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EMJ Neurology

Review of
EAN Congress 2022

Editor's Pick
Adiposity and Neurological Disorders: A Review

Interviews
Cathy Stinear

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

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

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Welcome letter

Koutsouki

Evgenia Koutsouki
Editor

I am delighted to welcome you to the 2022 issue of *EMJ Neurology*, highlighting key topics in the field and showcasing this year's European Academy of Neurology (EAN) Congress, which took place in Vienna, Austria, at the end of June.

As always, this year's EAN Congress provided a first-class insight into the latest developments in neurology. New guidelines were presented on invasive treatments for Parkinson's disease, which we have summarised in this issue, alongside some exciting findings from the keynote lecture. We are delighted to also feature an interview with the winner of the 2022 EAN Tournament for Neurologists in Training Abstract for Best Presentation in Basic Neurology, as well as an interview with the Director of the Clinical Neuroscience Laboratory at the University of Auckland, New Zealand.

Of course, the issue would not be complete without the top quality selection of articles, among which are a systematic review of sex-related differences in symptoms of patients presenting with acute stroke, and a review evaluating established and emerging evidence for the link between adiposity and a range of neurological disorders. In addition, in this issue you can read several exciting case reports that add value to our understanding of the manifestation and management of neurological diseases.

I would like to close by acknowledging the valuable contribution of the EMJ team, and everyone else who played a part in bringing this content together, from the reviewers and the Editorial Board to our highly valued authors and interviewees. I hope you have a pleasant read through the journal, and I look forward to attending next year's EAN Congress in Budapest, Hungary.

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Foreword

Dear Colleagues,

I am thrilled to present a wealth of excellent content in the newest issue of *EMJ Neurology*, including a focus on the 8th Congress of the European Association of Neurology (EAN), 25th–28th June 2022. Held in the beautiful city of Vienna, Austria, the congress provided the first opportunity for neurology specialists across Europe to gather together in person since the onset of the COVID-19 pandemic.

My Editor's Pick is a fascinating article by Haboubi et al., whose review explores the link between adiposity and various neurological phenomena. With a rapid increase in obesity, healthcare professionals on a global scale are facing many related challenges. The authors evaluate the chronic inflammatory state created by obesity, which results in complex health issues for many patients.

Of interest in this issue is the presentation of sex differences in patients with acute stroke. Evidence suggests that females tend to experience unique symptoms in comparison to males presenting with acute stroke, with more likelihood of experiencing fatigue and headache, and less of presenting with trouble speaking and loss of balance. Whilst the overlap of symptoms between sexes is substantial, these differences can unfortunately delay timely medical treatment. This paper by Spooner et al. is a valuable contribution to the literature, focusing on 11 observational studies between 1946 and 2021.

This issue also includes the focused case study of a young patient with early-onset Parkinson's disease found to have a mutation in their *PINK1* gene, by Venkateshwari et al., and an insightful interview with Cathy Stinear, Director of the Clinical Neuroscience Laboratory at the University of Auckland, New Zealand.

For those clinicians who were unable to attend the EAN Congress 2022 in person, the featured congress review is highly recommended. Here, you can expect abstract review highlights, summaries of the key research, and a captivating feature, as well as late-breaking research presented.

I congratulate all authors, interviewees, Editorial Board members, and reviewers who have contributed to this superb issue of *EMJ Neurology*. I sincerely hope that this journal will prove an inspiring and invaluable read.

Natan M. Bornstein

Director, Brain Division, Shaare-Zedek Medical Center, Jerusalem, Israel;
Vice President, World Stroke Organization (WSO).

EAN 2022

Review of the European Academy of Neurology (EAN) 2022 Congress

Location: Vienna, Austria

Date: 25th–28th June 2022

Citation: EMJ Neurol. 2022;10[1]:8-14. DOI/10.33590/emjneurol/10140243. https://doi.org/10.33590/emjneurol/10140243.

THE CURTAIN OPENED on the 8th European Academy of Neurology (EAN) 2022 Congress on 25th June 2022 in Vienna, Austria, with EAN President Claudio Bassetti welcoming more than 8,000 neurologists from around the world. This year's congress saw EAN return to a truly hybrid model, with in-person attendance after the 2 years of primarily virtual congresses. Bassetti highlighted the importance of the personal connections that in-person attendance allows in the wake of the separation of COVID-19, reflecting on the opportunity that crisis and challenge presents for growth.

EAN 2022 saw 5,300 onsite participants, with a further 2,700 online attendees. The congress featured 380 lectures and over 2,200 abstracts were submitted, with a new e-learning platform that featured over 1,000 items. Bassetti used his introduction to highlight the vision and mission of the EAN: to be the home of neurology and to reduce the burden of neurological diseases. Underlining what reducing this burden might mean, Bassetti described the reasons why neurology must be a public health priority. Neurological disorders (ND) were quoted as the number one cause of disability and the number two cause of mortality worldwide, with at least one in three people having an ND. Crucially, however, NDs can be prevented, with up to 40% of stroke cases, 40% of dementias, and 25% of epilepsy cases potentially preventable.

The priorities of EAN were highlighted as science, education, membership, and advocacy, all aiding in the facilitation and availability of high-quality healthcare. Science is understood by the EAN co-ordinating scientific panel as producing high level guidelines, as well as promoting and conducting studies that address overarching topics such as neuro-COVID-19, the economic burden of neurological disease, and neuro-data sharing. Education is promoted through annual congresses, fellowships, and the launch of the e-learning platform, with membership growing from national societies,

"EAN 2022 saw 5,300 onsite participants, with a further 2,700 online attendees. The congress featured 380 lectures and over 2,200 abstracts were submitted."

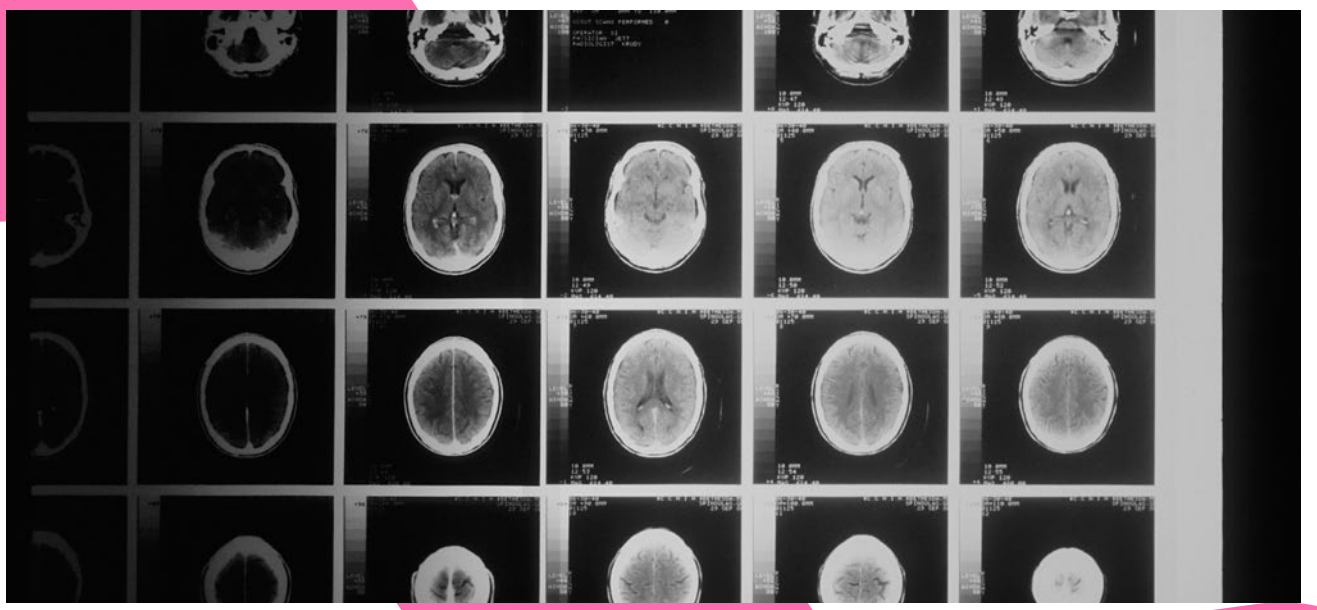
students, membership programmes, and the launch of a diversity and gender task force. Finally, advocacy is achieved through online sources, activities with industry, and collaboration with non-governmental organisations.

Discussing the future of EAN, Bassetti highlighted the priorities of the academy moving forward to support international co-operation alongside implementation at the national level. "We need to talk about education and awareness among the stakeholders and among the general population," he stated. Sustainability in neurology was emphasised alongside the implementation of the Global Action Plan, a novel research agenda, pre-graduate curriculum, and the leadership programme.

The opening ceremony featured a keynote lecture from Baroness Susan Greenfield, Founder and CEO of Neuro-Bio Ltd., Abingdon, UK. Greenfield's research has focused on brain physiology and mechanisms in Parkinson's and Alzheimer's disease. Primarily a research scientist, Greenfield focused her presentation on the marriage between neuroscience and neurology. Discussing the unique brain, Greenfield explained the core underlying value of plasticity, using experiments in rats to communicate the effects of an 'enriched' versus a 'standard' environment on the growth, plasticity, and the proliferation of a single brain cell. She emphasised the role of this process for moving from a sensory to a cognitive world. Greenfield broke down the core factors she believes drives the 21st century mind: a world driven by constant external stimuli; consciousness as a continuously variable spectrum; and, finally, the decline of the mind through Alzheimer's and other degenerative diseases.

The session closed with a final welcome from Bassetti, wishing guests an enjoyable stay in Vienna and highlighting the importance of communication and information exchange at the face-to-face congress. ●

"Science is understood by the EAN co-ordinating scientific panel as producing high level guidelines, as well as promoting and conducting studies that address overarching topics such as neuro-COVID-19, the economic burden of neurological disease, and neuro-data sharing."



COVID-19 and the Risk of Developing Neurodegenerative Disorders

RESEARCH presented at EAN Congress 2022 has shown that outpatients who tested positive for COVID-19 are at an increased risk of various neurodegenerative disorders compared with those who tested negative for severe acute respiratory syndrome coronavirus 2.

The research team analysed the health records of over half the Danish population. In total, 919,731 individuals tested for COVID-19 within the study. Of these, the 43,375 people who tested positive had a 3.5-, 2.6-, 2.7-, and 4.8-times increased risk of being diagnosed with Alzheimer's disease, Parkinson's disease, ischaemic stroke, and intracerebral haemorrhage, respectively.

The researchers studied in- and outpatients in Denmark between February 2020 and November 2021 as well as patients with influenza from the corresponding pre-pandemic period.

Lead author Pardis Zarifkar, Department of Neurology, Rigshospitalet, Copenhagen, Denmark, highlighted the relevance of the study: "More than 2 years after the onset of the COVID-19 pandemic, the precise nature and evolution of the effects of COVID-19 on neurological disorders remained uncharacterised. Previous studies have established an association with neurological syndromes, but until now it is unknown whether COVID-19 also influences the incidence of specific neurological diseases and whether it differs from other respiratory infections."

Interestingly, the heightened risk of most neurological diseases was no greater in patients who had tested positive for COVID-19 relative to those diagnosed with influenza or another respiratory illness. Furthermore, the frequency of Guillain–Barré syndrome, multiple sclerosis, myasthenia gravis, and narcolepsy was not found to increase after COVID-19, influenza, or pneumonia.

Zarifkar summarised the relevance of the research findings: "We found support for an increased risk of being diagnosed with neurodegenerative and cerebrovascular disorders in COVID-19 positive compared to COVID-negative patients, which must be confirmed or refuted by large registry studies in the near future. Reassuringly, apart for ischaemic stroke, most neurological disorders do not appear to be more frequent after COVID-19 than after influenza or community-acquired bacterial pneumonia." He added: "These findings will help to inform our understanding of the long-term effect of COVID-19 on the body and the role that infections play in neurodegenerative diseases and stroke." ●

"These findings will help to inform our understanding of the long-term effect of COVID-19 on the body and the role that infections play in neurodegenerative diseases and stroke."

Increased Reports of Adolescent Headaches: An Unanticipated Effect of the COVID-19 Pandemic

ONLINE learning delivered to adolescents during the COVID-19 pandemic could have contributed to increased headache aetiology, new research suggests. A multicentre study including 851 adolescents aged 10–18, presented on 25th June 2022 at EAN Congress 2022 by lead researcher Ayşe Nur Özdag Acarli, Ermenek State Hospital, Türkiye, revealed that headache frequency and severity increased in response to school closure and the delivery of online learning.

Of the 851 participants enrolled, 756 (89%) reported headaches during the study period. New onset headaches were reported by 10% and worsening of headaches were reported by 27%. No change in headaches and headache improvement were reported by 61% and 3%, respectively.

The risk factors associated with new onset and worsening headaches were identified as prolonged exposure time to computer screens, lack of suitable conditions for online learning from home, anxiety regarding COVID-19 itself, and school exams. Those who reported new onset or worse symptoms were experiencing headaches on average 8–9 times per month, and analgesic use was higher in these groups (43%) compared with those who reported no change in headaches (33%).

The authors discuss that those who developed new or worse headaches had significantly higher depression and anxiety scores than those with stable headaches. In addition to this, the study participants felt that their headaches had negatively affected the quality of their schoolwork.

Whilst previous short-term studies have shown a reduction in adolescent headaches as a result of school closure and online learning, this longer-term study highlights the opposite and is an example of COVID-19's evolving impact.

Overall, the findings from this study reveal that school closure and online learning during the pandemic led to an increase in adolescent headaches, and that the aetiology of this was multi-factorial. Further work analysing indirect effects of the pandemic could be performed for better understanding of the long-term impact that the pandemic has had on adolescents.

"The risk factors associated with new onset and worsening headaches were identified as prolonged exposure time to computer screens, lack of suitable conditions for online learning from home, anxiety regarding COVID-19 itself, and school exams."

Undiagnosed Risk Factors Found in Patients with Ischaemic Stroke

ISCHAEMIC stroke is the most common type of stroke, occurring when a blood clot, or another type of blockage, cuts off blood supply to the brain. A new study presented by André Rêgo from the Centre Vaudois, Lausanne, Switzerland, at the EAN Congress 2022 on 26th June 2022, highlighted that patients with ischaemic stroke typically have previously undetected health conditions.

Before this study, there was limited clinical information on the frequency, patient profiles, and stroke mechanisms in patients with acute ischaemic stroke and previously undiagnosed major risk factors (UMRF). The results show that 67.7% of patients with stroke and previously UMRF had one major risk factor, and Rêgo believes that this study provides significant insights into previously UMRF.

The researchers analysed the health records of 4,354 patients with stroke between 2003 and 2018 from the ASTRAL registry. Out of all these patients, 1,125 had UMRF. The most common vascular risk factor was dyslipidaemia, which is an imbalance of blood fats (e.g., high cholesterol or raised triglyceride levels), with 61.4% of patients having this condition. Other common risk factors included high blood pressure, which was detected in 23.7% of patients, and atrial fibrillation, which causes a fast and irregular heartbeat and was detected in 10.2% of patients.

There were several positive associations in patients with UMRF and risks, including a younger age; Black and minority ethnic ethnicities; the use of contraceptives in females aged 55 and younger; and smoking in patients aged 55 and over. However, the researchers found that the use of antiplatelet before a stroke and a higher BMI have negative associations.

"Our findings underline the importance of testing and treating blood fat imbalances such as high cholesterol and triglyceride levels, as well as blood pressure and identifying and treating those with atrial fibrillation and Type 2 diabetes," Rêgo stated.

"Before this study, there was limited clinical information on the frequency, patient profiles, and stroke mechanisms in patients with acute ischaemic stroke and previously undiagnosed major risk factors."

Parkinson's Disease Survival Length Affected by Gene Variants

RESEARCHERS have discovered that the length of time a patient with Parkinson's disease survives for could be the result of specific gene mutations. New research presented at EAN Congress 2022 has been collated by four institutes in Paris, including the specialist Paris Brain Institute at the Sorbonne Université, France.

Records of 2,037 patients diagnosed with Parkinson's disease were included in the study, beginning at their initial hospital visit. It was found that genetic variants could be the answer in establishing the speed of Parkinson's disease progression in patients, with research focused here on cases where the disease consists of a single gene.

The hazard ratios included in the study give the ability for investigators to compare survival rates of those with a genetic mutation to a control group, none of whom have a genetic mutation. Patients discovered to have either *LRRK2* or *PRKN* mutations tended to have a longer survival time than those without a gene mutation (hazard ratio: 0.5 and 0.42, respectively). However, those patients found to have *SNCA* or *GBA* gene mutations had a shorter survival time than those who did not present with a gene mutation (hazard ratio: 10.20 and 1.36, respectively).

Monogenic forms of Parkinson's disease, caused by a single gene variant, make up around 5% of all cases, and most occur without hereditary reason. Researchers believe that the most common genetic variant in Parkinson's disease is that of the *LRRK2* gene. Those who carry this variant tend to develop the degenerative disease later in life, with 70% of individuals diagnosed by the age of 80 years.

Aymeric Lanore from the Paris Brain Institute, Francelead researcher of the study, commented that this was the first study of its kind to compare survival times of patients with Parkinson's disease who carried these particular four genes. He remarked: "The results suggest the shorter survival of *SNCA* and *GBA* patients may be related to faster motor progression of the disease and earlier development of cognitive impairment." He then declared: "These are important new insights, which could help the development of new drugs targeting these genetic variants to slow down or stop the disease."

"These are important new insights which could help the development of new drugs targeting these genetic variants to slow down or stop the disease."

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EMJ

Highlights from EAN 2022

Authors: Evgenia Koutsouki, Editor

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This year's European Academy of Neurology (EAN) Congress offered a plethora of sessions in different areas of neurology. Of particular interest were the plenary sessions offering insights into the biological basis of the mind and mechanisms of Alzheimer's Disease (AD), as well as the presentation of the new guidelines for invasive therapies in Parkinson's Disease (PD).

EAN 2022

THE INTERSECTION OF NEUROSCIENCE AND NEUROLOGY

This year's plenary lecture at the EAN Congress was given Susan Greenfield, Neuro-Bio Ltd, Abingdon, UK, who focused on the intersection of neuroscience with neurology. In her talk, Greenfield stated that the biological basis of the mind is the personalisation of the brain through unique dynamic configurations of neuronal connections, which are driven by unique experiences. Greenfield explained that a stimulating environment will increase the extent of the dendrites in the human brain, thereby facilitating the formation of connections that help the brain to make the transition from a sensory state to a cognitive one.

Greenfield went on to explain the differences between a sensory and cognitive state. A sensory state of mind is when the mind is dominated by external stimuli and is a state driven by dopamine action, which acts as an inhibitor for the pre-frontal cortex and enables an individual to be the passive recipient of their senses. This is a very prominent state for infants and children, who have high levels of dopamine. In contrast, a cognitive state of mind is mostly encountered in adults who have formed the necessary connections in the brain to be able to navigate the world and looking beyond face value. In a cognitive state, the mind is dominated by internal stimuli and is characterised by lower levels of dopamine. Contrary to the cognitive state of mind, a proactive state is observed in a cognitive state of mind.

New Frontiers in Alzheimer's Disease

Greenfield also discussed a novel approach to AD that moves away from the amyloid hypothesis, which prevailed until recently. Greenfield suggested that the amyloid feature is a downstream effect and not the core driver in the brain in AD, and went on to present research suggesting that a hub of cells in the brain, termed the isodendritic core, might show early vulnerability to AD neurofibrillary lesions and could be the primary cells lost in AD. This hub could, therefore, represent a unique candidate for a viable therapeutic intervention.

The isodendritic core shows robust plasticity and high sensitivity to environmental factors. Greenfield suggested that the enzyme acetylcholinesterase, which can be found in areas where there is no cholinergic transmission, seems to be function through the vulnerable

"The biological basis of the mind is the personalisation of the brain through unique dynamic configurations of neuronal connections, which are driven by unique experiences."

areas in AD as a signalling molecule. Research from Greenfield's laboratory has identified a peptide called T14, which might be the salient part of acetylcholinesterase that is active in promoting functions outside the cholinergic transmission, which are seen in primarily vulnerable cells. Low levels of T14 can drive cell growth, whereas it can become toxic for the cells in high levels. This toxicity can also be influenced by the duration of application but, more interestingly, can be affected by age. As shown in the case of an agent such as calcium, which is normally a trigger for growth. In a mature system, it can be taken up by the mitochondria where it compromises electron transport; the formation of free radicals; and destabilises the membranes, resulting in death. An agent that might, in developmental ages, be a trophic agent, can be toxic in the context of age. Greenfield then went on to suggest that "neurodegeneration is an aberrant form of development with T14 as the crucial feature."

Hub cells selectively retain a growth mechanism driven by T14, which is normally only active during brain development. If these cells are damaged, T14 is mobilised to compensate and, in a mature adult, this develops and mental mechanisms turn toxic. Cognitive impairment starts when the toxicity spreads to the hippocampus and cortex; this is when people present for diagnosis.

Greenfield's group aims to develop a biomarker that detects degeneration before symptoms appear and they are examining T14 as a pre-symptomatic biomarker. Preliminary data from Greenfield's laboratory have demonstrated an increase in T14 brain levels at the pre-symptomatic stage. Greenfield's group aims to develop a saliva test or skin biopsy to reflect

progression of AD before the onset of symptoms. They are also developing a drug to block T14 called NBP14, which is a cyclated version of T14 and acts by displacing T14. This has been tested in mouse models and demonstrated encouraging results.

In her closing remarks, Greenfield highlighted the importance of the partnership between neuroscience and neurology, stating that this is the kind of science that we can expect to bear fruits.

GUIDELINES FOR INVASIVE THERAPIES IN PARKINSON'S DISEASE

In a session presenting the new neurological guidelines, Katarzyna Śmiłowska, Department of Neurology, University Hospital Schleswig-Holstein (UKSH)-Kiel Campus, Christian-Albrechts-University, Germany, summarised the guidelines on invasive therapies for PD management, which were formed in collaboration with EAN and the European Section of the International Movement Disorders Society (MDS-ES). In what is a first for PD, these guidelines cover all invasive therapies, both lesional and non-lesional. The approaches included are deep brain stimulation (DBS), pump therapies, and lesional therapies such as radiofrequency thermocoagulation and radiosurgery magnetic resonance imaging–guided focused ultrasound surgery (MRgFUS).

The first strongest recommendation of the guidelines, explained Śmiłowska, is to use DBS of the subthalamic nucleus (STN) for advanced PD with medically unresponsive fluctuations or medically unresponsive tremor if fluctuations or tremor are not satisfactorily controlled with medication or cannot be controlled with medication. The data demonstrate that STN-DBS probably results in a large improvement on quality of life (QoL) and activities of daily living, as well as in motor impairment, with a moderate increase in 'on' time and moderate reduction in daily 'off' time.

Another strong recommendation is that STN-DBS should not be offered to people with early PD without fluctuations, as the data failed to show a difference in critical outcomes for the DBS group. The change in medication from baseline to 24 months was not significantly different between DBS and the best medical treatment.

Other recommendations in different subtypes of patients include to consider offering STN-DBS to people with early PD and early fluctuations. For advanced PD with fluctuations, both STN-DBS and globus pallidus pars interna-DBS are effective in treating symptoms, but there can be a higher reduction in dopaminergic medication with STN-DBS.

Regarding pump therapies, the use of levodopa or carbidopa intestinal gel infusion resulted in a significant improvement in activities of daily living and QoL. These results were compared with oral treatment, and the recommendation is to consider offering levodopa/carbidopa intestinal gel infusion for people with advanced PD if fluctuations are not satisfactorily controlled with medication.

"In what is a first for PD, these guidelines cover all invasive therapies, both lesional and non-lesional."

Apomorphine infusion for advanced PD demonstrated no relevant effect on QoL, or the motor score in the on condition; however, there was a moderate improvement in the daily on time without troublesome dyskinesia in the apomorphine group compared with MD. Therefore, the recommendation is to consider offering an apomorphine pump infusion for people with advanced PD if fluctuations are not satisfactorily controlled with medication.

The final recommendation is to consider offering unilateral pallidotomy with radiofrequency thermocoagulation to people with advanced PD who experience troublesome fluctuations, and for whom DBS or pump therapies are not treatment options.

Invasive Therapies Are Not Supported by Evidence

The recommendations also include a number of clinical consensus statements to summarise recommendations for therapies that are not supported by randomised controlled trials (RCT).

The taskforce does not recommend unilateral radiofrequency thermocoagulation of the thalamus for parkinsonian tremor or advanced PD if safer treatments are available, due to the lack of data from RCTs. For the same reasons using unilateral radiofrequency thermocoagulation of the STN is not recommended for people with PD. Lesioning of the STN with radiofrequency thermocoagulation is also not recommended due to lack of RCTs.

RCTs for unilateral gamma radiation radiosurgery of any of the three target nuclei are not available for people with PD; therefore, this again not recommended as a treatment. Despite promising preliminary data, the recommendation is that unilateral thalamotomy with MRgFUS; however, should only be applied within clinical studies or registries for thalamus or medically resistant tremor in PD due to the lack of sufficient RCTs. Similarly, unilateral pallidotomy with MRgFUs is not recommended for pallidum in advanced PD with fluctuation outside clinical studies. Regarding unilateral lesioning of the STN with MRgFUS, there are still limited data on this new treatment, so the recommendation is to only use it in people with distinctly unilateral PD, and only within clinical studies or registries.

In her closing remarks Śmiłowska thanked the members of the guidelines taskforce and remarked that she believes that a challenge that healthcare professionals face is that not all treatment options are available in every country; therefore, this could pose a challenge for these recommendations in practice.

Implications of the First *Ex Vivo* Gene Therapy Approved for Treating Early-Onset Metachromatic Leukodystrophy

This scientific symposium took place on 21st June 2021, as part of the 7th Congress of the European Academy of Neurology (EAN) – Virtual 2021

Chairpeople:	Laura Campbell[1]
Speakers:	Laura Campbell,[1] Francesca Fumagalli[2,3]

1. Orchard Therapeutics, London, UK
2. Paediatric Immunohematology Unit, Ospedale San Raffaele - Telethon Institute for Gene Therapy (OSR-TIGET), Milan, Italy
3. Department of Neurology, Ospedale San Raffaele - Telethon Institute for Gene Therapy (OSR-TIGET), Milan, Italy

Disclosure:	Campbell is an employee of Orchard Therapeutics. Fumagalli is the principal investigator of gene therapy clinical trial for metachromatic leukodystrophy, sponsored by Orchard Therapeutics; the marketing authorisation holder of Libmeldy (atidarsagene autotemcel); and has been and ad-hoc consultant for Orchard Therapeutics and Takeda advisory boards.
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Meeting Summary

Laura Campbell from Orchard Therapeutics, London, UK, opened the session by explaining the objectives of the symposium and providing some background information on metachromatic leukodystrophy (MLD). MLD is a rare and life-threatening inherited disease of the body's metabolic system. MLD is caused by a mutation in the *ARSA* gene, which results in the accumulation of fats called sulfatides in the brain and other areas of the body, including the liver, gallbladder, kidneys, and spleen. Over time, the nervous system is damaged and children with MLD experience progressive neurological symptoms, including motor, behavioural and cognitive regression, severe spasticity, and seizures. Patients with MLD gradually lose the ability to move, talk, swallow, eat, and see. MLD is estimated to occur in approximately one in every 100,000 live births.[1,2] The prognosis for MLD is extremely poor. Most children within the late infantile (LI) form die by the age of 5 years; the juvenile (JU) form progresses to death within 10–20 years; and those affected by the adult form typically die 25 years following the onset of symptoms.[1] Approval of Libmeldy (atidarsagene autotemcel, [arsa-cel]; Orchard Therapeutics, London, UK), a gene therapy containing an autologous CD34+ cell

enriched population, which contains haematopoietic stem and progenitor cells transduced *ex vivo* using a lentiviral vector encoding the human *ARSA* gene, for the treatment of early-onset MLD,[3] opens up tremendous new possibilities for eligible children with MLD faced with this devastating disease, where previously no approved treatment options existed. Libmeldy is the first product approval for Orchard Therapeutics, a global gene therapy leader dedicated to rare diseases through the development of gene therapies.[4] Francesca Fumagalli from the Paediatric Immunohematology Unit and Department of Neurology, Ospedale San Raffaele - Telethon Institute for Gene Therapy (OSR-TIGET), Milan, Italy, shared the evidence on the efficacy and safety of Libmeldy in patients with MLD. The clinical trial investigating Libmeldy started more than 10 years ago at OSR-TIGET. Campbell closed the symposium by providing several educational resources to support clinicians managing children with MLD.

"MLD is a heart-breaking disease that causes immeasurable suffering and robs children of the chance of life. As a community, we have been desperate for a treatment for young patients with MLD, and we are incredibly excited to now have such a ground-breaking option approved in the European Union (EU)." Georgina Morton, Chairperson of ArchAngel MLD Trust[4]

Libmeldy is indicated for the treatment of MLD characterised by biallelic mutations in the *ARSA* gene, leading to a reduction of the arylsulfatase A (ARSA) enzymatic activity in children with LI or early juvenile (EJ) forms, without clinical manifestations of the disease, and in children with the EJ form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.

