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EAN Virtual 2021

EDITOR'S PICK

A Successful Treatment of Chronic Migraine with Hyperbaric Oxygen Therapy

INTERVIEWS

Interviews with Sergio Baranzini, Kristian Steen Frederiksen, and Riccardo Soffietti

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Editorial Board

VIEW IN FULL ←

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.

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EMJ Neurology 9.1

Welcome

Dear Readers,

Welcome to the latest issue of *EMJ Neurology*, an online journal that outlines the latest important progress in this field. With the European Academy of Neurology (EAN) hosting its 7th annual congress in the midst of the COVID-19 pandemic, it was a pleasure to attend and share in the fully-virtual EAN 2021. Enclosed within this eJournal are the most recent developments in neurology, in the form of peer-reviewed articles, and exclusive interviews with leading specialists in the field, alongside our congress review highlights from EAN Virtual 2021.

In this issue, readers can expect summaries of the key content delivered at EAN 2021, as well as abstracts written by the presenters themselves, ranging in theme from MRI assessment of cerebellar damage in multiple sclerosis to connectivity changes in the pons of patients with migraine, among other topics. Also included are feature articles sharing insights from the most significant congress sessions, of which there were more than 200, contributed to by close to 12,000 individuals.

Inside *EMJ Neurology* are a host of innovative peer-reviewed articles discussing the most recent advances in this sector, such as Becerra et al. investigating Turner syndrome and Craniosynostosis, and an intriguing report by Arriaga Rocha et al. demonstrating subacute combined degeneration as a manifestation of pernicious anaemia.

For this issue, Sergio Baranzini and Kristian Steen Frederiksen shared with us what has motivated them to conduct their respective research works, some of their career highlights, and which emerging topics to watch out for in the field in their interviews with EMJ. We also leapt at the opportunity to speak with Riccardo Soffietti, Chair of the Education Committee for EAN, to discuss his role and influence within EAN, how the event has adapted to virtual, the impact the congress has on the community, and recent significant advances in neurology.

Without the contributions from the Editorial Board, authors, peer-reviewers, interviewees, and Editorial team it would not be possible to produce such high-quality content. I would like to express my gratitude to all of these groups as I turn finally to you, the readers, for your loyalty, as we continue to strive towards being the go-to place for healthcare professionals. We hope you enjoy this latest issue of *EMJ Neurology.*

Spencer Gore

Chief Executive Officer, EMG-Health

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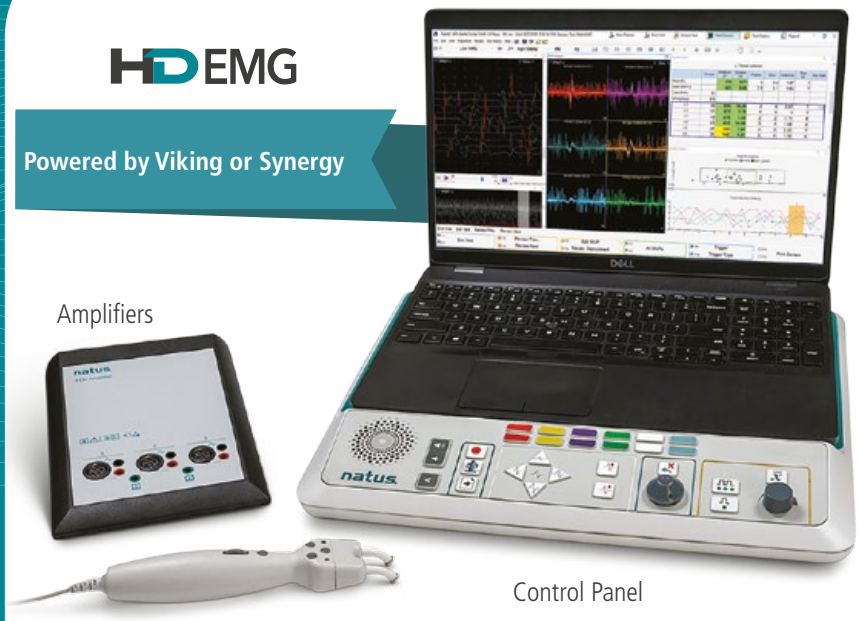

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Foreword

Dear Friends and Colleagues,

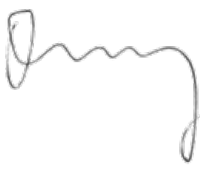
I am delighted to welcome you to the 2021 issue of *EMJ Neurology*, covering the latest updates from European Academy of Neurology (EAN) 2021, alongside a series of key articles focussing on current topics in neurology.

EAN 2021, taking place virtually, covered a plethora of topics presented by the top leaders in the field, with a plenary session focusing on precision neurology. Covering different aspects of neurology, the congress once again brought together the neurology community across Europe in a highly engaging programme. With COVID-19 having an ongoing effect on both organisational aspects and neurology practice, the message ringing clearly from the congress was that the neurology community in Europe has built a strong resilience for approaching clinical practice at this challenging time.

In our congress review for this issue, you will be able to catch up on the highlights and stories from EAN 2021. You will also be able to read an interview with Riccardo Soffietti, Chair of the Education Committee at EAN. The issue also contains summaries of selected abstracts presented at EAN 2021, alongside coverage of a fascinating congress session on chrononeurology.

For my Editor's Pick in this year's issue, I have selected an article by Shafee et al. where the authors describe treating a patient who presented with migraine with hyperbaric oxygen. This case report highlights hyperbaric oxygen treatment as a potential treatment path for analgesic-resistant migraine.

I would like to take this opportunity to thank everyone who has participated in bringing this issue together, and I hope that it makes an enjoyable and engaging read. I look forward to seeing you in person for next year's EAN Congress.



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Congress Review

Review of European Academy of Neurology (EAN) Virtual 2021

Location: EAN 2021

Date: 19th–22nd June 2021

Citation: EMJ Neurol. 2021;9[1]:13-20. Congress Review.

VIENNA was the virtual home of the 7th Congress of the European Academy of Neurology (EAN), taking place from 19th to 22nd June. In what is the second year in a virtual setting, Claudio Bassetti, President of the EAN, welcomed the attendees by highlighting the vision of the EAN to be the voice of neurology in Europe, with its mission to reduce the burden of neurological and brain diseases. Bassetti highlighted the impact of neurological conditions as the third most common cause of death and disability in Europe.

In his introductory remarks on COVID-19, Bassetti highlighted the high variability in the levels of care and vaccination in countries around the world, and emphasised the importance of collaboration among partners and the importance of encouraging resilience and making care people-centric. Bassetti also highlighted the importance of digitalisation and data sharing as key elements in fighting COVID-19. "We have learnt that the health, social, [and] economic structures are interdependent and that these systems must work in a dynamic and systematic approach to solve the problem," Bassetti outlined when discussing the lessons learnt from the COVID-19 pandemic.

It was exciting to hear about the activities of the EAN, especially the EAN Science School, which is devoted to bridging the gap between basic science and clinical medicine. The first School, taking place in March 2021, focused on a number of topics including immune neurological disorders, stroke, and epilepsy. Bassetti also highlighted the neuro-COVID-19 research initiative comprising a group of people from 34 sites collecting data to shed light on manifestations and complications of COVID-19. It is worth mentioning that the EAN has published an impressive set of data since it started: 107 guidelines, with 7 very new guidelines and 22 more in the pipeline.

"This is only the beginning of finding treatments for Alzheimer's Disease"

This year's EAN virtual platform introduced a live TV channel, live interactive sessions, networking areas, translation in Spanish and Russian, and many sessions around the clock with partners outside Europe, e.g., the Academies of Neurology of Brazil and India. This year's plenary session covered the overarching theme of precision neurology, and the President's Symposium covered the future of sleep medicine. With almost 12,000 attendees taking part and a high number of presented abstracts, the congress offered a plethora of highly engaging sessions. In this issue of *EMJ Neurology* we have covered a session on chrononeurology and rhythmicity in primary headache disorders.

The viewers of the opening ceremony also had the pleasure of watching the opening lecture, given by Jürgen Knoblich, Director of the Institute of Molecular Biotechnology, Vienna, Austria, who introduced the concept of cerebral organoids and how development of the human brain can be modelled in 3D cell cultures, giving an insight into potential future practices of neurology.

Like every other year, the opening ceremony was not complete without the honorary membership awards. Günther Deuschl, Professor of Neurology, Christian-Albrechts University Kiel, Germany, was the first recipient; among his numerous achievements, Deuschl is the founding president of the EAN, author of over 700 original publications, and among the top 1% of scientists worldwide. Bassetti hailed Deuschl as a pioneer in diagnostic and pathophysiological studies on tremor, who changed the way we look at deep brain stimulation in Parkinson's disease. Phillip Scheltens, Professor of Cognitive Neurology and Director of Alzheimer Centre, VU University Medical Centre Amsterdam, the Netherlands, was the second recipient, in recognition of his work on dementia and Alzheimer's disease and particularly for his work on early biomarkers of Alzheimer's disease. Upon acceptance of his award and reflecting on the evolution of the field from barely being an area of neurology to the first approved treatment for Alzheimer's disease, Scheltens expressed his belief that "This is only the beginning of finding treatments for Alzheimer's disease."

Plans are already in place for the 8th EAN Congress in 2022, which will again take place in Vienna. The plans for next year's Presidential Symposium have already been made, with speakers from Sweden, Austria, the UK, and USA already having been confirmed. The key theme of next year's congress will be translating evidence into practice, with a plenary symposium on improving lives and reducing disease burden. ■

EAN 2021 REVIEWED →

Headache Highlights from EAN 2021 Presentations

"In terms of monoclonal antibody therapy, Goadsby summarised the 5-year data for erenumab."

ON DAY 4 of this year's EAN 2021, Peter Goadsby, Professor of Neurology, King's College London, UK, summarised highlights from the headache presentations, with a focus on the variety of new preventative and acute migraine therapies.

Goadsby drew the audience's attention to a randomised, double-blind, placebo-controlled study designed to assess the efficacy and consistency of lasmiditan over four migraine attacks. Patients were randomised to one of three treatment groups: lasmiditan 200 mg, lasmiditan 100 mg, or a control group that received placebo for three attacks and lasmiditan 50 mg for either the third or fourth attack. The incidence of treatment-related adverse events was highest during the first attack. The most common adverse events included dizziness, paresthesia, and fatigue, which were typically mild or moderate in severity. In addition, both of the primary endpoints (pain freedom at 2 hours [first attack] and pain freedom at 2 hours in at least two of three migraine attacks) were met for lasmiditan. Similarly, all gated secondary endpoints, such as pain relief, disability freedom, and sustained pain freedom, were met. Overall, these results indicate the efficacy of lasmiditan.

In terms of monoclonal antibody therapy, Goadsby summarised the 5-year data for erenumab. Three hundred and eighty-three patients initially treated in a placebo-controlled trial were entered into an open-label extension phase. At 5 years, there were 214 patients who had completed the study. In total, 71% of patients reported a ≥50% reduction in mean monthly migraine days, 47% of patients reported a ≥75% reduction, and 36% of patients reported a ≥100% reduction. Eptinezumab, a calcitonin gene-related peptide monoclonal antibody, has also been shown to effectively prevent migraines. Patients were randomly assigned to receive either eptinezumab (n=238; 100 mg administered intravenously) or placebo (n=242) for treatment of an acute attack. At 2 hours after infusion, headache pain freedom was achieved by 23.5% of patients receiving eptinezumab and 12.0% of patients given the placebo (p=0.0009). Furthermore, the absence of most bothersome symptoms was achieved by 55.0% of eptinezumab-treated individuals and 35.8% of placebo patients (p=0.0001).

In conclusion, Goadsby emphasised that this was an exciting time to be a headache specialist because of the recent advances in safe and effective migraine treatment. ■

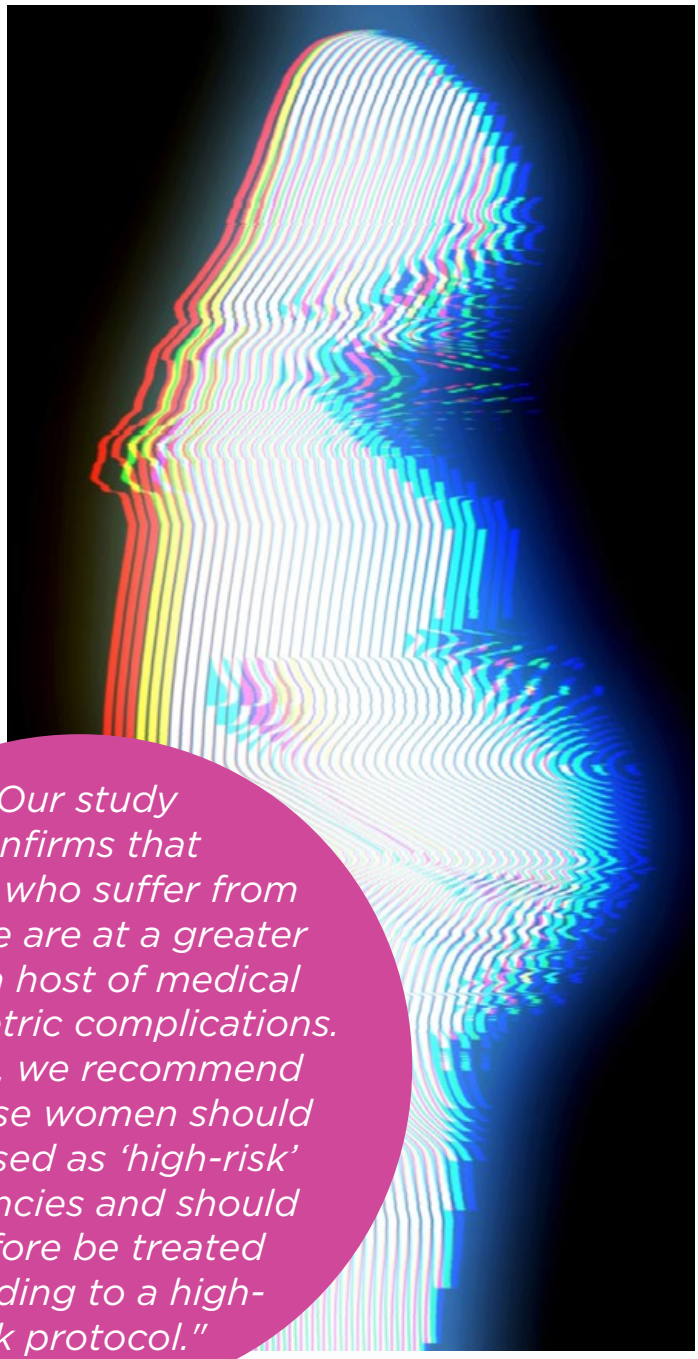
Migraine in Pregnancy at High Risk of Complications

CONCERNING the development of obstetric and post-partum complications, research in Israel led by Nirit Lev, shared at EAN 2021, has found that pregnant women who experience migraines are at increased health risk. Affecting mostly individuals of reproductive age, and one of the most prevalent disabling neurological disorders worldwide, the study aimed to evaluate the characteristics of this relationship and identify medical needs to direct action.

Between 2014 and 2020, the study analysed the pregnancies of 145,102 females, investigating mode of delivery, medical and obstetric complications, and the use of medication throughout. Within this population, 12,222 experienced migraine, of which 1,576 were migraine with aura. Findings included increased risk scores for pregnant migraine patients relating to gestational diagnosis of diabetes, hyperlipidaemia, and blood clot. Higher rates of epidural anaesthesia were also noted during the labour of females with migraine; however, this category was not particularly at risk of assisted delivery.

Lev commented: "Our study confirms that women who suffer from migraine are at a greater risk of a host of medical and obstetric complications. As such, we recommend that these women should be classed as 'high-risk' pregnancies and should therefore be treated according to a high-risk protocol," drawing these conclusions based on their data, which highlight a 6.9% increased risk of admittance to 'high-risk' departments in those with migraine, and 8.7% in those with both migraine and aura.

The main action point this study hopes to convey, and provoke future action upon, is a provision of special monitoring and care throughout pregnancy in migraine-affected individuals; in the same way as would take place in those affected by diabetes, epilepsy, or high-blood pressure. In addition to this, "Migraine sufferers were also found to have a greater risk of developing depression during their pregnancy and after giving birth," explained Levi, recommending a focus for any upcoming long-term initiatives. "As a result, they should also be offered a neurological consultation during pregnancy and adequate follow-up support after giving birth." Future studies should build on these important conclusions, and also incorporate observation of the hormonal changes related to menstruation, menopause, and childbirth exhibiting effects to worsen migraine activity. ■



"Our study confirms that women who suffer from migraine are at a greater risk of a host of medical and obstetric complications. As such, we recommend that these women should be classed as 'high-risk' pregnancies and should therefore be treated according to a high-risk protocol."

Treating Fatigue and Other Conditions in Multiple Sclerosis

FATIGUE is one of the most common yet understudied symptoms in multiple sclerosis (MS). Christian Enzinger from the EAN Organising Committee shared the presentations and studies he found most inspiring relating to fatigue and other conditions in MS at EAN 2021.

A new paper aimed to measure the impacts of fatigue in patients with MS using a novel disease-specific scale called FSIQ-RMS. The study is still in progress, but initial findings show that fatigue is one of the most reported symptoms that cause impactful disruption on a day-to-day basis in patients with MS. Thus far, the results demonstrate that FSIQ-RMS helps with improving understanding and management of fatigue. Enzinger expressed his enthusiasm for the promising results and believes this is an area that needs further research.

Another paper showed a unique approach in efforts to improve fatigue using bright light therapy (BLT) in a randomised controlled trial. BLT has been known to improve fatigue in other conditions such as depression. BLT is a fascinating alternative to medication as benefits include affordability and little to no side effects. The results showed that BLT had a placebo effect and improved the cognitive aspect of fatigue.

In another study, a team assessed work productivity and activity impairment (WPAI) in patients with relapsing–remitting MS treated with ocrelizumab. WPAI scores were recorded, and the results showed that there was a significant improvement in WPAI, which was maintained over 2 years. There was also a positive correlation between this change in scores and the reduction of the physical and psychological impact of MS.

The speaker briefly described a handful of other MS studies where objective measures of upper limb function and clinically isolated syndrome were suggestive of MS. Finally, he examined genetic differences in MS. One study included MRI results that showed brain volume differences in BDNF Val66Met polymorphism carriers compared to wild-type individuals. These structural differences were significantly associated with function and performance.

Enzinger concluded that there are many interesting studies in MS and young neurologists share in an important and distinctive approach to treating symptoms associated with MS. He noted that some of these studies had a small sample size but overall provided a great foundation for the future of treating fatigue and corresponding symptoms of MS. ■

"Initial findings show that fatigue is one of the most reported symptoms that cause impactful disruption on a day-to-day basis in patients with MS."

The Road So Far in Various Neurodegenerative Diseases

APPRAISING the latest updates in neurodegenerative diseases, Elisabeth Stögmann provided insight at EAN 2021 for current practice and the direction in which neurological treatment is travelling.

Stögmann described U.S. Food and Drug Administration (FDA) approval of a drug for Alzheimer's disease (AD) a "seismic event for our field," praising the potential for a treatment of this nature whilst recognising that approval is still required from the European Medicines Agency (EMA). The past decade was described as a critical period in advancing diagnosis of dementia and more specifically AD, during which findings from genetic studies have suggested optimum treatment is administered before the onset of symptoms. Going forwards, reading into subtle changes in cognition is recommended as a focal point.

Specific cognitive deficits in spatial memory, orientation, and navigation were discussed as early signs of preclinical AD, and could be used in the future as pre-emptive biomarkers for neurological disorders. Real progress has been made in this field over the last 5 years, such as in Henrik Zetterberg's study of the diagnostic accuracy of fluid biomarkers; highlighting the highest AD intensities can be reflected by faster decline in cerebrospinal fluid (CSF) dynamics. Neurofilament light CSF seems to be a better marker for neurodegeneration; with increased presence across a host of diseases, it could be a helpful marker in monitoring progression, particularly for patients with mild cognitive impairment. Both of these tie into the Amyloid/Tau/Neurodegeneration (ATN) classification system, briefly mentioned as an unbiased classification scheme for AD biomarkers.

"Specific cognitive deficits in spatial memory, orientation, and navigation were discussed as early signs of preclinical AD, and could be used in the future as pre-emptive biomarkers for neurological disorders."

Plasma biomarkers under investigation by Femke Bouwman were presented, including plasma amyloid, serum p-Tau, neurofilament light, and glial fibrillary acidic protein. p-Tau181, and particularly p-Tau217, were clearly elevated in AD, highlighting their potential as prognostic markers. Plasma biomarkers presented good accuracy; although not as strong as CSF, obtaining blood samples is more patient-friendly and practical. Future studies may guide plasma biomarker use for patient selection for therapies and could prove helpful for general population screening and offering a personalised medicine approach.

Recent developments in genetic testing have involved a shift from single-gene testing to a panel method; this requires careful patient consultation and a long waiting period before receiving results. There is much work to be done in this area; when delivering results, the discovery of other genetic predispositions and mutations, aside from only AD, must be explained to the patient. There is limited ability to assess expansion genes at present, and there is regular discovery of variants with unknown significance that cannot yet be explained.

Bringing the discussion to a close, and answering the question: 'Why diagnose familial forms of dementia?' Stögmann described participation in well-designed clinical trials as having the opportunity to provide support, information, and treatment to patients. This will promote understanding of neurodegenerative diseases and guide future research, helping to shape initiatives such as preimplantation of genetic diagnosis for family planning and other longitudinal generation-based therapies. ■

COVID-19 Leads to Significant Cognitive Disturbances and Behavioural Problems

COVID-19 took the world by surprise in late 2019 as countries all over the globe entered strict lockdowns and curfews to prevent the spread of the virus. Since then, researchers continue to better understand how COVID-19 works and new symptoms continue to come to light. Surprisingly, it is not only the respiratory system that is severely affected by this contagious disease; recent studies shared at EAN 2021 show that the brain is also severely affected in both physiological and psychological ways, including post-traumatic stress disorder, memory issues, and brain stem damage.

A new study by Massimo Filippi, Scientific Institute and University Vita-Salute San Raffaele, Milan, Italy, explored the cognitive disturbances and psychopathological symptoms in a cohort of patients with COVID-19 at different phases: 2 months and 10 months. The researchers recruited 49 patients aged between 40 and 75 years; these individuals had to meet set criteria in order to be included such as hospital admission with confirmed diagnosis of COVID-19, objective cognitive disturbances, and MRI consent. Filippi and their team examined white matter and grey matter MRI changes in patients and performed correlations between neurological scores and brain features to obtain the results in this study.

At the 2-month (sub-acute) phase, >50% of patients showed cognitive disturbances. One of the biggest of these issues, seen in 16% of patients, was executive dysfunction including problem-solving, planning, and attention. Other disturbances affected spatial awareness and memory. A large percentage had a combination of these cognitive impairments. The study also showed that >30% of patients had mental health issues including PTSD and depression. Surprisingly, low performance in the memory test was linked to higher levels of white matter changes in the brain, while low performance in information processing was related to higher severity of respiratory symptoms.

Further down the line at the 10-month follow-up, the results showed a decrease in cognitive disturbances from 53% to 36%. However, there was very little change in PTSD and depression in patients who had these symptoms at the sub-acute phase. The latest research confirms that COVID-19 leads to significant cognitive disturbances and behavioural problems. Larger sample sizes and longer duration of follow-up could help answer how long-term these neurological impairments from COVID-19 might be. ■

"At the 2-month (sub-acute) phase, >50% of patients showed cognitive disturbances."

The Mozart Effect in Epilepsy

ACOUSTIC qualities-based analysis of stereoelectroencephalography (SEEG) and the benefits of Mozart's music in patients diagnosed with epilepsy was one of the highlights of EAN 2021, presented by Ivan Rektor, Masaryk University, Brno, Czech Republic, on 19th June 2021.

The Mozart effect is the influence of Mozart's Sonata for two pianos in D major K. 448 on brain activity in the process of spatial learning. Rektor started the presentation by sharing previous research that stated that Mozart's sonata enhanced spatio-temporal reasoning by activating areas in the brain that were task-relevant. Rektor played Mozart's sonata in the background during the session and emphasised the repetition in melody played an important role in brain activity when listened to by patients diagnosed with epilepsy. Dastgheib et al. proposed that long-term listening could produce new pathways in the brain, which may alter patterns exhibited by an epileptic brain and release different neurotransmitters like dopamine in the brain.

