EMJ NEUROLOGY

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+ EAN CONGRESS 2020

Reviewed

+ EDITOR'S PICK

Current Paradigms to Explore the Gut Microbiota Linkage to Neurological Disorders

+ ABSTRACT REVIEWS

Reviews of abstracts presented at EAN 2020 covering topics such as oligonucleotide therapies, telemedicine, and novel tools for disease monitoring.

+ INTERVIEWS

Prof Claudia Sommer speaks about her role as Chair of the EAN Teaching Course Sub-Committee, and Prof Michael Barnes discusses medicinal cannabis for neurological disorders.

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"Within the following pages we have accumulated what we believe are the most important and innovative developments from across the neurological field."

Spencer Gore, CEO

Editorial Board

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Aims and Scope

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

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

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EMJ Neurol.

Welcome

It is with great pleasure, humility, and honour that I welcome you, our readers, to this year's issue of *EMJ Neurology*. Within the following pages we have accumulated what we believe are the most important and innovative developments from across the neurological field.

Prepare yourselves for peer-reviewed articles, exclusive interviews, our congress review from the 6th Congress of the European Academy of Neurology (EAN), as well as summaries of abstracts presented virtually at EAN.

Peer-reviewed articles in *EMJ Neurology 8.1* cover the topics of the gut microbiota linkage to neurological disorders, treatment of meningitis and encephalitis, and clinical controversies in amyotrophic lateral sclerosis.

Despite the EAN congress having to be conducted virtually, the standard of the scientific programme was second-to-none and our editorial team at EMJ thoroughly enjoyed attending the event. If you missed the congress, or could not make it to several sessions, we have our comprehensive congress review enclosed within this eJournal. Summaries of the sessions "EAN/[American Academy of Neurology]AAN Session on COVID-19" and "The Neurological Implications of COVID-19" are both included in our write-up, as well as key information and updates on the effects of increased risk of repeat stroke with disturbed sleep, medical students increased use of psychostimulants, and how research into 2,149 epilepsy-related deaths could lead to changes in epilepsy care.

Complementing our EAN review, we have a special congress interview with Prof Claudia Sommer who discusses with us her Presidency of the German Pain Society, her responsibilities as Chair of the EAN Teaching Course Sub-Committee, and COVID-19 and the possibility of the neuroinvasive potential of the virus.

In the current medical climate, we are well aware that many of our readers, editorial board members, and authors are all working tirelessly on the front-line to ensure patients are given the care and treatment they need during this time. I would like to thank you all for all that you do, and I hope that you all are able to learn from the contents of the journal.

Spencer Gore

Chief Executive Officer, EMG-Health

Foreword

Dear Friends and Colleagues,

The unexpected start to 2020 set the year to be one of uncertainty, but the spirit exuded from those on the frontline directly treating patients with COVID-19 and those supporting from the sidelines has been inspirational. Scientific collaboration has been crucial in elucidating the clinical aspects of COVID-19, many of which have neurological implications. It is therefore with great pleasure that I introduce to you *EMJ Neurology 8.1*, a journal that actively supports collaboration across the field to facilitate progress in neurology.

The inability to hold physical medical congresses could not stop the European Academy of Neurology (EAN) from hosting a magnificent event. The scientific programme was rich in sessions presenting the innovative developments made over the last year. On the following pages, you can find the congress review of EAN; inside contains news stories covering the biggest news from the event, a collection of summaries of excellent abstracts presented at the congress, and a feature on what is known so far about the neurological implications of COVID-19.

Staying on the topic of EAN, you can also find an interview with Prof Claudia Sommer, in which she discusses her role as the Chair of the EAN Teaching Course Sub-Committee and provides insights from her area of expertise, pain pathophysiology. Another interviewee featuring in the journal is Prof Michael Barnes, CMO of Lyphe Group and Chair of The Medical Cannabis Clinicians Society (MCCS). Prof Barnes was instrumental in the obtainment of the first prescription of medicinal cannabis-based products in the UK.

My Editor's Pick for this year's issue is Sharma et al. "Current Paradigms to Explore the Gut Microbiota Linkage to Neurological Disorders." It was found that the metabolites produced by gut microbiota are often perturbed as a result of neurological disorders. The review focusses on the impact of altered gut microbiota on brain functions. Therefore, better understanding of the difficult mechanisms underlying the gut–brain axis is very important for clinical practice.

Articles included cover a spectrum of neurological disorders: Smail and Simon delineate the evidence surrounding clinical controversies in amyotrophic lateral sclerosis and Bowers and Mudrakola provide an overview of the presentation, diagnosis, and treatment of neuroinfections.

I hope you all enjoy reading *EMJ Neurology 8.1*, an issue which I believe to be of interest to you all.

Professor László Vécsei

University of Szeged, Szeged, Hungary

Congress Review

Review of the European Academy of Neurology (EAN) Virtual Congress 2020

Location: EAN Virtual Congress 2020

Date: 23rd May – 26th May 2020

Citation: EMJ Neurol. 2020;8[1]:10-18. Congress Review

This year, the 6th Annual Meeting of the European Academy of Neurology (EAN) took place virtually as a result of the ongoing COVID-19 pandemic. The hard work that the academy invested behind the scenes was proven by the quality of the platform, which was built in an expeditious 8 weeks. An impressive 42,000 people from over 150 countries registered to attend the congress, making it the largest neurological meeting in history. Registration fees were waived for this year's congress, making the meeting even more accessible to those eager to learn the latest in neurology.

The opening ceremony commenced with an inspirational message: "In a time when the world is facing an unprecedented storm, solidarity becomes crucial and our humanity is more important than ever. Together we will adapt, overcome, find new ways, and use today's technologies to share our ideas wherever we are. This is a changing time. A time full of challenges, new opportunities, forward thinking, love, community, and dedication, for a future that is ours to shape." Acting President Prof Claudio Bassetti then introduced attendees to the ceremony, wishing the EAN President Prof Franz Fazekas good health after he was taken ill earlier in the year. Among Prof Bassetti's many encouraging words in the opening ceremony, he said: "Difficult times ask for creative and courageous decisions, which may open new avenues for a better future."

Prof Yann LeCun, considered to be one of the founding fathers of artificial intelligence and deep learning, delivered the opening lecture. In this he explained that: "Deep learning has its root in neuroscience; people in the '40s and '50s were inspired by the brain to design machines that were capable of learning." Adding to this, he commented that the type of model that is currently very popular is called artificial neural networks (i.e., deep learning), the structure of which is often likened to the brain with simple elements and weights being the equivalent of neurons and synapses, respectively.

The presidential symposium was delivered by the three respective award winners. The Moritz Romberg Lecture was presented by Prof Giorgio Cruccu, in which he discussed the pathophysiology of pain and the importance of being familiar

with it to effectively treat patients. Prof Steven Laureys delivered The Charles-Édouard Brown-Séquard Lecture, in which he described the current understanding of chronic disorders of consciousness and challenged the outdated view that consciousness is all or nothing. Finally, the Brain Prize Lecture given by Prof Hughes Chabriat detailed the journey that led to the discovery of CADASIL and our understanding of the disease today.

The overarching theme of the congress this year could not have been more relevant: "Time for Action: Predict, Prevent, Repair." Presentations throughout the congress captured the importance of the theme, but in particular the plenary session covered the role of inflammation in stroke prevention, the basic science and clinical care for the prevention of disability progression in multiple sclerosis, the evidence surrounding when is best to perform surgery in patients with epilepsy, and halting neurodegeneration and inducing repair in Huntington's disease.

Dissemination of breakthroughs in neurology was further achieved by the delivery of over 300 sessions, more than 1,000 posters, and the EAN Brain Challenge, all of which covered the big seven: epilepsy, stroke, headache, multiple sclerosis, dementia, movement disorders, and neuromuscular disorders.

In the opening ceremony, Prof Bassetti commented that the success of the virtual congress may lead to the consideration of hybrid congresses in the future, providing the opportunity for those that are not able to attend the face-to-face meeting to still attend the sessions online around the world. We look forward to being able to attend what will sure to be another great meeting next year in Helsinki, Finland; until then, please enjoy the following review of EAN's 2020 Virtual Meeting.

"Deep learning has its roots in neuroscience; people in the '40s and '50s were inspired by the brain to design machines that were capable of learning."

EAN VIRTUAL CONGRESS 2020 REVIEWED →

Increased Risk of Repeat Stroke with Disturbed Sleep

DISTURBED sleep–wake cycles following stroke can contribute to the risk of recurrent stroke. Complications following stroke can commonly include sleep–wake disturbances, however a Swiss study presented at the European Academy of Neurology (EAN) virtual congress showed that those patients with sleep–wake disturbances post-stroke have an increased risk of repeat stroke or other cardio-cerebrovascular events in the 2 years following their stroke.

Sleep–wake disturbances complicate post-stroke recovery for many patients, such as insomnia, restless leg syndrome, sleep-disordered breathing, or extreme long or short sleep duration. More than one-third of patients in a study in Switzerland met criteria for insomnia, 26% were found to have sleep-disordered breathing, 8% met criteria for restless leg syndrome, and approximately 15% reported longer sleep duration. These sleep–wake disturbances were collated to describe a 'sleep burden index' for each patient. Those with a high sleep burden index were more likely to have a cerebro-cardiovascular event in the 2 years post-stroke (odds ratio: 2.10 per index unit, 95% confidence interval: 1.34–3.30, $p<0.01$).

The study of 438 patients aged 21–86 years followed these patients for 2 years after acute ischaemic stroke or transient ischaemic attack. The study assessed sleep-disordered breathing in the immediate post-stroke period with respirography, collated symptoms of sleep disturbance at 1, 3, 12, and 24 months, and tracked rates of cardio-cerebrovascular events over the 2 years.

Dr Martijn Dekkers and Dr Simone Duss from the University of Bern, Bern, Switzerland explained the background to their study: "We know that people who have had a stroke often experience sleep disorders, and that these are associated with worse stroke recovery outcomes." They went on to explain the intent behind their study: "What we wanted to learn from this study was whether sleep–wake disturbances in particular are associated with worse outcomes after stroke."

These findings further the understanding that sleep disturbances are common complications for patients following ischaemic stroke and should be considered in their comprehensive management. Identifying the increased risk of recurrent stroke or cardio-cerebrovascular event associated with these sleep–wake disturbances is a first step. Future studies could determine the value of assessment and improvement of sleep patterns for potentially reducing the risk of recurrent stroke or improving long-term outcomes following stroke.

Those with a high sleep burden index were more likely to have a cerebro-cardiovascular event in the 2 years post-stroke

Social Isolation Can Increase Cardiovascular Events by Over 40%

"This observation is of particular interest in the present discussion on the COVID-19 pandemic, where social contacts are or have been relevantly restricted in most societies."

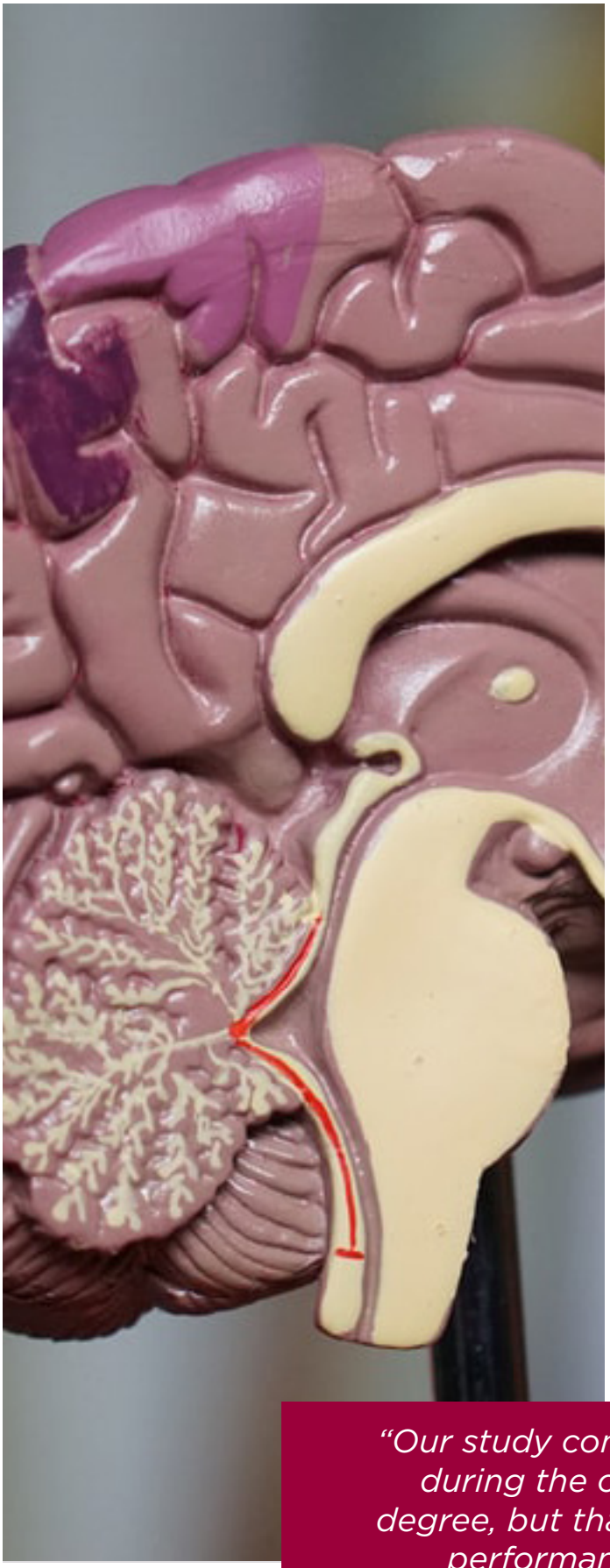
SOCIAL isolation has been linked to an increase in the risk of heart attacks, strokes, and death from all causes, according to an EAN press release dated 22nd May 2020. The study was led by Dr Janine Gronewold and Prof Dirk Hermann of the University Hospital in Essen, Germany, which found that those who are socially isolated are almost 50% more likely to die from any cause and over 40% more likely to have a cardiovascular event.

In total, 4,316 individuals, with an average age of 59.1 years, were involved in the Heinz Nixdorf Recall study, and were followed-up for an average of 13.0 years. None of the study participants entered the trial with known cardiovascular disease and data were collected initially on the types of social support they received, as well as their marital status and cohabitation, contact with close friends and family, and membership of community organisations.

Analysing the study data revealed that 339 cardiovascular events, such as heart attacks and strokes, occurred during the follow-up, alongside 530 deaths. The researchers adjusted for standard cardiovascular risk factors that could have contributed to these events and the results showed that a lack of social interaction was associated with increases in future risk of cardiovascular events by 44% and risk of death from all causes by 47%. An additional finding was that lack of financial support was linked to an increase of risk of cardiovascular events by 30%. Dr Gronewold remarked that strong social relationships play a similar role to "classical protective factors such as having a healthy blood pressure, acceptable cholesterol levels, and a normal weight."

Prof Karl-Heinz Jöckel, a co-author of the study, noted the importance of these findings in the current climate: "This observation is of particular interest in the present discussion on the COVID-19 pandemic, where social contacts are or have been relevantly restricted in most societies." The researchers disclaim that they do not yet understand why socially isolated individuals have poorer health outcomes, but that by effectively increasing social interaction we can improve overall health and longevity.

Medical Students Are Increasingly Using Psychostimulants



PSYCHOSTIMULANT use by medical students who are in training is reportedly widespread and increasing, according to a study conducted by a team of researchers from the Istanbul Science University, Istanbul, Turkey, and presented in a press release at EAN dated 24th May 2020.

In the study, 194 medical students completed an online survey which included questions that evaluated their use of stimulants and the side effects they experienced, in addition to their academic performance grades. The results from the students in their first year of study (n=93; control group) were compared with those in their fourth, fifth, and sixth year of study (n=101; study group).

Dr Suna Ertuğrul, Istanbul Science University, explained that over the last two decades, university campuses have been concerned about the non-medical use of prescription stimulants. Dr Ertuğrul commented that: "Medicine is one of the longest and most competitive degrees to study for and many students believe that using stimulants helps to enhance their academic performance and live an active life."

Psychostimulants, such as methylphenidate and modafinil, were used by 16.1% of those in the study group, compared with 6.8% of the control group. Side effects including insomnia, high heart rate, and agitation were reported in three-quarters of the study group. There were no differences in the academic performance between the groups, a notable finding given the common belief that psychostimulants would improve academic outcome.

Dr Ertuğrul summarised by saying: "Our study confirms that stimulant use increases during the course of studying for a medical degree, but that this does not improve academic performance as these students believe."

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Research into 2,149 Epilepsy-Related Deaths Could Lead to Changes in Epilepsy Care

REASONS for the higher risk of early death faced by patients with epilepsy are currently unclear. This chronic disease affects 50 million individuals worldwide and can cause seizures and confusion, and patients often experience stigmatisation and discrimination. The Scottish Epilepsy Deaths Study (SEDS) aimed to identify the burden of potentially avoidable epilepsy-related deaths and found that mortality rates for epilepsy-related deaths did not decrease between 2009 and 2015. This is according to findings presented at the EAN Virtual Congress in a press release dated 25th May 2020.

The study suggested that there remains an increased risk of epilepsy-related deaths in young adults despite new developments in treatment of the disease. Exposing preventable risk factors could lead to advancements in epilepsy care with the long-term goal of reducing total number of deaths from epilepsy. The researchers identified 2,149 epilepsy-related deaths between 2009 and 2016. The mortality rate for these deaths in 2009 was 6.8 per 100,000, while in 2015 the mortality rate was calculated to be 9.1 per 100,000. Young adults in their early 20s and 30s were at the highest risk of death, and those aged 16–24 years had a six-fold increased risk of mortality. Of the epilepsy-related deaths under the age of 55 years, 78% were considered to be potentially avoidable. In the years before their death, most patients (n=1,276) had a seizure- or epilepsy-related incident resulting in hospital admission; however, only 516 patients were cared for in a neurology clinic. Sudden unexpected death in epilepsy, aspiration pneumonia, cardiac arrest, congenital malformation, and alcohol-related deaths were among the most common causes of death reported in the study. This research is a breakthrough of epilepsy care and will help to identify which factors most place patients at risk of death; the data will be compared with living patients with epilepsy of the same age and sex to achieve this.

Dr Gashirai Mbizvo, one of researchers from the study conducted at The University of Edinburgh, Edinburgh, UK, outlined his ambition for the trial: "We hope that we can use this data to learn lessons and reduce the burden of epilepsy-related deaths in the future, many of which we believe are likely to be avoidable."

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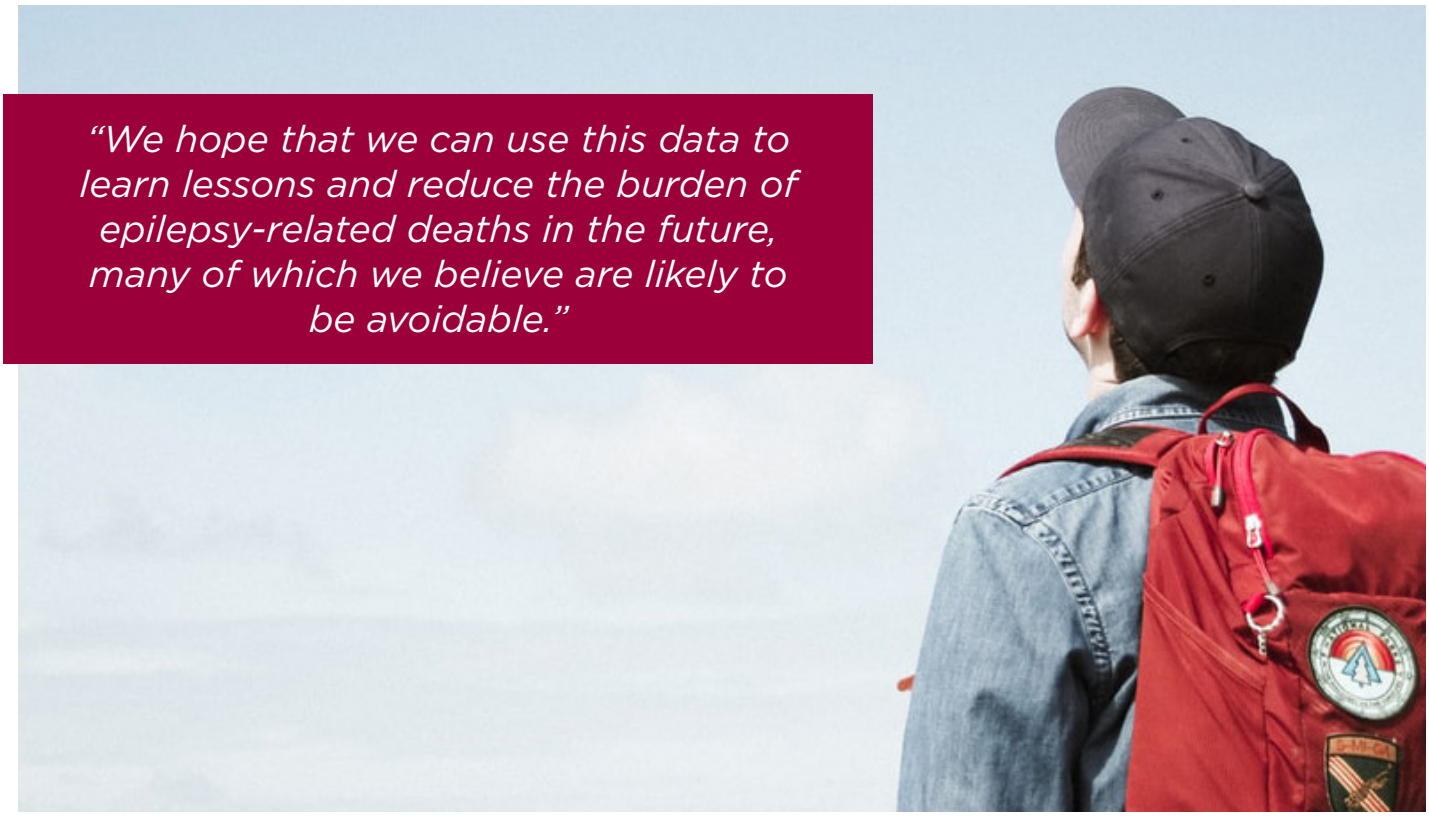


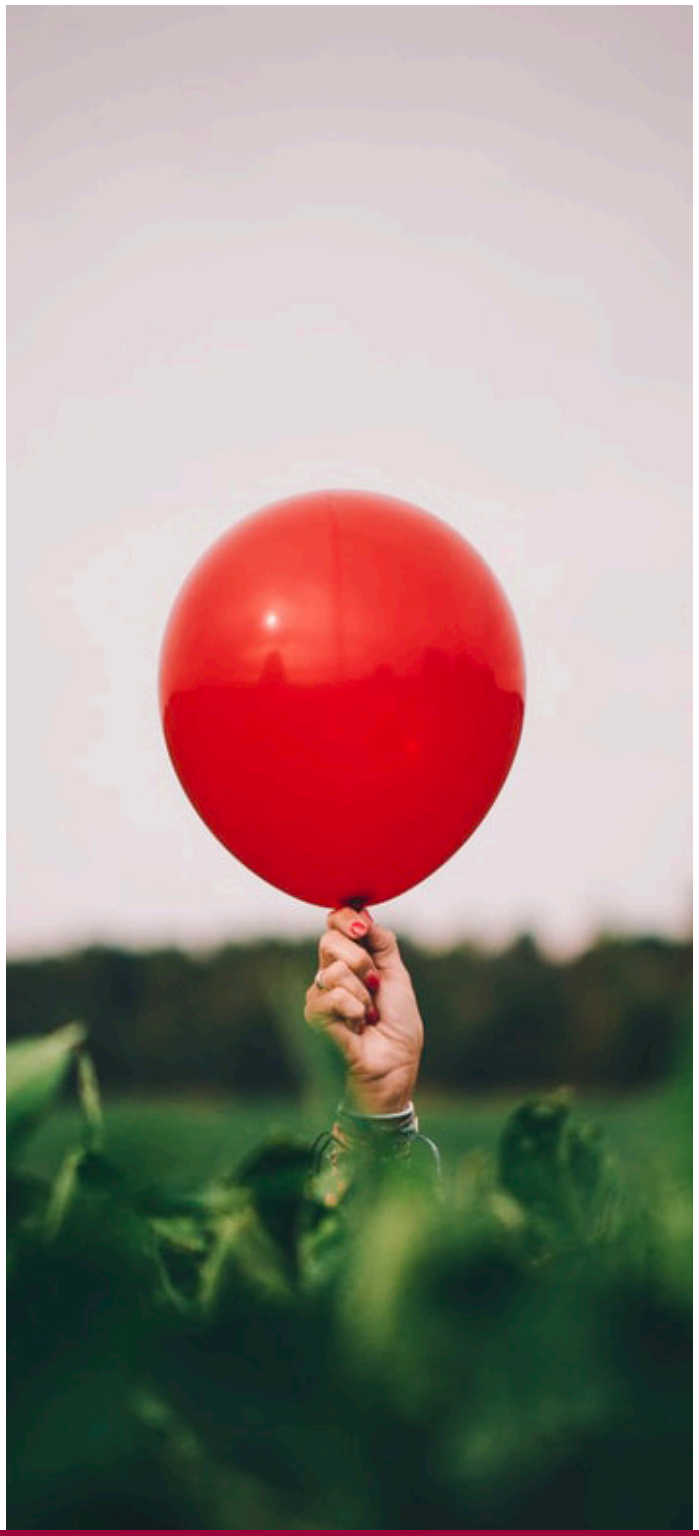
Recreational Use of Laughing Gas is Associated with Neurological Issues

LAUGHING GAS, or nitrous oxide, is used as an anaesthetic agent in dental practice and during labour. However, its use recreationally is increasing, with growing numbers of patients reporting to specialists and emergency rooms with neurological issues associated with its use, according to a study from the Netherlands and stated in a press release from EAN 2020 dated 24th May.

The study conducted by Zuyderland Medical Center, Heerlen, the Netherlands, included 13 patients who had been treated at the centre between 2017 and 2019. The average age of the patients was 21 years. Paraesthesias (tingling and numbness in the hands, legs, arms, and feet) and weakness in the lower limbs were the most common symptoms reported by the patients. The clinical diagnosis of axonal polyneuropathy was made in eight patients (62%), while two patients (15%) demonstrated evidence of spinal cord degeneration, and three (23%) showed clinical symptoms of both conditions. Vitamin B12 supplementation was given to all patients, and they were advised to stop using laughing gas.

Dr Anne Bruijnes, Zuyderland Medical Center, the presenter of the study, commented that in their neurological practice they are seeing an escalating number of patients with neurological problems from recreational use of laughing gas. Dr Bruijnes added that although most of their patients make a full recovery, some patients continued to experience minor symptoms and three had difficulties carrying out everyday activities and had to be referred to rehabilitation physicians.

An important factor in the increasing use of laughing gas is that many users are unaware of the potential consequences, which can also include paranoia, breathing problems, and even death. Dr Bruijnes concluded: "Whilst this study is on a relatively small sample, we know that laughing gas use is on the increase. We now know that it causes a vitamin B12 deficiency, which can affect the spinal cord and lead to permanent damage if not treated promptly."



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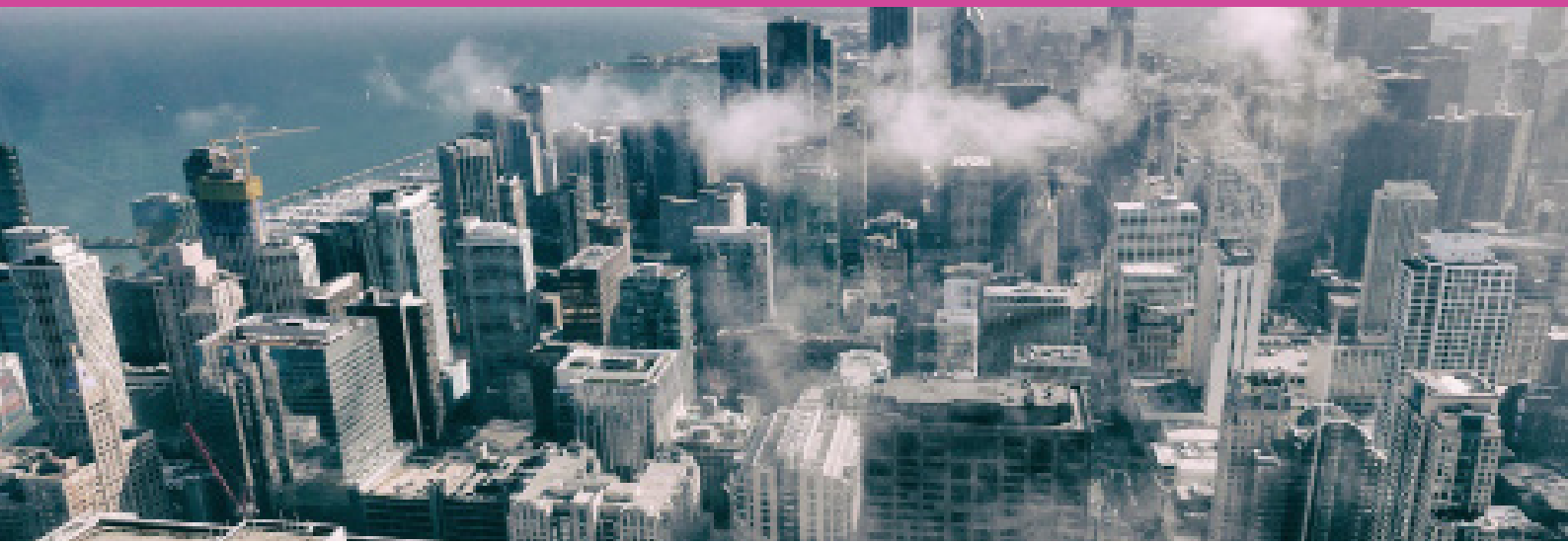

Association Between Urbanisation and the Increased Risk of Multiple Sclerosis

VARIOUS genetic and environmental risk factors have been studied extensively and associated with the development of multiple sclerosis (MS). Environmental factors at the centre of research include vitamin D levels and smoking; however, according to findings from an Italian study presented in a press release at EAN 2020 Virtual dated the 23rd May, air pollutants may be a risk factor for MS.

"In the higher risk areas, we are now carrying out specific analytical studies to examine multiple environmental factors possibly related to the heterogeneous distribution of MS risk."

The study results suggested that air pollution interacts through several mechanisms in the development of MS, therefore the researchers recruited a study sample of over 900 MS patients in Lombardy, Italy. Within the region, winter is the season with the highest pollutant concentration so the analysis was conducted then. According to the World Health Organization (WHO), 4.2 million deaths are attributed yearly to ambient air pollution. Particulate matter (PM), the sum of all solid and liquid particles suspended in air, can be divided into two categories; PM_{10} and $PM_{2.5}$, which include particles with a diameter of ≤10 µm and ≤2.5 µm, respectively, are both considered major pollutants and have been previously linked to heart and lung disease, cancer, and respiratory issues.

The analysis compared three different areas within the Lombardy region based on their levels of urbanisation and found that two were above the European Commission threshold for air pollution. The study further revealed that MS rates in the region rose from 16 cases per 100,000 inhabitants in 1974 to approximately 170 cases per 100,000 inhabitants today. Although this increase could be a result of the improved survival rates for MS patients, it may also be linked to greater exposure to risk factors. The study correlated a reduced risk for MS in individuals residing in rural areas that have lower levels of PM, and showed that the MS risk, adjusted for urbanisation, was 29% higher among individuals living in more urbanised areas.

According to lead researcher Prof Roberto Bergamaschi, these findings support the hypothesis that air pollutants are involved in the development of MS. He further noted: "In the higher risk areas, we are now carrying out specific analytical studies to examine multiple environmental factors possibly related to the heterogeneous distribution of MS risk." With the number of people affected by MS growing globally, findings from these future studies may provide a better insight into the prevention and management of the disease.

COVID-19-Associated Neurological Manifestations

Layla Southcombe
Editorial Assistant, EMJ

Citation: EMJ Neurol. 2020;8[1]:19-21.

SINCE the first observations of neurological manifestations were reported in China in April 2020, concerns over the impact of COVID-19 on the nervous system have been growing. Evidence has been mounting, with many clinicians publishing case reports of their patients who had exhibited a variety of neurological complications associated with the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus. In a bid to collate and summarise the findings to date, the European Academy of Neurology (EAN) held two sessions at the 2020 EAN Virtual Congress specifically dedicated to the neurological manifestations of COVID-19.

SYMPTOMS AND PREVALENCE

Preliminary data from published papers suggest that the presence of neurological manifestations in hospitalised patients with COVID-19 was relatively frequent, with a reported prevalence of 36.4%, which increased in those with severe COVID-19.[1] In the first session titled "EAN/AAN Session on COVID-19," Prof Elena Moro from Grenoble Alpes University, Grenoble, France, presented the preliminary results from registries and surveys recording the neurological implications associated with COVID-19 across Europe. Of note, the most frequent neurological manifestations are headache, anosmia (loss of the sense of smell)/ageusia (loss of taste function), cerebrovascular events, and encephalopathies, with many others having been reported.

DIRECT CENTRAL NERVOUS SYSTEM INFECTION

In the second COVID-19-dedicated session "The Neurological Implications of COVID-19," Prof Renaud Du Pasquier from Lausanne University Hospital, Lausanne, Switzerland, explained that SARS-CoV-2 binds to the receptor angiotensin-converting enzyme-2 (ACE-2) via its spike protein. Prof Du Pasquier later provided mRNA-based evidence that ACE-2 is present in the brain, suggesting that there is a possibility that cells of the central nervous system (CNS) can be infected with SARS-CoV-2.[2]

The olfactory nerves have been hypothesised to be one potential SARS-CoV-2 entry route into the CNS. Prof Du Pasquier commented that: "The high number of COVID-19 patients with anosmia clearly suggests that this virus has a tropism for this part of the brain." He added that there would be more evidence of CNS infection in patients with SARS-CoV-2 if this were the predominant mechanism, acknowledging that there have been limited reports of cerebrospinal fluid being positive for SARS-CoV-2 in patients with COVID-19-associated neurological manifestations.

The consequences of such direct SARS-CoV-2 CNS infection have emerged as encephalitis and meningoencephalitis, and potentially myelitis. Prof Du Pasquier exemplified the possibility of psychiatric symptoms in patients positive for SARS-CoV-2 in a case of a 64-year-old woman who presented to his clinic with acute psychotic

symptoms despite having no psychiatric history. After a full work-up and positive nasopharyngeal swab for SARS-CoV-2, the manifestation was diagnosed as meningoencephalitis, most likely related to COVID-19.

INDIRECT INFECTIOUS EFFECTS ON THE CENTRAL NERVOUS SYSTEM

Hypercoagulable states in patients with COVID-19 have been reported at alarming frequencies, with many resulting in the occurrence of stroke, even in those without any cerebrovascular risk factors. This hypercoagulability is thought to be a result of the activation of inflammatory and thrombotic pathways from SARS-CoV-2 interaction with ACE-2 on endothelial cells, evidenced by pathology studies shown by Prof Moro.

In an autopsy study of 12 patients who died from COVID-19, Prof Du Pasquier highlighted that more than seven had undiagnosed deep vein thrombosis and that four died as a direct result of pulmonary embolism.[3] There is clearly a trend towards a procoaguable state, he commented, which puts patients at a high risk of stroke. Prof Kenneth Tyler from the University of Colorado School of Medicine, Denver, Colorado, USA, a speaker in the first session, presented studies that reported a delay in cerebrovascular event occurrence, which happened 8–24 days after the onset of COVID-19 symptoms.[4]

In mild COVID-19, the virus is rapidly cleared by the immune response and the infection is contained; however, in severe disease the viral clearance is suboptimal and a proinflammatory response takes place. Instead of a direct infectious effect of the virus, this SARS-CoV-2-triggered mass release of proinflammatory cytokines such as IL-6, IL-β, and TNFα, the so-called cytokine storm, is another possible cause of the meningoencephalitis seen in patients with COVID-19. A Kawasaki-like disease associated with COVID-19 has also been reported. Prof Tyler presented a published case series in which two patients also had neurological symptoms, mostly in the form of meningeal symptoms.[5] Prof Tyler added: "This raises the possibility that there are going to be new syndromes emerging with COVID-19 that we haven't yet covered, potentially including vasculitic ones."