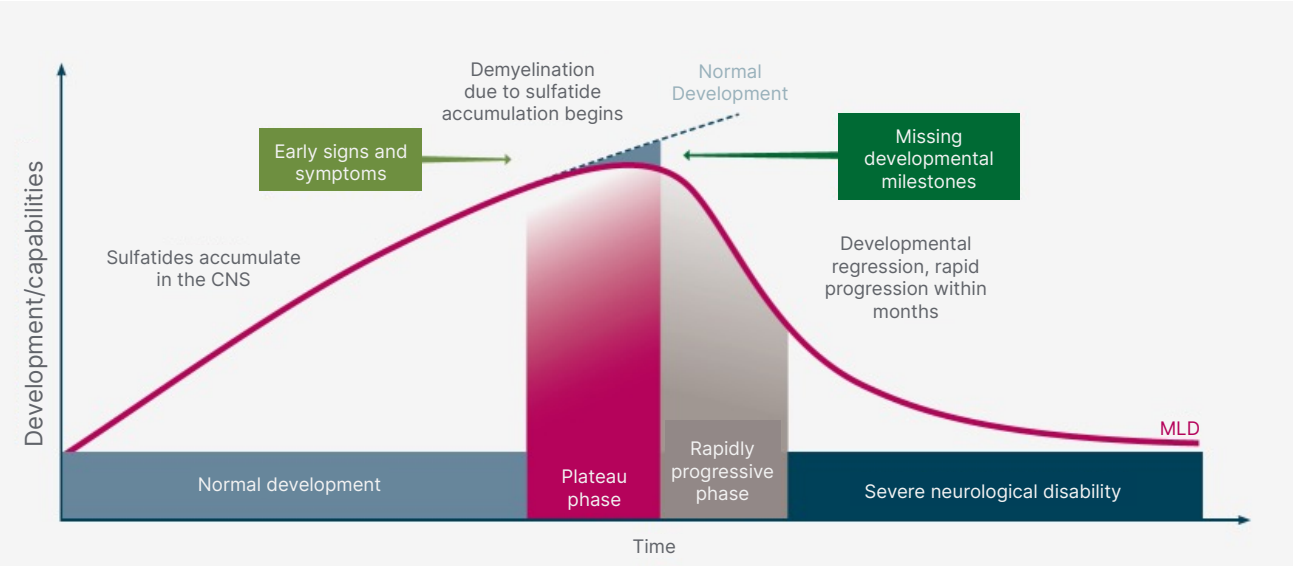
Early Signs and Symptoms of Metachromatic Leukodystrophy

Laura Campbell

MLD is caused by an accumulation of sulfatides in various organs and predominantly the central nervous system (CNS). Patients have an initial period of normal development, then experience developmental delay or stagnation (Figure 1).[5] When ARSA is deficient, sulfatides build up to high levels in the protective myelin sheath surrounding nerves, disrupting the myelin structure, and causing demyelination to occur in both the CNS and in the peripheral nervous system (PNS). The sulfatides will also build up in the visceral organs (such as the kidneys and gallbladder).[6,7] At this point, patients deviate from the previous development path and the normal trajectory of their peers, into a plateau phase. For example, they may stop progressing in their efforts towards walking; a patient with LI MLD may never learn to walk. After this period, patients begin to lose previously learned skills and will begin to exhibit more obvious symptoms of disease such as muscle weakness and neurocognitive changes. After these early signs and symptoms, patients then enter a rapidly progressive phase where they have rapid developmental regression and disease progression within months. After a noticeably short period of time, months or, in some cases, a few years, these patients will then enter a phase of severe neurological disability.[5]

The most common early signs and symptoms reported by caregivers in patients with LI MLD include motor symptoms such as difficulty in walking/running, clonus/tremor, co-ordination/balance, and unilateral muscle weakness. Initial symptoms reported in patients with JU MLD include a mix of motor and developmental/behavioural problems such as difficulty in walking/running, change in behaviour/personality, and lack of awareness.[8] These initial symptoms often manifest as a lack of developmental progress,

Figure 1: Clinical course of metachromatic leukodystrophy.



Adapted from von Figura K et al.[5]

CNS: central nervous system; MLD: metachromatic leukodystrophy.

or what is termed 'persistent toddler' or 'developmental stagnation', where a child had previously reached developmental milestones normally, but is now no longer progressing as expected, which should trigger immediate further investigation. The indication from parents and other caregivers that something is amiss is an important tool in recognising the early stages of MLD. The reason that this is so important is that once MLD has taken hold in a patient, demyelination and progression of disease is extremely rapid and can lead to early disability, as well as early death.[9] Therefore, it is vital that clinicians are aware of the early signs and symptoms of MLD in order to be able to identify these patients early and refer them to a specialist for appropriate treatment to improve morbidity and mortality outcomes for patients.

"[Patients with LI form of MLD] rapidly experienced psychomotor deterioration, bulbar dysfunction, and seizures, with loss of trunk control and dysphagia occurring concomitantly, and resulting in a substantially reduced survival."[9]

The Trial Results of Libmeldy (Atidarsagene Autotemcel) for the Treatment of Early-Onset Metachromatic Leukodystrophy

Francesca Fumagalli

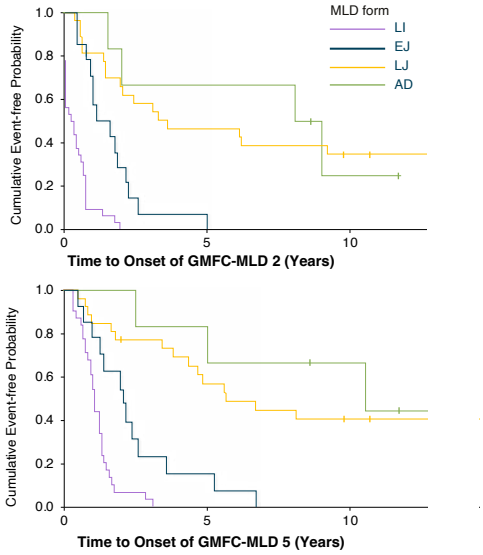
MLD is a rare, autosomal-recessive lysosomal sphingolipid storage disorder disease, caused by a mutation in the *ARSA* gene.[1,10-12] This leads to the accumulation of toxic substrates, sulfatides, in different tissues, but in particular in myelin-forming cells of the CNS and PNS, resulting in progressive demyelination and neurodegeneration.[9] The disease can be considered a phenotypic continuum caused by common underlying pathophysiological mechanisms, but it has historically been classified in different variants according to the severity, and based on a combination of the age of onset of symptoms and genotype. Three main clinical phenotypes have been described: the LI (age at symptom onset: 0–30 months) form (50% of cases), usually associated with two 0 alleles, and characterised by early motor impairment, rapid psychomotor regression, and premature death (mean age of death: 4.2 years). JU (age at symptom onset: 30 months–17 years) form (35% of cases)

is characterised by a combination of motor and cognitive/behavioural deficits at onset and a more heterogenous progression than LI and premature death (mean age of death: 17.4 years). Patients with JU MLD are commonly subdivided into EJ and late juvenile (LJ), and together LI and EJ MLD are termed 'early-onset MLD' (onset prior to seventh birthday). The disease course of early onset MLD is very rapid, with a fatal outcome within a few years after symptom onset. Adult onset MLD (age at symptom onset: >17 years) form (15% of cases) presents with cognitive decline, behavioural and psychiatric disturbances, and with variable outcomes (mean age of death: 43.1 years).[1,11-15]

The Gross Motor Function Classification in MLD score (GMFC-MLD) is commonly used to describe the progressive loss of motor function in children with MLD,[2] and Figure 2 clearly describes how rapidly untreated children lose their ability to walk independently (corresponding to Level 2) and reach a very severe disability with the loss of trunk control (Level 5) a few years after symptom onset. In parallel with motor decline, severe spasticity, epilepsy, dysphagia, as well as loss of speech, hearing, and sight can occur.[16] For that reason, the treatment of these children is usually only supportive, and based on palliation of symptoms in the symptomatic phase. The most important challenge in the development of effective treatments for MLD is the need to cross the blood–brain barrier and target the CNS.[10,14,17,18] Treatment options for MLD have, therefore, been limited. Allogeneic haematopoietic stem cell transplantation (HSCT) has been used in other diseases for decades and is based on the principle of the migration of physiologically functional donor cells to the CNS, which provide metabolic cross-correction. However, reports of allogeneic transplant outcomes for MLD in the medical literature are relatively few and conclusions are mixed. HSCT has shown some efficacy in modifying disease course in later onset (late juvenile and adult) variants, but has not demonstrated benefits in early onset MLD (LI and EJ), which are the more aggressive and most common forms, even when administered pre-symptomatically.[14,17] In the past few years, advances in translational research have brought hope to patients affected by MLD, with different therapeutic strategies showing promising results in slowing disease progression.[19-25] However, the evaluation of efficacy of such treatments is sometimes hindered by the complexity and variability of the disorder.[2,26,27]

Figure 2: GMFC-MLD level description and motor disease progression in MLD

Gross Motor Capabilities	GMFC-MLD Level
Walking without support with quality and performance normal for age	0
Walking without support but with reduced quality of performance (i.e., instability when standing or walking)	1
Walking with support Walking without support not possible (fewer than 5 steps)	2
Sitting without support and locomotion such as crawling or rolling Walking with or without support not possible	3
Sitting without support but no locomotion or Sitting without support not possible, but locomotion such as crawling or rolling	4
No locomotion nor sitting without support, but head control is possible	5
Loss of any locomotion as well as loss of any head and trunk control	6



Adapted from Kehrer C et al.[2,14]

AD: adult; EJ: early juvenile; GMFC-MLD: Gross Motor Function Classification for metachromatic leukodystrophy; LI: late infantile; LJ: late juvenile; MLD: metachromatic leukodystrophy.

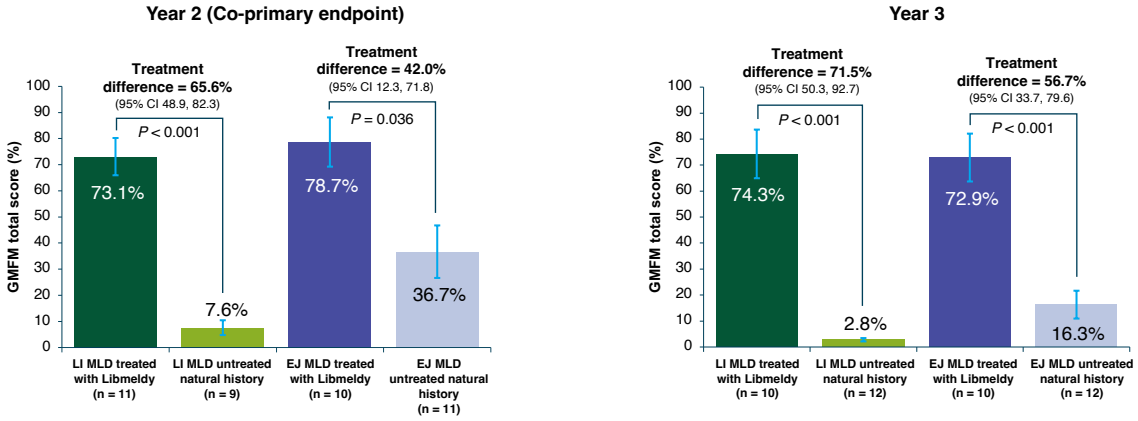
Libmeldy is an *ex vivo* autologous haematopoietic stem cell gene therapy. The first in human clinical trials with arsa-cel started in 2010, and Libmeldy was approved for use by the European Commission in children with LI or EJ forms of MLD on 17th December 2020.[3] This was closely followed by approval from the Medicines and Healthcare products Regulatory Agency (MHRA) on 1st January 2021.[28] Libmeldy is currently the only approved treatment for MLD. With Libmeldy, a patient's own HSCs are collected, and functional copies of the *ARSA* gene are inserted into the genome of the HSCs using a self-inactivating lentiviral vector. Then, these genetically modified cells are infused back into the patient. Gene-corrected HSCs are able to migrate across the blood–brain barrier into the brain, engraft, and express functional enzyme, which has the potential to persistently correct the underlying disease with a single treatment.[3]

The approval of Libmeldy was based on the results of the NCT01560182[29] and NCT03392987[30] clinical trials and patients treated in expanded access frameworks (EAF). As of June 2021, 39 patients have been treated in the clinical development program with Libmeldy (20 in NCT01560182; 9 in EAFs; and 10 in NCT03392987). Eligible patients included those with early-onset MLD, with either pre-symptomatic LI variant or pre- or early-symptomatic EJ variant. In NCT01560182, early-symptomatic-EJ was defined as having an intelligence quotient (IQ) of ≥70 and the ability to walk independently for ≥10 steps.[29] Based on preliminary results, this definition was amended to stricter criteria to 'free from cognitive impairment' (IQ: ≥85) and able to walk independently without support (GMFC-MLD Level 0 or 1) in NCT03392987.[30] The objectives of these clinical trials were to evaluate the safety and efficacy of Libmeldy. The primary efficacy endpoints of NCT01560182 were improvement in Gross Motor Function Measure (GMFM) score, as well as a restoration of ARSA activity at 2 years after treatment compared with baseline. The studies also evaluated the short- and long-term safety of gene therapy, treatment effects on cognitive function, and brain atrophy and demyelination in the CNS and PNS (assessed by MRI and nerve conduction velocity).

There were 16 patients with the LI form (15 pre-symptomatic, and one who became symptomatic between enrolment and treatment) and 13 patients with EJ MLD (five pre-symptomatic and eight early-symptomatic) participants in NCT01560182 and the EAFs with a median length of follow-up of 3.16 (0.64–7.51) years. Additional data, particularly on safety and pharmacodynamics, are available for patients more recently treated with the cryopreserved formulation. The results in the 29 participants treated with the fresh formulation were compared with an untreated natural history cohort of 31 patients with early-onset MLD, who were followed with the same clinical and instrumental tools. All 29 patients showed persistent and stable engraftment of corrected cells. At 1-year post-treatment, the mean percentage of lentiviral vector-positive bone marrow progenitor cells was 55% (range: 20–100%). Stable vector copy number in $CD34^+$ cells was seen throughout the follow-up period. Notably, the transduced progenitors were detectable starting from 1 month post-gene therapy. This resulted in a rapid increase of ARSA activity in peripheral blood that stabilised within 3–6 months post-gene therapy at normal to supranormal levels in all patients. The study confirmed that ARSA activity in the cerebrospinal fluid, undetectable at baseline, was detected from the first measurement performed at 3 months after gene therapy treatment, reached normal levels by 6–12 months post-gene therapy, and remained within the normal reference range up to the longest follow-up available (60 months).[31]

The effects of Libmeldy treatment on motor function was assessed using the GMFM and GMFC-MLD. The GMFM is a motor function scale that ranges from 0 to 100, where 100 is normal function in a child of 5-years-old. A co-primary efficacy endpoint was an improvement in >10% in GMFM at 2 years post-treatment, compared with the age and disease subtype-matched natural history control (Figure 3).[31] A statistically significant difference far exceeding the pre-defined 10% threshold was found in both patients with the LI and EJ MLD at 2 years ($p<0.001$ and $p=0.036$, respectively), which further increased at 3 years ($p<0.001$ for both LI and EJ), compared with the natural history cohort. Most of these patients displayed motor development similar to or slightly below normally developing children, or had stabilisation of motor function or delayed motor decline compared with the natural history group.

Figure 3: Gross Motor Function Measure scores in patients treated with Libmeldy versus untreated natural history



Note: vertical error bars are SE of the adjusted mean and p-values are from a two-sided 5% hypothesis test with null hypothesis of ≤10% difference.

Adapted from Fumagalli et al.[31]

CI: confidence interval; EJ: early juvenile; GMFM: Gross Motor Function Measure; LI: late infantile; MLD: metachromatic leukodystrophy; SE: standard error.

Severe motor impairment was defined as reaching GMFC-MLD Level 5 (loss of trunk control). The study demonstrated that severe motor impairment or death was prevented or delayed compared with natural history in the majority of patients, including patients with EJ MLD who were treated in an early symptomatic phase.[31]

Most patients maintained normal cognitive functioning in terms of performance score and acquired cognitive skills in line with the chronological age. Furthermore, four out of five children with EJ MLD treated in the early-symptomatic phase, who would have fit the current approved indication at the time of treatment (able to walk independently [GMFC: 0 or 1] and before the onset of cognitive decline [IQ: ≥85]), achieved development and acquisition of cognitive abilities in the normal range during long-term follow up. The observed clinical efficacy was further supported by imaging tests using an adapted Loes score,[32] to quantify the extent of white matter abnormality and the progression of brain atrophy. Brain MRI total scores for patients with LI MLD who were treated with Libmeldy stabilised at levels significantly below those observed in the natural history cohort, hence demonstrating lower levels of brain atrophy and demyelination in treated patients. Brain MRI scores also stabilised in the majority of patients with EJ MLD at lower levels than natural history patients with untreated EJ MLD, although at slightly higher levels than in patients with treated LI MLD.[31]

Regarding PNS involvement in MLD, the LI variant is associated with a very severe peripheral neuropathy, presenting early in the clinical course with a rapid decrease to very low nerve conduction velocities. PNS involvement in LI MLD has been refractory to correction with allogeneic HSCT.[20] In contrast, in patients with LI MLD who were treated with Libmeldy, after an initial decline in the first months after gene therapy, nerve conduction velocity stabilised at statistically significant higher levels than in the untreated natural history patients in the deep peroneal and ulnar nerves (both p<0.0001) throughout the follow-up period. This suggests a positive treatment effect of Libmeldy on progressive peripheral demyelination in LI MLD.[33]

A detailed analysis of treatment outcomes was conducted to identify clinical factors that could influence the level of treatment benefit with Libmeldy and optimise the recommended use of the treatment. This analysis identified four treatment failures. As anticipated, in the LI group, one child who was symptomatic at treatment progressed at the same rate as the natural history

group after treatment. Therefore, only patients with LI MLD without clinical manifestations of the disease are within the indicated population for treatment with arsa-cel. In the patients with early-symptomatic-EJ MLD, three patients treated with Libmeldy showed deterioration in both motor and cognitive functions comparable with that observed in untreated natural history patients, and progression of the disease led to death in two of these patients. Their clinical history showed that they either had an IQ of <85, a GMFC of ≥2 at baseline, or experienced deterioration of disease between screening and treatment, suggesting they had entered the rapid phase of disease progression before gene-modified cells were able to engraft. Taking these results into consideration, treatment with Libmeldy in patients with the EJ form of the disease is restricted to those who still have the ability to walk independently, and before the onset of cognitive decline.[32] In the summary of the product characteristics of Libmeldy, it is noted that the physician will reassess for disease progression between initial evaluation and drug infusion; if the disease has worsened, the child many not benefit from Libmeldy and the doctor may recommend against treatment.[32]

As of data cut for this analysis, the safety of Libmeldy was evaluated in 35 patients with MLD. The median duration of follow-up in the integrated safety data set of 29 patients treated with the fresh (investigational) formulation was 4.51 (range: 0.64–7.51) years, and in the six patients treated with the cryopreserved formulation was 0.87 (range: 0.00 to 1.47) years. There were three deaths among the treated group: two related to disease progression and one due to an ischaemic stroke; none were considered to be related to Libmeldy treatment. Treatment with Libmeldy was generally well-tolerated, with most adverse events attributed to busulfan conditioning or MLD disease progression. Treatment-related adverse events included anti-ARSA antibodies, which were reported in five patients. Titres were generally low and resolved spontaneously or after treatment with rituximab, with no apparent impacts observed on clinical efficacy or safety outcomes. No malignancies occurred; however, there is a theoretical risk of leukaemia or lymphoma after treatment with Libmeldy and patients should be monitored for 15 years after treatment, in line with other gene therapies.[31,32]

Treatment with Libmeldy is preceded by medical interventions, namely HSC collection through bone marrow harvest or peripheral blood mobilisation with granulocyte colony-stimulating factor, with or without plerixafor followed by apheresis, and myeloablative conditioning (busulfan is recommended), which are associated with well characterised but potentially serious risks. The safety profile and product information of the medicinal products used for peripheral blood mobilisation and myeloablative conditioning should be considered, in addition to the risks linked to the gene therapy. For further (or detailed) safety information, refer to the EMA summary of product characteristics for Libmeldy.[32]

Libmeldy must be administered in a qualified treatment centre with experience in HSCT. The long-term efficacy and safety of Libmeldy are currently unknown. Patients are expected to enrol and be followed in a long-term follow-up study in order to better understand the long-term safety and efficacy of Libmeldy for up to 15 years following treatment. Five treatment centres are qualified in Europe: Ospedale San Raffaele, Milan, Italy; Children's Hospital, University of Tübingen, Germany; Royal Manchester Children's Hospital, UK; APHP Robert Debré Hospital, Paris, France; and University Medical Center, Utrecht, The Netherlands.

Fumagalli concluded that the results from this interim analysis of 35 patients demonstrated a favourable benefit-risk profile of Libmeldy in the treatment of early-onset MLD, followed for up to 7.5 years post-treatment. There have been no serious adverse events related to Libmeldy reported to date. All patients treated with the fresh formulation achieved stable levels of haematological engraftment and reconstitution of ARSA activity in peripheral blood and in cerebrospinal fluid to normal to supranormal levels. Similar results have been seen for the cryopreserved formulation and within the range of results observed for the fresh formulation. Treatment effects observed in gross motor function and cognition suggest that Libmeldy provides clinically meaningful benefit in pre-symptomatic patients with LI and EJ MLD and patients with EJ MLD in the early symptomatic stages of MLD. Libmeldy may support the prevention, stabilisation, or delay of hallmark progressive CNS damage of early-onset MLD, consistent with treatment effects observed on motor function and cognition. The long-term follow-up of patients treated with Libmeldy is ongoing.

Conclusion

There is an urgency to diagnose, refer, and treat patients with early-onset MLD as there is a limited treatment window for this fatal disease. Lack of developmental progress, when previously reaching milestones normally (i.e., the persistent toddler should be recognised early, requiring immediate further investigation and referral for appropriate life-saving treatment). There is now a beneficial treatment option available in Europe for early-onset MLD, a population for whom options were previously limited or absent. Libmeldy has a positive effect on the neurological symptoms and motor skills following a single administration. These data presented by Fumagalli clearly highlight that early treatment can bring hope to patients.

Great progress is being made in MLD research to better understand the disease, its presentation, the importance of new-born screening, and available treatments. Recently, the academic led MLD initiative used a modified Delphi procedure to achieve consensus and harmonisation on core data to be collected to support research and to facilitate compliance with regulatory requirements.[34] There are several resources available to support clinicians, including the reference list at the end of this article and a series of educational webinars with world leading experts in the field, offered by Excellence in Pediatrics (EiP), which covers the diagnosis and management of MLD.[35]

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Abstract Reviews

Late-breaking abstracts on the latest research in neurology.

Huntingtin as a Presymptomatic Regulator of Alzheimer's Disease

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BACKGROUND AND AIMS

The identification of pathological elements that drive disease progression, so-called regulators, is essential when studying progressive diseases. Several neurodegenerative diseases are associated with such disease regulators, key examples being huntingtin in Huntington's disease and Aβ and τ in Alzheimer's disease (AD).[1,2]

When AD presents with symptoms, irreversible neuronal damage has already occurred.[3] This fact highlights the need to discover new disease regulators, which can be used for therapeutical development. Targetable intervention and therapy are needed to address presymptomatic processes, and regulatory proteins are a key part of disease progression and represent potential targets.[4]

Due to the multifactorial pathology of AD, a multimodal approach is needed in order to identify disease regulators. In these studies, the authors used unbiased proteomics coupled with bioinformatics and microscopy methods in order to discover novel disease regulators in AD.

MATERIALS AND METHODS

Proteomics and subsequent Ingenuity Pathway Analysis (IPA) were performed on a knock-in mouse model for AD (*App*$^{NL-F/NL-F}$), which specifically produced increased levels of the neurotoxic peptide Aβ42, making it suitable for studies of Aβ42-driven pathology.

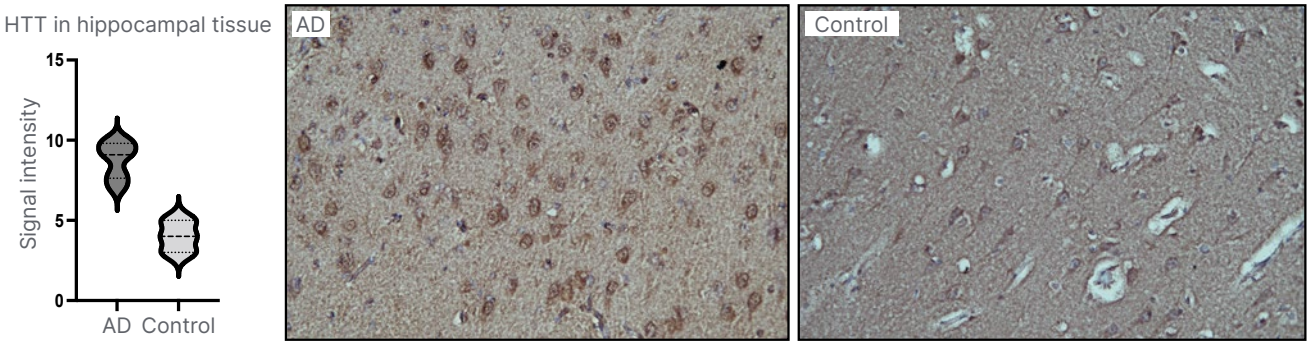
The levels of huntingtin in human and mouse brains were quantified using immunohistochemistry (IHC) and the subcellular huntingtin location was determined by fluorescence microscopy. Potential colocalisation between reactive astrocytes, τ tangles, and huntingtin was determined in human AD tissue by using confocal microscopy.

RESULTS

By using IPA, huntingtin was identified as a presymptomatic regulator of disease progression in a proteomics data set from cortex and hippocampus taken at four different ages (3, 6, 9, and 12 months) from the *App*$^{NL-F/NL-F}$ mouse. Several known Aβ42-associated proteins were also detected.

By using semi-quantitative IHC, huntingtin levels were shown to be highly increased in *App*$^{NL-F/NL-F}$ compared with wild type mice at 6 months of age (3 months before the appearance of amyloid

Figure 1: Huntingtin in the brain of patients with Alzheimer's disease.



Huntingtin is increased in the hippocampal tissue when compared with controls.

AD: Alzheimer's disease.

plaques). The huntingtin levels increased over time in wild type mice but not in *App*$^{NL-F/NL-F}$ mice and at 25 months, there was no difference in the levels of huntingtin. Moreover, IHC showed increased levels of huntingtin in pyramidal neurons in the hippocampus and frontal cortex in patients with AD relative to controls (Figure 1).

In contrast to Huntington's disease, huntingtin did not colocalise with reactive astrocytes in AD brain, as demonstrated by confocal microscopy. Huntingtin levels were increased in pyramidal neurons in AD brain. There was no significant colocalisation of huntingtin with phosphorylated τ.

CONCLUSION

Huntingtin accumulates in the brain of patients with AD and is distinct from the huntingtin accumulation seen in Huntington's disease. Huntingtin accumulation precedes AD pathology in *App*$^{NL-F/NL-F}$ mice.

These findings implicate huntingtin in the pathology of AD and warrant further studies. Huntingtin regulation could be a potential treatment for AD due to the numerous clinical trials aimed at Huntington's disease. The process by which huntingtin regulates AD pathology needs to be established. Mechanistic studies of huntingtin in neuronal cell cultures will shed light on the relationship between huntingtin and AD pathogenesis.●

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MRI Response Assessment in Patients with Glioblastoma Treated with Dendritic Cell-Based Immunotherapy

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Keywords: Glioblastoma (GB), immunotherapy, immunotherapy response assessment in neuro-oncology (iRANO), modified response assessment in neuro-oncology (mRANO), radiologic response criteria, volumetric measurements.

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BACKGROUND AND AIMS

In glioblastoma (GB), patients' reliable response assessment criteria are crucial in order to accurately compare the responsiveness of different therapies in clinical trials, and to differentiate between therapy-induced changes and true tumour progression. Radiochemotherapy and immunologic strategies, as well as radiologic phenomena such as pseudoprogression (PsP), challenge the current imaging response criteria.[1] In 1990, the MacDonald criteria were introduced, using two-dimensional tumour measurements, as well as corticosteroid use and the clinical performance of the patient for response assessment.[2] The Response Assessment in Neuro-oncology (RANO) criteria[3] additionally utilise T2-weighted or fluid-attenuated inversion recovery image sequences to account for non-enhancing tumour components and therapy-induced MRI changes.[3,4] To better account for the phenomenon of PsP, the modified RANO (mRANO) criteria were proposed in 2017.[5] In consideration of unique patterns of PsP during immunotherapy of GB, the immunotherapy RANO (iRANO) criteria[6] were developed.

The aim of this study was to compare the different response criteria in patients with GB treated by dendritic cell immunotherapy in addition to standard of care, and in order to detect the best response criteria for prediction of progression-free survival (PFS) and overall survival (OS).

MATERIAL AND METHODS

The authors retrospectively analysed imaging data from 76 patients with newly diagnosed GB World Health Organization (WHO) Grade IV, treated with either standard of care (SOC), or SOC plus a personalised dendritic cell-based vaccine. For 2D, response-assessment criteria MacDonald,[2] RANO,[3] mRANO,[5] and iRANO,[6] were

used, and for 3D assessment methods Vol-mRANO[5] and Vol-RANO[7] were applied to each available MRI scan obtained from each patient (postoperative and follow-up MRI). In order to calculate tumour volume, tumour segmentation was performed using a semiautomated active contour method (ITK-SNAP 3.8.0).[8] Differences in PFS among the assessment criteria were calculated by the Kruskal–Wallis test, and results were corrected for multiple comparison (Bonferroni's adjustment). For correlation analysis between PFS and OS, the Spearman test was used.