"...long-term listening could produce new pathways in the brain, which may alter patterns exhibited by an epileptic brain"

A meta-analysis of 12 publications also showed the reduction of epileptiform discharges (ED) in 84% of patients who were listening to the Mozart composition. However, this methodology is controversial and further research is required to apply to clinical practice.

Rektor then discussed his study carried out on 18 patients diagnosed with epilepsy with implanted SEEG to observe ED. The aim of the research was to compare the impact of listening to Mozart and Haydn Symphonie No. 94, by observing the spikes in ED to reveal differences leading to the effects on epileptiform activity.

Results showed that listening to Haydn's music reduced EDs only in the female participants but increased in the male participants. Furthermore, the effect on the ED depended on the acoustic characteristics (rhythm, dynamics, and timbre) of the compositions. The males were more sensitive to dissonance and high-frequency content, whilst the female participants were sensitive to the energy of the composition. In conclusion, the SEEG recordings revealed overall suppressed ED following exposure to classical music. An anti-epileptic effect was observed after listening to Mozart's sonata; however, the suppression of ED is different in males versus females due to acoustic characteristics of the compositions. ■

Rhythmicity in Primary Headache Disorders

Evgenia Koutsouki
Editor

Citation: EMJ Neurol. 2021;9[1]:21-23.

AMONG the many engaging sessions in this year's European Academy of Neurology (EAN) Virtual 2021 was the session on chrononeurology discussing rhythmicity in neurological disorders. In a presentation given by Christoph Schankin, Bern University Hospital, Switzerland, the main topic addressed was rhythmicity in headache disorders.

CHRONOBIOLOGY AND RHYTHMICITY IN THE HUMAN BODY

In his introductory remarks, Schankin explained the concept of chronobiology, which studies biological periodic phenomena that occur in cycles, giving rhythm to processes. Examples of such cycles that are adapted by environmental stimuli include the circadian rhythm, which is a 24-hour-long circle, and similarly, circaseptan cycles, which are cultural and based on the 7-day week, which includes weekends and work days. Another type of rhythm is the natural phenomenon of the moon phase lasting 28 days, which is important for the hormonal cycle in females, and finally the circannual rhythm, which refers to the year, the seasons, the length of the daytime, and temperatures.

Schankin explained that the circadian rhythm is present at a single-cell level and has a number of transcriptional products, among which are the CLOCK protein, Period 1 and 2, and Casein Kinase 1, which influence each other. The body organs formed by cells act as a single circadian unit or peripheral clock, each of which runs independently and is synchronised by a central pacemaker, the suprachiasmatic nucleus (SCN). The SCN is a region in the hypothalamus that is calibrated by light via pituitary adenylate cyclase activating polypeptide (PACAP). Food, temperature, exercise, and circadian hormones, such as steroids and melatonin, are other calibrators of the SCN.

RHYTHMICITY IN MIGRAINES

When it comes to migraines, Schankin continued, there is clear evidence of a circadian rhythmicity, shown in that most migraine attacks start at noon or 1 pm. Further to this, a 2007 study on those affected by migraine distinguishing between early risers and late risers showed that early risers experience their migraine attacks earlier in the day, whereas, typically, late risers experience their migraine attacks later in the day. Interestingly, there is also evidence of circaseptan rhythmicity in migraines, as fewer migraines occur on Sundays than any other day. Finally, there is evidence of monthly migraine rhythmicity in females who are not on oral contraceptives, as it has been shown that they often experience their migraines on the first or second day of their menstrual period.

MIGRAINE TRIGGERS

When discussing the underlying causes for this rhythmicity, Schankin emphasised the importance of the premonitory (early) phase of the migraine attack, which can start hours to days before the main headache phase. The hypothalamus, cortical, and subcortical areas are key areas implicated in this phase, as are neurotransmitters and neuropeptides such as noradrenaline, orexins, and dopamine. Discussing a study in which migraine attacks were triggered in patients using nitroglycerine infusions, and scanning the brain during the premonitory phase, Schankin explained that hypothalamic activation was observed. According to Schankin, one working theory is that the hypothalamus suppresses trigeminal cervical complex activity and any information that comes from the meninges is suppressed by this hypothalamic activity and not perceived as head pain. During a migraine attack, it is believed that there is a dysfunction in this hypothalamic suppressive activity and, as a result, patients perceive signals from the meninges as head pain. Similar mechanisms are involved in response to sound, light, and gastrointestinal function.

Although little is known about the involvement of neurotransmitters, Schankin presented an animal study that has shown differential involvement of orexins A and B in the trigeminal transmission mechanism.

It is not well-known which molecules might be involved in the migraine attack mechanism at a cellular level; however, Schankin highlighted casein kinase as an important player. People that carry a mutated form of this protein experience an early sleep phase syndrome and this is co-segregated with migraine with aura. An animal study by Brennan in 2013 found that there was a lower threshold for triggering migraine attacks in animals that carry this mutation compared to wild-type animals.

RHYTHMICITY IN CLUSTER HEADACHES

The rhythmicity of cluster headache has been extensively studied and it has now been shown that the majority of cluster headaches happen at night (1 or 2 am). When performing statistical analyses of the chrono-distribution of attacks to determine the oscillation period, a 2018 study found that the most prevalent oscillation period was the 24-hour period, followed by the 12-hour and 4.8-hour periods. Comparison of patients with episodic or chronic cluster headaches showed that these three periods were only present in patients with episodic cluster headaches, whereas the patients with chronic cluster headaches had a more diverse chrono-distribution of their headaches. In interpreting these results, Schankin explained that the group with chronic cluster headaches had a more disturbed chronobiology. In addition to this, cluster headaches appear to have a clear circannual rhythmicity. It is believed that cluster headaches occur in bouts when there are extremes in day length (summer and winter solstice). Other kinds of rhythmicities are observed in groups of patients who never get their cluster headaches in summer, or other patients who get their headaches on the winter or summer equinox.

UNDERLYING CAUSES OF RHYTHMICITY

Studies have looked into whether the causes for this rhythmicity could be genetic. Studies looking at the *CLOCK* gene and its variants found an association between some variants and the incidence of cluster headaches. Orexins are another factor that has been studied; reduced levels of orexin A were found in cerebrospinal fluid in cluster headaches. The orexin receptor has also been studied. A study from Italy and another from Germany found strong correlations between a mutation in the receptor and cluster headaches; however, other studies have not shown such a correlation. Schankin commented that the receptor might play an important role, however, the geographical area as well as the genetic background of the patient might also play a part. Finally, studies have shown that the *PACAP* gene variant is more prevalent in individuals that suffer from cluster headaches compared to controls.

THE ROLE OF SLEEP AND THE HYPOTHALAMUS

When it comes to studying the link between headache rhythmicity and sleep, Schankin explained that there seems to be a higher

likelihood of having a cluster headache during rapid eye movement (REM) sleep, with 30% of cluster headaches occurring at this period compared to 17% during non-REM sleep.

The hypothalamus also seems to play a role in cluster headaches as there appear to be be functional and structural alterations in the hypothalamic region and there are differences in melatonin excretion. Melatonin levels are increased in healthy patients at night, whereas with patients with cluster headaches have no such change in melatonin between the day and night.

THE HYPNIC HEADACHE

The hypnic headache, which occurs exclusively during sleep and causes awakening, is a type of headache likely to be REM-sleep-related as patients report it occurring during vivid dreams. Another possibility is that there is a chronobiological link as they usually occur at the same time in the night (mostly 2–3 am) and could involve the suprachiasmatic nucleus part of the hypothalamus and reduced melatonin secretion. However, a study by Holle in 2013 failed to find an association with REM sleep or any differences in melatonin secretion. What this study did show, however, was hypothalamic involvement in the hypnic headache, finding decreased grey matter density in the hypothalamus in patients with hypnic headache compared to controls.

TREATMENT OPTIONS AND CONCLUDING REMARKS

When putting this evidence together, Shankin explained that chronobiology plays a major role in primary headache syndromes and there is some evidence on the involvement of the hypothalamus and its major mediators. With regard to the role of sleep, it appears to be a two-way mechanism as sleep affects headaches and vice versa.

When it comes to treating rhythmicity in headaches, lithium is used for cluster and hypnic headache prophylaxis as it is an inhibitor of glycogen synthase kinase 3 β. Valproic acid is another therapy used as it shifts timing of Period2 protein. Randomised controlled trials in this topic from the 1990s have shown that melatonin is able to significantly reduce the number of cluster headaches and a recent study by Oberman confirmed that steroids were helpful in cluster headache prophylaxis.

With regard to orexin A and B, however, no differences have been shown between placebo and an orexin inhibitor. Similarly, a study using PACAP antibody versus placebo showed no difference when used as migraine prophylaxis.

In his concluding remarks, Schankin said that medications altering rhythmicity could be helpful for treatment; however, a lot of evidence is still lacking. ■

Motor Fluctuation Management in Parkinson's Disease: Now and What Next?

This satellite symposium took place on 20th June 2021, as part of the 7th Congress of the European Academy of Neurology – Virtual 2021

Chairperson: Fabrizio Stocchi[1]

Speakers: Joaquim Ferreira,[2] Mónica Kurtis,[3] Francesca Morgante,[4] Heinz Reichmann[5]

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Meeting Summary

Motor fluctuations (MF) are still under-recognised and under-treated in patients with Parkinson's disease (PD). End-of-dose wearing-off is a considerable problem in the overall management of PD and is a result of the decreased therapeutic effect of levodopa/dopa-decarboxylase inhibitors (DDCI). It can be present in the early stages of PD and be difficult to recognise. During a routine neurological clinical evaluation, key questions and specific rating scales for fluctuations can be helpful to gain insights into a patient's movements throughout their day. Wearable technology has been developed to overcome the shortfalls of frequent home diary entries for patient ON-/OFF-times, and can measure daytime variations of bradykinesia, tremor, dyskinesia, and freezing of gait. Telemedicine also provides physicians with a 'window' into their patients' daily lives. Treatment decisions for newly-identified MF should consider current PD treatments, which adjunctive to add first (for levodopa/

DDCI monotherapy), or which adjunctive to add next (for combination therapy). Choice of adjunctive therapies include catechol-O-methyltransferase (COMT) inhibitors, such as opicapone, monoamine oxidase-B (MAO-B) inhibitors, and dopamine agonists. Opicapone 50 mg has shown efficacy as a first-line adjunctive to levodopa/DDCI in patients with end-of-dose MF (OFF-time reduction: 68.8 minutes; ON-time increase: 79.8 minutes) versus placebo (p=0.0161 and p=0.0049, respectively), with a two-fold greater reduction in OFF-time versus placebo for both low-dose and higher-dose levodopa regimens, and significant OFF-time reductions in patients receiving <4 (-124.5 minutes; p=0.0397) or ≥4 levodopa intakes (-114.1 minutes; p=0.0001) versus placebo. Further data from four ongoing opicapone studies are eagerly anticipated.

Introduction from the Chair

Fabrizio Stocchi

Here the speakers present highlights of a virtual satellite symposium at the 7th Congress of the European Academy of Neurology – Virtual 2021, reviewing the practicalities of identifying motor fluctuations in patients with Parkinson's disease (PD), including the use of tools and wearable technology, and considerations to meet the challenges of virtual clinics. The speakers go on to look at therapeutic options currently available for the management of MF, focussing on the role of the catechol-O-methyltransferase (COMT) inhibitor opicapone as an adjunct to levodopa/dopa-decarboxylase inhibitors (DDCI) in the management of early MF.

Identifying Motor Fluctuations: Present and Future

Fabrizio Stocchi, Mónica Kurtis, and Francesca Morgante

Levodopa remains the gold standard of symptomatic efficacy for the treatment of motor symptoms in patients with PD;[1] however, as the disease progresses, patients develop motor response oscillations such as end-of-dose wearing-off and levodopa-induced dyskinesias.[2,3] Wearing-off, a result of decreased therapeutic effect of levodopa/DDCI, represents a major source of disability for patients with PD, impacting on quality of life.[4] Wearing-off also presents a considerable problem in the overall management of PD. Key to the timely detection and management of wearing-off is the ability to recognise that it can be present in the early stages of this disease.

Motor Fluctuations Occur Early in Parkinson's Disease Progression

Fabrizio Stocchi presented a patient case, including the patient describing her symptoms during a routine clinical evaluation. Wearing-off was characterised by non-motor symptoms (tiredness) and motor symptoms (tremor, bradykinesia), despite the early disease stage (4 years since diagnosis) (Table 1).

Wearing-off is investigated during a clinical evaluation in a number of ways. DEEP, a multicentre, observational study in 617 patients with PD, showed that wearing-off during the first years of PD (2.5–5 years' disease duration) was identified through a neurologist evaluation in 36.2% of patients and in 54.6% of patients using the Wearing-Off Questionnaire (WOQ-19).[4] A recent market research survey of 420 European healthcare professionals found that MF were most frequently identified by asking the patient (82%) or hearing directly from the patient about their wearing-off symptoms (56%) (Bial, unpublished data). Only 4% of those interviewed used the WOQ-19 tool, despite one-third of healthcare professionals recognising that MF are underdiagnosed, and one-quarter feeling that MF can be hard to diagnose during a routine neurological clinical evaluation (Bial, unpublished data). These data highlight the importance of assessment techniques in the recognition of early MF during a routine neurological clinical evaluation.

Timely Identification of Motor Fluctuations

Key patient questions to identify motor fluctuations

As part of a routine clinical evaluation, a selection of key questions can help neurologists

Table 1: Case study of wearing-off in early Parkinson's disease.

Patient history	Patient's description of her symptoms
59-year-old female 4 years since PD diagnosis 3 years since levodopa initiation Current levodopa regimen: • Total dose 300 mg • Dose schedule 100 mg TID (taken at 5-hour intervals) Other PD medication: rasagiline 1 mg (one tablet)	Coinciding with the time before her next levodopa dose the patient describes: • Return of some tremor • Fatigue, tiredness • Movement becomes a bit slower • No mood changes during this time These symptoms occur once or twice per day; once the patient has taken another levodopa intake, these symptoms disappear and do not re-occur until the next dose is due

PD: Parkinson's disease; TID: three times daily.

to identify MF; similar questions phrased in different ways and the use of diagrams may also help to gain insights into a patient's movements throughout their typical day (Figure 1).

Screening and rating instruments to identify fluctuations

There are a number of rating scales for fluctuations, including UPDRS-IV, Part B;[5] the Non-Motor Fluctuation Assessment (NoMoFA) Questionnaire;[6] and the WOQ-19.[7] The UPDRS-IV, Part B can be used to screen a patient for time spent in the OFF-state, and has advantages in that it can be used to screen for the functional impact of fluctuations and complexity of MF.[5] The NoMoFA rates the severity of non-motor symptoms and whether these are worse during ON- versus OFF-time; the NoMoFA is potentially more useful in the research setting.[6] The WOQ-19 is an easy-to-use questionnaire based on patient-reported outcomes and includes items for both MF and non-MF.[7] Using this tool can save time during a clinic visit as it can be filled in by the patient in the waiting room before the consultation.

In the case study described, the WOQ-19 questionnaire would be a useful tool to identify both the patient's motor and non-motor symptoms, including item 1 (tremor), item 6 (weakness), item 8 (slowness of movement), and item 5 (mood changes). However, the WOQ-19 does not offer any insights on severity of each fluctuation symptom or on sleep-related fluctuations.[7]

It is important to note that none of these instruments provide an understanding of fluctuation timings during the day and this information is needed to precisely adjust medication doses.

Telemedicine during the COVID-19 era: motor fluctuations on show

Telemedicine offers improvements to the quality of care[8] by providing clinicians with an opportunity to 'step into the homes of their patients' and presenting a 'window' into patients' daily lives.[9] In Mónica Kurtis' experience, observing a patient on-screen is preferable to a phone consultation. Being able to see the patient in a video call can remove the 'performance bias' that may occur during a routine clinic visit, enable a physician to see a patient when they are OFF (which rarely happens during a clinic visit), and offers an opportunity to pinpoint the types of spaces that can cause movement difficulties; for example, freezing of gait is often triggered when passing through narrow spaces/passages such as doorways.[10] Practical tips for conducting telemedicine consultations are given in Table 2.

In the case study described (Table 1), a telemedicine consultation coinciding with the patient's next levodopa dose may allow the physician to observe the patient's tremor and slowness of movement.

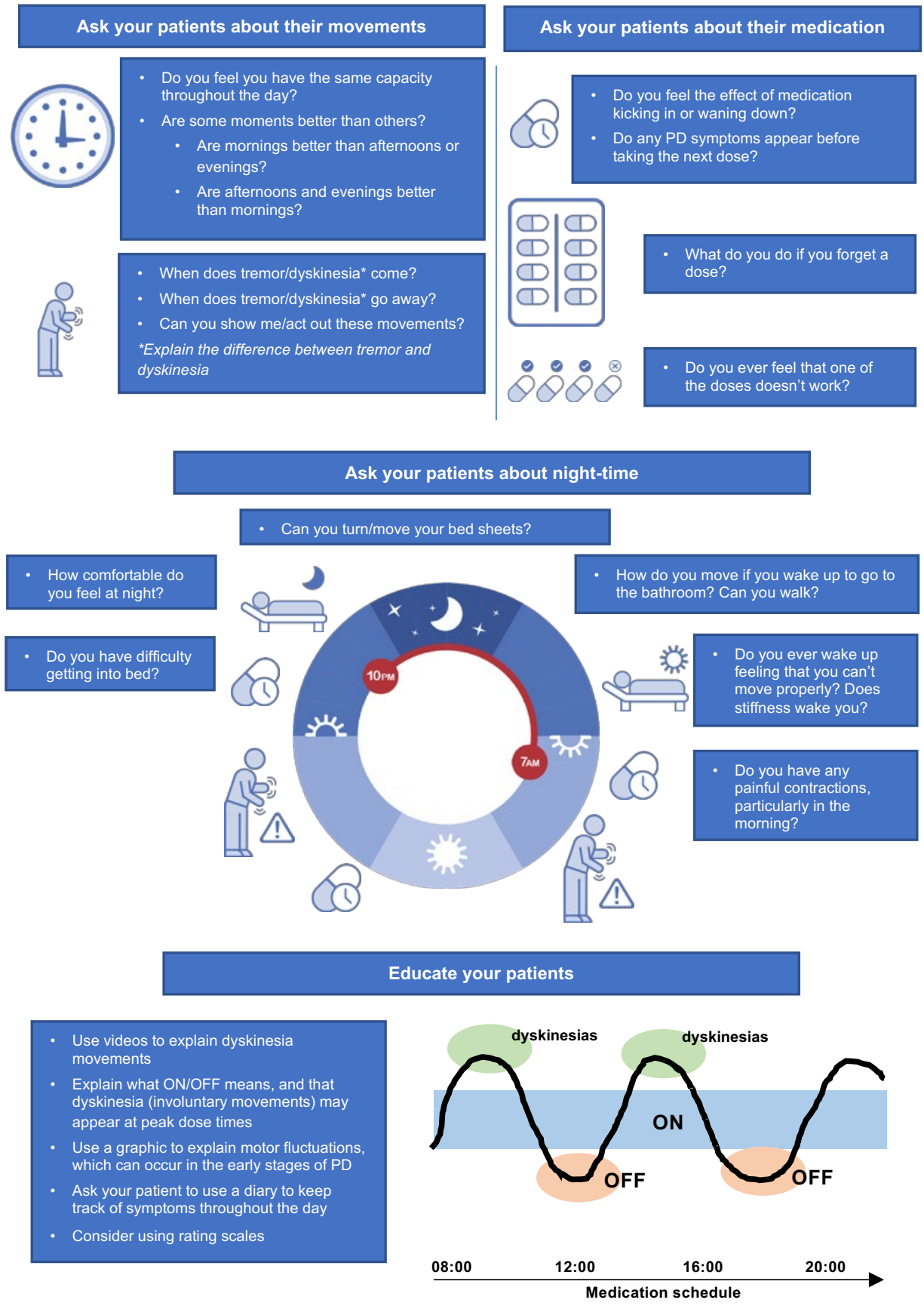

Figure 1: Key questions: identifying motor fluctuations in early Parkinson's disease.

PD: Parkinson's disease.

Table 2: Telemedicine practical tips for a virtual home consultation.

Preparing your patient before the consultation	Preparing your patient on the day of the consultation
Ask your patient to note down: • Problems since their last consultation (e.g., hospitalisations, falls) • Their main complaints • Any fluctuations (diary entries) Ask your patient to: • Have their medication schedule at hand • Sign the informed consent for a telemedicine follow-up	Ask your patient to: • Give themselves enough time to get set up • Get connected to the internet before the consultation • Ensure adequate lighting • Choose one device (laptop, computer, tablet, or phone) and to use this device for subsequent consultations • Choose one platform (e.g., Skype, Zoom, Teams) compliant with privacy, and to use this platform for subsequent consultations To enable a good view of your patient, ask them to: • Choose a place where they can sit on a chair in front of the camera • Stand up with nothing in front of them • Make sure that there is enough space to walk and be visible on camera

Other advantages telemedicine can provide are an increased accessibility to movement disorder specialists, a decrease in the caregiver burden, and cost savings.[8,9] There are, however, disadvantages. In Kurtis' experience, it is not possible to assess muscle tone and even with a high-definition camera it is difficult to examine eye movements in detail. While telemedicine does limit personal contact, ties with the patient can be strengthened by meeting family members/pets and getting to know the patient's environment. It is important to note that individual institutions and countries have their own regulations for remote consultations.

Novel technologies to detect motor fluctuations

Wearable technology, such as smartwatches or actigraphs, has been developed to overcome the shortfalls of patient ON/OFF home diaries,[11] including the need for diary entries every 30 minutes; assumptions that patients know the difference between ON, OFF, and ON with troublesome dyskinesia; and the lack of distinction between different types of fluctuations.

Such technology can measure daytime variations of bradykinesia, tremor, and dyskinesia.[12] Wearables are also able to detect freezing of gait,[13] and have been recently shown to detect fall events.[14] While these are real advances in detecting and monitoring fluctuations, the ideal wearables need to be easy to understand from the patient perspective, be eligible for reimbursement, provide measures for non-MF, and be able to record the full spectrum of night-time symptoms.

Therapeutic Options for Newly Detected Motor Fluctuations

Fabrizio Stocchi, Heinz Reichmann, and Joaquim Ferreira

Treatment Considerations for Newly Identified Motor Fluctuations

During a consultation, treatment goals should be discussed with the patient. These goals are different for individual patients and should include improving the most troublesome symptoms; for example, improving Parkinsonism symptoms, reducing OFF-time and increasing ON-time, and improving non-motor symptoms such as tremor, fatigue, and anxiety.

After considering patient factors such as age, severity of motor complications, dyskinesia, cognitive impairment, and neuropsychiatric

problems,[15] there are two key questions for choice of treatment for end-of-dose wearing-off: what treatments is the patient already receiving; and which treatment to add first (in the case of levodopa/DDCI monotherapy) or which treatment to add next (if the patient is already receiving adjunct therapy)? Treatment decisions for choice of adjunct class (COMT inhibitor, MAO-B inhibitor, or dopamine agonist), as well as within-class, should be based on evidence for efficacy and acceptable tolerability, as well as ease of administration and titration. However, regarding which treatment to start first, there is currently no clear-cut evidence to suggest one particular medicine over another.[15]

Whenever a new adjunct treatment is added, apart from providing explanations and education to the patient about MF, wearing-off, and dyskinesia, possible side effects of treatments should also be discussed. Heinz Reichmann suggested an early appointment 2–4 weeks following a new adjunct treatment being initiated to discuss side effects such as dyskinesia, dizziness, or hallucinations.

