment of patients with advanced common *EGFR* mutation-positive NSCLC Afatinib and osimertinib should be considered as the treatment of choice for uncommon *EGFR* mutations, excluding the ex20ins mutations, for which platinum-based regimen should be recommended while waiting for specific targeted inhibitors to reach the market.

The growing understanding of the mechanisms responsible of the progression, growth, and metastatic diffusion of lung cancer cells leads to a genomic profiling knowledge for the development of targeted therapies able to control and change the natural history of the disease since the first diagnosis. The development of next-generation sequencing platforms and targeted gene panels analyses may play an essential role in detecting early signals of drug resistance. In this way, there is the opportunity to switch to an alternative treatment to overcome relevant subclonal progression. However, this approach might be challenging due to the possible difficulty in reaching the tumour lesion, especially in patients with NSCLC, with the need of invasive and potentially harmful procedures. In this regard, the increasing development and optimisation of liquid biopsies, based on blood sampling, may noninvasively detect targetable genomic alterations, thus guiding the corresponding targeted therapy. Furthermore, liquid biopsy might be particularly useful in monitoring the response to treatment, detecting the onset of genetic changes as an early signal of resistance. All these efforts are first steps towards precision medicine, defined as the right drug to the right patient but also at the right moment.[50]

References

1. Citri A, Yarden Y. EGF-ERBB signalling: towards the systems level. Nat Rev Mol Cell Biol. 2006;7(7):505-16.
2. Kris MG et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. JAMA. 2014;311(19):1998-2006.
3. Shi Y et al. Molecular epidemiology of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology - mainland China subset analysis of the PIONEER study. PLoS One. 2015;10(11):e0143515.
4. Lee SY et al. Somatic mutations in epidermal growth factor receptor signaling pathway genes in non-small cell lung cancers. J Thorac Oncol. 2010;5(11):1734-40.
5. Tokumo M et al. The relationship between epidermal growth factor receptor mutations and clinicopathologic features in nonsmall cell lung cancers. Clin Cancer Res. 2005;11(3):1167-73.
6. Xu J et al. EGFR tyrosine kinase inhibitor (TKI) in patients with advanced nonsmall cell lung cancer (NSCLC) harboring uncommon EGFR mutations: a real-world study in China. Lung Cancer. 2016;96:87-92.
7. Klughammer B et al. Examining treatment outcomes with erlotinib in patients with advanced non-small cell lung cancer whose tumors harbor uncommon EGFR mutations. J Thorac Oncol. 2016;11(4):545-55.
8. Mitsudomi T et al. Mutations of the epidermal growth factor receptor gene predict prolonged survival after gefitinib treatment in patients with non-small-cell lung cancer with postoperative recurrence. J Clin Oncol. 2005;23(11):2513-20.
9. Mitsudomi T et al.; West Japan Oncology Group. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol. 2010;11(2):121-8.
10. Inoue A et al.; North-East Japan Study Group. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin–paclitaxel for chemo-naïve non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). Ann Oncol. 2013;24(1):54-9.
11. Patil VM et al. Phase III study of gefitinib or pemetrexed with carboplatin in EGFR-mutated advanced lung adenocarcinoma. ESMO Open. 2017;2(1):e000168.
12. Rosell R et al.; Spanish Lung Cancer Group in collaboration with Groupe Français de Pneumo-Cancérologie and Associazione Italiana Oncologia Toracica. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012;13(3):239-46.
13. Zhou C et al. Final overall survival results from a randomised, phase III study of erlotinib versus

chemotherapy as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer (OPTIMAL, CTONG-0802). Ann Oncol. 2015;26(9):1877-83.