POST-INFECTIOUS NERVOUS SYSTEM COMPLICATIONS

Guillain-Barré syndrome (GBS) is an immune-mediated neurological complication that can occur following infection. Numerous small case series on GBS associated with COVID-19 have already been published, but Prof Tyler highlighted one article specifically, in which five patients developed a clinical syndrome compatible with GBS 5–10 days after COVID-19 symptom onset.[6] He added that further post-infectious complications have been reported, such as acute disseminated encephalomyelitis and acute haemorrhagic necrotising encephalopathy, but these have been single case reports.[7,8]

"We learned a lot, but much more is to be learned."

indirect infectious manifestations, whether these complications can be treated in similar fashions to other neuroinvasive and neurotrophic infections, and if there is brainstem involvement in the worsening of acute respiratory distress syndrome.

"This raises the possibility that there are going to be new syndromes emerging with COVID-19 that we haven't yet covered, potentially including vasculitic ones."

Resources like the EAN Survey on Neurological Symptoms in Patients with COVID-19 could help characterise these neurological manifestations and quantify their prevalence. What all the presenters and chairs agreed upon was perfectly encapsulated by Prof Claudio Bassetti, the EAN Acting President and chair of the first session, who gave the closing remark: "We learned a lot, but much more is to be learned."

Prof Du Pasquier also supported the existence of GBS associated with COVID-19 and presented a case from his clinic in which the patient was diagnosed with severe GBS, a type of acute inflammatory demyelinating polyneuropathy, which occurred in the wake of COVID-19 infection. Prof Du Pasquier commented on the likelihood of GBS in patients infected with SARS-CoV-2: "It is not surprising. Indeed, it is usual to see GBS after infectious viral disease."

SUMMARY

From the presented data, along with the plethora of published cases, it is evident that there are numerous neurological complications associated with SARS-CoV-2 infection. There is still speculation about the ratio between direct and

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Congress Interview

Professor Claudia Sommer

University of Würzburg, Würzburg, Germany
Chair of the European Association of Neurology (EAN) Teaching Course Sub-Committee

Q1 You started your career studying medicine, now you are an expert neurologist. What were the reasons that prompted you to specialise in neurology?

I was always fascinated by the nervous system. When I stared studying medicine, my motivation for this was to go into brain research. Later, I learnt that working with patients, trying to decipher their diseases, and finding treatments was a fascinating task. So, I combined my interest in the nervous system with my wish to work with patients, and I became a neurologist and a neuroscientist.

Q2 One of your key areas of expertise includes the pathophysiology and treatment of pain. What is it about this field of research that interests you?

When you study pain, you can study the entire nervous system, from the very distal nociceptors in the skin, over the afferent tracts in the spinal cord, and to the pain-processing areas in the brain, also the psychological underpinnings and consequences. Additionally, almost every human being knows pain, it is a very prevalent problem.

Q3 You recently co-authored the paper 'Pain-related evoked potentials in patients with large, mixed, and small fiber neuropathy,' what were the main findings from this research?

Classical neurophysiology tests the large nerve fibres, the Aβ fibres, and motor neurons. Pain is transmitted by the small unmyelinated C fibres and the thinly myelinated Aδ fibres. Pain-related evoked potentials are a method to evaluate the function of Aδ fibres and their afferent connections. Thus, they are a great tool to find out whether, in any condition, Aδ fibres are affected. Here, we found that in what we clinically consider as a large fibre neuropathy, Aδ fibres were also damaged. We also used this tool in our research on fibromyalgia, a chronic pain condition. The Aδ fibre potentials are greatly affected in this condition, even though fibromyalgia is not usually considered a neurological disease.

Q4 As the President of the Deutsche Schmerzgesellschaft e.V. (German Pain Society), could you delineate what your role entails and what the associations main objective is?

The Deutsche Schmerzgesellschaft e.V. is the scientific society in Germany for everyone studying or treating pain, and a Chapter of the

What I would like to achieve is that every participant who joins a teaching course finishes it really having learnt something that will help them in their clinical practice or research.

International Association for the Study of PAIN (IASP). We are an interdisciplinary association, and our aim is to bring together specialists from all disciplines to improve patient care. For example, we provide information for patients and caregivers, we foster pain research, support young pain researchers and clinicians, work on guidelines, and organise an annual congress and a range of other regular activities to enhance the visibility of the problem of pain in society.

Q5 The Deutsche Schmerzgesellschaft e.V. aims to further extend their partnership networks. As the president of the association, could you tell us about plans you have put in motion to achieve this?

We have networks with all related medical-scientific societies in Germany, for example with the German Neurological Society (DGN), the Anesthesiology Society (Deutsche Gesellschaft für Anästhesiologie & Intensivmedizin [DGAI]), and many more. Delegates from the societies form our "Fachbeirat," i.e., an advisory board that gives counsel to our leadership from the points of view of each speciality. Of course, we network with the patient associations in Germany and across Europe.

Q6 What responsibilities does the EAN Teaching Course Sub-Committee have, and how does this fit into the bigger picture of EAN's goals?

The EAN Teaching Course Sub-Committee has several tasks. One is to plan the teaching courses, and this includes all the different formats at the annual EAN Congress. This is a major endeavour, in particular because we try to harmonise the teaching course content with the core curriculum of the European Board of Neurology (EBN), the knowledge that is required to pass the European Board exam in neurology. However, we are also in charge of the spring schools, autumn schools, EAN days, and other different educational formats that are spread out over the European countries over the course of the year, including the sub-Saharan Africa regional teaching course. Furthermore, we oversee the clinical fellowships and research fellowships.

Q7 In your role as Chair of the Teaching Course Sub-Committee of EAN, what is the biggest achievement you wish to accomplish during your term?

During my term, we introduced a number of innovative course formats, such as the interactive sessions, the case-based workshops, and we

greatly increased the number of hands-on courses. I am also very proud of our big quiz, the Brain Challenge, in which two teams, one from the host country and one entirely international, compete against each other, and with the audience. What I would like to achieve is that every participant who joins a teaching course finishes it really having learnt something that will help them in their clinical practice or research.

Q8 In response to COVID-19, does EAN or the Teaching Course Sub-Committee plan to increase the number of educational programmes available to neurologists?

We are making major efforts to provide all courses that would have been given at the 2020 Congress in Paris, France. This will be an unprecedented wealth of material available online, with up-to-date information for trainees, early career neurologists, and advanced neurologists.

Q9 It is hypothesised that the respiratory dysfunction caused by COVID-19 is a result of the neuroinvasive potential of the virus. What are your thoughts on this?

This is a very interesting question. What is particularly interesting is that the early loss of smell might indicate an invasion of the nervous system. With other viruses, such as those that cause a common cold, the loss of smell is caused by nasal congestion and excess nasal secretions, and the sense of smell recovers quickly after recovery from the cold. With COVID-19, hyposmia may even occur in the absence of nasal congestion and might thus be a primary consequence of the virus binding to the olfactory epithelium. We will certainly have to learn more about this.

Q10 Has COVID-19 directly or indirectly impacted your research, and what actions have been taken to adapt to the current situation?

Indeed, with the current restrictions, there is considerable impact on our research. All patient-centred research had to be paused. Also, the laboratory-based research is impacted by the fact that our labs are in the hospital. So, many students and physician researchers had to pause their practical work and are instead studying the literature or analysing their data. Medical student researchers have volunteered in the hospitals and are drawing blood from COVID-19 patients, working as patient guides and at telephone hotlines, or are helping us to set up digital teaching to make up for the loss of face-to-face teaching in this summer term.

Interview

Professor Michael Barnes

CMO of Lyphe Group and Chair of The Medical Cannabis Clinicians Society (MCCS)
Director of Maple Tree Med Can Consultancy Ltd., Newcastle, UK

Q1 You started your career as a neurologist then specialised in neurorehabilitation. Where did your interest in medicinal cannabis stem from?

I became interested whilst working in multiple sclerosis clinics roughly 20 years ago. Some of my patients came to the clinic and told me that they were using cannabis for their pain and spasticity. I (informally) asked all those attending the clinic about their cannabis use, and about 50% said they were using cannabis. At about that time GW Pharmaceuticals (Cambridge, UK) also asked me to be involved in the development of Sativex®, the first cannabis medicine. Thus, my interest is long-standing.

Q2 As the founding Chair of The Medicinal Cannabis Clinicians Society (MCCS), could you tell us about your role and the society's aims?

I started the society as a 'home' for clinicians (not just medical doctors) to learn and share information about cannabis as a medicine. We put on a series of roadshows around the country, an annual conference, newsletters, and provide our members with updates on available products. We run a mentoring scheme to support doctors new to prescribing. Soon, we will have a comprehensive database of published studies on efficacy and side effects for members to search. We now have around 100 members. It is run day-to-day by Hannah Deacon, the mother of Alfie Dingley who was the first child to obtain a license for cannabis, and our communications director, Kate Thorpe.

Q3 You were instrumental in securing the first prescription of medicinal cannabis in the UK. What were the biggest challenges involved in receiving approval for this?

It was quite a bit of work with the Home Office for over 3 months, but I have to say that they were very helpful and supportive. We were all working together to achieve something that had not been done before. In the end it was a 64-page, comprehensive document that covered the product we wanted to use and the clinical governance arrangements around that prescription. It was the catalyst that changed the law.

Q4 Specialist physicians have been able to officially prescribe medicinal cannabis in the UK since November 2018, yet only a handful of prescriptions have been issued. In your opinion, why do believe this to be the case?

"We were all working together to achieve something that had not been done before"

Several reasons. First, lack of knowledge about the subject. Doctors have never been taught about cannabis and the endocannabinoid system. We need more training programmes, like the Academy of Medical Cannabis.[1] Second, guidelines for cannabis-based medicinal products by bodies such as the Royal College of Physicians (RCP) and the British Paediatric Neurology Association (BPNA), and more recently the National Institute for Health and Care Excellence (NICE), need to be significantly improved to be more informative and useful for clinicians. These are visibly anticannabis and try to push cannabis-based products down a pharmaceutical approval route, in which it doesn't fit. The MCCS have recently published more balanced guidelines.[2] Third, we do need more evidence of efficacy, but in my view there is sufficient evidence for many indications (especially pain, anxiety, sleep, spasticity, and epilepsy); however, clearly more evidence is needed. Let's prescribe the medicine (which is remarkably safe) and learn as we go. Finally, it is an unlicensed medicine and many medics are reluctant to prescribe for that reason, of which in my view they shouldn't be.

Q5

What lessons can countries where medicinal cannabis is not legalised learn from those where it is, in regard to both the establishment of legalisation and building of infrastructure into healthcare?

We must learn from countries that are further ahead, such as Canada, some states in the USA, and Germany. They have developed robust prescribing systems. We can certainly learn that we need a UK industry because at the moment it is all import and that causes supply delays and higher costs than are unnecessary. Many countries have developed an Office of Medicinal Cannabis to coordinate supply, approvals, prescribing, evidence, etc. That seems an excellent solution rather than relying on the pharmaceutical systems, which do not lend themselves to a plant product.

Q6

The main indication for medicinal cannabis use has been for multiple sclerosis and severe epilepsy. What data are there for its use in other neurological diseases?

The best evidence is for pain; there is no doubt about that. Cannabis also has opioid sparing effects, which is very helpful in these days of opioid over-prescribing. There is also good evidence for its use for anxiety and sleep disorders.

Q7

What qualifies a patient to become a recipient of medicinal cannabis? And what aspects of a patient's health should be taken into consideration when making the decision?

A specialist doctor can prescribe cannabis for any condition (preferably within their own area of expertise, of course). The patient needs to have tried all reasonable licensed alternatives in my view, and then if they haven't worked sufficiently or are limited by side effects, then cannabis could be tried for those indications with a good evidence base. Like any other medicine, the doctor needs to take into account the condition of the patient and there are some contraindications, such as a history or family history of psychosis, some cardiac rhythm problems, and a few other relative contraindications. Other concomitant medication needs to be borne in mind as well. A low cannabidiol (CBD) compound is best at first, and then a slow titration of tetrahydrocannabinol (THC) as needed.

Q8

What are the biggest risks associated with the prescription of medicinal cannabis for a patient with a neurological disease?

There are few risks. As above, a history of psychosis or of some cardiac dysrhythmias needs to be taken into account, and concomitant drugs need consideration. A careful cannabis physician will always 'start low and go slow' with dosing, trying a high-CBD/low-THC product first before a gradual titration upwards of dose and product type.

Q9

Products only containing CBD have gained the most traction on the road to approval, but there is now a movement from the medical community to include low levels of THC alongside CBD in products. Are there benefits of including both CBD and THC in a formula, and if so, what are they?

"The law has been changed and now we need less restrictions from the medical hierarchy and better guidelines"

CBD should usually be tried first. Some epilepsies and pain conditions will benefit from addition of some THC and indeed some pain problems need relatively high THC. There seems to be benefit in many symptoms for CBD and THC in combination. There is also some evidence that isolates, for example pure CBD, are less efficacious than a 'full extract' product that contains other minor cannabinoids and terpenes; this is the entourage effect. More research is needed, but that seems to be the pattern.

Q10

Clinical trials establishing the safety and efficacy of a drug are essential for the approval by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA). How does the current clinical infrastructure pose as a challenge for medicinal cannabis clinical research?

Many medical authorities are assuming that cannabis can follow the classic pharmaceutical route. The plant, which has 113 cannabinoids and over 100 terpenes and flavonoids, simply does not fit the standard 'single molecule' pharmaceutical assessment process. We need a system of approval and appraisal of a botanical product. It can go through trials like any other medicine, but let's not be obsessed with the double-blind placebo-controlled model. Other forms of evidence need to be taken into account, for example good quality observational trials and N-of-1 trials.

Q11

What are the next steps for securing access to those in need of medicinal cannabis?

We urgently need NHS prescriptions. These are legal through specialist doctors. The law has been changed and now we need less restrictions from the medical hierarchy and better guidelines. There are doctors interested in this medicine and see its value. Let them prescribe and let us learn as we go. After all, many people who would benefit from cannabis are being affected by intractable pain and resistant epilepsy, for example. It is immoral to deny them a medicine that may be useful and is remarkably safe if prescribed by a knowledgeable doctor.

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Moving from The Periphery to The Core of The Matter – Where Does Opicapone▼ Fit in Parkinson's Disease?

This symposium took place on 24th May 2020, as part of the European Academy of Neurology (EAN) 2020 Virtual Congress

Chairperson: Bastiaan R. Bloem[1]

Speakers: Werner Poewe,[2] Georg Ebersbach[3]

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Meeting Summary

After five decades, levodopa is still considered the gold standard for the treatment of motor symptoms in patients with Parkinson's disease (PD). However, after the initial years of levodopa therapy many patients develop motor response oscillations such as end-of-dose wearing-off and levodopa-induced dyskinesias. The mechanisms underlying the development of levodopa response fluctuations are multifactorial, but perhaps the most important factor contributing to the end-of-dose wearing-off phenomenon is levodopa's short half-life. Limitations in the bioavailability of levodopa have led to dopa-decarboxylase inhibitor (DDCI) use in combination with levodopa as standard practice since the mid-1970s. Key to the treatment of PD symptoms is the maintenance

of low and sustained levels of levodopa to reduce the severity and impact of response fluctuations. Through understanding the mechanism of action of catechol-O-methyltransferase (COMT) inhibitors, it is a logical step that adding a COMT inhibitor will optimise levodopa bioavailability in the periphery and increase the benefit of each levodopa dose. Opicapone is a COMT inhibitor indicated as adjunctive therapy to preparations of levodopa/DDCI in adult patients with PD and end-of-dose motor fluctuations that cannot be stabilised using this combination alone. Data from post hoc analyses of the pivotal BIPARK-I and -II studies reinforced the suitability of opicapone as a treatment option across the spectrum of motor fluctuations in PD. Real-world clinical data from the OPTIPARK study further supported the efficacy and safety of opicapone 50 mg, confirming its clinical utility as an adjunct to levodopa/DDCI in patients with PD and motor fluctuations.

Introduction from The Chair

Professor Bastiaan R. Bloem

Presented here are highlights of a virtual satellite symposium from the European Academy of Neurology (EAN) 2020 Virtual Congress. The optimisation of levodopa bioavailability in the periphery in patients with PD was reviewed, with a focus on the role of COMT inhibition. The latest data on the efficacy and safety of opicapone 50 mg as an adjunct to levodopa/DDCI in the management of the full spectrum and duration of motor fluctuations were then discussed, together with emerging real-world experience of opicapone use.

Improving Levodopa Delivery: Let's Move to The Periphery

Professor Werner Poewe

Levodopa is rightfully referred to as a revolutionary drug in the treatment of PD, and after five decades it is still considered the gold standard of symptomatic efficacy for the treatment of motor symptoms.[1] Almost all patients with PD will eventually require levodopa and the first few years of treatment of newly diagnosed cases are often referred to as the 'honeymoon period', during which symptoms often improve to near normality.[2] This period is the most rewarding for both patients and the treating neurologist, but unfortunately becomes compromised when patients develop motor response oscillations such as end-of-dose wearing-off and levodopa-induced dyskinesias.[2-4]

Risk Factors for Motor Complications Associated with Levodopa Therapy

Risk factors for the development of motor complications include a younger age at disease onset, levodopa dose, and disease duration.[5-7] Findings from both the ELLDOPA and the STRIDE-PD studies showed a dose–response relationship for both the development of dyskinesias and wearing-off motor fluctuations.[6,8] In STRIDE-PD, the frequency of dyskinesia and wearing-off after 208 weeks was greatest in patients treated with >600 mg/day of levodopa (55.8% and 72.6%, respectively).[6]

More recent findings provide clear evidence that motor fluctuations and the development of levodopa-induced dyskinesia are associated with a longer duration of PD and with increased levodopa dose rather than duration of exposure to levodopa therapy.[7] Cilia et al.[7] were able to compare the temporal evolution of motor complications in response to levodopa in two cohorts of patients with PD: one from Ghana, where access to PD medication is limited, and diagnosis and initiation of levodopa therapy are often delayed by many years relative to disease onset, and the other from Italy, where levodopa is initiated soon after diagnosis. Both cohorts were followed for 4 years and despite much later introduction of levodopa therapy relative to disease onset in the Ghanaian cohort (4.2 years versus 2.4 years in Italy), wearing-off and dyskinesia occurred at a similar disease duration in both populations: wearing-off at 5.5–6.0 years and dyskinesia at 6.5–7.0 years,[7] thus clearly revealing duration of disease as more relevant than duration of exposure to levodopa.

The mechanisms underlying the development of levodopa response fluctuations are multifactorial, but perhaps the most important factor contributing to the end-of-dose wearing-off phenomenon is levodopa's short half-life, which is a result of its metabolism by aromatic L-amino acid decarboxylase and COMT in the periphery.[9,10] Drugs capable of inhibiting levodopa decarboxylation in the periphery, thereby increasing its bioavailability in the brain, have led to the use of DDCI in combination with levodopa as standard practice in patients with PD.[9]

The Role of Catechol-O-Methyltransferase Inhibition in Improving the Bioavailability of Levodopa

To further prevent the peripheral metabolism of levodopa, thereby enhancing its availability in the periphery, transportation through the blood–brain barrier, and subsequent duration of therapeutic effect, COMT inhibition in combination with levodopa/DDCI was investigated as far back as the 1970s.[9,11] Metabolism of levodopa by COMT is a second, important degradation pathway leading to the conversion of levodopa to 3-O-methyldopa; inhibiting COMT enables prolongation of levodopa half-life.[9]

The first-generation COMT inhibitors had little value as pharmacological agents because of their unfavourable pharmacokinetics, poor selectivity, or toxicity.[11] Second-generation COMT inhibitors were introduced into clinical practice in the late 1990s. Tolcapone, with its central and peripheral mode of action, was the first-in-class COMT inhibitor to be approved for clinical use in 1997 as add-on therapy to levodopa. However, as a result of liver toxicity it was withdrawn from many European markets and its use is now second-line under strict liver function monitoring.[9,12] Entacapone, a peripheral COMT inhibitor, was approved for clinical use in 1998 and has been used routinely as add-on therapy to levodopa/DDCI or in a triple combination tablet (levodopa/carbidopa/entacapone) in patients with motor fluctuations.[9,13] Common adverse events (AE) reported with entacapone and tolcapone therapy related to increases in plasma concentration of levodopa include dyskinesia, nausea, and orthostatic hypotension. Furthermore, some patients experience diarrhoea and urine discolouration with entacapone therapy.[12,13]

The efficacy of enhancing peripheral availability of levodopa/DDCI with COMT inhibition to reduce wearing-off fluctuations has been demonstrated in multiple randomised controlled trials in patients with PD and motor complications.[14]

Second-Generation Catechol-O-Methyltransferase Inhibitors

Limitations of the efficacy of entacapone,[15] as well as side effects such as troublesome diarrhoea,[15] have stimulated research into new types of COMT inhibitors, which has recently led to the development of opicapone, a long-acting, purely peripheral COMT inhibitor.[16] Opicapone has a high binding affinity for COMT, and a constant, slow dissociation rate of the enzyme–substrate complex, leading to a long (>24 hour) duration of action *in vivo*.[16,17] A pharmacokinetic study found that after 11 days of dosing, opicapone 50 mg decreased 3-O-methyldopa exposure to a greater degree than entacapone 200 mg: mean C_{max} was 361 ng/mL and 785 ng/mL, respectively.[18] Improving oral levodopa delivery through COMT inhibition is now an established adjunct to levodopa/DCCI to manage wearing-off. How opicapone has advanced COMT inhibitor therapy was discussed by Prof Ebersbach in the second presentation of the symposium.

Opicapone's Latest Insights

Professor Georg Ebersbach

Opicapone is a COMT inhibitor indicated as adjunctive therapy to preparations of levodopa/DDCI in adult patients with PD and end-of-dose motor fluctuations who cannot be stabilised on those combinations.[17]

The clinical efficacy and safety of opicapone as an adjunct therapy to levodopa has been demonstrated in two large, Phase III, multinational, randomised, double-blind studies with open-label extension periods. BIPARK-I was an active comparator (entacapone) and placebo-controlled study (N=600), and BIPARK-II a placebo-controlled study (N=427).[19-21] In BIPARK-I, the primary endpoint was change in

baseline to end of study treatment in absolute OFF time. Treatment with opicapone 50 mg was superior to placebo (mean difference in change from baseline: -60.8 min; 95% confidence interval [CI]: -97.2 to -24.4; p=0.0015) and noninferior to entacapone (mean difference: -26.2 min; 95% CI: -63.8 to 11.4; p=0.0051 for noninferiority test).[19] In BIPARK-II, the primary efficacy outcome in the double-blind phase was change from baseline in absolute OFF time versus placebo. The adjusted treatment difference versus placebo was significant for opicapone 50 mg (treatment effect: -54.3 min; 95% CI: -96.2 to -12.4; p=0.008).[21] Opicapone was generally well tolerated with the most common AE associated with opicapone treatment including dyskinesia, insomnia, constipation, and dry mouth.[19,21]

Opicapone in Patients Who Have Recently Developed Motor Fluctuations

Building on these Phase III data, exploratory post hoc analyses evaluated the efficacy and safety of opicapone in patients with PD treated with levodopa/DDCI with ≤1 year duration of motor fluctuations (recent motor fluctuations [RMF]), as well as >1 year duration of motor fluctuations (long-standing motor fluctuations [LMF]).[22]

Data from matching treatment arms in BIPARK-I and -II were combined for the placebo and opicapone 50 mg groups and analysed. Key baseline patient characteristics, including age, disease duration, and daily OFF time, were similar for opicapone (RMF: n=85; LMF: n=162) and placebo (RMF: n=71; LMF: n=174) groups in both RMF and LMF patients.[22] Mean daily levodopa dose was slightly higher for LMF (placebo: 742.3 mg; opicapone 50 mg: 739.3 mg) compared with RMF (placebo: 585.4 mg; opicapone 50 mg: 616.6 mg).[22] Changes in absolute OFF and ON time were significantly greater for opicapone versus placebo in both RMF and LMF. Opicapone reduced absolute OFF time by approximately 1 hour for RMF and LMF versus placebo (least squares mean RMF: -65.2 min; least squares mean LMF: -60.5 min) (Figure 1).[22]

Dyskinesia was the most frequently reported potentially related treatment-emergent AE (TEAE), with a 2-fold increase in dyskinesia for late versus recent motor fluctuators in the opicapone groups (23.5% versus 11.8%).[22] This could be because of longer disease duration and higher daily levodopa dose in the late fluctuators.[22] These data support the use of opicapone regardless of duration of onset of motor fluctuations, but with a lower incidence of dyskinesia in the first year of motor fluctuations.[22]

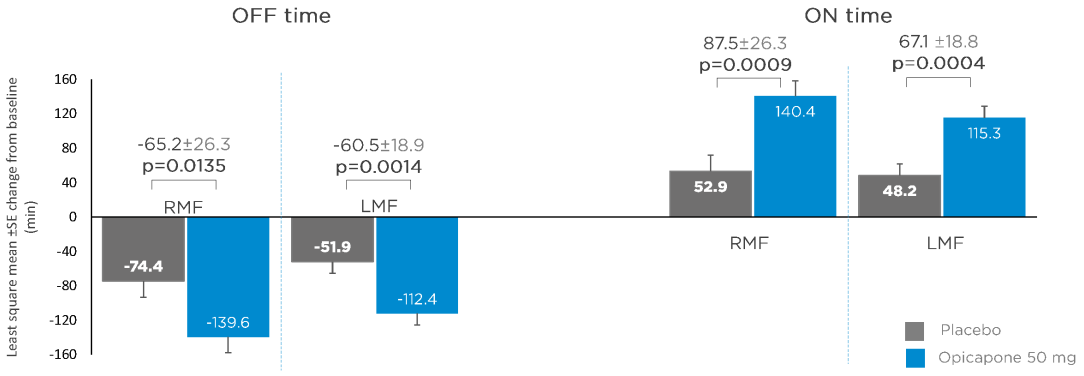

Figure 1: Changes from baseline in absolute OFF and ON time in recent and long-standing motor fluctuations on opicapone 50 mg or placebo.

LMF: long-standing motor fluctuations; RMF: recent motor fluctuations; SE: standard error.

Adapted from Ebersbach G et al.[22]

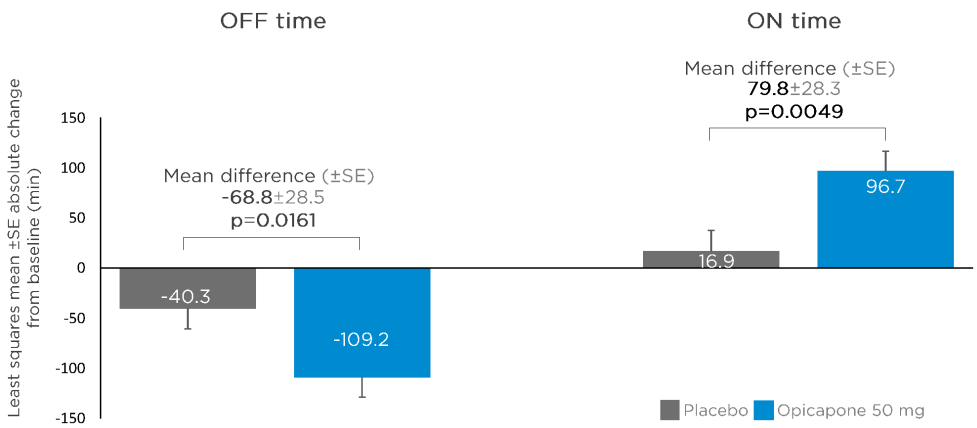

Figure 2: Changes from baseline in absolute OFF and ON time in patients treated with levodopa/dopa-decarboxylase inhibitor alone* and opicapone 50 mg as first-line adjunctive therapy.

*Without dopamine agonists or monoamine oxidase-B inhibitors.

SE: standard error.

Adapted from Ferreira JJ et al.[23]

Opicapone As First Add-On to Levodopa/Dopa-Decarboxylase Inhibitor in Patients With Motor Fluctuations

A post hoc analysis evaluating opicapone as first add-on in patients with PD with end-of-dose motor fluctuations treated with levodopa/DDCI only at baseline (i.e., without dopamine agonists or monoamine oxidase-B inhibitors) was conducted in 127 patients.[23] Baseline characteristics in the opicapone (n=68) and placebo (n=59) groups were comparable, with mean levodopa dose 730.3 mg and 718.3 mg/day, respectively.[23] Opicapone significantly improved OFF and ON time in patients treated with levodopa/DDCI alone compared with placebo, with mean changes from baseline in absolute OFF time reduced by 68.8 min (p=0.0161), and ON time increased by 79.8 min (p=0.0049) (Figure 2).[23]

The incidence of potentially related TEAE leading to discontinuation were comparable for opicapone 50 mg (n=5 [7.4%]) and placebo (n=5 [8.5%]).[23] The most frequently reported (≥5% of patients) potentially related TEAE were dyskinesia (opicapone: n=8 [11.8%]; placebo: n=1 [1.7%]), constipation (opicapone: n=4 [5.9%]; placebo: n=0 [0.0%]), and nausea (opicapone: n=1 [1.5%]; placebo: n=4 [6.8%]).[23] These data show that opicapone is effective and generally well tolerated as a first-line adjunctive therapy in levodopa-treated patients with PD and motor fluctuations.[23]

Opicapone in Patients With Advanced Complications of Levodopa Treatment

A further post hoc analysis was conducted to investigate levodopa dose reductions seen with opicapone 50 mg in the BIPARK-I and -II studies.[24] Opicapone efficacy was assessed in levodopa-treated patients with PD whose levodopa dose was reduced during the double-blind adjustment period. Overall, 41 out of 265 patients treated with opicapone 50 mg had levodopa dose reductions, either as a proactive dose reduction (n=11), or because of dopaminergic AE (n=30).[24]

Patients with these levodopa dose reductions had a longer mean (standard deviation [SD]) disease duration (10.1 [4.6] years) than the overall opicapone 50 mg population (7.7 [4.3] years; n=265), and higher mean (SD) daily doses of levodopa: 842 (344) mg/day and 698 (322) mg/day, respectively.[24] Although the mean daily levodopa dose decreased by an average of

23.4% (842 mg to 650 mg), these patients still experienced motor response and quality of life (QoL) improvements from baseline in absolute OFF time (mean decrease of 131.2 min), ON time (increase of 125.4 min), Unified PD Rating Scale (UPDRS) II and III scores (-3.3 and -1.7, respectively), and PD Questionnaire (PDQ) 39 items (PDQ-39 score; -2.8).[24] These findings show that dopaminergic AE emerging with opicapone can be managed by reduction of levodopa dose and that improvements for patients are still provided after reduction of levodopa.[24]

Opicapone as a Treatment Option Across the Spectrum of Motor Fluctuations

In summary, data from the BIPARK-I and -II post hoc analyses have shown that opicapone 50 mg improves OFF and ON time in patients with RMF (≤1 year of motor fluctuations) as well as patients with LMF, and that there is a lower incidence of dyskinesia in RMF compared with LMF.[22] Opicapone significantly improved OFF and ON time as a first adjunctive therapy in patients with motor fluctuations.[23] Dopaminergic AE emerging with opicapone can be managed by levodopa dose reduction, with improvements in motor response and QoL still present.[24] Opicapone was generally well tolerated in all subgroups.[22-24]

Opicapone in Clinical Practice: OPTIPARK, a Phase IV Open-Label Study

Real-world evidence from the recently published OPTIPARK study added further credence to the utility of opicapone 50 mg in clinical practice.[25] Full details of the OPTIPARK study have been described elsewhere.[25] In brief, OPTIPARK was a Phase IV, real-world, prospective, open-label, uncontrolled, single-group trial in adults with PD with wearing-off motor fluctuations conducted in the UK (6 months) and Germany (3 months). Main inclusion criteria were Stage I–IV of disease severity (modified Hoehn and Yahr Scale) in the ON state, and treated with 3–7 daily doses of levodopa/DDCI or levodopa/DDCI/entacapone. Total daily levodopa/DDCI dose could be adjusted according to the individual's condition throughout the trial (except on Day 1). Patients treated with entacapone before trial entry were to discontinue entacapone at the baseline visit; patients previously or currently treated with tolcapone and/or opicapone were excluded from the study.[25]

The primary efficacy endpoint was Clinician's Global Impression of Change (CGI-C) at 3 months, and secondary endpoints included Patient's Global Impression of Change (PGI-C), Wearing-off Questionnaire (WOQ)-9 assessments, UPDRS, PDQ-8, and Non-Motor Symptoms Scale (NMSS).[25]

Patient characteristics

A total of 495 patients were included in the safety set. Mean (SD) age was 67.7 (8.98) years, disease duration was 8.5 (4.97) years, and duration of motor fluctuations was 2.5 (3.16) years. Mean (SD) total levodopa daily dose was 580.1 (289.1) mg. Overall, 393 patients completed 3 months; 109 patients terminated the study prematurely, mainly due to nonserious AE (n=76).[25]

Efficacy results

After 3 months' treatment with opicapone 50 mg in a clinical setting, there were improvements in global PD condition: 71.3% of patients showed clinical improvement as rated by the CGI-C (primary endpoint), with 43% reported as much or very much improved,[25] and 76.9% self-reported a clinical improvement rated by PGI-C (secondary endpoint), with 48.1% of patients reporting they were much or very much improved (Figure 3).[25,26]

Opicapone also significantly improved UPDRS Part II (activities of daily living) and III (motor) scores, QoL (PDQ-8 total score), and Non-Motor Symptoms Scale (NMSS) scores after 3 months (Figure 4).[25,26]

Safety results

The majority of drug-related TEAE were reported during the first week.[27] In the 74.9% of patients who experienced TEAE, the majority were mild or moderate in severity. Dyskinesia was the most common at least possibly-related TEAE (11.5%) but had a low impact on patient discontinuation (1.0%). The most common reason for withdrawal was nausea, affecting 2.0% of patients.[25] Overall, observed AE in this large open-label study were comparable to AE data from the two pivotal clinical trials.[19,21]

Conclusion

In summary, these real-world clinical data support the efficacy and safety of opicapone 50 mg observed in Phase III studies and post hoc analyses. OPTIPARK confirms the clinical utility of opicapone 50 mg as an effective and generally well-tolerated adjunct option in patients with PD with motor fluctuations.[25]

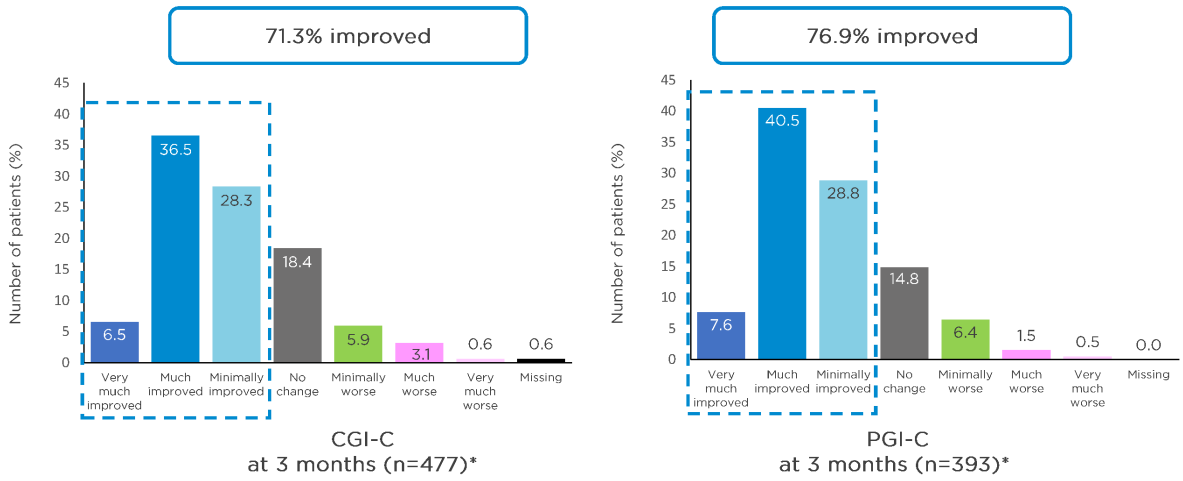

Figure 3: Clinician's Global Impression of Change (CGI-C) and Patient's Global Impression of Change (PGI-C) at 3 months in OPTIPARK.