Opicapone as an Early Treatment Option for Motor Fluctuations

The clinical efficacy and safety of opicapone as an adjunct therapy to levodopa has been demonstrated in two large, Phase III, multinational, randomised, double-blind studies with open-label extension periods. BIPARK-I was an active comparator (entacapone) and placebo-controlled study (n=600), and BIPARK-II was a placebo-controlled study (n=427).[16-18] In both trials, the primary endpoint was change from baseline to end of study treatment in absolute OFF-time.[16,18] In BIPARK-I, treatment with opicapone 50 mg was superior to placebo (mean difference in change from baseline: -60.8 min; 95% confidence interval [CI]: -97.2 to -24.4; p=0.0015), and non-inferior to entacapone (-26.2 min; 95% CI: -63.8 to 11.4; p=0.0051 for the non-inferiority test).[16] In BIPARK-II, the adjusted treatment difference versus placebo was significant for opicapone 50 mg (treatment effect: -54.3 min; 95% CI: -96.2 to -12.4; p=0.008).[18] Opicapone was generally well tolerated, with the most common adverse events associated with opicapone treatment including dyskinesia, insomnia, constipation, and dry mouth.[16,18]

Opicapone in patients with recent and long-standing motor fluctuations

Building on these Phase III data, exploratory *post hoc* analyses evaluated the efficacy and safety of opicapone in levodopa/DDCI-treated patients with PD with ≤1 year duration of MF (recent motor fluctuators; RMF), as well as >1 year duration of MF (long-standing MF; LMF).[19] Data from matching treatment arms in BIPARK-I and -II were combined for the placebo and opicapone 50 mg groups and analysed.[19]

Baseline patient characteristics, including age and daily OFF-time, were similar for opicapone (RMF: n=85; LMF: n=162) and placebo (RMF: n=71; LMF: n=174) groups in both RMF and LMF patients.[19] The LMF group had a longer mean disease duration (placebo: 8.5 years; opicapone 50 mg: 8.6 years) compared to RMF (placebo: 5.8 years; opicapone 50 mg: 5.9 years),[19] as well as higher mean daily levodopa dose (LMF placebo: 742.3 mg; opicapone 50 mg: 739.3 mg) than RMF (RMF placebo: 585.4 mg; opicapone 50 mg: 616.6 mg) patients.[19] Remarkably, changes in absolute OFF- and ON-time were significantly greater for opicapone versus placebo in both RMF and LMF, with opicapone reducing absolute OFF-time by approximately 1 hour in both groups versus placebo (Figure 2).[19]

Moreover, in the opicapone group, dyskinesia was reported almost half as frequently in RMF versus LMF patients (11.8% versus 23.5%), despite similar reductions in OFF-time;[19] this might be due to longer disease duration and higher daily levodopa dose in the LMF group.

Opicapone as first-line adjunctive therapy in patients with end-of-dose motor fluctuations

A *post hoc* analysis evaluating opicapone as first add-on in patients with PD with end-of-dose MF treated with levodopa/DDCI only at baseline (i.e., without dopamine agonists or MAO-B inhibitors) was conducted in 127 patients.[20] Baseline characteristics in the opicapone (n=68) and placebo (n=59) groups were comparable, with mean levodopa doses 730.3 mg/day and 718.3 mg/day, respectively.[20]

Opicapone significantly reduced absolute OFF-time by 68.8 minutes (p=0.0161) and increased

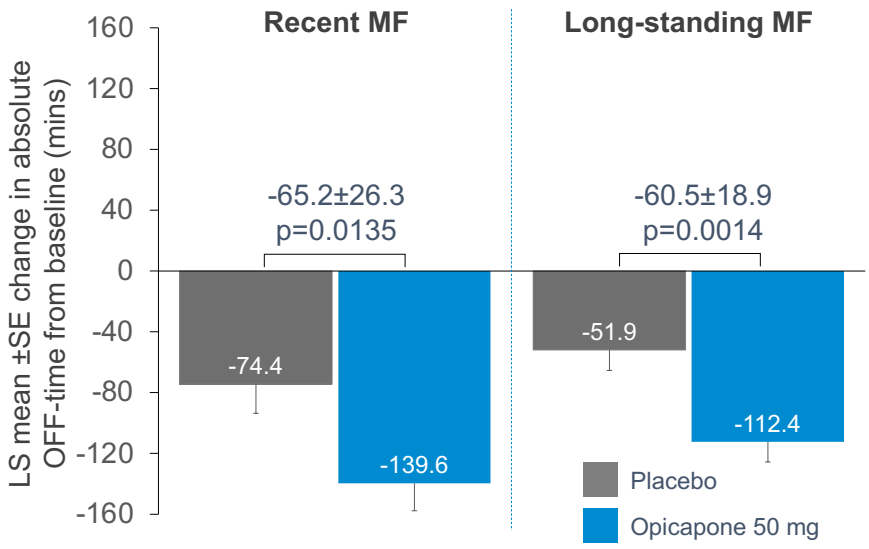

Figure 2: Mean changes in OFF-time in recent and long-standing motor fluctuators: opicapone versus placebo.

LS: least squares; SE: standard error.

Adapted from Ebersbach G et al.[19]

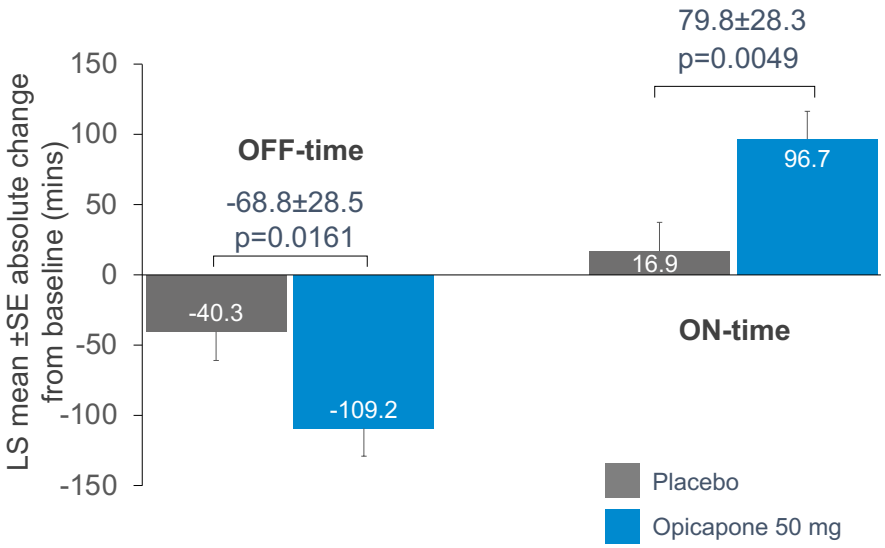

Figure 3: Mean changes in OFF- and ON-time: opicapone as first-line adjunctive therapy versus placebo.

LS: least squares; SE: standard error.

Adapted from Ferreira J et al.[20]

ON-time by 79.8 minutes (p=0.0049) compared to placebo (Figure 3),[20] while the incidence of potentially related treatment-emergent adverse events leading to discontinuation was similar for opicapone 50 mg (n=5, 7.4%) and placebo (n=5, 8.5%).[20] The most frequently reported (≥5% of patients) potentially related treatment-emergent adverse event was dyskinesia (opicapone: n=8, 11.8%; placebo: n=1, 1.7%).[20]

These data show that opicapone is effective and generally well-tolerated as a first-line adjunctive therapy in levodopa-treated patients with PD and MF.[20]

Opicapone efficacy in patients with low levodopa doses (300–400 mg) or <4 levodopa intakes

Two further analyses provide evidence of opicapone utility in the treatment of early MF. By combining matching efficacy data for opicapone 50 mg and placebo from the pivotal Phase III studies, different levodopa regimens were evaluated in a subgroup analysis (n=239 patients).[21] Improvements in OFF-time were observed for both low-dose and higher-dose levodopa regimens on addition of opicapone 50 mg, with at least a two-fold greater reduction in mean OFF-time versus placebo (Figure 4).[21]

Another analysis demonstrated a significant improvement in absolute OFF-time from baseline, regardless of whether patients were receiving <4 (-124.5 min; p=0.0397 versus placebo) or ≥4 levodopa intakes (-114.1 min; p=0.0001 versus placebo).[22]

Reichmann ventured that in the case study described (Table 1), consideration for using opicapone in this patient is backed up by this therapy's efficacy with low-dose levodopa.[21] Opicapone may be useful to keep levodopa doses in the optimised range[16] and its once-daily dosing regimen[23] might aid adherence, since the more levodopa doses per day, the more adherence inconsistencies.[24]

Ongoing Opicapone Trials: Supporting Evidence-Based Choices in Treating Motor Fluctuations

Four studies are ongoing to further elucidate the best use of levodopa and opicapone in treating MF and MF-related non-motor symptoms in clinical practice. These trials are being conducted at European sites.

The ADOPTION study is a Phase IV, randomised, prospective, open-label exploratory trial with patients recruited from Germany, Italy, Portugal, Spain, and the UK.[25] The aim of this study is to explore the potential of opicapone to optimise levodopa/DDCI as a first-line approach to treat wearing-off (stable treatment plus addition of opicapone 50 mg versus an additional 100 mg levodopa) in 100 adults with signs of wearing-off for <2 years, and treated with 3–4 daily oral levodopa doses up to 600 mg. The primary endpoint is change from baseline in OFF-time at 4 weeks, according to Hauser's home diary.

The aim of the Phase II, open-label 203 trial[26] is to assess the effect of opicapone 50 mg on

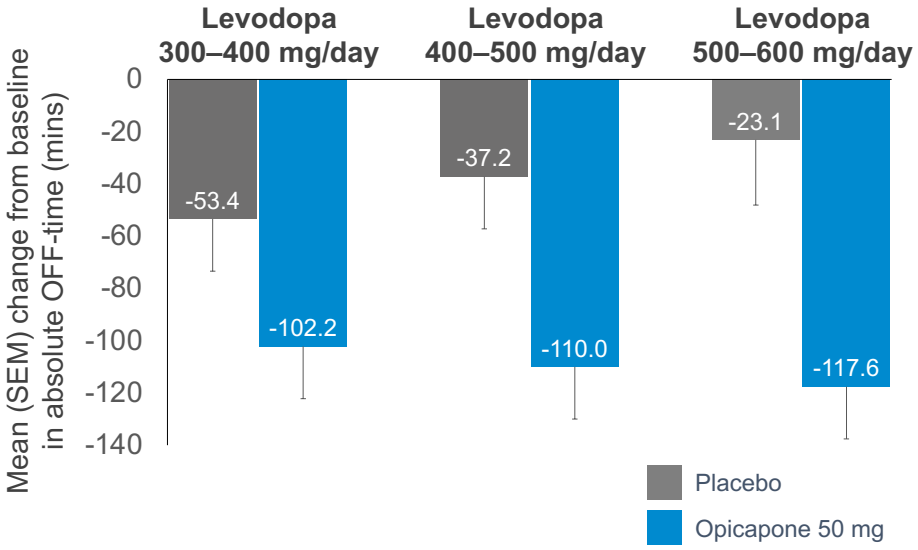

Figure 4: Mean changes in OFF-time by different levodopa regimen: opicapone versus placebo.

SEM: standard error of the mean.

Adapted from LeWitt PA J et al.[21]

levodopa pharmacokinetics in different levodopa/carbidopa treatment regimens in patients with end-of-dose MF. Twenty-four patients will receive five intakes of 500/125 mg levodopa/carbidopa dose for 2 weeks. They will then be randomised 1:1 to either four or five intakes of 400/100 mg levodopa/carbidopa plus opicapone 50 mg for 2 weeks. The primary endpoint compares the pharmacokinetics of levodopa at the end of both 2-week treatment periods.

The OCEAN study is a Phase IV, randomised, double-blind, placebo-controlled trial.[27] The aim of this study is to evaluate the effect of opicapone 50 mg with levodopa/DDCI in 140 patients with PD with end-of-dose MF and associated pain, recruited from 50 European sites. The primary endpoint is change from baseline in the King's Parkinson's Disease Pain Scale (KPPS), domain 3 (fluctuation-related pain) at 24 weeks.

Finally, the OASIS study is a Phase IV, open-label, single-arm pilot trial.[28] The aim of this study is to evaluate the impact of opicapone 50 mg as adjunctive therapy to levodopa/DDCI on PD-associated sleep disorders in 30 patients with wearing-off and sleep disorders, at sites in Germany and Portugal. The primary endpoint is change from baseline in Parkinson's Disease Sleep Scale 2 (PDSS-2) total score at 6 weeks.

Conclusion

Fabrizio Stocchi

In summary, MF are still under-recognised and under-treated in patients with PD. Newer strategies in the form of wearable technologies are now available to help identify MF during a typical patient day. How to integrate and make the most of these technologies together with the 'new normal' of virtual clinics in recognising and treating early MF will be key to optimising patient management. While wearable technologies are a welcome addition, mastering gathering a precise patient history with complete description of symptoms, whether by asking key questions or questionnaires, will continue to be paramount for a routine clinical evaluation.

The current evidence supporting opicapone as a potential first-line adjunctive treatment to levodopa/DDCI in patients with PD with early MF is robust. Significant OFF-time reductions have been demonstrated, including for both low-dose and higher-dose levodopa regimens versus placebo, as well as in patients receiving <4 levodopa daily intakes. Data from four further studies, including the potential of opicapone to optimise levodopa/DDCI as a first-line approach to treat wearing-off, in end-of-dose MF-associated pain, and in wearing-off and sleep disorders, aim to consolidate the evidence base for opicapone in routine clinical practice.

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Abstract Reviews

Sharing insights and updates from a selection of abstracts presented by leading experts in the field of neurology at the European Academy of Neurology (EAN) Virtual Congress 2021

Classifying and Characterising Multiple Sclerosis Disease Phenotypes with Functional Connectivity and Machine Learning

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Keywords: Functional connectivity (FC), machine-learning, multiple sclerosis (MS), network analysis, phenotypes, resting state (RS).

Citation: EMJ Neurol. 2021;9[1]:34-36. Abstract Review No. AR1.

BACKGROUND AND AIMS

Multiple sclerosis (MS) is a chronic, inflammatory, and neurodegenerative disease of the central nervous system, characterised by non-uniform clinical manifestations. Resting state (RS) functional MRI (fMRI) studies of patients with MS often showed trends towards higher functional connectivity (FC) at the earliest disease stages, followed by a gradual RS FC reduction in progressive MS (PMS).[1,2] However, complex patterns of regional increased and decreased RS FC in critical brain networks have been described across MS phenotypes. Moreover, RS FC abnormalities do not have a straightforward relationship with the severity of clinical and cognitive symptoms.[1,2] Network-based methods on RS fMRI data are helping to shed light into brain functional reorganisation in MS[3,4] and, combined with machine-learning, may produce important clues to support automated classification of patients with MS. Against this background, the aim of this study was to develop advanced machine-learning methods to analyse RS FC data and classify patients with MS according to their disease phenotype.

MATERIALS AND METHODS

RS fMRI scans were obtained from 46 right-handed healthy controls (HC) and 113 MS patients (62 relapsing-remitting MS [RRMS] and 51 PMS).

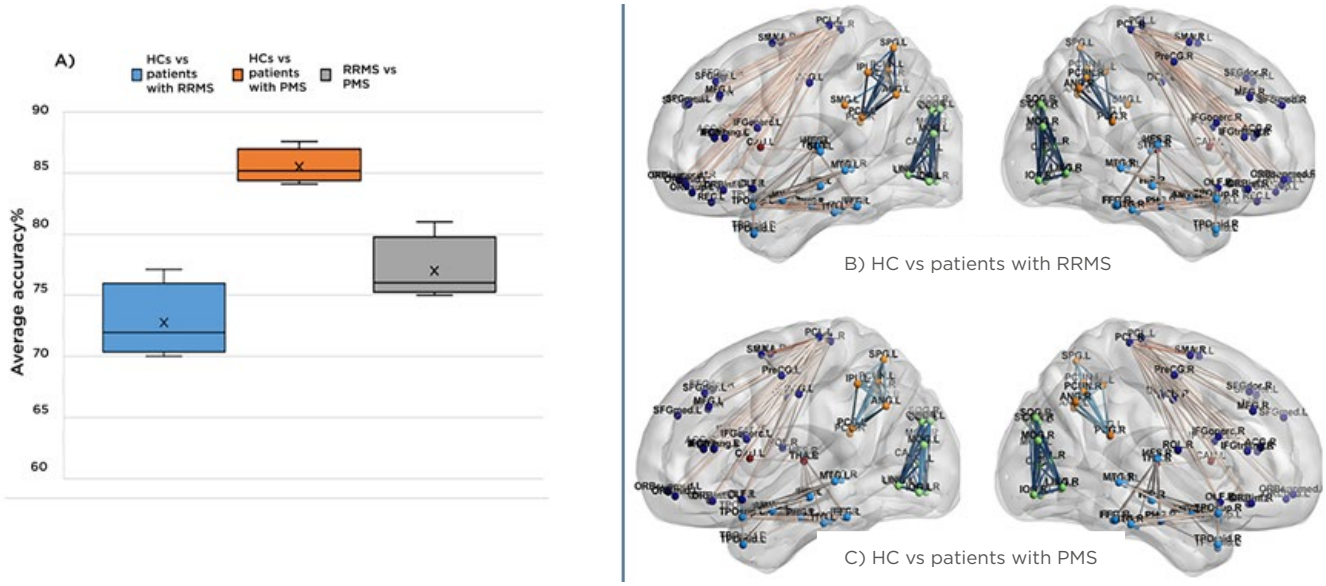

Figure 1: Results from machine-learning tool to classify patients with relapsing-remitting multiple sclerosis and progressive multiple sclerosis from healthy controls.

A) Boxplot representing the average cross-fold validation accuracy for the following classification tasks: HCs versus RRMS (blue), HCs versus PMS (orange), and patients with RRMS versus patients with PMS (grey). **B,C)** Illustrative example of RS FC differences within the main sub-networks of the brain (parcellated according to cortical lobe) contributing to the classification task: **B)** RS FC differences between HCs and patients with RRMS. **C)** RS FC differences between HCs and patients with PMS. RS FC decrease in patients versus HCs is colour-coded in blue, while RS FC increase is colour-coded in orange-red.

FC: functional connectivity; HC: healthy control; PMS: progressing multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; RS: resting state; vs: versus.

After RS fMRI pre-processing, RS FC matrices were created by means of pair-wise covariance between RS fMRI time series extracted from the automatic anatomical labelling atlas. RS FC matrices were then clustered into groups with dominant-set clustering exploiting the geodesic metric. Each cluster represents a group of subjects with some similarity in their FC. A reference connectome (geodesic mean) was determined for each cluster, and each RS FC matrix was then represented by a set of geodesic distances from cluster representatives. This representation was used to classify subjects (HC, RRMS, and PMS) using a linear support vector machine, executed 100 times with a 5-fold cross-validation scheme. Finally, a sensitivity analysis on the trained classifier was used to identify clusters and connections more relevant for classification.

RESULTS

The described machine-learning tool was able to classify patients with RRMS from HCs with an accuracy of 72.5%, patients with PMS from HCs with an accuracy of 85.2%, and patients with PMS from patients with RRMS with an accuracy of 76.0% (Figure 1). The sensitivity analysis on trained support vector machines found that increased RS FC in the basal ganglia subnetwork (peculiarly involving the bilateral thalami) and abnormal RS FC in the frontal subnetwork contributed to an accurate classification of both patients with RRMS and PMS from HCs (Figure 1). Moreover, decreased RS FC in occipito-temporal subnetworks contributed to differentiate patients with RRMS from HCs, while decreased RS FC in the parietal sub-network (especially involving the precunei and posterior cingulate cortices) contributed to differentiate patients with PMS from patients with RRMS.

CONCLUSION

A combination of different machine-learning principles allowed to classify patients with MS with different clinical phenotypes from HCs with a good accuracy. Increased RS FC in the basal ganglia sub-network contributed to an accurate classification of both patients with RRMS and PMS from HCs, suggesting that altered thalamic and frontal RS FC may be a hallmark of MS disease, occurring in all MS phenotypes. Conversely, the peculiar involvement of occipito-temporal subnetworks in patients with RRMS might be secondary to damage of associative sensory regions, while the peculiar involvement of the posterior cingulate cortex and precuneus in PMS suggests a spreading of damage to high-order, associative regions, leading to impaired network integration. ■

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Clinical Relevance of Multiparametric MRI Assessment of Cerebellar Damage in Multiple Sclerosis

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Keywords: Cerebellum, MRI, multiple sclerosis.

Citation: EMJ Neurol. 2021;9[1]:37-38. Abstract Review No. AR2.

BACKGROUND AND AIMS

Cerebellar involvement is common in multiple sclerosis (MS),[1,2] with pathological evidence of extensive white matter (WM) and grey matter (GM) damage, especially in patients with progressive MS (PMS).[3,4] MRI studies confirmed higher cortical lesion number and volume in PMS compared to patients with relapsing–remitting MS (RRMS)[5] and more prominent GM atrophy with increasing disability.[6] Atrophy of anterior cerebellar lobes correlated with physical disability and atrophy of posterior lobes correlated with cognitive impairment.[7-9] However, the cerebellum is a highly interconnected structure, whose functioning is critically dependent onto input and output pathways. Using a multiparametric MRI approach (studying atrophy, lesions, and WM microstructural abnormalities), the authors aimed to quantify cerebellar damage and identify predictors of physical disability and cognitive dysfunction in patients with MS, and to characterise patients with cerebellar disability.

MATERIALS AND METHODS

One hundred and sixty-four patients with MS (89 RRMS and 75 PMS), and 68 age- and sex-matched healthy controls underwent brain and cervical spinal cord (CSC) 3T MRI with pulse sequences for assessing lesions and atrophy in the brain (separately for cerebellum, brainstem, and supratentorial areas) and CSC; and microstructural damage (with diffusion-tensor metrics) of the cerebellar peduncles. Subjects underwent neurological examination and neuropsychological assessment with the Brief Repeatable Battery. Domain-specific z-scores were averaged, yielding a cognitive z-score. MRI predictors of clinical variables were identified with random forest models.

RESULTS

According to random forest analysis, informative predictors of higher Expanded Disability Status Scale score were: lower cord GM and global areas, brain volume, GM volume (GMV), cortical GMV, cerebellum lobules I–IV and vermis GMV, and higher cord GM and brainstem lesion volume (LV) in patients with MS (out-of-bag [OOB]-R^2=0.83); higher brainstem and CSC GM LV, lower CSC

global area, higher MCP, and cerebellum WM LV in patients with RRMS (OOB-R^2=0.35); lower CSC GM area, lower cerebellum lobules I–IV GMV, lower normalised brain volume, and lower brain GMV in patients with PMS (OOB-R^2=0.31).

Informative predictors of lower cognition z-score were: higher supratentorial and superior cerebellar peduncle LV and lower brain, thalamus, and basal ganglia volumes, GMV, cerebellum lobule VIIIBm, and Crus II GMV in patients with MS (OOB-R^2=0.25); lower thalamus volume, higher supratentorial and SCP LV, lower normalised brain volume, lower posterior cerebellum and cerebellum Crus II GMV, and higher cerebellum WM LV in patients with RRMS (OOB-R^2=0.21); lower basal ganglia volume, lower brain GMV, lower cerebellum lobule VIIIb GMV, lower thalamus volume, higher supratentorial, and lower cerebellum Crus II GMV in patients with PMS (OOB-R^2=0.22).

In patients with cerebellar disability, the authors found three clusters with homogenous MRI metrics: patients with high brain LV (including cerebellar peduncles), those with marked cerebellum GM atrophy, and patients with severe CSC damage.

CONCLUSIONS

In this multiparametric MRI study, the authors found that damage to cerebellum GM and connecting structures explains a significant proportion of physical disability and cognitive dysfunction in patients with MS. Among patients with cerebellar disability, the authors identified three homogeneous MRI-subgroups, which is a step forward in MRI-clinical correlations. ■

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Human Spinal Cord-like Organoids to Model *C9orf72* Amyotrophic Lateral Sclerosis and Test New Therapies *In Vitro*

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Keywords: Amyotrophic lateral sclerosis (ALS), *C9orf72*, neural organoids, spinal cord, 3D cultures.

Citation: EMJ Neurol. 2021;9[1]:39-41. Abstract Review No. AR3.

BACKGROUND AND AIMS

Amyotrophic lateral sclerosis (ALS) is an incurable neurodegenerative disease. Underlying genetic pathomechanisms include the *C9orf72* hexanucleotide GGGGCC repeat expansion, the most frequent genetic cause of ALS (C9-ALS) in Western countries.[1]

Neurodegeneration in C9-ALS is supposedly associated with two mechanisms: a loss- and a gain-of-function mechanism.[1] They are not mutually exclusive and depend on the site of transcription start. The former refers to reduced transcription and translation of the C9orf72 protein. The latter involves the increased transcription and translation of hexanucleotide repeat expansion, leading to the generation of foci of transcribed RNA and the accumulation of translated toxic dipeptide repeat proteins.[1] Another pathological hallmark is represented by TDP-43, a ubiquitous intranuclear protein that can translocate and accumulate in a phosphorylated form into the cytoplasm of glial cells and neurons.[2] Despite recent progress in unravelling C9-ALS pathogenesis, reliable disease models and disease-modifying therapies are still lacking.