14. Wu Y-L et al. First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. Ann Oncol. 2015;26(9):1883-9.
15. Shi YK et al. First-line icotinib versus cisplatin/pemetrexed plus pemetrexed maintenance therapy for patients with advanced EGFR mutation-positive lung adenocarcinoma (CONVINCE): a phase 3, open-label, randomized study. Ann Oncol. 2017;28(10):2443-50.
16. Sequist LV et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol. 2013;31(27):3327-34.
17. Wu YL et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol. 2014;15(2):213-22.
18. Paz-Ares L et al. Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial. Ann Oncol. 2017;28(2):270-7.
19. Mok TS et al. Improvement in overall survival in a randomized study that compared dacomitinib with gefitinib in patients with advanced non-small-cell lung cancer and EGFR activating mutations. J Clin Oncol. 2018;36(22):2244-50.
20. Ramalingam SS et al.; FLAURA Investigators. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. N Engl J Med. 2020;382(1):41-50.
21. Ding PN et al. Risk of treatment-related toxicities from EGFR tyrosine kinase inhibitors: a meta-analysis of clinical trials of gefitinib, erlotinib, and afatinib in advanced EGFR-mutated non-small cell lung cancer. J Thorac Oncol. 2017;12(4):633-43.
22. Camidge DR et al. Acquired resistance to TKIs in solid tumours: learning from lung cancer. Nat Rev Clin Oncol. 2014;11(8):473-81.
23. Mok TS et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med. 2017;376(7):629-40.
24. Wu Y-L et al.; ADAURA Investigators. Osimertinib in resected *EGFR*-mutated non-small-cell lung cancer. N Engl J Med. 2020;383(18):1711-23.
25. Nagasaka M et al. Beyond osimertinib: the development of third-generation EGFR tyrosine kinase inhibitors for advanced EGFR+ NSCLC. Ann Oncol. 2021;16(5):740-63.
26. Zhang Y et al. Patients with exon 19 deletion were associated with longer progression-free survival compared to those with L858R mutation after first-line EGFR-TKIs for advanced non-small cell lung cancer: a meta-analysis. PLoS One. 2014;9(9):e107161.
27. Passaro A et al. Recent advances on the role of EGFR tyrosine kinase inhibitors in the management of NSCLC with uncommon, non exon 20 Insertions, EGFR mutations. J Thorac Oncol. 2021;16(5):764-73.
28. Park K et al. Amivantamab in EGFR exon 20 insertion-mutated non-small-cell lung cancer progressing on platinum chemotherapy: initial results from the CHRYSALIS phase I study. J Clin Oncol. 2021;39(30):3391-402.
29. Markham A. Mobocertinib: first approval. Drugs. 2021; 81(17):2069-74.
30. Morgillo F et al. Mechanisms of resistance to EGFR-targeted drugs: lung cancer. ESMO Open. 2016;1(3):e000060.
31. Jackman D et al. Clinical definition of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. J Clin Oncol. 2010;28(2):357-60.
32. Gandara DR et al. Acquired resistance to targeted therapies against oncogene-driven non-small-cell lung cancer: approach to subtyping progressive disease and clinical implications. Clin Lung Cancer. 2014;15(1):1-6.
33. Rossi A, Galetta D. Systemic therapy for oligoprogression in patients with metastatic NSCLC harboring activating EGFR mutations. Cancers. 2022;14(3):832.
34. Sequist LV et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci Transl Med. 2011;3(75):75ra26.
35. Ferrer L et al. A brief report of transformation from NSCLC to SCLC: molecular and therapeutic characteristics. J Thorac Oncol. 2019;14(1):130-4.
36. Marcoux N et al. EGFR-mutant adenocarcinomas that transform to small-cell lung cancer and other neuroendocrine carcinomas: clinical outcomes. J Clin Oncol. 2019;37(4):278-85.
37. Weingertner N et al. Correlation between MET protein expression and MET gene copy number in a Caucasian cohort of non-small cell lung cancers according to the new IASLC/ATS/ERS classification. Pathology. 2015;47(4):320-8.
38. Paik PK et al. Tepotinib in non-small-cell lung cancer with MET exon 14 skipping mutations. N Engl J Med. 2020;383(10):931-43.
39. Wolf J et al.; GEOMETRY mono-1 Investigators. Capmatinib in MET exon 14-mutated or MET-amplified non-small-cell lung cancer. N Engl J Med. 2020;383(10):944-57.
40. Lu S et al. Once-daily savolitinib in Chinese patients with pulmonary sarcomatoid carcinomas and other non-small-cell lung cancers harbouring MET exon 14 skipping alterations: a multicentre, single-arm, open-label, phase 2 study. Lancet Resp. 2021;9(10):1154-64.
41. Wu YL et al. Phase Ib/II study of capmatinib (INC280) plus gefitinib after failure of endothelial growth factor receptor (EGFR) inhibitor therapy in patients with EGFR-mutated, MET factor-dysregulated non-small-cell lung cancer. J Clin Oncol. 2018;36(31):3101-9.
42. Sequist LV et al. Osimertinib plus savolitinib in patients with EGFR mutation-positive, MET-amplified, non-small-cell lung cancer after progression on EGFR tyrosine kinase inhibitors: interim results from a multicentre, open-label, phase 1b study. Lancet Oncol. 2020;21(3):373-86.
43. AstraZeneca. Osimertinib plus savolitinib in EGFRm+/MET+NSCLC following prior osimertinab (SAVANNAH). NCT03778229. https://clinicaltrials.gov/ct2/show/NCT03778229.
44. EMD Serono Research & Development Institute, Inc. A study of tepotinib plus osimertinib in osimertinib relapsed MET amplified NSCLC (INSIGHT 2). NCT03940703. https://clinicaltrials.gov/ct2/show/NCT03940703.
45. Ramalingam SS et al. Mechanisms of acquired resistance to first-line osimertinib: preliminary data from the phase III FLAURA study. Ann Oncol. 2018;29(Suppl 8):VIII740.

46. Reita D et al. Molecular mechanism of EGFR-TKI resistance in EGFR-mutated non-small cell lung cancer: application to biological diagnostic and monitoring. Cancers. 2021;13(19):4926.
47. Planchard D et al.; ESMO Guidelines Committee. Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Suppl 4):iv192-237.
48. Hanna NH et al. Therapy for stage IV non-small-cell lung cancer with driver alterations: ASCO and OH (CCO) joint guideline update. J Clin Oncol. 2021;39(9):1040-91.
49. Wu Q et al. First-generation EGFR-TKI plus chemotherapy versus EGFR-TKI alone as first-line treatment in advanced NSCLC with EGFR activating mutation: a systematic review and meta-analysis of randomized controlled trials. Front Oncol. 2021;11:598265.
50. Rossi A. Immunotherapy and NSCLC: the long and winding road. Cancers (Basel). 2020;12(9):2512.

Gastric Pouch Gastrointestinal Stromal Tumour Post-Roux-en-Y Gastric Bypass: A First Reported Case

Authors:	Wissam Dib,[1] Melissa Kyriakos Saad,[1] Georges El Hachem,[2] Bassim Sawan,[3] Elias Saikaly[1] 1. Department of General Surgery, Saint George Hospital University Medical Center, University of Balamand, Beirut, Lebanon 2. Department of Hematology and Medical Oncology, Saint George Hospital University Medical Center, University of Balamand, Beirut, Lebanon 3. Department of Histopathology, Saint George Hospital University Medical Center, University of Balamand, Beirut, Lebanon

Disclosure:	The authors have declared no conflicts of interest. A written informed consent was obtained from the patient to publish their case along with any associated radiological, histological, and intraoperative photos.
Received:	22.03.22
Accepted:	14.09.22
Keywords:	Gastric gastrointestinal stromal tumour (GIST), GIST post-gastric bypass, resection of gastric GIST.
Citation:	EMJ. 2022; DOI/10.33590/emj/10094129. https://doi.org/10.33590/emj/10094129.

Abstract

Gastric gastrointestinal stromal tumour is an extremely rare condition to occur after bariatric surgery. To the authors' knowledge, only two cases of gastric gastrointestinal stromal tumours after Roux-en-Y gastric bypass have been reported in the medical literature, both occurring in the excluded gastric remnant. Herein, the authors report the third case of gastric gastrointestinal stromal tumour post-Roux-en-Y gastric bypass, and the first case to occur in the gastric pouch, which was managed surgically by laparoscopic resection. From here, combining the observations of clinicians treating and following up patients post-bariatric surgery in an international database will be beneficial to patients, and aid in development of surveillance guidelines.