*Data from full analysis set. Missing values for CGI-C at visit 4 were imputed using the last observation carried forward method.

Adapted from Reichmann et al.; OPTIPARK investigators.[25,26]

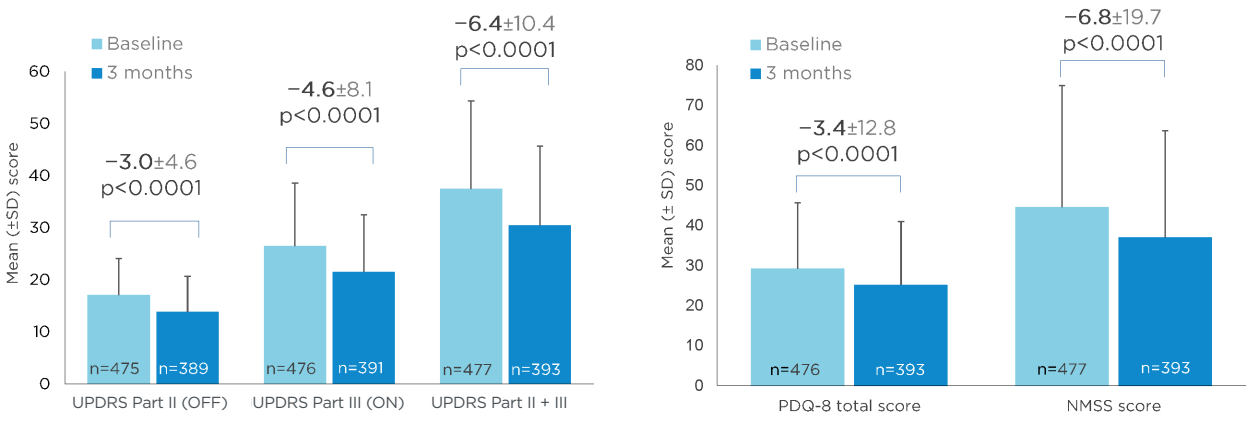

Figure 4: Activities of daily living and motor scores (UPDRS Parts II and III), and Quality of Life (PDQ-8) and Non-Motor Symptoms Scale (NMSS) scores at 3 months in OPTIPARK.

NMSS: Non-Motor Symptoms Scale; PDQ: Parkinson's Disease Questionnaire; SD: standard deviation; UPDRS: Unified Parkinson's Disease Rating Scale.

Adapted from Reichmann et al.; OPTIPARK investigators.[25,26]

Symposium Panel Discussion

Professor Bas Bloem, Professor Werner Poewe, and Professor Georg Ebersbach

At the end of the well-attended live-streamed satellite symposium, delegates were able to ask questions to the panel. A selection of questions pertinent to the clinical use of opicapone 50 mg as an adjunct to levodopa/DDCI in the management of the full spectrum and duration of motor fluctuations in patients with PD, which were answered by the expert speaker panel, are presented here.

Opicapone Therapy and Onset of Efficacy in Improving Motor Fluctuations

In response to the question: "How long is the wait before adjunct opicapone therapy starts to take effect, and in order to see an improvement in motor fluctuations?," Prof Ebersbach replied that the first effects can be expected to appear within the first few days of treatment, with the full effect becoming present and obvious after 1–2 more weeks of opicapone treatment.[28]

In a follow-up question enquiring when to reduce the dose of levodopa following the addition of opicapone (i.e., should this be an immediate reduction of levodopa, or is it best to wait for dyskinesia to happen before reducing the levodopa dose?), Prof Ebersbach responded that this depends on the risk profile of the individual patient. If a patient is prone to dyskinesia with any rise in levodopa dose, then the dose could be lowered prophylactically (i.e., at the same time as introducing the opicapone). However, in a patient who has not previously experienced dyskinesia, the levodopa dose does not necessarily need to be lowered in anticipation of this possible side effect, which only occurs in a subgroup of patients following the addition of opicapone (20.4% with opicapone 50 mg in the pooled double-blind Phase III trials [n=265][29]). According to the clinical condition of the patient, it is often necessary to adjust the daily dose of levodopa within the first few days to first weeks after initiating treatment with opicapone.[17] In 41 out of 265 patients treated with opicapone 50 mg who had levodopa dose reductions during the double-blind phase of BIPARK-I and -II, the mean daily levodopa dose decreased by an average of 23.4% (from 842 mg to 650 mg).[24]

Conversion Factor for Levodopa and Opicapone

With levodopa as the gold standard, conversion factors can be used to calculate levodopa-equivalent doses (LED) for comparison of drug regimens. Prof Poewe's response to a question about the LED conversion factor for opicapone was that it is proposed to be 1.5, in comparison with entacapone's LED conversion factor of 1.3. Thus, opicapone's LED is 140–150 mg for a 100 mg levodopa dose.[30]

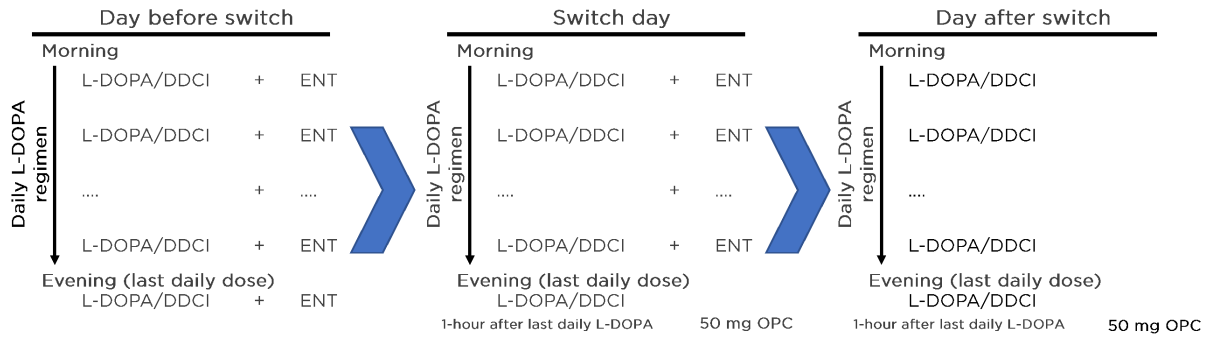

Figure 5: Practical switch from entacapone to opicapone 50 mg.

DDCI: dopa-decarboxylase inhibitor; ENT: entacapone; L-DOPA: levodopa; OPC: opicapone.

Adapted from Ferreira J et al.[31]

Switching From Entacapone to Opicapone

Prof Poewe's answer to a question asking for a recommendation on how to switch from entacapone to opicapone came from experience in the BIPARK-I study (Figure 5).[31]

Entacapone's half-life is similar to the half-life of levodopa, so the switch can be made in 1 day. On the day of the switch, the last daily dose of levodopa/DDCI should be taken without entacapone, and opicapone 50 mg started on that same night, at least 1 hour apart from the last dose of levodopa/DDCI.[31] This recommendation was confirmed by Prof Ebersbach.

Long-Term Effectiveness of Opicapone

In reply to a question asking whether the effect of opicapone decreases after several months of treatment as a result of loss of intrinsic efficacy, or whether this is attributable to worsening of the underlying PD, Prof Poewe responded by highlighting evidence from the pooled analysis of data from BIPARK-I and -II, and their associated open-label extension studies. Opicapone does not give any indication of loss of benefit over time and persistent benefit has been shown in the open-label extension after 1 year.[32] In Prof Poewe's experience, there are many reasons for reduced benefit with treatments in general, including disease progression, psychology, and low compliance.

Opicapone as Adjunct Therapy to Levodopa in Patients With Parkinson's Disease

How would you describe the ideal patient for opicapone? In response to this question, Prof Ebersbach outlined two types of suitable patients. In a patient with recent motor fluctuations, the addition of opicapone is usually straightforward and often does not need any adjustment to co-medication.

On the other end of the spectrum, patients with severe motor response fluctuations are likely to benefit but, in this situation, levodopa dose may have to be adjusted.[22-24]

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Opicapone▼ Prescribing Information

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Abstract Reviews

Herein, you will find a collection of reviews of abstracts from this year's EAN Virtual Congress, written by the presenters themselves.

A Multicenter Retrospective Study Evaluating Brivaracetam in the Treatment of Epilepsies in Clinical Practice

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Keywords: Brivaracetam (BRV), clinical practice, epilepsy, therapy.

Citation: EMJ Neurology. 2020;8[1]:39-41. Abstract Review No: AR1.

BACKGROUND AND AIMS

Brivaracetam (BRV) is the latest approved antiepileptic drug and acts as a synaptic vesicle protein 2A ligand.[1] The aim of the present study was to evaluate the efficacy and tolerability of BRV in everyday clinical practice.

METHODS AND MATERIALS

In this retrospective, observational, multicentre study, data from epilepsy patients receiving BRV any time from January 2018 to July 2019 were analysed. Patients aged ≥16 years affected by a variety of epilepsy types and having at least one follow-up (1–6 months) after dose titration were included.

Table 1: Patients' characteristics.

Characteristics	Baseline
N=156	
Age (years), M (SD)	39.69 (13.63)
Gender, n (%)	
Male	82 (52.6)
Female	74 (47.4)
Period of follow-up (months), M (SD)	3.9 (2.7)
Epilepsy duration (years), M (SD)	21.4 (13.7)
Drug resistant epilepsy, n (%)	
Yes	61 (39.1)
No	95 (60.9)
Cosponsored AED, M (SD)	2.28 (1.40)
BRV monotherapy	9 (5.8)
Types of seizures, n (%)	**N=156 (%)**
Focal seizures	88 (56.4)
Focal seizures with secondary generalisation	39 (25.0)
Generalised seizures	25 (16.0)
Unclassified seizures	4 (2.6)
Syndromes, n (%)	**N=156 (%)**
Idiopathic epilepsy	69 (44.2)
Symptomatic epilepsy	71 (45.5)
Juvenile myoclonic epilepsy	4 (2.6)
Special syndromes	12 (7.7)

AED: antiepileptic drug; BRV: brivaracetam; M: mean; SD: standard deviation.

RESULTS

The study included 156 consecutive patients. Patients' demographic characteristics are shown in Table 1. There were 82 males and 74 females. The mean age was 40 years of age (16–84 years), the mean duration of epilepsy was 21 years, and 39% had drug-resistant epilepsy. Of the 156 patients, 81% were diagnosed with focal onset epilepsy, 16% with generalised seizures, and 3% had unclassified seizures. The mean cosponsored drugs with the BRV treatment were 2.28 at baseline. Of the patients, 102 patients were treated with levetiracetam (LEV) in the past, 85 (83%) of whom were treated with LEV at the baseline. Nine patients received BRV as monotherapy as a switching therapy, mainly after LEV.

After BRV treatment, the rate of ≥50% response was 36%. Seizure freedom was achieved in 56 (39%) patients, while 15% remained unchanged. Six patients (4%) were recorded with increased seizure frequency, while the remaining 9% had a response less than 50%.

Twenty-six patients (17%) showed clinically significant adverse events, but none were life threatening. Among them, 18 patients had non-behavioural side effects (headache, fatigue, etc.) and eight patients had behavioural changes (such as aggressiveness and depression). Sixteen patients discontinued BRV after the first follow-up. The reasons for discontinuation were lack of efficacy (two patients), adverse events (10 patients), or both (four patients).

CONCLUSION

BRV appears to be an effective, easy to use, and safe antiepileptic drug in the clinical setting.

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Role of Routine Cerebrospinal Fluid and Serum Parameters in Adult 5q-SMA Type 2/3 Treated with Nusinersen: A Prospective Observational Study

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Cerebrospinal fluid (CSF), neurodegenerative biomarkers, nusinersen, spinal muscular atrophy (SMA).

Citation: EMJ Neurol. 2020;8[1]:41-43. Abstract Review No: AR2.

BACKGROUND AND AIMS

Spinal muscular atrophy (SMA) is an autosomal, neurodegenerative disease of the motor neurons with onset in childhood or adolescence. Nusinersen is an antisense oligonucleotide, intrathecally administered and approved for the treatment of children and adult SMA patients.[1] The aim of this cross-sectional and longitudinal study was to analyse therapy-related changes in cerebrospinal fluid (CSF) and serum parameters to evaluate the efficacy and safety of the treatment.

MATERIALS AND METHODS

Nine adult patients with SMA type 2–3, with a mean age at baseline of 42.78 ± 13.95 years, were included in the study. For each intrathecal administration of 5 mL of nusinersen, 5 mL of CSF had been previously withdrawn. CSF was collected in polypropylene tubes and analysed with a simultaneous blood sample at baseline (T0), after loading dose at Day 63 (T1), after the first (T2) and second (T3) maintenance doses, at Days 180 and 300, respectively. There was one patient who voluntarily dropped-out at T3. Serum creatinine levels, CSF leukocyte count, CSF to serum glucose ratio, CSF to serum albumin ratio (Q_{alb}), and isoelectric focussing on agarose gels with subsequent immunoblotting were performed. Neurofilament light chain (NfL), tau, phosphorylated tau, and β-amyloid 1–42 were assayed in all CSF samples, except for NfL in three patients at T3. Motor function was assessed using the Hammersmith functional motor scale–expanded (HFMSE) and revised upper limb module (RULM) scores.

Ten subjects, matched for sex and age and without neurodegenerative or inflammatory neurological diseases, underwent lumbar puncture and were assumed as controls. Comparisons were performed by Mann–Whitney test and paired t-test. Relations between clinical and serum or CSF parameters were assessed with Pearson's correlation.

Table 1: Longitudinal serum and cerebrospinal fluid parameters in spinal muscular atrophy patients

Nusinersen (number of patients)	Serum creatinine mg/dL* (M±SD)	Q_{alb}>6.5 x10^3 (patients)	Systemic OB (patients)	CSF OB (patients)	CSF NfL pg/mL (M±SD)	CSF tau pg/mL (M±SD)	CSF ptau pg/mL (M±SD)	CSF β-amyloid 1–42 pg/mL (M±SD)
T0 (9)	0.22±0.08	3 of 9	5 of 9	1 of 9	501.38±116.40	176.1±78.43	34.50±16.30	577.25±227.98
T1 (9)	0.24±0.11	4 of 9	8 of 9	1 of 9	512.25±153.76	166.50±84.45	37.50±20.06	604.00±253.08
T2 (9)	0.24±0.15	4 of 9	8 of 9	1 of 9	417.88±128.97	167.63±90.42	31.85±13.48	634.63±266.02
T3 (8)	0.35±0.24	3 of 8	7 of 8	1 of 9	333.80±104.95	165.75±73.9	31.63±19.40	627.62±250.80

*Serum creatinine reference range: 0.67–1.17 mg/dL

CSF: cerebrospinal fluid; M: mean; NfL: neurofilament light chain; OB: oligoclonal bands; ptau: phosphorylated tau; Q_{alb}: cerebrospinal fluid to serum albumin ratio; SD: standard deviation; SMA: spinal muscular atrophy; T0: baseline timepoint; T1: timepoint 1, after loading dose at Day 63; T2: timepoint 2, after first maintenance dose at Day 180; T3: timepoint 3, after second maintenance dose at Day 300.

RESULTS

CSF cell count and CSF to serum glucose ratio were within the normal range in each sample. Persistent blood–brain barrier dysfunction, expressed by Q_{alb}>6.5, was detected in three patients from T0 and in one further patient from T1. Persistent systemic oligoclonal bands (OB) were found in five patients from T0 and in three more patients during the follow-up; one patient showed intrathecal OB from T0. Serum creatinine levels were consistently much lower than normal reference values. CSF NfL, tau, phosphorylated tau, and β-amyloid 1–42 levels at T0 in patients with SMA did not differ from those in controls, without any significant longitudinal changes (Table 1). HFMSE and RULM improved significantly, only between T0 and T1 (confidence interval: 95%; p=0.032 and p=0.017, respectively).

At T0, serum creatinine values strongly correlated to HFMSE (r=0.93; p<0.001) and RULM (r=0.799; p=0.001) at T0 and at the follow-up. Neuronal biomarkers did not correlate with functional scales at each timepoint.

CONCLUSION

These findings of the immunological impairment in patients with SMA are consistent with other evidence of defects in multiple systems beyond motor neurons, including immune cells.[2] However, the development of systemic OB during treatment could depend on changes of the immune responses induced by nusinersen against common antigens, or a drug-induced specific immune response.[3] The blood–brain barrier damage may reflect a CSF flow dysfunction related to spinal stenoses of scoliosis, frequent in patients with SMA, or it may result from repeated lumbar punctures. Finally, with partial agreement with previous studies,[4,5] the lack of change in the neurodegenerative biomarkers during the first year of treatment in this adult SMA cohort does not support their prognostic role.

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External Carotid Artery Stenting – A Good Strategy to Preserve Cerebral Circulation in a Patient with Ipsilateral Internal Carotid Artery Occlusion

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Keywords: External carotid artery (ECA), internal carotid artery (ICA) occlusion, revascularisation, stenosis, stenting.

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BACKGROUND AND AIMS

Ipsilateral external carotid artery (ECA) may supply the cerebral circulation through collateral vessels in patients with internal carotid artery (ICA) occlusion; at least 10–15% of the middle cerebral artery blood flow may be provided by ECA.[1] Silent or symptomatic, permanent or transient, and retinal or cerebral ischaemic events could be triggered by emboli originating from the ICA or ECA or by a haemodynamic mechanism.[2] Furthermore, it was observed that isolated ECA plaque was an independent predictor of all-cause mortality.[3]

As angiographic studies revealed that different cerebral regions depend on ipsilateral ECA contribution, different procedures for revascularisation have been tried during the last decades; some of them, such as surgical ICA and ECA bypass, did not show any benefit.[4] There are numerous reports regarding endarterectomy for ECA stenosis alone or simultaneous to ICA revascularisation, but stenting has rarely been reported.

The aim of this paper is to present the case of a patient with ECA stenosis and ipsilateral ICA occlusion in whom stenting of the ECA was performed.

MATERIALS AND METHODS

A 73-year-old male was admitted for the first time to the author's neurology department 3 years ago for angiographic examination of carotid and vertebral artery stenoses. The patient had medical history of a right frontal and insular ischaemic stroke, arterial hypertension, dyslipidaemia, peripheral artery disease, and mild neurocognitive impairment.

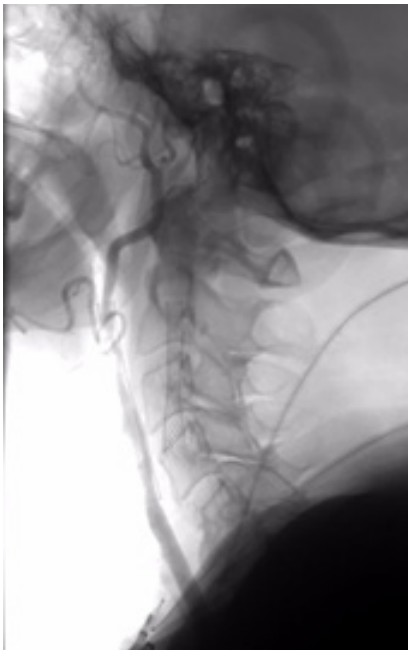

Figure 1: Digital sutraction angiography of the cervical and cerebral arteries showing intra-stent restenosis of the right external carotid artery. Left internal carotid artery stent can also be observed.

Neurologic examination revealed slight left central facial palsy and hemiparesis. Digital subtraction angiography of the cervical and cerebral arteries revealed the presence of a right ICA occlusion, 60% right ECA stenosis, 80% left ICA stenosis, and 90% left vertebral artery stenosis with intracerebral filling of right middle and anterior cerebral arteries from the left ICA. Left ICA stenting was performed due to an increased risk of stroke.

One year later, digital subtraction angiography of the cervical and cerebral arteries showed progression of right ECA stenosis under best medical treatment, with intracerebral filling of the right middle cerebral artery from the right ECA. Additionally, the cerebral CT depicted extension of the hypodensity located in the territory of the right middle cerebral artery and right anterior cerebral artery. As a result, ECA stenting was decided.

RESULTS

One year later, the ultrasonographic examination of the cervical arteries showed increased velocities and endothelial proliferation at the ECA stent site, confirmed by digital subtraction angiography of the cervical and cerebral arteries; balloon angioplasty was performed with optimal results. There was no evidence of worsening of the scores obtained at the neuropsychological examination follow-up.

CONCLUSION

This case highlights the importance of revascularisation therapy and follow-up in patients with stenoses of cervical arteries. This approach maintains the patency of these arteries and prevents further ischaemic events and vascular cognitive impairment. As these cases are not so frequent, it is important to gather evidence regarding the best approach and treatment strategy.

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Young Onset Stoke: A Cause for Concern

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Aetiology, cryptogenic, ischaemic stroke, young stroke.

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BACKGROUND AND AIMS

The incidence of 'young strokes' (stroke affecting people under the age of 45) has been on the rise internationally, accounting for approximately 10% of total strokes.[1] There is a number of reasons for this, and the increasing use of MRI is one contributing factor. Traditional stroke risk factors, such as obesity and hypercholesterolaemia, are increasingly more prevalent in young people.[1]

Despite improvements in diagnostic abilities, a large proportion of young strokes are cryptogenic. The prevalence of this has been reported to be up to 50% in some studies.[1] It is likely that there is a complex interplay between environmental and genetic predispositions, as well as unconventional factors such as migraine.[2] Paradoxical embolism through a patent foramen ovale must also be considered, particularly in combination with prothrombotic mutations. However, there is a paucity of evidence to implicate this as an aetiological factor.[3]

Most studies of ischaemic strokes in young adults employ the TOAST criteria to assign mechanism. No specific guidelines exist for the investigation or management of ischaemic strokes. Assessment of young strokes with no obvious cause often include CT or MR angiography, comprehensive cardiac workup, and serum testing for vasculitis, connective tissue diseases, prothrombotic syndromes, and infections.[4]

The authors aimed to analyse all acute stroke presentations under the age of 45 years over a 10 year period and to identify the mechanism.

METHODS

A retrospective review was undertaken on all patients under the age of 45 years presenting with acute stroke from 1st January 2010 to 30th September 2019 to a tertiary stroke referral centre. Details regarding presentation (ischaemic or haemorrhagic), vascular territory affected, use of thrombolysis or thrombectomy, as well as imaging, cardiac, and laboratory results were gathered. The TOAST criteria were applied to assign stroke mechanism.

RESULTS

The authors' institution had a total of 3,420 patients presenting with acute stroke over the 10-year period. Of these, 2,530 (74.0%) were ischaemic strokes, and 117(3.4%) of these occurred in patients under the age of 45. The largest proportion were cryptogenic (26.0%). 'Other determined aetiology' accounted for 21.0%, 11.0% were secondary to small vessel disease, 11.0% were cardioembolic, and 4.0% were from large vessel occlusion. Six patients were thrombolysed (0.5%) and two underwent thrombectomy. The other determined aetiology was made up of carotid and vertebral artery dissection, hypercoagulability, antiphospholipid syndrome, vasculitis, and substance abuse. No patients had an iatrogenic cause for the stroke.

CONCLUSION

There is a high number of strokes as a result of modifiable risk factors, and aggressive targeting of these could lead to a decline in stroke incidence. A frequent mistake is the diagnosis of cryptogenic strokes in patients who have had incomplete investigations for rare causes, for example, vasculitis, hypercoagulability, and autoimmune conditions. Repeating investigations such as cardiac monitoring, angiography, and serum testing should be considered.[4] Although the data are limited, small studies have suggested a favourable prognosis with cryptogenic strokes in the young with the recurrence rate for ischaemic strokes being less than 2% annually.[5]

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Carpal Tunnel Syndrome Symptoms Correlate with Strength-Duration Time Constant

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Keywords: Carpal tunnel syndrome (CTS), strength-duration time constant (SDTC).

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BACKGROUND AND AIMS

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy of the upper extremities, causing pain, paraesthesia, numbness, and weakness in the territory corresponding to the median nerve.[1-3] Although nerve conduction studies have been proposed for use in its diagnosis, the electrodiagnostic severity of CTS may not be associated with its clinical severity. The strength-duration time constant (SDTC) is a property of nodal membrane and, while it depends on a number of factors, its measurement may shed light on axonal properties when taken in conjunction with measurements of axonal excitability.[2] For example, SDTC increases with demyelination as the exposed membrane is enlarged by inclusion of the paranodal and internodal membrane, it decreases with hyperpolarisation, and it increases with depolarisation.[3] The Boston carpal tunnel questionnaire (BCTQ) is an easy, brief, self-administered tool for assessing symptom severity and functional status in CTS; recently, a Greek version has been validated.[1] The aim of this study was to correlate BCTQ with electrodiagnostic measurements including nerve axonal excitability.

MATERIALS AND METHODS

BCTQ was administered to 29 consecutive patients (25 females, four males; age: 57.48±15.48 years) referred to the authors' laboratory with symptoms consistent with CTS. All of the patients and 19 age-matched control subjects underwent motor conduction study and excitability measurements using Qtrac software.

RESULTS

For the 29 patients with CTS, the average SDTC was 0.54±0.13 µsecs and median nerve compound muscle action potential (CMAP) was 11.62±3.27 mV. Only SDTC was found to be strongly correlated with the BCTQ score, whereas the latency and amplitude of CMAP were not. The amplitude of CMAP correlated only with the functional status scale of the BCTQ.

CONCLUSION

A previous study compared the strength-duration behaviour of motor and sensory fibres in human subjects, determined the best method for deriving a SDTC, and evaluated the reproducibility of time-constant measurements to determine whether they could be suitable for clinical use.[4] The precise value of the time constant depends on a complex interaction of biophysical variables and on experimental technique. However, such measurements may prove a useful additional tool for probing the pathophysiology of peripheral nerve disorders in human subjects, particularly when combined with other measures of axonal properties such as excitability, latency, or CMAP. In this study, these measurements of SDTC may shed light on axonal properties in patients with CTS and could constitute a useful, relatively simple technique in clinical practice.

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Differences in Performance on Clock-Drawing Tasks as Predictive Measurements for Disease Classification Amongst Patients with Parkinson's Disease and Essential Tremor

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Clock drawing (CD) test, essential tremor (ET), Parkinson's disease (PD).

Citation: EMJ Neurol. 2020;8[1]:47-48.
Abstract No: AR6.

INTRODUCTION

Non-motor symptoms are widely recognised in both Parkinson's disease (PD) and essential tremor (ET). Clock-drawing (CD) tests appear to be impaired relatively early on during the progression of cognitive (executive) decline in PD.[1] However, the optimal measures for detecting cognitive changes in patients with ET have not been established.[2-4] This study examined whether the CD test could provide the opportunity to quickly predict visuospatial deficits in patients with ET.

METHOD AND RESULTS

Visuospatial performance was assessed in 58 consecutive patients with ET, 75 patients with PD, and 22 healthy controls (HC), all of whom had visited two specialised memory clinics in Athens, Greece. The 'CD and copy' (CC) tasks in the Parkinson's Disease-Cognitive Rating Scale (PD-CRS) were used as a test of visuospatial function.

Both CD and CC scores were lower for patients with ET compared to those with PD and HC ($p<0.001$ for both comparisons). A binomial

logistic regression showed that both CD and CC tasks could predict if participants had ET or PD with high sensitivity (94.7%), specificity (87.9%), and an area under the curve of 0.980 (95% confidence interval: 0.962–0.997). The model was able to explain 86.1% (Nagelkerke R2) of the variance in the disease variable (ET/PD) and correctly classified 91.7% of the cases.

CONCLUSION

These results showed for the first time that patients with ET have more frontal and visuospatial deficits compared to PD; similar previous studies have not shown this. In the study by Lombardi et al.,[5] the patients with PD exhibited poorer performance in visuospatial tasks compared to ET. Moreover, Gasparini et al.[6] reported that patients with PD performed worse in some verbal fluency and executive tasks than patients with ET. In the Benge et al.[7] study, the 15 patients with PD displayed a poorer performance in executive function tests than the 11 patients with ET. The results are, however, in agreement with the Lombardi et al.[5] functional MRI study which showed decreased functional connectivity in visual and frontoparietal network in patients with ET compared with those with HC. It could be speculated that these functional changes in ET may be an early marker of non-motor cognitive manifestations that are related to ET. However, additional studies are required before this hypothesis can be confirmed.

Patients with ET have more visuospatial deficits compared to those with PD. CD testing appears to be a robust predictor of ET, after adjustment for age and education. These findings suggest that the CD test may be an easy and useful tool to track cognitive changes in non-dementia patients with ET in clinical practice.

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A Novel Machine Learning Algorithm to Predict Lewy Body Dementia Using Clinical and Neuropsychological Scores

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Lewy body dementia (LBD), machine learning algorithm, Parkinson's disease dementia (PDD).

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BACKGROUND AND AIMS

Parkinson's disease dementia (PDD) and Lewy body dementia (LBD) are dementia syndromes that overlap in many clinical features, making their diagnosis difficult in clinical practice, particularly in advanced stages.[1,2] The authors propose a highly predictive machine learning algorithm, based on noninvasive procedures and predicators easy to attain within the clinic, to identify these disorders.

METHODS

The algorithm was developed using datasets from two specialised memory centres, employing a sample of 58 PDD and 28 DLB patients whose diagnostic follow-up was available for at least 3 years after the baseline assessment. A restricted set of information regarding clinico-demographic characteristics and six neuropsychological tests (Mini–Mental State Examination [MMSE], Parkinson's Disease-Cognitive Rating Scale [PD-CRS], Brief Visuospatial Memory Test-Revised [BVMT-R], Symbol Digit Modalities Test [SDMT], Wechsler Adult Intelligence Scale [WAIS], Trail Making Test [TMT] Parts A and B) were used as predictors. Two classification algorithms (logistic regression and K-Nearest Neighbors) were investigated for their ability to successfully predict whether patients had PDD or LBD.

RESULTS

The K-Nearest Neighbors classification model scored an accuracy of 91.2% of overall cases based on the 15 best clinical and cognitive features, achieving 96.42% sensitivity and 67.00% specificity on discriminating between the two conditions. Regarding the binomial logistic regression classification model, it achieved an accuracy of 87.50% on average based on the 15 best features, showing 93.93% sensitivity and 57.00% specificity. Previous machine learning studies achieved promising results for predicting other types of dementia;[3,4] however, these models have been shown to have moderate discriminatory capabilities with area under the curve (AUC) ranging from 0.60 to 0.78. The accuracy of 91.2% AUC and a sensitivity of 96.0% in the authors' model indicates that this version is able to prescreen patients for follow-up diagnosis or evaluate their suitability for clinical trials. Most of the previous models cannot address the issue of lack of precision in data collection, limiting their performance and generalisability to other settings. Furthermore, because each work used different methods (e.g., bagging decision tree, support vector machine, nearest mean classifiers), no safe conclusion can be made concerning the most suitable model to use in clinical practice. Nevertheless, the results obtained support the application of the proposed algorithm in clinical practice for clinicians in PDD and DLB diagnosis.

CONCLUSION

The proposed algorithm has a high prognostic performance to predict PDD and LBD with high accuracy using easy to calculate neuropsychological scores. Furthermore, it improves the recruitment in clinical trials, which could potentially be used as additional decision-making tool in clinical practice.

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The Potential of Asymmetric Stimulation Frequency in Subthalamic Stimulation for Parkinson's Disease

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Disclosure: Prof Defebvre has served on the advisory board, served as a consultant, and given lectures for AbbVie, Orkyn', and Aguettant. Dr Kreisler declared that there are no conflicts of interest relevant to this work and reports personal fees from Allergan France SAS, Merz Pharma France, and grants and personal fees from Ipsen outside the submitted work. Prof Devos has received PHRC grants from the French Ministry of Health and research funding from the ARSLA charity, the France Parkinson charity, and European Commission (H2020). He has served on the advisory board, served as a consultant, and given lectures for ApoPharma, Orkyn', Air Liquide, Aguettant, Ever Pharma, and Boston Scientific. Dr Moreau has received grants from the France Parkinson charity and honoraria from Orkyn', ApoPharma, and Boston Scientific for consultancy and lectures on Parkinson's disease at symposia. The remaining authors have declared no conflicts of interest.

Keywords: Deep brain stimulation (DBS), Parkinson's disease (PD), tremor.

Citation: EMJ Neurol. 2020;8[1]:50-52. Abstract Review No: AR8.

BACKGROUND AND AIMS

Subthalamic deep brain stimulation (STN-DBS) is an effective treatment for motor fluctuations in Parkinson's disease (PD). Several parameters can be controlled to improve the clinical outcomes. Among them, frequency has variable clinical effects,[1] perhaps owing to the differential impact on downstream networks. High-frequency stimulation (HFS) (i.e., above 100 Hz) is classically the best choice to control the segmental PD symptoms[2] and may also improve akinesia and tremor. Higher frequencies (i.e., 130–180 Hz) can further improve the tremor;[1] however, they may also worsen axial symptoms in late-stage PD patients as exemplified in gait.[3] Thus, there is a potential benefit to fine-tune stimulation frequency independently in both hemispheres to account for asymmetric symptom expression. Beyond directional leads[4] the Cartesia-Boston® system for STN-DBS (Vercise Cartesia™, Boston Scientific, Santa Clarita, California, USA) allows configuring different frequencies of stimulation between left and right hemispheres (called differentiated frequency).[5] The authors sought to explore if differentiated frequency can improve the asymmetrical tremor in patients with STN-DBS.

METHODS

Seventeen PD patients with STN-DBS (implanted with the Cartesia-Boston® system) were assessed under four conditions (stimulation on/medication off, stimulation off/medication off, stimulation off/medication on, stimulation on/medication on) 1 year after implantation. All patients participated in the PREDI-STIM study,[6] a multicentre study of the predictive factors of the therapeutic response to subthalamic stimulation on the long-term quality of life in 700 people with PD. Four of these patients (Table 1) were not satisfied with their DBS outcomes because of persistent asymmetrical tremor. All patients were initially programmed with a stimulation frequency of 130 Hz bilaterally. The persistent tremor was not resolved with medication changes, increased stimulation amplitude, or stimulation on different contacts (including directional stimulation). Pulse width was reduced in two patients.

Table 1: Clinical features of the four patients and DBS parameters proposed to relieve their tremor.

Patient	Age	Sex	Disease duration (years)	LEDD change (mg)	MDS-UPDRS III worst off	MDS-UPDRS III best on	Left side parameters				Right side parameters			
							Contact configuration	Amplitude (mA)	Frequency (Hz)	Pulse width (µ secs)	Contact configuration	Amplitude (mA)	Frequency (Hz)	Pulse width (µ secs)
1	68	F	16	-1700	75	14	5 (23%), 6 (23%), 7 (24%), 8 (30%)	4.1	185	30	13 (33%), 14 (33%), 15 (34%)	4.7	140	30
2	58	M	17	-416	49	6	5 (20%), 6 (20%), 7 (20%), 8 (40%)	4.2	140	30	13 (16%), 14 (17%), 15 (17%), 16 (50%)	3.6	185	30
3	56	M	12	-445	54	14	5 (33%), 6 (33%), 7 (34%)	3.6	140	60	10 (100%)	3.0	185	60
4	64	M	25	-627	87	8	5 (33%), 6 (33%), 7 (34%)	4	130	60	10 (33%) 11 (33%), 12 (34%)	4.0	174	60

Best on condition: stimulation on/medication on; F: female; LEDD change: levodopa equivalent daily dose change between pre- and post-DBS implementation; M: male; MDS-UPDRS: Movement Disorder Society-unified Parkinson's disease rating scale; worst off condition: stimulation off/medication off.