RESULTS

Overall, there was a significant difference in median PFS between mRANO (8.6 months) and Vol-mRANO (8.6 months) compared with MacDonald (4.0 months), RANO (4.2 months) and Vol-RANO (5.4 months). In the audencel subgroup, there was a significant difference in median PFS between mRANO (8.1 months) and Vol-mRANO (8.6 months) compared with MacDonald (4.2 months). The best correlation between PFS and OS was detected for Vol-mRANO (r=0.69) and mRANO (r=0.65), followed by MacDonald (r=0.44), RANO (r=0.45), Vol-RANO (r=0.46), and iRANO (r=0.50). The impact of progressive disease on median OS at the 4-month landmark time was most distinct for mRANO, Vol-mRANO, and iRANO, and at the 8-month landmark time for mRANO and Vol-mRANO. For those criteria, the greatest difference in OS between stable disease and progressive disease at the specific landmark time was observed. By applying mRANO, 19 patients (25.0%) had confirmed PsP. When iRANO was applied to patients treated with SOC plus audencel, four patients (11.1%) had confirmed PsP.[9]

CONCLUSION

mRANO criteria are superior to MacDonald and RANO for predicting progression in patients with newly diagnosed GB treated with SOC±additional audencel-based immunotherapy. Moreover, the best correlation between PFS and OS was seen for mRANO and Vol-mRANO. ●

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Brain Tumour-Related Epilepsy: Impact of Grading and Treatments in a Cohort of Molecularly Defined Lower-Grade Gliomas

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BACKGROUND AND AIMS

Brain tumour-related epilepsy (BTRE) is associated with diffuse lower-grade gliomas (DLGG) in up to 70–90% of cases.[1] Several factors may affect seizure outcome and control, some of which are related to tumour characteristics (such as tumour location, histotype, molecular features, tumour growth, and progression), while others are the consequences of tumour treatment (extent of surgery, radiation therapy, chemotherapy, and the use of target agents).[2-6] The authors' study aimed to describe the natural history of BTRE in a real-life cohort of patients with DLGGs, to correlate the presence of seizures to tumour and patient characteristics, and to assess the impact of surgery and adjuvant treatments on seizure control.

MATERIALS AND METHODS

The authors retrospectively collected clinical data of patients with DLGGs, aged ≥18 years of age, with a history of BTRE. They retained information about seizure freedom after surgery, adjuvant treatments, and recurrence. The authors' main endpoints were seizure freedom after surgery, adjuvant treatments, and recurrence.

RESULTS

This study included 280 patients (median age: 40) with DLGGs who were diagnosed between 1988 and 2021. Out of the 280 patients, 106 (54.9%) had oligodendrogliomas *IDH*-mutant 1p19q-codeleted, 40 (20.7%) had astrocytomas *IDH*-mutant, and 47 (24.4%) had *IDH*-wildtype. There were 199 (71.1%) patients with Grade 2 tumours and 81 (28.9%) patients with Grade 3 tumours. Gross total resection (GTR) accounted for 117 (41.8%) cases.

Seizure freedom at 30 days after surgery was seen in 144 out of 280 (51.4%) patients, and in 97 out of 151 (64.2%) patients after 6 months after starting adjuvant treatment. One-hundred and thirty-four (59.6%) patients displayed seizures as a symptom of recurrence. Patients with seizure persistence after surgery were significantly more likely to be of a younger age and have oligodendroglial tumours, Grade 2 histology, temporal lobe location, and incomplete surgery.

Furthermore, seizure freedom after adjuvant treatment prevailed among patients displaying an objective Response Assessment in Neuro-oncology (RANO) response to adjuvant treatments (being achieved in 84.2% versus 59.4% patients with complete/partial response versus stable/progressive disease; p=0.040). In a multivariable model (Table 1), seizure freedom after surgery was positively related to age ≥40 (odds ratio [OR]: 1.027; p<0.001) and GTR (OR: 1.788; p=0.049), and negatively related to Grade 2 histology (OR: 0.301; p<0.001). Similarly, Grade 2 histology (OR: 0.232; p=0.011) and temporal lobe location were negative predictors of seizure freedom after adjuvant treatments (OR: 0.318; p=0.041). Previous radiotherapy significantly reduced the risk of seizures at recurrence (OR: 0.233; p=0.026).

Table 1: Multivariable model of factors affecting seizure freedom after surgery, after adjuvant treatments, and at recurrence.

	Seizure-freedom after surgery				Seizure-freedom after adjuvant treatment				Seizures at recurrence			
	OR	95% CI		p	OR	95% CI		p	OR	95% CI		p
		Lower	Upper			Lower	Upper			Lower	Upper	
Age	1.027	1.011	1.044	<0.001	1.053	1.016	1.091	0.005	0.989	0.968	1.010	0.312
Temporal lobe versus other	0.612	0.297	1.261	0.183	0.318	0.106	0.956	0.041	0.624	0.292	1.335	0.224
GTR versus non-GTR	1.788	0.101	3.460	0.049	1.170	0.368	3.719	0.791	1.043	0.498	2.183	0.911
Grade 2 versus Grade 3	0.301	0.156	0.580	<0.001	0.232	0.075	0.717	0.011	2.294	1.070	4.919	0.033
Histomolecular diagnosis												
O. IDHmt, 1p19q-codel	1.000	N/A	N/A	0.460	1.000	N/A	N/A	0.690	1.000	N/A	N/A	0.047
A. IDHmt	0.902	0.383	2.122	0.813	1.823	0.455	7.311	0.397	1.537	0.611	3.866	0.361
A. IDHwt	0.579	0.245	1.371	0.214	1.414	0.334	5.981	0.637	4.895	1.379	17.373	0.014
Adjuvant temozolomide	N/A	N/A	N/A	N/A	0.556	0.124	2.493	0.443	1.298	0.595	2.832	0.513
Adjuvant radiotherapy	N/A	N/A	N/A	N/A	0.530	0.122	2.304	0.397	0.233	0.065	0.839	0.026
Objective RANO response (CR/PR versus SD/PD)	N/A	N/A	N/A	N/A	2.108	0.313	14.184	0.443	N/A	N/A	N/A	N/A

A: astrocytoma; codel, codeleted; CI: confidence interval; CR: complete response; GTR: gross total resection; IDH: isocitrate dehydrogenase; mt: mutant; O: oligodendrogliomas; OR: odds ratio; PD: progressive disease; PR: partial response; RANO: Response Assessment in Neuro-oncology; SD: stable disease; wt: wildtype.

CONCLUSION

In the authors' study, younger age, Grade 2 histology, oligodendroglial phenotype, and temporal lobe involvement were baseline factors associated with a worse seizure control in patients with DLGGs. The extent of resection and adjuvant treatments affected seizure control at different levels: GTR correlated with a higher rate of seizure freedom after surgery; objective RANO responses to MRI (complete/partial response) prevailed among seizure-free patients after adjuvant treatments; and adjuvant radiotherapy was associated with a lower risk of seizures at recurrence. These data should be validated in larger prospective studies and the analysis should be extended to the new entities of the 2021 (World Health Organization) WHO Classification of brain tumours (astrocytomas *IDH*-mutant Grade 4 with *CDKN2A/B* homozygous deletion and astrocytomas *IDH*-wildtype with molecular features of glioblastoma).

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Seizure Forecasting with Non-invasive and Minimally Invasive Mobile Devices: The Epilepsy Foundation's My Seizure Gauge Study

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Keywords: Epilepsy, mobile devices, mobile health, seizure detection, seizure forecasting, wearable technology.

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BACKGROUND AND AIMS

Seizure unpredictability is consistently reported as one of the most disabling aspects of living with chronic epilepsy. Reliable forecasting systems could have far-reaching consequences for patients, from allowing protection at times of high seizure risk to improving confidence during everyday life at times of low seizure risk.[1,2] The feasibility of forecasting has been demonstrated with chronic intracerebral electroencephalographic (EEG) recordings;[3] however, invasive devices carry significant risks and are not appropriate for all patients.

The Epilepsy Foundation's My Seizure Gauge Project is an ongoing multicentre study aiming to determine the feasibility of seizure forecasting with non-invasive and minimally invasive mobile devices (Figure 1).

MATERIALS AND METHODS

Adult patients with active (>10 seizures/6 months) drug-resistant epilepsy were enrolled for ultra-long-term (>8 months) monitoring. Patients were asked to self-report their seizures on an electronic diary (Seer app [Seer, Melbourne, Australia]) while using a wearable device (Empatica E4 [Empatica, Boston, Massachusetts, USA], Fitbit Charge 4/HR [Fitbit, San Francisco, Calirfornia, USA], or Fitbit Inspire) and simultaneous chronic ambulatory EEG monitoring (RNS [NeuroPace, Mountain View, California, USA], 24/7 EEG™ SubQ [UNEEG, Allerød, Denmark] or Epi-Minder sub-scalp [Bionics Institute, Melbourne, Australia] systems). Recorded data from these multiple modalities was analysed via traditional machine learning or deep learning methods, together with the identification of patient-specific circadian and multiday seizure risk cycles to forecast seizures.

RESULTS

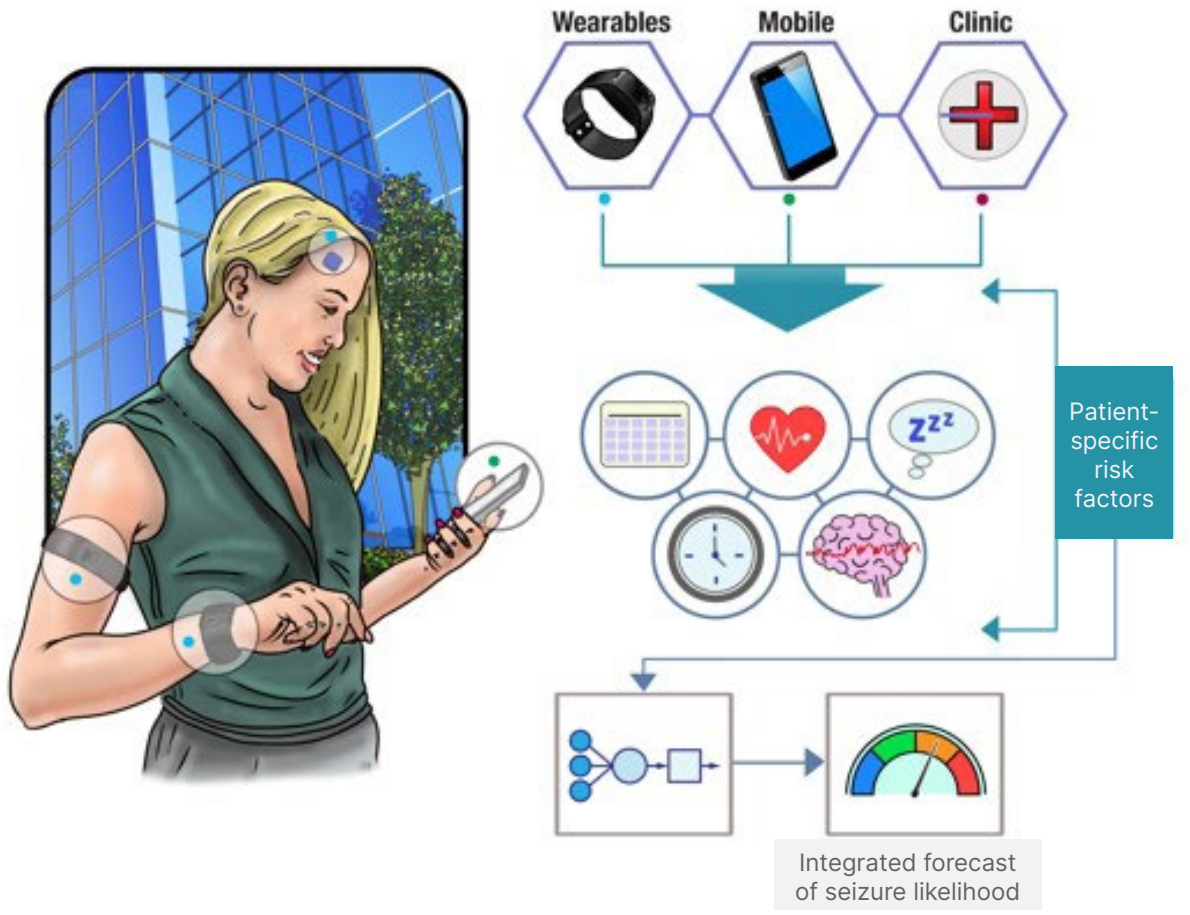
To date, 40 enrolled subjects have recorded over 11,400 days (>31 years) of ambulatory data, and over 1,700 seizures have been annotated. Nine patients left the study prematurely due to device malfunctions, complications, poor adherence, poor data quality, or unanticipated seizure freedom. However, 20 patients are continuing to record data and 11 have completed the study.

Selected results from analysis of this cohort have been presented. Circadian and multiday seizure cycles were detected with ultra-long-term subcutaneous EEG.[4,5] Heart rate circadian and multiday cycles were also detected in a high proportion of patients using a commercial fitness tracker (Fitbit), and were found to correlate with self-reported seizure likelihood.[6] Using data from a multimodal wearable device (Empatica E4), electrodermal activity, heart-rate, and accelerometery data were significantly correlated with electrographic seizures detected by the RNS device in 11 patients. In another group of 11 subjects, patient-specific seizure forecasts trained on Fitibit data were found to be significantly better than chance in 91–100% of subjects.[7] Seizure forecasting was also better than chance in five out of six patients using the Empatica E4 data, validated on RNS-detected seizures.[8] Finally, seizure forecasting using ultra-long-term subcutaneous EEG data was significantly better than chance in at least 50% of patients in a six-patient cohort.[9,10]

CONCLUSION

This project has established the feasibility of forecasting seizures using seizure cycles, wearable devices, and subcutaneous EEG.

Figure 1: The overarching goal of the Epilepsy Foundation's My Seizure Gauge project is to establish the feasibility of seizure forecasting using non-invasive and minimally invasive mobile devices.



Multimodal data can be incorporated into patient-specific forecasts of seizure risk.

Seizure cycles are common in patients with epilepsy. They are measurable across a range of non-invasive wearables, minimally invasive EEG, and intracranial EEG devices, and they are strong forecasts of seizure likelihood. The next steps in this project are to establish a freely available data science competition for forecasting using wearable data, and to trial a prospective seizure forecasting smartphone app (Seer), which is now available to the public.

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Prefrontal Transcranial Direct Current Stimulation in Patients with Disorders of Consciousness: A Multicentre, Randomised, Double-Blind, Sham-Controlled Clinical Trial

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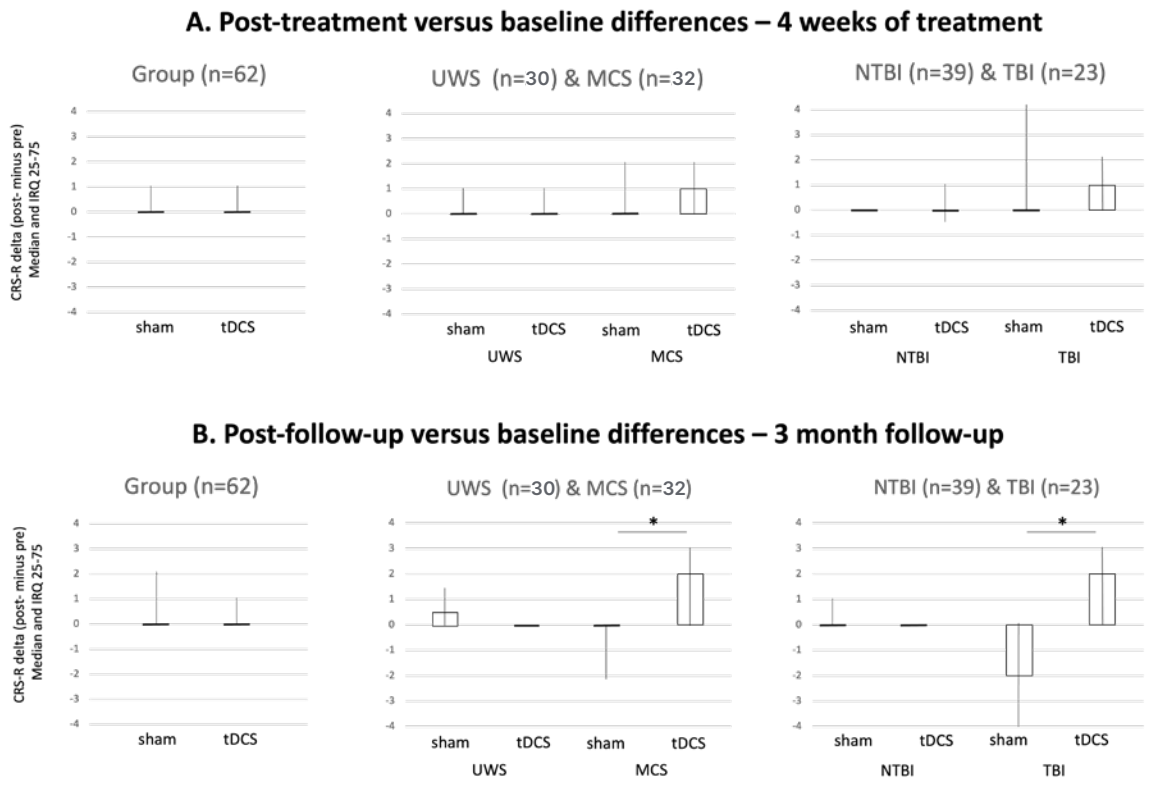
BACKGROUND AND AIMS

Transcranial direct current stimulation (tDCS) applied over the left dorsolateral prefrontal cortex has shown to transiently improve the level of consciousness of severely brain-injured patients in disorders of consciousness,[1] and seems to be effective especially for patients in minimally conscious state (MCS) compared with patients in unresponsive wakefulness syndrome.[2] However, no large-sample multicentre study confirmed its efficacy or inefficacy in both subgroups of patients when applied during rehabilitation.

Figure 1: Results of the Mann–Whitney tests for the group and subgroups analyses.



Boxplot of active and sham tDCS at Week 4 (A. treatment period) and Month 3 (B. follow-up). Black lines represent the medians of the delta of the CRS-R total score between baseline and after active or sham tDCS; boxes represent the interquartile range; lines represent minimum and maximum.

CRS-R: Coma Recovery Scale-Revised; IQR: interquartile range; MCS: minimally conscious state; NTBI: non-traumatic brain injury; TBI: traumatic brain injury; tDCS: transcranial direct current stimulation; UWS: unresponsive wakefulness syndrome.

MATERIALS AND METHODS

In this parallel sham-controlled, double-blind, randomised trial, the authors investigated whether 4 weeks of tDCS could enhance signs of consciousness in patients in prolonged disorders of consciousness whilst in rehabilitation. TDCS (or sham) was applied at 2mA for 20 minutes over the left dorsolateral prefrontal cortex once a day, five days per week for 4 weeks, for a total of 20 sessions. The authors used the Coma Recovery Scale-Revised weekly during the treatment period (4 weeks), and at 1-, 2-, and 3-month follow-ups to objectify behavioral changes. They used a mixed general linear model to evaluate behavioral changes during the treatment period (4 weeks) and the follow-up period (3 months) between active and sham groups, accounting for diagnosis, aetiology, and time since injury. Differences (i.e., deltas) between baseline and the end of the treatment period (4 weeks), as well as baseline and the end of the follow-up period (3 months), were analysed with a Mann–Whitney test. Analyses were conducted at the group level, and by subgroup levels based on the diagnosis (MCS and unresponsive wakefulness syndrome) and the aetiology (traumatic or non-traumatic).

RESULTS

A total of 62 patients (44±14 years old; 37±24.5 weeks post-injury; 18 females [29%]; 32 MCS

[52%]; 39 non-traumatic aetiology [63%]) were randomised. Thirty three patients were allocated to the active group, and 31 of them received the treatment (two dropped out right after randomisation). The remaining 29 patients were allocated to the sham group, where there was no drop out. Baseline demographic characteristics were similar between both groups. None of the patients experienced any serious adverse events related to the intervention. At the group level, the generalised linear mixed model did not reveal any treatment effect during the treatment period (p=0.21), nor during the follow-up (p=0.85). Subgroup analyses revealed a significant improvement for the active compared to the sham group for patients in MCS (p=0.020; improvement of 1 [0–3] for the active group and 0 [-2–0] for the sham group) and for traumatic brain-injured patients (p=0.021; improvement of 2 [0–3] for the active group and -2 [-4–0] for the sham group) at Month 3. No other subgroup comparisons were significant.

CONCLUSION

The authors' results suggest that at the group level, tDCS applied during rehabilitation does not significantly enhance patients' signs of consciousness during the treatment period. The subgroups of patients with MCS and traumatic brain injury, however, demonstrated a better recovery in the active compared to the sham group at 3-month follow-up. In this context, tDCS could be included in the rehabilitation programs of these subgroups of patients to promote their recovery. ●

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Haemodynamic Determinants of Supine Hypertension in Neurogenic Orthostatic Hypotension

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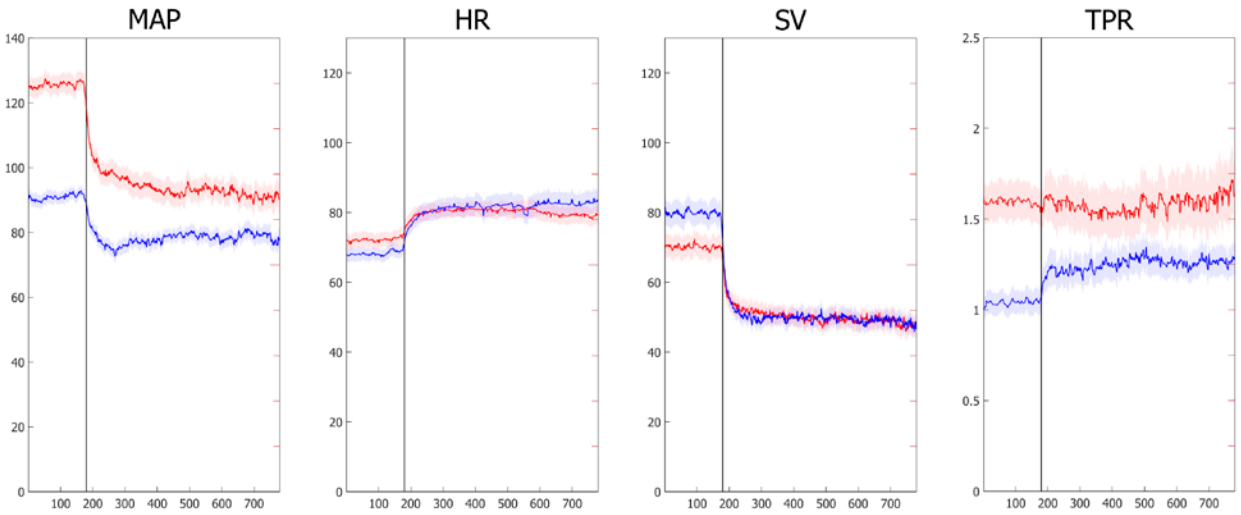
BACKGROUND AND AIMS

Patients with classic orthostatic hypotension (cOH) suffer from an abnormally large blood pressure (BP) fall upon standing due to baroreflex dysfunction. cOH, particularly in the absence of BP-lowering drugs, often has a neurogenic cause (neurogenic orthostatic hypotension [nOH]). In approximately half of all patients with nOH, this coincides with supine hypertension (i.e., systolic BP [SBP] ≥140 mmHg, diastolic BP ≥90 mmHg, or both);[1] however, the underlying mechanisms of this complication are poorly understood.[2] Supine hypertension is thought to aggravate low BP complaints in cOH due to increased overnight pressure natriuresis, resulting in relative hypovolaemia in the morning.[1,3] Supine hypertension is a risk factor for cardiovascular disease in the general population and it is also associated with increased cardiovascular risk in nOH.[3,4]

Figure 1: Time course of haemodynamic parameters in patients with classic orthostatic hypotension according to supine systolic blood pressure.



Lines indicate average±standard error, the point of tilt is indicated by the horizontal line visible at 180 seconds.

Red: high supine systolic blood pressure; blue: low supine systolic blood pressure.

HR: heart rate; MAP: mean arterial pressure; SV: stroke volume; TPR: total peripheral resistance.

The authors aimed to investigate the haemodynamic mechanisms of supine hypertension in patients with cOH.

MATERIALS AND METHODS

The authors performed a retrospective analysis of continuous BP patterns in 65 patients with cOH (53 of these individuals had nOH) and 39 age-matched controls who underwent a tilt test. The authors compared the means of two periods: -180 seconds to -20 seconds before and 170 seconds to 190 seconds after the head-up tilt. Modelflow was used to analyse mean arterial pressure (MAP) and its constituent heart rate, stroke volume (SV), and total peripheral resistance (TPR). Both groups were split based on the median supine SBP of 150 mmHg, dividing them in a high supine SBP group and a low supine SBP group.

RESULTS

Patients with cOH and a relative high supine SBP, and therefore MAP, had a significantly higher supine TPR than those with a relative low supine SBP ($p<0.0001$), while supine heart rate and SV did not differ between groups (Figure 1). The upright position yielded a more pronounced MAP fall ($p<0.0001$) and smaller SV decrease ($p=0.001$) in those patients with cOH and higher supine BP relative to those with lower supine BP. Notably, in those with cOH and high supine SBP, the larger BP fall upon tilting was not accompanied by a more marked TPR response, suggesting a ceiling effect of TPR in this group (Figure 1). Interestingly, when comparing the relative high and relative low supine SBP control groups, the authors did not find contrasts in either supine or standing TPR.

CONCLUSION

Supine hypertension in cOH is primarily driven by a high TPR in supine position and a larger BP fall caused by an inability to increase TPR beyond supine levels, which is slightly counteracted by a smaller decrease in SV. Supine hypertension in nOH may result from long-term influences affecting BP homeostasis. The inability to increase TPR upon standing suggests more

widespread baroreflex failure. Non-autonomic humoral mechanisms could be considered to explain the relative high supine TPR in supine hypertension and nOH.

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Congress Interview

EMJ interviewed award-winning abstract author Einar August Høgestøl, hearing his thoughts on the 2022 European Academy of Neurology (EAN) Congress, the current state of multiple sclerosis research, and the future of innovative neurology research.

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EAN 2022

Einar August Høgestøl

Associate Professor, Department of Psychology, University of Oslo, Norway; Doctor-in-Training, Department of Neurology, Oslo University Hospital, Norway; 2022 Author of the Best Presentation in Basic Neurology at the European Academy of Neurology (EAN) Tournament for Neurologists in Training

Q1 What led you to pursue a career in neurology and psychology?

This is always a tricky question to answer. As a student, I shifted a lot based on the topics we were going through at the time. At one point I was certain I would be a paediatrician, while later it was geriatrician. When I finally had the opportunity to choose my course, I applied for a lot of different residencies in a plan to move closer to my hometown. Quite surprisingly, the first contract I was offered came from the neurosurgical department, where I started my career and spent the next year and a half. Even though this was a very exciting and all-consuming career, I wanted to combine research with more neurological insights. I was lucky that a new opportunity came along, and back in 2015, I was accepted as a full-time PhD candidate at the university. Since then, I've never looked back, and have enjoyed a mix of advanced imaging research in neurology and psychology, which later combined with a clinical residency in neurology. I have always jumped on the next opportunity, building on previous experience, but always going forward.

Q2 You completed your PhD thesis on MRI and biomarkers for early multiple sclerosis (MS). What initially sparked your interest in this particular area of neurology?

Since I was a young kid growing up with computers and the exploding technological evolution, I have always had a special interest in computational science. When going into medical school in Norway back in 2006, the bioinformatics and computational advances were not deeply included as part of the curriculum. I guess this was just the way things had been done for years, but when finishing medical school, I felt that part of me was never utilised to its full potential. For my

PhD topic, I was lucky to find the right supervisor at the right time. Professor Harbo saw potential in me, and I was able to mix together the project to follow my interests. We knew I had to do a follow-up study on patients with MS, but mixing this with advanced imaging research was both a suggestion from Professor Harbo and a wish on my part. We then joined forces with Professor Westlye and his team at the Multimodal Imaging Group at the Norwegian Centre for Mental Disorders Research (NORMENT) in Norway, which we knew was at the forefront of imaging research, and had great potential for future collaborations.

"One of the main tasks as a researcher is disseminating knowledge to people, and not just to other colleagues that you encounter on an almost daily basis."

Q3 You run a Facebook page for your MS research group in Oslo. Can you talk about its purpose and why it provides value?

In Norway, we have many young adults with MS. One of the main tasks as a researcher is disseminating knowledge to people, and not just to other colleagues that you encounter on an almost daily basis. I noticed early on that young people with MS in Norway had a lot of questions, and no specific platform for voicing them within the MS research community. They had their own, closed Facebook group called 'MS-friends', a place that I knew from my patients had a lot of discussions on MS research and rumours. Also, the national MS union had their own Facebook page with a lot of followers, but their standing was more of a political one.