Key Points

1. Obesity is a global problem in healthcare and is growing in prevalence, with gold standard treatment being metabolic and bariatric surgery to aid weight loss.

2. Most literature on gastric gastrointestinal stromal tumours Roux-en-Y gastric bypass indicates that incidence of obesity-related cancers decreases after bariatric surgery. Only two cases have been reported in the literature and this is considered extremely rare.

3. As gastrointestinal stromal tumours after bariatric surgery are so rare, there are no guidelines; therefore, the authors note that an international database on these cases would be beneficial in producing guidelines.

INTRODUCTION

Obesity is a rising global epidemic with a growing prevalence. A well-known association between obesity and increased overall mortality has been established. In addition, obesity is firmly linked to an increased risk of cancer. Metabolic and bariatric surgery is the gold standard treatment for long-term weight loss and resolution of associated comorbidities. With this in mind, the number of patients with previous history of bariatric surgery is continuously rising.

On the other hand, the association between intentional weight reduction through bariatric or metabolic surgery and reduced cancer risk remains poorly understood, with limited knowledge and conflicting data in the medical literature. Most studies report a decrease of obesity-related cancers in patients undergoing bariatric surgery. In fact, only a few cases of gastric cancer post-bariatric surgery have been reported in the medical literature, with the majority being gastric adenocarcinomas and two cases of gastric gastrointestinal stromal tumours (GIST); however, evidence is lacking concerning the link between gastric cancer and bariatric or metabolic surgery.[1-3] From here, physicians caring for patients post-bariatric surgery should suspect malignancy in any patient who presents with vague epigastric symptoms, unexplained anaemia, gastrointestinal bleeding, and excessive weight loss. Herein, the authors report the third case of gastric GIST post-Roux-en-Y gastric bypass (RYGB) and the first gastric pouch GIST post-RYGB.

PATIENT INFORMATION

A 40-year-old male patient with a previous surgical history of RYGB 12 years ago, as treatment for morbid obesity with a BMI of 57.59 kg/m^2 (195.00 kg; 1.84 m), and a normal initial pre-operative gastroscopy, presenting with the complaint of fatigue, melena, and *de novo* weight loss of 10 kg over a 2-month period. They reported that the nadir weight achieved was 125.00 kg at 2 years after their surgery, which was maintained for 3 years. This was followed by a weight regain of 30.00 kg, from which they lost the unintentional 10.00 kg, with the current weight being 145.00 kg, for a BMI of 42.82 kg/m^2.

CLINICAL FINDINGS

Vital signs were stable and the physical exam was normal.

DIAGNOSTIC ASSESSMENT

Consequently, the patient was investigated by blood workup showing iron deficiency anaemia with a haemoglobin level of 7.5 g/dL (norm: 13.0–17.3 g/dL), haematocrit level of 29.6% (norm: 39.0–50.0%), iron level of 20 µg/dL (norm: 35–150 µg/dL), ferritin level of 2.85 µg/L (norm: 20.00–250.00 µg/L), vitamin B12 level of 363 pg/mL (norm: 191–800 pg/mL), and folic acid level of 5.66 ng/mL (norm: 5.00–20.00 ng/mL). This was followed by a gastroscopy (Figure 1), which showed a peri-anastomotic bleeding ulcer and a 5 cm round submucosal tumour in the lesser curvature of the gastric pouch, just proximal to the gastro-jejunal anastomosis. In addition, the endoscopist noted a large anastomosis and a long blind loop. Biopsies were taken from the ulcer and did not reveal any malignancy.

Then, an endoscopic ultrasound was performed (Figure 2A), revealing a 60×59 mm hypoechoic and homogeneous, gastric, subepithelial lesion with regular margins. The lesion originated from the muscularis propria layer of the gastric wall, with a clear cleavage plane separating the tumour from the remnant stomach and adjacent organs. No peri-tumoural lymph nodes were noted. Fine needle biopsy was done, revealing the presence of spindle cell tumour suggestive of GIST, mildly to moderately cellular, without evidence of mitosis, necrosis, or cellular atypia.

This was followed by a CT scan with intravenous and oral contrast (Figure 2B) confirming the

Figure 1: Endoscopic findings of a large 5 cm subepithelial tumour in the gastric pouch above the gastro-jejunal anastomosis with smooth regular borders and a bleeding anastomotic ulcer.

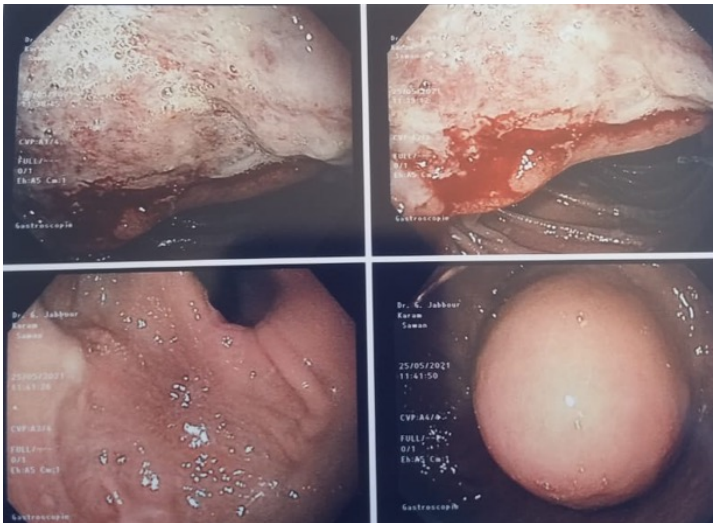
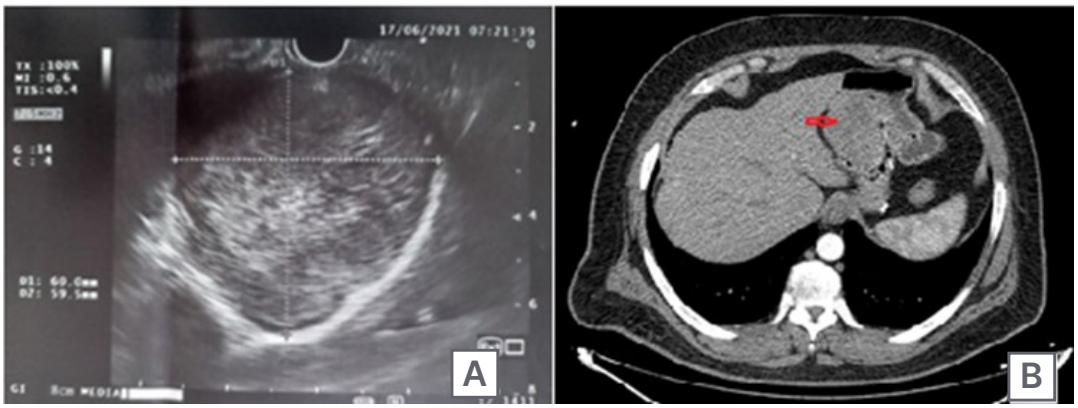