Increasing the frequency of stimulation reduced the asymmetrical tremor, but all four patients reported worsening of the akinesia and hypertonia on the opposite side. Therefore, differentiated frequency was proposed with the higher frequency programmed contralateral to the side with the persistent tremor. To assess the efficacy of tremor reduction on the most affected side, the authors calculated a tremor subscore corresponding to the sum of the following items of the Movement Disorder Society-unified Parkinson's disease rating scale (MDS-UPDRS) Part III: 3.15 (postural tremor of the hands), 3.16 (kinetic tremor4.0of, the hands), 3.17 (rest tremor amplitude for upper and lower limb), and 3.18 (constancy of rest tremor).

RESULTS

With differentiated HFS, (185 Hz versus 140 Hz for three patients, 174 Hz versus 130 Hz for the last one) tremor subscore decreased for three patients (Table 1). Patient clinical global impression improved one point for three patients in comparison with symmetrical HFS (130 Hz on both sides). One patient did not report any change and no worsening of the total MDS-UPDRS III was observed.

CONCLUSION

Expanded programming flexibility with the opportunity to programme different frequencies for each side could be optimal for certain patients to reduce tremor and maintain a good control of the other symptoms. Despite this proof of concept, further clinical trials remain necessary because of interpatient variability.

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Effective Long-Term Treatment with Incobotulinum Toxin After Immunoresistance to Abo- or Ona-Botulinum Toxin in Patients with Cervical Dystonia

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Keywords: Complex proteins, incobotulinumtoxinA (incoBoNT/A), low antigenicity, neutralising antibodies (NAB) formation, secondary treatment failure.

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Table 1: Comparison of demographic and treatment-related data in the AB-pos- and AB-neg-group.

	AB-pos-group	AB-neg-group	p value
n	16	34	
Female/male	11/5	21/13	
Age at therapy onset (years) (mean/SD)	48.98/11.15	47.79/8.75	n.s.
STSUI (mean/SD)	8.19/2.63	8.00/3.57	n.s.
SDose (uDU) (mean/SD)	294/66	243/74	0.023
ATSUI (mean/SD)	6.44/2.00	5.29/3.28	n.s.
ADose (mean/SD)	384/82	338/91	n.s.
TSATSUI (days) (mean/SD)	2633/1103	2822/1130	n.s.
IMP (%) (mean/SD)	18/43	54/23	0.009

AB-neg-group: patient group that were negative for neutralising antibodies; AB-pos-group: patient group that were positive for neutralising antibodies; ATSUI: TSUI-score at present; IMP: the improvement of cervical dystonia since the switch to incobotulinumtoxunA; n.s.; nonsignificant; SD: standard deviation; SDose: dose at switch; STSUI: TSUI minus the score at switch; TSATSUI: time period from switch to the present time; uDu: unit dose uniformity.

BACKGROUND AND AIMS

Popularity of the use of botulinum neurotoxin Type A (BoNT/A) is rapidly increasing.[1] The production of antibodies (AB) against various parts of this BoNT/A complex can be induced, which is hard to avoid during long-term treatment.[2] Some AB can reduce the biological function of BoNT/A (neutralising AB [NAB]), others cannot. NAB first reduce duration of efficacy; later, with increasing titres, complete treatment failure occurs.

The onabotulinumtoxinA (onaBoNT/A; Botox®, Coolock, Ireland) and abobotulinumtoxinA (aboBoNT/A; Dysport®, Ipsen, Paris, France) contain the entire botulinum toxin Type A complex with all its different biologically inactive complex proteins. In contrast, the more recently licensed incobotulinumtoxinA (incoBoNT/A; Xeomin®, Merz Pharma, Frankfurt, Germany) only contains the pure BoNT/A toxin. Therefore, the protein load during treatment with incoBoNT/A is very low, as is its antigenicity.[3]

During long-term treatment of over 10 years with aboBoNT/A or onaBoNT/A for cervical dystonia (CD), induction of NAB occurs in up to 14% of patients. It has been recommended that BoNT/A therapy should be stopped and deep brain stimulation should be performed when a secondary treatment failure has developed.

This cross-sectional study investigated the effectiveness of switching to incoBoNT/A in patients with CD who were partially resistant under treatment with aboBoNT/A or onaBoNT/A.

METHODS AND MATERIALS

In this study, 50 patients with CD with the development of a progressive, clear-cut partial secondary treatment failure (PSTF) after aboBoNT/A or onaBoNT/A treatment who had been switched to incoBoNT/A years prior were recruited. Blood samples were taken for determination of the presence of NAB using the mouse hemidiaphragm assay and demographic as well as treatment-related data were extracted

from the charts. Furthermore, patients had to assess the improvement of CD since the switch to incoBoNT/A.

RESULTS

NAB were detected in 16 (32%) of the patients (AB-pos-group). In 34 (68%) patients, no NAB could be detected by means of the mouse hemidiaphragm assay (AB-neg-group). On the day of the switch, the mean severity of CD (STSUI), measured by the TSUI-score, did not differ significantly between both AB groups. However, the dose of incoBoNT/A that had been chosen years earlier to initiate incoBoNT/A was significantly lower ($p<0.023$) in the AB-neg- compared to the AB-pos-group. Duration of incoBoNT/A treatment did not differ between both groups (7.3 years in the AB-pos- and 7.8 years in the AB-neg-group) (Table 1).

During incoBoNT/A, severity of CD scored by means of the TSUI-score was significantly improved by 21.4% ($p<0.05$) in the AB-pos- and by 33.9% ($p<0.01$) in the AB-neg-group ([STSUI minus the TSUI-score at present] divided by STSUI). Dose at switch was significantly increased by 90 mouse units incoBoNT/A in the AB-pos ($p<0.05$) and by 95 mouse units ($p<0.01$) in the AB-neg-group. The outcome (TSUI-score at present) between both groups did not differ significantly. However, the patient's global assessment of the treatment effect was significantly better in the AB-neg- compared to the AB-pos-group.

CONCLUSION

In patients with CD and progressive PSTF after abo- or onaBoNT/A therapy, switch to incoBoNT/A can play a prominent role in the level of improvement and should have higher priority over deep brain stimulation in the treatment plan. The improvement observed after the switch to incoBoNT/A is long-lasting with a mean duration of over 7 years, in contrast to the short-lasting improvement observed after the switch to rimabotulinumtoxinB. Furthermore, persistence of NAB after the switch to incoBoNT/A appeared to have a negative influence on long-term outcome in patients with CD and PSTF after abo- or onaBoNT/A treatment.

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Foramen Magnum Meningioma Presenting as Cervical Myelopathy in a Patient with Seronegative Neuromyelitis Optica Spectrum Disorder Overlapping with Primary Sjögren's Syndrome

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Keywords: Foramen magnum meningioma, neuromyelitis optica spectrum disorder (NMOSD), primary Sjögren's syndrome (SS).

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BACKGROUND

Meningiomas are the most common primary tumours of the central nervous system,[1,2] with a prevalence of 97.5 per 100,000 population.[1] They are typically benign and cause symptoms by compression. Foramen magnum meningiomas account for 1.8–3.2% of all meningiomas.[3,4] Neuromyelitis optica spectrum disorders (NMOSD) are inflammatory autoimmune diseases of the central nervous system, primarily targeting the optic nerves and spinal cord, with a prevalence as high as 10.0 per 100,000 population.[5] Approximately 20% of people with NMOSD are seronegative for aquaporin-4 antibodies and up to 75% of these patients are also seronegative for myelin oligodendrocyte glycoprotein antibodies.[6] NMOSD may coexist with other organ-specific or systemic autoimmune disorders, including Sjögren's syndrome (SS). Whilst the exact prevalence of this overlap is unknown, SS, systemic lupus erythematosus, and myasthenia gravis are the most frequently reported systemic autoimmune diseases associated with NMOSD.[7-9]

CASE REPORT

The authors report the case of a 52-year-old male who had had recurrent cervical and thoracic myelitis for 12 years, compatible with seronegative NMOSD overlap with primary SS. He achieved sustained clinical remission following immunosuppression with cyclophosphamide (pulses: 8; total dose per pulse: 800 mg/m^2; no notable side-effects). He was admitted for paresthesia in the cervical dermatomes and limb weakness, which had developed over the previous month. The neurological examination revealed bilateral C2 hypoesthesia, tetrameric hypopallesthesia, and mild tetraparesis predominantly in the lower limbs. MRI of the cervical spine showed a voluminous contrast-enhancing epidural mass, consistent with a foramen magnum meningioma, that was compressing the C1–C2 spinal cord and medulla. Mild signal changes consistent with myelopathy were also present in the corresponding spinal cord segments. High-dose methylprednisolone brought no significant improvement and did not preclude the clinical progression. The patient underwent minimally invasive surgery with complete excision of the tumour. The neuropathology diagnosis was benign meningioma. Postoperatively he recovered completely.

DISCUSSION

Foramen magnum meningiomas are rare, representing 2.5% of all meningiomas. The mean age at the time of diagnosis is 55 years, similar to this present case. However, they can occur in any age group. There is no established association between meningioma and NMOSD or primary SS. On account of the patient's history of recurrent cervical and thoracic myelitis, the possibility of cervical myelitis was also considered. Nevertheless, the lack of signal change in the cervical cord suggesting recent myelitis and the complete remission following removal of the meningioma argue against this diagnosis. The predominance of weakness in the lower limbs is atypical considering the somatotopy of the corticospinal tracts with the pattern expected with spinal cord compression from periphery to centre and from the posterior to the anterior facet. In this case, it might be inferred that changes from previous myelitis may have resulted in the clinical expression of an otherwise subclinical lesion.

CONCLUSION

This case illustrates the importance of accurate clinical assessment and that of ascertaining anatomoclinical correlation for an early diagnosis and prompt therapeutic management.

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A Case Report of a Patient with T-Lymphoblastic Leukaemia/Lymphoma

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Keywords: Cerebrospinal fluid, flow cytometric (FCM) immunophenotyping, meningeal syndrome, T-lymphoblastic lymphoma (T-LBL).

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BACKGROUND

T-lymphoblastic lymphoma (T-LBL) is a neoplasm of immature T-cell precursors or lymphoblasts.[1] This neoplasm tends to occur in older adolescents, with a male predominance.[1] T-LBL usually presents as an anterior mediastinal (thymic) mass with supradiaphragmatic lymphadenopathy and variable splenic, hepatic, and bone marrow involvement (with leukaemic phase of the illness).[2] T-cell acute lymphoblastic leukaemia localised to the central nervous system (CNS) represents <5% of cases, and does not have the subsequent systemic evolution of usual cases of acute lymphoblastic leukaemia.[2-4]

METHODS AND MATERIALS

Multiple diagnostic tests can be undertaken in assessment of suspected cases of T-LBL: somatic and neurological examination; laboratory tests including flow cytometric (FCM) immunophenotyping of cerebrospinal fluid, antiphospholipid antibody, rapid plasma reagin, and HIV testing; MRI of the head; X-ray of the thorax; coronary angiogram; lymphocytic choriomeningitis testing; and trepan biopsy of bone marrow.

CLINICAL CASE

This summary presents a clinical case of a 44-year-old patient admitted to the emergency department with complaints of progressively increased headache, stiffness of the neck, impaired co-ordination, nausea, vomiting, and irritation from noise and light. Consent to publish this case was obtained from the patient's family. The patient had a meningeal syndrome, and MRI showed a tumour in the left cavernous sinus area.

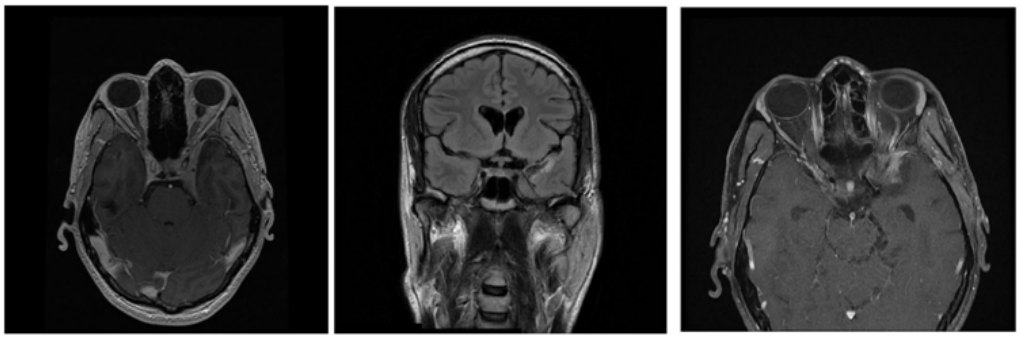

Figure 1: T-lymphoma MRI images.

The patient had a history of peripheral facial nerve palsy, and MRI showed extra-axial tumour formation in the left cavernous sinus area and retro-orbital area (Figure 1). Biopsy was performed 3 months earlier and the histology showed partially hyalinised connective tissue. Blood testing showed a slightly increased troponin I at 1,761.4 pg/mL, C-reactive protein of 25.4 mg/L, a negative QuantiFERON-TB Gold test, negative tests for hepatitis B and C, antiphospholipid antibody, and HIV, and negative rapid plasma reagin test. The X-ray of the thorax was without pathological changes.

Because of the laboratory constellation of results, coronary angiography was performed; no stenosis or thrombosis were observed. A lumbar puncture was performed because of the meningeal syndrome; examination of the cerebrospinal fluid showed lymphocytic pleocytosis and atypical cells in different phases of mitosis, with a negative result for lymphocytic choriomeningitis. Trepan biopsy of bone marrow was without pathological changes. FCM of cerebrospinal fluid was diagnostic for T-lymphoblastic leukaemia/lymphoma. Intrathecal chemotherapy was started.

CONCLUSION

CNS T-LBL is a rare disease with an incidence of approximately 51 cases per 10 million per year.[5,6] Differential diagnoses include aseptic meningitis, brainstem glioma, granulomatous angiitis, neurological infections, neurosarcoidosis, and neurosyphilis.[5] FCM of cerebrospinal fluid could help to make the right diagnosis.[7] FCM is a highly sensitive technique capable of detecting malignant cells.[7,8,9] FCM can detect CNS disease before the manifestation of clinical symptoms; the routine use of flow cytometry and cytology may permit the earlier detection of neoplasm.

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Ubiquilin-2 Gene Mutation Presenting with Adult-Onset Ataxia and Spasticity: Report Of A Novel Phenotype Case

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INTRODUCTION

UBQLN2 is a member of the ubiquitin-like protein family and plays a critical role in protein clearance pathways including the ubiquitin–proteasome system.[1,2] It also functions to modulate autophagy, cell signalling, cell-cycle progression, and cytoskeletal association.[2] *UBQLN2* mutations cause a small subset of amyotrophic lateral sclerosis (ALS), and ALS-frontotemporal dementia (ALS–FTD) cases.[3-6] More widespread is the presence of UBQLN2-positive inclusions in the affected neurons of some familial and sporadic ALS and ALS-FTD cases, indicating a pathogenic role for *UBQLN2* in these diseases.[1,5-8]

CASE PRESENTATION

A 35-year-old female with normal developmental milestones and an unremarkable personal and family history presented with oscillopsia, dizziness, and unstable gait with subacute onset and gradual progression.

The neurological examination revealed mild cognitive impairment, diplopia, dysarthric speech, marked tremor, limb and gait ataxia, along with evident spasticity. In the first 2 years, the patient deteriorated, evolving difficulty in swallowing thin liquids as well as urinary incontinence, fasciculations, and required bilateral assistance for walking.

Blood examinations were notable for iron deficiency anaemia. Cerebrospinal fluid analysis was normal and examination for autoimmune and metabolic diseases was insignificant. Brain and spinal cord MRI scans were normal initially and on follow-up, while the electroencephalographic examination recorded mild diffuse slowness with rare lateralised epileptiform discharges on the right hemisphere without deterioration. A wide panel for antibodies causative of autoimmune and paraneoplastic encephalomyelitis was negative, as well as investigation for underlying malignancy with full body CT and PET scan. Genetic testing for common modalities causing ataxia and/or spasticity showed no pathology. Needle electromyography was consistent with mild denervation in the first dorsal interosseous muscle of the right hand. The patient received first-line immunotherapies, with no amelioration of signs and symptoms.

Whole exome sequencing was performed, revealing a mutation in the *UBQLN2* gene in X-chromosome [c.1019G>T (p.Ser340Ile)]. Genetic testing was performed for the patient's parents, revealing the same mutation in her father, who is asymptomatic at the age of 65 with the same neurophysiologic findings in needle electromyography.

Following the initial deterioration, the patient had a stable disease course at 5-years follow-up and is receiving symptomatic treatment for tremor and spasticity.

DISCUSSION

Studies have revealed that *UBQLN2* plays a pathogenic role in X-linked ALS with or without FTD.[3,5-7] The course of familial ALS is slower than that of sporadic cases.[9] *UBQLN2* mutations have been associated with ALS with onset from third to seventh decade, with spasticity, muscle weakness, dysphagia, and dysarthria. Women tend to manifest milder phenotypes, with late onset and decreased penetrance.[3,9,10]

CONCLUSION

Here is presented a case with clinical features of predominant ataxia with evident spasticity but without muscle weakness, and with stable disease course after the initial progression after a 5-year follow-up. This phenotype has not previously been documented in association with a mutation in the *UBQLN2* gene.

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Could Telemedicine Improve Neurocognitive Disorders Detection and Diagnosis in Nursing Homes?

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Keywords: Cognitive disorders diagnosis, dementia, long-term care, nursing home, telemedicine (TLM).

Citation: EMJ Neurol. 2020;8[1]:59-61. Abstract Review No. AR13.

Table 1: Benefits of neurocognitive disorders aetiological diagnosis for nursing homes' patients: a tool proposed by « ACT ON DEMENTIA » to support neurocognitive disorder diagnosis in nursing homes.[2]

	NCD diagnosis benefits	Benefit depending on NCD aetiological diagnosis?	Benefit applicable for nursing homes' patients?
For the patient	Right to know	Yes (but also the right not to know) Less for severe stages	Applicable
	Plan for the future	Yes Less for severe stages	Rarely applicable Depending on life expectancy, dependence, stage
	Other NCD diagnosis	Yes Less for severe stages	Applicable
	Appropriate dementia diagnosis and appropriate care	Yes Less for severe stages	Applicable
	Access to 1/2/3 prevention and post diagnosis support	Partially Better adapted when aetiological diagnosis	Applicable If post diagnosis support for NH patients
	Prevent/early manage BPSD	Partially Better adapted with aetiological diagnosis	Applicable
	Reduce dangerous behaviours	Yes	Rarely applicable Mostly dependant patients, already safe environment
For the family carer	Providing emotional support to the patient	Partially Better with aetiological diagnosis	Rarely applicable Patient living in NH
	Competences improvement	Yes Less for severe stages	Rarely applicable Competences already exists in NH
	Genetic counselling/ research programmes	Yes	Applicable
For the healthcare professional	Giving a personalised treatment, avoiding iatrogenic consequences	Yes	Applicable Particularly for antipsychotics and Lewy disease
	Facilitate access to appropriate support services, care pathway	Yes Less for severe stages	Applicable If post diagnosis support for NH patients
	Facilitate access to genetic counseling	Yes	Applicable For family carers

BPSD: behavioural and psychological symptoms of dementia; NCD: neurocognitive disorder; NH: nursing home.

In Europe, there is a lack of detection of neurocognitive disorders (NCD) in primary care, particularly in nursing homes. Obstacles in nursing homes include general practitioners' limited time, unawareness of diagnosis guidelines and tools, and difficulties to refer patients who are disabled to NCD specialist doctors. Telemedicine (TLM) could improve access to specialist doctors and increase NCD diagnosis.

In the context of the "Act On Dementia" European Joint Action, three countries (Bulgaria, France, and Greece) tested TLM for NCD detection and diagnosis in six nursing homes (one in Bulgaria, three in Greece, and two in France). NCD detection tools for patients were shared as well as satisfaction and dementia attitude questionnaires for nursing homes staffs. The experiments were planned from April 2018 to June 2018.

The six nursing homes were faced with various legal, ethical, and practical requirements before TLM could be implemented. Results at 3 months varied. In Greece, the nursing homes' staffs were trained about NCD via a 30-hour tele-educational programme. In France, despite altered Mini-Mental State Examination (MMSE) scores and current TLM for behavioural disorders (behavioural and psychological symptoms of dementia [BPSD]), there were few requests for NCD diagnosis, probably a result of unawareness of diagnosis benefits for nursing homes' residents. In Bulgaria, nursing homes' staff training and 17 teleconsultations for NCD diagnosis took place and led to mild-to-major NCD diagnosis, including aetiological diagnosis in 16 cases. Despite the challenges, all the nursing homes' teams were satisfied with TLM. The dementia attitude scale results were similar between the different nursing homes, countries, and health professionals and other nursing homes' professionals.

Each country identified facilitators to improve NCD diagnosis in nursing homes, e.g., a shared tool explaining the benefits of NCD aetiological diagnosis for nursing homes' patients (Table 1) to be included in the NCD educational programme for nursing homes' staff and general practitioners, which represents a crucial step for a successful TLM programme.The first request for TLM for NCD in nursing homes was for BPSD; NCD detection and diagnosis in nursing homes could be improved by TLM when combined with BPSD evaluation.

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Driving Behaviour in Alzheimer's Disease and Amnestic Mild Cognitive Impairment Carriers of the *Apolipoprotein E4* Allele

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Keywords: Alzheimer's disease (AD), *APOE4*, driving behaviour.

Citation: EMJ Neurol. 2020;8[1]:61-63. Abstract Review No: AR14.

BACKGROUND AND AIM

Patients with Alzheimer's disease (AD) indicate impaired driving behaviour and their driving profile is described as conservative, although they maintain the ability to operate a vehicle.[1] According to previous research, patients with mild cognitive impairment (MCI) are generally considered safe drivers, however, they also have driving performance deficits.[2] Literature regarding the severity of driving impairments in MCI and mild AD has not yet reached a consensus. A recent meta-analysis suggested that the severity of cognitive decline appears to have important predictive utility over driving ability in patients with AD and patients with MCI.[3] The *apolipoprotein E4* (*APOE4)* allele, a well-documented genetic risk factor for AD, affects cognition of carriers within the clinical stages of MCI and AD, as reported by studies comparing them with non-carriers. The aim of the current study was to compare the driving behaviour of carriers and non-carriers of *APOE4* in the clinical stages of mild AD or amnestic MCI (aMCI).

MATERIALS AND METHODS

Included in the study were 36 active drivers with aMCI or mild AD. Of whom, 18 were carriers of *APOE4* and 18 were non-carriers. Each group included 13 aMCI and five mild AD. The two groups had no significant differences in age, years of education, general cognitive ability, and driving experience.

All patients underwent a thorough medical, ophthalmological, neurological, and neuropsychological assessment, and participated in a driving simulation experiment which included a rural environment with low- and high-traffic-volume conditions. Plasma samples were used for *APOE* genotyping.

RESULTS

The application of independent samples t-test indicated that in high traffic volume, *APOE4* carriers had significantly lower average speed (mean [M]= 32.6; standard deviation [SD]= 7.0) than non-carriers (M=38.2; SD=6.1; t[30]=2.40; p=0.023; d=0,85). *APOE4* carriers had also lower speed variation (M=7.7; SD=1.5) than non-carriers (M=11.2; SD=2.8; t[30]=4.36; p<0.001; d=0.70). Nonetheless, after the application of the Bonferroni correction the only difference that survived was the measure of speed variation. In low traffic volume there were no significant differences. Regarding the neuropsychological measures, the independent samples t-test detected a significant difference only in the domain of episodic memory. *APOE4* carriers had more severe episodic memory disorders (M=5.4; SD=3.3) than non-carriers (M=7.7; SD=2.6; t[27]=2.31; p=0.027; d=0.80). However, this result did not survive after the application of Bonferroni correction.

CONCLUSION

To the authors' knowledge, this is the first study to investigate the possible effect of *APOE4* to driving behaviour. The study found that *APOE4* genotype moderates the behaviour of the carriers in a cognitively demanding condition like driving. It should be highlighted that the driving simulator experiment was able

to depict a robust significant difference in terms of speed variation despite the absence of significant differences in a variety of neuropsychological measures.

Lower speed variation could sometimes reflect a strategy of compensation that is utilised by drivers in order to avoid driving errors.[4] Along this vein, the lower values of the *APOE4* carriers could be regarded as a compensatory behaviour for an underlying attentional deficit that was not depicted by the applied neuropsychological measures. Future studies could expand the conclusions of the current study by utilising larger samples as well as by investigating the driving behaviour of *APOE4* carriers in preclinical stages.

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An Evaluation of the Studies on the Therapeutic Effects of Yoga in People with Dementia

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INTRODUCTION

The global population is ageing, and the prevalence of dementia is increasing. Current conventional drug therapy lacks efficacy; therefore, there is growing interest in nonpharmacological interventions of complementary and alternative medicine.[1,2] Yoga is an ancient Indian practice which is characterised as a mind–body medicine modality according to the National Center for Complementary and Integrative Health (NCCIH).[1] Yoga therapy is an inherently holistic approach including asana (the physical posture), pranayama (breathing exercise), meditation, and guided imagery. Yoga has many therapeutic benefits for individuals with a broad range of chronic diseases such as cancer, asthma, diabetes, arthritis, fibromyalgia, anxiety, and depression. Various physical postures, such as yogic breathing (voluntary control of abdominal breathing) and meditation yoga exercises, stretch and relax muscles while other exercises balance the body and mind to reach a state of mind–body integration.[1] Many programmes for people with dementia combine yoga with physical and occupational therapy including tai-chi and dance in community settings based on specific techniques: a) repetition with variations, b) progressive and functional movements, c) step-by-step instructions, d) goal orientation, e) physical care, mindfulness, and breathing, and f) social interaction.[1] By integrating mindfulness into dementia practice, yoga can promote calmness and improve balance, mobility, and strength for patients.

Although yoga has been used as a complementary health approach for enhancing wellness and physical health, little is known about the impact of yoga on cognitive function in adults with dementia. So far there are only two systematic reviews. In 2017, Du and Wei[3] conducted a systematic review of the therapeutic effects of yoga in individuals with dementia, which included one related study,[2] and found that yoga significantly improved cognitive and motor functions and behavioural issues.[3] In 2018, Brenes et al.[4] reviewed four yoga intervention studies of dementia patients with beneficial effects on cognitive domains, particularly attention and verbal memory (Table 1);[4] however, these conclusions should be considered with caution.

LIMITATIONS OF THE INCLUDED STUDIES

The first critical issue is the methodology to establish the diagnosis of dementia. Most studies examined mild-to-moderate dementia based on the Mini-Mental State Examination (MMSE)[2,5] or Short Portable Mental Status Questionnaire (SPMSQ).[6]

Table 1: Summary of yoga intervention studies for individuals with dementia in two systematic reviews.

	Fan, Chen[2] 2011	Litchke et al.[6] 2014	Paller et al.[10] 2015	Barnes et al.[5] 2015
Study type	Quasi-experimental	Quasi-experimental	Quasi-experimental	Quasi-experimental
Sample size (n)	68	19	17	12
Participants	Mild-to-moderate dementia	Mild-to-severe Alzheimer's disease	Mild cognitive impairment, Alzheimer's disease, frontotemporal dementia, subjective cognitive complaints	Dementia
Control group	NA	NA	NA	Usual care
Yoga programme (duration, frequency/ week)	Silver yoga/hatha (55 min, 3x/12 weeks)	Lakshmi Voelker Chair Yoga (60 min, 3x/10 weeks)	Gentle yoga, loving-kindness practice, meditation (1.5 hours, 1x/8 weeks)	Body awareness, chair-based exercises adapted from tai-chi, yoga, and Feldenkrais (45 min, 3x/18 weeks)
Adherence (%)	90.9	70.3	NA	72.2
Cognitive measurements	MMSE	SPMSQ	RBANS Trail Making Test Parts A and B	MMSE, ADAS-Cog
Biomarkers	No	No	No	No
Adverse events	NA	NA	NA	Dizziness/nausea, legs buckling, hip pain
Main outcomes	Improvement of neuropsychiatric and physical symptoms	No significant improvement of cognitive symptoms and activities of daily living	Improvement of neuropsychiatric, cognitive, and physical symptoms and quality of life	Improvement of cognitive symptoms, caregiver distress, and quality of life

ADAS-Cog: Alzheimer's Disease Assessment Scale–Cognitive Subscale; MMSE: Mini-Mental State Examination; NA: not available; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; SPMSQ: Short Portable Mental Status Questionnaire.

However, the content of the MMSE is highly verbal, lacking sufficient items to adequately measure visuospatial and/or constructional praxis. Litchke et al.[6] used the SPMSQ as a sensitive and specific screening test for moderate-to-severe dementia; therefore, it should not serve as the sole criterion for dementia diagnosis or for differentiating between various forms of dementia.[7] Furthermore, the included studies did not use any specific clinical criteria for dementia subtyping. According to the updated criteria for the diagnosis of Alzheimer's disease,[8] to better characterise these patients, neuroimaging data of genetic and blood/ cerebrospinal fluid (amyloid and tau) biomarkers are required to support the diagnosis of dementia in future studies.[9]

A second limitation is the lack of specific neuropsychological measurements to detect changes in different cognitive domains.[2] In the study of Paller et al.,[10] patients with dementia were assessed based on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) for each of the five domains tested (immediate memory, visuospatial/ constructional, language, attention, and delayed memory) and Trail Making Test (TNT) (Part A [processing speed]).[10] There was no assessment of executive function, phonemic fluency, or motor responses.[10] Barnes et al.[5] used the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) that includes direct assessment of learning (word list), naming (objects), following commands, constructional praxis (figure copying), ideational praxis (mailing a letter), orientation

(person, time, place), recognition memory, and remembering test instructions. Measurement of these neuropsychological variables at multiple time points would have been more informative as cognitive domains can have differential trajectory of change. Additionally, the authors did not use any other tests to assess quality of life or anxiety, which may affect cognition and mental wellbeing before and after the yoga intervention.[2,5,6] Finally, it would be more appropriate to combine neuropsychological and fluid biomarker data to accurately measure the cognitive changes produced by yoga programmes, as was previously suggested for other neurodegenerative disease (e.g., Parkinson's disease).[11]

Third, there are several factors that may limit the generalisability of the above studies. The study sample size was small, which limited the applicability of the results to a broader population. In all studies, expectation bias may have existed because participants were aware of the treatment allocation. In both studies, participants were enrolled through convenience sampling, thus, selection bias should also be considered. In the study of Fan and Chen,[2] possible differences in characteristics might have existed that were not captured in this study including a cluster effect. There might have been a potential bias based on dropout rate (n=33), particularly with the moderate sample size,[2] and furthermore, the randomisation was not entirely perfect in the included studies resulting in a female predominance. In future studies, an experimental design with three groups (yoga group, standard exercise group, and control group) using pre- and post-test comparisons should be applied. Furthermore, the results of these reviews were based on a unique population of people with mild-to-moderate dementia who attended short follow–up sessions.

Finally, there is wide variability in the type and method of yoga used for intervention and few studies report the training type/level of their instructors. While this is reflective of the fact that there are several different types of yoga disciplines and practices, it limits the generalisability of results. Frequency and intensity (hours, weeks) of intervention periods generally fell within the 8–12-week range. This variability of yoga programmes does not permit the monitoring of intervention fidelity and these disparities negatively impact the conclusions on dose–response relationships.

IMPLICATIONS FOR FUTURE STUDIES

More consistent documentation of the intervention, instructor training, and frequency and intensity will elevate the quality of yoga research. There is a need for future multicentre yoga studies to incorporate a multidisciplinary programme including physicians, nurses, social workers, and psychologists. The key message of yoga is to encourage and enable people with dementia to remain physically active for as long as possible so they can reap the many benefits.[1] All health providers may consider recommending yoga to individuals with dementia as a safe and potentially beneficial complementary health approach. Considering that dementia limits the ability to perform a mental programme such as yoga, healthcare professionals should target patients who are in the mild and moderate stages of dementia. The latter allows the proposition of yoga programmes characterised by a simple language, with clear and repetitive instructions, e.g., using imitation as a starting point. Given the lack of mechanistic studies that support the practice of yoga in the context of dementia, these studies are important to elucidate stress-related pathways and improve behavioural mediated disorders in the future.

CONCLUSION

Overall, the evidence on the effects of yoga in patients with dementia is limited and conflicting in some cases. Although promising, studies that combine yoga have methodological limitations (small sample, absence of biomarkers/follow up, brain MRI, different protocols/measures). Although their effectiveness is rather modest, the absence of serious side effects allow us to encourage their use in addition to standard treatments. Nevertheless, the preliminary nature of the existing evidence highlights the need for longitudinal studies with a rigorous methodology to define the optimal frequency and intervals of yoga, and to evaluate the cost-effectiveness for people with dementia. Given these considerations and the increasing availability of yoga in community settings, clinicians may consider recommending yoga to individuals with dementia. Future rehabilitation programmes with yoga could consider integrating more skills (sleep routine, exercise, healthy

dietary habits) into physical and mental therapy to enhance the holistic wellbeing of people with neurodegenerative conditions.

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Current Paradigms to Explore the Gut Microbiota Linkage to Neurological Disorders

EDITOR'S PICK

The investigation of gut microbiota in neurological disorders is a very exciting field of future neurology. My Editor's Pick for this year's issue is by Sharma et al. This paper details what is known about the link between gut dysbiosis and neurological disorders and provides examples that showcase this. Understanding the interactions between microbiota and the brain may open up a new avenue of therapeutic approaches for hard-to-treat neurological disorders. We hope you enjoy reading this timely article.

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Abstract

It has been suggested that an intricate communication link exists between the gut microbiota and the brain and its ability to modulate behaviour of an individual governing homeostasis. Metabolic activity of the microbiota is considered to be relatively constant in healthy individuals, despite differences in the composition of microbiota. The metabolites produced by gut microbiota and their homeostatic balance is often perturbed as a result of neurological complications. Therefore, it is of paramount importance to explore the link between gut microbiota and brain function and behaviour through neural, endocrine, and immune pathways. This current review focusses on the impact of altered gut microbiota on brain functions and how microbiome modulation by use of probiotics, prebiotics, and synbiotics might prove beneficial in the prevention and/or treatment of neurological disorders. It is important to carefully understand the complex mechanisms underlying the gut–brain axis so as to use the gut microbiota as a therapeutic intervention strategy for neurological disorders.

INTRODUCTION

The human body harbours a diverse community of symbiotic, commensal, and pathogenic micro-organisms including bacteria, viruses, and fungi, collectively known as the microbiota. In recent times, the relationship between brain and gut microbiota has become an important component of wider research studies. The microbiome consists of the combined genetic material of the micro-organisms in a particular environment that may constitute the whole body or a specific part of the body. There exists a bidirectional microbiome gut–brain axis communication, which enables the gut microbiota to interact with the brain and vice versa.[1] This communication between the microbiota and central nervous system (CNS) is established through autonomous, neuroendocrinological, gastrointestinal, and immunological systems. Pathological complications are known to alter the levels of neurotransmitters, and therefore the balance between them, exacerbating the hypothalamus–pituitary–adrenal (HPA) axis activity and leading to chronic inflammation.[2] The intestinal secretions, porousness of the gut, and gut motility, along with the structure–function activity relationship, are also greatly influenced by the CNS. Conversely, the gut microbiota, by secreting certain chemicals, are known to affect the brain functions as well.[2] Even anxiety/stress and social issues are reported to affect bile secretions by altering the genes responsible for bile production.[2]

Many preclinical studies have suggested that the microbiome and the microbiota could be the key regulators in predisposing organisms towards various disorders, including neurodegenerative disorders, because alterations to the composition of the human gut microbiota are linked to a variety of neuropsychiatric conditions including depression, autism, Alzheimer's disease (AD), multiple sclerosis (MS), and Parkinson's disease (PD). However, studies are limited and it is not confirmed whether there is a direct link between the microbiota and brain disorders, or if microbiota indirectly influence by virtue of secondary effects.[3] It has been shown that one may improve the gut microbiota by the intake of probiotics, fermented foods, and prebiotic fibres in the diet; a healthy lifestyle; reducing sugar consumption; avoiding antibiotic use; and decreasing stress.