I felt obligated to start a Facebook group that had its basis in our research group, mostly to inform on ongoing research both locally, nationally, and internationally. I felt it was often necessary to 'translate' new research to people with the disease, and to put it in context. It has also been a way to inform on the views or standpoints of fellow neurologists and researchers on important matters that also affect people with MS. People with MS are often very up to date on their disease, and I hope that our page on Facebook has been helpful in some way.

Q4 You are set to present an abstract of your novel research, 'Brain age estimation by machine learning outperforms brain parenchymal fraction as imaging marker in multiple sclerosis', at the EAN's 2022 Congress. Could you tell us a little about this research and its implications?

Since 2017, NORMENT and the MS research group has had a growing interest in the application of modern artificial intelligence (AI) methods in imaging research. Estimating age based on MRI scans is nothing new, and was first done in 2004. Recently, large imaging repositories and improved computational efficacy has enabled us to develop more sophisticated models to apply in a research setting. We published the first paper on brain age estimation in MS back in 2019, but have since collaborated together with NORMENT and also the Karolinska University Hospital, Stockholm, Sweden, to expand and explore this in a much larger cohort of people with MS, using an established machine learning model based on a training set of over 35,000 healthy individuals. This enabled us to dig into a unique, real-world MS cohort to discover robust associations with many clinical features. It was especially important for us to be able to compare this model with the established imaging marker in MS, brain volume. We hope this will spur even more interest across the MS research community, and then in the future as a potential imaging marker to improve future MS care, both from the onset of the disease and throughout the disease course, as a supplementary imaging tool being supplied at each MRI scan any person with MS undergoes (or any other person undergoing an MRI scan of the head).

"With the EAN congress, I can both attend the presentations that I'm most interested in, while also being able to get a broader update across many of the different branches of neurology."

Q5 How widespread do you think knowledge is of machine learning and its implications in MS diagnosis and treatment?

The application of AI methods has been a hot topic over the last 5–10 years in the MS community, yet it has still only been applied in a research setting. Some efforts have, as far as I know, been made to explore it in advanced imaging research by mixing different imaging modalities to capture disease progression. Already, across different medical topics, like skin biopsy, X-ray diagnoses, gastroenterology with colonoscopy, or a CT scan to investigate for stroke, there have been many large diagnostic breakthroughs incorporating different AI methods as supplementary tools.

Q6 As a contributor to the EAN Congress 2022, can you talk about the impact the EAN has on neurologists and patients?

I have been attending the EAN congress each year since it was organised here

in Oslo in 2019, which was the fifth time this congress was held. That year, I was part of the local committee, and helped to organise the site visit at our hospital. To combine the complete neurological field in such a far-reaching congress is extremely hard. There are other congresses which are more specific, such as the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS, organised for the 38th time in autumn 2022), and the European Stroke Organisation Conference (ESOC, organised for the eighth time in May 2022). Such conferences have a greater impact on specific fields of research. With the EAN congress, I can both attend the presentations that I'm most interested in while also being able to get a broader update across many of the different branches of neurology. This benefits us as researchers and clinicians more directly, but also patients down the line, when the clinicians travel back home to our hospitals fresh with new knowledge on current state-of-the-art techniques.

Q7 What topics are you hoping to see in focus at this year's EAN Congress?

For this year's EAN congress, I, first of all, am looking forward to meeting up in person again with great colleagues from across Europe, and to get a general update across different neurological branches, such as epilepsy, stroke, headache and migraine, MS, and movement disorders. I hope that there will be time to see some small glimpses of the great city of Vienna, Austria, where I have not been previously. Regarding MS research, I have always had a sweet spot for advanced imaging research, but am also looking very much forward to the Camillo Golgi Lecture by Professor Hans Lassmann, with the title 'The Contribution of Neuropathology to Multiple Sclerosis'. There are also some other topics on MS treatment with high-efficacy treatment that will be very interesting to attend, where we can compare how the Norwegian approach aligns with the bigger countries in terms of strategy and also in terms of what we focus on for signs of disease progression. An update on the 'real MS', also known as 'smouldering MS', is also a special favourite of mine, as many

people with MS experience progression independent of relapse activity, and we currently lack the complete picture of what causes this.

Q8 You are currently working in collaboration with NORMENT. Could you tell us about the work you do there?

After completing my PhD thesis and defence, I was approached by Westlye in the Multimodal Imaging Group of NORMENT to join their team in two large studies on brain imaging in the BRAINMINT project. This is a European Research Council (ERC)-founded project that focuses on brains and minds in transition, with a special focus on two important transitions in life, namely adolescence and pregnancy. We take a broad approach to both of these two groups, and in addition to MRI scans of the brain and body, we also perform electroencephalogram, blood sampling including genetics, neuropsychological tests, and general screening. For the pregnancy study we are recruiting females who plan to become pregnant in the near future, and will examine them before and after pregnancy, with a control group of those not becoming pregnant. As of now, we already have over 400 females and over 400 teenagers recruited, and we are looking very much forward to digging into these datasets when they become more complete.

Q9 Much of your extensive published work has focused on MS. What do you believe are the current gaps in the literature, and what topics merit greater attention?

In MS research, there are many new avenues that will be given increased focus for research in the coming years. From what I know, and from my perspective, I hope there will be an increased focus on the neurodegenerative part of the disease. In a couple of years, we will also see the results from all of the ongoing haematopoietic stem cell transplantation randomised control trials, to finally get the answer to which people with MS should be treated with haematopoietic stem cell transplantation from the beginning, compared to when we see progression of the disease. The term smouldering MS is catching hold of researchers, and to disentangle this aspect of MS will potentially give new insights and new treatment possibilities. Also, how we monitor people with MS has to be more adapted to the digital era, with home monitoring, digital screening, and the inclusion of patient-reported outcome measures in the follow-up of MS care. We need to include new biomarkers in MS care, such as neurofilament, cognitive screening, potentially genetic guidance, and supplementary tools for MRI scans of the brain. Last but not least, new research avenues opened after some big breakthroughs following the Epstein–Barr virus (EBV) papers from 2021 and 2022. Could we potentially avoid getting MS by developing and incorporating an EBV-vaccine in the children's vaccine programme? Or could targeted EBV-treatment for those with MS be a new potential treatment approach?

Q10 Are there any innovations on the horizon in neurology, and more specifically in MS, that you think are particularly noteworthy?

As mentioned in the last question, I hope to see some targeted treatment possibilities for the neurodegenerative aspect of MS, and also some EBV-related treatments. During the COVID-19 pandemic, I have also shifted many of my follow-up appointments to video calls or just a telephone call. This implies that there is no current need to investigate patients, but in that case, I hope there will be more opportunities for home-monitoring, digital screening for MS symptoms, and cognitive performance. With MS being effectively countered for many with the early high-efficacy treatment, we need more sensitive tools for monitoring the

disease. As of today, we are merely asking for side effects of the current treatment, looking for clinical relapses, and reviewing the neuroradiological assessment of annual MRI scans. Based on what the research has shown us in the last decade, we need to include many more aspects in the follow-up of MS patients. This is, however, impossible with the lack of resources and time each patient gets with their neurologist, so here we need to explore and develop new tools to simplify and implement this in a clinical setting. Lastly, I really hope we can see some effective treatments for fatigue, as this is not only a MS-specific symptom, but a debilitating symptom across the medical field.

Q11 As a researcher, where can we expect to see your focus lie in the coming years?

I was appointed subgroup leader of the MRI group in the MS research group here in Oslo last year. I have many ongoing projects across advanced imaging research, and hope to also broaden my perspective a bit to include stroke, motor neurone disease, and neuro-COVID. I get to be part of the forefront of imaging research through my position at NORMENT, which I also hope to be able to bridge across to other neurological diseases. Brain health includes all disorders affecting the brain, so in that understanding, I'm just bridging two parts of brain health aspects together where they belong. I always try to recruit and collaborate with people more capable than myself in a specific field of research; then we find common ground on the topic in focus to move the research field a bit further. As for MS, my big focus at the moment lies in AI methods and imaging research. Here, I hope we will see some big breakthroughs, both for MS but also across other parts of neurology. As of now, we are merely scratching the surface of the data being available from a clinical MRI scan of the brain by relying on the visual assessments alone. There is much more information in brain scans that will help us to better tailor treatment and understand the diseases, to improve patient care. I hope to be a part of this in the coming years.

Interview

Cathy Stinear

Director of the Clinical Neuroscience Laboratory in the Department of Medicine, University of Auckland, New Zealand; Chair of the Neurological Foundation of New Zealand's Council

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Cathy Stinear shared her thoughts and experiences within the field of neuroscience, focusing on the challenges of stroke recovery, changes within the field, and her role as Chair of the Neurological Foundation of New Zealand's Council.

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

Neuroscience is my third career, so it might have been a process of elimination!

> "The work that we do involves whole human beings, usually people in the hospital who have recently experienced a stroke."

Q2 Do you think there are any misconceptions about your speciality?

When people think about neuroscience they often imagine people in white coats working at lab benches. And it's true that a lot of great neuroscience looks exactly like this. The work that we do involves whole human beings, usually people in the hospital who have recently experienced a stroke. We use neurophysiological and neuroimaging techniques to understand how the brain is affected by stroke and the biology of recovery. People are sometimes surprised at the sophisticated neuroscience research that can be done with patients. It's very rewarding to work directly with patients, rather than with animal models or cell cultures that are many steps removed from the problems we're trying to solve.

Q3 You have specialised in predicting and promoting motor recovery after stroke. What are some of the unique challenges associated with stroke recovery?

It can be very difficult to make accurate predictions for individual patients. While it is true that most people with initially mild stroke symptoms usually have a good outcome, recovery can be much harder to predict for people with initially moderate to severe impairments. Some people with initially severe haemiparesis make very little improvement, while others go on to make a substantial recovery and have a good outcome. The problem is that you can't know what to

expect using clinical examination and experience alone. So the challenge is to make judicious and efficient use of motor system biomarkers to make accurate predictions for individual patients and then use these predictions to tailor rehabilitation plans and manage expectations. We have developed the PREP2 prediction tool that combines clinical and biomarker information within days of the stroke to accurately predict upper limb outcomes, 3 months after stroke. Our work has shown that this helps with setting appropriate rehabilitation goals and reduces the length of stay. We have also developed the TWIST prediction tool that combines clinical information 1 week after stroke to accurately predict both whether and when a patient will recover to independently walking.

Q4 One of your interests is the translation of neuroscience discoveries to clinical practice. Could you tell us more about what this often requires?

Understanding the problems that clinicians are trying to solve is an important first step. My research team is very fortunate to work in the hospital setting, in both acute and rehabilitation wards. Around half of the team are practicing clinicians in these wards, with first-hand knowledge of what's needed to improve patient care. Embedding our research in the clinical environment, and embedding clinicians in our research team, means we're asking good questions and coming up with practical answers. We have a big head start on translation and implementation because our discoveries are co-designed with clinicians and made with patients in the real-world clinical environment.

Q5 What are the most significant changes you have seen in the field of movement neuroscience since completing your PhD in 2004?

Technologies for capturing movement kinematics and measuring real-world activity have become widely accessible at lower cost, allowing researchers and clinicians to better understand the ways that people move in their daily lives. The challenge is making sure that the vast amounts of data that can be generated produce insights that are meaningful for patient care.

Q6 There has been interest from all areas of life science and healthcare towards artificial intelligence (AI). Is there room for AI in neuroimaging tools for predicting stroke outcomes for individual patients?

There's exciting work underway using machine learning methods to predict stroke outcomes based on standard clinical imaging. It's always important to think carefully about what is being predicted, how useful the prediction is, and how it will be communicated to patients and families.

> "We find that most patients want to know what to expect, even when it's going to be a poor recovery."

Q7 What are some points of emphasis you incorporate into practice to be the best researcher and educator you can be?

Clinicians are sometimes discomfited by the idea of giving predictions to patients and families, for fear of demotivating them if the prediction is negative. However, prediction information can be safely shared with patients and families when clinicians have appropriate training for these conversations. We find that most patients want to know what to expect, even when it's going to be a poor recovery. They are adults and deserve the opportunity to adjust their plans for life after stroke based on realistic information. If they don't know what to expect, they can labour under false hopes for many months, even years, before finally coming to the realisation that they're not going to make further improvements. By this time they have usually left our care, and we're no longer available to support them as they come to this realisation. Delivering prediction information requires considerable skill, and when delivered in the first week or two of recovery it can help patients and families adjust more effectively to life after stroke, with rehabilitation therapies and our support.

Q8 Since your appointment as Chair of the Neurological Foundation of New Zealand's Council, what has your proudest achievement been?

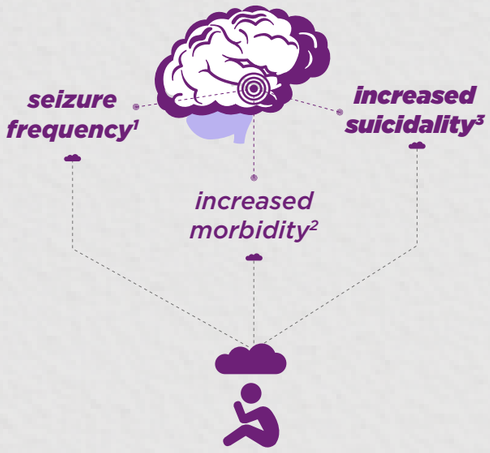
The Foundation supports PhD students with scholarships. These have had a similar value to the scholarships offered by the rest of the tertiary sector. Unfortunately, the sector has held these scholarships at an amount less than the minimum wage for several years. I'm very proud that the Foundation has increased the value of its PhD scholarships so they are now more than the minimum wage, and are equivalent to the living wage. The Foundation is the first scholarship provider in New Zealand to achieve this goal, and I'm very proud of our investment in tomorrow's neuroscientists.

DEPRESSION IN PEOPLE WITH EPILEPSY

This content was funded by LivaNova PLC.

You may know:

Depression in Patients with Epilepsy is frequent and associated with:



Effect of epilepsy treatments on depression

Epilepsy treatments that may have...

Negative effects on depression[4,5]

- Barbiturates
- Felbamate
- Tiagabine
- Topiramate
- Vigabatrin
- Zonisamide
- Pregabalin
- Deep Brain Stimulation*

Positive effects on depression[6,7]

- Lamotrigine
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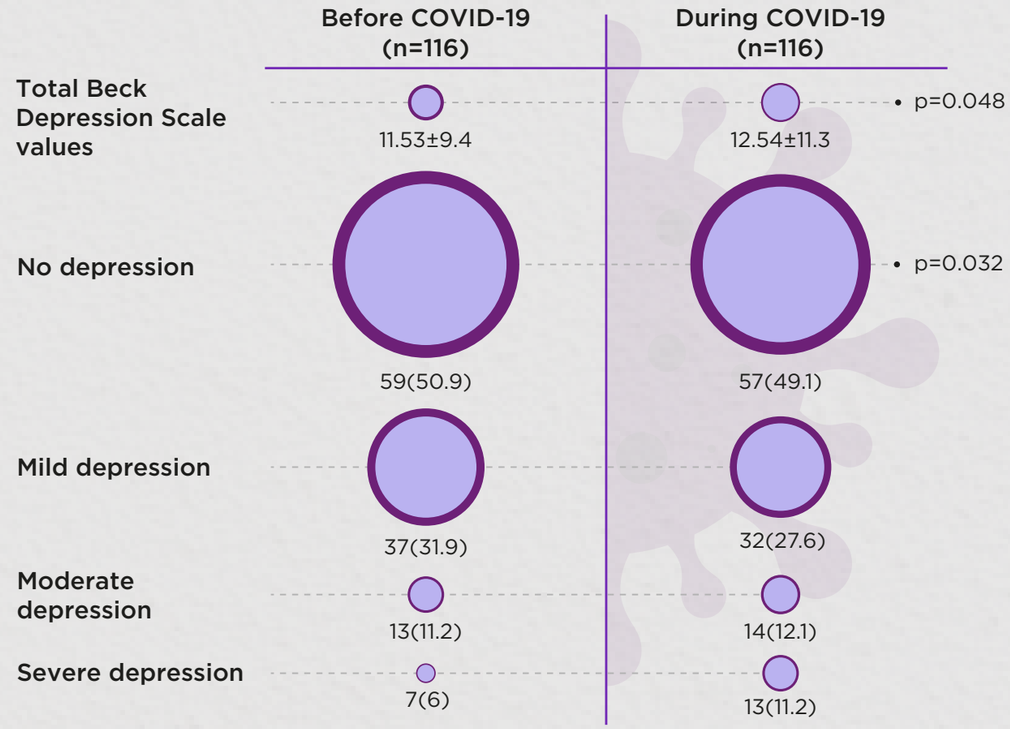
Did you know:

In a cohort of 116 pwE at a epilepsy specialized center BDI scores increased from 11.5 to 12.5 ($p < 0.05$) during the pandemic.[8,9]



Epidemiology of depression in PwE

Life Time Prevalence for Major Depressive Disorder (MDD)

31.6%

in pts with **refractory focal epilepsy**[10]

17.4%

In pts with **epilepsy**[11]

Screening increases diagnosis: **10-fold** more likely to diagnose depression[12]

View our references here

Depressive Symptoms:

30% pts with **controlled epilepsy**[13]

60% pts with drug-resistant **epilepsy**[14]

50-60% of **PwE & MDD in epilepsy** specialists clinics do not get treated for MDD[15,16]

...It takes less than two minutes to screen for MDD in PwE

Neurological Disorders Depression Inventory for Epilepsy (NDDI-E): Developed for PwE

Please input the answer that best describes you within the past two weeks, including today. (Please tick the relevant box)

	How much of the time...	Always or Often	Sometimes	Rarely	Never
1	Everything is a struggle	4	3	2	1
2	Nothing I do is right	4	3	2	1
3	Feel guilty	4	3	2	1
4	I'd be better of dead	4	3	2	1
5	Frustrated	4	3	2	1
6	Difficulty finding pleasure	4	3	2	1

Download form now

Conclusion:

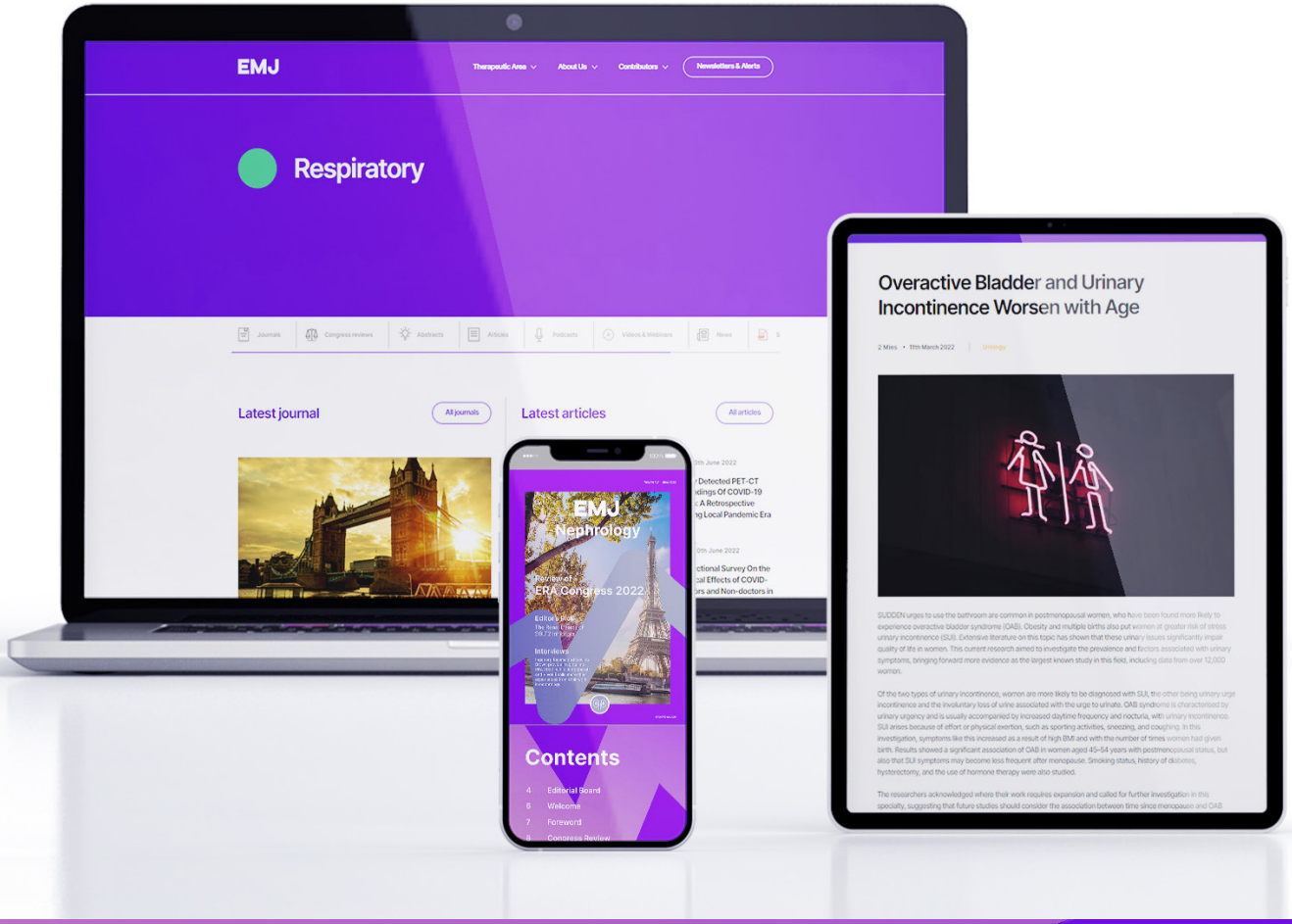
There is a **high prevalence of depression and depressive symptoms in patients with epilepsy (PWE)** and depression in PWE is associated with increased morbidity, suicidality and seizure frequency

The Covid-19 pandemic has exacerbated depression and anxiety in PwE.

4 Key Factors to Consider

Antiepileptic therapies can have positive or negative effects on depression, and therefore should be chosen with this impact on depression in mind in patients with epilepsy to avoid aggravation of depressive symptoms and the detrimental consequences thereof.

You CAN help: **Screening for depression takes less than 2 minutes** and can be conducted by any healthcare provider



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Adiposity and Neurological Disorders: A Review

Editor's Pick

My Editor's Pick is a fascinating article by Haboubi et al., whose review explores the link between adiposity and various neurological phenomena. With a rapid increase in obesity, healthcare professionals on a global scale are facing many related challenges. The authors evaluate the chronic inflammatory state created by obesity, which results in complex health issues for many patients.

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Abstract

The rapid increase in the global incidence of obesity presents an ever-expanding set of medical, social, and economic challenges. Obesity is a complex disease, with the emphasis of current research aimed at unravelling its link with a range of health conditions.

The chronic inflammatory state created by obesity is frequently postulated as the driving force behind its pathophysiological consequences in a number of health conditions. Specifically, there is expanding evidence linking obesity to the development of a number of central and peripheral nervous system disorders.

This review evaluates established and emerging evidence for the link between adiposity and a range of neurological phenomena. Knowledge of the pathological mechanisms of obesity may prove useful in determining the most effective treatments of obesity-induced neurological disorders.

Key Points

1. Obesity is a complex disease linked to a range of health conditions, including neurological conditions affecting both the CNS and PNS. The recent rapid increase in its global incidence presents expanding medical, social, and economic challenges.

2. The chronic inflammatory state created by obesity is frequently postulated as the driving force behind pathophysiological processes in a range of neurological phenomena.

3.The increasing prevalence of obesity necessitates further investigation into the pathways behind potential nervous system damage caused by obesity, and highlights the need for comparing already established dietary, physical, pharmacological, and surgical weight loss interventions.

INTRODUCTION

Obesity is defined by the National Institute of Health and Care Excellence (NICE) as a body mass index (BMI) greater than 30 kg/m^2. Recognised as a chronic and progressive disease, obesity is linked with a number of comorbidities that have a detrimental impact on health. The current obesity epidemic is a major public health problem across the world. In 2016, approximately 13% of the world's adult population were obese, with the incidence of obesity almost tripling between 1975 and 2016.[1] It is estimated that by 2050, 60% of males and 50% of females will be obese.[2] A considerable burden on health services is anticipated, due to the increasing incidence of Type 2 diabetes, hypertension, cardiovascular disease, stroke, osteoarthritis, sleep apnoea, and certain cancers, amongst other conditions linked to obesity. The social and economic impacts of obesity are equally recognised.[2]

Expanding evidence now associates obesity as a risk factor for an array of neurological disorders.[3] Obesity-driven dysfunction drives central and peripheral nervous system (PNS) damage via complex mechanisms.[4] It is well known that visceral adiposity has metabolic and endocrine implications, impacting on various organs, including the liver, pancreas, and vasculature, resulting in hyperinsulinemia, hyperglycaemia, dyslipidaemia, and hypertension.[5] This review describes the link between obesity and disorders of the central and peripheral nervous system (PNS). The authors outline the recent research in this field, whilst examining how lifestyle and surgical interventions can reduce the incidence of neurological conditions, where obesity is a known risk factor.

SEARCH STRATEGY

A literature search was performed using Medline and PubMed for papers published between 2000 and 2021. The following keywords were used in various combinations: 'obesity', 'BMI', 'high fat diet', 'neurological disorders', 'inflammation', 'Alzheimer's disease', 'autonomic nervous system', 'peripheral nervous system', 'bariatric surgery', 'dyslipidaemia', and 'adiposity'. Studies that were not written in English were excluded, as well as those which did not contain more than one of the keywords in the title. Furthermore, studies with small sample sizes and those with abstracts not relevant to the search were excluded.

PATHOPHYSIOLOGY OF OBESITY AND NEUROLOGICAL DYSFUNCTION

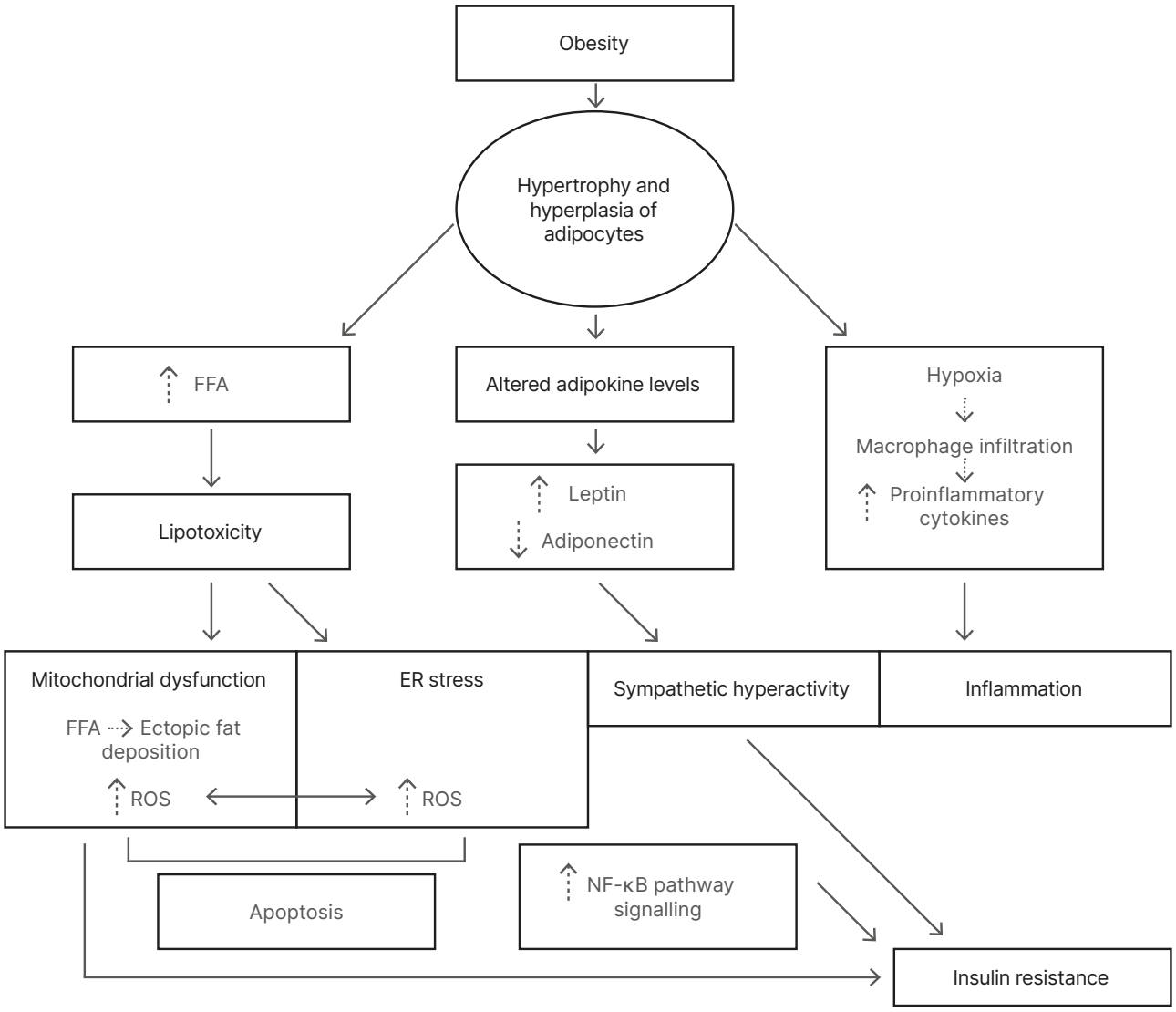
Adipose tissue regulates whole body homeostasis and is a key organ in the modulation of energy storage. Its involvement in metabolic and immune processes is thought to play a leading role in obesity-induced complications. A high-fat diet and reduced energy expenditure yields an overall positive energy balance. Excess lipid accumulation in adipose tissue, and increasing visceral adipose mass, prompts hypertrophy and hyperplasia of adipocytes, triggering their dysfunction.[6] Metabolic inflammation occurs in hypertrophied adipocytes due to activation of stress signalling pathways. This results in the release of free fatty acids (FFA), proinflammatory cytokines, and altered adipokine levels. A hypoxic state in adipocytes is created, triggering the infiltration of macrophages, which further contributes to the release of cytokines.[7,8]

Obesity is characterised by a chronic low-grade inflammation, which is considered the driving force behind obesity-induced neurological disorders.[4] The pathophysiology behind neuronal damage is complex and multifactorial, with multiple pathways involved, including lipotoxicity, insulin resistance, and oxidative stress (Figure 1). Alterations in these signalling pathways result in damage to cells, and eventually in neuronal loss. Below are four postulated mechanisms.