Figure 2: Endoscopic ultrasound (A) and CT scan (B) findings of the tumour.



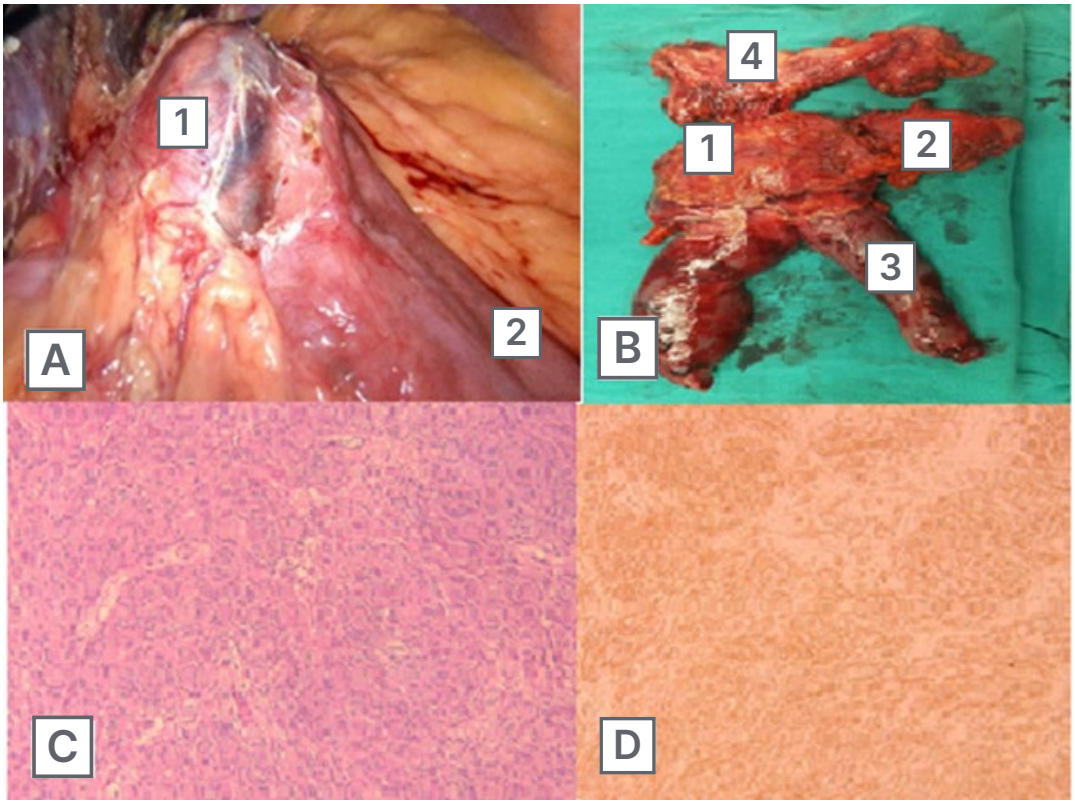
A) Endoscopic ultrasound finding of a submucosal tumour originating from the muscularis propria layer of the gastric wall, measuring 60.0×59.5 mm, with regular borders. **B)** CT-scan with intravenous and oral contrast showing the tumour (marked by the red arrow) within the gastric pouch.

presence of a 5 cm heterogeneous mass in the gastric pouch above the level of the gastro-jejunal anastomosis, associated with thickening of the lesser curvature, without contrast enhancement, lymphadenopathy, or distant metastasis. The patient was diagnosed with gastric pouch GIST post-RYGB and weight recidivism.

THERAPEUTIC INTERVENTION

Consequently, the patient was scheduled for laparoscopic resection of the gastric pouch GIST along with revisional bariatric surgery. Intra-operative findings (Figure 3A) included a large cystic-solid and hypervascular tumour around 6×6 cm in size, occupying most of the gastric pouch, extending proximally, with its epicentre on the lesser curvature of the pouch. The tumour was locally invading the anterior surface of the

Figure 3: Intra-operative findings.



A) Intra-operative findings of the tumour (1) in the gastric pouch with a relatively long jejunal candy cane (2). **B)** Post-operative specimen showing the tumour (1) in the gastric pouch (2) with adequate margins, the jejunal candy cane (3), and the remnant stomach (4).

C and **D** are representative images of the tumour. **C)** Epithelioid and spindle tumour cells arranged in fascicles stained with haematoxylin and eosin (magnification x10). **D)** Diffuse membranous and cytoplasmic staining of tumour cells with CD117 (magnification x10).

excluded stomach. Furthermore, a large gastric pouch, an abnormally long blind loop (candy cane), an alimentary limb length of 150 cm, and a biliopancreatic limb length of 100 cm were noted.

Laparoscopic en bloc resection of the gastric pouch GIST was performed, with grossly negative margin of 3 cm, incorporating the gastro-jejunal anastomosis and the excluded stomach. Refashioning of a 30 cc gastric pouch was done with a new gastro-jejunal anastomosis (Figure 3B). The post-operative course was uneventful and the patient was discharged on Day 4 after surgery with a gastrografin swallow test negative for leak and stenosis.