Organoids refer to 3D cultures derived from induced pluripotent stem cells that present a complex cytoarchitecture with a layered structure, dynamically resembling some phases of early human development.[3] Neural organoids consist of diverse cellular subpopulations, including proliferating, differentiating, migrating, and self-organising pools of neural progenitors, enabling the study of cell-to-cell communication, the patterning of peripheral and central nervous system regions, and the evaluation of neural connectivity.[4] Their generation, coupled with genome editing, microfluidics, live imaging, and single-cell genomics, has allowed the modelling *in vitro* of different neurological disorders,[5] including neurodegenerative diseases such as Huntington's disease,[6] Alzheimer's disease,[7] and Parkinson's disease.[8] To date, an organoid model of C9-ALS is still lacking.

Here, the authors aim to model C9-ALS *in vitro* using 3D human spinal cord organoids (SCOs).

MATERIALS AND METHODS

The authors differentiated C9-ALS induced pluripotent stem cells and isogenic controls using a free-floating 3D culture method with a multi-stage protocol involving various differentiation factors. They generated SCOs with a modified Lancaster's protocol,[9] promoting neural caudalisation (Wnt signalling and retinoic acid) and ventralisation (sonic hedgehog signalling). Long-term growth was achieved using spinning flasks. The authors treated C9-ALS SCOs with morpholino antisense oligonucleotides against *C9orf72* repeat expansion. Finally, they assessed the differentiation of organoids at different time points with immunohistochemical and real-time quantitative PCR (qPCR) analysis.

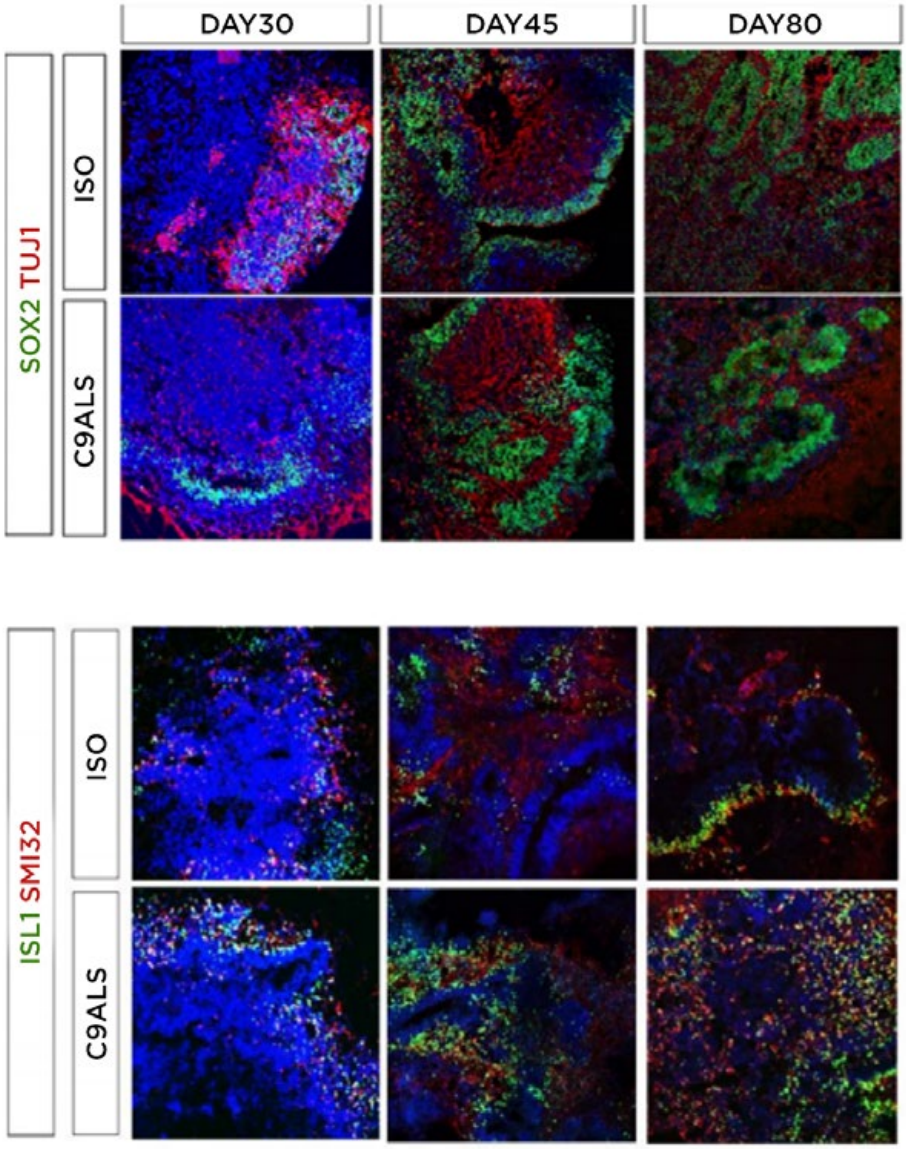

Figure 1: Immunohistochemical characterisation of C9-ALS spinal cord organoids.
Isogenic and C9-ALS spinal cord organoids stained for neuronal precursors, post-mitotic, and motor neuron markers. Time-course of SOX2/TuJ1 (neural precursor/post-mitotic) as well as motor neuron markers ISL1/SMI32 on isogenic and ALS organoids at Days 30, 45, and 80.

C9-ALS: *C9orf72* hexanucleotide GGGGCC amyotrophic lateral sclerosis; ISO: isoquercetin.

RESULTS

The authors obtained isogenic and C9-ALS SCOs displaying different co-existing neuronal sub-populations at different time points (at Days 30, 45, and 80). SCOs expressed neural progenitor, pan-neuronal, astrocyte, motor neuron, and rostrocaudal markers, including markers of cervicobrachial spinal cells (Figure 1). Compared to controls, C9-ALS organoids exhibited increased dipeptide repeat proteins levels, DNA damage markers associated with *C9orf72* expansion, and cytoplasmic inclusions of translocated TDP-43. Gene expression analysis using qPCR confirmed the expression of neural precursors, post-mitotic neural, and motor neuron-related genes in both C9-ALS and isogenic

spinal cord organoids. Preliminary results on qPCR reported differential expression of genes associated with DNA damage and motor neurons in morpholino antisense oligonucleotides treated C9-ALS organoids.

CONCLUSION

SCOs represent a valuable system for modelling some neuropathological hallmarks of C9-ALS, investigating C9-ALS pathomechanisms, and testing possible new treatments *in vitro.* ■

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Relevance of Neurite Orientation and Dispersion Density Imaging to Characterise Microstructural Abnormalities of Multiple Sclerosis Cortex and Cortical Lesions *In Vivo*: A 3T Study

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Keywords: Cortex, cortical lesions, grey matter, MRI, multiple sclerosis (MS), neurodegeneration, neurite orientation and dispersion density imaging (NODDI).

Citation: EMJ Neurol. 2021;9[1]:41-43. Abstract Review No. AR4.

BACKGROUND AND AIMS

Pathology has shown that cortical abnormalities are extensive in multiple sclerosis (MS),[1] whereas recent MRI studies have demonstrated that cortical damage is one of the best predictors of clinical disability and cognitive impairment in these patients.[1,2] The definition of MRI measures more specifically the pathological processes affecting MS cortex might improve our understanding of the relationship between structural damage and disease clinical manifestations, thus providing novel outcome measures for monitoring MS. Neurite orientation dispersion and density imaging (NODDI) is a promising multi-compartment diffusion model to better evaluate the complexity of brain neuroanatomical microarchitecture.[3] The NODDI model allows the evaluation of quantitative measures including the intracellular volume fraction (considered a measure of neurite volume), the extracellular volume fraction (representing the extracellular space), and orientation dispersion index (reflecting neurite orientation variability).[3]

At present, the investigation of normal-appearing grey matter abnormalities in MS using NODDI has provided conflicting and inconclusive findings.[4-9] Accordingly, the application of NODDI in larger cohorts of patients with MS is necessary to provide more consistent pieces of information to better typify cortical damage in MS *in vivo* and to demonstrate the clinical relevance of NODDI measures.

In this study, the authors used NODDI to characterise the microstructural abnormalities of normal-appearing cortex and cortical lesions and their relations with disease phenotypes and clinical disability in a relatively large cohort of patients with MS.

MATERIALS AND METHODS

One hundred and seventy-two patients with MS (101 relapsing-remitting and 71 progressive) and 62 healthy controls underwent a brain 3T acquisition. Brain cortex and cortical lesions were segmented from 3D T1-weighted and double inversion recovery, respectively. Using NODDI, on diffusion-weighted sequence, intracellular volume fraction, extracellular volume fraction, and orientation dispersion index were assessed in normal-appearing cortex and cortical lesions.

RESULTS

The authors found that 117 out of 172 (68%) patients with MS had at least one cortical lesion. Patients with MS with normal-appearing cortex had significantly lower intracellular volume fraction versus the healthy controls' cortex (false discovery rate [FDR]: $p<0.001$). Cortical lesions showed significantly increased extracellular volume fractions (FDR: $p<0.001$) and decreased intracellular volume fraction and orientation dispersion index versus a normal-appearing cortex of both healthy controls and patients with MS (FDR: $p\leq0.008$). Compared with relapsing-remitting, patients with progressive MS had a significantly decreased normal-appearing cortex intracellular volume fraction and orientation dispersion index (FDR: $p=0.049$ and FDR: $p=0.033$, respectively). No cortical lesion microstructural differences were found between progressive and relapsing-remitting patients with MS. Multiple sclerosis normal-appearing cortex intracellular volume fraction, extracellular volume fractions, and orientation dispersion index were significantly correlated with disease duration, clinical disability, white matter and cortical lesion burden, and brain, grey matter, and cortical volumes (from -0.51 to 0.71; FDR: from $p<0.001$ to 0.049).

CONCLUSION

The authors' study suggested that a significant neurite loss occurs in multiple sclerosis normal-appearing cortex. Cortical lesions show a further neurite density reduction, an increased extracellular space, possibly reflecting inflammation and cellular loss, and a reduced orientation dispersion index suggesting a

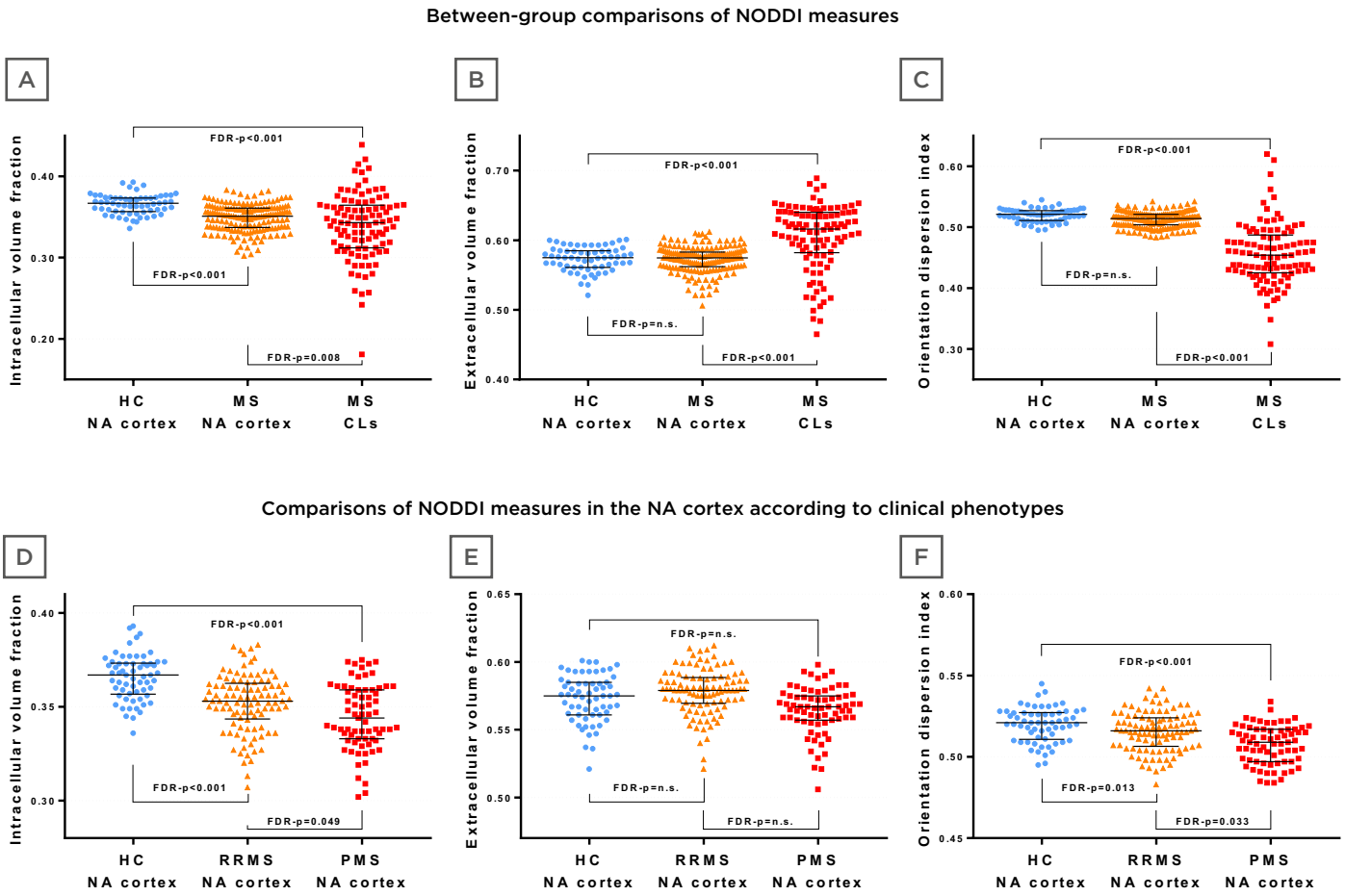

Figure 1: Comparing healthy control groups to patients with multiple sclerosis.

CL: cortical lesion; FDR: false discovery rate; HC: healthy control; MS: multiple sclerosis; NA: normal-appearing; NODDI: neurite dispersion and density imaging; PMS: progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis.

simplification of neurites complexity. NODDI is relevant to investigate *in vivo* the heterogeneous pathology affecting multiple sclerosis cortex. ■

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Magnetic Resonance T2-relaxation Time as an Indirect Measure of Brain Water Content and Disease Activity in Neuromyelitis Optica Spectrum Disorders

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Keywords: Magnetic resonance imaging (MRI), neuromyelitis optica spectrum disorders (NMOSD), relaxometry.

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BACKGROUND AND AIMS

Neuromyelitis optica spectrum disorders (NMOSD) are a group of conditions affecting the central nervous system.[1] Most patients present a seral antibody targeting the aquaporin-4 channel on astrocytes, at the blood–brain barrier interface.[1] During relapses, it is possible to observe radiological signs suggesting increased water permeability, such as the presence of bright spotty lesions and posterior reversible encephalopathy syndrome.[2,3] However, at state of the art, no biomarkers to predict relapses and monitor the disease course are available.[4] Following the hypothesis that, in NMOSD, astrocytes damage could determine subclinical brain water accumulation, possibly varying according to disease activity (relapses), this work aimed to estimate brain water content indirectly by measuring T2-relaxation time (T2rt) in NMOSD patients. The authors also assessed whether T2rt differs in patients having a short-term relapse.

MATERIALS AND METHODS

The authors recruited 77 aquaporin-4-positive patients with NMOSD and 84 age-matched healthy controls (HC) from two European centres (Milan, Italy, and Belgrade, Serbia), undergoing a standardised MRI protocol. The clinical evaluation included the assessment of the Expanded Disability Status Scale (EDSS).[5] The authors also annotated the time from the last and subsequent relapse with respect to the date of MRI acquisition.

The T2rt was calculated from brain dual-echo turbo spin-echo images assuming a monoexponential decay to obtain T2rt maps of the normal-appearing white matter (NAWM), grey matter (GM), and basal ganglia. Short-term relapses were defined as occurring within one month before or after MRI scan. Differences between the patients with NMOSD and the HC were assessed with age-, sex-, and site-adjusted linear models. Receiver operating characteristic analyses were run to identify discriminators between stable and short-term relapsing patients.

RESULTS

HC and patients were comparable in age (mean age 41 versus 44 years, respectively), whereas the female to male ratio was higher in patients than HC (62/15 versus 50/34; p=0.004). Compared to HC, patients had significant atrophy of the brain (1482 ml versus 1582 ml; p<0.001), white matter (747 ml versus 780 ml; p=0.007), and GM (732 ml versus 803 ml; p<0.001). In addition, patients with NMOSD had increased T2rt in the GM (103 ms versus 97 ms; p<0.001), NAWM (88 ms versus 84 ms; p<0.001), and putamen (75 ms versus 72 ms; p<0.001) compared to HC. Short-term relapses occurred in 20/77 (26%) of patients. At receiver operating characteristic analysis, higher values

of T2rt in the NAWM were able to discriminate between short-term relapsing and stable patients with good accuracy (area under the curve: 0.70; p=0.027).

CONCLUSION

Patients with NMOSD had increased T2rt values, suggesting a subclinical water accumulation in this disorder. The burden of T2rt alterations might be a helpful index of disease activity. ■

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Long-term Safety Outcomes with Inebilizumab Treatment in Neuromyelitis Optica Spectrum Disorder: The N-MOmentum Trial

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Paul has received research support, speaker fees, and travel reimbursement from Bayer, Biogen Idec, Merck Serono, Novartis, Sanofi Genzyme, and Teva; is supported by the German Competence Network for Multiple Sclerosis and the German Research Council (DFG Exc 257); has received travel reimbursement from the Guthy–Jackson Charitable Foundation; and serves on the steering committee of the OCTIMS study sponsored by Novartis. Kim has received a grant from the National Research Foundation of Korea; consultancy/speaker fees or research support from Alexion, AprilBio, Celltrion, Eisai, HanAll BioPharma, Horizon Therapeutics, MDimune, Merck Serono, Novartis, Sanofi Genzyme, and Teva-Handok; serves on a steering committee for MedImmune/Horizon Therapeutics; and is a co-editor for the Multiple Sclerosis Journal and an associate editor for the Journal of Clinical Neurology. 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Fujihara serves on scientific advisory boards for Alexion, Bayer Schering, Biogen Idec, Chugai, Horizon Therapeutics, MedImmune, Merck Serono, Mitsubishi Tanabe Pharma, Nihon Pharmaceutical, Novartis, and Ono; has received funding for travel and speaker fees from Asahi Kasei Medical, Astellas, Bayer Schering, Biogen Idec, Daiichi Sankyo, Dainippon Sumitomo, Eisai, Mitsubishi Tanabe Pharma, Nihon Pharmaceutical, Novartis, and Takeda; and research support from Asahi Kasei Medical, Bayer Schering, Biogen Idec, Chemo-Sero-Therapeutic Research Institute, Chugai, Genzyme Japan, the Ministry of Education, Culture, Sports, Science and Technology of Japan, the Ministry of Health, Welfare and Labor of Japan, Mitsubishi Tanabe Pharma, Nihon Pharmaceutical, Ono, Teijin, and Teva. **Cutter** has received personal fees for participation on data and safety monitoring boards from AstraZeneca, Avexis Pharmaceuticals, BioLineRx, Brainstorm Cell Therapeutics, Bristol Myers Squibb/Celgene, CSL Behring, Galmed Pharmaceuticals, Hisun Pharmaceuticals, Horizon Therapeutics, Mapi Pharma, Merck, Merck/Pfizer, Neurim, NHLBI (Protocol Review Committee), NICHD (OPRU oversight committee), Novartis, OncoImmune, OPKO Biologics, Orphazyme, Reata Pharmaceuticals, Sanofi-Aventis, Teva, and Vivus; personal fees for consulting or advisory board participation from Biodelivery Sciences International, Biogen, Click Therapeutics, Genentech, Genzyme, GW Pharmaceuticals, Immunic, Klein-Buendel Incorporated, MedDay, MedImmune, Neurogenesis, Novartis, Osmotica Pharmaceuticals, Perception Neurosciences, Recursion/Cerexis Pharmaceuticals, Roche, and TG Therapeutics; is employed by the University of Alabama at Birmingham; and is President of Pythagoras, Inc., a private consulting company based in Birmingham, AL, USA. 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Green reports grants from the Conrad N Hilton Foundation and the Tom Sherak MS Hope Foundation; other financial relationships (for activities as expert witness, associate editor, advisory board/steering committee participation, and endpoint adjudication) with Bionure, Inception Sciences, JAMA Neurology, MedImmune/Horizon Therapeutics, Mylan, Synthon, and Trims Pharma; and personal fees from and other financial relationships with Pipeline Therapeutics. Drappa, She, Cimbora, Rees, and Katz are employees of Horizon Therapeutics. Ratchford was an employee of Horizon Therapeutics at the time of this study. The study was funded by Horizon Therapeutics (formerly Viela Bio) and MedImmune.

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Keywords: Adverse events, B-cell depletion, CD19, inebilizumab, long-term, neuromyelitis optica spectrum disorder (NMOSD), N-MOmentum, safety outcomes.

Citation: EMJ Neurol. 2021;9[1]:45-48. Abstract Review No. AR6

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BACKGROUND AND AIMS

Neuromyelitis optica spectrum disorder (NMOSD) is a severe autoimmune disease characterised by recurrent inflammation of the optic nerve, spinal cord, and/or brain or brainstem.[1,2] N-MOmentum was a multi-centre, double-blind, randomised, placebo-controlled Phase II/III study, with an optional open-label period (OLP), of the efficacy and safety of inebilizumab, a humanised anti-CD19 monoclonal antibody, in NMOSD.[3] During the randomised controlled period (RCP), inebilizumab showed good tolerability and rates of treatment-emergent adverse events (TEAEs), serious adverse events, and infusion-related reactions (IRRs), similar to placebo.[3] The aim is to evaluate the long-term safety of inebilizumab in participants with NMOSD.

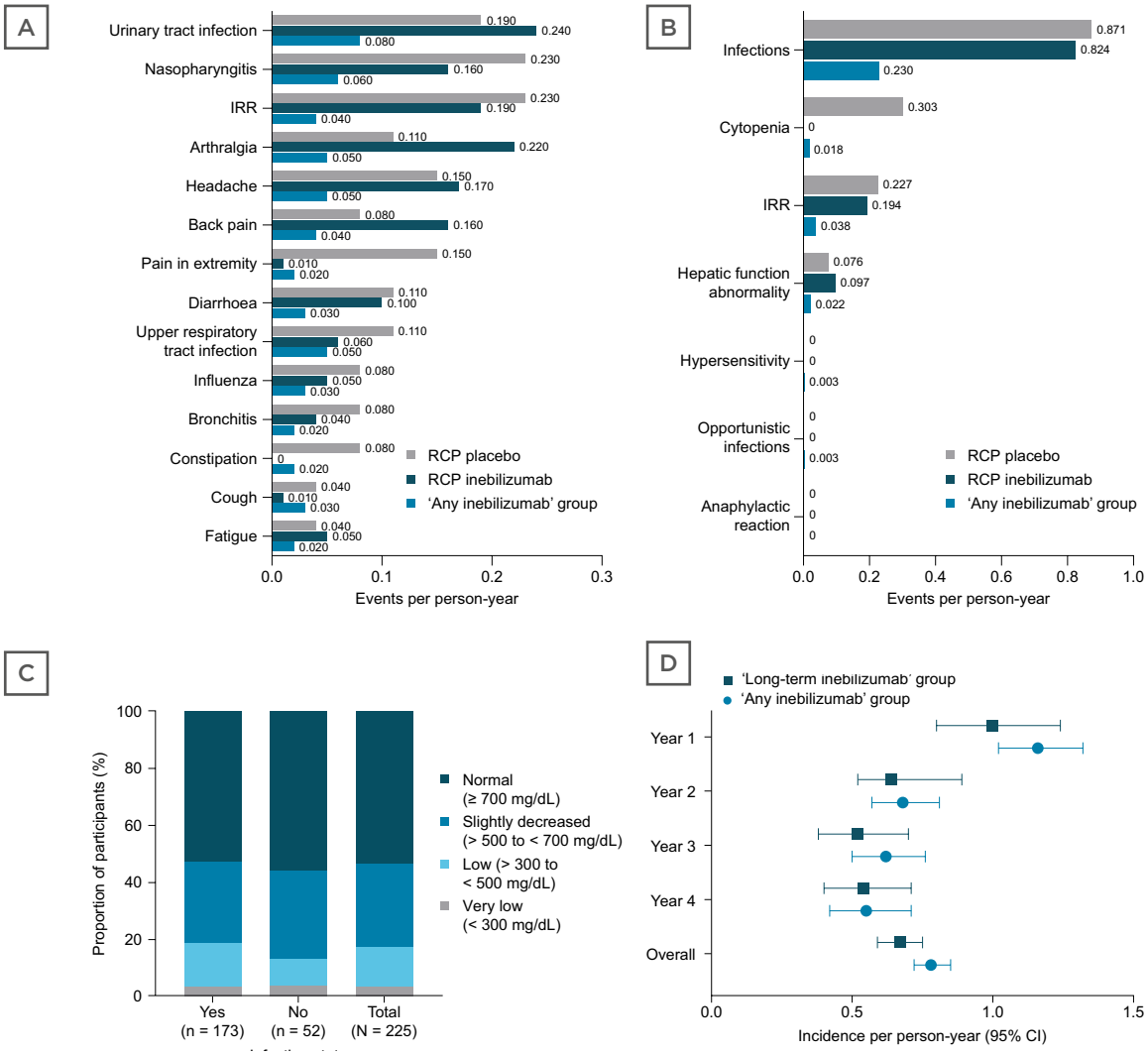

Figure 1: Rates per person-year.