Neuroinflammation

Obesity results in the release of proinflammatory cytokines such as TNFα, IL6, and IL-1β, which trigger neuroinflammation and result in subtle changes in brain morphology.[8] Such neuroinflammation has been associated with lower cortical grey and white matter volumes and the onset of cognitive impairment.[9,10] Thaler et al.[11] put forward hypothalamic inflammation as the first stage of neuroinflammation in the central nervous system, as proinflammatory cytokines and FFAs increase the permeability of the blood–brain barrier.

Figure 1: Pathological mechanisms of obesity induced dysfunction in the central nervous system



ER: endoplasmic reticulum; FFA: free fatty acid; ROS: reactive oxygen species.

With regard to the peripheral nervous system (PNS), the blood–nerve barrier, dorsal root ganglion, and free nerve endings are susceptible to injury via inflammatory mechanisms in the context of normoglycaemia and hyperglycaemia, leading to polyneuropathy in the population with obesity.[12] It is the chronic inflammation caused by obesity that is injurious to peripheral nerves and underlies the pathogenesis of neurological disorders associated with obesity.

Adipokine Levels

Obesity induces changes in circulating adipokine levels from adipose tissue.[13] Adipokines play a homeostatic role as intermediaries between metabolic and immune function. Mice with obesity demonstrate decreased levels of adiponectin, a cytokine released from white adipose tissue, which is able to cross the blood–brain barrier to exert anti-inflammatory effects.[14] The suppression of the adiponectin receptor 1 contributes to insulin resistance in the brain. A long-term high-fat diet can thus impair insulin signalling, which is important for synaptic plasticity and glucose homeostasis, resulting in death of neuronal cells and exacerbating neurodegeneration. Animal studies have substantiated the association between insulin resistance, cognitive impairment, and neurodegenerative diseases.[14,15] Mice deficient in adiponectin present with reduced spatial memory and decreased synaptic protein levels.[15]

In contrast, increased levels of leptin, visfatin, and resistin are found in patients with obesity. Both visfatin and resistin have been shown to contribute to insulin resistance.[16] Obesity decreases the responsiveness to leptin, resulting in a leptin-resistant state, which contributes to synaptic loss, and consequently neurodegeneration.[17] Leptin receptors in the ventromedial hypothalamic nucleus are desensitised as a consequence of persistently elevated leptin levels, leading to dysregulation of leptin signalling pathways. A vicious circle arises as leptin resistance causes a compensatory increase in leptin release, which further worsens obesity due to the effects of increased sympathetic activity, and suppression of leptin's anorexigenic function.[6] There is still a lack of knowledge on the exact pathogenic mechanisms that adipokines play in obesity. Many mice studies provide an enhanced understanding, with Qatanani et al.[16] showing the role of adipokines being assignable to human disease.

Free Fatty Acids

Obesity increases basal lipolysis and the generation of FFAs in adipose tissue. Increased cellular uptake of FFAs causes lipid overload, thereby resulting in lipotoxic effects on nerve cells. The consequences of this include promotion of insulin resistance via ectopic fat deposition in the pancreas and muscles, as well as dyslipidaemia via FFA-induced liver dysfunction.[7] These effects lead to metabolic syndrome and are responsible for the increased risk of stroke in the population with obesity.[18]

Mitochondrial Dysfunction and Endoplasmic Reticulum Stress

Mitochondrial dysfunction is a cause and consequence of lipotoxicity and inflammation. Failure of synaptic remodelling has damaging effects on cells, leading to neurodegeneration and, thus, brain atrophy.[7] The lipotoxic state observed in obesity creates an excess of FFAs, which alter the structure of mitochondria, leading to increased mitochondrial depolarisation. Consequently, impaired oxidative phosphorylation causes an increase in reactive oxygen species and decreased adenosine triphosphate production, triggering apoptosis of neurons.[19]

Moreover, increased FFAs in peripheral nerves contribute to endoplasmic reticulum (ER) stress.[20] The ER and mitochondria function together to maintain cellular homeostasis. FFA-induced dysfunction of the ER and mitochondria leads to dysregulated calcium signalling between the two structures, promoting a proapoptotic state, resulting in nerve damage.

CENTRAL NERVOUS SYSTEM

An increased risk of cognitive decline is present in individuals with obesity.[9,21] Meta-analyses have exhibited a convincing link between obesity and dementias, including Alzheimer's disease and vascular dementias.[22,23]

Studies indicate the consumption of a high-fat diet leads to widespread oxidative damage,[24] which is involved in the pathology of neurodegenerative diseases. As demonstrated in mice studies, a high-cholesterol diet can increase amyloid-β protein deposition.[25] These

changes are reinforced by an insulin-resistant state, which incites Tau hyperphosphorylation and the accumulation of amyloid-β protein.[26] These changes are accepted as pathognomonic of Alzheimer's.

Other theories propose a correlation between obesity and reduced dopaminergic response.[27] There is a perceived vicious cycle between insulin resistance and mitochondrial dysfunction, which prompts increased reactive oxygen species levels and neuronal loss. As demonstrated in the substantia nigra, insulin resistance is understood to promote a loss of dopaminergic neurons and augment the expression and signalling of α-synuclein protein, which are hallmarks of Parkinsonian pathology.[28,29] Also related to altered function of dopamine in the central nervous system (CNS) is the link between obesity and restless legs syndrome.[30] A meta-analysis reveals that it is more prevalent amongst individuals with obesity.[31]

EPILEPSY

It is postulated that epilepsy is related to metabolic dysfunction. One study by Daniels et al.[32] has demonstrated obesity to be more prevalent in children with diagnosed epilepsy, prior to treatment, compared with controls. Although the relationship between the two is not clear, it suggests that obesity could induce changes in the CNS, leading to increased seizure susceptibility.[33] Furthermore, it is widely hypothesised that altered hormone levels lead to altered seizure threshold. Adiponectin-deficient mice fed a high-fat diet demonstrate increased seizure activity, suggesting a protective role against seizures for adiponectin, which is known to be downregulated in obesity.[33]

NARCOLEPSY AND CATAPLEXY

There is a significant association between the chronic sleep disorder narcolepsy and higher BMIs.[34] Inocente et al.[35] found 50% of children diagnosed with narcolepsy were obese. An explanation for this may lie in the deficiency of hypocretin, which is a neurochemical involved in the regulation of the sleep–wake cycle and is proposed to impact on energy homeostasis due to its other roles in body adiposity regulation.[34]

MIGRAINE

The relationship between migraine and obesity has been extensively researched. A meta-analysis demonstrates increased prevalence of migraine in individuals with BMI within the obese range, with age and sex as important variables within this relationship.[36] A population-based study has shown that increased total body and abdominal obesity is associated with higher prevalence of migraine.[37] It is suggested that proinflammatory cytokines and altered adipokine levels cause neurogenic inflammation, leading to migraine.

IDIOPATHIC INTRACRANIAL HYPERTENSION

The link between a high BMI and idiopathic intracranial hypertension (IIH) is widely recognised, with weight loss considered the only cure for this condition.[38] The exact mechanism behind obesity leading to raised intracranial pressure is unclear but is related to hormonal change. A lesser-known theory suggests that increased visceral adiposity leads to a rise in intrathoracic and central venous pressure, causing a decrease in intracranial blood flow, resulting in IIH.[39]

RELATIONSHIP WITH AUTOIMMUNE DISEASES

Evidence suggests a correlation between obesity in adolescence and a higher risk of developing multiple sclerosis (MS).[40] This study demonstrates adolescents with a BMI >27 kg/m^2 having a higher risk of developing MS, compared with those of a BMI 18.5–21.0 kg/m^2. Also, there is a correlation between the MS risk gene HLA-DRB1*15 and adolescent obesity. There are many potential mechanisms for this relationship, with leptin playing a leading role in linking metabolic changes with immune dysfunction. It is proposed that leptin favours the induction of an inflammatory state, which underlies the pathology of MS, by inducing Th1 responses and decreasing the activity of regulatory T cells, contributing to the development of autoimmune diseases.[41]

Dyslipidaemia can also be linked to the onset of autoimmune disease. A study by Wu et al.[42] demonstrates higher levels of triglycerides may worsen the prognosis of the rare condition neuromyelitis optica. Increased levels of cytokines and chemokines have been identified in the pathogenesis of both MS and neuromyelitis optica.[43] Therefore, it is plausible that the inflammatory state created by obesity could play a pathophysiological role and worsen patient outcomes in these neuro-inflammatory conditions.

NEUROPSYCHIATRIC DISORDERS

A rodent study suggests a high-fat diet could induce core symptoms of depression, such as anxiety and anhedonia.[27] In this case, diet duration played a key role in the changes propagated by obesity. Further evidence indicates obesity is associated with neuropsychiatric diseases such as bipolar disorder and schizophrenia, in part due to obesity-induced mitochondrial dysfunction and inflammation.[4,21,44]

PERIPHERAL NERVOUS SYSTEM

The PNS is composed of autonomic and somatic divisions that have also been demonstrated to be vulnerable to the pathophysiological consequences of obesity. The somatic nervous system functions to control the body's voluntary movements. Obesity can trigger damage to sensory and motor nerves, as illustrated in Figure 2.

A sensory nerve consists of a bundle of neurons surrounded by supportive connective tissue. Neurones are comprised of axons, dendrites, and cell bodies in the dorsal root ganglion. Cell bodies are dependent on mitochondria for energy to function, such that damage to mitochondria can heavily impact on normal nerve function. This is one postulated mechanism leading to polyneuropathy.[19] It is well documented that diabetes is an important risk factor for polyneuropathy, typically causing sensory and motor deficits in a distal to proximal manner.[19] However, emerging data now elucidates obesity to be one of the principal metabolic triggers for polyneuropathy, independent of diabetes and pre-diabetes. A cross-sectional study shows a significant association between waist circumference and neuropathy.[12] Chemokines C-C motif ligand 7 and C-X-C motif chemokine ligand 10 are known to be released in a distal symmetric polyneuropathy.[45] High levels of these chemokines can result in nerve structure damage and are thought to contribute to pain in polyneuropathy.

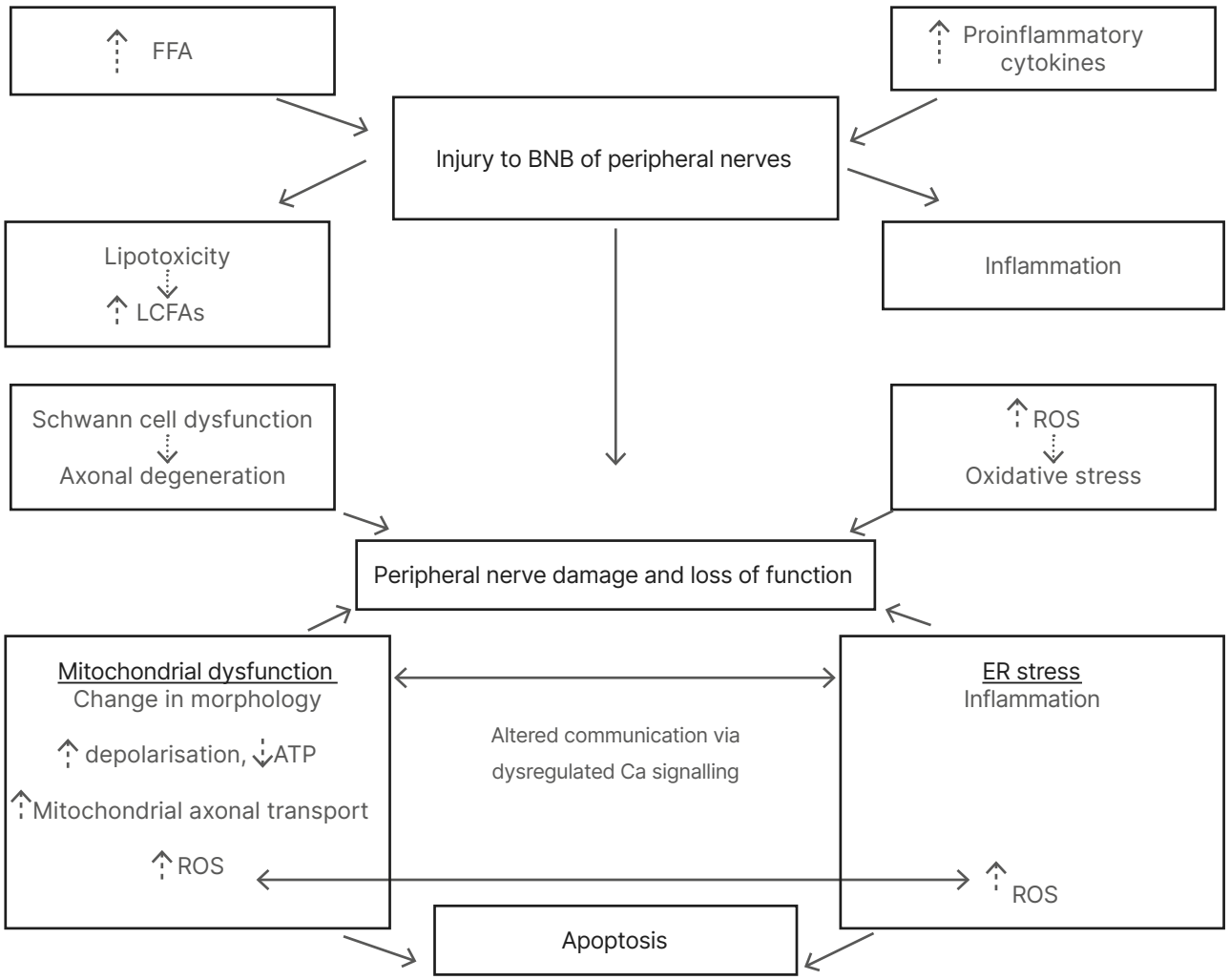
A prospective analysis shows a correlation between higher BMI and waist circumference, and an increased risk of Guillain–Barré syndrome.[46] Likewise, a positive correlation between high BMI and Bell's palsy has been demonstrated in a case control study.[47] A slower recovery rate in patients with obesity and Bell's palsy has been demonstrated.[48] These relationships could be, in part, plausibly explained by the pre-disposing inflammatory state created by obesity.

Obesity is additionally associated with an increased incidence of mononeuropathies. A relationship is demonstrated between raised BMI and carpal tunnel syndrome, as well as meralgia paresthetica.[49,50,51]

AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system is divided into sympathetic and parasympathetic divisions and plays a role in homeostatic energy balance by regulating food intake and energy expenditure. Studies demonstrate the presence of autonomic nervous system dysfunction in individuals with obesity.[52] Obesity is perceived to provoke a selective hyperactivity of the sympathetic divisions via an impaired baroreceptor reflex and increased leptin and insulin levels.[53] Both leptin and insulin bind to receptors in the CNS, which are selective for the regulation of sympathetic tone. This overactivity causes increased stimulation of β-adrenergic receptors in neuro-adipose junctions, promoting lipolysis and increased FFA levels.[54] Greater sympathetic stimulation of skeletal muscles also precipitates insulin resistance, due to changes in glucose metabolism.[52] (Figure 3).

Figure 2: Pathological mechanisms of obesity induced dysfunction in the peripheral nervous system.



ATP: adenosine 5'-triphosphate; BNB: blood–nerve barrier; Ca: calcium; ER: endoplasmic reticulum; FFA: free fatty acid; LCFA: long-chain fatty acid; ROS: reactive oxygen species.

A two-way relationship is observed between obesity and autonomic nervous system dysfunction. Obesity can trigger changes to autonomic nervous system signalling, resulting in metabolic and cardiovascular consequences; conversely, increased sympathetic stimulation can propagate metabolic dysfunction. Studies demonstrate that weight loss in individuals with obesity causes a decrease in sympathetic activity in muscles, further supporting this relationship and the potential for therapy that targets the sympathetic nervous system to improve metabolic profile.[55]

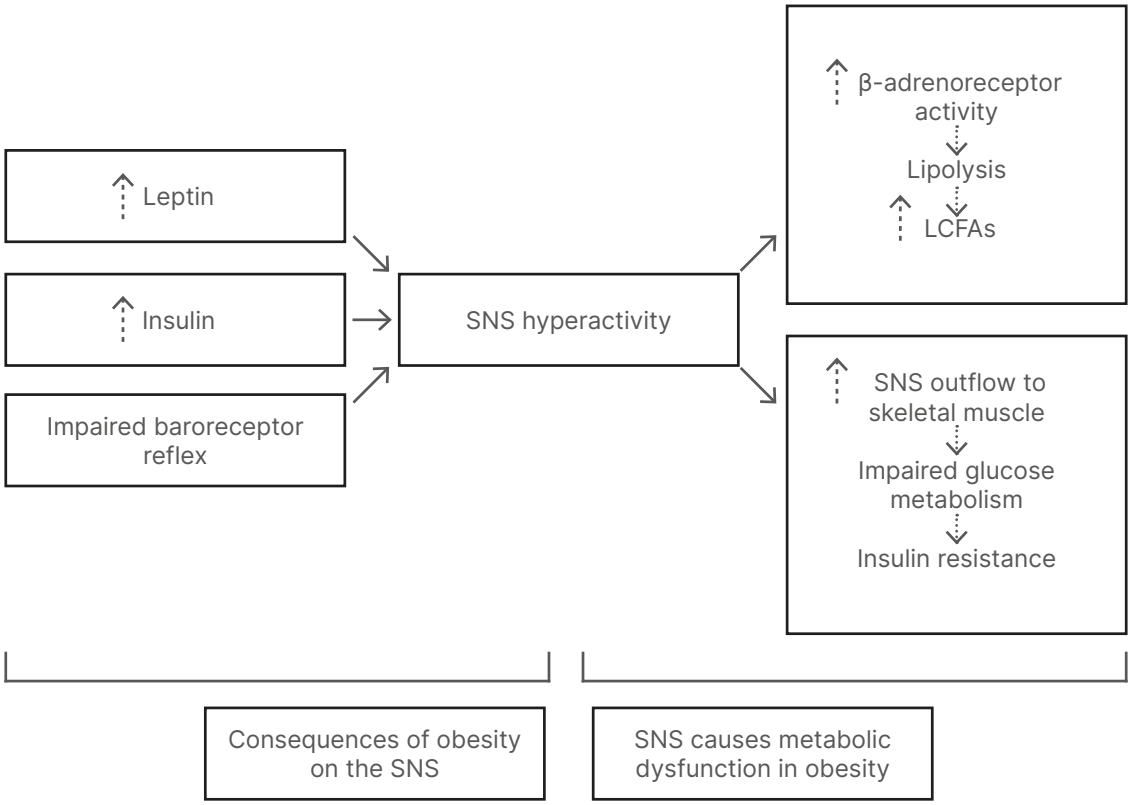
NEUROLOGICAL DISORDERS ASSOCIATED WITH OBESITY

Overall, from the extensive data analysed, it is evident that obesity has a pathological role in CNS and PNS dysfunction. There are numerous neurological disorders known to be associated with obesity, which are summarised in Table 1.

TARGETING OBESITY IN NEUROLOGICAL DISORDERS

It is widely recognised that targeting obesity can generate considerable health benefits in

Figure 3: Pathological mechanisms of obesity induced dysfunction in the sympathetic nervous system.



LCFA: long-chain fatty acids; SNS: sympathetic nervous system.

Table 1: List of neurological disorders associated with obesity.

Central nervous system	Peripheral nervous system

• Alzheimer's disease
• Anxiety disorders
• Bipolar disorder
• Cognitive impairment
• Dementia
• Epilepsy
• Glioma
• Idiopathic intracranial hypertension
• Meningioma
• Migraines
• Multiple sclerosis
• Narcolepsy associated with cataplexy
• Neuromyelitis optica
• Parkinson's disease
• Restless legs syndrome
• Schizophrenia
• Stroke
• Vascular dementia
	• Autonomic nervous system dysfunction
	• Bell's palsy
	• Guillain–Barré Syndrome
	• Mononeuropathies
	  • Carpal tunnel syndrome
	  • Meralgia paraesthetica
	• Polyneuropathy

an individual, attributable to the physiological benefits that arise, such as improved glucose homeostasis, lipid levels, and vascular function. This leads to enhancements in the overall systemic and metabolic health of an individual. Given the multiple chronic diseases correlated with obesity, its prevention can be seen as essential in minimising their risk.

Improved cognitive performance is demonstrated when obesity is targeted.[56] A combination of dietary and exercise mediations are preferred means in tackling obesity and its complications. A 2-year randomised controlled trial has demonstrated that increased exercise, cognitive training, and changes to diet are successful in preventing cognitive decline.[57]

Nonetheless, compliance with these lifestyle changes can sometimes be difficult, and this is when pharmacological and surgical methods are sometimes required. Bariatric surgery has proven to be an extremely effective treatment for patients with morbid obesity. Various studies demonstrate improvements in neurological function following this procedure.[58] One study has illustrated decreased inflammation and amyloid precursor protein expression following bariatric surgery.[59] These are hallmark changes in Alzheimer's disease and indicate that weight loss after such interventions could have beneficial effects on brain structures, leading to improved cognitive function. Furthermore, IIH in an obese subject is an absolute indication for bariatric surgery, which is effective in producing significant improvements in symptoms, or complete remission.[60]

Bariatric surgery is highly successful in treating weight loss but carries with it multiple complications.[59] Many complications, such as polyneuropathy, are driven by the after-effects of nutrient deficiency. Adequate vitamin and micronutrient supplementation is required post-operatively to prevent such neurological complications.

CONCLUSION

Obesity has been demonstrated as a risk factor for a range of neurological disorders, affecting both the CNS and PNS. A complex set of mechanisms is shown to be involved in the development of neurological dysfunction. The inflammatory state created by obesity is the driving force behind the pathology, and other mechanisms of insulin resistance, lipotoxicity, mitochondrial dysfunction, ER stress, and sympathetic hyperactivity all interact to provoke further damage.

With the prevalence of obesity ever-increasing, further research is necessary in determining the pathways of potential nervous system damage, as well as comparing the already established interventions of dietary, physical, pharmacological, and surgical weight loss in promoting the best possible health outcomes and reducing the incidence of neurological disorders.

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Improving The Management of Non-dystrophic Myotonia to Benefit Care Delivery and Improve Patient Outcomes

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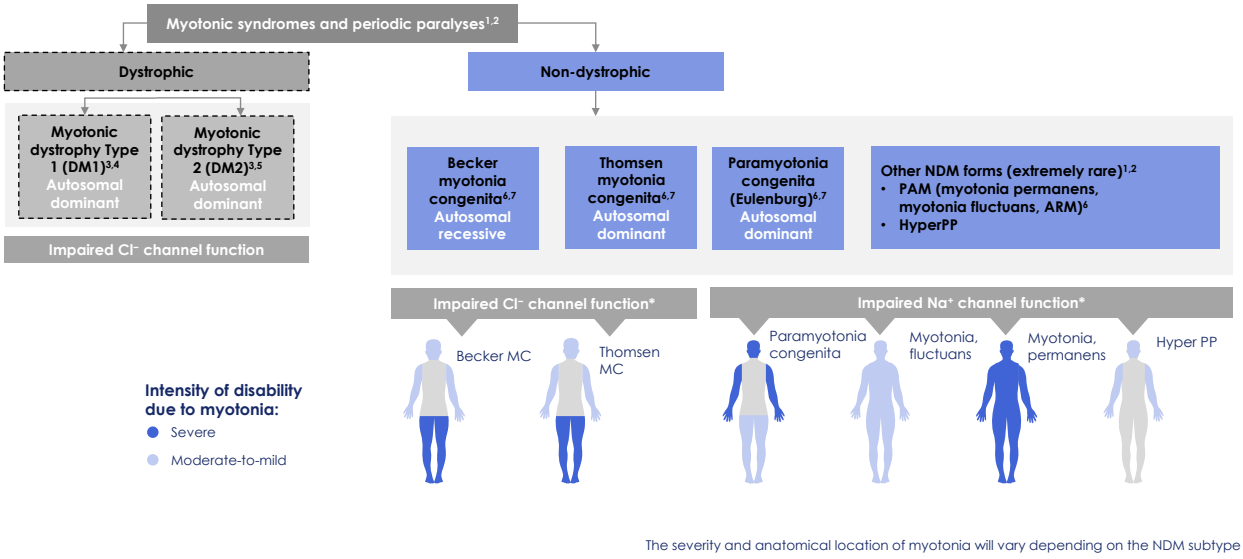
Abstract

Non-dystrophic myotonias (NDM) are rare muscle disorders caused by mutations in skeletal voltage-gated muscle channels leading to delayed muscle relaxation after voluntary contraction. They are subdivided into sodium channelopathies, when the mutation is in the *SCN4A* gene, and chloride channelopathies, when the mutation is in the *CLCN1* gene. Symptoms, which may differ according to subtype, exacerbating factors, and over disease course, can include muscle stiffness, pain, fatigue, muscle hypertrophy, myalgia, and weakness. The severity of NDM symptoms varies widely, from being barely noticeable to causing considerable disability that impacts health-related quality of life. People with NDM may remain undiagnosed for several years, potentially due to a lack of awareness of NDM among many healthcare professionals. The symptomatic treatment for NDM predominantly involves sodium channel blockers, such as mexiletine. Randomised, placebo-controlled trials have shown mexiletine can reduce muscle stiffness and pain, and improve health-related quality of life. Patient and clinician surveys, as well as national guidelines, place this medication as one of the first choices for pharmaceutical treatment of myotonia. Other choices include lamotrigine, carbamazepine, acetazolamide, ranolazine, and flecainide, though clinical evidence is limited, and all are used on an off-label basis. Herein, the challenges in recognising and treating myotonia symptoms in people with NDM are reviewed, along with strategies to increase awareness of the disease and its potential treatment.

INTRODUCTION

Non-dystrophic myotonias (NDM) are a group of rare muscle disorders with a reported prevalence of 0.75–1.7 per 100,000 population (Figure 1).[1,2] They are due to pathogenic variants in genes coding for skeletal voltage-gated muscle channels that cause ion channel dysfunction. These mutations lead to increased muscle membrane excitability,[3] clinically manifesting as delayed muscle relaxation after voluntary contraction or percussion.[4-6] NDM symptoms and signs can include muscle stiffness, cramps, myalgia, transient weakness, fatigue, muscle hypertrophy, dysphagia, and dysphonia.[4] Depending on NDM subtype and exacerbating factors, these may differ in age of onset, body distribution, severity, and circumstances of occurrence.[4,7-9] Symptoms can lead to movement difficulties, such as in running, climbing stairs, or grip release after a handshake.[6,9] While NDM shares similarities with myotonic dystrophies, muscle weakness is typically more common in myotonic dystrophy

Figure 1: Non-dystrophic myotonia subtypes.



The severity and anatomical location of myotonia will vary depending on the NDM subtype

*Due to wide variability in affected regions experienced with all types of non-dystrophic myotonia, location of affected muscles is not an accurate indicator of NDM subtype.

ARM: acetazolamide responsive myotonia; Cl-: chloride ion; HyperPP: hyperkalaemic periodic paralysis; MC: myotonia congenita; Na+: sodium ion; NDM: non-dystrophic myotonia; PAM: potassium-aggravated mytonia.