Final histopathological examination revealed the presence of a 5.6×5.4 cm mesenchymal neoplasm, which was comprised of epithelioid and spindle cell patterns, presenting three mitotic figures per 50 high power fields, and showing no signs of necrosis. Surgical margins were negative for malignancy. No signs of neoplastic invasions in any of the lymph nodes identified. The tumour was classified as low grade G1 and T3NoMx according to the TNM classification. Immunohistochemistry showed CD17 (+), CD34 (+), and H-caldesmon (+). Molecular studies showed absence of pathogenic variants in *PDGFRA* exon 12 and 18 in the processed specimen. Because the sample was poor at reception, c-Kit analysis could not be carried out. The above readings established the diagnosis of GIST with epithelioid and spindle cells (Figure 3C and D). A multidisciplinary decision was made to initiate adjuvant imatinib.

Table 1: Timeline.

2009	January 2021	January 2021	January 2021	January 2021	January 2022
RYGB for morbid obesity	Fatigue, anaemia, and melena	Gastroscopy showing a subepithelial tumour in gastric pouch	CT scan showing the tumour with no metastasis or lymphadenopathy EUS with biopsy confirmed the diagnosis of gastric GIST in pouch	Laparoscopic resection plus adjuvant imatinib	Disease- and symptom- free at 1-year follow-up

EUS: endoscopic ultrasound; GIST: gastrointestinal stromal tumour; RYGB: Roux-en-Y gastric bypass.

FOLLOW-UP AND OUTCOMES

Currently, 1 year post-surgery, the patient is disease-free, with no evidence of local recurrence nor distant metastasis on imaging. They report a weight loss of 28 kg (Table 1).

DISCUSSION

The first gastric bypass for treatment of morbid obesity was performed in 1966.[4] Since then, there has been a dramatic increase in the number of procedures for treatment of obesity. This was followed by the emergence of a minimally invasive approach to perform RYGB, which further escalades the utility of weight loss surgery for treatment of morbid obesity. However, bariatric and metabolic surgery is not a complication-free surgery, and the association between intentional weight reduction through bariatric or metabolic surgery and the reduced cancer risk remains poorly understood. There is limited knowledge and conflicting data in the medical literature, with most studies reporting a decrease in the risk of cancer in patients who undertook weight loss surgery. In fact, merely a few cases of gastric cancer post-bariatric surgery have been reported in the medical literature, with the majority being gastric adenocarcinomas and two cases of gastric GIST, but evidence is lacking concerning the link between gastric cancer and weight loss surgery.[1,3]

GIST is a rare pathology occurring post-weight loss surgery. Even rarer is gastric pouch GIST. In fact, to the best of the authors' knowledge, this is the first reported case of gastric pouch GIST post-RYGB. The authors believe that gastric pouch GIST and gastric GIST, in general, after bariatric surgery are a challenge to the unaware. This challenge is partly due to the rarity of this disease and also due to the wide spectrum of presenting symptoms. Having said this, there is an overlap in symptoms between gastric GIST and what can be attributed to normal complaints post-bariatric surgery. In fact, gastrointestinal bleeding is the most common complaint. In addition, patients may report abdominal pain, anaemia, and melena, as seen in this case. Moreover, patients with gastric GIST may be diagnosed incidentally in asymptomatic patients or those complaining of dysphagia, as described by de Roover et al.[5-8]

The cornerstone for treatment of gastric GIST is surgery with the aim to resect the entire tumour with intact pseudo-capsule, and with special attention not to rupture the tumour as this is directly related to poor prognosis.[9] Laparoscopic approach is as effective as the traditional open surgery, especially for tumours that are smaller than 8 cm, and this was the approach in this case.[10,11] From here, the prognosis of patients with gastric GIST is satisfactory, and the 5-year survival rate reaches 65%. Factors influencing the prognosis include age, site of tumour, mitotic index, size of tumour, and curative surgery. Furthermore, some studies show the relation between prognosis and immunohistochemistry, such as c-Kit and CD34 positivity, as a possible better prognostic factor.[12,13]

CONCLUSION

Gastric GIST post-RYGB is a rarely reported entity, and this makes its diagnosis a challenge to the unaware. Furthermore, its rarity dictates absence of universal guidelines. From here, combining the observations of clinicians treating and following up patients post-bariatric surgery in an international database will be beneficial to patients and aid in development of surveillance guidelines.

PATIENT PERSPECTIVE

The patient reports being asymptomatic with a good quality of life.

References

1. Ostlund MP et al. Risk of obesity-related cancer after obesity surgery in a population-based cohort study. Ann Surg. 2010;252(6):972-6.
2. Adams TD et al. Cancer incidence and mortality after gastric bypass surgery. Obesity (Silver Spring). 2009;17(4):796-802.
3. Orlando G et al. Gastric cancer following bariatric surgery: a review. Surg Laparosc Endosc Percutan Tech. 2014;24(5):400-5.
4. Mason EE, Ito C. Gastric bypass and obesity. Surg Clin North Am. 1967;47:1355.
5. Søreide K et al. Global epidemiology of gastrointestinal stromal tumours (GIST): a systematic review of population-based cohort studies. Cancer Epidemiol. 2016;40:39-46.
6. de Roover A et al. Report of two cases of gastric cancer after bariatric surgery: lymphoma of the bypassed stomach after Roux-en-Y gastric bypass and gastrointestinal stromal tumour (GIST) after vertical banded gastroplasty. Obes Surg. 2006;16(7):928-31.
7. Abellán I et al. Incidental gastric gastrointestinal stromal tumour (GIST) in the excluded stomach after Roux-en-Y gastric bypass: a case report and review of the literature. Surg Obes Relat Dis. 2014;10(1):e13-4.
8. Miettinen M et al. Gastrointestinal stromal tumours of the stomach: a clinicopathologic, immunohistochemical, and molecular genetics study of 1765 cases with long-term follow-up. Am J Surg Pathol. 2005;29(1):52-68.
9. Joensuu H. Gastrointestinal stromal tumour (GIST). Ann Oncol. 2016;17(Suppl 10):x280-6.
10. Karakousis GC et al. Laparoscopic versus open gastric resections for primary gastrointestinal stromal tumours (GISTs): a size-matched comparison. Ann Surg Oncol. 2011;18(6):1599-1605.
11. Huang CM et al. Can laparoscopic surgery be applied in gastric gastrointestinal stromal tumours located in unfavorable sites?: a study based on the NCCN guidelines. Medicine (Baltimore). 2017;96(14):e6535.
12. Liu X et al. Prognostic factors of primary gastrointestinal stromal tumours: a cohort study based on high-volume centers. Chin J Cancer Res. 2018;30(1):61-71
13. Rizzo FM et al. Parallelism of DOG1 expression with recurrence risk in gastrointestinal stromal tumours bearing KIT or PDGFRA mutations. BMC Cancer. 2016;16:87.