There are a number of mechanisms that support the interaction between the brain and gut microbiota, either in relation to neural, endocrine, immune, or metabolic signalling pathways. There is also a significant bridging between the brain and gut microbiota at the chemical level, as has been seen through the use of various hormones such as corticotropin-releasing hormone in the pituitary and the neurotransmitters dopamine, serotonin, and GABA.[3]

GUT MICROBIOTA–BRAIN CROSS TALK

Gut microbiota are thought to be greatly influenced by stimulating the HPA axis and sympathetic nervous system. The stimulation of the HPA axis is a major constituent of stress response, which has been well established through genetic and post-delivery environmental factors.[4] Past studies in mouse models have observed variations in host behaviour in the stress stimuli response. The observations indicated that the gut microbiota can influence the progression of the HPA reaction to stressors.[5]

Significant behavioural alterations have been known to be caused by a diverse range of micro-organisms. In mice, toxoplasmosis and bacterial infections altered the behaviour of the mice in such a way that they became unresponsive to the smell of cats, meaning the mice could be easily preyed upon.[6] There are some probable pathways involved in the association between the gut microbiota and brain that could help the transmission of information from gut to brain. The information can be processed for better understanding through the roles of short-chain fatty acids (SCFA) and neuroglia, and tryptophan and its metabolites, as well as accessing pathways at the neural level.[7] At neural levels, the conduction of information from the intestine to the CNS through nerves/neurons, has been successfully demonstrated in mice.[8] In one study, *Bifidobacterium infantis* administration to germ-free mice resulted in increased expression of *c-Fos*,[9] a principal alteration in the brain that changes the conversion of short-term incitements into long-term responses. The enhanced expression was moderately

repressed by treatment with capsaicin.[10] It was observed that the serotonin released from enterochromaffin-like cells, which originate in the gastric gland, act upon serotonin Type 3 receptors, and lead to the transfer of information engendered in the gut to the brain.[5-11]

SHORT-CHAIN FATTY ACIDS AND CHANGES IN MICROGLIA

Dietary fibres, upon absorption in the gut, have been reported to yield SCFA. These SCFA have been shown to be absorbed through the colon, and are used as an energy source. More recently, some receptors have been identified which has led to the novel, functional characterisation of SCFA. Butyric acid and its impact on the CNS has been observed previously in animal studies, because it functions as an antidepressant.[12]

Tryptophan and its Metabolites

Tryptophan is an essential amino acid found in the digestive system. It acts as a precursor in serotonin biosynthesis, blood platelets biosynthesis, and for numerous molecules in the CNS.[13] The kynurenine pathway is known to be controlled by the enzyme indolamine 2, 3-dioxygenase, in which the majority of tryptophan is involved in. Further, the cytokine levels reportedly boost the tryptophan-kynurenine route in the pathway. The metabolic products of kynurenine have been reported to affect the functioning of neural cells.[14] Kynurenic acid (KYNA), produced by kynurenine, acts antagonistically at the broad-spectrum ionotropic glutamate receptors. In case of neurological complications such as schizophrenia, the levels of this tryptophan metabolite are elevated in the brain and cerebrospinal fluid. KYNA is known to antagonise the function of α7 nicotinic and N-methyl-d-aspartate (NMDA) receptors, both of which are required for cognitive processes and normal brain development. Therefore, KYNA levels are very critical for the predisposition towards neurological disease.[15]

Similarly, carbohydrates levels are thought to influence the mood and behaviour of humans. Carbohydrates in our diet are known to stimulate insulin discharge in the body; they lead to the release of blood sugar into cells and the production of energy, simultaneously triggering the entry of tryptophan into the brain which has a pronounced effect on neurotransmitters levels. As the production of serotonin and tryptophan in the brain aid mental wellbeing, some studies suggest a diet low in carbohydrates to alleviate depression.[16]

FUNCTIONAL ASPECTS OF GUT MICROBIOTA

The human microbiome is composed of viruses, bacteria, protozoa, and fungi and the interaction network of these microbiota plays an essential role in overall health. In humans, the microbes are present externally, on the skin, mouth, intestine, etc., and internally, in the digestive system, lungs, etc.[17] Bacteria are the most predominant members of the microbiome community; they are highly dense in the gut, predominantly the colon. Firmicutes and Bacteroidetes are the most abundant phyla and are major constituents in functioning with reference to the microbiome, while Proteobacteria, Verrucomicrobia, Actinobacteria, and Fusobacteria are reportedly present at lower levels.[18] All the microbes associated with the gut microbiome have a vast range of functions with respect to the human body as they aid digestion, develop the immune system, and support mental health.[19]

The key communication route between CNS and gut microbiota is via the vagus nerve, which acts as a thread between them. Fluctuation in the signal of the nerve can result in immunoregulation effects and dysfunction of the nervous system. This may lead to gastrointestinal diseases, intestinal distress, anxiety, depression, diseases such as irritable bowel syndrome, MS, AD, PD, and inflammatory bowel disease (IBD), etc.[20] Several studies have evidenced the improvement in levels of cytokines by vagal stimulation.[21,22] Enteroendocrine cells transmit biological signals from the gut to the brain via stimulation by bacterial metabolites, hormones such as cholecystokinin, peptide YY, and serotonin. These mediators bind to chemoreceptors and upon binding, activate the neural afferent fibres. In another study, subtypes of enteroendocrine cells were reported to complete the signal by direct communication with the gut through vagal afferent fibres.[23]

Table 1: Some of the major disorders associated with altered gut microbiota.

Disease associated	Disease type/subtype	Characteristics	Reference
Alzheimer's disease	Chronic and irreversible neurodegenerative disease	Central nervous system dysfunction	24-26
Multiple sclerosis	Inflammatory disease	Immune-mediated demyelination of the neural axon	
Parkinson's disease	Neurodegenerative disorder	Multifactorial motor symptoms	
IBS	Bowel disorder	Abdominal discomfort, adaptations in bowel habits	27
	IBS with diarrhoea	Loose, frequent stools; abdominal pain; and uneasiness, gastric, etc	
	IBS with constipation	Chronic or persistent constipation	
	Mixed or cycling	Digestive complications: cramping, belly pain, and bloating	
	Unsubtyped IBS	Problems associated to motion/movement through the gastrointestinal tract	
Inflammatory bowel disease	Bowel disease	Inflammation in the gut subsequent to the grouping of environmental and inherited factors	28,29
	Paediatric Crohn's disease	Enlarged profusions of Enterobacteriaceae, Pasteurellaceae, Fusobacteriaceae, Neisseriaceae, Veillonellaceae, and Gemellaceae, reduced profusions of Bifidobacteriaceae, Erysipelotrichaceae, Clostridiales, and Bacteroidales	
Cardiovascular disease	Heart disease	Microbiota-dependent pathway	29

IBS: irritable bowel syndrome.

DISORDERS ASSOCIATED WITH ALTERED GUT MICROBIOTA

The CNS is sensitive to microbiota changes occurring through numerous pathways, which has an important role in the progression of neurological disorders (Table 1).[24-29] Human Type I IFN, NF-κB, and the inflammasome are the major components associated with the above pathways and play an important role in influencing the microbiota.[29]

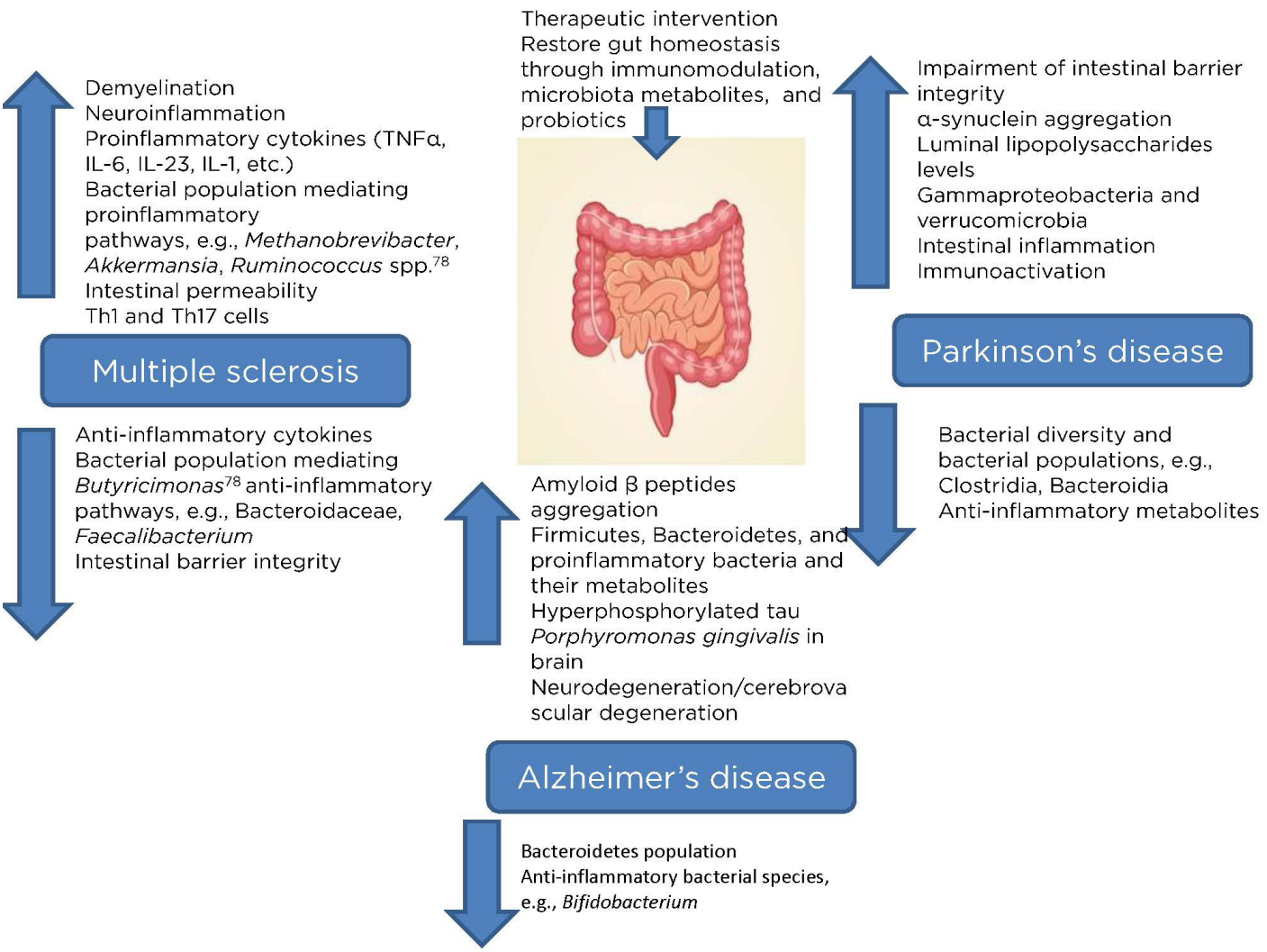

Figure 1: Microbiota dysbiosis due to pathological complications of major neurological disorders (multiple sclerosis, Alzheimer's disease, and Parkinson's disease) providing a therapeutic window via restoring microbiota homeostasis.

Multiple Sclerosis

MS is an immune-mediated inflammatory ailment in which myelin loss results in neurological complications, including damages at the visual, motor, sensual, autonomous, and cognitive level. There are a variety of general factors reported to be associated with MS that are responsible for damage to the insulating covers of the nerve cells in the brain and spinal cord, resulting in physical, neurological, and sometimes psychiatric problems (Figure 1).[24]

The gut microbiome is said to play a vital role in the development of MS, as evidenced by the differences in the specific gut microbial taxa present in patients with this autoimmune disease in comparison to healthy individuals.[25] Autoimmunity is known to have direct control over the response of the immune system towards the gut microbiota, thus altering the overall composition of the resident microbiota.[26] Significant microbial alterations in the gut, as a result of the presence of the major microbial population associated with proinflammatory pathways, enhance the pathogenesis of MS. Gut microbial dysbiosis further increases the intestinal permeability, microbial translocation, and local and systemic inflammation, resulting in MS. Additionally, neuroinflammation and demyelination are involved, along with a significant impact on the natural killer T cell population.[27] Firmicutes and Bacteroidetes populations, as well as the class of alphaproteobacteria, were reportedly reduced as a result of the disease, while there was an increase in the

class of gammaproteobacteria.[28] Therefore, the interaction between the gut microbiota and MS appears bidirectional, providing itself a potential therapeutic window for early intervention with probiotics or metabolites produced from the microbiota.[30,31] Faecal microbiota transplantation (FMT) has been recently utilised, wherein the host aberrant gut microbiome could be replenished in order to replace the aberrant microbiome with a healthy one.[32-34] A case study demonstrated the effectiveness of FMT in a 61-year-old patient with secondary, progressive MS with a history of several episodes of enterocolitis.[26,35] The Expanded Disability Status Scale (EDSS) of the patient was stabilised, but FMT had limited efficacy in this case.[26,36]

There are several environmental factors that play an important role in the pathogenesis of MS including geographical location, smoking, vitamin A and D, retinol, sodium, body mass, and obesity. At higher latitudes, the difference in sunlight exposure may lead to a decrease in vitamin D levels,[37] which is significant because vitamin D has been reported to prompt anti-inflammatory immune cells.[38] Disease risk is doubled by smoking because of the higher levels of cotinine.[39] Another study disclosed that the immune-regulatory characteristics of vitamin A might be pertinent to MS because the transitional levels of retinol binding protein have an association with lower incidence of disease risk.[40,41]

Plasma cells of the gut and IgA antibodies were reportedly found to migrate to the CNS, resulting in an anti-inflammatory effect as observed in a mouse model and in human patients with MS.[41] MS is known to be driven by B and T cells, and it was found in one study that drugs targeting B cells may alleviate MS.[41] The same study demonstrated that IgA-producing B cells can move from the gut to the brain, paving a way for novel treatments for MS and other related neurological disorders.[42]

Alzheimer's Disease

AD is a neurodegenerative, progressive disease caused by CNS dysfunction, which may be described as an advanced death of brain cells that takes place over time and results in excessive neuroinflammation. Memory loss and cognitive decline, along with loss of vision, confusion, depression, anxiety, and fearfulness are the symptoms associated with the disease. One of the key factors attributed to the cause of disease appears to be gut microbiota dysbiosis, as a decrease in microbial diversity in the gut microbiota is observed alongside an increase in profusion of Bacteroidetes (Figure 1).[43] Dysbiosis, neural loss, and damages to synaptic function, along with the accumulation of tau protein and amyloid-β (Aβ) in excess, may lead to neuronal cellular apoptosis in AD.[44] More recently, the role of the gut microbiome was considered as a dynamic factor in the aetiology of the disease because metabolites derived from microbiota in the cerebral spinal fluid of patients with AD were recognised.[45]

The gut microbiome is a rich source of amyloids, which are present on the surface of bacterial cells. Amyloid fibres can be accumulated, leading to unrestricted immune system activation. Treatment with bacterial amyloids (curli-producing *Escherichia coli*) has been shown to exhibit amplified neuronal α-synuclein accumulation at both the gut and the brain level.[46] In another study, the use of injectable bacterial lipopolysaccharide into the brain demonstrated the occurrence of numerous inflammatory features observed in AD.[47] Microbiota have also been shown to have a therapeutic role in some tumour types: Bifidobacterium, a member of the bifidobacteria species, was shown to be an antitumour agent in a mouse model where the oral administration of Bifidobacterium eliminated the tumour consequence.[48]

An amyloid precursor protein that produced an Aβ peptide lacking glutamic acid at position 22 (E693Δ Osaka mutation) was found to be associated with AD through the excessive oligomerisation of the Aβ.[49] Similarly, the microtubule-associated tau protein is known to keep microtubules straight and strong in a healthy human brain. In AD, it was found that the microtubules were no longer able to sustain the transport of nutrients and other essential substances in the nerve cells, which eventually led to cell death.[50] The hyperphosphorylation of the tau protein detached it from the microtubules and it combined with other associated fragments, resulting in the accumulation of Aβ plaques, leading to neurodegeneration and AD.[51]

Parkinson's Disease

PD is a neurodegenerative disorder that disturbs movement. Symptoms of PD include tremors in the limbs, hands, or fingers; rigid muscles; loss of automatic activities; fluctuations in tongue movement; and difficulty in walking, balance, and co-ordination, with the brain cells or neurons being the initial starting point of the disease.[52,53]

There are also many inherent and environmental features that are involved in the commencement of the disease.[54] There are many alterations in the brain of individuals such as the manifestation of Lewy bodies and unusual clumps of the protein α-synuclein, which are considered microscopic disease causing markers of PD (Figure 1).[54] Age, sex, heredity, and exposure to toxins (herbicides and pesticides) are some of the risk factors that are associated with the disease. In recent studies, it has been reported that α-synuclein action in the nervous system during the initial stages of disease could be correlated to the digestive complications.[55] α-synuclein overexpression in the mouse model advocates the significant role of microbiota in the disease progression. On the other hand, α-synuclein overexpression in the germ-free mouse model with antibiotic treatment displayed decreased incidence of PD.[56]

NEUROIMAGING METHODS EMPLOYED FOR DIAGNOSIS

Neuroimaging refers to the imaging of structural, functional, or pharmacological features of the nervous system. There are various methods that have been employed for neuroimaging.

MRI

MRI is an extensively used technique which demonstrates properties of the brain at various levels. There is a voluntary transformation among preclinical and clinical backgrounds in this technique.[57] The major focus of MRI at the structural level is on the assessment of grey matter in the brain, along with demarcation of structural differences with reference to the patient population. Voxel based morphometry is another technique employed for neuroimaging, which is based upon MRI.[58] Voxel based morphometry explores the principal differences in the brain along with the assessment of grey matter volumes.

Diffusion Tensor Imaging

Diffusion tensor imaging is subsequent to diffusion-weighted imaging, wherein structural details at the microscopic level are available in reference to the white matter *in vivo*. Moreover, the same technique has the capability to enumerate the extent of water diffusion.[59]

Fractional Anisotropy

Fractional anisotropy helps to access the measure of manoeuvring consistency of water dissemination in the tissues, which aids understanding of the white matter at the structural level. In order to define the white matter tracts, other methods such as fibre tracking and three-dimensional visualisation are used, which help to analyse the different diseases/disorders among different population groups.[60]

NEUROIMAGING TECHNIQUES AT FUNCTIONAL LEVEL

In reference to imaging and measuring the functional changes, numerous techniques can be employed.

Functional MRI Analysis

Functional MRI relies upon the blood oxygenation level-dependent (BOLD) analysis. The signals transmitted from BOLD are used for understanding the basics of the neural system in both healthy and dysfunctional brains.[61] Functional MRI and its task specificity help to measure the alterations in neural activities, which defines the response of the brain to external stimulation (stimulus can be sensory, auditory, visual, etc.). In contrast to the working of the human brain, it has also been reported that the brain is functional beneath resting or relaxed states. The resting state uses the BOLD signal for investigating the natural fluctuations in the brain, along with the brain networks centred on the acknowledged interactions.

Functional Connectivity

Functional connectivity demonstrates the resting-state networks amongst the brain regions with definite functions. Results have been successfully derived from the resting state networks using statistical methods.

Table 2: Effect of gut microbiome on human health and factors associated with the improvement of the gut microbiome.

Health effects	General characteristics	Reference
Whole body	Bifidobacteria in a newborn baby aids the digestion of the sugars in breast milk. Short-chain fatty acids absorption by bacteria. Regulatory check of gut bacteria over contaminants or pathogens and brain functions.	61-64
Cardiovascular	Gut microbiome assists in promoting 'good' HDL cholesterol and maintaining triglycerides to healthier levels.	
Effects on diabetic complications	Regulation of blood sugar levels restricting diabetic complications by the gut microbiome.	
Neurological effects	Gut microbiome assists in neurotransmitter secretions in the brain.	
Factors associated with the advancements/building of the gut microbiome		
Diet	**Derived benefits and recommendations**	
Diverse range of foods	Variations in the food intake. Diet enriched with diverse microbiota. Inclusion of vegetables, legumes, beans, and fibrous fruits.	65-70
Addition of fermented foods in the diet and reduction in the levels of marketed sugars in diet	Yogurt, sauerkraut, and kefir, all contain healthy bacteria. *Lactobacilli* in diet can reduce disease causing agents.	
Addition of prebiotic foods, fibrous foods in the diet	Some food products such as chicory root, artichokes, bananas, leeks, asparagus, oats, onions, garlic, and apples. They should be included in the diet to help in the stimulation of beneficial bacteria. The fibrous foods and advantageous carbohydrates like β-glucan are beneficial for humans. Gut bacteria assist in digestion of food further reducing the risk of cancer, diabetes, and other disorders.	

Default Mode Network

Default mode network displays high levels of activity throughout the resting state and neutralises during the enactment.[62]

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy provides the neural substrate information of the brain, accessing the levels of choline, creatine, glutamate, glucose, and N-acetyl aspartate.

With magnetic resonance spectroscopy, some key investigations can be performed in cases of neurological or neurosurgical disorders.[63,64]

Brain Iron Deposition Imaging

Iron is a metal that is fundamental to basic processes such as DNA synthesis, respiration in mitochondria, and oxygen transportation. The paramagnetic nature of iron, as determined through advanced MRI techniques, has led to new insights into the iron testimony in vivo in the human brain.[65]

MICROBIOTA VERSUS DISEASE-GENETIC PREVIEW

There are variety of factors that have been reported to be associated with the improvement of the gut microbiome that impact the human health (Table 2).[61-70]

Disease/disorder may lead to alteration in the microbial composition of the gut microbiota, leading to mutations in genes and resulting in immune-level irregularities. Predisposition at the genetic level has been shown to result in the progression of IBD, which is thought to occur because of polymorphisms in the *NOD2* gene that codes for a receptor that recognises causative pathogenic micro-organisms.[66] Mutations in *ATG16L1* and *IRGM* genes have been found to be associated with Crohn's disease, because of eradication of the intracellular bacteria. Acute inflammatory response was found to be associated with other *NOD2* variant genes such as *L1007X*, *R702W, G908R*, and *ATG16L1 T300A*.[66] Similarly, some IL such as IL-10, IL-19, IL-27, IL-1RL1, IL-2RA, IL-12RL2, and IL-18R1 and chemokines CCL2 and CCL7 have been found to impact acute inflammatory response.[67] In another study, determination of microbial factors were studied in reference to host genetics. DNA extraction and amplification studies were performed using general bacterial primers and terminal restriction fragment length polymorphism fingerprints were generated to establish microbial community profiles similar to those seen in nature.[68]

There are many factors that can affect the microbial flora inhabiting the gut, but recent findings discovered that specific host genetic variants influence an individual towards microbiome dysbiosis.[69] The host regulates the composition of the gut microbiome through the secretion of IgA, antimicrobial peptides, and microRNA.[70]

Genes encode many proteins that shape the microbiome by appropriately regulating the availability of nutrients, and the level of the immune response generated. The secretion of antimicrobial peptides was found to be decreased with mutations in *NOD2*, *ATG16L1*, and *LRRK2* genes.[71,72]

The abundance of *Lactobacillus* spp. is found to decrease because of variants in the *CLEC7A* and *CARD9* genes, resulting in altered activities of dendritic cells and macrophages. Increased abundance of *Escherichia* spp. and *Bacteroides vulgatus* alongside a decrease in *Faecalibacterium* spp. was associated with variants in *NOD2*.[73,74] The increased production of IgG and IgA against commensal microbiota has been associated with impaired A*TG16L1* signalling, resulting in a loss of tolerance to intestinal microbes. Polymorphisms in *MHC Class II* or *HLA* genes were seen to affect production of IgA in response to microbes. Defects in mucus production were seen in altered intestinal microbiome, while also increasing susceptibility to colitis.[75]

There was a significant variation in the gut microbiota of healthy individuals with a high genetic risk for IBD. *Roseburia intestinalis* is one of the 20 most abundant species present in the gut microbiota. The IBD genetic risk score was significantly associated with a decrease in *Roseburia* in the gut microbiota of patients with IBD.[76] Increased variants in genes involved in bacterial handling (*NOD2*, *IRGM*, *ATG16L1*, *CARD9*, and *FUT2*) have been found to be associated with a decrease in *Roseburia* spp. *Roseburia* spp. were specifically seen to colonise the mucins, directing mucosal butyrate production. Butyrate derived from clostridium clusters IV, VIII, and XIVa (to which *Roseburia* spp. belong to) has been shown to induce T-cell regulators, affecting intestinal inflammation.[76]

CHALLENGES AND LIMITATIONS OF THE MICROBIOTA RESEARCH

The impact of the microbiota on human health has been significant in guiding us to newer diagnostic and therapeutic approaches to treat neurological disorders (Figure 1); however, concrete clinical studies or large cohorts of randomised trials are lacking. Also, complex intricacies of host microbial interactions, microbial environment, the underpinning human microbiome, and how additive, subtractive, or modulatory strategies influence such interactions, are not completely understood. Additionally, there is a lack of knowledge so far about comprehensive understanding of the rules governing invasion, resilience, and succession in a host-associated microbial environment, which is quintessential for the development of long-term cell-based therapeutics.[77] The majority of studies pertaining to microbiota have been tested in rodents which are correlated to humans in a generalised fashion, despite having differences in their respective microbiomes. Effective therapeutic studies considering microbiota as a

biomarker are still to be carried out. Moreover, genetic engineering approaches to enable the modification of a wide range of bacterial hosts, along with the creation of disease-relevant sensors, are still at infancy.

Natural commensals like *Bacteroides* or Clostridia could have the potential to be developed as microbiota-based therapies, but again, pharmacological and safety issues are the major concerns, which are yet to be addressed. Furthermore, microbiota research has been limited to short-term therapies so far, and long-term cellular therapies and how the engineered microbiota establishes at the target site with respect to time and changing environment are still at large. Newer and advanced genetic engineering techniques are required in order to overcome these challenges.

CONCLUSIONS AND FUTURE PERSPECTIVES

Healthy humans differ from each other in terms of microbiome composition, but the metabolic activity of the microbiome remains relatively constant. Immune response is affected as a result of active transport or diffusion of metabolites produced in the gut. When perturbations in the microbiome occur as a result of disease/disorder, the immune-homeostasis equilibrium is altered, further impacting the drug-metabolic capacity of the host as well.[78,79] Metabolites such as neurotransmitters, neuromodulators, and SCFA produced by gut microbiota are known to reduce the secretions of proinflammatory cytokines while inducing T-cell regulators development and IL-10 secretions. Some SCFA may also cross into the CNS. Additionally, the integrity of the blood–brain barrier is disrupted during neuroinflammation through the action of IL-1, IL-6, and TNFα, resulting in neurological complications.[80] Therefore, the gut microbiota greatly influence the brain function and behaviour through neural, endocrine, and immune pathways (Figure 1). Modulation of the microbiome by use of probiotics, prebiotics, and synbiotics might prove beneficial in the prevention and/or treatment of neurological disorders. To fully harness the influence of gut microbiota for the therapeutic intervention in neurological diseases, future research should improve our understanding of the complex mechanisms underlying the gut–brain axis. Moreover, large-cohort studies are required to investigate the therapeutic potential of long-term modulation of the gut microbiota on brain diseases.

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Clinical Controversies in Amyotrophic Lateral Sclerosis

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Abstract

Amyotrophic lateral sclerosis is a devastating neurodegenerative condition with few effective treatments. Current research is gathering momentum into the underlying pathology of this condition and how components of these pathological mechanisms affect individuals differently, leading to the broad manifestations encountered in clinical practice. We are moving away from considering this condition as merely an anterior horn cell disorder into a framework of a multisystem neurodegenerative condition in which early cortical hyperexcitability is key. The deposition of TAR DNA-binding protein 43 is also a relevant finding given the overlap with frontotemporal dysfunction. New techniques have been developed to provide a more accurate diagnosis, earlier in the disease course. This goes beyond the traditional nerve conduction studies and needle electromyography, to cortical excitability studies using transcranial magnetic stimulation, and the use of ultrasound. These ancillary tests are proposed for consideration of future diagnostic paradigms. As we learn more about this disease, future treatments need to ensure efficacy, safety, and a suitable target population to improve outcomes for these patients. In this time of active research into this condition, this paper highlights some of the areas of controversy to induce discussion surrounding these topics.

INTRODUCTION

Motor neurone disease (MND) encompasses a group of disorders affecting the anterior horn cells and includes the most common form, termed amyotrophic lateral sclerosis (ALS). The inexorable decline in function leading to death for these conditions, in often otherwise healthy people, has emphasised the unmet need for better diagnostic and treatment paradigms. With awareness of these conditions increasing in the public consciousness, and increasing research funding, this is an excellent opportunity to improve outcomes for these patients.

While previously considered a neuromuscular disorder of the anterior horn cells, greater research in recent years into brain cortical dysfunction, and also identification of deposition of TAR DNA-binding protein 43 (TDP-43) in the brain, has altered the perception of this condition into the category of multisystem neurodegenerative disease. On one end of the spectrum lies

predominant anterior horn cell damage and lower motor neuron (LMN) signs. On the other end is cortical TDP-43 deposition leading to behavioural-variant frontotemporal dementia (FTD).

In this review, recent advances in the understanding of the diagnosis and treatment of this condition are discussed. This information is posed as a series of 'controversial statements' for which evidence may be conflicting. While the authors have no claim to answer these questions, they hope this will encourage readers to question their own diagnostic and therapeutic preconceptions and generate increased consideration of the underlying issues.

CLASSIFICATION

Amyotrophic Lateral Sclerosis is the Same Disease as Progressive Muscular Atrophy and Primary Lateral Sclerosis

MND encompasses a family of disorders affecting the anterior horn cells, of which ALS is the most common form, demonstrating both upper motor neuron (UMN) and LMN features. Other phenotypes of the disease such as primary lateral sclerosis (PLS) and primary muscular atrophy (PMA) are less common, featuring UMN and LMN deficits, respectively. Even within ALS there is significant variation in the anatomical location and progression of the disease.[1] Within ALS, patients may have an UMN- or LMN-predominant symptomatology. There are other phenotypic variants such as the flail arm or flail leg syndrome, and rarer variants such as spinal or diaphragm onset.[2,3] From the point of origin, different patterns of disease spread have been characterised.[1] Bulbar-onset disease accounts for approximately one-third of ALS cases, and carries a poorer prognosis. Specific genetic changes may influence phenotype and prognosis, but there is significant pleiotropy whereby a mutation may cause a variety of phenotypes, even within the same family.[4] Some have incorporated clinical, phenotypic, and genetic factors into a prognostic model.[5] A clear indication of prognosis is helpful for patients.

In the absence of a distinguishing biomarker, there has been controversy as to what extent ALS, PMA, and PLS should be defined as a single entity, or to classify them as separate conditions.[6] Often with time, other UMN or LMN features become apparent, and the diagnosis is revised to ALS.[7,8] In the authors' opinion, these conditions are likely to be the same pathophysiological condition, albeit with differing location of predominant pathology (and different emphasis on pathological processes) leading to the spectrum of symptoms that they consider in PMA, ALS, and PLS. Some have proposed that a definite diagnosis of PMA or PLS is only made >4 years after symptom onset to ensure that there has been no emergence of ALS signs.[6] Even if patients exhibit solely UMN or LMN signs, often at biopsy there is evidence of more widespread neural loss, which would support the hypothesis that this is all the same condition. Although some distinction of the phenotypes is helpful to define prognosis, often the terminology can be confusing for patients. Subjective interpretation of the criteria may impact patients' entry into clinical trials. Others have proposed alternative classifications to improve prognostic accuracy and to allow clearer description of the patient's status for other clinicians and in clinical trials. Not only would this classification involve a description of UMN or LMN predominance and El Escorial category, but also diagnostic modifiers such as genetic mutation, presence of frontotemporal dysfunction, and stage of disease.[6]

Amyotrophic Lateral Sclerosis and Frontotemporal Dementia are on a Spectrum of TDP-43 Deposition Neurodegenerative Disease

There are conditions that have been associated with MND, such as FTD. Frontotemporal dysfunction occurs in up to 50% of ALS patients, reaching FTD criteria in 15%.[9] TDP-43 has been found in both ALS and FTD. It is a RNA-binding protein which has been shown to be mislocalised in ALS patients. Restoration of the stathmin 2 gene (*STMN2*) allows microtubule stabilisation, and in turn allows recovery of axons in TDP-43-depleted motor neurons. This can indicate *STMN2* as a target for future therapy.[10] Some patients may also develop cerebellar or autonomic problems, possibly related to TDP-43 deposition in those areas of the nervous system. These associated features are not included in current clinical classifications. There is again controversy as to whether ALS–FTD is a separate entity compared

to ALS with some executive dysfunction, because there appears to be differences in TDP-43 deposition and microglial activation.[11] Furthermore, TDP-43 deposition is variable, and many ALS patients do not demonstrate obvious cognitive impairment, most notably Prof Stephen Hawking.

It is more easily conceivable to understand the TDP-43 deposition in the brain leading to UMN dysfunction. To what extent TDP-43 causes LMN dysfunction, such as in PMA, is unknown. Several pathological processes have been proposed in ALS, affecting both UMN and LMN. It may be that MND pathologies are numerous, and different emphasis on pathological mechanisms leads to the different symptomatology experienced.

Further clarification about the description of the diagnosis and phenotype has been proposed.[6] This will assist in both research recruitment endeavours and being able to communicate information about diagnosis and prognosis to patients.

Amyotrophic Lateral Sclerosis is Solely A Motor Neuronopathy

The concept of ALS only being a motor neuron condition has also been questioned. Not only have there been significant cerebral cortex changes mentioned above, there is recent research suggesting that sensory nerves are also affected.[12,13] Somatosensory evoked potentials are also abnormal, suggesting sensory pathways in the spinal cord or brain are affected.[14] Small-fibre neuropathy has also been demonstrated in ALS patients, though it is unclear how this correlates with phenotype and prognosis.[15,16]

Amyotrophic Lateral Sclerosis Can Be Split into Sporadic and Familial Subtypes

Approximately 10% of ALS cases have been described as 'familial'.[17] However, there remains significant numbers of so-called 'sporadic' cases which have something of a genetic basis.[18] Contributory genetic variations and mutations are being identified, and their contribution to the pathway leading to ALS is gradually being understood.[19] While cases such as those associated with *SOD1* mutations follow an autosomal-dominant pattern, other heritable genetic traits may be involved in a less obvious manner in sporadic cases without obvious family history. The development of ALS has been shown to be a multi-step process involving both genetic and environmental risk factors.[20] Family history itself may be difficult, since ALS is a disease of older age, and family members may have died before symptoms manifested. A positive family history is also affected by family size.[21] Furthermore, penetrance of some genetic forms, such as the *C9orf72* hexanucleotide repeat expansion, remains below 100%. The *C9orf72* expansion is the most common genetic abnormality, found in approximately 40% of familial cases. It is also found in 4–8% of sporadic ALS cases (in a European and USA cohort).[22] Approximately one-third of ALS and FTD will have a pathogenic *C9orf72* expansion.[23] Other relevant conditions such as FTD may not be diagnosed or recalled correctly when a family history is being sought. It has been shown that the risk of ALS in relatives of patients with sporadic disease is higher than in those without affected relatives.