Type I than NDM. There are overlapping phenotypes with myotonic dystrophy Type 2, but cold-exacerbation of symptoms is highly suggestive of paramyotonia congenita (PMC) and people with myotonic dystrophy Type 2 may have temperature-sensitive pain and myotonia.[8]

Chloride channelopathies (NDM-ClC) arise due to mutations in the chloride channel *CLCN-1* gene, and include the autosomal dominant Thomsen myotonia congenita (TMC)[10] and the autosomal recessive Becker myotonia congenita (BMC).[11] Typically starting in childhood (TMC) or adolescence (BMC), both are present with myotonia that decreases or vanishes with repetitive motion. BMC tends to be more severe than TMC and is associated with episodic and occasionally progressive weakness.[4,6,11,12] Triggers in both conditions can include cold, psychological stress, exercise, and alcohol consumption.[7]

Sodium channelopathies (NDM-NaC) are due to autosomal dominant *SCN4A* gene mutations affecting the NaV1.4 channel, and include sodium channel myotonia and PMC, as well as hyperkalaemic periodic paralysis and severe neonatal episodic laryngospasm. With a typical onset around age 5 years, symptoms differ according to diagnosis but can include episodic weakness, pain, and isolated facial stiffness. These can be exacerbated by cold temperatures, potassium consumption (depending on subtype), menstrual cycle, and, for PMC especially, repetitive contractions. While weakness may be present, it is most prevalent in hyperkalaemic periodic paralysis and can last for days.[4,12,13]

Although there are many shared symptoms in NDM, patient surveys reveal that clinical and percussion myotonia, stiffness, muscle hypertrophy, and pain may be more prominent in NDM-ClC, with muscle weakness, hand grip myotonia, paradoxical eyelid myotonia, cramping, and cold exacerbation more prevalent in NDM-NaC.[7,8,12,14] However, this does not always hold true, with one patient survey finding subjective muscle weakness reported by 75.0% of people with NDM-ClC and 36.7% of those with NDM-NaC.[15]

To understand experiences of NDM diagnosis, symptoms, treatment, health-related quality of

life (HRQoL), and support, two surveys were carried out among patients with NDM and their caregivers. The 2020 IMPACT (Impact of non-dystrophic Myotonia on PAtients and Caregivers' qualiTy of life) patient (n=181) and caregiver (n=59) surveys included responses from several European countries and the USA.[16,17] The 2018 European Myotonia Observation Survey of Patient Access to therapy avoiding Harm (MyoPath) survey involved 390 people with a variety of myotonic disorders and included 43 people with NDM (data on file, Lupin Neurosciences).[18] Results of a roundtable expert panel discussion on the IMPACT survey findings are also included herein. This involved seven Europe-based clinicians experienced in managing adults with NDM.

DIAGNOSIS OF NON-DYSTROPHIC MYOTONIA

While NDM typically first manifests in childhood, symptoms may be mild and not recognised as burdensome, resulting in diagnostic delay and misdiagnosis.[9] For instance, a difference in gait or fall frequency may be dismissed as normal for the spectrum of childhood movement.[19] Patients themselves may not recognise NDM symptoms that have been present since infancy or are not perceived to impact their life.[3] The expert panel also highlighted how families affected by similar symptoms might not notice them as being unusual. Conversely, as NDM can be familial, symptoms may be more readily recognised by family members.[5] Symptoms may, however, be aggravating, debilitating, and progressive or, in TMC, first appear or worsen during pregnancy.[9,20]

In the IMPACT survey, diagnostic delay was reported by 64% of respondents, who experienced symptoms for ≥10 years before diagnosis.[16,17] Similarly, a German study found average delays of 15–17 years.[7] The IMPACT survey showed that diagnostic delay might be due to incorrect referral to a specialist not experienced enough in NDM to recognise the symptoms, including a general neurologist, orthopaedist, or rheumatologist, instead of to a neuromuscular specialist.[17] The expert panel also discussed how patients may experience difficulties in describing their symptoms, and a discrepancy between the language used by patients and healthcare professionals (HCP) might lead to misunderstanding and incorrect referrals.

Education to raise awareness of NDM among HCPs to help ensure patients receive a correct and timely diagnosis was a need highlighted by the expert panel. They emphasised the necessity for organisational structures that included a high level of collaboration among stakeholders to refer and diagnose patients quickly. The panel also suggested a need for a red flags list for easier NDM recognition, such as myotonia, myalgia, and, in some cases, increased serum creatine kinase levels.

NDM diagnosis involves observations of NDM signs and symptoms, as well as neurological and neurophysiological examinations and genetic testing.[4] Action myotonia can be detected by asking the patient to open their eyes after holding them tightly closed for a few seconds or by assessing grip release ability following a firm handshake. Percussion myotonia can be elicited in the muscles using a reflex hammer.[4-6] The presence of exacerbating factors, which can vary both between patients and over time, can be assessed via a symptom diary.[21] Family history is also useful in those with autosomal dominant NDM subtypes such as TMC.[4-6]

NDM can also be assessed using physical ability measures with best test–retest agreement being shown for the Timed Up and Go test,[22] Borg's Category-Ratio Scale,[23] and the Myotonic Behaviour Scale,[24] along with patient-rated symptom scales and 14-day stiffness diaries.[25] However, few of these tests have been specifically validated to measure myotonia severity or other NDM symptoms, which contributes to diagnostic delay and suboptimal assessment of disease symptoms.

HRQoL can be measured using the Individualised Neuromuscular Quality of Life (INQoL) measure, a patient-completed questionnaire that includes four domains regarding how symptoms affect HRQoL, how NDM limits life domains, how treatment affects symptoms, and overall HRQoL.[26]

Testing of muscle function in NDM involves needle electromyography (EMG) to ascertain myotonic discharge presence in affected muscle

fibres (i.e., electrical myotonia), which may be present without clinical symptoms. EMG has a high sensitivity for myotonia detection; however, detection of electrical myotonia is not specific for NDM and, in the case of a positive test, other disorders, such as myotonic dystrophies, need to be eliminated. The short exercise test, at room temperature or after cooling, helps distinguish between NDM-NaC and NDM-ClC.[5,14,25] The combination of EMG with compound muscle action potentials changes after short or long exercise tests produces distinct Fournier patterns that might help toward differentiating NDM subtype.[14,27] EMG testing cannot, however, assess symptom severity,[5,25] and may not be generally available.

Although costly, the only way to definitively confirm NDM subtype is with gene panel testing.[4] Muscle MRI can reveal NDM-related muscle abnormalities, such as fatty changes and oedema, that are distinct from those shown in other myotonic disorders, but is not a useful tool for diagnosis.[27,28] Future research with muscle MRI is needed to ascertain its use in distinguishing patterns of involvement or monitoring treatment response.

NEGATIVE EFFECTS OF NON-DYSTROPHIC MYOTONIAS ON HEALTH-RELATED QUALITY OF LIFE

Overall, people with NDM report an inferior health status and HRQoL compared with control populations.[15,29] This may be related to specific symptoms such as muscle stiffness, pain, and fatigue.[12,15,29] For example, in a patient study,[15] over a quarter of patients with NDM-ClC and over half with NDM-NaC characterised myotonia as painful, and reported that it negatively affected general health perception, physical and social functioning, and vitality. Around half of respondents experienced fatigue, which inversely correlated with vitality and physical health scores.[15]

A study utilising the INQoL questionnaire (n=66) found particular impacts of weakness, 'muscle locking', pain, and fatigue. Such impacts were evidenced in daily life, work, and leisure activities as well as on independence. Scores were slightly higher (greater impact) for those with NDM-NaC. This study also showed that 6.3% of patients with NDM-ClC and 23.5% of those with NDM-NaC were disabled due to their condition, and 3.1% and 14.7%, respectively, were unemployed due to NDM symptoms.[12] Another study utilising this measure also found greater HRQoL impacts for people with NDM-NaC with greatest impacts on activity limitations, independence, and emotions.[14]

Another important finding of the IMPACT survey was that over a quarter of respondents rated their HRQoL as low. Participants reported that NDM interfered with social, practical, physical, and work or study related realms, in areas such as communicating with others, using public transport, undressing, and carrying out their chosen profession. Emotional impacts of NDM were also reported, with many respondents saying that they felt helpless, isolated, and alone.[16,17] Further, 42% of respondents in the IMPACT caregiver survey reported negative impacts on their mental health and 25% on their physical health.[17]

MANAGEMENT OF NON-DYSTROPHIC MYOTONIA SYMPTOMS

Pharmacological treatment for NDM primarily centres around sodium channel blockers. In the IMPACT survey, of those who had received treatment, symptoms reduced by such medications included muscle stiffness, pain, and tiredness.[17] However, 41% of respondents had not received NDM-specific medications.[16,17] The reasons for this are multifactorial and include the perception that symptoms are mild, poor awareness by patients and HCPs regarding treatment options, unavailability of some medications in some countries, and reluctance to start treatments that are also indicated in non-NDM conditions.[3]

The expert panel agreed that they might not offer medication to patients whose symptoms are described or perceived as minimal or appear non-significant and where HRQoL is not perceived to be impacted. They may also not offer medication to patients with comorbidities, especially cardiac problems, a history of drug allergies, previous treatment failure, or pain explained by other factors. They discussed

how the decision to initiate medication might be patient-led, based on how much they can tolerate their symptoms versus their concerns regarding potential treatment-related adverse events (AE). It was noted that patients are usually more likely to want treatment following specialist clinic consultation.

Table 1 details several of the current treatments for NDM and provides some guidance for switching from off-label medications to mexiletine, which has among the highest level of evidence using in NDM. Mexiletine, a Class 1B antiarrhythmic sodium channel blocker, is the only European Medicine Agency (EMA) approved antimyotonic drug for NDM. It reduces sodium influx, allowing faster inactivation and repolarisation of sodium channels.[4] As mexiletine is less potent than other antiarrhythmic sodium channel blockers, and recovery from sodium channel binding is faster, it has a safer cardiac action compared to Class IA and Class IC sodium channel blockers.[37]

NDM does not affect the cardic muscle,[38] as cardiac muscles do not significantly express the NaV1.4 sodium channel isoform affected in NDM,[39] and very few CLC-1 chloride ion channels.[40] The effectiveness of mexiletine in managing symptoms, including muscle stiffness, pain, and weakness, and improving HRQoL, has been shown in several trials (Table 2).[21,41-43] Due to its actions on the heart,[44] as with any antiarrhythmic drugs for managing myotonia, cardiac evaluation prior to prescription and annually/every 2 years is a requirement for administration.[45] For mexiletine, while in one randomised controlled trial one patient had asymptomatic bradycardia that resolved without study withdrawal on follow-up ECG,[41] in other studies, no ECG conduction abnormalities were reported.[21,42,43] Mexiletine administration has not

Table 1: Medications utilised for the treatment of myotonia in non-dystrophic myotonias.

Drug; level of evidence[3]	Licensed indication	Safety considerations	Important drug interaction and cardiac considerations	Comments
European Medicines Agency (EMA)-approved medication				
Mexiletine[30] I (Systematic review of randomised controlled trial or n-of-1 trials)	NDM, ventricular arrhythmias	GI discomfort, dizziness, tremor, ataxia	Contraindicated with other antiarrhythmics, cardiogenic shock or 2nd/3rd-degree AV block (without pacemaker)	Not recommended in lesser arrhythmias or asymptomatic ventricular premature contraction
Off-label medications				
Lamotrigine[31] II (Randomised controlled trial or observational study with dramatic effect)	Epilepsy, bipolar disorder	Skin rash, headache, fatigue, nausea, rare life-threatening adverse events†	Contraindicated with carbamazepine, cardiac conduction disorders, ventricular arrhythmias, cardiac disease/ abnormality. Caution needs to be taken for patients taking oral contraceptives	Slow titration required due to life-threatening risk of Stevens–Johnson syndrome; treatment weaning needed if stopped as abrupt withdrawal may precipitate seizures; recommended 7–8 days washout period
Carbamazepine[32] III (Non-randomised controlled cohort/ follow-up study)	Epilepsy, trigeminal neuralgia paroxysmal pain, manic depressive psychosis prophylaxis	Skin rash, endocrinological effects, hyponatraemia, hypothyroidism, anticholinergic effects, psychiatric effects	Rare: cardiac conduction disorders; very rare: arrhythmia, AV block with syncope, bradycardia, congestive cardiac failure, coronary artery disease aggravation	Abrupt withdrawal may precipitate seizures; recommended 4 days washout period‡

Table 1 continued.

Drug; level of evidence[3]	Licensed indication	Safety considerations	Important drug interaction and cardiac considerations	Comments
Flecainide[33] III (Non-randomised controlled cohort/ follow-up study)	AV nodal reciprocating tachycardia, certain arrhythmias	Dizziness, visual impairment, proarrhythmic, dyspnoea, fatigue, asthenia, pyrexia, oedema	Contraindicated with Class I–IV antiarrhythmics	Ensure adequate washout period of 4–5 days before initiating Class I–IV antiarrhythmics. Regular cardiac safety evaluations and follow-up appointments needed
Ranolazine[34] III (Non-randomised controlled cohort/ follow-up study)	Angina pectoris	Chronic angina, dizziness, headaches, constipation, nausea, asthenia	Contraindicated with CYP2A4 inhibitors, Class IA or III antiarrhythmics, hepatic impairment, renal impairment	Caution in those with history/family history of long QT syndrome, acquired QT interval prolongation, drugs affecting QTc interval
Acetazolamide[35] IV (Case-series, case-control studies, or historically controlled studies)	Glaucoma, abnormal fluid retention, epilepsy	Glaucoma, fluid retention	Contraindicated with carbamazepine; may impact dose requirements of cardiac glycosides and hypertensive agents	Switch to mexiletine considered for acetazolamide non-responsive myotonia; recommended 2–3 days washout period[37]

†Stevens–Johnson syndrome, toxic epidermal necrolysis, aplastic anaemia, bone marrow depression, pancytopenia.

‡Based on 5.5 elimination half-lives to clear a medicine from the system.

AV: atrioventricular; CYP: cytochrome P450; GI: gastrointestinal; NDM: non-dystrophic myotonia.

been shown to lead to QT interval prolongation in people with a healthy heart.[37]

The most common AEs in mexiletine studies were gastrointestinal.[21,41-44] In a long-term study of 63 patients (mean follow-up: 4.8 years [range: 0.5–17.8 years]), this predominantly manifested as dyspepsia, leading to treatment discontinuation in four patients.[43] No clinical studies have been carried out regarding mexiletine use during pregnancy, though case studies have described the successful use of such.[46]

Most of the expert panel considered mexiletine as first-line treatment for NDM in patients without contraindications. However, challenges to prescribing mexiletine included unavailability of cardiologists to conduct the cardiac assessment, uncertainties of the cardiac problems associated with mexiletine, and access issues such as reimbursement cost and paperwork burden. In another study, a panel of experts was convened to investigate healthcare utilisation regarding mexiletine. They discussed how treatment with mexiletine led to decreased need and frequency of use of NDM-related resources including physiotherapy, occupational therapy, mental health support, and walking stick use.[47]

Table 2: Mexiletine studies.

Study	MYOMEX 2017[42]	Statland 2012[41]	Stunnenberg 2018[21]	Suetterlin 2015[43]
Design (N)	Double-blind, crossover RCT (N=26)	Double-blind, crossover RCT (N=59)	Aggregated N-of-1 randomised trials (N=30)	Retrospective review (N=63)
Dosage	600 mg/day	600 mg/day	600 mg/day	Up to 600 mg/day
Comparator	Placebo	Placebo	Placebo	Best supportive care
Duration	18 days	4 weeks	4 weeks	Mean follow-up: 4.8 years (range: 0.5–17.8 years)
Trial period	2011–2014	2008–2011	2014–2015	Not reported
Countries	France	USA, Canada, UK, Italy	Netherlands	UK

RCT: randomised controlled trial.

The MyoPath survey was conducted to maintain the orphan drug designation of mexiletine by the EMA.[48] The outcomes discussed an improvement in muscle stiffness and increased mobility in patients with NDM receiving mexiletine. Patients also reported a positive impact on HRQoL domains including emotional wellbeing, confidence in their abilities, and simple daily tasks. Treatment interruptions worsened myotonia and were associated with fatigue, pain, dysphagia, breathing difficulties, impaired digestion, and poor sleep quality. Anxiety about mexiletine's availability was expressed by 36/54 (67%) of currently-treated patients. Lack of mexiletine awareness was also reported, but this was an expected finding as MyoPath was undertaken before mexiletine was approved for NDM in 2018 (data on file, Lupin Neurosciences).[18]

Another treatment prescribed for NDM symptom alleviation is the sodium channel blocker lamotrigine, though its use is off-label (Table 1). Lamotrigine use for NDM is supported by a placebo-controlled, crossover trial (n=12 with PMC; n=14 with myotonia congenita) where administration of up to 300 mg/day for 8 weeks reduced MBS scores by 29%. Significant between-group differences favouring lamotrigine were also shown in a Timed Up and Go test, a 14-step stair test, hand and eye relaxation tests, and overall patient self-assessment of health (including physical and social functioning and role limitations due to physical health). AEs included headache, skin rash, fatigue, and muscle pain.[31,49] The expert panel described how they would prescribe lamotrigine first line for symptomatic patients with cardiac-related mexiletine contraindications or an abnormal ECG; hepatic problems; co-existing depression, generalised/focal epilepsy, or mood disorders; intolerance to mexiletine; had altered potassium/magnesium blood levels; or were planning a pregnancy. The recent U.S. Food and Drug Administration (FDA) warning on the potential increased risk of arrhythmias with lamotrigine was noted by the panel.[50]

Several other medications are used for NDM treatment, though all are off-label (Table 1).[4] Precautions need to be taken when switching between medications due to potential cardiac AEs. Flecainide, a Class IC antiarrhythmic drug, was viewed by the expert panel as more widely available and nearly as effective as mexiletine in those with a suitable NDM subtype. While it is considered the preferred first line treatment for severe neonatal episodic laryngospasm,[51] efficacy has only been shown via case reports.[52] Limitations though include the potential for occurrence of arrhythmias and an increased incidence of cardiac disease with prolonged use.[3,53] The antianginal drug ranolazine can reduce EMG-detected myotonia and patient-

reported stiffness as well as decrease weakness and pain. Mild light headedness and constipation were reported as AEs.[54,55]

Carbamazepine is a voltage-gated sodium channel blocker that was a choice expressed by the expert panel after failure of mexiletine, lamotrigine, or lacosamide, with only case reports available to assess use in NDM.[3,56,57] Also used by the expert panel in some NDM subtypes was acetazolamide if other treatments were not well-tolerated or effective. An observational study of use in NDM (n=9) showed that administration decreased myotonia. AEs included paraesthesia and, in one case, potentially, renal calculus,[58] though this has not been shown in other studies.[59] According to the expert panel, lacosamide was used if mexiletine and lamotrigine failed; however, to date there have been no randomised controlled trials of its use in NDM.

In a survey including 70 patients with NDM, the three most prescribed drugs were mexiletine, carbamazepine, and flecainide, with fewer patients taking lamotrigine or acetazolamide along with several other antimyotonic drugs. The greatest patient perceived efficacy scores were given to mexiletine and lamotrigine.[7] Another survey, including 37 people with NDM who took mexiletine, lamotrigine, ranolazine, or acetazolamide, revealed that lack of efficacy and AEs were the main reasons for medication discontinuation of any of these medications.[8]

The IMPACT survey revealed that 29% of respondents had not received any type of treatment for NDM and 34% were not satisfied with how their condition was managed.[16,17] Both the IMPACT[17] and MyoPath (data on file, Lupin Neurosciences)[18] surveys highlighted the symptoms that patients most wanted improved included overall mobility problems, muscle stiffness, fall frequency, persistent tiredness, and pain. This was mirrored by a need for a reduction in HRQoL impacts.

Historically, for those with NDM symptoms defined as mild, practical help and advice to avoid triggers and exercise according to NDM subtype was the main therapeutic approach recommended by the expert panel; however, due to the nature of the condition, such avoidance is not always possible.[3,12,60] They suggested that drug treatment for myotonia be offered to all patients with NDM even if they report symptoms to be mild, or the HCP perceives them as such as many will have had symptoms since childhood and may not be aware of how much they are interfering with their daily lives.[3]

The expert panel discussed several solutions for improving NDM management, including discussions with stakeholders, multidisciplinary approaches, multicentre collaboration, and further data collection. Multidisciplinary teams were seen as key to NDM management to help facilitate a holistic and individualised approach to care. The exact team composition may vary according to patient need but could include a neuromuscular specialist, physiotherapist, pain specialist, rheumatologist, and psychologist.

UNMET NEEDS

While understanding and treatment of NDMs are progressing, there are still unmet needs. For example, a study of patient-reported outcomes in NDM highlighted a need for a treatment strategy that targets mutation-specific biophysical abnormalities to better control symptoms. This would require greater understanding of how the affected ion channels function.[12] The mechanism of pain within NDM is also poorly understood.[60] As pain may be refractory to treatment, and is associated with HRQoL impact,[15] it is important to elucidate the molecular pathways involved to tailor treatment approaches.[60]

Overall, the expert panel highlighted a need to increase awareness of NDM and confidence in recognising and treating this condition, as well as fostering a multidisciplinary approach to NDM care. Development needs to be undertaken of verified diagnostic tools and disease monitoring tools such as smartphone applications. The panel also suggested building on the findings of the IMPACT survey to further investigate what other medications patients with NDM were taking, including painkillers, to assess if treatment leads to a reduction in pain symptoms. Additionally, the panel wanted to understand how satisfied patients were with their current treatment and how caregivers were burdened and suggested that patient-reported outcome measures and HRQoL scales, potentially via smartphone applications, could be used to measure and

monitor the effectiveness of drug treatment on symptoms over time.

With regard to increasing awareness of myotonia treatment, while most of the expert panel did not think mexiletine had a negative safety profile, they highlighted the need for pharmacodynamic studies to better understand mexiletine's mechanism of action as well as patient registry studies to capture long-term efficacy and safety. This would help in the discussion with patients and other HCPs regarding the use of such therapy. They also discussed a need for further understanding of cardiologists' opinions on long term use of mexiletine and other off-label treatments, and to clarify whether such medications are associated with cardiac risks in the NDM setting, as some panel members reported cardiac issues associated with mexiletine, lamotrigine and carbamazepine. A working group between cardiologists and NDM specialists has been formed in France, with the intention to publish the outcomes of the project.

The IMPACT survey revealed that fear of AEs was one reason given by patients who were not taking pharmaceutical treatments. This, the expert panel agreed pointed to a need to increase patient understanding of the advantages and disadvantages of antimyotonic medication, and align on treatment expectations.

Currently, mexiletine is only indicated for adults with NDM, as clinical studies did not include children. To address this, an 8-week clinical trial is underway including participants aged 6–17 years old. This will involve a 4-week titration phase up to age-appropriate bodyweight doses of mexiletine.[61]

CONCLUSION

Symptoms of NDM may differ according to NDM subtype and exacerbating factors, and may progress over time. While for some people symptoms may not impact daily aspects of life, for others, they can be disabling and severely disruptive.[12,16,17] Although there are several pharmacological treatments utilised for NDM, only mexiletine effectiveness has been demonstrated in a number of clinical trials of NDM,[21,41,42] and is the only approved drug for NDM,[30] with lamotrigine effectiveness demonstrated in a small clinical trial.[49] The expert panel highlighted how unmet needs include validated screening and monitoring tools, HCP education regarding NDM diagnosis and treatment, and multidisciplinary teams to tackle physical, emotional, and practical aspects of NDM.

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Sex-Related Differences in Symptoms Among Patients Presenting with Acute Stroke: A Systematic Review and Meta-analysis

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Abstract

Background: Recognising acute stroke symptoms is crucial in providing timely treatment. However, evidence suggests that females often experience unique symptoms compared with males, resulting in delays to seeking medical attention and treatment. This systematic review and meta-analysis evaluated whether sex is associated with differences in acute stroke symptoms.

Methods: Searches from 1946 to 7th September 2021 were carried out using MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Cochrane Library. Studies reporting acute stroke symptoms in adult females and males were eligible for inclusion. Eleven observational studies met the inclusion criteria. Methodological quality was assessed using the Newcastle–Ottawa scale (NOS). Data were meta-analysed using a random-effects model.

Results: Compared with males, females had higher odds of experiencing headache (odds ratio [OR]: 1.27; 95% confidence interval [CI]: 1.01–1.59); change in level of consciousness (OR: 1.36; 95% CI: 1.13–1.63); fatigue (OR: 1.53; 95% CI: 1.04–2.25); and incontinence (OR: 1.44; 95% CI: 1.29–1.60). In contrast, females were at lower odds of experiencing trouble speaking (OR: 0.79; 95% CI: 0.64–0.96); trouble walking, loss of balance, or co-ordination (OR: 0.55; 95% CI: 0.39–0.76); and dizziness (OR: 0.77; 95% CI: 0.64–0.94) compared with males. No difference was found in confusion, difficulty understanding speech, trouble seeing in one or both eyes, mental status change, and nausea or vomiting.

Discussion: Sex differences do exist in some acute stroke symptoms. At the same time, the overlap in symptoms between sexes was substantial. Healthcare professionals and public health campaigns should continue to promote classic symptoms of acute stroke, whilst taking into account the less common symptoms and the potential differences in symptoms experienced by females and males.

Key Points

1. As recently as 2020, the World Health Organisation (WHO) published data showing that acute strokes were the second leading cause of death worldwide.

2. This systematic review and meta-analysis of 11 studies of 15,465 patients with acute stroke revealed considerable overlap in symptomology between male and female patients for both 'traditional' and 'non-traditional' symptoms, suggesting these terms are outdated.

3. While significant sex differences in stroke presentations weren't found by this analysis, better community knowledge of atypical symptoms of acute stroke could improve earlier hospital presentation for affected patients, regardless of sex.

INTRODUCTION

In recent years, acute stroke mortality has decreased due to advancements in treatment, lifestyle changes, and an increased focus on primary prevention; however, rates are still considerably high globally.[1] In 2020, the World Health Organization (WHO) published data that showed acute stroke to be the second leading cause of deaths at a global level in 2019, instigating approximately 11% of the total deaths.[2] This number is set to rise exponentially due to ageing and growth of the population, as well as improvements in treatment leading to better survival rates.[3,4]

Recognising acute stroke symptoms is crucial in providing timely treatment. Patients who receive rapid treatment are more likely to have better outcomes and recovery, even if the initial stroke is relatively severe.[5] As a result, establishing the time of onset of symptoms is imperative.

Previous studies have reported that acute stroke symptomology can differ between females and males, leading to differences in acute stroke outcomes.[6] In particular, females have been documented to present with different, unique symptoms of acute stroke rather than those considered 'traditional' or 'typical' (e.g., numbness and weakness).[7,8] These unique symptoms are often labelled as 'non-traditional' or 'atypical', and cover a broad spectrum.[8]

To date, there is no consensus as to which symptoms can specifically be classified as 'non-traditional'. This lack of consensus means that these unique symptoms are often not recognised as acute stroke symptoms, and their manifestation can result in delays to medical attention, under-diagnosis, and under-treatment, which in turn can exacerbate adverse outcomes of acute stroke.[9]

Potential differences in acute stroke symptoms can contribute towards the delay in seeking medical assistance in females, making diagnosis more difficult and delaying effective treatment or therapy.[10] Current campaigns to increase awareness are based on typical or traditional symptoms of acute stroke.[10–12] In order to minimise the time between symptom onset and seeking medical attention, a more sustainable public health campaign needs to be established and addressed through theory-based interventions targeting the entire range of acute stroke symptoms, as opposed to the most common.[13]

A systematic review was conducted to understand better if and how acute stroke symptoms differ between sexes. Such information is required for the development of effective health campaigns to educate both the public and healthcare professionals on recognising alternative symptoms of acute stroke and prompt further research.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in all aspects of this systematic review.[14] This study was submitted for registration on the International Prospective Register of Systematic Reviews (PROSPERO), under registration number CRD42020220866.

Search Strategy

Keywords and medical subject headings related to acute stroke, ischaemic stroke, haemorrhagic stroke, cerebrovascular accident, sex, and symptoms were identified.

Searches were carried out on MEDLINE, Embase, CINAHL, and the Cochrane Library. The following search strategy was employed on the OVID platforms and modified for other databases:

(((sex OR gender) adj2 (distribution OR different* OR dispuarit* OR factor* OR inequality* OR specific))) OR (((male* or men) and (female* or women)).ti.) AND (((stroke) adj2 (ischaemic OR intracerebral OR intraparenchymal OR subarachnoid OR haemorrhage*)) OR (cerebrovascular accident OR CVA OR brain attack)) AND (symptom* OR presenting OR presentation OR sign* OR character* OR manifestation)

Grey literature searches were conducted using OpenGrey and ProQuest-Digital Dissertations and Theses.

Eligibility Criteria

Original, quantitative studies (randomised or quasi-randomised controlled trials), interventional studies, and observational studies (cohort, cross-sectional, and case-control studies) that reported on acute symptom presentation in females and males aged ≥18 years presenting to hospital with acute stroke, as confirmed by a physician or neurologic examination and/or radiological scan, were included. Acute stroke was defined as a clinical syndrome, consisting of rapidly developing clinical signs of focal (or at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin, including either ischaemic or haemorrhagic stroke. Outcomes of interest were traditional and non-traditional symptoms of acute stroke.

Traditional acute stroke symptoms were identified using the five main categories, which are classified by the Centers for Disease Control and Prevention (CDC) as sudden numbness or weakness in the face, arm, or legs, especially on one side of the body; sudden confusion, trouble speaking, or difficulty understanding speech; sudden trouble seeing in one or both eyes, sudden trouble walking, dizziness, loss of balance, or lack of co-ordination; and sudden, severe headache.[7]

Further to this, the following symptoms commonly classified as non-traditional were identified from existing literature: general weakness; pain, including facial or hemi-body pain; change in level of consciousness; mental status change; fatigue; nausea or vomiting; and incontinence.[8,15-17]

Studies were not limited by date of publication. Diagnostic studies, qualitative studies, editorials, commentaries, review articles, case reports, and letters without quantitative data were not included. Only studies in English were included due to resource limits. As transient ischaemic attacks do not typically cause lasting damage, they are often seen as a precursor to acute stroke rather than an acute stroke subtype.[18] Therefore, studies that reported symptoms of transient ischaemic attacks were excluded. Conference abstracts and reviews were also excluded.

Risk of Bias

Due to the observational methodology of the included papers, the quality assessment was based on the Newcastle–Ottawa scale (NOS).[19]

Data Extraction

The following data were extracted from all eligible studies: study participants' demographic information; study characteristics, including design, methodology, and geographical location; sample size; eligibility criteria; diagnostic criteria; the proportion of females and males with acute stroke symptoms; and the proportion of females and males with each symptom, both traditional and non-traditional.