Cutaneous Mucormycosis Co-infection in a Patient with COVID-19

Authors: *Raham Rahgoshai, Peter Goldberg, Rayhaneh Rahgoshai, Shadi Zain

McGill University Health Centre, Montreal, Canada
*Correspondence to raham.rahgoshai@muhc.mcgill.ca

Disclosure: The authors have declared no conflicts of interest.

Received: 22.03.22

Accepted: 11.08.22

Keywords: Case report, co-infection, COVID-19, cutaneous mucormycosis, dermatology.

Citation: EMJ. 2022; DOI/10.33590/emj/10098860. https://doi.org/10.33590/emj/10098860

Abstract

Mucormycosis is a life-threatening fungal infection usually seen in patients who are immunocompromised; however, to date, it has been rarely described in patients with COVID-19, although more recently, reports from India have described an increased incidence of these infections. This report describes a patient with COVID-19 who developed a fatal dermatologic mucormycosis infection. The patient, whose history included therapy for diffuse large B-cell lymphoma, had an incidental positive screening test for COVID-19 in February 2021 after exposure to a family member who had tested positive. They then presented to the emergency room a few weeks later exhibiting progressive dyspnoea and fever. A CT scan of the chest revealed ground glass opacities. They were intubated approximately 2 weeks later and their course was complicated by renal failure, for which continuous renal replacement therapy was started, and by refractory hypoxaemic and hypercapnic respiratory failure in which they were placed on venovenous extracorporeal membrane oxygenation. During their course in the intensive care unit (ICU), they developed a right thigh haematoma, thought to be related to the previous insertion of a femoral arterial pressure monitoring catheter. Several days before the patient's death, the wound noted to be covered by a brown-black eschar was cultured on April 30 and returned positive for *Rhizopus oryzae* and *Staphylococcus epidermidis* on May 5. The patient was immediately started on liposomal amphotericin and posaconazole and taken urgently taken to the operating room for a radical debridement. Unfortunately, their post-operative course was characterised by fulminant haemodynamic collapse and multiple system organ failure, from which the patient died.

Key Points

1. The authors examine the case of a rare co-infection between mucormycosis, a life-threatening fungal infection, and COVID-19 in a 54-year-old male.

2. Invasive fungal infection such as mucormycosis often presents in one of four clinical syndromes, which affect the lungs, skin, sinuses, or presents as disseminated disease.

3. Cutaneous mucormycosis in patients with COVID-19 has a significant mortality rate, requiring swift diagnosis and immediate treatment.

CASE REPORT

A 54-year-old male tested positive in late February on a screening COVID-19 test performed after a family member's test had become positive. A few weeks later, they presented to the emergency room at a different hospital centre with shortness of breath and fever. Their oxygen saturation in room air was 63%. A CT scan of the chest confirmed bilateral ground glass opacities with intralobular and interlobular septal thickening, predominantly in the lung bases. They were transferred to the intensive care unit (ICU), where they were intubated several days later for worsening respiratory failure.

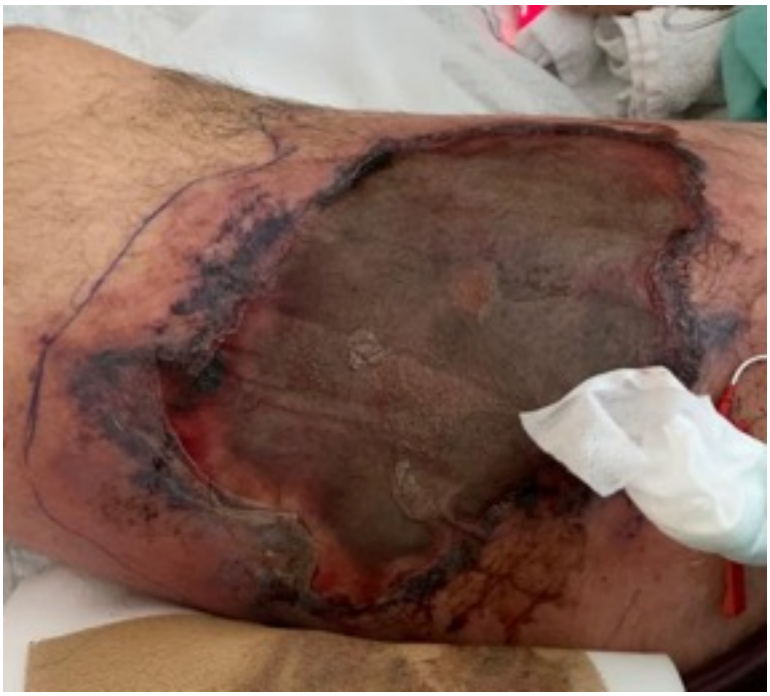
The patient had been diagnosed with follicular lymphoma in 2015, which later that year had transformed into diffuse large B-cell lymphoma. The patient subsequently underwent several courses of chemotherapy in 2018–19, including a rituximab-cyclophosphamide-hydroxydaunorubicin-oncovin-prednisone (R-CHOP) regimen; rituximab-gemcitabine-dexamethasone-cisplatin (R-GDP) chemotherapy; polatuzumab vedotin; and finally chimeric antigen receptor T-cell (CAR-T) therapy, the latter in August 2020. A PET scan in 2020, however, demonstrated an excellent response, albeit with some residual foci in the left axilla and right thigh. Three months later, a follow-up PET scan showed a slight progression of the disease in the right thigh.The patient also had laryngeal cancer, which had been treated with radiotherapy in 2012.