A) TEAEs occurring in ≥10% of participants in the 'any inebilizumab' group.

B) AESIs during the N-MOmentum trial.

C) IgG level changes during the study in participants who did ('Yes') and did not ('No') experience an infection.

D) Incidence per person-year of treatment-emergent infections in the 'any inebilizumab' and 'long-term inebilizumab' groups.

AESI: adverse event of special interest; CI: confidence interval; IRR: infusion-related reaction; RCP: randomised controlled period; TEAE: treatment-emergent adverse event.

MATERIALS AND METHODS

Participants with NMOSD (aged ≥18 years with an Expanded Disability Status Scale [EDSS] score of ≤8 and a recent history of attacks) were randomised 3:1 to inebilizumab or placebo monotherapy in the RCP for 28 weeks or up to attack occurrence, after which they could enter the OLP for a minimum of 2 years. During the OLP, participants received inebilizumab (300 mg intravenous infusion) every 28 weeks for a maximum of 5.5 years. Long-term safety endpoints included TEAEs, adverse events of special interest (including severe and opportunistic infections and IRRs), anti-drug antibodies, and Ig level changes. Participants were grouped into two groups for analysis: 'any inebilizumab' (who received inebilizumab at any point during the study) and 'long-term inebilizumab' (who received inebilizumab for at least 4 years). Data from participants at the end of the RCP were also used for context.

RESULTS

Overall, 165/174 participants (94.8%) randomised to inebilizumab and 51/56 participants (91.1%) randomised to placebo in the RCP entered the OLP, with a total of 225 participants receiving 'any inebilizumab'. Mean treatment duration was 3.2 years (standard deviation: ±1.4 years) and 36.8% of participants were treated for more than 4 years; total inebilizumab exposure was 730.36 person-years. During the OLP, there were three deaths: one due to a severe NMOSD attack, one due to a central nervous system event of unclear aetiology, and one related to COVID-19 after 7,224 and 1,225 days of inebilizumab exposure, respectively.

'Any inebilizumab' participants did not have higher incidences of the most common TEAEs than those found during the RCP (TEAE rate per person-year: 'any inebilizumab', 0.28; RCP inebilizumab, 1.54; RCP placebo, 1.55 [Figure 1A]). Compared with placebo, inebilizumab did not increase the incidence of adverse events of special interest, including IRRs and opportunistic infections, during the RCP or with multiple dosing in the OLP (Figure 1B).

'Any inebilizumab' participants had decreased Ig levels, which were 28.8% lower than baseline with long-term treatment. However, Ig depletion did not increase infection rates. There was no correlation between infection and levels of IgG depletion (Fisher exact test, p>0.05 [Figure 1C]), and rates of infection in participants from the 'long-term inebilizumab' group were not higher than in the 'any inebilizumab' group (Figure 1D). Moreover, incidence of anti-drug antibody formation remained low during the study and did not increase with inebilizumab treatment or multiple dosing (participants with anti-inebilizumab antibodies: RCP inebilizumab, 2.9% [n=5]; RCP placebo, 7.1% [n=4]; OLP, 6.5% [n=14]).

CONCLUSION

Long-term data from the OLP of N-MOmentum demonstrated that treatment with inebilizumab was generally well tolerated for at least 4 years. No new safety signals were identified and rates of infection or serious infection did not increase with prolonged inebilizumab treatment. ■

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Resting State Functional Connectivity Changes of the Pons in Patients with Migraine: A Cross-Sectional and Longitudinal Study

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Keywords: Longitudinal functional MRI, migraine, pathophysiology, pons.

Citation: EMJ Neurol. 2021;9[1]:49-50. Abstract Review No. AR7.

BACKGROUND AND AIMS

Previous studies support a pivotal role of the pons during the pain phase of a migraine attack.[1-3] An altered activation of the pons during trigeminal nociceptive stimulation, as well as resting state functional connectivity (RS FC) alterations between the pons and pain processing cortical areas has been demonstrated in patients with migraine during the interictal phase.[4,5] This study aimed to elucidate the role of the pons in migraine pathophysiology using a longitudinal study design and investigate the association between pontine RS FC changes and the clinical characteristics and disease progression of patients with migraine.

MATERIALS AND METHODS

Using a 3.0 Tesla scanner, RS functional MRI and 3D T1-weighted scans were acquired from 91 headache-free patients with episodic migraine and 73 controls at baseline. Twenty-three patients and controls agreed to be re-examined after a median follow-up of 4.5 years. Maps of pontine RS FC were obtained from each subject using a seed-region correlation approach.[6] Using a general linear model and SPM12, a whole-brain analysis was performed to assess pontine RS FC changes. The correlation between functional MRI abnormalities and patients' clinical characteristics was also investigated.

RESULTS

During the follow-up, 11 patients reported a decreased number of migraine attacks, four patients had no changes in migraine attack frequency, and eight patients reported an increased number of attacks. At baseline, compared to controls, migraine patients showed a decreased RS FC between the left pons and left lingual gyrus, right cerebellar lobule V, and bilateral cerebellar crus I; while the right pons had a decreased RS FC with the left cerebellar crus I, right fusiform, and inferior temporal gyrus. Over the follow-up, compared to controls, patients with migraine developed an increased FC between the left pons and the cerebellar crus I, as well as a decreased FC between the left pons, ipsilateral cerebellar lobule VIII, and bilateral precuneus (Figure 1A). Patients with migraine also experienced a decreased right pontine RS FC with the ipsilateral superior temporal gyrus and bilateral precuneus (Figure 1B). The increased RS FC between the left pons and ipsilateral cerebellar crus I was associated to an increased migraine attack frequency over the years.

CONCLUSION

Similar to previous cross-sectional studies,[4,5] the authors confirmed that the pons modulates the activity of pain processing brain areas in patients with migraine. Their findings also highlighted an interaction between the pons and extrastriate visual areas during the interictal phase, supporting their key role in migraine pathophysiology.

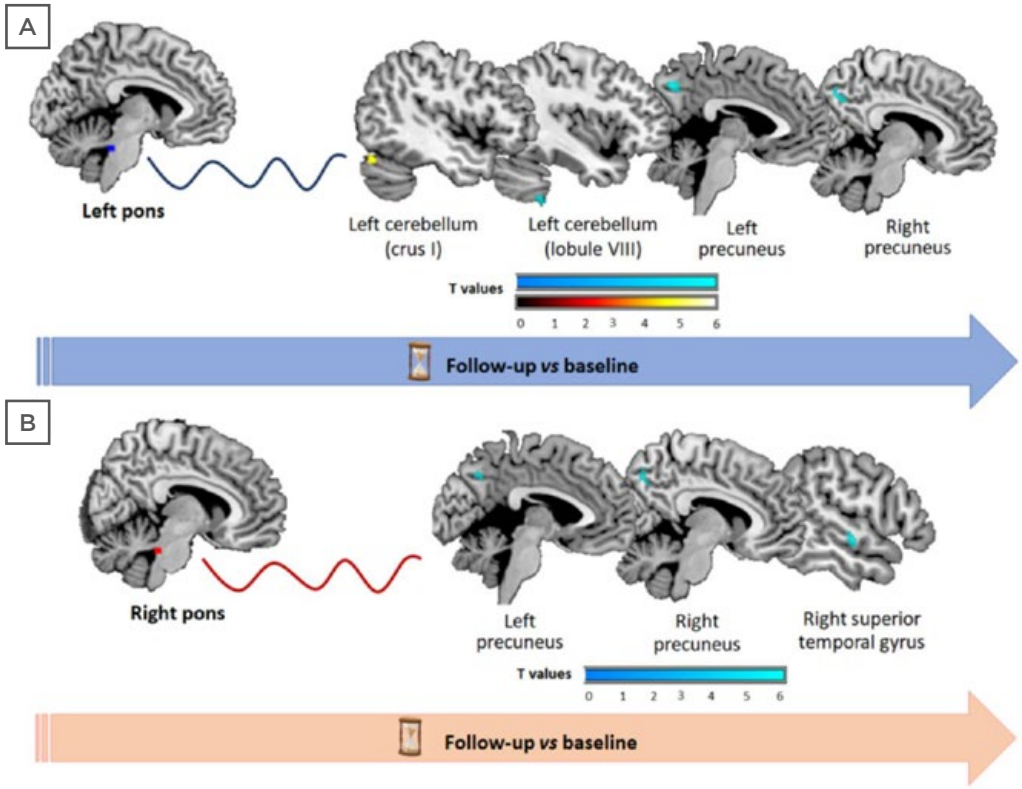

Figure 1: Brain regions showing significant longitudinal resting state functional connectivity changes of the left (A) and right (B) pons in patients with migraine compared to controls at follow-up versus baseline.

Areas of decreased RS FC are colour-coded in blue, and areas of increased RS FC are represented in red, according to their t values. The left pons is represented in blue, and the right pons is represented in red.

RS FC: resting state functional connectivity; vs: versus.

In this cohort, the RS FC of the pons changes dynamically over time. After 4 years, the RS FC between the pons and precuneus, a region known to be involved in sensory integration, is decreased. Compared to controls, patients with migraine developed both decreased and increased RS FC between the pons and the cerebellum, suggesting that distinct adaptive responses might occur over time at the level of the cerebellum. Some of the cerebellar changes might represent a maladaptive response, contributing to migraines worsening. ■

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The Effects of Great Occipital Nerve Block Over Photophobia in Patients with Migraine

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Keywords: Greater occipital nerve (GON), migraine, photophobia

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BACKGROUND AND AIMS

Photophobia is a sensory disturbance provoked by light commonly seen in several headache disorders. Photophobia affects as much as 80% of patients with migraine, presenting even outside of migraine attacks.[1] In the Migraine in America Symptoms and Treatment (MAST) study, 49.1% of participants reported photophobia as the most bothersome symptom.[2]

For a greater characterisation of the photophobia impact in daily activities, several clinical scores have been validated, such as the 8-item Korean Photophobia Questionnaire (KUMC-8)[1] and the 12-item Utah Photophobia Symptom Impact Scale (UPSIS-12).[3] KUMC-8 consists of eight yes-no questions, with seven of them relating light aversion with pain in the migraine phase and the last one about photophobia in the out-of-pain phases of migraine. Photophobia between the migraine attacks gains more relevancy in UPSIS-12, representing 40 out of a maximum score of 55.

To date, most of the recommended treatments for photophobia are based on case-reports or a few studies with small sample sizes. New therapies are still needed to improve this bothersome symptom.

MATERIALS AND METHODS

The authors conducted a prospective case-control observational study with a successive recruitment of patients with migraine and photophobia. Data was collected in two visits: the baseline visit (V1) and the follow-up visit (V2), which was scheduled 7 days after V1. Greater occipital nerve (GON) block and other migraine therapies were used following the current guidelines of the Spanish Society of Neurology. Cases were defined as patients in which GON block was performed. As per usual clinical practice, GON block was offered to patients with an ongoing migraine attack at the time of the visit, frequent attacks in the previous week, a headache frequency that exceeded 15 days per month in the last 3 months despite adequate treatment, and to patients that had reported a good previous response to GON block in terms of pain. All patients completed UPSIS-12, KUMC-8, the Hospital Anxiety and Depression Scale, and the Migraine Specific Quality of Life Questionnaire (version 2.1) both in V1 and V2.

RESULTS

For this study, 41 patients were recruited: 28 (68.3%) cases and 13 (31.7%) controls. At V1, there was no significant difference in the median (p25–p75) score of UPSIS-12 in cases versus controls (32.0 [21.0–34.0] versus 30.5 [22.0–37.0]; p=0.497) or KUMC-8 (6.5 [5.5–7.0] versus 7.0 [6.0–8.0]; p=0.463). At V2, cases experimented a significant improvement in UPSIS-12 of -5.5 ([-8.8]-[-1.3]) and in KUMC-8 of -0.5 ([-2.0]-0), while there were no significant changes in the control group. Patients with aura migraine scored higher on UPSIS-12 at V1 (33.5 [24.5–37.0] versus 26.0 [16.0–35.0]) and experimented lesser improvement at V2 after GON block compared with patients without aura migraine (-4.0 [(-6.0)–(-1.0)] versus -8.0 [(-17.0)–(-2.0)]), although statistical signification was not achieved (p=0.643 and p=0.122, respectively). There was no significant variation in the remaining scales.

CONCLUSION

GON block improves migraine-associated photophobia, measured with UPSIS-12 and KUMC-8. Patients without aura may exhibit a greater improvement. Physicians could consider GON block for management of photophobia in patients with migraine. ■

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Congress Interview

Riccardo Soffietti

Chair of the Education Committee at the European Academy of Neurology (EAN) 2021; Head of the Neuro-Oncology Department, University Hospital of Turin, Italy; and Professor of Neurology and Neuro-Oncology, University of Turin Medical School, Italy

Riccardo Soffietti, Chair of the Education Committee at the European Academy of Neurology (EAN) 2021, spoke to EMJ about his motives to research in neurology, recent publications in the field, the influences and activity of the EAN, and what lies ahead for his career.

Q1 Was there a particular event or person that encouraged you to pursue a career in neurology?

I was attracted early on in my graduation period by neuroanatomy, neurochemistry, and neurophysiology.

Q2 Do you think there are any misconceptions about your speciality? What excites you most about the field of neurology?

Still, there is some confusion in the clinical practice between neurology and psychiatry. Molecular and neuroimaging advances in clinical neurosciences have been dramatic and exciting.

Q3 What was the key message of your recently published review "Primary prevention of COVID-19: advocacy for vaccination from a neurological perspective"?

Aside from acute neurological complications from COVID-19, mainly linked to the systemic disease, we are increasingly seeing more subtle and delayed cognitive and emotional disturbances. In this regard, vaccination is even more important.

Q4 Is there anything that you or the EAN learnt from the first virtual EAN congress last year, that will be carried into this year's congress?

We learned that a virtual congress that is easily accessible worldwide may enhance the spread of science and knowledge.

Q5 What are you hoping to achieve through the launching of a new eLearning platform and mentorship programme for young neurologists at EAN?

The e-Learning platform will cover all subfields of neurology in a dynamic fashion, as it will be continuously updated. The platform will be instrumental for both the European Board Examination of young people but also useful for continuous medical education of certified neurologists. The Mentorship programme will

enhance the relationships between expert academic neurologists and young residents fond of receiving advice for their advancements in career.

Q6 What are the most significant changes you have seen in the field of neurology and neuro-oncology during your time working with the field?

I cannot list all changes in all subfields. However, new treatments in multiple sclerosis and headaches, and progress in basic science of movement disorders and brain tumours impressed me most.

Q7 How much of an impact do you believe the EAN congress has, both directly on neurologists at different stages in their careers and indirectly on patients?

EAN is increasingly reaching neurologists not only in Europe, but also worldwide, especially in Africa and South America. This will benefit the skills of neurologists in taking care of their patients.

Q8 Where do you hope to focus next, and what continues to energise your work in the field?

As the Chair of the Education Committee, I will work on new initiatives, such as the development of a Leadership Programme and a Fellowship for talented students during graduation in Medicine.

As a neuro-oncologist, I will further enhance my activity in translational neuro-oncology, including the design of clinical studies on new targeted agents. ■

"The Mentorship programme will enhance the relationships between expert academic neurologists and young residents fond of receiving advice for their advancements in career"

Interviews

We spoke to respected researcher Dr Sergio Baranzini and neurologist Dr Kristian Steen Frederiksen to find out about their clinical interests and the translation of their research focusses into bedside care.

Sergio Baranzini

Associate Professor In-Residence, Department of Neurology, University of California San Francisco (UCSF), California, USA

Q1 What inspired you to pursue a career in scientific research?

Both my parents were clinical biochemists, and ran their lab next to our house, so I grew up in between microscopes, electrophoretic apparatuses, and centrifuges. Later, when I took my first courses in genetics and molecular biology, I was fascinated with the complexity of living organisms and wanted to dedicate my career to solving some of the puzzles that human diseases represented to me.

Q2 After completing your undergraduate and postgraduate degrees in biochemistry, what influenced your decision to specialise in neurology and neurogenetics?

During my PhD, I focused on understanding the phenotypic effects of different mutations that caused Duchenne muscular dystrophy. I shifted the attention of my work to multiple sclerosis (MS), in part because I was motivated by the challenge posed by complex diseases, where small effects from multiple genes converge in shaping risk. If one thinks about the two most complex systems in the human body, the likely choices are the brain and the immune system. Both of them are composed of billions of cells interacting in non-linear ways, producing emergent behaviours (i.e., emotions, fighting pathogens, etc.). In that regard, since MS involves an autoimmune attack on central nervous system myelin, it could be considered the most complex disease ever described. Contributing to understanding MS pathogenesis and devising new therapeutic options were the main two pillars of my decision.

Q3 The work at the Baranzini Lab at UCSF is half computational and half experimental research; how does this strategy of an equally weighted investment into the two strengthen the lab's position in the field and the research it produces?

I strongly believe that a modern laboratory needs to incorporate data science to do relevant work and be successful. This is because we are relying more and more on high-throughput data from our instruments (e.g., 'omics', large-scale electronic health records, real-time monitoring, imaging, etc.). Thus, at the beginning of my career, I needed to decide whether I wanted to collaborate with a bioinformatics lab or become one. Because of my training as a bench scientist, I considered the best option was to build a hybrid lab that could analyse the data it produced.

"I strongly believe that a modern lab needs to incorporate data science to do relevant work and be successful."

Q4 Computational and bioinformatic tools over the past few decades, and artificial intelligence and machine learning in the past few years, have significantly advanced scientific research; how do you see these tools aiding in the research and development of therapies for MS?

I think they will be critical. In my view, biomedicine is lagging behind other fields (e.g., banking, e-commerce, etc.) when it comes to effective utilisation of sophisticated statistics and artificial intelligence. One of the reasons is that biomedicine is more complex, and the standards to trust a given health-related prediction need to be higher than whether a bank will grant a loan to a customer or not. If an algorithm outputs a given treatment for a patient, the doctor needs to know why a given prediction is suggested; it cannot be a black box. Thus, in the near future, we will see more applications of artificial intelligence and machine learning to biomedicine, with the particularity that they will have to be explainable.

Q5 Could you explain the possibility of personalised medicine based on data-driven insights in the management of MS?

Doctors today need to process more information than ever before. New laboratory tests, imaging modalities, and additional patient-derived data (including real-time monitoring, wearables, etc.) further complicate making an accurate diagnosis and deciding on the best course of action for a particular patient. The reality is that no doctor (or for that matter, no human being) can recall, interpret, integrate, and process this colossal amount of information in order to respond adequately (and in real-time) to complex scenarios to achieve the best care for their patient. This is why artificial intelligence will likely be a companion to make sure all possibilities are considered, given the patient's history, to make the best possible decision.

Q6 There has recently been a substantial focus on the link between gut microbiome dysbiosis and numerous diseases, including MS. In your opinion, what is the therapeutic potential of gut microbiome-targeted therapy in the case of MS? What challenges does this field of research still face?

We are still beginning to understand the extent of the role the gut microbiota plays in human diseases; however, I anticipate it will not be minor. Therapeutic options that involve modification of the gut microbiota are not only pharmacological but also involve next-generation probiotics and dietary interventions. In the case of MS, the many therapeutic options already available may limit the applicability of microbial therapies. On the other hand, these may represent a more natural approach, with a more favourable adverse events profile, and thus be attractive to some patients.

Q7 Looking back across your impressive career, do you have a standout or proudest moment?

We all live very busy lives and sometimes do not take time to reflect on ourselves. I will be proud if anything I help discover can make the life of a patient suffering from a chronic disease even a little better.

Kristian Steen Frederiksen

Consultant Neurologist, Danish Dementia Research Centre, Department of Neurology, Rigshospitalet, University of Copenhagen, Denmark

Q1 What influenced your decision to specialise in Alzheimer's disease (AD) and vascular dementia?

Since medical school I have had a special interest in cognitive neurology and higher cortical functions, and actually started out doing a small pre-graduate research project in biological psychiatry. However, I quickly discovered that it was within neurology that my future lay. Being interested in cognitive neurology led to AD and vascular dementia specialisation. I like working with common diseases and that is probably why I chose to focus on these two dementia disorders.

Q2 In July 2020 you were the first author of a manuscript entitled 'A European Academy of Neurology guideline on medical management issues in dementia'. Could you summarise the main points addressed in this article?

This guideline comes from the realisation that despite the fact that AD and other dementia disorders are not curable, they are manageable in the sense that we can improve the quality of life for patients with dementia and perhaps slow the progression of disease by managing risk factors and associated medical conditions. For example, treating vascular risk factors is likely to reduce progression rates, but nevertheless patients will not always receive the appropriate treatment, sometimes perhaps due to a nihilistic attitude on behalf of the physician, or for fear of side effects. In the guideline, we further give guidance on management of pain, epilepsy, aggression, and agitation in patients with dementia and give recommendations on systematic medical follow-up.

Q3 Given that a research interest of yours includes the role of exercise as a potential adjunct to pharmacological treatment of AD, what are the effects of physical activity on Alzheimer's disease biomarkers and what are the new developments in this field?

Physical exercise is a promising supplement to pharmacological therapies. Findings in the last 10–15 years have underscored the preventive effect of exercise in terms of incident dementia, but also improvements of dementia symptoms in patients with dementia; specifically regarding effects on AD pathology reflected by biomarkers, for example, results are still sparse. Since the early 2000s there have been a lot of promising results in AD animal models demonstrating substantial reductions in β-amyloid, reduced hippocampal atrophy, and also effects on phospho-tau following exercise. In humans, there is a growing evidence base showing some effects on brain volume, but most are in healthy elderly persons or in mild cognitive impairment (MCI). Studies in patients with AD are relatively few, and the findings are somewhat contradictory, for example regarding effects on hippocampal volume. We performed a study in patients with AD in which we investigated the effects of exercise on β-amyloid measured using carbon-11-labelled Pittsburgh compound B (11C-PiB)-PET, and were not able to demonstrate an effect. This is the only study so far to examine the hypothesis that exercise may clear β-amyloid. Our findings do in no way dispel the hypothesis amongst other reasons for the fact that the intervention was relatively short, but also since further studies need to replicate the finding.

Q4 Aside from physical activity and exercise, what other non-pharmacological interventions for AD do you believe merit greater attention?

It is always a bit difficult discussing so-called non-pharmacological interventions as they are very different and are difficult to delineate from things such as care. In general, these interventions are difficult to prove effective, some because they are not effective, but in other instances for other reasons. If I should point to one intervention it would undoubtedly be cognitive stimulation, which has convincingly been shown to be effective in MCI and mild dementia. The most well-examined form is cognitive stimulation therapy. Another really interesting intervention is transcranial stimulation, where an electrical current is applied on the cranium to elicit currents on the surface of the brain. I think this, in the future, may be a possible adjunct therapy for patients with dementia. Lastly, multi-modal therapy combining exercise, diet, and cognitive stimulation (or other combinations) also looks promising.

Q5 Could you highlight the principal findings and wider relevance of your paper 'European Academy of Neurology/European Alzheimer's Disease Consortium position statement on diagnostic disclosure, biomarker counselling, and management of patients with mild cognitive impairment'?

This paper endeavours to give guidance to clinicians diagnosing and managing patients with MCI. MCI is a tricky diagnosis in many respects. Firstly, it is easily misinterpreted as a disease when in actual case it is a syndrome. The consequence of this is that the clinician should always strive to identify the underlying cause of the syndrome. There are many possible causes of MCI, some reversible, some associated with a high risk of progression to dementia, for example in the case of AD. Another issue is that conveying a diagnosis of MCI is not easy. It may be misconstrued as dementia or the physician may not be sure what the patient is experiencing. We also give recommendations on how to discuss whether to do biomarker studies with the patient and how to convey the results of biomarker sampling and their meaning for the patient and their prognosis.