Terminologies or symptoms that were considered synonymous with the symptoms identified in the outcomes were combined. Where studies grouped symptoms using an umbrella term, such as 'speech symptoms' or 'visual deficits' without further description or definition, this information was not extracted as it was not possible to disaggregate which symptoms were included. Data were combined if one symptom or another was reported such as 'nausea or vomiting'. Where studies reported one symptom and another, such as nausea and vomiting, the prevalence of both were extracted where possible.

Statistical Analysis

Effect measures were expressed as odds ratios (OR) with 95% confidence intervals (CI) to formally test the female–male differences in the prevalence of acute stroke symptoms. The OR was the ratio of the odds of an event, such as an acute stroke symptom, occurring in males to the odds of the event occurring in females. An OR of 1 implied that a symptom was experienced equally in both females and males; an OR of >1 implied that the event was more likely in females; and a ratio of <1 implied that the event was less likely in females.[20] As a certain degree of heterogeneity was expected in the observational studies included in this review in terms of study designs, patient populations, data analysis methods, and outcomes, a Mantel–Haenszel model for random effects was used.[21,22] A p value of <0.05 was considered statistically significant.[21]

Statistical heterogeneity was assessed using the Chi-squared test (significance level of 0.1) and I^2 statistic. I^2 values of <40% were considered to represent low heterogeneity, 40–60% moderate heterogeneity, 60–90% substantial heterogeneity, and >90% as considerable heterogeneity.[22]

Sub-group analyses were not performed as none of the meta-analyses included at least 10 studies for each characteristic modelled and, therefore, were unlikely to produce useful findings.[22] Similarly, it was established *a priori* that funnel plots would be used to assess for publication bias when 10 or more studies were combined. None of the analyses combined a sufficient number of studies to produce such funnel plots; therefore, the effects of publication bias could not be determined.

All statistical analyses were performed using Review Manager (Cochrane, London, UK), version 5.4.1 for Mac.[23]

RESULTS

Study Selection

The literature search returned 2,877 results in total. Search results from each database were deduplicated. Two investigators independently screened the titles and abstracts of the studies. Any discrepancies in study assignments were solved through discussion and consensus between the two investigators. If no consensus could be reached, a third-party reviewer was available for consultation. In total, 11 studies fulfilled the inclusion criteria and were included in the meta-analysis. Figure 1 summarises the study selection process.

Characteristics of Included Studies

Eight cohort studies and three cross-sectional studies involving 15,465 individuals in total were included, 7,763 (50.2%) of whom were female and 7,702 (49.8%) were male. Study participants were all recruited from hospitals from 13 countries, predominantly from the USA (n=4). The years during which data were collected ranged between 1985–2010. The mean age of female participants was 71 years, while the mean age of male participants was 65. Three of the studies included patients presenting with ischaemic stroke only. One study investigated patients with haemorrhagic stroke only. The remaining seven studies included both ischaemic and haemorrhagic stroke patients. The full study characteristics are summarised in Table 1.

Risk of bias in studies

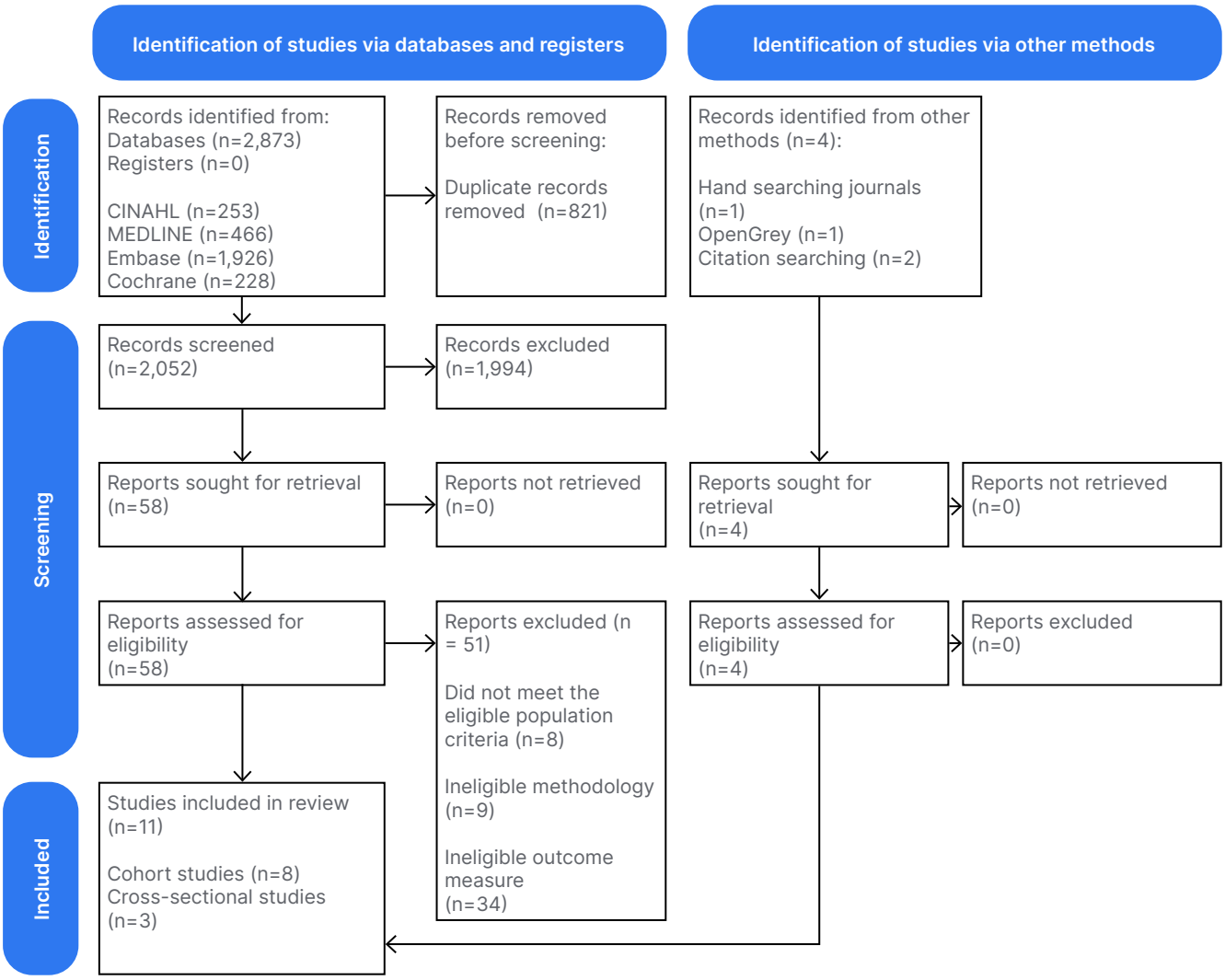
The quality of the eight included cohort studies was variable, whilst the quality of the three included cross-sectional studies was considered good.

Results of syntheses

Table 2 provides the pooled crude ORs for sex differences in each examined symptom of patients presenting with acute stroke.

Numbness or weakness in the face, arms, or legs, especially on one side of the body

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of selection of studies for inclusion in the review.[14]



Due to the variability in reported symptoms for this outcome, it was deemed inappropriate to pool data between all four studies that reported 'weakness' as a symptom.[25,28,30,33] Instead, symptoms that more than one study reported data for were identified and analysed, including facial weakness and limb weakness.

No significant sex difference was noted in presentation with facial weakness (OR: 1.05; 95% CI: 0.72–1.53).[25,30,33] There was a significant, moderate level of statistical heterogeneity between these studies (I^2: 61%; Chi-squared: 5.07; p=0.08).

Similarly, no significant sex difference was found in presentation with limb weakness (OR: 0.90; 95% CI: 0.73–1.11).[25,28] No heterogeneity was noted (I^2: 0%; Chi-squared: 0.58; p=0.45). This may be due to the size of this meta-analysis; it is not always possible to estimate heterogeneity with much precision in small meta-analyses.[34]

Confusion

No significant sex difference was noted in the overall pooled OR for confusion (OR: 1.13; 95% CI: 0.95–1.35).[12,25,26] A low but non-significant level of heterogeneity was noted between these studies (I^2: 30%; Chi-squared: 2.85; p=0.24).

Trouble speaking

Females had a significantly lower odds of presenting with trouble speaking than males (OR: 0.79; 95% CI: 0.64–0.96).[12,25,26,28,33] The I^2

value of 42% suggested a moderate level of heterogeneity between these studies, but this was not statistically significant (Chi-squared: 6.90; p=0.14).

Difficulty understanding speech

Overall, there was no significant sex difference in presentation with symptoms that resulted in difficulty understanding speech (OR: 1.14; 95% CI: 0.94–1.39).[12,25,26,28,31,33] Statistical heterogeneity was substantial, as evidenced by the I^2 value of 74% and statistically significant Chi-squared test results (Chi-squared: 18.99; p=0.002).

Trouble seeing in one or both eyes

Overall, there was no significant sex difference in presentation with the symptom of trouble seeing in one or both eyes (OR: 0.64; 95% CI: 0.41–1.00).[26,30,33] Heterogeneity was low and non-significant (I^2: 31%; Chi-squared: 2.90; p=0.23).

Trouble walking or loss of balance or co-ordination

Overall, females had significantly lower odds of presenting with the symptom of trouble walking or loss of balance or co-ordination than males (OR: 0.55; 95% CI: 0.39–0.76).[25,26,28,30,32] There was a significant, moderate level of statistical heterogeneity between these studies (I^2: 64%; Chi-squared: 11.21; p<0.02).

Dizziness

Females had significantly lower odds of presenting with dizziness than males (OR: 0.77; 95% CI: 0.64–0.94).[25,26,29,30] Low heterogeneity was noted; this was non-significant (I^2: 0%; Chi-squared: 0.82; p=0.5).

Headache

Females with acute stroke had significantly lower odds than males of presenting with headache (OR: 1.27; 95% CI: 1.01–1.59).[24-28,30,32,33] The I^2 value of 75% and significant Chi-squared statistic of 31.54 (p=0.0001) suggested a substantial level of statistical heterogeneity between these studies.

General weakness

Only one study reported general weakness as a symptom of acute stroke in females and males; therefore, a pooled OR could not be calculated.[26] The OR calculated from the prevalence of females and males who experienced general weakness on presentation with acute stroke in this study showed that females had significantly higher odds of presenting with general weakness than males (OR: 1.84; 95% CI: 1.19–2.85).

Pain

Only one study that reported pain as an acute stroke symptom; therefore, a pooled OR could not be calculated.[26] The OR calculated from the descriptive statistics provided in the study showed no significant sex difference in presentation with pain in acute stroke (OR: 0.57; 95% CI: 0.27–1.20).

Change in level of consciousness

Overall, females had significantly higher odds of presenting with a change in level of consciousness than males (OR: 1.36; 95% CI: 1.13–1.63).[12,24,25,27-29,33] Statistical heterogeneity was moderate as evidenced by the I^2 value of 57% and statistically significant Chi-squared test results (Chi-squared: 13.83; p=0.03).

Mental status change

Overall, there was no significant sex difference in presentation with mental status change as an acute stroke symptom (OR: 1.62; 95% CI: 0.71–3.70).[26,32] The I^2 value of 89% and significant Chi-squared statistic of 9.17 (p=0.002) suggested a substantial level of statistical heterogeneity between these studies, most likely because of the small size of the meta-analysis.[34]

Fatigue

Overall, females had significantly higher odds than males of presenting with fatigue (OR: 1.53; 95% CI: 1.04–2.25).[26,32] Low heterogeneity was noted; this was not significant (I^2: 1%; Chi-squared: 1.01; p=0.32). As noted above, this may be due to the size of this meta-analysis.[34]

Nausea or vomiting

Overall, no significant sex difference in presentation with nausea or vomiting as an acute stroke symptom was found (OR: 1.02; 95% CI: 0.80–1.30).[25,26,32,33] Low heterogeneity was noted, but this was not significant (I^2: 0%; Chi-squared: 2.98; p=0.40).

Incontinence

Overall, females with acute stroke had higher odds of presenting with incontinence than males (OR: 1.44; 95% CI; 1.29–1.60).[12,25,26,28] No significant heterogeneity was observed (I^2: 0, Chi-squared: 1.86; p=0.60).

Table 1: Summary of characteristics of included studies.

Study	Study design	Country	Study years	Data collection method	Diagnostic criteria	Stroke type	Sample size	Mean age (years)	NOS score*
Alves et al.,[24] 2012	Prospective cohort (multicentre)	Brazil	2009–2010 (16 months)	Medical records	Neuroimaging (CT and MRI)	H	n=364 F=173 M=191	F=66.3 M=59.3	8
DiCarlo et al.,[12] 2003	Prospective cohort (multicentre)	England, France, Germany, Hungary, Italy, Portugal, and Spain	1993 (12 months)	Medical records and patient interviews	Neuroimaging (CT)	I and H	n=4,499 F=2,260 M=2,239	F=74.5 M=69.2	8
Gall et al.,[25] 2010	Prospective cohort	Australia	1996–1999	Medical records patient interviews	Neurologist	I and H	n=1,316 F=731 M=585	F=76.0 M=72.0	7
Jerath et al.,[26] 2011	Cross-sectional (registry)	USA	1985–1989	Medical records	Neurologist	I	n=449 F=268 M=181	F=79.0 M=70.0	9
Kapral et al.,[27] 2005	Prospective cohort (registry)	Canada	2001–2002 (6 months)	Medical records and patient interviews	Neurologist	I and H	n=3,323 F=1,527 M=1,796	Unknown	9
Khan and Ibrahim,[28] 2018	Prospective cohort (secondary analysis)	Qatar	2004–2005 (12 months)	Patient interviews	Neurologist and neuroimaging (CT and MRI)	I and H	N=270 F=73 M=197	F=61.3 M=55.6	6
Madsen et al.,[29] 2016	Cross-sectional	USA	2010 (12 months)	Medical records	Physician	I	n=1,991 F=1,097 M=894	F=74.0 M=67.0	5
Rathore et al.,[30] 2002	Retrospec-tive cohort	USA	1987–1997	Medical records	Physician	I and H	n=474 F=224 M=250	Overall= 62.5	7
Roquer et al.,[31] 2003	Prospective cohort	Spain	1995–2002	Medical records	Physician	I and H	n=1,581 F=772 M=809	F=74.6 M=68.8	8
Stuart-Shor et al.,[32] 2009	Cohort (cross-sectional)	USA	1999-2004	Medical records	Neurologist	I	n=1,107 F=608 M=499	F=75.8 M=69.7	5
Watila et al.,[33] 2011	Prospective cohort	Nigeria	2005–2009	Patient interviews	Neuroimaging (CT and MRI)	I and H	n=91 F=30 M=61	F=55.6 M=56.2	5

The overall population age (years) where individual mean age for females and males is not stated.

*The NOS was out of a maximum of 9 stars. NOS 0–3: very high risk of bias (low quality); 4–6: high risk of bias; and 7-9: low risk of bias (high quality).

F: female H: haemorrhagic stroke; I: ischaemic stroke; M: male; NOS: Newcastle–Ottawa scale.

Table 2: Aggregated meta-analysis for all included symptoms of acute stroke.

Symptom	Analysis of crude OR			
	Number of studies	Pooled OR (95% CI)	I^2	Chi-squared p
Facial weakness	3	1.05 (0.72–1.53)	61%	0.08000
Limb weakness	2	0.90 (0.73–1.11)	0%	0.45000
Confusion	3	1.13 (0.95–1.35)	30%	0.24000
Trouble speaking	5	0.79 (0.64–0.96)	42%	0.14000
Difficulty understanding speech	7	1.14 (0.94–1.39)	74%	0.00200
Trouble seeing in one or both eyes	3	0.64 (0.41–1.00)	31%	0.23000
Trouble walking or loss of balance or co-ordination	5	0.55 (0.39–0.76)	64%	0.02000
Dizziness	4	0.77 (0.64–0.94)	0%	0.85000
Headache	9	1.27 (1.01–1.59)	75%	0.00001
General weakness	1	N/A	N/A	N/A
Pain	1	N/A	N/A	N/A
Change in level of consciousness	7	1.36 (1.13–1.63)	57%	0.03000
Mental status change	2	1.62 (0.71–3.70)	89%	0.00200
Fatigue	2	1.53 (1.04–2.25)	1%	0.32000
Nausea or vomiting	4	1.02 (0.80–1.30)	0%	0.40000
Incontinence	4	1.44 (1.29–1.60)	0%	0.60000

CI: confidence interval; N/A: not applicable; OR: odds ratio.

DISCUSSION

This systematic review and meta-analysis of 11 studies, including 15,465 patients, shows that sex differences exist in some acute stroke symptoms. At the same time, overlap in symptoms between females and males with acute stroke was substantial.

A causal relationship between sex and acute stroke symptoms cannot be inferred from these results, particularly as age, ethnicity, and stroke subtype may have had a confounding effect. Moreover, these results are not indicative of sex differences in traditional acute stroke symptoms commonly known by the public and healthcare professionals. However, these results do provide

evidence to suggest that females are more likely to present with non-traditional symptoms than males, with considerable overlap of traditional symptoms between both sexes. This is important for the applicability of public awareness campaigns to increase recognition of acute stroke in the community, irrespective of sex. It is imperative to continue promoting the awareness of traditional or classic acute stroke symptoms, as they appear to present in females and males. However, both the public and healthcare professionals should also be aware of the possibility of less commonly known symptoms of acute stroke manifesting, such as headache, change in level of consciousness, fatigue, and incontinence, so as not to delay treatment.

Implications for Future Research and Clinical Practice

Based on these findings, researchers and healthcare professionals should use caution when labelling acute stroke symptoms as traditional or non-traditional or 'female/male-specific' and instead focus on the established differences and overlap in symptom presentation between females and males. Furthermore, these results demonstrate the potential to revise national and international public health campaigns to highlight less common acute stroke symptoms and the possible differences in acute stroke symptom presentation between women and men. Alongside this, healthcare professionals need to be educated to recognise and explain these sex differences in acute stroke symptoms to patients presenting with acute stroke and those identified as at risk of acute stroke. Given the importance of age and ethnicity as explanatory factors, it is recommended that any future studies adjust for age and ethnicity, testing for interactions and adjusting for risk factors in a standardised way to allow for comparisons between studies.

Strengths and Limitations

This is the first systematic review and meta-analysis to examine sex differences in acute stroke symptoms. Scrupulous searching meant that relevant studies were identified; hence, results and conclusions of this systematic review are likely to be based on a synthesis of the available evidence. In addition to this, a rigorous risk of bias assessment was performed to help establish transparency of evidence synthesis results and findings.

As well as strengths, there are also limitations to this systematic review and meta-analysis to take into consideration. First, a limited number of publications looked into sex differences in acute stroke symptoms, rather than just sex differences in acute stroke outcomes or severity, representing a limitation within the current body of evidence. Secondly, the investigators could only read English; therefore, only studies published in English were included, which may have excluded potentially relevant articles. Finally, comparability of individual studies was hampered by the use of different definitions and combining of stroke symptoms in individual studies.

CONCLUSIONS

This systematic review and meta-analysis show that whilst there may be sex-related differences in some acute stroke symptoms, there is also significant overlap between the sexes in others. Moreover, there is little evidence to indicate sex differences in traditional and non-traditional acute stroke symptoms, suggesting that these terms are outdated. Instead, the data from this systematic review and meta-analysis suggest that public health campaigns and professionals should continue to focus on the classic symptoms of stroke for both sexes whilst also reflecting a broader spectrum of possible symptoms. Potential differences in symptom presentation between females and males should be taken into account to aid early recognition and avoid delays in treatment. Future studies should aim to shed light on the relationship between age, sex, ethnicity, and acute stroke symptoms.

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Never Too Late to Treat NMDAR Encephalitis: A Paediatric Case Report and Review of Literature

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Abstract

Background: Anti-N-methyl-D-aspartate receptor antibody encephalitis is an immune-mediated disorder characterised by a complex neuropsychiatric syndrome that often can be initially misdiagnosed. A small subset of the population is refractory to both first- and second-line therapies. These reasons make delays to the correct therapy a major concern, as early treatment may lead to better outcomes in children. Nevertheless, there is still benefit in additional medication courses despite a prolonged refractory state. The authors provide an illustrative case report and review of literature.

Case Presentation: The authors describe a 5-year-old female with 5 days of change in mental status; choreoathetoid movements were found to have positive anti-GluN1 antibodies in their cerebral spinal fluid. They failed first-line intravenous steroids and intravenous Ig and second-line rituximab, but then were discharged to rehabilitation without improvement over 3 months. Despite the time frame, they had a complete response to 12 sessions of plasma exchange with concomitant pulse steroids and subsequent intravenous Ig.

Conclusion: The authors' case report and review of literature supports practices that prompt additional therapy for incomplete or failure of response in anti-N-methyl-D-aspartate receptor encephalitis despite prolonged symptom duration. Extended plasma exchange therapy may be beneficial in some treatment refractory cases.

Key Points

1. The authors present an illustrative case study of a commonly misdiagnosed complex neuropsychiatric syndrome, anti-N-methyl-D-aspartate receptor antibody encephalitis, in a 5-year-old patient.

2. The patient presented with altered mood, abnormal movements, difficulty with motor control, and unintelligible speech. They were initially misdiagnosed with several differential diagnoses, including stroke, meningitis, and Sydenham's chorea.

3. Early treatment can lead to better outcomes in paediatric patients; however, additional courses of medicine may provide benefit, and ought to be strongly considered even in cases of prolonged refractory state.

INTRODUCTION

Dysfunction of N-methyl-D-aspartate receptors (NMDAR) have been proposed as the aetiology for multiple neuropsychiatric diseases. While overactivity of NMDA receptors causing excitotoxicity has been implicated in epilepsy, dementia, and stroke, low activity may produce symptoms resembling those of schizophrenia.[1] Autoimmune disruption to the NMDA receptors in anti-NMDAR antibody encephalitis is caused by the presence of cerebrospinal fluid (CSF) antibodies against the GluN1 subunit of the NMDA-R, leading to rapid deterioration in a patient's psychiatric and neurologic state. The authors describe a 5-year-old female with typical presentation and positive anti-GluN1 antibodies, failing first-line intravenous steroids and intravenous Ig (IVIg) and second-line rituximab, but then discharged to rehabilitation without improvement over 3 months. Despite the time frame, they had a complete response to 12 sessions of plasma exchange with concomitant pulse steroids and subsequent IVIg.

CASE REPORT

A 5-year-old developmentally normal female, with no significant past medical or contributory family history, who was born at 27 weeks gestation, initially presented to an outside tertiary academic centre in autumn 2020 with 5 days of change in mental status and abnormal movements. Their mood had significantly tempered, yet they had continued superimposed episodes of inappropriate laughter, followed by difficulty with motor control, restless legs during sleep, and trouble grasping a pencil. Head CT was unremarkable, and serum white blood cell was elevated at 15.2×10^9 cells/L.

Their exam on presentation demonstrated prolonged periods of somnolence with rapid slurred and unintelligible speech, requiring significant stimulation to rouse. Non-suppressible choreoathetoid movements, characterised by intermittent abduction at the right hip and writhing movements with inversion at the right ankle, were present in the right lower extremity. Their left toe was upgoing.

The initial differential diagnosis included Sydenham's chorea, autoimmune encephalitis, diffuse cerebral structural lesions, stroke, toxin exposure, metabolic derangement, and meningitis. Work up was normal or negative for urine drug screen, metabolites, head CT, and contrast enhanced brain MRI. Electroencephalography studies did not show epileptiform discharges or delta brush activity. For mildly elevated anti-streptolysin O titres of 400 IU/mL (anti-deoxyribonuclease B and throat cultures were negative, with a normal echocardiogram), they received 10 days of penicillin V for possible Sydenham's chorea. Despite treatment, the encephalopathy progressed. Further CSF studies demonstrated a white blood cell of 14×10^9 cells/L, 90% lymphocytes, and negative CSF BioFire PCR (BioFire Diagnostics, Salt Lake City, Utah, USA) and aerobic cultures with gram stain. Encephalopathy autoimmune evaluation using cell-based assay confirmed NMDA-R antibody positivity in both serum and CSF, with titres of 1:2 in the CSF and 1:120 in the serum. An abdomen/pelvis MRI revealed a left ovarian focus of fat suspicious for teratoma, a possible paraneoplastic source for anti-NMDA-R encephalitis, but pathology following oophorectomy revealed normal ovarian tissue.

For worsening choreiform movements, increased agitation, and psychosis, the patient received IVIg 2 g/kg over 5 days and methylprednisolone 30 mg/kg daily over 5 days. They further received lorazepam, valproic acid (30 mg/kg/day divided in two doses), and clonazepam (1.75 mg/day in divided doses) for agitation and seizure prophylaxis. Given their lack of response during the first month after presentation, the decision was made to start

second-line therapy, so the patient received 4 doses of weekly rituximab (375 mg/m^2/dose). They continued to deteriorate with two prolonged episodes of unresponsiveness. A repeat brain MRI was unremarkable and repeat video electroencephalography showed only intermittent slowing. For worsening agitation and new onset nocturnal visual hallucinations, they received quetiapine (10 mg/kg/day in divided doses), which subsequently improved their sleep. Their clinical presentation deteriorated into a nonverbal state, with lack of eye contact and urinary incontinence, and extreme lethargy. They received a repeat course of 5 days IVIg (2 g/kg divided over 5 days) with pulse methylprednisolone (30 mg/kg/day). Second-line therapy cyclophosphamide was avoided due to concerns for infertility given the solitary remaining ovary. The patient was subsequently transferred to inpatient rehabilitation 1.5 months after symptom onset.

A second opinion was requested at 3 months post-symptom onset during inpatient rehabilitation. Consequently, they received 12 sessions of plasma exchange (PLEX), given every other day, with concomitant 30 mg/kg daily methylprednisolone and subsequent IVIg (2 g/kg divided over 3 days) after observing improvement following the second PLEX session. Repeat abdomen, pelvis, and chest MRI showed no evidence of malignancy. A brain MRI now demonstrated mild diffuse cerebral volume loss.

Following the sixth session, the patient demonstrated increased awareness of their environment, began speaking, and followed simple requests. Sedatives were tapered. One month follow-up post-hospital discharge, the patient made a complete recovery (Figure 1).

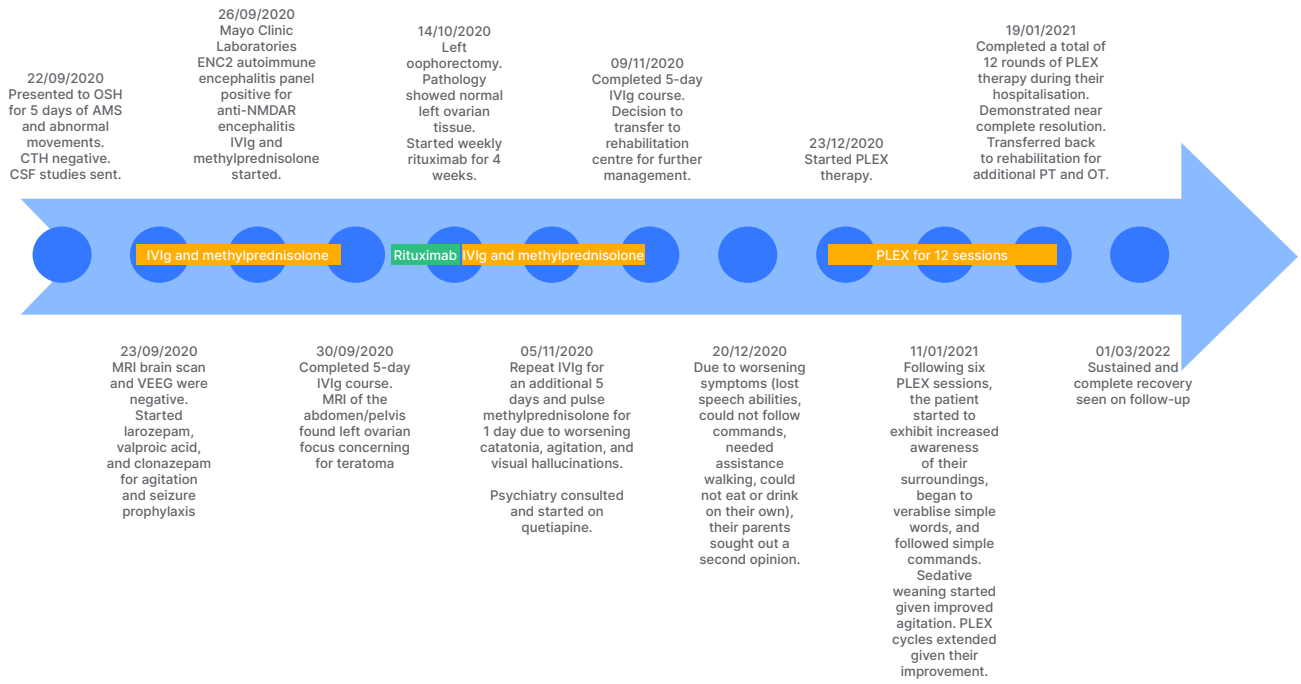
DISCUSSION

Typical management of anti-NMDAR encephalitis involves the escalation of immunotherapy, starting with first-line therapies such as steroids, IVIg, and/or PLEX, and supplementing or transitioning to second-line therapies such as rituximab, cyclophosphamide, and, less commonly, azathioprine or mycophenolate mofetil as needed.[2] In a large study by Titulaer et al.,[2] almost half of the patients improved after first-line therapies. Of the patients who did not, nearly half improved after second-line therapies. Of the patients who remained refractory to both first- and second-line therapies, third-line therapy such as bortezomib, a proteasome inhibitor, or tocilizumab, an IL-6 receptor antagonist have been suggested.[3,4] In other case reports, intrathecal administration of rituximab or methotrexate-dexamethasone with the rationale of improved CSF antibody removal has demonstrated success.[5-7] Similarly, low dose IL-2, which aims to restore regulatory and effector T cells, has also been suggested for treatment-refractory anti-NMDA-R encephalitis.[8] Smaller studies investigated daratumumab, an anti-cluster of differentiation 38 monoclonal antibody typically used in refractory myeloma treatment, and tofacitinib, a JAK inhibitor with good central nervous system penetration, and offered them as therapeutic options for refractory anti-NMDAR encephalitis.[9,10]

Numerous retrospective studies indicate a good prognosis, including fewer relapses, with early diagnosis and treatment of anti-NMDAR encephalitis.[11,12] A large cohort study indicated that treatment delay greater than 4 weeks was associated with worse 1-year functional status.[13] However, timely treatment is not always possible, given the complex presentation that may lead to psychiatric or non-autoimmune epileptic misdiagnoses, and lack of proven treatment options in refractory cases. Despite the common consensus that early diagnosis leads to better outcomes, some studies found no association between time to immunotherapy and outcome, suggesting that even delayed treatment could be of major benefit.[14-17] One recent study indicated treatment delay did not affect neuropsychological outcomes, namely no long-term worsening of sustained attention, long-term verbal memory, or fatigue.[18]

Among second-line therapies, rituximab is believed still efficacious when initiated months or even years after disease onset. In a large multicentre retrospective study, 41% of 39 patients anti-NMDA-R failing first-line therapies had a definite benefit after receiving rituximab, on average, at around 1.2 months post-disease onset, but ranging from 0.05 to 5.10 years.[19] Dou et al.[20] studied eight children with refractory disease, where rituximab was given after a median disease duration of 57

Figure 1: Patient treatment timeline.