Therapy in the ICU at the referring center included empiric therapy with piperacillin plus tazobactam, azithromycin, remdesivir, and dexamethason. Additionally, trimethoprim plus sulfamethoxazole, later switched to atovaquone and primaquine plus clindamycin, had been introduced given concerns over the possibility of *Pneumocystis jiroveci* pneumonia. Intravenous immunoglobulin therapy was also administered given concerns over B-cell dysfunction consequent to the CAR-T therapy.

The patient was transferred to the authors' centre for treatment of their worsening respiratory failure, and was subsequently placed on venovenous extracorporeal membrane oxygenation in early April. Cannulas were inserted in the right internal jugular and left femoral veins. An arterial pressure monitoring line was inserted into the right femoral artery from which the patient bled, developing a visible superficial haematoma on the right thigh, approximately 20 cm by 12 cm. A CT scan of the right thigh on April 28 revealed ill-defined fat stranding of the subcutaneous tissues without any evidence of either discreet collections or gas. The patient's condition stabilised but the wound, covered by a brown-black eschar, failed to heal. A culture of the wound, taken on April 30, was reported on May 5 to be growing *Rhizopus oryzae* and *Staphylococcus epidermidis*.

The patient was immediately started on liposomal amphotericin and then taken to the operating room that evening with a diagnosis of tissue necrosis secondary to mucormycosis (Figure 1). A diagnosis suspected on visual inspection; however, when a radical debridement of the right thigh was performed diagnosis was confirmed. Unfortunately, that procedure was followed soon thereafter by distributive haemodynamic collapse requiring very large doses of vasopressors and inotropes. Posaconazole was added, but the patient ultimately died from multiple system organ failure.

Figure 1: Cutaneous mucormycosis infection, 20 cm by 12 cm wound on right thigh of a COVID-19 positive 54-year-old male with cutaneous mucormycosis co-infection 3 months following ICU admission.



DISCUSSION

While opportunistic fungal infections, primarily *Aspergillus* superinfection of the lungs,[1] have emerged as a growing clinical problem in patients with COVID-19, mucormycosis remains uncommon in this patient population, albeit a growing concern.[2,3]

Mucormycosis refers to the invasive fungal infection by saprophytic environmental fungi most usually, as in this case, by *Rhizopus* although other related fungi such as *Mucor* and *Cunninghamella* have also been identified. Such invasive fungal infections usually present in one of four clinical syndromes involving the sinuses, the lungs, the skin, and as disseminated disease, although gastrointestinal tract involvement has also been reported.[4,5] Usually cited risk factors for these infections include uncontrolled diabetes, haematologic malignancies, and immune-incompetence. This includes patients with both solid and haematologic transplants, those receiving immunocompromising medications such as systemic steroids, and those patients exposed to potential nosocomial sources, in particular bandages and intravascular devices. Certain studies have linked specific risk factors with a particular clinical presentation.[5] The four cornerstones of therapy include: rapid diagnosis which presupposes a high index of suspicion; reversal of underlying predisposing factors, if possible; appropriate antifungal medication; and surgical debridement, the latter deemed necessary given the propensity of this organism for angio-invasion, resulting in necrosis and poor drug penetration into devitalised tissues.[2,4] Mortality is high, ranging from 30–50%, with increased survival associated with a longer duration of antifungal therapy and combined medical-surgical treatment.[2,4,5]

Mucormycosis, specifically in patients with COVID-19 infections, is still relatively uncommon, but is subject to an increasing number of clinical reports.[2,3] Most recently, in addition to European countries,[6] it has been reported that patients with COVID-19 in India are presenting primarily with rhino-orbital or rhino-orbital-cerebral infections, but reports of life-threatening infections of the skin by this fungus in the patient population remain rare. In their report, Khatri et al.[7] described a heart transplant patient who, after developing COVID-19, died after contracting

cutaneous mucormycosis. In their review of the literature, they identified an additional seven cases of mucormycotic superinfection in patients with COVID-19, none of whom had cutaneous mucormycosis, but all of whom died.[7]

This patient did not suffer from diabetes. In fact, their blood glucose was relatively well controlled between 5.5–7.8 mmol/L for most of their stay in the ICU. However, it must be recalled that the haematoma had been related to the insertion of an arterial catheter, an intravascular device, identified as a risk factor for this infection.

However, the patient likely did suffer from a significant level of immune incompetence. Firstly, COVID-19 infection itself has been linked to immune suppression.[8] Although they never received tocilizumab, they did receive steroids as a part of their anti-COVID-19 treatment. Parenthetically, in this regard, PCR of the patient's lower respiratory tract secretions continued to be positive for COVID-19 throughout the entire 70-day course of illness. The authors are unable to comment on the status of the patient's underlying malignancy; however, it is a possible contribution to their impaired immune status based on the PET scan findings in 2020 that showed increased right thigh activity. Although the patient had received significant immunosuppressive chemotherapy during 2019, the authors believe it unlikely that the immunosuppression resulting from those treatments played a significant role so long after their administration.

However, this patient had received CAR-T therapy in August 2020, approximately 7 months prior to the onset of this opportunistic fungal infection. CAR-T therapy is a relatively new immune effector cell therapy used primarily in refractory or relapsed haematologic malignancies such as in diffuse large B-cell lymphoma, similar to this patient's case. B-cell aplasia is usually a delayed complication of this therapy and is reported to persist for as long as 3 years following therapy.[9] Given the relative newness of this therapy, the risks of delayed infections have yet to be clearly elucidated; however, recent studies have pointed to several risk factors including the incidence of cytokine release syndrome immediately accompanying CAR-T therapy, the presence or absence of haematopoietic transplantation, the type of accompanying chemotherapeutic agents, and the persistence of hypogammaglobulinaemia. As noted above, this patient had received intravenous immunoglobulins during their most recent hospitalisation. One study cited the cumulative incidence of infections at 1 year following CAR-T therapy to be 63% with bacterial infections being most frequent (57%); viral infections(45%); and fungal infections (4%) being less frequent.[9]

