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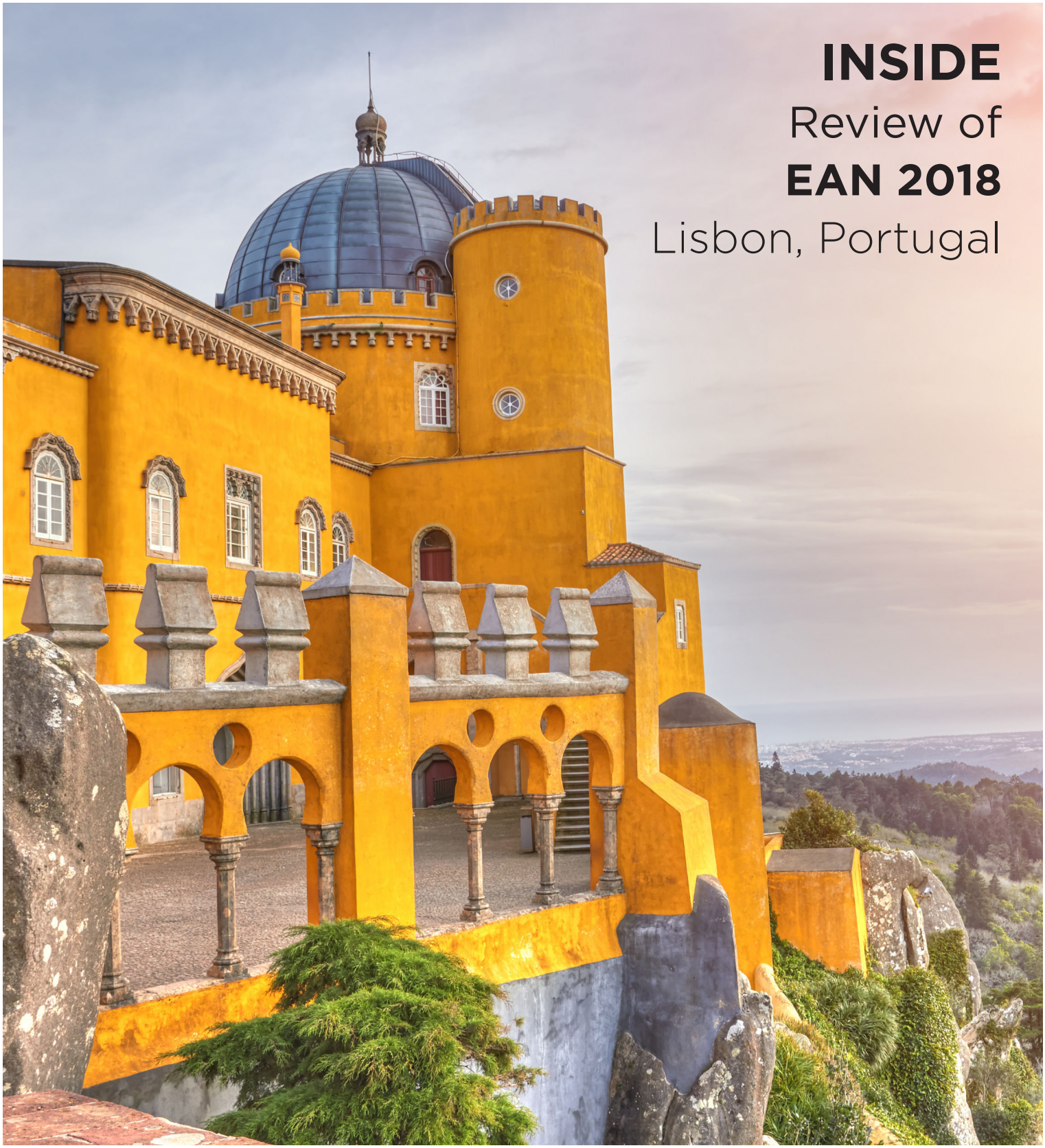

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Review of

EAN 2018

Lisbon, Portugal

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Spencer Gore, CEO

Editorial Board

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Aims and Scope

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

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

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

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

EMJ also publishes 16 therapeutic area journals, which provide concise coverage of salient developments at the leading European congresses. These are published annually, approximately 6 weeks after the relevant congress. Further details can be found on our website: www.europeanmedical-journal.com

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

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This Publication

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Front cover and contents photograph: Lisbon, Portugal, home of the EAN 2018 Congress.

EMJ Neurol.

European Medical Journal 3.1

This edition is packed with an assortment of peer-reviewed articles from a body of therapeutic areas, including reproductive health, dermatology, and cardiology, to name a few.