AMS : altered mental state; CSF: cerebrospinal fluid; CTH: computed tomography of the head; ENC2: encephalopathy, autoimmune/paraneoplastic evaluation of spinal fluid; IVIg: intravenous immunoglobulin; LP: lumbar puncture; NMDAR: N-methyl-D-aspartate receptor; OSH: outside hospital; OT: occupational therapy; PLEX: plasma exchange; PT: physical therapy; VEEG: video electroencephalography.

days (range: 50.50–113.75 days). They found the use of rituximab led to a significant reduction in modified Rankin scale (mRS) and serum cluster of differentiation CD19+ B cells. Five patients (62.5%) had a good outcome (mRS≤2), including four patients (50%) who showed complete recovery (mRS=0) at last follow-up.[20]

The initiation of cyclophosphamide months from disease onset also has been shown to be beneficial in treating refractory disease. Kashyape et al.[21] reported on two paediatric patients with refractory disease on steroids and IVIg, who had complete resolution of their movement disorders and a dramatic sustained clinical improvement of other symptoms in the domains of cognition, language, and behaviour following initiation of cyclophosphamide at Days 73 and 64 of symptom onset.

Similarly, among third-line therapies, treatment with bortezomib months to years after symptoms may also be beneficial in refractory disease. In a cohort study conducted by Scheibe et al.,[22] five patients with refractory disease showed clinical improvement or disease remission despite delayed treatment with 1–6 cycles of bortezomib, initiated from 3 to 69 months since symptom onset. Another study reported that initiation of bortezomib 3 months into symptom onset in a 22-year-old female with refractory disease to both first- and second-line therapies showed rapid improvement in neurological deficits soon after the first injection.[23] In a case report by Behrendt et al.,[3] two patients who were severely affected with anti-NMDAR were treated with bortezomib at 7 months and 2.5 years from symptom onset, respectively, also showed significant clinical improvement.

Lengthier delays to efficacious therapy have been documented in several case reports. Sulentic et al.[11] discussed that, despite delayed diagnosis and therefore immunotherapy

ranging from 13 months to 8 years after initial presentation, three patients only had minimal residual cognitive deficits compared with their pre-morbid baselines. Another case report reviewed three patients with treatment refractory disease receiving tocilizumab 2–4 years post-symptom onset, with substantial recovery months after treatment initiation.[4]

The patient achieved complete remission on an extended course of PLEX therapy, an established empirical treatment with growing evidence for efficaciousness, at over 3 months post-symptom onset. PLEX likely filters harmful antibodies and proinflammatory cytokines to enable recovery in immune-mediated diseases.[24] As a first-line therapy, PLEX is widely studied.[24,25] In addition, in the paediatric population, there have been case reports suggesting remarkable success after PLEX therapy.[26-28] A cohort study by Pham et al.[24] identified that earlier initiation of PLEX therapy and PLEX followed by IVIg were able to provide the best outcomes for anti NMDAR encephalitis. In a large systematic literature review, Suppiej et al.[25] identified the combination of PLEX, steroids, and IVIg to be the most efficacious option, with a mean of 7.3 exchanges in 62 patients.

The authors' patient responded to a prolonged course of PLEX, eliminating the need for further costly inpatient rehabilitation. Although not well studied, longer courses of PLEX therapy in a number of small studies have emerged supporting its successful use. Simabukuro et al.[28] described an 18-year-old with refractory anti-NMDAR encephalitis who failed first- and second-line therapies, but responded to 19 rounds of PLEX initiated on Day 45 after symptom onset.[28] A report by Agrawal et al.[26] described a 22-month-old infant who responded after 20 rounds of PLEX. In a review by Suppiej et al., the longest course of PLEX was 21 cycles.[25] In another cohort study by Zhang et al.,[25] the longest course of PLEX was 15 cycles in patients with refractory anti-NMDAR.[29] The authors' case report supports the mounting evidence that prolonged PLEX therapy should be a viable option when confronted with refractory disease.

Response to PLEX in the authors' case was supported by the extended duration of time without improvement following initial hospital discharge. However, a potential delayed onset of action from rituximab could be postulated.

Nevertheless, this case study and review of literature highlight that delayed treatment must still be contemplated and offered to significantly symptomatic individuals prior to dismissal to in- or outpatient rehabilitation. This may be in opposition to other autoimmune disorders of the central nervous system, where classically the acute phase is considered concluded by 3 months. However, the distinction between subtle active disease and neuropsychological sequelae remains a challenging topic for this population.

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A Rare Case of Multiple Cranial Nerve Palsies as the First Presentation of Hepatocellular Carcinoma: A Case Report and Review of Literature

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Abstract

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. It mainly occurs in patients with chronic liver diseases such as cirrhosis caused by hepatitis B or C infections, as well as chronic alcoholics. HCC is one of the highly malignant neoplasms. Extrahepatic metastases are seen in 64% of patients with HCC, but metastases to the brain and skull are extremely rare. Here, the case of a 45-year-old male who presented with left III, IV, VI, IX, X, and XII cranial nerve palsies is reported. These were revealed to be caused by a distant metastasis from an unnoticed HCC with a background of previously undiagnosed chronic alcoholic liver disease. Physicians should be aware of the metastatic potential of HCC, in addition to its uncommon presentations, while encountering patients with an underlying liver disease. This case report elucidates that metastatic HCC can lead to a rare, but possible, new onset of cranial neuropathy.

Key Points

1. HCC is a highly malignant neoplasm; extrahepatic metastases are common, however, metastases in the brain and skull are extremely rare.

2. HCC with brain metastasis has limited treatment options and is life-threatening due to the risk of haemorrhage.

3. Increased awareness might prevent deaths from neurological causes in HCC patients with metastatic brain tumours by increasing the chance of early diagnosis and potentially improving the chances of curative surgical resection.

INTRODUCTION

The highest incidence rates of hepatocellular carcinoma (HCC) are found in Asia and sub-Saharan Africa. Overall, liver cancer accounts for 7% of all cases of cancer (approximately 850,000 new cases each year), while HCC, which frequently metastasises to the lungs, regional lymph nodes, and the skeletal system, represents 90% of primary liver cancers.[1] Cirrhosis from any aetiology is the strongest risk factor for HCC, and most cases of HCC are secondary to either viral hepatitis (hepatitis B or C) or alcoholic cirrhosis. HCC in a young patient with no previous evidence of cirrhosis or fibrosis is a relatively rare condition. In an analysis of 770,000 cases of HCC occurring worldwide, over 50% of cases were attributed to chronic hepatitis B, and 20% of cases were attributed to chronic hepatitis C infection.[2] Alcohol-related liver disease is the most prevalent type of chronic liver disease (CLD) worldwide, accounting for 30.0% of HCC cases, whilst alcoholic liver disease is responsible for 5.4% of HCC-related deaths.[3]

An excessive alcohol intake may result in fatty liver, acute or chronic hepatitis, and/or cirrhosis, and eventually lead to HCC. Extrahepatic metastases are seen in 64% of patients, while brain metastases from HCC are extremely rare, with a reported frequency ranging from 0.2–2.2%.[4-7] The interval between the diagnosis of primary cancer and the detection of a brain metastasis ranged from 2–54 months; the mean survival period was only 3 months after the diagnosis of brain metastasis. The attributed cause of death in patients with HCC with a metastatic brain is, therefore, neurological failure rather than hepatic failure.

CASE REPORT

This case report describes a 45-year-old male patient from Uttar Pradesh, India, who presented to the authors' medical outpatient department with a history of fever that had a usual duration of 1 day. Upon further evaluation, the patient also reported a history of headaches, tongue deviation towards the left side, hoarseness of voice, difficulty swallowing, and drooping of the left eyelid over the preceding 2 months. The patient also described a loss of appetite for the last 2 months, which caused them to lose approximately 20 kg of weight. He denied having any evidence of a pre-existing liver disease; however, he used to drink alcohol occasionally. He was a non-smoker and denied any usage of intravenous recreational drugs. The patient gave no history of chronic medical illness or any significant family history. He had not undergone any surgical procedures in the past or received any blood transfusions.

On physical examination, the patient appeared moderately built, poorly nourished, fully conscious with a Glasgow coma scale score of 15/15, and oriented to time, place, and person, with no cognitive impairment. He had presented with pyrexia on admission, with a body temperature of 101 °F, but displayed no pallor, icterus, clubbing, cyanosis, or oedema. On systemic examination, an abdominal examination revealed distension of the abdomen with no stigmata of CLD or any peripheral signs of hepatic failure. A respiratory examination revealed bibasilar crepitations. The cardiovascular examination was unremarkable.

A neurological examination revealed ptosis of the left eye, restricted left eyeball movement, left side soft palatal movement, dysphagia, hoarseness, and deviation of the tongue to the left side with left vocal cord palsy, which suggested that the patient had left III, IV, VI, IX, X, and XII cranial nerve palsies. Other cranial nerve examinations, sensory functions, motor functions, and cerebellar functions were all normal. The laboratory studies of the patient's blood that were undertaken on admission are seen in Tables 1 and 2. A serological examination for viral hepatitis, including hepatitis B and C, was negative, and the results from the iron panel test, renal function test, and electrolyte test were all normal.

A triple-phase abdominal CT scan of the liver was performed (including an arterial phase, a portal venous phase, and a late washout phase). The scan showed hepatomegaly with multiple hypodense irregular lesions, with the largest lesion in right lobe showing enhancement on arterial phase (Figure 1). The imaging and washout on portal venous phase (Figure 2) were suggestive of HCC with metastasis and CLD. The dilated portal vein appeared with an intraluminal filling defect in intra- and extra-hepatic segments involving both its branches, showing a post-contrast enhancement that was suggestive of portal vein thrombosis with portal hypertension and moderate ascites.

Table 1: Abnormal liver function test with a reference range.

Test name	Result value	Reference range
Total bilirubin	2.0 mg/dL	0.2–1.3 mg/dL
Direct bilirubin	1.14 mg/dL	0–0 mg/dL
Indirect bilirubin	1.08 mg/dL	0.00–1.00 mg/dL
	216 U/L	0–40 U/L
SGPT	98 U/L	0–50 U/L
Alkaline Phosphate	629 U/L	38–126 U/L
Serum albumin	2.8 g/L	3.5–5.0 mg/dL
PT/INR	14.0/1.7 sec	9.5–16.5/1.0 sec

INR: international normalised ratio; PT: prothrombin time; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase.

Table 2: Test values for alpha-fetoprotein, erythrocyte sedimentation rate, and D-Dimer with a reference range.

Test name	Result value	Reference range
Alpha-fetoprotein	65,000 IU/mL	<7 IU/mL
ESR	35 mm/hour	0–15 mm/hour
D-Dimer	>4 µg/L	0.0–0.5 µg/L

ESR: erythrocyte sedimentation rate.

An MRI scan of the brain (Figure 3) revealed a well-circumscribed, rounded lesion adjacent to the left cerebellopontine angle, abutting the medulla medially and causing mild compression over it. The enhancement that showed on post-contrast imaging was suggestive of a brain metastasis.

A high-resolution CT scan of the chest (Figure 4) revealed a hyperdense, well-circumscribed lesion with irregular margins in the posterior-basal segment of the left lower lobe peripherally, showing mild post-contrast enhancement that was likely to be suggestive of pulmonary metastasis.

DISCUSSION

HCC is one of the most common causes of cancer-related deaths worldwide.[8] The presence of brain metastases is associated with significant morbidity and mortality, and considerable research is focused on improving both the survival and quality of life of these patients. Brain metastases are most frequently diagnosed in patients with lung, breast, and melanoma primary tumours.[9] However, brain metastases from HCC is extremely rare, with a reported frequency ranging from 0.2–2.2% at autopsy.[5-8] The prognosis of the patients with a

Figure 1: Axial plan of an abdomenal CT scan in the arterial phase, showing an irregular iso-hypodense mass lesion (indicated by the white arrows) occupying the right lobe of the liver, with mild contrast enhancement

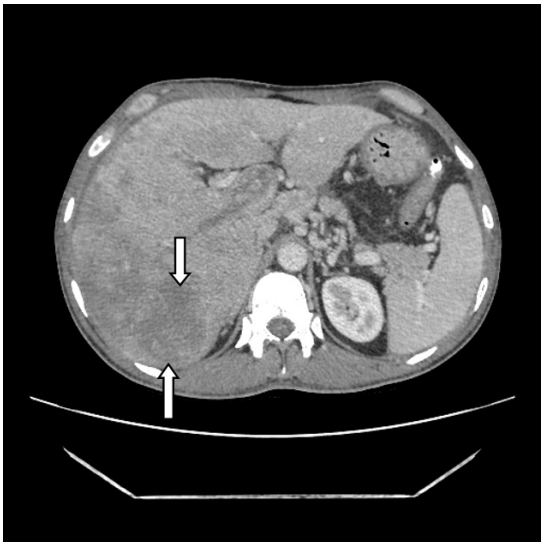
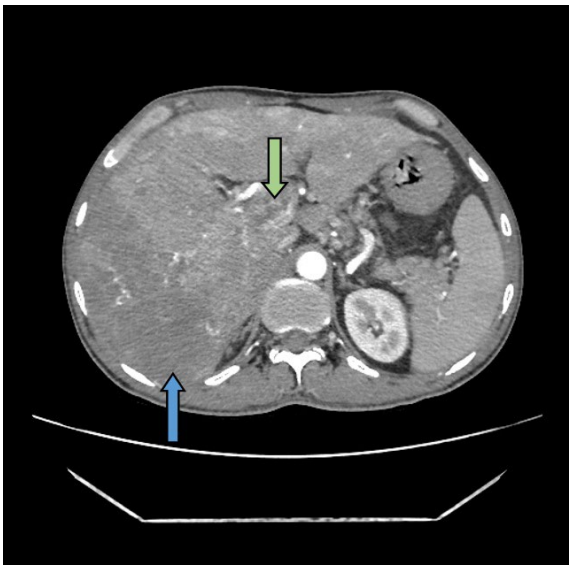


Figure 2: Axial plane of abdominal CT scan in the portal venous phase, showing washout from the mass lesion (blue arrow).



The proximal part of the portal vein is dilated, with an intraluminal filling defect showing post-contrast enhancement (green arrow).

brain metastasis is extremely poor, with a median survival of only 1–2 months.[5,10,11] To date, only a few studies from Asia, as well as some small studies from the USA and Europe, on brain metastases with HCC have been reported.[5,6,10-15]

In the present case, although a histological examination was not performed, the diagnosis was considered to be brain metastases from HCC, based on the following radiological and laboratory findings. Radiological diagnosis is achieved with a

Figure 3: This brain MRI axial section reveals a well-circumscribed rounded lesion (white arrow), adjacent to the left cerebellopontine angle, abutting the medulla medially, causing mild compression on it and showing enhancement on the post-contrast imaging, suggestive of a brain metastasis.

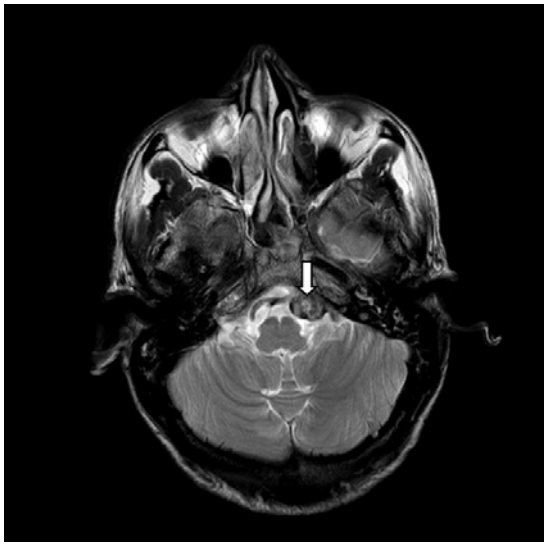
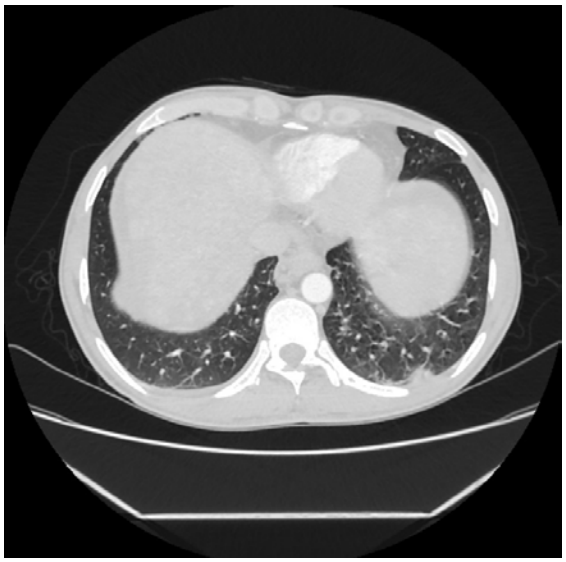


Figure 4: High-resolution chest CT revealing a hyperdense, well-circumscribed lesion with irregular margins in the posterior-basal segment of the left lower lobe peripherally, showing mild post-contrast enhancement, likely suggestive of a pulmonary metastasis.



high degree of confidence if the lesion is ≥2 cm in diameter and shows the radiological hallmarks of HCC by one imaging technique. Using contrast-enhanced imaging techniques, the typical hallmark of HCC is the vascular uptake of the nodule in the arterial phase with washout in the portal venous or delayed phases. This radiological pattern captures the hypervascular nature that is characteristic of HCC. In these scenarios, the diagnostic specificity is approximately 95–100% and a biopsy is not necessary.[16] Alpha-fetoprotein was taken as an accessory biomarker to aid the diagnosis of HCC. However, a liver biopsy could not be performed in the patient as they did not give consent, which was considered a limitation of the study.

In the patient case outlined here, the findings of the triple-phase abdominal CT scan and the extremely elevated levels of alpha-fetoprotein (60,500 IU/mL) suggest a diagnosis of HCC. Patients with HCC are assessed using the Barcelona Clinic Liver Cancer (BCLC) staging system, which incorporates the number and size of tumours in the liver, performance status, and liver function. A Child—Pugh score was used to assess the liver function, and an Eastern Cooperative Oncology Group (ECOG) score was used to determine performance status. The patient was determined to be at BCLC stage D, with a Child—Pugh score C, and an ECOG performance status of 3. Patients with BCLC stage D HCC, which is often referred to as terminal stage, have a median survival of less than 3 months[6,9,10] and can be offered palliative supportive care, as disease-directed treatments are not available for patients with terminal HCC. Palliative care should be offered early in order to meet the complex medical, social, and psychological needs of these patients.

CONCLUSION

HCC with brain metastases is a life-threatening condition due to the added risk of haemorrhage and the limited treatment options available. Since there is no standard therapeutic strategy available to date, an early diagnosis would certainly improve the chance of curative surgical resection, thus increasing survival in patients with unresectable tumours. The rarity of this presentation with no clinical signs of chronic liver stigmata should alert physicians to be diligent when they are confronted with an abnormal radiological liver finding. There are studies available on brain metastases caused by HCC; however, there are very few studies related to multiple cranial nerve palsies. This case report may, therefore, be of importance due to the rarity of this condition and the need to create awareness in order to prevent deaths from neurological causes in patients with HCC who have metastatic brain tumours.

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A Case Report on a Novel *PINK1* Gene Mutation in a Female with a Neurodegenerative Disorder

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Abstract

Introduction: Parkinson's disease (PD) is a progressive neurological disorder that affects both motor and non-motor skills in an individual. Both familial and sporadic cases of PD can be caused by mutations in the *LRRK2, PARK7, PINK1, PRKN*, or *SNCA* genes. However, mutations in genes *PINK1* and *LRRK2* are associated with early onset PD.

Case presentation: This study reports an 18-year-old female with early onset PD, where whole-exome sequencing showed a pathogenic missense variant p.R88W in the *PINK1* gene (NM_032409.2) resulting in the disease condition.

Conclusion: For cases like neurodegenerative disorders confirmed by an MRI or CT scan, it is always advisable to perform whole-exome sequencing or next-generation sequencing to detect the genes associated with the disease. Depending on the type of the symptoms, medication along with physical therapy can be advised to manage the condition.

Key Points

1. Mutations in *PINK1* are the most common genetic cause of autosomal recessive early onset Parkinson's disease.

2. These mutations result in mitochondria malfunctioning causing neurodegeneration through inflammation, apoptosis, and dendritic morphogenesis.

3. Comprehensive clinical diagnosis and advanced genetic testing procedures in neurodegenerative disorders will provide further evidence that can be used to understand the role of gene mutations in the aetiology of Parkinson's disease.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder attributed to the loss of dopaminergic neurons in the substantia nigra.[1] PD is considered to be the second most common neurodegenerative disease, affecting 4.6 million people worldwide.[2] Depending on the type of gene mutation, the inheritance pattern could be either autosomal dominant or autosomal recessive. The literature has shown 27 genes identified to be associated either with autosomal dominant, autosomal recessive, or with X-linked transmission.[3] However, *PINK1* mutations are the most common prevalent genetic cause of autosomal recessive early onset PD.[4,5]

The *PINK1* gene, located on chromosome 1 (*PARK6* locus), contains eight exons and encodes for a 581-amino acid protein that targets both mitochondrial and serine/threonine kinase domains, which were identified to be a cause of autosomal recessive PD.[6,7] The gene is, therefore, responsible for fine-tuning the network and energy metabolism of the mitochondria. It regulates parkin translocation in impaired mitochondria and drives their removal via selective autophagy.[2,8] The mutations in the *PINK1* gene result in the malfunctioning of the mitochondria, particularly when cells are stressed, causing neurodegeneration such as inflammation, apoptosis, or dendritic morphogenesis in humans.[9,10]

The purpose of the case study is to evaluate an 18-year-old female with an early onset neurodegenerative disease and a heterozygous gene mutation in the *PINK1* gene, which is reported here for the first time in India to the best of the authors' knowledge.

CASE PRESENTATION

History and Examination

An 18-year-old female, born to a non-consanguineous couple, was referred to the authors' institute for genetic evaluation. On clinical examination, the patient presented with left hand dystonia, progressive flexion contracture of the left hand and leg, difficulty writing, left hemi-dystonia, and left leg gait abnormality. Since the subject was 12 years old, their pupils have remained reactive to light and no Kayser–Fleischer rings have been observed under slit-lamp examination. MRI and CT scan evaluations showed normal reports. The levels of serum copper (136.5 µg/dL), serum ceruloplasmin (27.2 µg/dL), and urine copper (11.5 µg/day) were within normal range. Both parents of the index case and their sibling exhibited normal behaviour with no history of genetic disease.

Complimentary Examination

The index case was evaluated for whole-exome sequencing, using this massively parallel sequencing method to identify the molecular and genetic basis of suspected genetic conditions. Genomic DNA was enriched for the complete coding regions and splice site junctions of the genes of the specimen. Paired-end sequencing was performed with 2×100 and 2×150 chemistry on an Illumina platform (San Diego, California, USA). Reads were assembled and aligned to reference sequences based on National Center for Biotechnology Information (NCBI) RefSeq transcripts and the human genome build GRCh37 (hg19). Data was filtered and analysed to identify variants of interest and interpreted in the context of a single most damaging, clinically relevant transcript for the report, indicated as a part of variant details. Variant calling and filtering were performed by the OrionSeek algorithm (St. Louis, Missouri, USA), which is currently benchmarked to the Genome in a Bottle (GIAB) variant callset for these target regions.

Whole-exome sequencing results showed a heterozygous variant of uncertain significance with the *PINK1* missense variant p.R88W, which had not been previously reported as a pathogenic variant nor as a benign variant, to the authors' knowledge. The variant p.R88W was

observed in only two patients with early onset PD. These individuals presented in heterozygote form as per the genome aggregation database data (0.001%). Whole-exome sequencing details of the proband revealed the gene and transcript of PINK1 (NM_032409.2) at exon 1 location on chromosome 1p36.12, with a variant c.262C>T (p.Arg88Trp). This is classified as a heterozygous variant with an uncertain significance, inherited in an autosomal recessive inheritance pattern, leading to PD-6 with an early onset.

DISCUSSION

PD is the second most common neurodegenerative disease, affecting approximately 1% of people over 50 years of age worldwide.[11] During the fourth decade of life, the prevalence ranges from 41 per 100,000 people, compared with more than 1,900 per 100,000 for those 80 and above. PD is a long-standing progressive neurodegenerative disorder with the involvement of both genetic and non-genetic factors. It is outlined pathologically by the conspicuous and selective loss of dopaminergic neurons, projecting from the substantia nigra pars compacta to the striatum, and by the accumulation of intracytoplasmic proteinaceous inclusions known as Lewy bodies.[12] The present study revealed an unreported heterozygous mutation in the *PINK1* gene, causing impaired motor skills in the proband at an early age. The gene mutation at p.Arg88Trp in the *PINK1* gene of the proband may deregulate the protein synthesis, which could result in dopaminergic neuronal dysfunction.

The clinical features observed in the present study are in accordance with the earlier studies of Ibáñez et al.,[3] where flexion contracture of the left hand was reported. Valente et al.[4] observed that the *PINK1* gene is responsible for *PARK6*-associated autosomal recessive PD, with either a homozygous missense mutation (G309D) or a homozygous truncating mutation (W437X) in Spanish and Italian kindreds, respectively. A study by Gandhi et al.[13] indicated that the *PINK1* gene mutation in parkinsonism highlights two points: the molecular link between mitochondria and neurodegeneration in PD and the importance of the kinase signalling pathway in the pathogenesis of dopaminergic nigral cell death.[13]

Heterozygous mutations in genes causing autosomal recessive forms of parkinsonism (i.e., the DJ-1, parkin, and *PINK1* genes) have been identified in cases of sporadic PD where their contribution to disease causation remains unclear. Abou-Sleiman et al.[14] have identified heterozygous mutations in the *PINK1* gene in sporadic PD cases with a higher frequency than in control groups. One important hypothesis is that heterozygous mutations may have a functional effect on the encoded protein as a result of haploinsufficiency. Earlier studies have emphasised that PET scans of clinically unaffected relatives of cases who carry heterozygous mutations in the *PINK1* gene revealed a reduction of 18F-dopa uptake in their nigrostriatal neurons, indicating a degree of dopaminergic dysfunction.[15] Thus, it appears that the presence of a heterozygous mutation of the *PINK1* gene in the proband can exert a functional effect on the PTEN-induced kinase 1 protein and subsequently on dopaminergic neuronal dysfunction.

In a study conducted by Ibáñez et al.,[3] the mutation analysis of 177 cases for both *PINK1* and parkin gene mutations in Europe and North Africa for early onset PD revealed 7 cases with *PINK1* gene mutations with an early onset of the disease, and 90 cases with parkin gene mutation, which was reported to appear in the third decade of life. In comparison, the phenotypic representation of the individuals is similar for both of the gene mutations, except for that of the age of onset.[3] The symptoms observed in the proband may be due to the deregulated expression of the *PINK1* gene, resulting in the neurodegenerative disorder PD-6.

CONCLUSION

The study suggests that comprehensive clinical diagnosis, along with advanced genetic testing procedures in neurodegenerative disorders, will provide further evidence that can be used to understand the role of known and novel gene mutations in the aetiology of PD. Further treatment strategies can then be employed based on the obtained gene mutations, which may also help in offering genetic counselling.

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