"There is accumulating evidence that COVID-19 affects brain functions, at least during the acute infection. "

Q6 You recently published an article exploring the prevalence of acute delirium and other neuropsychiatric symptoms in patients with COVID-19. What biological mechanisms underlie the association between COVID-19 and cognitive impairment?

The relationship between COVID-19 and dementia is complicated and studies are limited. Nevertheless, it is an intriguing one. There is no doubt that having dementia increases your risk of contracting COVID-19, and also your risk of becoming seriously ill with COVID-19. However, it may also go the other way, i.e., that infection may increase your risk of developing dementia.

There is accumulating evidence that COVID-19 affects brain functions, at least during the acute infection. For example, delirium is common in the acute phase, and a number of other neurological symptoms have been reported, such as cognitive impairment. A few imaging studies have indicated that especially frontal and parietal regions are affected, but also luckily that these changes are reversible and almost resolve 6 months after the infection has been cleared. The mechanisms responsible for the neurological symptoms remain uncertain but may include direct invasion of the virus into the brain and neurons, cytokine storm, or the effects of critical illness and the need for intensive care unit treatments, or a combination of the three.

"I think we are missing a really beneficial effect of exercise for patients with dementia, and that is the immediate positive effects of exercise."

Q7 Could you share the key conclusions drawn from your recent paper, 'Comparison of the Clinical Impact of 2-[18F]FDG-PET and Cerebrospinal Fluid Biomarkers in Patients Suspected of Alzheimer's Disease'?

In this study, we addressed the issue of whether cerebrospinal fluid sampling or fluorodeoxyglucose-PET scanning was superior

in terms of improvement in diagnostic accuracy in patients with suspected AD. We found that the two examinations were equal. However, interpretation and application of biomarkers need to take the individual clinical question into account.

Q8 As a researcher, where can we expect to see your focus progress to in the coming years?

I still have a keen interest in exercise. I have plans for a study of the acute effects of a single bout of exercise on brain functions and cognitive functions as well as signalling molecules released from muscle. The aim is to tease out some of the basic mechanisms coupling exercise and effects on the brain. I think we are missing a really beneficial effect of exercise for patients with dementia, and that is the immediate positive effects of exercise. A kind of 'runner's high'. This possible effect is probably not picked up in longer intervention studies over weeks to months. The idea is partly fuelled by my own personal observations that if I manage to fit in a run, or I bike to work, I feel much more able to focus and stay attentive to what I am doing. Plus, my mind finds rest to explore many different ideas when I am running.

In terms of biomarkers, I am initiating a study on prognostic blood-based biomarkers. I find that there is a great need for prognostic biomarkers. This is something I am almost always asked about by patients who receive a dementia diagnosis: "What will I be like in 1-, 2-, or 3-years' time?" For this, we do not have very good answers. Lastly, I am leading a study on the prodromal symptoms in Lewy body dementia: a really interesting study that I hope will be a small piece in the burgeoning exploration of this fascinating disease.

A Successful Treatment of Chronic Migraine with Hyperbaric Oxygen Therapy

EDITOR'S PICK

The use of hyperbaric oxygen as treatment for pain has received considerable attention over the last few years. This issue's Editor's Pick is a case report by Shafee et al. in which the authors describe treating a patient who presented with migraine with hyperbaric oxygen, highlighting this as a feasible treatment path for analgesic-resistant migraine. We hope you enjoy reading this highly interesting article.

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Abstract

The World Health Organization (WHO) ranks migraine as the most prevalent and disabling neurological condition. Management of migraines can be broadly divided into lifestyle and trigger management, acute treatments, and preventive treatments. Despite pharmacological advances, this medical problem has remained undertreated.

A 40-year-old male presented to the authors' hospital and complained of severe, constant, and throbbing pain over the right side of his head. There was occasional photophobia but no visual disturbances. Oral analgesics were not helpful. After careful evaluation, he was advised to receive hyperbaric oxygen therapy sessions. He underwent one session per day, 5 days per week for 4 weeks. At the end of the 20 sessions, the patient reported an improvement in his symptoms, and did not require any oral medication. The authors concluded that hyperbaric oxygen therapy should be explored further as a treatment for pharmacologically resistant migraine.

INTRODUCTION

Migraines involve intense head pain, which severely affects the activities of daily living, and is the is the third most common disease in the world.[1] Migraines affect approximately 15% of the general population in England[2] and the World Health Organization (WHO) ranks migraine as the most prevalent and disabling neurological condition.[3] Patients with migraine usually complain of pain over half of the head. The pain is generally throbbing in nature and worsens with movement.

Table 1: Phases of migraine.

Phases	Time period	Symptoms
Prodome	A few days to hours	Irritability, depression, yawning, increased need for urination, food craving, sensitivity to light and sounds, difficulty concentrating, fatigue, difficulty speaking/reading, nausea, difficulty sleeping
Aura	5–60 min	Visual disturbances, temporary loss of sight, numbness and tingling on part of the body
Migraine attack	4–72 hours	Throbbing pain, burning sensation, nausea, vomiting, giddiness, insomnia, nasal congestion, anxiety, depressed mood, sensitivity to light/smell/sound, neck pain and stiffness
Postdrome	24–48 hours	Inability to concentrate, fatigue, depressed mood, euphoric mood, lack of comprehension

It is typically accompanied by nausea, dizziness, extreme sensitivity to lights and noises, lack of appetite, disturbances of bowel function, and occasionally aura.[4] There are four phases of migraine,[5] which have been summarised in Table 1.

PATHOGENESIS

The exact pathogenesis of migraine is unknown. The current state of knowledge suggests that a primary neuronal dysfunction leads to a sequence of changes intracranially and extracranially.[6,7] This primary neuronal dysfunction has features of cortical spreading depression, activation of the trigeminovascular system, onset of inflammation, and sensitisation.

The once-popular vascular theory of migraine, which suggested that migraine headache was caused by the dilatation of blood vessels, while the aura of migraine resulted from vasoconstriction, is no longer considered viable.[8-10] Vasodilatation, if it occurs at all during spontaneous migraine attacks,[10] is probably an epiphenomenon resulting from instability in the central neurovascular control mechanism.

Currently considered to be a neurological condition, migraine is more likely caused by inflammation in response to the release of neuropeptides. The release of neuropeptides, such as Substance P, calcitonin gene-related peptide, and neurokinin A, is associated with the process of neurogenic inflammation, which is thought to be important in the prolongation and intensification of the pain of migraine.[11] This neurogenic inflammation can lead to sensitisation: a process in which neurons become increasingly responsive to stimulation and the pain threshold decreases. Sensitisation is thought to be responsible for many of the clinical symptoms of migraine, including the throbbing quality of the pain and worsening of the pain with coughing, bending, or sudden head movements.[12-14]

Management of migraines can be broadly divided into three: lifestyle and trigger management, acute treatments, and preventive treatments. Some examples of the acute treatment for migraine are paracetamol, nonsteroidal anti-inflammatory drugs, opioids, and triptans. Tricyclics, β-blockers, anticonvulsants, and botulinum toxin (botox) injections are some options for preventive treatments; however, despite advances in pharmacology, migraine has remained undertreated.[4] Besides pharmacological treatment, there are other modalities that are emerging to be treatment options to treat migraine. Among these modalities, hyperbaric oxygen therapy (HBOT) is gaining popularity. The authors present a case of a patient with chronic migraine, managed successfully with HBOT.

CASE DESCRIPTION

A 40-year-old male patient complained of frequent severe, constant, and throbbing pain over the right side of his head. There was occasional photophobia but no visual disturbances. He had a history of migraine for >10 years. Initially, the attacks occurred two to three times per month, but had increased to more than 15 times per month in the preceding 6 months. Each pain episode would last for 1–2 hours. The patient's Numerical Rating Scale (NRS) pain score during the attack had also increased over the years, from 6/10 to 10/10. Over the years, he had a history of taking oral sumatriptan, nonsteroidal anti-inflammatory drugs, antiepileptics, and opioids. None of the pharmacotherapy helped to reduce his pain or frequency of attacks.

Upon examination, the patient was alert and orientated. His vital signs were within normal range. His motor and sensory examinations and reflexes for both upper and lower limbs were healthy. Examination of his cranial nerves was also normal. There were no visible lesions on his face or eye and brain MRI was normal. Based on the International Classification of Headache Disorders 3rd edition (ICHD-3) guidelines, a diagnosis of chronic migraine was made. The patient presented to the authors' clinic requesting for an alternative treatment for his migraine. He was unhappy with his existing pain control. After careful evaluation, he was advised to receive 20 sessions of 90-minute HBOT at 2 atmosphere absolute (ATA). The plan was to administer one session per day, 5 days per week, for a duration of 4 weeks.

A single-person-chamber was used for the treatment. During the treatment in the chamber, the patient did not have any discomfort or complaints and was comfortable in the chamber. No unwanted effects of HBOT were recorded following sessions. At the end of the 20 sessions, the patient reported an improvement in his symptoms. His pain score reduced to 2/10. He did not require analgesics or any prophylactic medication. He was able to continue with his daily activities and work without any complaints. A follow-up review of the patient 6 months later showed good pain control, with a pain score ranging from 1 to 3 during his migraine attacks. The frequencies of attack were also reduced to one or two episodes per month. He did not require any analgesics or any more HBOT maintenance.

DISCUSSION

The Undersea and Hyperbaric Medical Society (UHMS) defined HBOT as an intervention in which an individual breathes near 100% oxygen intermittently while inside a hyperbaric chamber that is pressurised to greater than sea level pressure (1 ATA).[15] If the lungs are healthy, an arterial partial pressure of oxygen in the range 1000–15000 mmHg is generally achieved at 2–3 ATA. This will create an oxygen partial pressure in the tissues of between 200 and 400 mmHg or more, which will induce a controlled oxidative stress causing activation of various pathways. This will result in multiple potential clinical benefits, including diminished inflammatory responses.[16] In a monoplace chamber, an individual patient breathes in directly pressurised 100% oxygen. In the multiplace chambers with more than one patient, the patients will be pressurised with air, and breathe 100% oxygen indirectly via a head hood, mask, or endotracheal tube.[17] HBOT is approved for 14 indications, summarised in Table 2;[15] however, besides these standard indications, several studies have demonstrated many other benefits of HBOT, including the management of migraines.

There have been several published studies regarding the use of HBOT to treat migraine. There was a similar case report recently showing a successful treatment of migraine in a 23-year-old patient.[18] The authors used a treatment of 1.5 ATA in a chamber for 40 sessions. This protocol will reduce the treatment time by 50%, as the authors only held 20 sessions with the patient instead of the documented 40 sessions. The 20-session intervention protocol had the added advantage of less disruption to the patient's routine and productivity as well as faster positive outcome. Despite a higher ATA, the patient was comfortable without any complaints. This protocol had a good outcome in the patient. The authors will continue to use this treatment protocol for future patients with severe migraine.

Oxygen is presumed to have the ability to constrict distal cerebral vessels;[19] therefore, oxygen administered at higher pressures will produce even further vasoconstriction.

Table 2: Indications for hyperbaric oxygen therapy.

Air or gas embolism
Carbon monoxide poisoning
Gas gangrene
Crush injury, compartment syndrome
Decompression sickness
Arterial insufficiencies: central retinal artery occlusion, wounds
Severe anaemia
Intracranial abscess
Necrotising soft tissue infections
Refractory osteomyelitis
Delayed radiation injury
Compromised grafts and flaps
Acute thermal burn injury
Idiopathic sudden sensorineural hearing loss

The supply of oxygen dissolved within the plasma, however, is not compromised and the net effect of tissue oxygen is maintained because of hyperoxia.[20] This suggests that HBOT may be a favourable treatment for vascular migraines.[21] Furthermore, the pain relief effects of HBOT for those with migraine may also be attributed to the correction of local hypoxia.

If the current projections about the pathophysiology of migraine are correct, inflammation plays a central role, and vasodilatation is an epiphenomenon. Hyperbaric oxygen has been shown to modulate the immune cytokines in multiple conditions, including decompression illness and air embolism; that would be the likely mechanism of benefit in patients with migraine.[22]

The use of HBOT is not without risk.[15] The most common side effects of HBOT are middle ear barotrauma and sinus squeeze, which appear in almost 2% of treated patients.[23] Another frequent complaint is claustrophobia, which may occur in monoplace and multiplace chambers. Multiple exposures to HBOT can also lead to oxygen toxicity. Oxygen toxicity may lead to progressive myopia and pulmonary symptoms such as cough and inspiratory pain. When higher oxygen pressures are used, especially in treatment of acidotic patients, for example, those with carbon monoxide poisoning, oxygen-induced seizures may also occur. For these reasons, a thorough medical history and physical examination should precede every HBOT. By doing this, subjects who are at risk of complications can be identified, and the right treatment protocol can be tailored to the patient.[15]

CONCLUSION

Migraine can be a very debilitating problem. Migraines affect approximately 15% of the general population in England and the WHO ranks migraine as the most prevalent and disabling neurological condition. Management of migraines can be broadly divided into lifestyle and trigger management, acute treatments, and preventive treatments. Despite pharmacological advances, this medical problem has remained undertreated. HBOT can be an alternative treatment for patients with migraine who are not responding to traditional pharmacotherapy. Despite the risk of using HBOT, patients at risk can be identified early before the treatment protocol; however, more studies are needed before HBOT can be a mainstream treatment of persistent migraine in the near future.

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A Case Report: Internal Carotid Artery Dissection Presenting as Hoarseness Secondary to Vocal Cord Palsy

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Abstract

Internal carotid artery (ICA) dissection is a rare cause of a cranial nerve X palsy. Patients more commonly present with stroke or transient ischaemic attacks. An undetected and untreated ICA dissection can have serious consequences. Here, the authors present two cases of ICA dissection presenting with isolated vagal nerve palsy presenting with hoarseness. CT scans provided good evidence of ICA in both cases. The patients were treated with antiplatelet agents and made a good recovery with complete resolution of symptoms.

INTRODUCTION

Vocal cord paralysis or weakness can be a symptom of malignancy, caused by viral infection, iatrogenic, a result of trauma, idiopathic, or a result of brainstem infarction, in particular lateral medullary syndrome.[1] Internal carotid artery (ICA) dissection is a rare cause of an X cranial nerve palsy. This particular nerve palsy is present in only 16% of ICA dissection cases.[2] Isolated cranial nerve palsies are an unusual presentation of ICA dissection. Patients more commonly present with stroke or transient ischaemic attacks. They can also present with multiple lower cranial nerve palsies and other concurrent neurological deficits, such as Horner's syndrome, due to compression of sympathetic nerves around the ICA by a thrombus.[2] An undetected and untreated ICA dissection can have serious consequences.[3] Here, the authors present two cases of ICA dissection with isolated vagal nerve palsy.

CASE 1

Presentation

A previously healthy male, who occasionally smoked, presented at the age of 42 with a sudden onset of hoarseness and swallowing difficulties, but with no history of trauma. They also reported pain over the right side of their head and face. They were initially treated in primary care with antibiotics, but there was no improvement. A contrast-enhanced CT scan of

their chest and abdomen did not reveal the cause of their symptoms. They were then referred to the otolaryngology service where a right vocal cord palsy was found on fibreoptic laryngoscopy. Due to some concern about the appearance of the right piriform fossa, they underwent examination under general anaesthetic, but this was unremarkable.

Investigation

A further CT scan was requested in order to investigate a potential cause of the vocal cord palsy in the head and neck. The standard protocol for contrast CT of the neck alone for otorhinolaryngological (ear, nose, and throat) pathology in the authors' local department was utilised. This is a split bolus technique: 45 mL of Omipaque™ (GE Healthcare, Chicago, Illinois, USA; iohexol) 300 administered at a rate of 1.5 mL/sec, with a further 45 mL bolus at the same rate with an inter-bolus delay of 30 secs. This resulted in neck images being acquired with good soft tissue and vascular contrast at 90 secs following the start of the first contrast injection. Axial coverage was from above the frontal sinuses to the clavicles. This CT scan demonstrated a thickening of the right ICA at the skull base with narrowing of the vessel lumen and eccentric hypodensity, strongly suggestive of arterial dissection (Figure 1). An MRI was also performed using axial fat-saturated sequences and this revealed corresponding eccentric T2 iso- or hyperintensity around the right ICA true lumen, confirming the suspicion of dissection (Figure 2).

Treatment and Outcome

Antiplatelet therapy was commenced for a period of 6 months. Over the next 6 months, their vocal cord palsy persisted but their left vocal cord was compensating very well, allowing them to produce a stable and strong voice. They were referred to the speech and language therapy team, and a year after their first presentation their right vocal cord had fully recovered.

CASE 2

Presentation

A 29-year-old female patient, previously healthy, presented with a sudden onset of difficulty swallowing. Shortly after the onset of their dysphagia, they developed hoarseness. Although their physical activities were not affected, they found themselves more breathless walking up the stairs and found it difficult to complete sentences. They also noticed a left-sided pulsatile tinnitus when lying on their left side. They attended their general practitioner and were treated with two courses of antibiotics. They reported no history of trauma. Onward referral was made to the otolaryngology service. Further investigation was arranged due to the unresolved cause of the issue. Fibreoptic examination revealed impaired left vocal cord movement.

Investigation

A CT scan was organised, and the split-bolus contrast CT showed narrowing of the lumen of the left ICA and eccentric mural thickening, consistent with a left ICA dissection (Figure 3). The same split-bolus sequence was used. A 75 mL bolus was administered at 2.5 mL/sec and the thorax was scanned at 65 secs delay with arms up. This was quickly followed by a 50 mL bolus at 2.0 mL/sec and the neck was scanned with arms down at 25 secs delay. The result was a split-bolus neck scan at approximately 100 secs following the start of the first injection.

Treatment and Outcome

Following the diagnosis, the individual was referred to the stroke team and began antiplatelet therapy for a duration of 6 months to reduce the risk of thromboembolism.[4] Follow-up CT angiogram revealed a near-complete resolution. When reviewed a few months later, the patient reported that their swallowing and voice symptoms had completely resolved. The only residual symptom was the awareness of intermittent pulsatile tinnitus in their left ear at night. Genetic testing was carried out and no underlying genetic connective tissue disorder was discovered.

DISCUSSION

ICA dissection can be either intracranial or extracranial. Although rare with an incidence between 2.6 and 2.9 per 100,000, extracranial ICA dissection is still more common than intracranial ICA in the adult European population.[5] It is also more common in males, usually aged 50–59.[6]

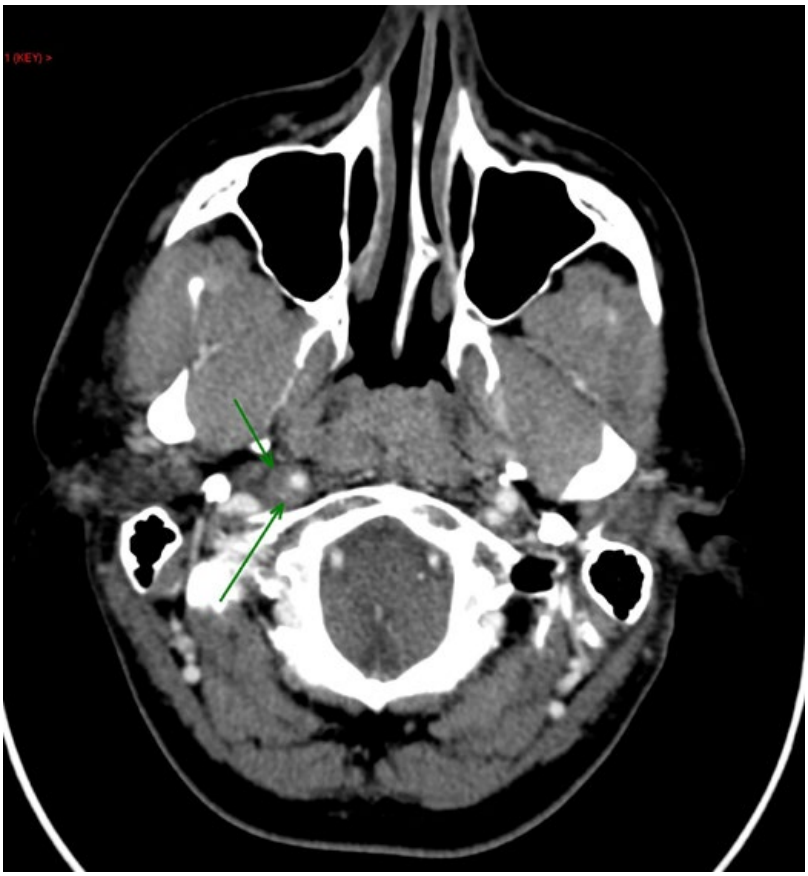

Figure 1: Axial CT image depicting the intramural haematoma.

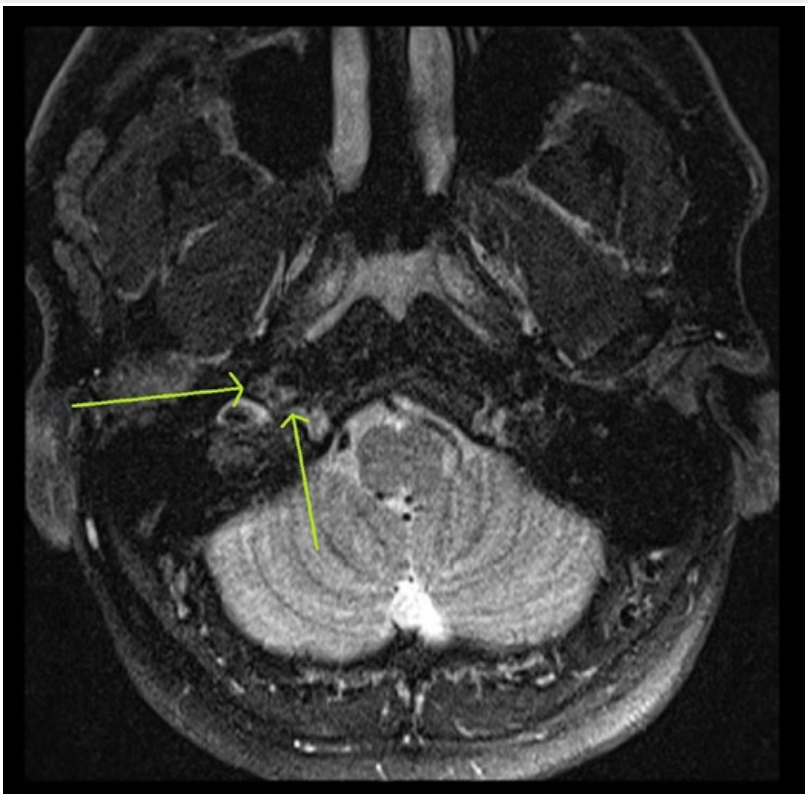

Figure 2: Axial MRI image of the intramural haematoma.

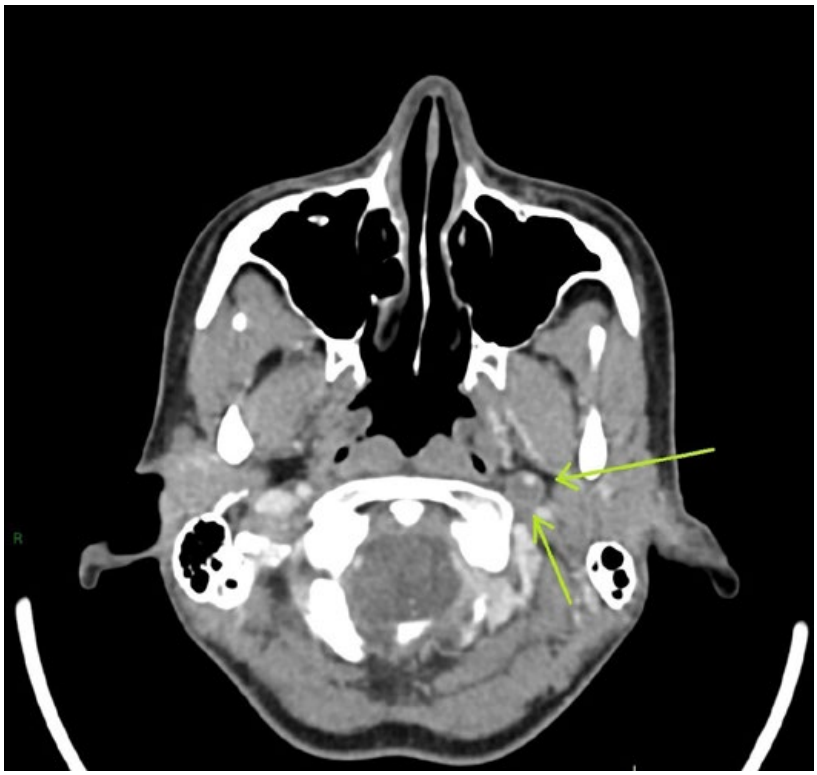

Figure 3: Axial CT image depicting the intramural haematoma.