Some now advocate a broader genetic screening for ALS patients with apparent sporadic disease.[23] With the advent of antisense oligonucleotide therapy trials, identification of a mutation may lead to therapy. Greater adoption of genetic testing may also broaden the database of disease-causing mutations or expansions and increase our understanding of phenotypic presentations of different mutations. In the familial ALS cohort, different phenotypes and prognoses are already known: *C9orf72* expansions are associated with more cognitive (FTD-type) deficits, whereas *SOD1* mutations less so. Certain mutations may also confer a favourable prognosis.[24]

DIAGNOSIS

Current Diagnostic Criteria are Outdated and Do Not Include Consideration of New Diagnostic Techniques

Correct diagnosis of ALS is essential to counsel patients regarding their future. Other motor neuromuscular disorders, such as multifocal motor neuropathy (MMN), have effective treatments and are important not to miss. Early on in the disease course, however, it is often difficult

to make a definite diagnosis of ALS; delays in diagnosis are common.[25] The sensitivity of the revised El Escorial criteria may only be 57% at the time of diagnosis.[26] Money and time can be spent on unnecessary treatments if the diagnosis is not made appropriately. First and foremost, diagnosis is made on clinical grounds, with supporting electrophysiological evidence. Imaging is used for exclusion of mimics, such a monomelic amyotrophy or multi-level polyradiculopathy.

The El Escorial Criteria (1994) were formed to standardise the diagnosis of ALS based on principally clinical parameters. It emphasised the need for UMN and LMN degeneration in the same region. There must be disease progression in the affected region, and there must be spread of degeneration to other body areas. It divides diagnosis into four categories: definite, probable, possible, and suspected. These criteria were revised in 1998.[27] The principal change was to place more emphasis on electrophysiological evidence, allowing electromyography (EMG) evidence of denervation rather than clinical evidence, i.e., muscle wasting. Further recommendations were made in Awaji, Japan, in 2008 to facilitate earlier diagnosis.[28]

Table 1: Advantages and disadvantages of various diagnostic modalities.

Diagnostic modality	Pros	Cons
Nerve conduction study	Exclude mimics Simple indices	Minimal UMN information, although H-reflex studies may provide some[36-38]
Needle EMG	The mainstay of diagnosis for identifying widespread denervation changes	No UMN information Painful Time-consuming
Peripheral nerve excitability	Insights into axonal function	Variability limits diagnostic specificity Requires hardware and operator experience Time-consuming
Motor unit number estimation	Allows monitoring of disease progression and prognosis	Patient-to-patient variability limits diagnostic use Limited muscles able to be tested accurately Requires specific expertise and training
Cortical excitability (transcranial magnetic stimulation)	Insight into UMN changes early in the disease process Differentiates ALS from mimics early in the disease	Requires hardware and operator experience
Nerve and muscle ultrasound	Quick, painless, body-wide screen for fasciculations Measurable muscle parameters allow disease monitoring Nerve ultrasound scan can distinguish ALS from mimics	Hardware and operator experience required Only limited information about UMN dysfunction
Blood and CSF biomarkers	Simple to obtain Good specificity versus controls, even early in disease course	CSF sampling difficult for longitudinal study Laboratory experience and equipment required, yet to be widespread May not distinguish easily from mimics

ALS: amyotrophic lateral sclerosis; CSF: cerebrospinal fluid; EMG: electromyography; UMN: upper motor neuron.

It allowed fasciculations in a chronically reinnervated muscle as evidence of LMN dysfunction along with fibrillations and sharp waves. This change increases diagnostic sensitivity by 12–20% on revised El Escorial criteria, without changing specificity.[29-31]

Diagnostic classification is useful for research purposes, but can be confusing when discussing the diagnosis with patients. For example, a patient may be defined by Awaji criteria as 'possible ALS', whereas the clinician is certain of the diagnosis based on the clinical presentation and exclusion of mimics. In a retrospective study of 399 standardised cases, there were large inter-rater variations in probable and possible categories.[32] Some patients were classified differently between revised El Escorial and Awaji Criteria in the probable-laboratory supported and possible categories. There is an inherent complexity in interpretation of both clinical and electrophysiological parameters for the different body regions.

The World Federation of Neurology (WFN) subgroup on ALS produced an updated consensus statement in 2015 attempting to clarify the diagnostic classification.[33,34] It took provided guidance on phenotypes not conforming to typical revised El Escorial criteria such as the flail arm or flail leg variant. Note was also made that there is a negligible false-positive rate in the possible cohort, and these can be considered for clinical trials (assuming appropriate exclusion of mimics). It also indicated that a pathogenic mutation in a known gene can substitute for UMN or LMN signs. These are all pragmatic recommendations recognising the heterogeneity of ALS and should allow easier access to clinical trials for patients earlier in the disease course. New consensus diagnostic criteria have recently been published which have sought to simplify the diagnosis of ALS by collapsing the previous definite, probable, and possible categories into a single diagnostic entity to facilitate clinical management and trial design.[35]

Diagnostic Modalities

Nerve conduction studies are necessary during ALS diagnostic workup for exclusion of mimics such as MMN (Table 1).[36-38] Some further diagnostic information may also be gained from nerve conduction studies: increased H reflexes (relative to M wave) can indicate UMN dysfunction.[36] A split-hand index can calculate the ratio of median compound muscle action potential (CMAP) compared to ulnar CMAP. A value <0.6 is indicative of the split hand phenomenon of ALS, and can be seen even when symptoms arise in another anatomical area.[1] Additionally, a split-leg index can also be used.[39] Unfortunately, CMAP amplitudes themselves are a blunt diagnostic indicator because they are preserved well into the disease course due to compensatory reinnervation. Motor unit number estimation provides more direct information about motor neuron loss, and several techniques have been developed for this. Some have the ability to distinguish ALS patients from controls at diagnosis.[40] Yet given the variability at diagnosis, this technique may be more useful to monitor patients longitudinally, to monitor progress (more accurately than Revised Amyotrophic Lateral Sclerosis Functional Rating Scale [ALSFRS-R]) and provide prognostic information. Although one study demonstrated the MScanFit program to be most accurate for monitoring motor unit decline, this requires software that may not be available to all neurologists.[41]

It is Likely that Cortical Excitability Will Prove To Be a Useful Diagnostic Tool

Motor evoked potentials (MEP) have been shown to be altered in ALS. MEP may be absent, decreased in amplitude, and may be delayed or dispersed (prolonged central motor conduction time [CMCT]).[42] Absent MEP are seen in patients with more severe UMN dysfunction. Abnormal MEP may be helpful in differentiating ALS from a pure LMN disorder such as MMN; however, early ALS patients may have CMCT that fall within normal limits (Figure 1).[43] Additionally, differentiating ALS from hereditary spastic paraparesis cannot be done on CMCT values, since both may be prolonged.[44] The use of dual-stimulation transcranial magnetic stimulation (TMS) allows two magnetic impulses to be created in quick succession. How the cortex then responds to these impulses under different conditions, and whether a motor signal is generated, can provide insights into what is occurring in the cortex on a neuronal level.

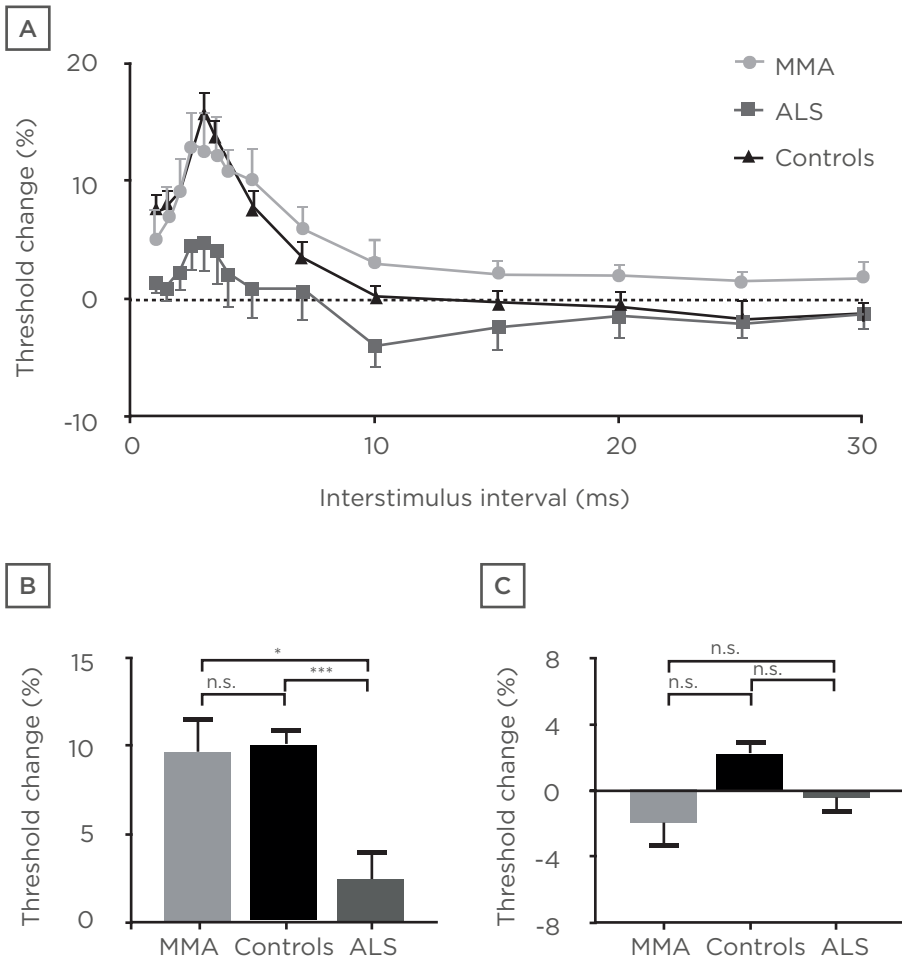

Figure 1: Cortical excitability in patients with monomelic amyotrophy compares with healthy controls and amyotrophic lateral sclerosis patients. Whereas the mimic (MMA) demonstrates normal cortical excitability, patients with amyotrophic lateral sclerosis demonstrate cortical hyperexcitability.

ALS: amyotrophic lateral sclerosis; MMA: monomelic amyotrophy; n.s.: nonsignificant.

*p≤0.005

***p≤0.001

Reproduced with permission from Matamala et al.[43]

Recent studies have focussed on cortical hyperexcitability as an integral component of ALS pathology. It is thought that cortical hyperexcitability occurs early in the disease process, and may result in anterior horn cell degeneration in a 'dying forward' process.[45,46] It has been established that a normal motor cortex has a refractory period (absolute then relative) whereby a second motor signal cannot be created. This is known as the short interval cortical inhibition period (SICI). In patients with ALS, this SICI has been shown to be decreased. In other words, the cortex is more ready to generate a second motor impulse, only shortly after one has been sent, and is indicative of a hyperexcitable motor cortex. This reduced SICI is the most robust TMS diagnostic variable.[47-49] This reduction in SICI occurs early in the disease process, occurring prior to symptoms in familial ALS[50] and certainly when symptoms are subtle in sporadic cases.[51] One series demonstrated that the number needed to test with TMS to diagnose an extra case of ALS was 1.8, demonstrating excellent diagnostic utility for the extra testing time. This was not affected by site of symptom onset.[46] The degree of reduced SICI has been shown to be a prognostic marker for shorter life expectancy.[52] A reduction in resting motor

threshold and decreased cortical silent period duration have also been shown, consistent with cortical hyperexcitability for the symptomatic side of the body.[47,48,53] These techniques can differentiate ALS from mimics,[43] and forms part of a proposed ALS diagnostic index to improve early diagnosis.[44,54] While the equipment may be expensive and requires operator experience, this will be a useful tool for earlier diagnosis.

Neuromuscular Ultrasound Complements Needle Electromyography and Should be Included in Future Diagnostic Criteria

Though not widely used when the El Escorial or Awaji criteria were devised, neuromuscular ultrasound is emerging as a useful diagnostic and prognostic test modality (Table 1).[55] Its attraction comes from its noninvasive nature. It is also generally time-effective, being able to sample a wide variety of muscles in a short time.

For diagnosis, ultrasound can identify fasciculations easily, and can identify fasciculations in deeper muscles compared to needle EMG.[56,57] It can also be used for initial screening of likely pathological muscles to increase needle EMG yield. The distribution of fasciculations may allow distinction of ALS compared to a benign fasciculation mimic or peripheral hyperexcitability syndrome.[58] It has also been shown to facilitate differentiation of large fasciculations from myoclonus.[59,60] However, it is inferior to EMG for defining the complexity of fasciculations, and fibrillations are better identified by needle EMG.[61] Nevertheless, quantitative fasciculation analysis allowed differentiation from mimics with high sensitivity and specificity.[57] Muscle ultrasound is particularly useful for bulbar evaluation, for which needle EMG of tongue muscles is painful and may be hindered by incomplete relaxation.[61,62] The use of muscle ultrasound scores may help simplify use in diagnosis.[63]

Not only do muscles atrophy, their characteristics are changed as the disease progresses, with increased deposition of fibrous-fatty tissue. These changes can be quantified with ultrasound measures of echo intensity, echovariation, grey-level co-occurrence matrix, and increased muscle stiffness on elastography (Figure 2). These have been demonstrated to be useful adjuncts to clinical parameters in trials, and in some cases has shown to improve diagnostic accuracy compared to clinical tests alone.[64,65]

Ultrasound has also been used to identify bulbar muscle dysfunction related to UMN dysfunction.[66] The ratio of muscle thickness from contracted to relaxed was shown to differ between bulbar ALS patients and controls. Further work is needed to determine how accurate this finding is on an individual level, and whether this can be added as a criterion for UMN deficit in the bulbar region. In a similar manner, thickness ratio changes of the diaphragm between inspiration and expiration have been used to identify weakness. This correlates with forced vital capacity, ALSFRS-R, and diaphragm CMAP. Diaphragm ultrasound is an attractive alternative to other measures because of its noninvasive nature and lack of requirement for good bulbar control to perform respiratory function tests.[67] It should be noted, however, that diaphragm thickness changes are only one component of respiratory dysfunction in ALS patients, with intercostal and bulbar dysfunction as well as central drive impairment being important to consider as well.

As a disease progression monitoring tool, ultrasound has shown some promise, but demonstration of additional benefit to measures of disability, such as the ALSFR-S score, is required before it becomes useful, and this is still lacking.[4]

Nerve ultrasound has also been studied in ALS. Nerve cross-sectional area is reduced because of LMN loss. This differentiation can be used in clinical scenarios such as differentiating PLS (solely UMN) from UMN-predominant ALS, which shows nerve atrophy.[68] Distal:proximal cross-sectional area ratios of peripheral nerves have been shown to reflect motor neuron atrophy typical of ALS and can be a diagnostic indicator.[69] Other mimics such as MMN or chronic inflammatory demyelinating polyneuropathy often have enlarged nerves.

There is a building body of evidence to support the use of ultrasound in both diagnosis and monitoring of ALS patients. Some uses, such as fasciculation identification, are simply diagnostic. Other measures may not be useful in the early stages, such as muscle atrophy, but may be useful to monitor for disease progression and assist prognosis.

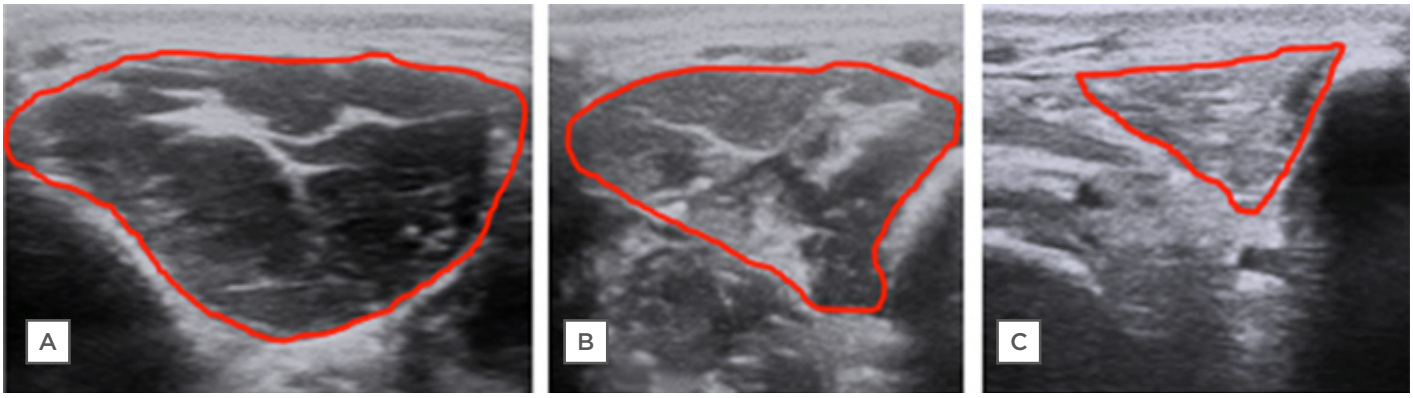

Figure 2: Ultrasound of the first dorsal interosseous muscle.

A) A healthy control; **B)** an ALS patient with minimal clinical hand weakness; and **C)** an ALS patient with severe hand weakness. Ultrasound demonstrates reduced muscle thickness/cross-sectional area and increased echogenicity with progressive denervation.

ALS: amyotrophic lateral sclerosis.

Standardisation of testing techniques for quantitative measures will be useful for both research and longitudinal patient monitoring. With machines improving in portability and cost, use of ultrasound is likely to become more widespread, and incorporation of ultrasound parameters in future diagnostic and prognostic paradigms is recommended.

MRI is a Useful Research Tool, But Adds Little to an Individual Diagnosis of Amyotrophic Lateral Sclerosis

MRI can be used for exclusion of mimics and is performed on most patients undergoing ALS diagnostic workup. Identification of corticospinal tract hyperintensity on T2-weighted imaging, as well as hypodensity on susceptibility-weighted imaging (SWI) in the motor cortex (the 'motor band sign') can be indicators for a diagnosis of ALS. One study identified the motor band sign in 78% of ALS patients on whom the SWI sequence was used, however numbers were small, and further research is required.[70] With SWI or gradient echo sequences becoming standard, this may be a helpful piece in the diagnostic puzzle. Both of these MRI findings are nonspecific however, so should not be overemphasised.

MRI has been a useful research tool to evaluate the cortical changes seen in ALS. Voxel-based morphometry and diffusion tensor imaging have shown accelerated loss of grey matter, particularly in the premotor cortex. Changes appear to be most prominent in the ALS-FTD cohort.[71] The corticospinal pathways are also disrupted. As the disease progresses, further loss is seen in frontotemporal areas outside the motor pathways.[72] These techniques allow ALS patients to be differentiated from controls with a 65% sensitivity and 67% specificity for ALS. However, this is only on a group level and no definite conclusions can be drawn on an individual level.[73]

Blood Biomarkers Will Support a Diagnosis of Amyotrophic Lateral Sclerosis in the Future, and Can Be Used for Monitoring of Disease Progression

Neurofilament light chain (NfL) protein is emerging as a potentially useful biomarker in many neurological conditions. It is released from neurons undergoing axonal damage. Studies have shown increased levels in ALS patients compared to controls, but more importantly has shown the ability to differentiate from mimics.[74-76] The titre has also been shown to vary with clinical stage, and therefore may aid in identifying disease progression. It appears to be higher in patients with UMN features and the level in cerebrospinal fluid (CSF) correlates with time to death, indicating use as a prognostic marker.[74] Further work is required on this, however, because levels will vary on a patient-to-patient basis,

and may also vary based on the site of disease manifestation. There is still an overlap between values in the ALS and mimic populations, therefore other diagnostic techniques should be used. Laboratory techniques have now improved to allow detection of NfL in the blood as well as CSF, and this will be important for its use to monitor disease progression, since serial CSF sampling is impractical. Though not as sensitive or specific as CSF for ALS diagnosis, serum or plasma levels still demonstrated good positive and negative-predictive values.[75,76]

Phosphorylated neurofilament heavy chain (pNfH) has also been studied and is similar to NfL with respects to sensitivity and specificity. A cut-off of 560 pg/mL yielded a sensitivity of 83% and a specificity of 80%. NfH did not change with disease progression in one small study, whereas a drop of NfH levels correlated with disease progression in another.[77] A small study has also indicated that pNfH concentrations in the CSF can help differentiate UMN-predominant ALS from common mimics such as hereditary spastic paraparesis and PLS on a group level.[78] There was significant overlap in groups on an individual level and therefore, again, this biomarker can only provide some supportive evidence for diagnosis. A limitation remains in the availability of a suitably validated immunofluorescence assay. Currently used at research centres, it may take time to become more widely available.

Numerous other blood and CSF biomarkers have been proposed for ALS.[79] Given the relationship to FTD, CSF levels of TDP-43 have been tested in ALS patients. The CSF level could differentiate ALS patients from neurological controls with a sensitivity of 59.3% and specificity of 96.0%. The indication that lower levels of TDP-43 heralded a poorer prognosis, and that there was no correlation with disease duration, needs further investigation in a larger trial. Plasma TDP-43 levels have also been found to be higher in ALS patients than controls, although there was significant overlap of the two groups.[80] Another study has shown that CSF metabolomics (eight selected metabolites) coupled with clinical parameters provided prognostic information in ALS patients.[81] Using a proteomic method to identify CSF biomarkers, Thompson et al.[82] identified three macrophage-derived chitinases that were more abundant in ALS patients and had some correlation with disease progression. Other CSF biomarkers of inflammation have also shown correlation with disease progression and some ability to delineate ALS cases from neurological controls.[83] Whether these research techniques are able to be replicated in other labs, and can be used on a more general basis, remains to be seen. Furthermore, as with most tests, on an individual level there may not be sufficient separation between an ALS patient and a mimic.

TREATMENT

The role of the multidisciplinary team, and the use of symptomatic management including palliative care, are recommended for all ALS patients and are incontrovertibly beneficial. American guidelines were published on the topics of symptomatic treatment, nutritional support, and respiratory support in 2009,[84,85] and similar guidelines exist in the UK (National Institute for Health and Care Excellence [NICE]) and Europe.[86] Appropriate feeding and breathing adjuncts such as percutaneous gastrostomy and noninvasive ventilation should also be discussed with patient and family. These have been shown to prolong survival, and the only controversy arises as to when these adjuncts should be instigated. Commonly, this is a decision led by the patient and their family. Significant variation occurs with regards to the uptake of respiratory support, and this variation is sometimes unexplained though may relate to cultural and patient factors.[87] The role of pharmaceutical agents for disease modification is more debatable.

Riluzole Should be Ceased in Later Stages of the Disease

Riluzole is a glutamate release inhibitor which has been used for more than 20 years. It has demonstrated tracheostomy-free survival benefit of between 2 and 3 months.[88,89] It remains generally well tolerated, but may cause increased fatigue and transaminase abnormalities. Since the original studies, the extent of drug effect has been questioned, with only some study outcome measures being positive, and lack of cost-effectiveness limiting previous use in some jurisdictions.[90,91] Some studies only identified a survival benefit in bulbar-onset rather than limb-onset ALS.[92] Some showed bulbar-onset ALS to be more responsive,[89,93] but this was contradicted

in other studies.[94] Its use at later stages of the disease is unclear and debated.[94] Riluzole was shown to have an effect on cortical and peripheral axon excitability, but it was transient.[95] Furthermore, studies suggest that riluzole is not effective following treatment for longer than 12 months.[89,93]

More recent retrospective trials, however, have indicated that riluzole works in advanced stages of disease, whereas the middle stages (King's Stages 2 and 3) did not demonstrate a benefit.[96,97] Given the possibility that riluzole is working in different ways at different stages of disease, some advocate continuing riluzole into the advanced stages and remains a preferred approach of many neurologists if the medication is tolerated.[98,99]

No Other Medications for Amyotrophic Lateral Sclerosis Have Been Shown To Be of Benefit

The antioxidant drug edaravone has been approved in Japan and the USA. Although the initial trial was negative,[100] a subsequent randomised trial in a subgroup of rapid progressors was positive.[101] Its use is limited by the requirement for intravenous infusion, its cost, and uncertainty regarding which patients will benefit. Other medications trialled have not demonstrated benefit, but hopefully there are more in the pipeline.[102]

Stem-Cell Therapy Represents the Future of Amyotrophic Lateral Sclerosis Treatment

As patients strive to find any effective therapy to slow or reverse their decline, they become susceptible to strong marketing for therapies which may be promising but have no evidence for benefit. Autologous stem-cell therapy ('transplants') has been used for immune reconstitution in multiple sclerosis and systemic sclerosis with good results, albeit with significant potential side effects. Patients are drawn to the idea of stem cells for its intuitive mechanism of action, and as a 'nonpharmacological' way of inducing their own body to repair itself. Private clinics are providing treatments to ALS patients with varying methods and standards.[17] A recently published study with appropriately standardised protocols using autologous bone-marrow-derived mesenchymal stem cell transplant found a small benefit in a cohort of ALS patients demonstrating rapid disease progression.[103] This was a Phase II study, and further studies are required before this onerous therapy becomes more mainstream. Patients should be encouraged to enrol in approved clinical trials to undertake experimental therapies, otherwise currently it is considered that potential harms of stem-cell therapy outweigh benefits.

CONCLUSION

This is an exciting time for ALS research, with understanding of pathological mechanisms increasing and diagnostic armamentarium evolving. Clinical trials for new therapeutics will come soon, and it is therefore important to improve diagnostic certainty early in the disease course for timely treatment. In this review, many of the uncertainties in the understanding of this heterogeneous condition have been demonstrated. It is clear that no single diagnostic test will identify all ALS cases. The diagnostic modalities described represent pieces of a puzzle, with each patient being sufficiently different to require a personalised diagnostic approach. The authors endorse the use of a proposed personalised diagnostic ALS index[54] and propose the utilisation of these diagnostic techniques to be included in future diagnostic criteria. Specifically, they recommend the additional incorporation of cortical excitability and ultrasound evidence into laboratory-supported diagnosis in future consensus guidelines. Blood and CSF biomarkers may play a role if uptake is widespread, but greater certainty regarding diagnostic accuracy is required. Incorporation of genetic information (where available) should also be considered. From a therapeutics point of view, disease-modifying treatments are still some way off, and there remains controversy as to how beneficial, and in whom, the current treatments work. There is a need to adequately test therapies in a well-defined patient population prior to approval to ensure cost-effectiveness.

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Neuroinfections: Presentation, Diagnosis, and Treatment of Meningitis and Encephalitis

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Abstract

Neuroinfections cause significant morbidity, mortality, and long-term disability. These infections rarely present with the classic signs and symptoms taught in textbooks. Due to the similarities in presentation between neuroinfections and many other disease processes, delayed diagnosis is common. Thus, it is important that care providers have a high clinical suspicion for potential cases because early diagnosis and treatment can significantly improve outcomes. This article serves as a review of the approach to a patient with suspected neurological infection with an emphasis on clinical presentation, diagnosis, and treatment of the major causes of meningitis and encephalitis. Additionally, patients in an immunocompromised state are vulnerable to a whole host of additional neuroinfections that present atypically and will also be addressed.

INTRODUCTION

Infections of the central nervous system (CNS) are varied in their causes, presentations, and prognosis. They can be sudden in onset and have the potential to cause significant morbidity and mortality. A particular clinical challenge for CNS infections is the relatively isolated nature of the CNS and its protective mechanisms. The blood–brain barrier is the main protective feature of the CNS and works to restrict the passage of pathogens and large molecules from the bloodstream into the cerebrospinal fluid (CSF). It is composed of a network of specialised brain endothelial cells as well as pericytes and astrocytes that support brain capillaries.[1,2] A specific challenge that arises as a result of this protective mechanism is the identification of the specific neurovascular space where the infection resides, be it the meninges, the epidural space, or the parenchyma itself. The extent of the neurovascular space involved in infections is often a spectrum extending from the meninges to the encephalon. An infectious agent that initially causes meningitis can easily progress to encephalitis, also known as meningoencephalitis. The extent of disease produced by a specific agent can also vary drastically between patients.

This article is a review on the initial approach to a patient with suspected neurological infection with emphasis on clinical presentation, diagnosis, and treatment of meningitis and encephalitis.

MENINGITIS

The meninges are a triple-layer membranous envelope composed of the pia mater, dura mater, and arachnoid space. Meningitis refers to inflammation of the leptomeninges and CSF within the subarachnoid space that exists between the pia mater and the arachnoid layers.[3] The exact cause of the inflammation, however, can vary. There is a myriad of infectious and noninfectious causes of meningitis, but for the purpose of this review, the focus will be acute infections of the meninges. Primary infectious causes include bacterial, viral, and fungal origins.

Meningitis secondary to a bacterial infection can cause significant morbidity and mortality as a result of the severe inflammation. The inflammation can cause significant oedema of the surrounding structures and increased intracranial pressure.[4] Many organisms, such as *Escherichia coli* and *Neisseria meningitidis*, are pyogenic and can cause a thick suppurative exudate that covers the brainstem and thickens the leptomeninges.[3] The main pathogenic bacteria implicated in meningitis varies by age and degree of immunocompromise. The most common causes of meningitis in neonates are *Streptococcus agalactiae* and *E. coli*. Whereas in children beyond the neonatal period, the most common agents are *N. meningitidis* and *Streptococcus pneumoniae*.[5] Common agents in adults include *N. meningitidis* and *S. pneumoniae*, but *Listeria monocytogenes* must also be considered, particularly in the elderly.

Another important pathogen to consider is *Haemophilus influenzae* type b (Hib). Widespread vaccination has significantly decreased the incidence of Hib meningitis by over 90% in some countries.[6,7] However, it remains a prevalent pathogen in underdeveloped and unvaccinated populations. Hib can cause severe bacterial meningitis in children with significant morbidity. Up to 20% of children that recover from Hib meningitis experience long-term neurological sequelae such as sensorineural hearing loss, developmental delay, seizures, and hydrocephalus.[8] Hib can also cause significant disease in immunocompromised and asplenic patients at any age.

Viral meningitis is usually less clinically severe than bacterial meningitis. Herpes simplex virus (HSV) and varicella-zoster virus (VZV) are two main examples of neurotropic viruses that can frequently cause disease. HSV-1 infection can cause severe encephalitis in adults whereas in children, HSV-2 tends to cause more serious infections. However, incidental and non-neurotropic viruses account for the majority of viral meningitis cases. Nonpolio enteroviruses account for more than 85% of all cases of viral meningitis.[9]

Clinical Presentation

Meningitis must be considered in any patient presenting with fever and headache. Diagnosis is complicated by the fact that the full triad of fever, nuchal rigidity, and meningismus is rarely present. A thorough history and physical exam to rule out other common aetiologies is paramount. Establishing pretest probability is important because the gold standard to diagnose meningitis, lumbar puncture (LP), and CSF culture, is an invasive and skilful procedure that can be difficult to perform under certain circumstances. Common historical features of patients with meningitis include headache, vomiting, and neck pain.[10] The presence of these symptoms alone has poor sensitivity, with the pooled sensitivity for headache being 50% (95% confidence interval: 32–68%) and 30% for nausea/vomiting (95% confidence interval: 22–38%).[10] However, the absence of fever, neck stiffness, and altered mental status effectively eliminates meningitis.[10] As far as physical signs are concerned, Kernig's and Brudzinski's signs were both described in the late 1800s and early 1900s, respectively. Most of the patients they studied had significant meningeal inflammation with underlying *Mycobacterium tuberculosis* and *S. pneumoniae* infections.[11] Multiple recent studies have shown poor sensitivity of these signs, even in the presence of jolt accentuation.[12,13] Despite poor sensitivity, these signs are quite specific (92–95%) for pleocytosis, which again demonstrates the importance of a detailed exam. Overall, clinical gestalt is the best guiding feature in pursuing a workup of meningitis and establishing the diagnosis.

Diagnosis

The hallmark diagnostic procedure for meningitis is LP. Serum laboratory markers can indicate overall presence of inflammation, but none can specifically diagnose meningitis. The specific technique and contraindications of the procedure

will not be discussed here, but it is important to note that the technique is invasive and that proper equipment along with patient positioning are vital to the success of the procedure. There has also been much discussion as to whether a noncontrast CT scan of the brain is necessary prior to performing the procedure because of the fear of underlying mass effect and increased risk of herniation with a LP. While one would think that head CT prior to LP is relatively harmless, obtaining a head CT when not indicated can delay definitive diagnosis and most importantly treatment of acute meningitis. In a recent study, Michael et al.[14] noted that unnecessary head CT caused significant delays in performing LP and thus decreased the utility of CSF culture in instances where antibiotics had already been started. There are specific clinical criteria for when head CT should precede LP. Per European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines, these are a Glasgow coma score <10 and focal neurological deficits other than cranial nerve palsies.[5] Based on the available data, in the absence of these clinical findings, it is safe to perform the LP without a preceding head CT.

The presence of increased cell counts in the CSF is known as pleocytosis and is strongly indicative of meningeal inflammation. The leukocyte differential can further hint towards the aetiology. Viral aetiologies tend to generate a lymphocytic predominance, whereas bacterial aetiologies generate a neutrophilic predominance. These trends and patterns in the cell count and differential are still nonspecific, but there are data suggesting that marked pleocytosis in itself is sensitive for bacterial meningitis. Agueda et al.[15] noted a cut-off value of 321 white blood cells/µL showed the best combination of sensitivity (80.6%) and specificity (81.4%) for the diagnosis of bacterial meningitis in a recent paediatric, retrospective study. The first reported measurements from CSF analysis are usually the CSF protein and glucose levels. While not diagnostic, trends in protein and glucose levels can hint towards whether the infectious cause is viral, bacterial, or fungal (Table 1).

The gold standard for diagnosis remains as CSF culture for identification of the pathogen. Culture results are diagnostic in 70–85% of cases prior to antibiotic exposure. Sensitivity decreases by 20% following antibiotic pretreatment.[16] However, cultures are time-consuming, and patients are often started on empiric treatment well before culture data results. A novel method for identifying the pathogen is through gene identification via PCR. PCR methods allow for rapid pathogen identification through amplification and matching of the pathogen's gene products.[17] This technology has evolved into multiplex PCR which allows for identification of multiple nucleic acid targets within a single reaction. This technology is rapid, sensitive, and specific. A recent multicentre, prospective study on >1,500 specimens by Leber et al.[18] revealed that the sensitivity and specificity of this method was well above 90% for the most common pathogens implicated in meningitis. Many institutions have adopted such a filmarray panel. Rapid identification of pathogens is important because it can decrease duration of antibiotic therapy and duration of hospitalisation.[19,20]

Table 1: Typical cerebrospinal fluid profiles for bacterial, viral, and fungal meningitis.

	Bacterial	Viral	Fungal
Opening pressure	Increased	Normal	Increased
Appearance	Cloudy to purulent	Clear	Clear or cloudy
CSF WBC	Raised	Raised	Raised
Differential	Neutrophilic	Lymphocytic	Lymphocytic
CSF protein	Increased	Mild increase	Increased
CSF glucose	Decreased	Normal-to-mild decrease	Mild decrease

CSF: cerebrospinal fluid; WBC: white blood cell.