CONCLUSION

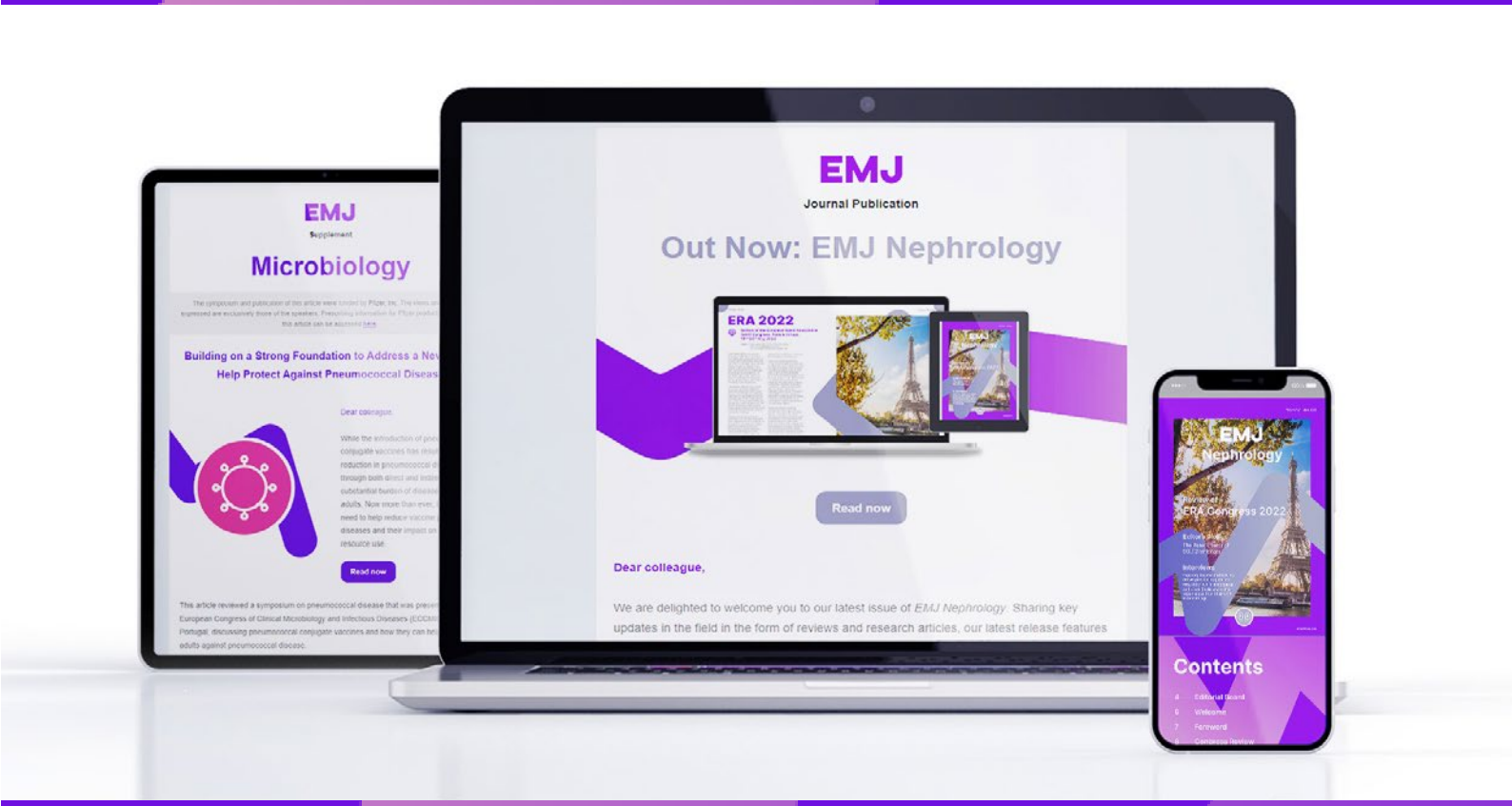
Although still uncommon, cutaneous mucormycosis in patients with COVID-19 is a highly serious condition with significant mortality. As such, a high index of suspicion combined with a rapid diagnosis is essential. And when diagnosed, immediate surgical debridement and appropriate anti-fungal medications are crucial.

The authors certify that they have obtained patient's substitute decision maker's (SDM) consent, as patient passed away. The SDM gave consent for the images and other clinical information to be reported in the journal. The SDM understands that the patient's name and initials will not be published, and due efforts will be made to conceal their identity.

References

1. Koehler P et al. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. Lancet Infect Dis. 2021;21(6):e149-62.
2. Singh AK et al. Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. Diabetes Metab Syndr. 2021;15(4):102146.
3. John TM et al. When uncontrolled diabetes mellitus and severe COVID-19 converge: the perfect storm for mucormycosis. J Fungi (Basel). 2021;7(4):298.
4. Patel A et al. A multicentre observational study on the epidemiology, risk factors, management, and outcomes of mucormycosis in India. Clin Microbiol Infect. 2020;DOI:10.1016/j.cmi.2019.11.021.
5. Jeong W et al. The epidemiology and clinical manifestation of mucormycosis: a systematic review and meta-analysis of case reports. Clin Microbiol Infect. 2019;25(1):26-34.

6. Drago F et al. Rhino-cerebral and cutaneous zygomycosis: an increasingly emerging life-threating infection. Dermatol Ther. 2020;33(6):e14379.
7. Khatri A et al. Mucormycosis after coronavirus disease 2019 infection in a heart transplant recipient - case report and review of the literature. J Mycol Med. 2021;31(2):101125.
8. Remy KE et al. Severe Immunosuppression and not a cytokine storm characterizes COVID-19 infection. JCI Insight. 2020;5(17):e140329.
9. Gutierrez C et al. Management of the critically ill adult chimeric antigen receptor-T cell therapy patient: a critical care perspective. Crit Care Med. 2018;46(9):1402-10.



Receive our free newsletters and alerts

Get the latest updates on all our upcoming journals and receive first-class insights into ground-breaking news and advancements in medicine across multiple therapeutic areas.

Join our mailing list

www.emjreviews.com

EMJ