It presents with stroke in 67% of cases and Horner's syndrome in 28–58% of cases.[7] Other symptoms include ipsilateral neck, facial or eye pain, ptosis, and visual disturbance.[1,3,8] Approximately 3–16% of patients with ICA dissection present with lower cranial nerve palsies. The most affected cranial nerves are X, XI, and XII.[3,8,9] As they exit the skull base through the jugular foramen and hypoglossal canal, these nerves travel in the carotid sheath and are therefore in close relation to the ICA, especially cranial nerves X and XII, which travel a longer distance along its length. In the neck, the vagus nerve can be found on both sides, and enters the carotid sheath and travels inferiorly between the common carotid artery and the internal jugular vein all the way to the base of the neck. The left vagus nerve then branches and gives rise to the left recurrent laryngeal nerve, which loops around the aortic arch, while the right vagus nerve branches at the level of the right subclavian artery to loop around it. The recurrent laryngeal nerves travel back up to provide motor innervations to the vocal cords. The vagus nerve also contributes to the oesophageal plexus by sending parasympathetic and afferent fibres. Mass effect from an ICA haematoma on the vagus nerve can give rise to hoarseness or dysphagia or both. It is interesting to note that ICA dissections that exhibit lower cranial nerve paralysis are less often associated with cerebral ischaemia.[3] The cervical plexus lies deep to the carotid sheath. It provides sensory innervations to the ear, scalp, neck, and upper part of the chest. Compression of these nerves could account for the head and face pain experienced by the first patient.[10] ICA is usually unilateral but can be bilateral in up to 10% of patients.[9] Compared to unilateral disease, bilateral disease causes a greater obstruction of cerebral blood flow and is more likely to lead to cerebral ischaemia. A concurrent vertebral artery dissection can also be found in more than one-fifth of cases.[11]

ICA dissection can occur spontaneously or can be attributed to trauma in 40% of cases.[1,3,12] The mechanism of injury is usually blunt force trauma, such as a direct blow to the neck or sudden neck movements.[13] Other risk factors for ICA dissection include systemic conditions and congenital tissue defects: fibromuscular dysplasia, Marfan's syndrome, Ehlers–Danlos syndrome, α-1 antitrypsin deficiency, Behçet's syndrome, and

osteogenesis imperfecta Type 1.[1,3,12] The disease is caused by a tear in the wall of the vessel creating a false lumen and the formation of a mural haematoma, thereby compressing and narrowing the true lumen.[3] Formation of a haematoma leads to mass effect on the surrounding structures, and in the case of a cervical ICA dissection, it impacts on the other structures within the carotid sheath.[14]

It has been suggested in the literature that ICA dissection should be diagnosed through duplex ultrasonography or MRI.[3,14] A further CT angiogram can then help localise and evaluate the extent of the ICA dissection.[2,14] In the case of a haematoma, MRI scans show hyperintensity on T1 and T2 images or a delineation around the blood clot.[2] One of the limitations of duplex ultrasonography is that unless there is a change in the blood flow caused by the dissection, the diagnosis can be missed.[15] In the authors' local practice, patients presenting with a vocal cord palsy are initially referred for a CT scan encompassing the skull base to the diaphragm. In both cases, contrast CT scans using split-bolus CT provided good evidence of ICA dissection. MRI was used in one case to confirm the diagnosis. This was supported by the findings of one study that showed that the evaluation accuracy of CT and MRI are comparable in the diagnosis of carotid and vertebral artery dissection.[16]

The prognosis of ICA dissection is generally good and there is full or almost full recovery of symptoms in up to 80% of cases.[7] Although it can resolve spontaneously in a large number of patients, ICA dissection is usually managed with antithrombotics to reduce the risk of stroke, usually antiplatelets or warfarin;[1,6,17] however, there is no compelling evidence to favour one over the other.[18] Although it is does not treat the dissection itself, the antithrombotic therapy leads to a higher rate of recanalisation within the first 2–3 months.[19] With the right management, the outcome of an ICA dissection is good.[1]

CONCLUSION

After excluding malignancy in a patient with vocal cord palsy, particularly in a sudden onset or if associated with facial or neck pain or headache, physicians should consider ICA dissection as another potential cause. Although rare, ICA dissection can lead to serious complications, such as embolic stroke, transient ischaemic attack, or aneurysms.[2,20,21] MRI scans have been suggested as the radiological investigation of choice, however, in both cases, split-bolus CT has shown to provide good evidence of ICA dissection. Prompt and appropriate treatment should be started using antithrombotics and, in most cases, this will lead to a good outcome.

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Turner Syndrome and Craniosynostosis: An Unusual Combination

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Abstract

This article describes a case of Turner syndrome (TS) associated with craniosynostosis due to an early closure of the sagittal suture. Skeletal anomalies are characteristic phenotypic findings, although the presence of associated craniosynostosis constitutes an unusual pathology with very few references in the literature. The case describes a 5-year-old patient who presented with failure to thrive, psychomotor retardation, and scaphocephaly. Genetic analysis showed an Xq isochromosome. Different genes have been identified in the pathogenesis of TS. The *SHOX* (short-stature homebox) gene and its interaction with other growth regulator genes is responsible for different bone anomalies in TS and in other skeletal dysplasias. Classic cephalometric studies have demonstrated marked alterations in the skull base in patients with TS. The association of abnormal cranial morphology together with the craniosynostosis could cause a decrease of volume in the posterior fossa. In this patient, the dynamic study of cerebrospinal fluid in flow MRI was normal; therefore, clinical, radiological, and ophthalmological follow-up was prescribed. Craniosynostosis is a rare entity in TS. The presence of premature closure of the skull sutures makes it necessary to rule out other abnormalities of the craniocervical junction.

INTRODUCTION

Turner syndrome (TS) is one of the most frequent chromosomal aberrations, caused by the partial or complete loss of one X chromosome.[1] The disorder leads to a conglomerate of phenotypical manifestations that often includes short stature, congenital lymphoedema, gonadal dysgenesis, or cardiovascular and renal congenital malformations.[2] Skeletal anomalies are a characteristic phenotypic finding, including disproportion between the upper and the lower body segments, cubitus valgus, scoliosis, genu valgum, short metacarpals, or congenital hip dislocation. Patients with TS may also have a variety of typical craniofacial manifestations such as sphinx facies, ogival palate, micrognathia, and

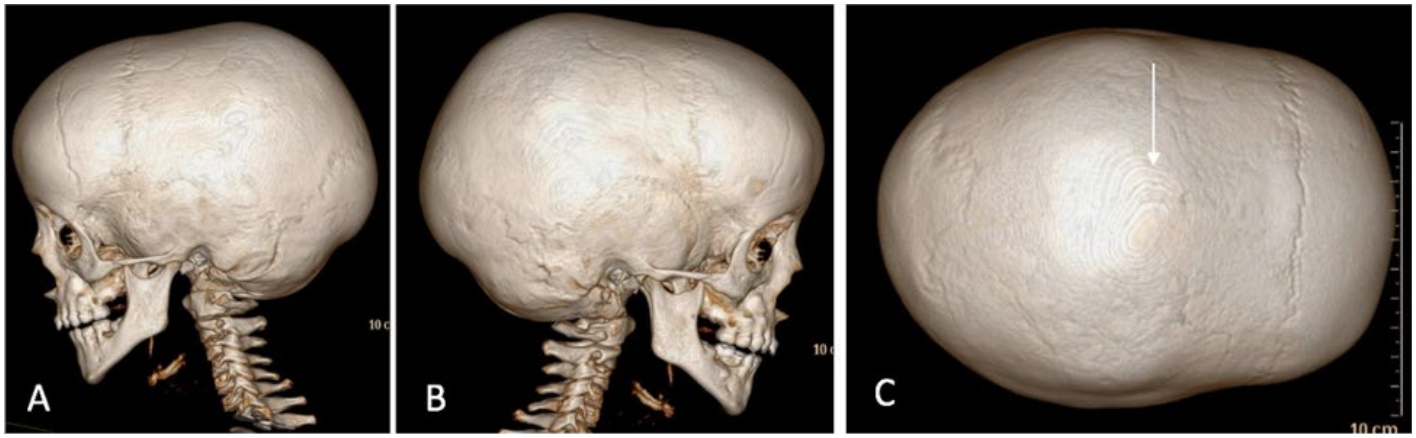

Figure 1: CT scan with 3D reconstruction showing: A–B) lateral view; C: vertex view.
The arrow shows a synostosis sagittal suture.

short neck due to hypoplasia of cervical vertebrae or pterigium colli.[3]

However, the presence of associated craniosynostosis constitutes an infrequent entity, with few clinical cases reported in the literature. In 1959, the first case of a patient with TS and cranial malformation was reported in the shape of turricephaly due to premature closure of the coronal and sagittal sutures; the turricephaly was of mild degree and no surgery was required.[4] In 1968, Calmettes et al.[5] reported a case of oxycephaly and corneal dystrophy in a patient with TS because of its unusual combination. Another case was described by Bozzola et al.[6] in 1986: their patient presented a complex craniosynostosis with the fusion of sagittal and bicoronal sutures; two surgical procedures were necessary to correct it.[6] One year later, Massa and Vanderschueren-Lodeweyckx[7] published the first case of monosutural craniosynostosis associated to TS. Radiological examination of the skull revealed a premature fusion of the sagittal suture and digital impressions on the parietal bones, although surgical management was not required.[7] In a recent study that focused on the incidence of systemic diseases and syndromic diagnoses in a cohort of patients with scaphocephaly, a single case of TS was identified.[8]

TS and craniosynostosis is an unusual concurrence. However, with the current evidence, simple or severe forms of craniosynostosis should be considered as a possible skeletal abnormality in TS. In addition, molecular researchers have identified some genes that could be involved in the different clinical expressions of this pathology.[2] This article describes a patient diagnosed with TS who presented an isolated sagittal synostosis. Likewise, morphological aspects in the development of the skull in the context of untreated craniosynostosis are reviewed and the possible genetic implications in this patient with TS is analysed.

CASE REPORT

History and Examination

The patient was a 5-year-old female, referred to the authors' department one year prior due to cranial deformity including scaphocephaly. The cephalic index was 70. Antenatal history was unremarkable and delivery was uncomplicated. There was no parental consanguinity. Clinical examination showed a decrease in growth velocity for her age; at 6 years old she weighed 14.40 kg and her height was 108 cm. No other remarkable musculoskeletal characteristics were identified. Mild developmental concerns were identified in visuospatial skills, non-verbal perceptual problems, and attention disabilities.

Complementary Examinations

Funduscopy was consistent with papillary paleness and visual evoked potentials and showed a very mild delay through the optic pathways. A CT scan revealed a craniosynostosis

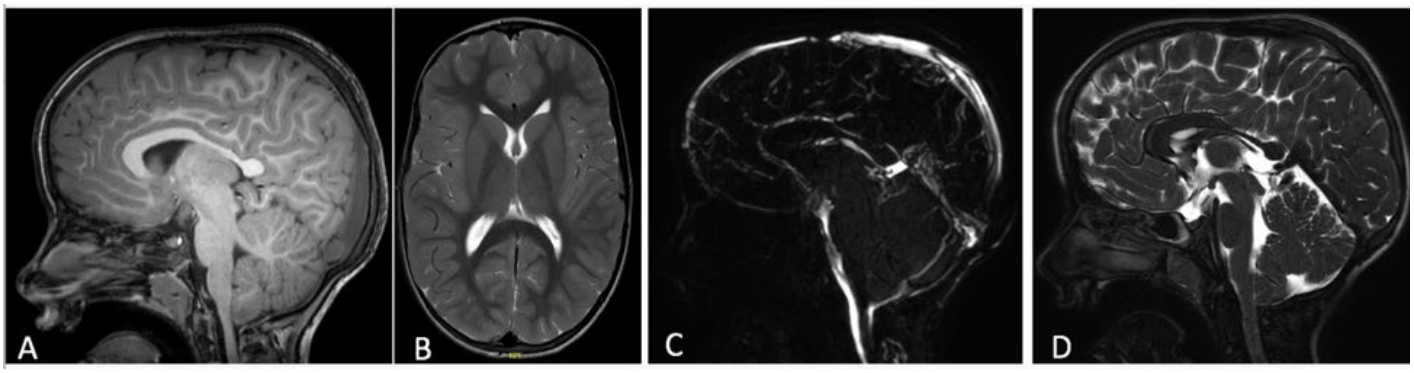

Figure 2: A–B) T1 sagittal and T2-weighted axial magnetic resonance brain images show a cranial deformity in the context of an early closure of the sagittal suture. There are no notable changes in the morphology and signal of the brain parenchyma; C) dynamic study of cerebrospinal fluid in flow MRI is normal, without any compromise of cerebrospinal fluid flow; D) T2-weighted sagittal magnetic resonance brain image demonstrates minor descent of the cerebellar tonsils through the foramen magnum at the lower limit of normality.

due to premature closure of the sagittal suture (Figure 1). MRI of the brain and cervical region showed a minor descent of the cerebellar tonsils through the foramen magnum, at the lower limit of normality.

No other abnormalities were found in the morphology or signal of the brain parenchyma (Figure 2A, B, and D). The dynamic study of the cerebrospinal fluid (CSF) in flow MRI did not reveal compromise of CSF flow at the occipitocervical junction level (Figure 2C).

Cardiovascular health issues were normal. Screening renal ultrasonography showed no renal malformations. Laboratory tests of renal function were normal. The patient initiated treatment with growth hormone due to short stature coupled with an insulin like-growth factor 1 value at the lower limit of normality (65 ng/mL) and a bone age ahead of 1 year, which caused a prognostic height below her target size. Neuropsychological and behavioural monitoring is ongoing due to developmental delays.

Conventional karyotyping showed a nonmosaic 45,X,i (X)(q10). In all metaphases (20), the presence of two X chromosomes, a structurally normal X, and an Xq isochromosome were observed, constituting a partial Xq trisomy and a partial Xp monosomy. Fluorescence *in situ* hybridisation probes showed two X chromosomes, one of them with a normal hybridisation pattern for both subtelomeric regions (one signal for Xpter/one signal for Xqter) and the second chromosome with an altered hybridisation pattern for the subtelomeric regions of the short and long arms of the X chromosome. No hybridisation signal was observed for the SRY region. Karyogram and fluorescence *in situ* hybridisation images are described in Figure 3. Array comparative genomic hybridisation analysis confirmed the existence of a probably terminal partial deletion of 53 Mb in the short arm of the X chromosome, as well as the presence of a partial duplication of 85 Mb of the long arm of the X chromosome, involving chromosomal bands Xq13–q28. Both of them altered the dose of several reference genes. The imbalances identified were compatible with the presence of a derivative X chromosome.

DISCUSSION

TS is a well-known chromosomal disorder caused by a partial or complete lack of one of the X chromosomes. The karyotype variation is large and complex.[1] The relationship between phenotype and genotype is being widely investigated. Clinical manifestations are not only related to the grade of deficit of X chromosomal material, but also depends on the expression of different genes and epigenetic and transcriptional factors.[9] The *SHOX* gene

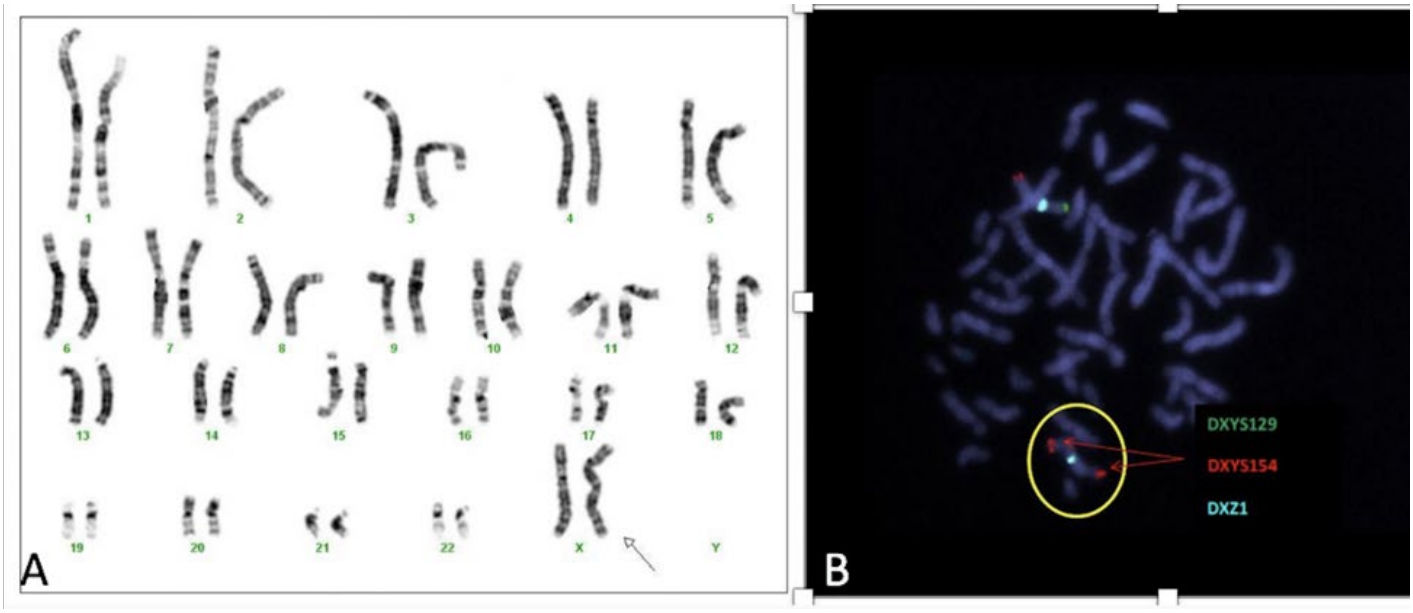

Figure 3: A) Karyotype of the patient, a non-mosaic 45,X,i (X)(q10); B) fluorescence *in situ* hybridisation showing a metaphase with two X chromosomes (DXZ1x2), one of them with a signal for each of the hybridised subtelomeric regions (DXYS129 +, DXYS154 +; pattern compatible with normal X chromosome) and the second chromosome (circled) with two signals for the subtelomeric region of the long arm of the X chromosome and no signal for the subtelomeric region of the short arm of the X chromosome (DXYS129, DXYS154 ++; pattern compatible with an X chromosome with qter duplication and pter deletion).

is situated in pseudoautosomal region 1, a chromosomal segment located on the short arm of the X and Y chromosomes (Xp22.3 and Yp11.3). This gene, a transcriptional regulator, is involved at the point of fusion of the growth plate and skeletal maturation.[10] The function of this gene is dose dependent and is associated with short stature and other skeletal anomalies.[9] In TS, the haploinsufficiency of the *SHOX* gene, located on the short arm of the X chromosome, is justified by the presence of isochromosomes from the long arms of the X chromosome. In fact, growth deficit tends to be more pronounced in X ring chromosome and isochromosome Xq karyotypes than 45X.[11] The karyotype of the patient was nonmosaic 45,X,i (X)(q10) and she had a short stature. Furthermore, preclinical investigations have identified a complex interaction between *SHOX* gene and other growth regulator genes such as fibroblast growth factor receptor 3, offering a possible theory about the different bone abnormalities in TS, as well as in other skeletal dysplasia (e.g., achondroplasia).[12,13]

Likewise, classic cephalometric studies have demonstrated marked alterations in the skull base in patients with TS. The clivus is shorter and the angle between the sphenoidal plane and the Sella-Nasion line is larger, similar to the angle between the foraminal and clival planes; however, measurements of anterior cranial fossa are normal.[14] Further research is needed to determine the genetic mechanisms behind craniosynostosis such as skull morphology in TS. In any case, the association of an abnormal cranial morphology together with the presence of scaphocephaly could cause a decrease in volume in the posterior fossa. Chiari malformation Type 1 has been described as a possible complication of untreated sagittal synostosis.[15] The early closure of the sagittal suture produces an increase in the skull in the axial plane and a restriction of the vertical growth of the cranial vault, resulting in a posterior fossa smaller than normal. Decreased supratentorial volume leads to the descent of the cerebellar tonsils, either directly or by intracranial hypertension associated with increased venous pressure due to

constriction of superior sagittal sinus in the bone groove.[15,16]

Thus, in any case similar to the patient with a diagnosis of TS and the occurrence of premature closure of the cranial vault sutures, a high suspicion of associated craniocervical malformations must be considered. In this patient, the dynamic study of CSF in flow MRI was normal and ophthalmological control did not detect papilledema, so clinical, radiological, and ophthalmological follow-up was prescribed.

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A Case of Subacute Combined Degeneration as a Manifestation of Pernicious Anaemia

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Abstract

Vitamin B_{12} deficiency affects multiple systems, including the central and peripheral nervous systems, producing a vast spectrum of neurological symptoms. It is particularly important due to its insidious presentation and because it can evolve to spastic paraplegia with permanent sequelae. The authors describe a case of a woman with asthenia, bilateral lower limb weakness, urinary retention, and faecal incontinence, with no structural cause on imaging studies. Blood tests showed anaemia (haemoglobin: 6.8 g/dL) and vitamin B_{12} deficiency (<100 pg/mL). After upper digestive endoscopy compatible with chronic atrophic gastritis and positive for anti-intrinsic factor antibodies was obtained, the diagnosis of subacute combined degeneration due to vitamin B_{12} deficiency in the context of pernicious anaemia was admitted. Although this entity is a rare cause of myelopathy, it is a frequent manifestation of vitamin B_{12} deficiency. Clinical suspicion is fundamental since the reversibility of the neurological lesion is dependent on early treatment.

INTRODUCTION

Vitamin B_{12} (cobalamin) deficiency is a highly frequent condition that affects approximately 6% of the population in developed countries, particularly institutionalised or malnourished elderly people (20% prevalence in >60 years old).[1] Despite often being asymptomatic, this deficiency may impact several organs and systems, with gastrointestinal, haematological, cardiovascular, psychiatric, and neurological manifestations.

Vitamin B_{12} deficiency is associated with a wide spectrum of neurological effects in central and peripheral nervous systems. Subacute combined degeneration (SCD), the myelopathy caused by this deficiency, initially affects the dorsal and lateral columns of the spinal cord, but it can extend to pyramidal tracts and lead to spastic paraparesis. It is thus critical to rapidly diagnose and treat vitamin B_{12} deficiency to prevent the development of serious and permanent neurological complications.[1,2]

Herein, the authors present a case of a woman with asthenia, lower limb paresis, urinary retention, and faecal incontinence, diagnosed with SCD due to vitamin B_{12} deficiency.

CASE REPORT

A 65-year-old melanodermic woman from Guinea-Bissau, autonomous in everyday life and with a medical history of Type 2 diabetes mellitus treated with metformin, without any other medication or drug allergies, presented to the emergency department with asthenia and bilateral lower limb weakness with 10 days of evolution, and recent complaints of low back and hypogastric pain associated with dysuria and decreased urine output.

On admission, she was conscious, normotensive (128/86 mmHg), normocardial (75 bpm), and apyretic (tympanic temperature: 36.8 °C). Heart and lung auscultation had no alterations. She had abdominal tenderness at hypogastrium palpation, with evidence of a mass that was suggestive of a bladder globe. She was catheterised, with urine drainage of 500 mL, suggesting urinary retention.

Neurological examination revealed symmetric ataxia of lower limbs and mild hyporeflexia, but unimpaired segmental and global strength as well as muscle tone. No significant alterations in pain sensitivity or sensitive level were detected. Bilateral apallesthesia, multiple proprioceptive errors, and marked gait instability were observed. The patient was oriented in time and space, without cognitive or speech alterations, as confirmed by a relative.

She had macrocytic anaemia with haemoglobin: 6.8 g/dL; mean corpuscular volume: 98.3 fL and normal numbers of other cells; creatinine: 1.21 mg/dL; urea: 43.6 mg/mL; protein-to-creatinine ratio: 22.34 mg/dL; and pyuria. No acute changes were observed in cranial CT, whereas lumbar spine CT revealed incipient degenerative skeletal changes with no apparent compromise at the root level or at the spinal channel. The patient was admitted to the hospital for further study of the neurological changes, treatment of serious anaemia, and likely urinary tract infection.