Table 2: Guidelines for empiric antibiotics for suspected bacterial meningitis based on age and common pathogens.[5]

Age group	Common pathogens	Empiric treatment	Intravenous dosing
Neonates <1-month-old	*Streptococcus agalactiae, Escherichia coli, Listeria monocytogenes*	Amoxicillin/ampicillin/ penicillin plus cefotaxime, or amoxicillin/ampicillin plus an aminoglycoside	**Age <1 week:** cefotaxime 50.0 mg/kg q8H; ampicillin/ amoxicillin 50.0 mg/kg q8H; gentamicin 2.5 mg/kg q12H.
			Age 1–4 weeks: ampicillin 50.0 mg/kg q6H; cefotaxime 50.0 mg/kg q6–8H; gentamicin 2.5 mg/ kg q8H; tobramycin 2.5 mg/ kg q8H; amikacin 10.0 mg/ kg q8H.
1 month to 18 years	*Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae*	Cefotaxime or ceftriaxone plus vancomycin or rifampin	Vancomycin 10–15 mg/ kg q6H to achieve serum trough concentrations of 15–20 µg/mL; rifampin 10 mg/kg q12H up to 600 mg/ day; cefotaxime 75 mg/ kg q6–8H; ceftriaxone 50 mg/kg q12H (maximum 2 g q12H).
Adults	*S. pneumoniae, N. meningitidis*	Cefotaxime or ceftriaxone plus vancomycin or rifampin	Ceftriaxone 2 g q12H or 4 g q24H; cefotaxime 2 g q4–6 H; vancomycin 10–20 mg/ kg q8–12H to achieve serum trough concentrations of 15–20 µg/mL; rifampin 300 mg q12H.
Elderly or risk of immunocompromise	*S. pneumoniae, N. meningitidis, L. monocytogenes, H. influenzae*	Cefotaxime or ceftriaxone plus vancomycin or rifampin plus amoxicillin/ampicillin/ penicillin G	Ceftriaxone 2 g q12H or 4 g q24H; cefotaxime 2 g q4–6H; vancomycin 10–20 mg/ kg q8–12H to achieve serum trough concentrations of 15–20 µg/mL; rifampin 300 mg q12h, amoxicillin, or ampicillin 2 g q4H.

Treatment

Treatment of meningitis is typically initiated based on clinical suspicion or abnormal CSF cell counts/differential because CSF cultures results can be obtained within a day or two. Any patient with concern for sepsis or septic shock should be started on an empiric regimen of broad-spectrum antibiotics and antivirals even before performing the LP in order to not delay treatment. Management of severe sepsis and shock should follow current sepsis guidelines.[21] ESCMID guidelines for empiric antibiotics based on age and common pathogens can be found in Table 2.[5]

Adjunctive steroids should be considered in patients with suspected bacterial meningitis because animal studies have shown reduced inflammation, and thus decreased neurological sequelae, with their use. Morbidity secondary to hearing loss is a known neurological sequela in cases of severe bacterial meningitis.[22] It is because of this that steroids are recommended to be given with the initial dose of antibiotics. Based on the Cochrane review by Brouwer et al.,[22] there is no difference in mortality with steroid administration, but there is significant decrease in hearing loss and neurological sequelae. The evidence for a clear benefit from steroids is not as strong in the paediatric population. However,

current guidelines do recommend administering steroids with the first dose of antibiotics when bacterial meningitis is suspected in paediatric patients.[23,24]

Treatment for viral meningitis is largely supportive. Adults are often treated with acyclovir but currently there are no studies that show a significant benefit in meningitis.

ENCEPHALITIS

Encephalitis is a syndrome in which the brain parenchyma is invaded by a pathogen or microorganism and presents with encephalopathy and evidence of CNS inflammation. Encephalopathy is defined as any altered level of consciousness present for at least 24 hours.[25] This includes lethargy, irritability, or a change in personality or behaviours. Evidence of CNS inflammation includes fever, focal neurological findings, seizures, CSF pleocytosis, electroencephalogram (EEG) abnormalities, and neuroimaging findings consistent with encephalitis.[25] An important distinction is the CNS inflammation that is caused by the infection, which differentiates encephalitis from other causes of encephalopathy.

Each year there are approximately 6,000 cases of encephalitis requiring hospitalisation in the UK.[26] Viruses are responsible for a vast majority, 20–50%, of which HSV is the most prevalent.[27,28] Of the cases remaining, close to one-half will have no identifiable cause.[27,29] In the past decade, antibody-mediated encephalitis caused by autoimmune or paraneoplastic processes has become the third most common type of encephalitis, responsible for as many as 20–30% of cases.[28,30] Anti-NMDA receptor encephalitis is the most common autoimmune encephalitis, with antibodies against LGI1 (leucine-rich glioma inactivated 1 protein) being the second most prevalent.[30]

On a worldwide basis, Japanese encephalitis has become a common pathogen, responsible for 30,000–50,000 cases of encephalitis annually.[31] Eradication and control of Japanese encephalitis is important; while it primarily affects certain endemic areas, the population density in those regions often leads to high morbidity and mortality rates.[32] Since the eradication of polio, Japanese encephalitis is now at the forefront of international focus due to its long-term neurological sequelae and high mortality rates.

Clinical Presentation

Initial evaluation should focus on a detailed history and examination because early diagnosis and treatment improves outcomes and decreases long-term disability. Important components of the patient's history include recent travel, animal exposure and bites, vaccinations, contact with people who have been ill, recent illness, and occupation. It is also vital to consider the patient's demographics, season of presentation, and any local community pathogens.

Physical examination findings such as fever, mental status changes, neurological deficits, memory impairment, behaviour changes, seizures, and exanthems are all commonly seen in encephalitis. While some classic associations exist, the overlap in symptoms between the various causes of encephalitis as well as many other disease processes complicates the diagnostic process.

The most common of the viral encephalitis aetiologies is HSV, which accounts for 50–75% of cases.[27] Studies comparing HSV to all other causes of encephalitis revealed that patients with HSV were likely to be older (88% versus 64%, respectively), febrile (80% versus 49%, respectively), and experience gastrointestinal symptoms (37% versus 19%, respectively).[33] They also found lower rates of ataxia and exanthems in the HSV group when compared with other causes of encephalitis.[33] Given that HSV is more than likely to affect the temporal lobe, it is common to see olfactory hallucinations, personality changes, and psychosis, making it important to inquire about any underlying history of psychiatric diagnoses.[28,34]

Another cause of encephalitis that can often initially be misdiagnosed as a psychiatric disorder is anti-NMDA receptor encephalitis. This antibody-mediated form of encephalitis typically presents with a vague influenza-like illness that, over the course of 1–2 weeks, progresses into altered mental status, paranoia, hallucinations, and bizarre behaviour.[35] Ninety percent of patients are young females, and ovarian teratomas are present in 60% of these patients.[35]

Table 3: Infectious causes of encephalitis.[27,28,30]

Viral	
Herpesviridae	Herpes simplex-1 (HSV-1/HHV1) Herpes simplex-2 (HSV-2/HHV2) Varicella zoster (HHV3) Epstein–Barr (HHV4) Human herpes-6 (HHV6) Human herpes-7 (HHV7)
Picornaviridae	Enterovirus 70 Enterovirus 71 Poliovirus Coxsackievirus
Orthomyxoviridae	Influenza
Paramyxoviridae	Measles Mumps
Bunyaviridae	La Crosse Toscana Jamestown Canyon California encephalitis
Flaviviridae	West Nile Dengue Zika Japanese encephalitis Powassan Saint Louis encephalitis
Togaviridae	Eastern equine encephalitis Western equine encephalitis Venezuelan equine encephalitis Chikungunya
Bacterial	*Bartonella henselae* *Borrelia burgdorferi* *Brucella* spp. *Chlamydia pneumonia* *Chlamydia psittacosaurus* *Listeria monocytogenes* *Mycobacterium tuberculosis* *Mycobacterium pneumoniae* *Pasteurella multocida* *Streptococcus pyogenes* *Streptococcus agalactiae* *Tropheryma whipplei*

Table 3 continued.

Autoimmune	
Antibody-mediated	NMDA AMPAR CASPR2 D2R DPPX $GABA_A$ receptor $GABA_B$ receptor LGI1 mGluR5 Neurexin-3α
Rickettsiae	*Anaplasma phagocytophilum* *Coxiella burnetii* *Ehrlichia chaffeensis* *Rickettsia rickettsii* *Rickettsia typhi*
Fungi	*Blastomyces dermatitidis* *Coccidioides immitis* *Cryptococcus* spp. *Histoplasma capsulatum*
Protozoan	*Acanthamoeba* spp. *Balamuthia mandrillaris* *Baylisascaris procyonis* *Naegleria fowleri*

Autonomic instability is identified late in the disease course, with 76% of patients developing seizures and 88% experiencing decreased consciousness and akinesis.[35]

There are numerous additional causes of encephalitis including viral, bacterial, fungal, mycoplasma, *Rickettsia*, protozoan, and autoimmune. For the purpose of this review, the authors chose to focus on common pathogens that all clinicians should be familiar with in order to appropriately workup a patient presenting with suspected encephalitis. A more extensive list of causes of encephalitis can be found in Table 3.[27,28,30]

Diagnosis

Differentiating encephalitis from the many causes of encephalopathy can be very difficult because their clinical presentations are all similar, often leading to delays in diagnosis and treatment. Common mimics of encephalitis include conditions of a metabolic (hypoglycaemia, hyponatraemia, hepatic encephalopathy, toxins), inflammatory (vasculitis, autoimmune diseases), infectious (sepsis, bacterial meningitis, opportunistic infections), neoplastic, psychiatric, and stroke origin.[29] Due to the overlap in symptomatology, evaluating for evidence of CNS inflammation is key to early diagnosis and treatment.

The major components of any encephalitis workup should include CSF analysis, neuroimaging, and EEG. All patients with suspected encephalitis should also undergo HIV testing because a positive result would significantly alter the differential diagnosis and workup.[29] Additionally, it is important for providers to keep in mind the many encephalitis mimics and work diligently to rule out other causes.

Many would argue the most important step in the evaluation of CNS inflammation is performing an emergency LP. As discussed prior, there are guidelines for when it is appropriate to delay LP for CT scan. However, every effort should be made to obtain CSF promptly because it is key to guiding management and confirming the diagnosis. In all cases, CSF studies should include cell count and differential, protein, glucose, Gram staining, cultures, cryptococcal antigen test/India ink staining, venereal disease research laboratory test, and PCR for HSV-1, HSV-2, VZV, and enterovirus. Additional testing may be required based on demographics, occupational, and environmental exposures. For this reason, it is recommended to send additional CSF to the lab in case more specific testing needs to be added as the workup evolves. Recently, next-generation sequencing has shown promise in the identification of cases of encephalitis with unknown aetiology; however, it is outside of the scope of this review article.

CSF analysis in viral encephalitis typically presents with a lymphocytic pleocytosis. However, early on in viral infections, neutrophils can predominate. Protein will be mildly elevated with a normal glucose (Table 1). HSV-1 and HSV-2 PCR has a sensitivity of 96% and specificity of 99%, however it can be negative early on in the disease progress.[36,37] If there is high clinical suspicion for HSV, many sources recommend repeat CSF analysis on subsequent days.[28,29,36,37] In regard to anti-NMDA receptor encephalitis, antiglutamate receptor NMDAR1 and antiglutamate receptor NMDAR2 antibodies are pathognomonic for the diagnosis.[38]

The preferred neuroimaging study in encephalitis is MRI because it has both a better sensitivity and specificity than CT.[28,29,36] In reality, most patients will first undergo CT brain imaging as part of their initial workup to exclude other causes. However, MRI abnormalities can clue care providers into specific aetiologies based on imaging patterns, characteristics, and locations of abnormalities.[28] One of the best examples of this is HSV encephalitis, in which an abnormal MRI is seen in up to 90% of cases.[29] Findings consistent with HSV include asymmetric hyperintense signal on T2-weighted and fluid-attenuated inversion recovery sequences in the temporal, orbitofrontal, or insular regions.[37] If there is a high suspicion for antibody-mediated encephalitis, further imaging to assess for a paraneoplastic process will be required.[29] In the case of anti-NMDA receptor encephalitis, due to the high association with ovarian teratoma, it is recommended to obtain a pelvic ultrasound or CT.[35]

EEG is commonly recommended in the workup for encephalitis; however, EEG findings alone are nondiagnostic.[29,36] Signs of encephalopathic change can help guide further workup as well as rule out encephalitis mimics such as psychiatric disease. HSV has been associated with generalised slowing, periodic discharges, and electrographic seizures.[36,37] Case reports of anti-NMDA receptor encephalitis have also shown that 80% of patients have generalised slowing on EEG and 50% have epileptic activity.[28]

Treatment

Similar to meningitis, treatment for encephalitis is initiated based on clinical suspicion because CSF testing for specific aetiologies will not yield same-day results. In addition to the disease-specific treatment, close monitoring for hypoglycaemia, increased intracranial pressure, and seizures is important. In all patients with encephalitis, it is recommended to start empiric intravenous acyclovir (Infectious Disease Society of America [IDSA] A-level recommendation) because it has a low side-effect profile and has been shown to reduce mortality in HSV encephalitis from 70% to 10–20%.[29,39] If the patient is HSV positive, acyclovir should be continued for a minimum of 2 weeks, at which time most sources recommend repeat LP to guide further management.[28,36,37] There is a lack of evidence to support the use of glucocorticoids in HSV, Epstein–Barr virus, or VZV encephalitis.[39] Treatment for anti-NMDA receptor encephalitis is immunotherapy and early tumour removal in the setting of paraneoplastic cases. Immunotherapy includes high-dose corticosteroids, intravenous immunoglobulin, and exchange transfusion.[29]

Prevention

Preventative measures against meningoencephalitis are vital in preventing epidemics. This is particularly true for viral aetiologies due to a lack of efficacious treatments for most neurotropic agents.[27] Prevention methods largely centre around adhering to vaccination guidelines, proper hygiene, and distancing, as with any infection. In infections

for which *N. meningitidis* or Hib is suspected, prophylactic antibiotic treatment of close contacts and exposed healthcare workers is key to prevention as well.

Opportunistic infections

Opportunistic infections of the CNS are most common in individuals with significant immunocompromise. Common scenarios include AIDS, post-transplant, and immunodeficiency syndromes. Most pathogens are inhaled and only cause systemic disease in the setting of significant immunosuppression.

Cryptococcal Meningitis

Cryptococcal meningitis is the most common cause of meningitis among those infected with HIV.[40] It is also one of the most common fungal infections in the post-transplant period.[41] Approximately 7–15% of patients with AIDS become infected with cryptococcus and it is responsible for up to one-fifth of AIDS-related mortality worldwide.[42]

Diagnosis requires a detailed physical exam and high index of suspicion. Due to underlying immunocompromise, classic symptoms such as fever and nuchal rigidity are not common. Rather, the most common symptoms are headache, altered mental status, and vision changes.[43]

The diagnostic pathway is similar to that described above, but it is important to measure an opening pressure when performing the LP, especially if there are clinical signs of increased intracranial pressure. CSF antigen testing is the gold standard for confirming diagnosis. The India ink stain has been studied as a useful screening test, especially in resource poor areas. However, it lacks specificity to serve as a confirmatory test (sensitivity: 90%; specificity: 50–75%).[44] Treatment consists of lowering intracranial pressure, if elevated, and antifungals. Specific agents should be chosen in consultation with local infectious disease guidelines.

Toxoplasmosis

Toxoplasmosis results from a parasitic infection of brain parenchyma. CNS infection typically occurs as a result of the reactivation of an old CNS lesion or haematogenous spread from an active infection. It is usually spread by consuming undercooked food that is contaminated with cysts; cat faeces is another common source.[45] The epidemiology of this disease varies greatly based on availability of antiretroviral treatment because it primarily affects patients with AIDS with CD4+ counts less than 200 cells/mm^3.[45] Clinical presentation again varies greatly due to underlying immunocompromise, but special note must be made of any movement disorder because toxoplasmosis has a propensity to invade basal ganglia.[46] Diagnosis differs from that of other CNS infections because of the tendency of toxoplasmosis to form ring-enhancing lesions and potentially increase intracranial pressure. LP should not be performed if there are any clinical signs of increased intracranial pressure. Definitive diagnosis is made with serological testing. Rapid PCR showed a sensitivity of 83.3% and specificity of 95.7%.[47] CT and MRI imaging with contrast can also reveal cystic lesions in the brain parenchyma. Similarly, treatment consists of addressing intracranial pressure, if elevated, as well as broad spectrum antibiotics. Agents should be selected in conjunction with infectious disease input.

CONCLUSION

Infections of the CNS require strong clinical suspicion and prompt workup to improve morbidity and mortality. Empiric treatment should not be delayed by imaging. However, it is important to understand that neuroimaging should precede LP in patients with focal neurological deficits, depressed Glasgow coma score, and clinical signs of increased intracranial pressure. Treatment should be initiated with broad spectrum antibiotics and tapered as possible. Suspected cases of encephalitis should be covered empirically with antivirals. Steroids have also shown benefit in improving neurological sequelae as well as hearing loss in the setting of meningitis; however, are not recommended in cases of viral encephalitis. Of special note are opportunistic infections of CNS, which must be considered in patients with significant immunocompromise.

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Case Report of Schwannomas: Benign Tumour of the Peripheral Nerve Sheath

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Abstract

Schwannomas, also known as neurilemmomas, are benign peripheral nerve sheath tumours arising from the Schwann cells surrounding the nerve. Incidence of peripheral nerve sheath benign tumours occurring in the lower extremities is rare (1–10%). The authors present two cases with solitary schwannomas from the peripheral nerves. In one case, the schwannoma arose from the sural nerve and in the other, from the tibial nerve. They were successfully surgically removed with the aid of a surgical microscope, with no intraoperative or postoperative complications.

INTRODUCTION

Schwannomas are benign, painless, firm nodules, 1–2 cm in diameter, that develop from the Schwann cells of peripheral nerve sheaths. They are tethered to a nerve and are therefore only laterally mobile. They are asymptomatic and nontender, and are not associated with any nodal involvement or malignant potential. The diagnosis is usually made histologically after excision of the tumour.[1] Malignant transformation of schwannomas is extremely rare.[2-5] Histologically, schwannomas are differentiated by the presence of a highly cellular Antoni A component that palisades Verocay bodies and myxoid hypocellular Antoni B components. These cases provide an insight into diagnosis and management of solitary schwannomas originating from peripheral nerves in adult males.

CASE PRESENTATION 1

A 39-year-old male presented with tender, palpable swelling and pain on the lateral aspect of the right mid-calf, shooting down the lateral aspect of the right leg to the ankle for 2 months. Physical examination revealed a tender, solid subcutaneous mass at mid-calf level measuring 20.0×20.0×15.0 mm, with no focal neurological deficits. The patient's past medical history was not significant. MRI of the right leg showed a well-defined, ovoid soft tissue mass lesion seen in the posterior aspect of the right leg. The lesion lay directly posterior to the myotendinous junction of the gastrocnemius muscle, causing overlying skin bulge. It measured approximately 14.3×13.7×11.1 mm at its maximal craniocaudal length (Figure 1). A benign nerve sheath tumour, such as schwannoma, was strongly suspected.

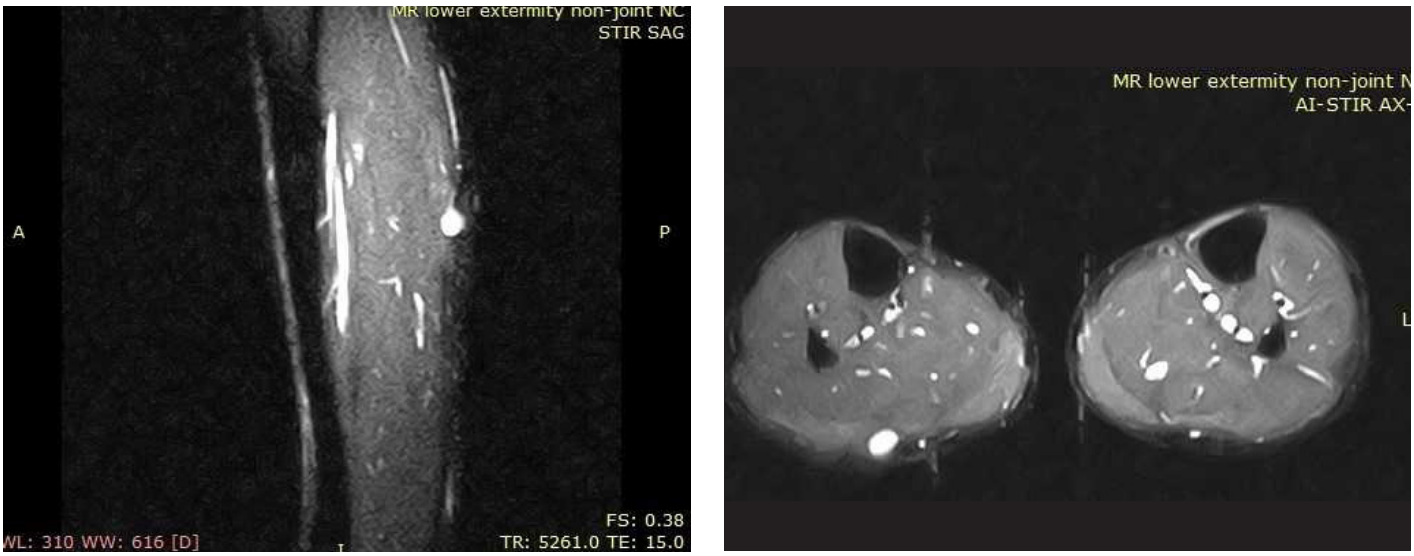

Figure 1: MRI revealed a well-defined, oval mass in the posterior aspect of the right leg.

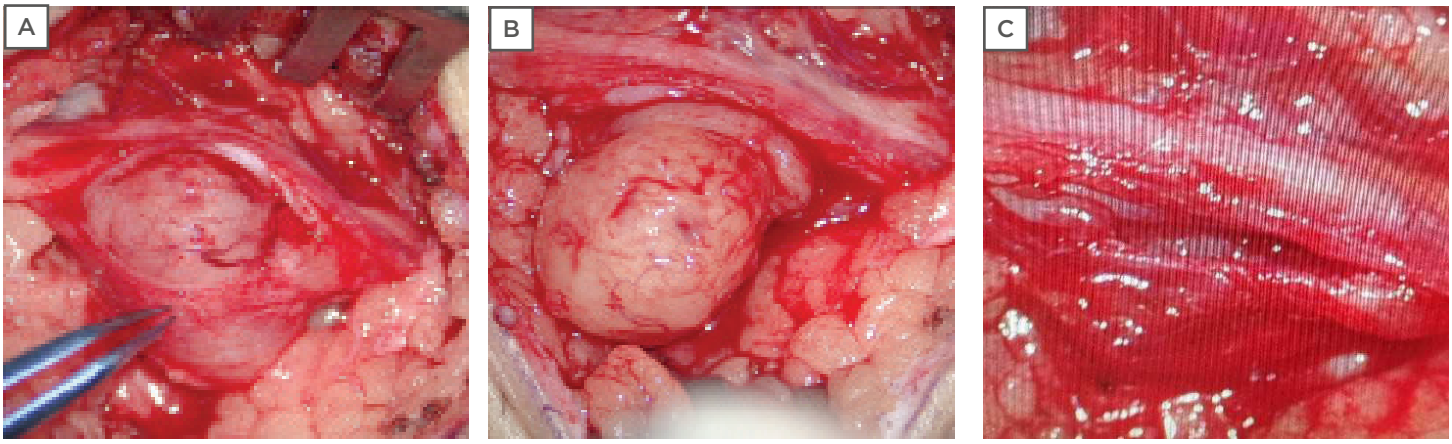

Figure 2: A) Isolation of the tumour with incision of the capsule; B) gradual enucleation of the tumour with nerve fibres intact; C) postexcision of schwannoma with intact sural nerve.

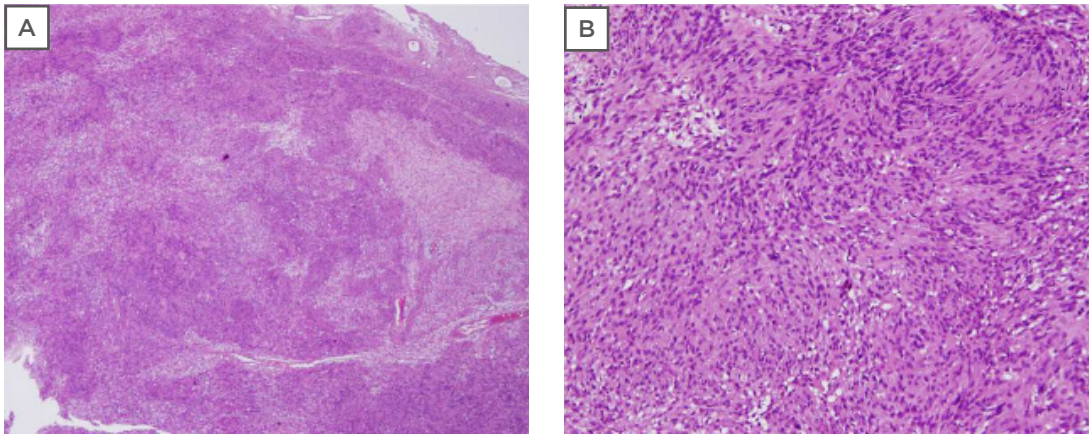

Figure 3: Histopathologic examination shows hypocellular Antoni (A) and hypercellular Antoni (B) Verocay bodies, confirming the diagnosis of benign schwannoma.

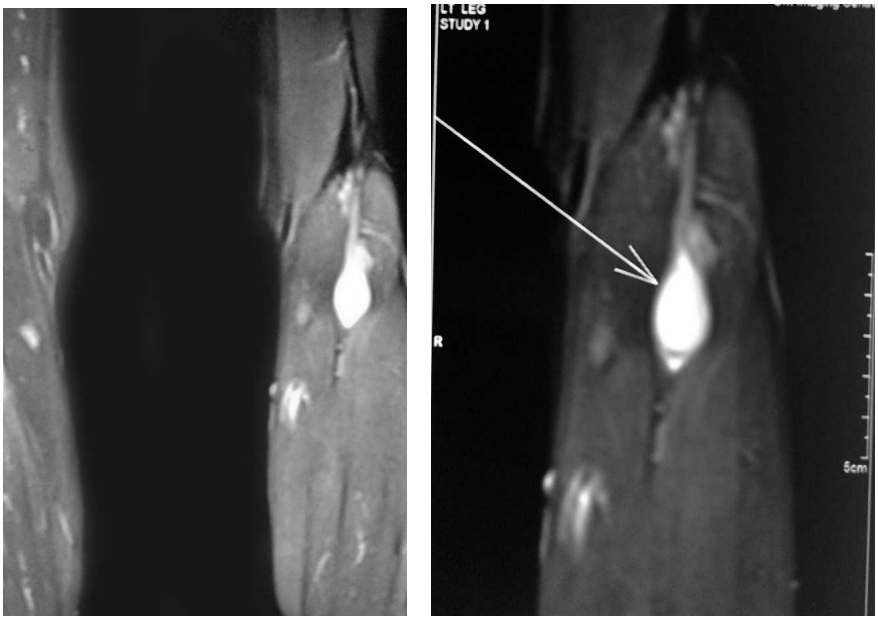

Figure 4: Well-defined, smooth, oval mass (depicted by arrow) with involvement of the posterior tibial nerve.

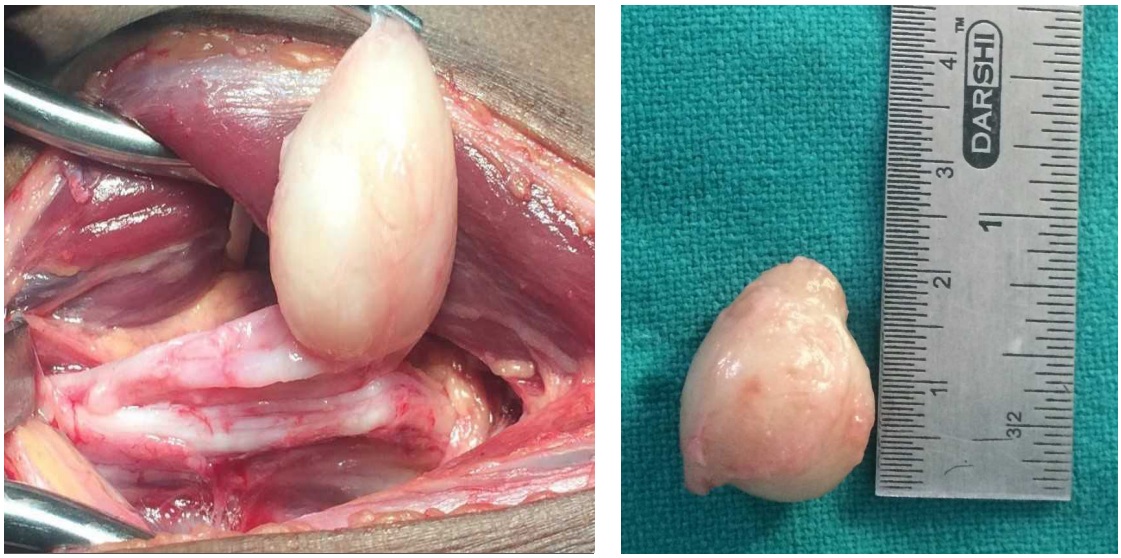

Figure 5: A) Complete enucleation of the schwannoma with nerve fibres intact; B) enucleated schwannoma measuring 22 mm.

The surgery was performed under local anaesthesia. Lidocaine 2% with adrenaline was injected subcutaneously at the site of the tumour. A 'lazy S' incision was made at the site to allow for exposure of the tumour to the level of deep fascia. The Capsule of the tumour was identified and gradually incised to dissect away the encapsulated tumour using sharp dissection. One fascicle of nerve was identified as entering the tumour, and was carefully excised. The tumour was completely removed and haemostasis was achieved. The wound was closed in layers with Monocryl® 5-0 sutures. Grossly, the tumour was firm, smooth-surfaced, and appeared pale yellow in colour (Figure 2A, B, C). Histopathology of the excisional biopsy confirmed benign schwannoma (Figure 3). The postoperative phase was uneventful.

CASE PRESENTATION 2

A similar case of a 40-year-old male presented with pain and claudication associated with a tender swelling on the posterior aspect of the upper calf of the left leg. Examination revealed a firm mass, mobile laterally, on the posterior aspect of the left leg, measuring approximately 2.5 cm in diameter.

MRI revealed a well-encapsulated oval mass in the posterior compartment of the leg: located in the infrapopliteal region. It showed marked T2-weighted hyperintense signal with smooth perilesional planes. Contrast-enhanced MRI showed homogenous marked enhancement in the lesion (Figure 4).

On exploration under regional anaesthesia and tourniquet control, the tumour was identified deep to gastrocnemius soleus, closely associated with fibres of the tibial nerve. The perineural sheath was carefully dissected under magnification, with preservation of all nerve fibres and complete tumour excision (Figure 5A, B). Histopathologic examination revealed benign schwannoma. Postoperatively, the patient had no complaints of sensory or motor weakness.

DISCUSSION

The differential diagnoses of such cases include neurofibroma and benign vascular tumours such as angioleiomyoma. Cystic hygroma, followed by lipoma, haemangioma, ganglion, and myxoma, are also commonly seen.[6] The sural nerve is a sensory nerve that passes down the posterolateral side of the leg and on to the dorsal aspect of the lateral side of the foot. The sural nerve runs with the small saphenous vein on the posterior leg, just lateral to the Achilles tendon. Its terminal branches consist of the lateral dorsal cutaneous nerve and the lateral calcaneal branches, whereas the tibial nerve branch of the sciatic nerve follows a course down the leg posterior to the tibia. It provides sensory innervation to the posterolateral side of the leg, the lateral side of the foot, and sole of the foot, and motor innervation to the posterior compartment of the leg. A solitary schwannoma arising from the tibial nerve is more common than from the sural nerve, which is reported to be a rare occurrence.[7-12] Despite its rare occurrence, schwannoma should always be included in the differential diagnosis.

Schwannomas or neurilemmomas are well-encapsulated, lobulated lesions without metastatic potential, particularly if they are located in the extremities. The lesions are mostly solitary, slow-growing, painless tumours and malignant transformation is a rare event. Schwannomas do not transverse through the nerve but remain in the sheath, unlike neurofibromas. Schwannomas can cause distal symptoms if found in the proximal aspect of the lower limbs.[13,14] Permanent nerve damage and soft tissue and bone deformity can be prevented by early diagnosis. MRI and sonography can help diagnose these lesions early.[15,16] The aim of treatment is total excision of the lesion without causing nerve damage that may lead to sensorimotor deficit.[17,18] In these cases, good magnification and good microsurgical technique under tourniquet control was extremely important to achieve this goal.

CONCLUSION

This report focusses on the early diagnosis of schwannoma by performing an MRI of the lower extremities. The cases were managed by complete excision of the benign tumour, preserving the peripheral nerve fibres with the aid of a surgical microscope, which provided better magnification of the operating field and meticulous dissection of the mass.

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Neuroinflammation: A Common Line Between the Wnt Pathway and Toll-Like Receptors

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Abstract

Neurodegenerative disorders constitute a worldwide concern attributable to the ageing of the human population. In this context, Alzheimer's disease (AD) accounts for up to 70% of dementia cases worldwide. With no effective treatment available, new therapeutic alternatives are under assessment. Recently, several researchers have highlighted the need to include the multifactorial aetiology of AD as part of the design and evaluation of novel AD-therapies. Thus, it is not enough to only understand the critical molecular events that occur during AD pathophysiology, but to unveil the crosstalk between these events as well as its interplay with different biological subsystems. This is the case for neuroinflammation, an extremely complex response, widely recognised as a main contributor of AD-linked neurodegeneration but poorly understood in terms of its physiological interactions. Accordingly, based on previous work regarding the relationship between the Wnt signalling pathway and toll-like receptor-mediated inflammatory response, this review provides an update to the integrative view of this communication and discusses future directions of research focussed on modulating the inflammatory response within the central nervous system of AD patients.

INTRODUCTION

Described in 1906, Alzheimer's disease (AD) has become a major burden to the human population. Highly correlated with ageing, it has been estimated that AD can account for up to 70% of dementia cases worldwide with a cost of over $800 billion to public health systems around the world.[1] Accordingly, substantial human and financial efforts have been committed to fight AD. Regrettably, even with our increased understanding of the molecular mechanisms of the disease, no success has been achieved in the different clinical trials developed during the last decade.[2] In this regard, there is an urgent need to reconsider the way we approach potential AD therapeutics, such as the reappraisal of already known drugs, but taking the multifactorial aetiology of the pathology into consideration. Notably, during the last years it has become evident that addressing the inflammatory process during AD is fundamental not only to properly understand the pathology but to depict future therapies.

ALZHEIMER'S DISEASE

AD is commonly associated with a progressive loss of memory; however, the disease usually begins earlier with almost imperceptible symptoms such as subtle abnormal social behaviours or mood changes. Therefore, memory alterations only become evident with the progression of the disease and when the underlying neuronal dysfunction is enough to alter brain function.[3-7] Although the accumulation of amyloid-β (Aβ) peptides and hyperphosphorylated tau aggregates have been defined as the molecular hallmarks of the disease,[7-9] it is currently widely accepted that additional pathological features of the disease, such as vascular alterations,[10] mitochondrial dysfunction,[11] and neuroinflammation,[12] are involved from the very beginning in the progression of the disorder and appear even earlier than the traditional hallmarks.

Alzheimer Amyloid-β Peptide

According to the amyloid hypothesis of AD,[6] Aβ is a pivotal factor regulating the aforementioned features including the neurofibrillary tangles. Indeed, our current understanding of the effects of Aβ on the cellular molecular system has improved significantly during the last decades.[13-15] Oxidative stress, mitochondrial alterations, hyperphosphorylation of tau protein, further Aβ production, synaptic disruption, and neuronal cell death have been linked with the direct effects of Aβ on different organelles and/or molecular cascades.[16,17]

In this regard, Aβ constitutes a 37–43 amino acids post-transcriptional product of the amyloid precursor protein (APP). APP processing involves two possible pathways: 1) The non-amyloidogenic processing is carried out by the α and γ secretases, leading to the release of the soluble APPα and p3 fragment; 2) the amyloidogenic pathway is carried out by the β and γ secretases, leading to the release of the soluble APPβ and the neurotoxic Aβ peptide.[18,19] Even when Aβ aggregates localise outside the cells they can also accumulate inside the neurons,[20] being found within the mitochondria pool.[21] Considering that APP is synthesised and processed within different subcellular compartments, finding Aβ within these structures is still possible. Moreover, it has been demonstrated that cells can uptake Aβ from the extracellular space through the α7-nicotinic acetylcholine receptor further supporting the intracellular accumulation of the peptide and that this can cause primary cellular alterations, including tau hyperphosphorylation and neurite atrophy.[18] Importantly, these features are the most relevant regarding the neuroinflammatory cascade triggered during AD pathophysiology.