She was given a transfusion of one unit of packed red blood cells with good transfusional yield, and amoxicillin plus clavulanic acid for 7 days to treat the infection due to a multi-sensitive *Escherichia coli*. Lower limb and pelvic girdle paresis as well as ataxia worsened, with urinary retention episodes and faecal incontinence. There was no evidence of structural lesions as assessed by cranial and spine MRI. Lumbar puncture revealed low cellularity, mainly mononuclear cells, with normal proteinorrachia and glychorrachia. HIV and venereal disease research laboratory test serologies were negative. Vitamin B_{12} levels were <100 pg/mL, suggesting a serious cobalamin deficiency.

Autoantibody serology was positive for anti-intrinsic factor antibodies and negative for anti-parietal cell antibodies. No macroscopic changes were observed in upper gastrointestinal endoscopy, but the anatomo-pathological examination showed chronic gastritis of the antrum, body, and fundus, without activity and with mild atrophy. These findings supported a diagnosis of SCD and megaloblastic anaemia due to vitamin B_{12} deficiency, in the context of pernicious anaemia.

Other vitamin deficiencies, particularly in group B, were not investigated since the patient did not have a clinical picture of malnutrition but rather a specific deficit in the absorption of vitamin B_{12}.

The patient was given daily intramuscular injections of 1 mg cyanocobalamin for 7 days, followed by weekly injections for a month, combined with muscle strengthening training, which resulted in significant progressive improvement. She was discharged 42 days after admission, exhibiting clinical improvement with autonomous although ataxic gait and no evidence of faecal incontinence or urinary retention. Monthly treatment with 1 mg cyanocobalamin and physiotherapy were prescribed. At re-evaluation 6 months later, she was asymptomatic, with no objective neurological deficits, haemoglobin 12.4 g/dL, and vitamin B_{12} levels >300 pg/mL.

DISCUSSION

B vitamins are a group of water-soluble vitamins that have some general similarities but are each unique with critical functions in the body. Collectively called B complex vitamins, they are sorted into eight chemically distinct entities: thiamine (B_1), riboflavin (B_2), niacin (B_3), pantothenic acid (B_5), pyridoxine (B_6), biotin (B_7), folate (B_9), and cobalamin (B_{12}). They are all co-factors for enzymatic reactions, providing important catalytic functionality to drive metabolic processes to completion, and cannot be synthesised in the human body.

Therefore, they must be consumed through food sources.[3]

Vitamin B_{12} is found in a wide variety of animal foods and fortified plant foods. Its absorption depends on intrinsic factor, a protein produced by parietal cells of the gastric mucosa. It forms a complex with vitamin B_{12} in the small intestine that is absorbed in the terminal ileum.[1,2] The main causes of significant vitamin B_{12} deficiency are related to malabsorption, either due to intrinsic factor deficiency (pernicious anaemia) or due to gastric (total or partial gastrectomy) or ileal pathology (Crohn's disease, ileal resection).[4]

Vitamin B_{12} is a co-factor required for the formation of tetrahydrofolate, a metabolite involved in purine and thymidine biosynthetic pathways, which are essential for DNA maturation in proliferating cells (excluding haematopoietic stem cells), as well as for conversion of homocysteine into methionine and for methylmalonic acid metabolism, both necessary to maintain neuronal homeostasis. Therefore, vitamin B_{12} deficiency is often associated with megaloblastic anaemia, with possible involvement of other cell lineages and neurological symptoms.[5]

Vitamin B_{12} deficiency is linked to progressive demyelination, the physiopathological mechanism of which remains poorly understood. It is thought that methylmalonic acid accumulation prevents normal myelin synthesis, leading to abnormal fatty acid accumulation in neuronal sheaths. Axonal loss due to vacuolar degeneration of white matter, as well as decreased synthesis of methionine-dependent neurotransmitters, might also be involved. The major affected areas include the spinal cord, brain white matter, peripheral nerves, and optic nerve.[6,7]

The myelopathy caused by vitamin B_{12} deficiency is characterised by the involvement of posterior and lateral columns of the cervical and thoracic spinal cord. Patients usually present with insidiously developing symptoms that start with paresthesia and progressively evolve into symmetrical sensory disturbances, areflexia, and ataxia. Lower limbs are typically affected before upper limbs, with gait impairment. In advanced stages of disease, paresis and stiffness may develop, as well as a dementia syndrome with possible psychotic symptoms.[2,6,7] MRI findings of the posterior columns, showing areas of abnormally increased T2 signal hyperintensity associated with spongy degeneration of myelin fibres, have been documented.[8]

SCD diagnosis is based on laboratory-confirmed absolute or relative vitamin B_{12} deficiency in people with suggestive neurological symptoms without any other cause. Anaemia is absent in 20% of the cases.[9] Vitamin B_{12} levels <200 pg/mL are specific of vitamin B_{12} deficiency and increase the probability of response to supplementation, although with a diagnostic sensitivity of 60–95%.[3] In patients with a borderline value of vitamin B_{12} (200–400 pg/mL) and/or suggestive symptoms, the quantification of methylmalonic acid is recommended, with levels >400 nmol/L displaying a sensitivity of 98% for clinically significant vitamin B_{12} deficiency.[10] Anti-intrinsic factor antibodies, which are present in 50% of patients with pernicious anaemia, have a very high diagnostic specificity when quantified before vitamin B_{12} supplementation.[3]

SCD is treated with vitamin B_{12} supplementation, which can be administered by parenteral or oral routes. Oral administration is given to healthy adults with vitamin deficiency, whereas parenteral administration is mandatory in patients with a vitamin B_{12} deficiency due to malabsorption or associated with severe symptoms, including neuropathy. Parenteral supplementation consists of intramuscular injections of 1 mg cyanocobalamin, in which approximately 10% of the dose is absorbed. In patients with anaemia, standard therapy is three injections per week for 2 weeks. Patients with neurological disorders should be subjected to a more intensive regimen, with daily or alternate injections until symptoms improve or until 3 weeks, followed by weekly injections. A monthly maintenance dose is also recommended of 1 mg in patients with continuous vitamin B_{12} absorption deficiency (excluding pernicious anaemia).[11]

In contrast with the rapid increase of reticulocyte counts after 1 week and megaloblastic anaemia resolution after 6–8 weeks, the improvement of neurological symptoms is slow, being more evident during the first 2 months after starting treatment and continuing for the following 6 months. The severity and duration of the neurological changes are related to the grade and speed of the patient's recovery.[12]

CONCLUSION

The case report presented here, which describes a rare but reversible cause of myelopathy, highlights the importance of early clinical suspicion of vitamin B_{12} deficiency as the aetiological agent of a wide range of neurological symptoms, given that neurological lesion reversibility is directly linked to an early diagnosis and correction of vitamin deficiency.

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Successful Management of Parsonage–Turner Syndrome with Steroids in the Post-acute Weakness Phase: A Case Report

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Abstract

Introduction: Parsonage–Turner Syndrome (PTS) is a rare disease of the brachial plexus of unclear aetiology. The limited data available typically describes involvement of branches of brachial nerves. The authors present a case of PTS with a rare combination of unilateral brachial plexus, phrenic nerve, and recurrent laryngeal nerve injuries. They also highlight successful treatment with pharmacological intervention despite several months' delay in diagnosis. The 35-year-old female presented with acute onset of severe left shoulder pain followed by severe progressive weakness of the left shoulder muscles, progressive weakness of her voice, nasal regurgitation of fluids, paroxysmal bouts of coughing, and exertional dyspnoea at rest. The symptoms remained undiagnosed for about 10 months. A clinical diagnosis of exclusion of PTS was finally made, and treatment with steroids, neurotropic drugs, and physiotherapy was started. The patient has recovered significantly since then and continues to improve.

Conclusion: The authors presented a case of PTS with a rare combination of brachial plexus, recurrent laryngeal nerve, and phrenic nerve injuries. This case was also remarkable for the significant improvement in her symptoms with treatment, despite the delay in diagnosis. This bears evidence that steroids and adjuvant therapy is useful even months after onset of the disease.

INTRODUCTION

Parsonage–Turner Syndrome (PTS) is a rare autoimmune disease of the peripheral nervous system. It is thought to occur in 1–3 people in 100,000; however, this incidence might be an underestimation because of underdiagnosis.[1,2] This condition, also known as brachial plexopathy, is centred around inflammatory damage to specific peripheral nerve bundles as evidenced by histopathologic and neurophysiologic studies (see Diagnostic Tests). While the typical presentation of PTS involves brachial plexus, other nerves like the lumbosacral plexus, phrenic nerves, and recurrent laryngeal nerves are rarely affected. The authors' case is only the second report in the medical literature that shows this unique combination of brachial plexus, phrenic nerve, and recurrent laryngeal nerve palsies.[3]

CASE DESCRIPTION

A 35-year-old female presented with pain and severe progressive weakness of the left shoulder. Her symptoms started about 10 months earlier as severe acute pain in the left shoulder, jaw, and chest. She had undergone a dental surgery for dental caries 2 weeks before the symptoms started. On Day 7 of symptom onset, she noticed gradual resolution in pain as well as onset of progressive weakness of the shoulder evidenced by drooping of the shoulder and weakness in lifting the arm above shoulder level, but no noticeable weakness of the forearm or hand. The symptoms were accompanied by a change in her voice, described as high-pitched and low volume, as well as a paroxysmal cough and breathlessness. She also reported regurgitation of liquids through her nose right after swallowing and difficulty swallowing liquids "unless she pushed through the left side of her throat."

Her symptoms remained undiagnosed for months and were treated unsuccessfully as laryngitis, tonsillitis, and pneumonia with non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics, which included 5-day courses of oral amoxicillin-clavulanic acid and oral azithromycin sequentially.

On presentation at the authors' hospital 10 months after the onset of symptoms, she appeared weak, anxious, and spoke in a low volume. She was breathless at rest and found it difficult to speak in complete sentences. Her left shoulder was drooping, with deltoid and supraspinatus muscles noticeably atrophied. There was no medial scapular winging that suggested that the long thoracic nerve was spared. The passive range of motion at the neck and shoulder joints was normal and not associated with the pain. Muscle strength on the left shoulder extension was 4/5, suggesting possible involvement of latissimus dorsi, teres major and posterior deltoid, and left shoulder abduction up to 90° was 3/5, indicating involvement of supraspinatus and deltoid muscles. Muscle strength on flexion and extension of the elbow and internal and external rotation of the left arm was 5/5. Muscle strength assessment on the right upper limb was normal. Touch, pain, and temperature sensation were normal in all the dermatomes, including the left C4–C5. The left biceps reflex was +1, and the brachioradialis and triceps reflexes were +2. Chest findings were significant for reduced air entry, vesicular breath sounds, and mild crepitations over the left lower lung zone. The rest of the physical examination was normal.

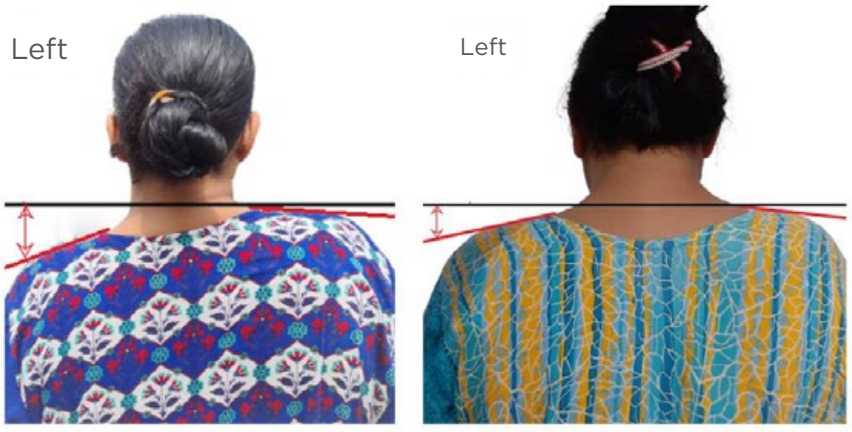

Figure 1: Appearance of patient at presentation and after treatment.

A) Shows the patient at presentation with left shoulder drooping. The red lines follow the slope of the shoulders and show that the left shoulder slope is steeper than the right. The black horizontal line is drawn through the base of the neck to show the drop in the height of the left shoulder. **B)** The patient after 1 month of treatment. There is improvement in the drop of the left shoulder, as seen by the reduction in the distance from the base of the neck to the slope of the shoulder.

Figure 1 compares the patient's appearance at presentation and after 1 month of treatment. Laboratory investigation showed normal complete blood count, comprehensive metabolic Panel, erythrocyte sedimentation rate. A cervical spine MRI showed mild intervertebral disc degeneration but with preserved disc height and normal vertebral body. There was no evidence of vertebral fracture or spondylolisthesis. The antero-posterior view of the chest radiograph was remarkable for a significant elevation of the left hemidiaphragm supporting the suspicion of left hemidiaphragm paralysis. Electromyography and nerve conduction studies could not be done in the authors' poor resource setting.

Table 1: Common differential diagnoses of Parsonage–Turner Syndrome.[4-6]

Neurological:
• Mononeuritis multiplex
• Brachial neuritis
• Motor neuropathy
• Entrapment neuropathy
• Complex regional pain syndrome
Musculoskeletal:
• Progressive muscular atrophy
• Facioscapulohumeral dystrophy
• Rotator cuff pathology
• Capsulitis
• Bursitis
• Tendinitis
• Osteoarthritis
Infectious:
• Lyme disease
• Poliomyelitis
Spinal:
• Vertebral fracture
• Cervical spondylosis with referred pain
• Cervical radiculopathy

After exclusion of differential diagnoses (Table 1), a clinical diagnosis of PTS was made, and the patient was started on prednisolone tablets at 1 mg/kg per day for 4 weeks to be tapered gradually. Nootropics were given as adjuvant treatment and included Nucleo CMP Forte® (Ferrer, Barcelona, Spain) and Neuropat® (Indus Life Sciences Pvt. Ltd., Chennai, India), containing high doses of nucleotides, cyanocobalamin, alpha lipoic acid, folic acid, thiamine, and pyridoxine. The patient was started on physical therapy with incentive spirometry and shoulder strengthening exercises. Within 2 weeks, the patient experienced remarkable improvement of her condition, evidenced by better shoulder muscle strength, reduced breathlessness and cough, and improved voice quality. She continues to improve with the above management.

DISCUSSION

Background

PTS is a type of neuralgic amyotrophy, named after the two doctors, M.J. Parsonage and J.W. Aldren Turner, who reported 136 cases of this condition in 1946.[4] Although it is commonly reported to occur in the brachial plexus, suprascapular nerve, long thoracic nerve, and axillary nerve, several other nerves such as anterior interosseous nerve, lateral antebrachial cutaneous nerve, superficial radial nerve, and even cranial nerves may also be involved. Both motor and sensory nerves are affected.[5] However, sensory symptoms may not be present in over one-third of patients. After analysing 246 cases of PTS, van Alfen et al. mention that 62.5% develop pain during the course; presentation is unilateral and asymmetric in 71.5% and 97.0%, respectively. In their analysis, they found that pain lasted longer in males than in females, but the outcome was poorer in females compared to males. They also found that in almost all cases, there were associated motor symptoms.[6] Recurrent laryngeal nerve was found to be involved in up to 18.6% of patients, more common among those with hereditary neuralgic amyotrophy than idiopathic neuralgic amyotrophy. Fransz et al. note that winging of the scapula is present in two-thirds of the patients diagnosed with PTS.[7] As these symptoms are non-specific, present in a variety of different neurological conditions, it is difficult to diagnose this condition.[6,8]

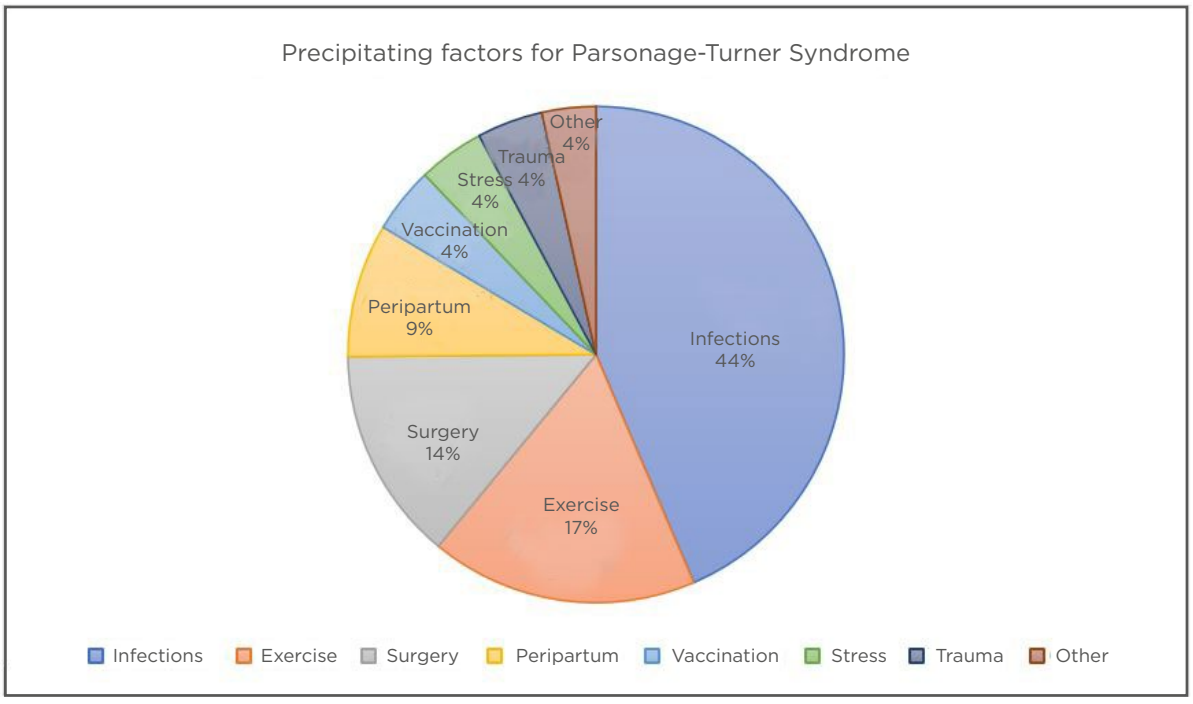

Figure 2: Pie Chart describing common precipitating factors for Parsonage–Turner Syndrome.[4,7,10]

Pathophysiology

Neurologists propose that this condition is precipitated when genetically predisposed individuals are exposed to certain precipitating events.[6] These triggers can be categorised into either infectious, accounting for about 25–55% cases,[9] environmental, or immunological, and stress either due to exercise or surgery (Figure 2).[8] The authors' patient experienced the symptoms 2 weeks after a dental surgery intrapartum. While PTS precipitated by surgical procedures has been widely reported, the authors found only one other case report in the medical literature of a 28-year-old female who was diagnosed with PTS following an orthognathic surgery. The association between oral surgery and PTS is postulated to be either because of mechanical injury from traction or inadequate head and neck position, or an immune-mediated brachial nerve injury in a genetically predisposed person.[11] Following a precipitating event, there is a multi-focal inflammation of the affected nerves. The immune pathogenesis is evidenced by the perineural thickening, neovascularisation, and focal fibre loss seen in nerve biopsies.[12] Recent studies with high resolution ultrasound of peripheral nerves in PTS supports the inflammatory process underlying the disease. The segmental swelling of axons indicates neuronal damage, while the hourglass constrictions and torsions suggest friable nerves which are further damaged by movement and abnormal positions.[13]

Diagnostic Tests

PTS is a clinical diagnosis. However, investigations are important both for exclusion of differential diagnoses and as supporting evidence for the disease. Standard tests, such as blood tests, and imaging such as CT and MRI are used to exclude other diseases, some of which are listed in Table 1. In the authors' patient, basic investigations that included complete blood count, to rule out any acute infection; comprehensive metabolic panel, to explore any underlying comorbidities such as diabetes mellitus, renal, or liver dysfunction; and erythrocyte sedimentation rate as an inflammatory marker, were all normal. The chest X-ray was done to investigate possible thoracic or neck masses compressing the brachial plexus. However, the only relevant finding on the chest X-ray was the marked elevation of the left hemidiaphragm, indicating a left hemidiaphragm paralysis. The cervical spine MRI was only significant for mild to moderate vertebral degeneration, but no evidence of soft tissue masses or injury was found. In the poor resource setting, electromyography and nerve conduction studies could not be done.

Diagnosis was made through a comprehensive clinical assessment. magnetic resonance neurography is a more sensitive imaging test than MRI for peripheral nervous system pathology. Its findings to be noted for PTS include thickening and diffuse high signal intensity in the brachial plexus trunks in coronal T1 weighted sequences. This is not very specific, however, because denervation can be seen in a variety of clinical settings like trauma, cervical spondylosis, neuropathy, amyotrophic lateral sclerosis, pernicious anaemia, and infections.[14,15]

Neurophysiologic studies are most helpful in aiding the diagnosis. They typically reveal evidence of severe plexopathy. Electromyography might show positive sharp waves and fibrillation in the acute phase, and early reinnervation with polyphasic motor unit potentials in the late phase. Nerve conduction studies reveal absent sensory nerve action potential, reduced compound motor action potentials, and prolonged F response in severe disease. However, both of these studies are sensitive only 2–3 weeks after the onset of the disease.[16] Due to this challenge and the varied clinical presentation of the disease, the diagnosis of PTS is often under-recognised or can be delayed.[17] An emerging diagnostic modality is high resolution ultrasound, which typically shows structural nerve abnormalities like segmental swelling, hourglass constrictions, and torsions, which are very specific for PTS.[13] However, its utilisation is currently limited since sufficient technological expertise is needed to accurately identify lesions.

Treatment

Most neurologists agree that though a person with PTS takes a long time to recover, conservative treatment will suffice. Ibrahim et al. suggest that physical therapy will suffice to treat the symptoms. While conservative treatment with analgesics and physical therapy is the generally accepted practice, studies done in recent years substantiate the efficacy of steroid use in the acute phase of the disease. In a case

series by van Alfen et al, addition of prednisolone 1 mg/kg per day in the treatment regimen of a cohort of patients with PTS during the acute phase of illness promoted recovery of patients compared to the untreated cohort, shortening the duration of pain and time until the onset of recovery from paresis (28% within the first month versus 6.3% in the untreated group; p=0.001).[18] In a few other studies too, oral and intravenous steroids and immunotherapy in the acute painful phase are seen to improve symptoms and accelerate recovery.[2,19,20] There has been a paucity of data on the use of steroids in the acute phase but especially in the post-acute weakness phase of PTS. Most of the studies done on PTS involve patients who presented and are treated within 1 month of disease onset. Lee et al. evaluated the effect of injected and oral prednisolone given at an approximate dose of 1 mg/kg per day to a group of six patients with PTS who presented in the post-acute weakness phase of the disease. They reported faster muscle strength recovery and return to work in the steroid group compared with a cohort treated with NSAIDs and physical therapy but no steroids.[21]

The authors used a similar treatment regime seen in most of the studies involving PTS management on their patient, with tapered 1 mg/kg per day dose of prednisone over 2–4 weeks[2,18,19] They also used nucleotides and vitamins as adjuvant therapy. While there has been no evidence of their use in PTS, use of these adjuvants, sometimes called nootropics, has been found beneficial in the treatment of peripheral neuropathies, neuromuscular diseases, and brain injuries.[22,23]

While the authors noted marked improvement in their patient after starting the treatment regimen (NSAIDs, prednisone, nootropics, and physical therapy), they cannot conclude which of the treatments was the most relevant in the resolution of the symptoms. It should also be considered the recovery period of PTS generally ranges from 1–3 years, making it difficult to exclude the natural course and resolution of the disease in their patient, who presented to them 10 months after disease onset. Large scale randomised clinical trials with different treatment modalities will be helpful in determining efficacy of therapies. However, the relatively low prevalence of the disease makes it difficult to conduct such studies. Surgical treatment with decompression and micro-neurolysis is also useful in patients with persistent symptoms.[17]

Outcome

An electrodiagnostic study of natural history of the disease on 26 patients with PTS showed complete recovery in about one-half of the patients at 1 year.[24] However, clinical studies vary in this assessment. Earlier studies suggest that about two-thirds of the patients have residual persisting pain and functional impairment for up to 3 years of follow-ups with subjective full recovery from symptoms only seen in <10% at 3 years.[25] More recent studies that evaluate the use of analgesics, steroids, and physical therapy have shown better recovery rates and return to functionality.[6,20,26]

SUMMARY

The authors present here a case of PTS with a rare involvement of brachial plexus, recurrent laryngeal nerve, and phrenic nerve. This case was remarkable for the significant improvement in her symptoms with their treatment regimen, despite the lateness of the presentation. This bears evidence that steroids and adjuvant therapy is useful even months after onset of the disease. Further larger, randomised trials will be required to establish the effectiveness of steroids in the weakness phase of PTS.

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