Aβ-DRIVEN NEUROINFLAMMATION AND THE ROLE OF TOLL-LIKE RECEPTORS

During the last decades it has become evident that sustained exposure to Aβ will lead to a chronic inflammatory state which ultimately will alter the brain microenvironment causing neuronal damage and/or neuronal death.[22,23] Aβ causes increased levels of several proinflammatory mediators including various members of the IL family (IL-1β, IL-6, IL-12), TNFα, COX2, and inducible nitric oxide synthase.[24-26] On the other hand, Aβ induces reactive oxygen species production through direct interaction with the mitochondria, not only affecting the metabolism of ATP but also leading to further production of proinflammatory mediators through NF-κB activation.[27-31]

These inflammatory mechanisms are exerted mostly via Aβ/toll-like receptor (TLR) interactions.[26]

The Brain and Toll-Like Receptors

Neurons are highly specialised cells with specific microenvironmental requirements. Accordingly, the central nervous system (CNS) remains a partially isolated domain with critical structures, such as the blood–brain barrier and the choroid plexus, and non-neuronal cells playing a fundamental role to sustain neuronal activity and protect the CNS from damage.[22,26,32] Astrocytes, oligodendrocytes, and microglia are recognised as the support cells for neuronal activity, with astrocytes and microglia as the main effectors of the response against inflammatory-related pathological processes in AD.[33] It is important to note that microglia remain the only representatives of the immune lineage within the CNS attributable to the colonisation of the brain by macrophages early during development.[34]

Beyond the different functions carried out by these cell types, each of them, including neurons, expresses different members of the TLR family. Thus, neuronal and non-neuronal cells cannot only respond to damaging insults but will also be affected by the presence of proinflammatory mediators.

The TLR family constitutes the main type of pattern recognition receptors which recognise the pathogen-associated molecular patterns and the damage-associated molecular patterns.[35,36] Up to 13 members have been described for the TLR family with different localisation within the cells. Relevantly, TLR1,2, and 4–6 are present in the plasma membrane, usually sensing or interacting with pathogen-associated molecular patterns; while TLR3 and 7–9 localise to endosomes and are able to sense damage-associated molecular patterns including ATP and nucleic acids.[36]

As mentioned previously, neurons and glial cells express TLR but with a different pattern. While the microglia and neurons express all TLR subtypes, astrocytes express TLR2–4, 9, and 11.[37,38]

The canonical molecular cascade linked to the activation of the TLR have been revised elsewhere; however, Figure 1A summarises the main events derived from such activation. For the purpose of this revision it is relevant to highlight that TLR activation will ultimately lead to increased release of proinflammatory mediators including IL, TNF, transforming growth factor, IFN, and complement proteins, among others.[39,40] In this context, it has been well established that Aβ triggers the inflammatory response mainly through direct interaction with TLR2 and TLR4, although it can interact with additional members of the TLR family.[21,40-43] Consequently, the permanent exposure to high levels of Aβ will result in the activation of the TLR in neuronal and non-neuronal cells causing a chronic condition with a vicious circle of activation of the inflammatory cascade. According to this information, it is not surprising that anti-inflammatory therapies are proposed to be re-evaluated because of their potential to control the inflammatory component of the disease. Therefore, one element that should not be overlooked during this approach is the crosstalk between the inflammatory cascade and critical signalling pathways for neuronal physiology, such as the Wnt pathway.

WNT SIGNALLING/TOLL-LIKE RECEPTORS AND THE INFLAMMATORY MILIEU

The Wnt pathway constitutes a complex cellular signalling system which has been related to cell proliferation and differentiation.[44,45] Wnt signalling can be divided in the canonical and the non-canonical Wnt pathways (Figure 1B). In the canonical pathway, Wnt proteins bind to the Frizzled receptor and low-density lipoprotein receptor-related protein 5/6, leading to the activation of dishevelled phosphoproteins and the interaction of low-density lipoprotein receptor-related protein 5/6 with axin. These events will cause the disassembly of the β-catenin destruction complex (adenomatous polyposis coli, axin, glycogen synthase kinase 3 beta [GSK-β3], and casein kinase 1), preventing the GSK-3β-mediated β-catenin phosphorylation. Then, the stabilised β-catenin can translocate to the nucleus where it will induce the expression of the Wnt target genes by binding to the T-cell factor and lymphoid enhancer-binding factor. The absence of Wnt ligands will define the turn-off of the system, causing the stabilisation of the destruction complex and the full activity of the GSK-3β, leading to β-catenin destruction.[46,47] On the other hand, the non-canonical Wnt pathway, which can be divided in the Wnt/planar cell polarity and the Wnt/$Ca2^{+}$ pathway, will lead to the activation of the c-Jun N-terminal kinase activity and to the rearrangement of cytoskeletal proteins,[48,49] and to the activation of calcium-related proteins such as protein kinase C and calcium/calmodulin-dependent protein kinase II.[48,49] Based on this division, it is possible to recognise two main types of Wnt ligands: those that activate the canonical pathway, including Wnt-1–3, 3a, and 8a; and those that are able to activate the non-canonical pathways, including Wnt-4, 5a, 5b, 6, 7a, and 11. However, this classification is not completely accurate since different ligands are able to activate depending on the physiological context, one way or another.[50] Furthermore, several elements of the Wnt cascade have been described as master switches that can be accessed through additional signalling pathways. Interestingly, the inflammatory master NF-κB pathway is one of the molecular cascades able to interact directly with Wnt signalling.[16]

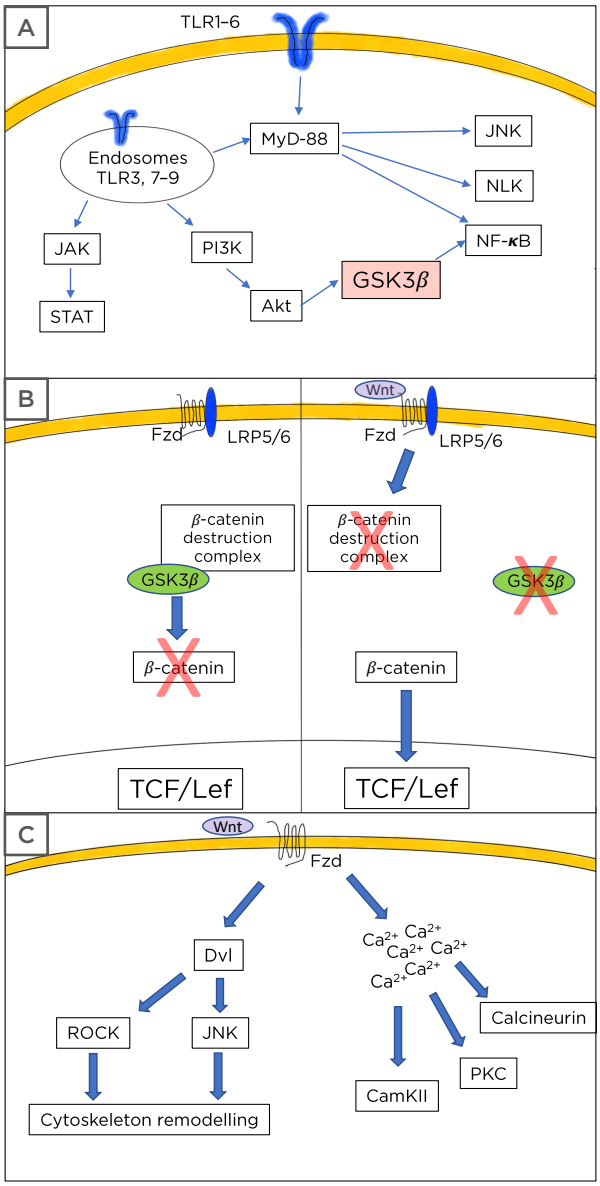

Figure 1: Toll-like receptor and Wnt pathway description.

A) Toll-like receptors (TLR) usually signal through the myeloid differentiation factor 88 leading to activation of the NF-κB pathway with the subsequent production and release of inflammatory mediators. Additionally, TLR also causes Nemo-like kinase and c-Jun N-terminal kinases activation. Some TLR can signal via the PI3K/protein kinase B/glycogen synthase kinase 3 β axis to induce further NF-κB activation. A third mechanism of TLR activity includes the JAK/STAT activation. **B)** Wnt signalling is composed of two main pathways. In the canonical, or Wnt/β-catenin dependent mechanism, the presence of Wnt ligands causes the activation of the Frizzled (Fzd)/low-density lipoprotein receptor-related protein 5/6 receptor leading to the disassembly of the β-catenin destruction complex and preventing the GSK-3β-mediated β-catenin phosphorylation. Thus, stabilised β-catenin can translocate to the nucleus and bind to the T-cell factor/lymphoid enhancer-binding factor transcription factor allowing the transcription of the Wnt target genes. In the absence of Wnt ligands, the system is turned-off and GSK-3β can phosphorylate β-catenin leading to its proteasomal destruction. **C)** The Wnt pathway also considers the non-canonical cascade, in which the presence of specific Wnt ligands will cause cytoskeleton rearrangement through dishevelled phosphoproteins followed by Rho-associated coiled-coil containing protein kinase and c-Jun N-terminal kinases activation in the planar cell polarity pathway. Similarly, the non-canonical activation can trigger the Wnt/Ca^{2}+ cascade leading to increased levels of calcium from intracellular storages and to the activation of several calcium dependent proteins, such as calcineurin, calcium calmodulin kinase II, and protein kinase C.

Akt: protein kinase B; CamKII: calcium calmodulin kinase II; JNK: c-Jun N-terminal kinases; Dvl: dishevelled; Fzd: Frizzled; GSK-3β: glycogen synthase kinase-3 β: Lef: lymphoid enhancer-binding factor; LRP: low-density lipoprotein receptor-related protein; MyD88: myeloid differentiation factor 88; NLK: Nemo-like kinase; PKC: protein kinase C; ROCK: Rho-associated coiled-coil containing protein kinase; Tcf: T-cell factor.

Wnt and Toll-Like Receptors Connection

In their previous work, the authors underlined the close relation and the reciprocal modulatory effect between TLR and Wnt signalling. Part of the molecular cascade triggered through TLR activation can be tracked down to the molecular switches present in the Wnt pathway. For example, TAK1, the controller of the IκB kinase complex, also activates the Nemo-like kinase and the c-Jun N-terminal kinase, both a factor and an end point of the activation of the canonical and non-canonical Wnt pathways.[51-53] Similarly, the potential regulation of GSK-3β through the TLR-PI3K-protein kinase B axis also contributes to solve the tight relation observed between Wnt signalling and the inflammatory response.[53] New research further supports this connection and underlines the critical role that Wnt signalling plays in the neuroinflammatory process.

In this context, the work of Song et al.[54] and Van Steenwinckel et al.[55] demonstrated not only the ability of Wnt signalling to modulate the activation of microglia, but to also downregulate the increase in the levels of critical proinflammatory mediators. Interestingly, the TWS119-induced inhibition of GSK-3β not only ensures canonical Wnt activity but also prevents the binding of NF-κB with the cyclic adenosine monophosphate response element binding protein-binding protein causing the blockade of the synthesis of several cytokines, a relevant issue beyond microglia activation. Indeed, TWS119 also acts as a regulator of the PI3K/protein kinase B/GSK-3β/reactive oxygen species axis.[56] The use of specific Wnt ligands, such as Wnt3a, has demonstrated significant anti-inflammatory effects including inducible nitric oxide synthase and TNFα downregulation.[56]

The work of Royer et al.[57] demonstrated the complementarity of the TLR/Wnt connection. In their work, the activation of TLR3 led to an increase in the levels of matrix metalloprotease 9 but in a mechanism absolutely dependent on the activation of the Wnt/β-catenin pathway. A similar complementary effect was also observed between the TLR4 and the Wnt/Dickkopf-related protein 3 axis.[58] This constitutes a relevant mechanism in tumour growth regulation in which the downregulation of the TLR4 will increase the activity of the Wnt pathway.

On the other hand, it has recently been demonstrated that the activation of Wnt signalling is closely related with the neuroprotection necessary in spinal cord injury. Moreover, this activation can be linked with several processes including blockade of apoptosis, tissue repair, and modulation of the inflammatory response.[59]

It is well known that Wnt signalling can exert different functions depending on the cellular context. Relevantly, this situation can also be observed regarding the inflammatory modulation exerted by some Wnt components. In this regard, different works have demonstrated that β-catenin, the main effector of canonical Wnt signalling, can be associated with several inflammatory conditions including infections and sterile processes such as colitis, liver injury, and myocardial infarction.[60-63] Furthermore, the work of Huang et al.[64] has recently demonstrated that β-catenin leads to the activation of the NOD-, LRR-, and pyrin domain-containing protein 3 inflammasome, a critical regulator of cytokine production.[64]

CONCLUSION

The role that Wnt signalling plays in inflammation or as an immunomodulatory agent has been largely known in the context of cancer and other pathological conditions. Recent research has also pointed out that these effects might be of relevance during the neurodegenerative process involving inflammation, such as AD. Previously, the authors depicted a common line between TLR and the Wnt pathway and have here provided information regarding recent findings that further suggest that these two molecular cascades are closely related and that they are fundamental in understanding the complexity of the neuroinflammatory process observed during AD neurodegeneration.

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Unilateral Facial Palsyin Guillain–Barré Syndrome, A Hyperreflexic Variant Case

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Abstract

Guillain–Barré syndrome (GBS) is a form of rapidly progressive, acute inflammatory demyelinating polyradiculopathy. Acute inflammatory demyelinating polyradiculopathy is the most common variant of GBS, especially in the western hemisphere. It is diagnosed without hesitation when it presents with its characteristic clinical features of ascending paralysis and areflexia. It is when an atypical presentation appears, with brisk or very brisk reflexes, that diagnosis becomes difficult. In this case, a patient who presented with progressive motor weakness, unilateral facial palsy, and hyperreflexia on examination is described in order to demonstrate a variant of GBS and its management. Keeping in mind that the management of the disease does not change with the variant, the diagnostic challenge that is put forward by those variants needs a focussed approach by physicians.

INTRODUCTION

Guillain–Barré syndrome (GBS) is a form of rapidly progressive, acute inflammatory demyelinating polyradiculopathy (AIDP). AIDP is the most common variant of GBS, especially in the western hemisphere.[1] This disease appears to be triggered by an infection or vaccination which disrupts self-tolerance, thereby leading to an autoimmune response which clinically presents as progressive motor weakness of one or more limbs with additional areflexia.[2] Facial paresis in GBS is another common clinical finding, which is mostly bilateral; however, a rare variant of unilateral facial paresis can also occur.[3] Sensory changes are also a common manifestation of most GBS variants. Bickerstaff's brainstem encephalitis, a rare postinfectious inflammatory disorder, also shares overlapping features of similar aetiology with GBS, and together with Miller Fisher syndrome, they are considered as variables of the same neurological disease spectrum.[4]

This case represents a rare variance of GBS in a young male who presented with weakness in all four limbs with hyperreflexia and a unilateral facial palsy. The hyperreflexia is another clinically variant symptom of GBS that can produce a diagnostic dilemma in a patient with acute paresis. While

most clinicians now accept that clinical variants, although rare, should be thoroughly investigated and pursued in the same manner as a usual case of GBS, on occasion a diagnostic dilemma can delay the management and worsen the prognosis with late intervention. In previous case studies there has been an argument to not expose the patients to immunotherapy in mild disease until there is absolute surety regarding the clinical diagnosis.[5,6] The counterargument is that the delay in intervention can worsen the prognosis; there are multiple cases discussed below that show benefits of early therapy, with complete resolution of symptoms.[7]

CASE PRESENTATION

A 16-year-old male with no known comorbidities presented with complaints of weakness in all four limbs for the previous 9 days and pain in the left shoulder for 1 day. The weakness was sudden in onset and started in the lower limbs, with the patient suddenly falling while walking. He required assistance when standing back up, as well as when trying to walk. The weakness progressed the following day, which resulted in him being unable to get out of his bed or to perform daily chores. The weakness then spread to his upper limb and the patient said that he could not change his clothes without assistance. The patient also developed pain in the left shoulder for 1 day which was muscular in character. The pain was sudden in onset and increased with attempts at activity and decreased with rest. In the 6 days prior to the onset of weakness, the patient also had a history of fever which resolved on its own. However, this fever did not coincide with the muscle weakness of acute presentation. There was also a history of fever and pustular eruptions on the hands and feet 2 months prior, which were itchy and likely to be lesions from scabies. The lesions were resolved after the use of over-the-counter emollient creams. In the following months, the patient had repeated hospital admissions for pain crises, abdominal pain, diarrhoea, and weight loss. For every admission he was treated with red blood cell exchange transfusions, intravenous hydration, antibiotics, and analgesics; haemaglobin S levels were maintained at <28%. A lactose-free diet was recommended, but the patient continued to have six to eight loose stools per day. A flexible rectosigmoidoscopy revealed areas of exudate and necrosis in the rectosigmoid colon with multiple blood clots, and biopsies obtained did not show any significant findings. Stool cultures and stool parasitology tests were negative. Abdominal T2-weighted MRI to assess iron overload showed no signs of secondary liver haemochromatosis, with liver iron being 1.1 mg/g (dry liver measurement), but significant liver hypertrophy and upper abdominal varices were suggestive of portal hypertension. CT evaluation of the abdomen revealed bowel distention, thickening of the intestinal wall, mesenteric lymph node enlargement, signs of liver cirrhosis, and presence of ascites. Liver elastography showed an elevated liver stiffness of 13.2 kPa, indicative of liver cirrhosis.

On initial examination, the patient's vital signs including body temperature, pulse rate, respiratory rate, and blood pressure were all in the normal ranges. Motor system examination revealed the muscle bulk and tone to be normal in all four limbs. For both the upper limbs, the grade of power was 2/5 in both the proximal and distal muscle groups. For the lower right limb, the grade of power was 2/5. For the lower-left limb, the grade of power was 4/5, which later decreased to 2/5 in both the proximal and distal muscle groups during another day of hospital stay. The deep tendon reflexes were brisk (+3) throughout all four limbs except for the patellar tendon reflex which had a very brisk response (+4). However, the plantar response was flexor, Hoffman's sign was negative in the upper limbs, and abdominal reflexes were normal. The cranial examination revealed left-sided lower motor neuron facial palsy, as well as an absent corneal reflex, while the rest of the cranial nerve examination was unremarkable. The involvement of lower motor neurons in GBS is probably a result of infectious polyneuritis, which might involve or spare isolated cranial nerves. There was a blink response on the right with left corneal stimulation, ruling out the involvement of the V1 branch of the left trigeminal in addition to the left seventh cranial nerve. Other sensory modalities such as fine and crude sensations, two-point discrimination, pain, temperature, vibration, and proprioception were all intact. Examination of the shoulder joint revealed muscular spasm, but other signs of tendon injury or rotator cuff pathology were negative. Other systemic examination segments revealed no abnormalities. The differential

diagnosis at this point was acute myelopathy (transverse myelitis), neurotoxic polyneuropathy (botulism, fish poisoning), spinal cord syndromes (postinfectious), toxic or vasculitic neuropathies, AIDP, and metabolic myopathies.

The laboratory workup findings were a haemoglobin count of 15.2 g/dL (normal 13.2–17.5 g/dL), erythrocyte sedimentation rate of 17 mm/hour (normal 0–15 mm/hour), total leukocyte count of 6.4x10^3/µL (normal 4.1–10.9x10^3/µL), platelet count of 342x10^3/µL (normal 150–400x10^3/µL), urea level of 32.3 mg/dL (normal 15.0–43.0 mg/dL), creatinine level of 0.62 mg/dL (normal 0.60–1.20 mg/dL), sodium level of 139 mmol/L (normal 134–144 mmol/L), chloride level of 100 mmol/L (normal 98–107 mmol/L), potassium level of 3.9 mmol/L (normal 3.6–5.0 mmol/L), bicarbonate level of 30 mmol/L (normal 23–30 mmol/L), total bilirubin of 0.34 mg/dL (normal 0.30–1.00 mg/dL), alanine aminotransferase level of 25 IU/L (normal 10–35 IU/L), aspartate aminotransferase level of 24 IU/L (normal <35 IU/L), alkaline phosphatase level of 154 IU/L (normal 44–147 IU/L), and γ-glutamyl transferase level of 18 IU/L (normal 15–80 IU/L). Viral serologies were negative for hepatitis, HIV, cytomegalovirus, Epstein–Barr virus, herpes simplex virus, and varicella-zoster virus. The West Nile virus and Lyme disease diagnostic tests were not available in the authors' region and therefore were not performed.

Nerve conduction studies performed in the initial week of symptoms onset were nonspecific to postinfectious pathology and revealed C8-T1 radiculopathy (Table 1). Needle electromyography was not performed in the patient. The lumbar puncture, preceded by a plain CT scan of the brain, revealed no findings and ruled out central nervous system inflammation (Figure 1). MRI (with contrast) of the cervical spinal cord was normal (Figure 2). Cerebrospinal fluid (CSF) examination on Day 10 of clinical onset revealed a cell count of 6 cells/mm^3 (normal 100–1,000 cells/mm^3), CSF protein level of 142 mg/dL (normal 15–40 mg/dL), CSF glucose level of 68 mg/dL (normal 40–70 mg/dL), CSF chloride level of 117 mEq/L (122–132 mEq/L), CSF white blood cell count of 0.001x10^3/µL (normal 0.000–0.005 10^3/µL), and no red blood cells or pus cells were detected, and hence was suggestive of albuminocytological dissociation.

No other features in the history and examination were suggestive of toxic ingestion or autoimmune illness, hence the diagnosis of the patient was established to be GBS, and prompt action was taken to begin the patient's treatment with one cycle of plasmapheresis every alternate day (40–50 mL/kg). The plasmapheresis was preferred instead of intravenous Ig in this patient strictly because of cost-effectiveness. The patient started improving greatly after the plasmapheresis cycles were commenced, and all signs of neuropathy and cranial nerve deficit began to decrease and almost completely disappeared in the following 2 weeks after completing five cycles of plasmapheresis. The patient was discharged and followed-up in the ambulatory clinical setting 2 weeks later and had complete resolution of symptoms. Ethical approval was taken in this study from the institutional review board, and consent to participate has been taken from the patient's guardian with informed verbal consent.

DISCUSSION

GBS is a group of syndromes that are classified into demyelinating and axonal forms based on their pathologies. Approximately 1.72 patients per 100,000 people per year are considered to be affected by GBS, with a further increase of 50% with every 10-year increase in age.[1] Despite this, it should be noted that although one of the fundamental features of GBS is hyporeflexia or areflexia, a patient presenting with preserved reflexes or hyperreflexia does not rule out GBS as a diagnosis.[1] Hyperreflexia is known to be seen in patients with a previous *Campylobacter jejuni* infection with prior history of abdominal pain and diarrhoea; however, the most common and repeatable results have been seen with the acute motor axonal neuropathy type of GBS, which is seen in approximately 48% of Chinese patients and 33% of Japanese patients.[2]

It is important to note that although hyperreflexia is known to be seen in patients with previous *C. jejuni* infections, the patient in this present case had no previous history of such infection and the onset of the disease was more unforeseen, presenting with sudden onset of lower-limb paralysis that progressively worsened to all involve all four limbs.

Table 1: Motor and sensory nerve conduction studies.

Sensory nerve conduction study																				
Nerve	Median				N	Ulnar				N	Radial				N	Sural				N
Latency (msec)	Right	2.4	Left	2.3	2.9–3.5	Right	2.2	Left	2.2	2.9–3.5	Right	1.8	Left	1.9	1.9–2.8	Right	-	Left	3.1	<4.2
SNAP Amplitude (uV)	Right	35.5	Left	32.3	>15	Right	35.4	Left	30.5	>15	Right	31.1	Left	33.2	>10	Right	-	Left	20.1	>5

Motor nerve conduction study																				
Nerve	Median					Ulnar					Peroneal					Tibial				
Segment	C8-T1					C8-T1					L4-S1					L4-S2				
Recording muscle	Thenar				N	Hypothenar				N	Extensor digitalis brevis				N	Abductor hallucis				N
CAMPS amplitude (mV)	Right	3.5	Left	4.8	>4.0	Right	1.3	Left	2.1	>4.0	Right	-	Left	4.4	>2.0	Right	-	Left	8.5	>3.0
Distal stimulus latency (msec)	Right	3.7	Left	3.8	<4.5	Right	2.5	Left	2.9	<4.2	Right	-	Left	4.2	<5.1	Right	-	Left	6.1	<6.1
Proximal stimulus latency / CMAP (msec, mV)	Right	7.5	Left	7.1	-	Right	8.4	Left	9.4	-	Right	-	Left	12.2	-	Right	-	Left	13.7	-
Conduction velocity (m/sec)	Right	60.6	Left	59.7	45.0–57.0	Right	46.6	Left	47.6	45.0–57.0	Right	-	Left	50.2	>40.0	Right	-	Left	55.7	>40.0
F-wave latency (m/sec)	Right	27	Left	26.7	21.0–31.0	Right	26.0	Left	26.6	21.0–32.0	Right	-	Left	-	38.0–57.0	Right	-	Left	43.2	41.0–57.0

N: normal.

This presentation shows that even though *C. jejuni* infection may show some correlation with hyperreflexia in patients, this rare presentation does not require a prior infection.[2]

The clinical course of GBS is usually aggressive and tends to involve respiratory muscles which may result in ventilatory failure and requirement of respiratory support in up to one-third of patients.[2] Most patients also complain of sensory disturbances such as paraesthesia and numbness.

Although the presentation of hyperreflexia in GBS is not common but known,[8] it is highly likely that it may be an associated finding in upper motor neuron dysfunction.

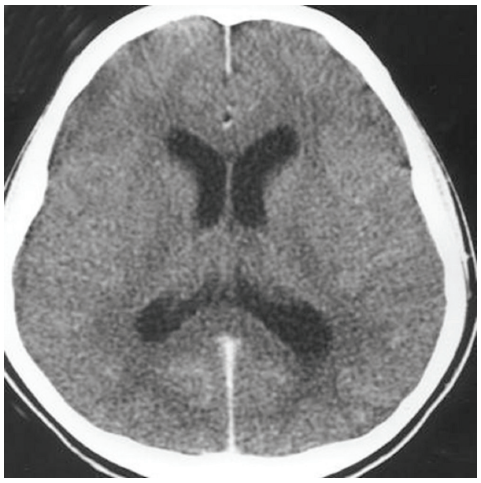

Figure 1: CT scan of the patient's brain (without contrast, showing normal findings).

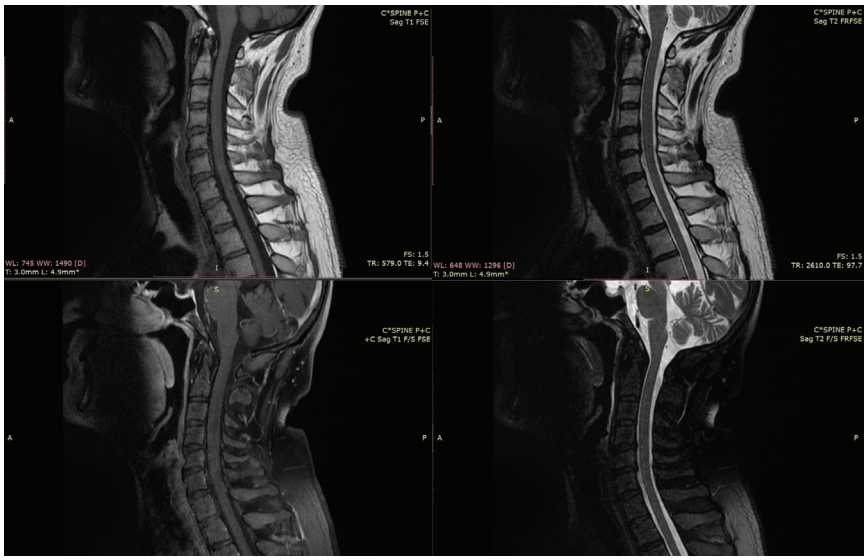

Figure 2: MRI of the patient's cervical spine (with contrast, showing normal findings).

A common theory was that the role of anti-GM1 antibodies could cause the hyperreflexia by damaging nerve roots and central axons of the spinal cord when entering the subarachnoid space through the blood–brain and blood–spinal cord barriers.[9]

However, the exact mechanism of hyperreflexia in GBS and why nerve root damage does not cause hyporeflexia or areflexia, even if there is upper motor neuron dysfunction, is still unknown but is postulated to be associated with spinal inhibitor intermediate neuronal dysfunction.[9] Few studies have shown that although there is a high incidence of antiganglioside (GM-1) antibodies being present in patients with hyperreflexia, it is still possible for patients to present with this rare variant without any antibodies present in their serum.[3] Most patients with GBS show increased protein counts in the CSF, but nerve conduction studies remain the most sensitive diagnostic tool. However, electrodiagnostic studies cannot be highly sensitive in diagnosing GBS in the early course of the disease, as mentioned by several studies.[10,11] The usual sensitivities to diagnose GBS with nerve conduction studies are 55–59%, according to two different studies.[10,11]

In literature, similar cases have been reported, and few of those discussed the need to withhold the immunotherapy till the second week to be

sure of the diagnosis.[5,6] Another review of two patients with facial palsy and hyperreflexia preceding *C. jejuni* infection and the presence of antiganglioside antibodies showed improvement with the administration of intravenous Ig.[7] Intensive physiotherapy can help to reach complete resolution within 2 weeks.[12] The role of intravenous methylprednisolone along with intravenous Ig was also discussed in one case.[13] Hyperreflexia can persist, with complete resolution of muscle strength potentially taking up to 1 year.[14,15] Follow-up nerve conduction studies usually show regenerative changes with the resolution of symptoms.[16,17] The paediatric population usually presents with such a variant type of GBS,[18,21] and it has been reported in women who are pregnant, but this is rare.[22] Asian and European populations are more commonly affected by this variant.[2,23] Bilateral facial palsy is rarely the only presentation of this variant;[24] although, almost one-third to one-half of the patients with GBS have facial palsy, either unilateral or bilateral.[14,15,25]

Hemiplegia and cranial nerve palsies are the other reported variants of GBS that are closely related.[26] The overall prevalence of this GBS variant is reported to be around 0.2–0.8%;[14,15,23,24] however, hyperreflexia can be present in 33–48% of AIDP cases.[20,26] Miller Fisher syndrome is another closely related variant, which can involve extraocular muscles and diminished reflexes, in contrast to this present case.[27] Bickerstaff's brainstem encephalitis, which consists of a triad of ophthalmoplegia, ataxia, and altered sensorium, is another closely related disorder that shares overlapping features and similar aetiology to GBS. The only feature that differentiates the two entities is altered level of consciousness, which was absent in the author's case.[4,28] Recent Zika virus outbreaks were also reported to be associated with GBS, hyperreflexia, and facial or bulbar palsy, but myelopathic forms appeared with different prognoses and high mortality.[29] The development of hyperreflexia at the knees and normoreflexia at the ankles in a teenage male can be attributed to many other causes, including medication and stimulant side effects, hyperthyroidism, electrolyte imbalance, serotonin syndrome, severe brain trauma, and Reye's syndrome. A specific cause has been recently identified as L5 nerve root injury.[30]

CONCLUSION

This case report shows that although areflexia and progressive motor weakness are both key elements of GBS, if a patient does not present with both, GBS should still be in the physician's working differentials. The aim of this case report is to increase the awareness regarding this different variant of GBS, which was not diagnosed with nerve conduction studies but by meeting other criteria. Although it is rare, prompt diagnosis and management showed worthiness in improving prognosis in various case studies.

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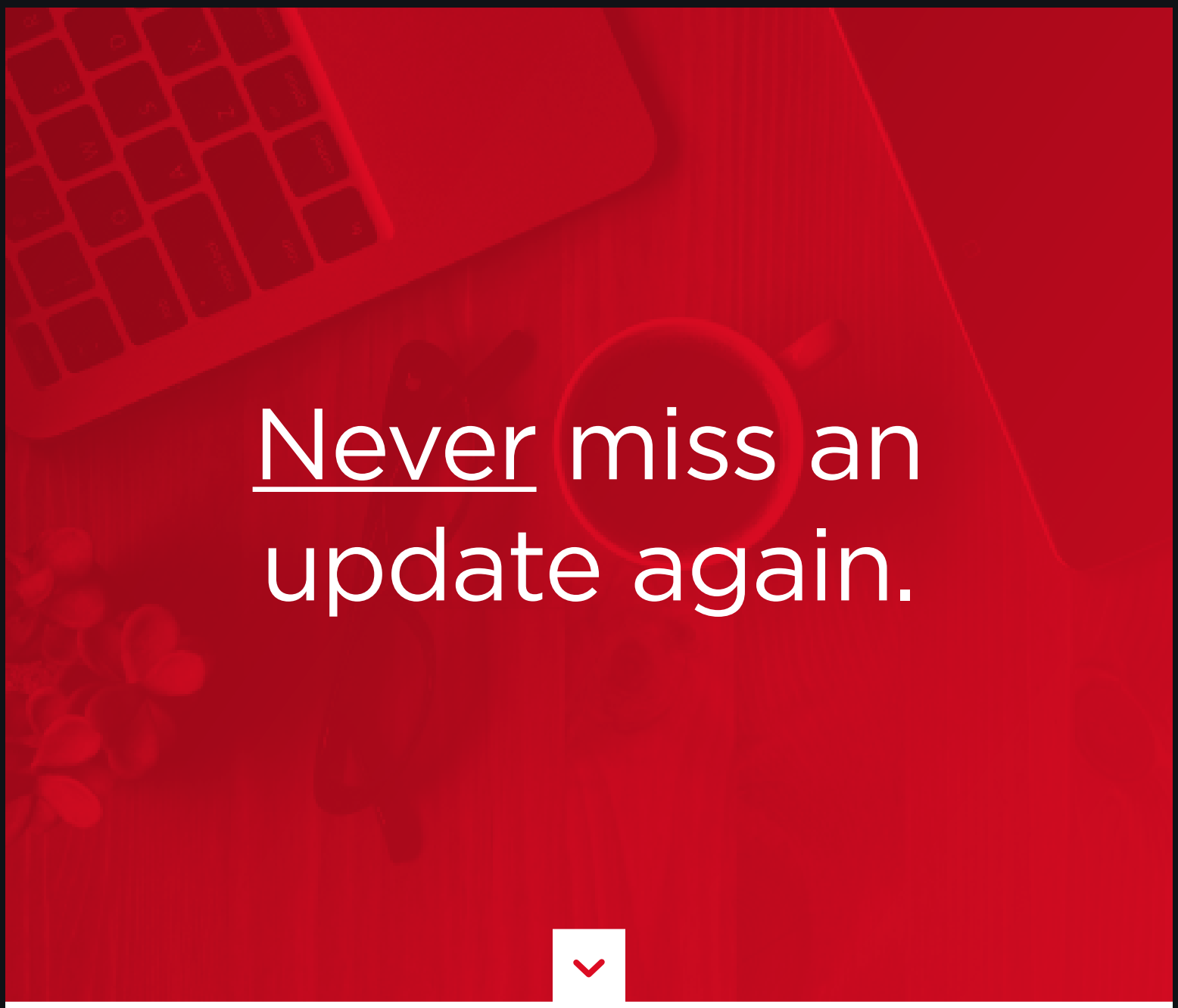

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