VIEW ALL JOURNALS ←

Welcome

Dear colleagues,

It is with great pleasure that I present to you *EMJ Neurology 6.1*. There is an astonishing array of content in this eJournal, with peer-reviewed, cutting-edge research papers alongside our unique Congress Review of the European Academy of Neurology (EAN) Congress; there really is something for everyone to enjoy in *EMJ Neurology 6.1*.

EAN 2018 was a highlight in the European Medical Journal's calendar. Set in the beautiful coastal capital of Lisbon, Portugal, the 4th EAN Congress included workshops, hands-on courses, and spectacular symposiums presenting the latest research from a myriad of neurological topics. Our Congress Review section encompasses the groundbreaking research released and presented at EAN 2018, including abstract summaries of work displayed at the congress, penned by the presenters themselves to give a unique perspective on these thought-provoking topics.

Delving deeper into *EMJ Neurology 6.1*, you will find our high-quality, peer-reviewed articles, beginning with the Editor's Pick by Hogden et al. that summarises the importance of an integrated palliative approach to care for people living with neurodegenerative conditions. I am sure that this narrative review will no doubt be of interest to those in the neurology healthcare profession, as well as further afield. Other contributions include a research paper by Armstrong on the link between tau-immunoreactive inclusion and the spread of pathogenic tau in a number of tauopathies, and a review of neuro-Behçet's syndrome by Uygunoglu et al.

Finally, I would like to whole-heartedly thank everyone who has contributed to the production of *EMJ Neurology 6.1*; it has been an absolute pleasure to work with you all on this publication. The ever-evolving field of neurology is advancing at a remarkable rate, with developments being made every day. The EMJ team is already looking forward to bringing you the highlights from EAN 2019 in next year's edition of *EMJ Neurology*.

Warm regards,

Spencer Gore

Chief Executive Officer, European Medical Group

ean congress Oslo 2019

5th Congress of the European Academy of Neurology

June 29 – July 2

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23 January 2019

Early registration deadline
10 April 2019

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Foreword

Dear friends, colleagues, and readers,

It is with a sense of great pride and pleasure that I present you with 2018's edition of *EMJ Neurology.* Read on to find a carefully curated package of peer-reviewed articles, interviews with Editorial Board members, the European Academy of Neurology (EAN) Congress Review, and invited abstract summaries from the EAN Congress 2018.

Did you travel to Lisbon, Portugal this year to attend the EAN Congress? Although the EAN was only created in 2014, this event has already become a lodestone for neurologists across Europe and the globe. In an increasingly interconnected scientific community, the importance of old-fashioned, face-to-face communication and networking cannot be overlooked. Whether catching up with old friends, making new connections, or simply attending talks, symposiums, and presentations, there are many valuable opportunities to be had. The event does an impressive job of bringing together all the various aspects of neurological diseases as well as facilitating the discussion of clinical practice and research.

"It is with a sense of great pride and pleasure that I present you with 2018's edition of EMJ Neurology."

The Congress Review within *EMJ Neurology* captures the outstanding atmosphere of this festival of neurology. Inside, you can catch up on many of the breaking news stories presented during the congress, including the latest developments in stroke treatment and the fascinating research into therapeutic options for dementia. This section is well worth a read.

I would also like to take a moment to thank all of you who played a role in the creation of this journal. There were many contributors, including my fellow colleagues on the Editorial Board, the authors who submitted their manuscripts, those who dedicated their time to peer reviewing, and the poster presenters who submitted their Abstract Reviews. Your work has made the publication of *EMJ Neurology* possible and played a vital part in the dissemination of neurological information.

I hope you enjoy this truly unique eJournal.

With warm regards and thanks,

Prof László Vécsei
University of Szeged, Hungary

Congress Review

Review of the European Academy of Neurology (EAN) 4th Annual Meeting 2018

Location: Lisbon, Portugal – Lisbon Congress Centre

Date: 16.06.18–19.06.18

Citation: EMJ Neurol. 2018;6[1]:10-32. Congress Review.

The 4th European Academy of Neurology (EAN) congress was held in the hilly, coastal capital of Lisbon, Portugal, on the 16th–19th June 2018. The over-arching theme of the congress was neurogenetics, with the meeting aiming to unravel these seemingly hidden diseases. Situated just a stone's throw away from the congress hall, the impressive 25 de Abril suspension bridge over the Tagus river symbolised the collaboration seen at this year's EAN congress, with attendees travelling from across the globe to revel in this magnificent event.

The programme for the 4th EAN congress was full of focussed workshops, hands-on courses, and spectacular symposiums presenting the cutting-edge research from a myriad of neurological topics. Some of the ground-breaking highlights from the congress are detailed in this Congress Review, including new treatment guidelines, an investigation into consciousness after stroke, and many more intriguing results.

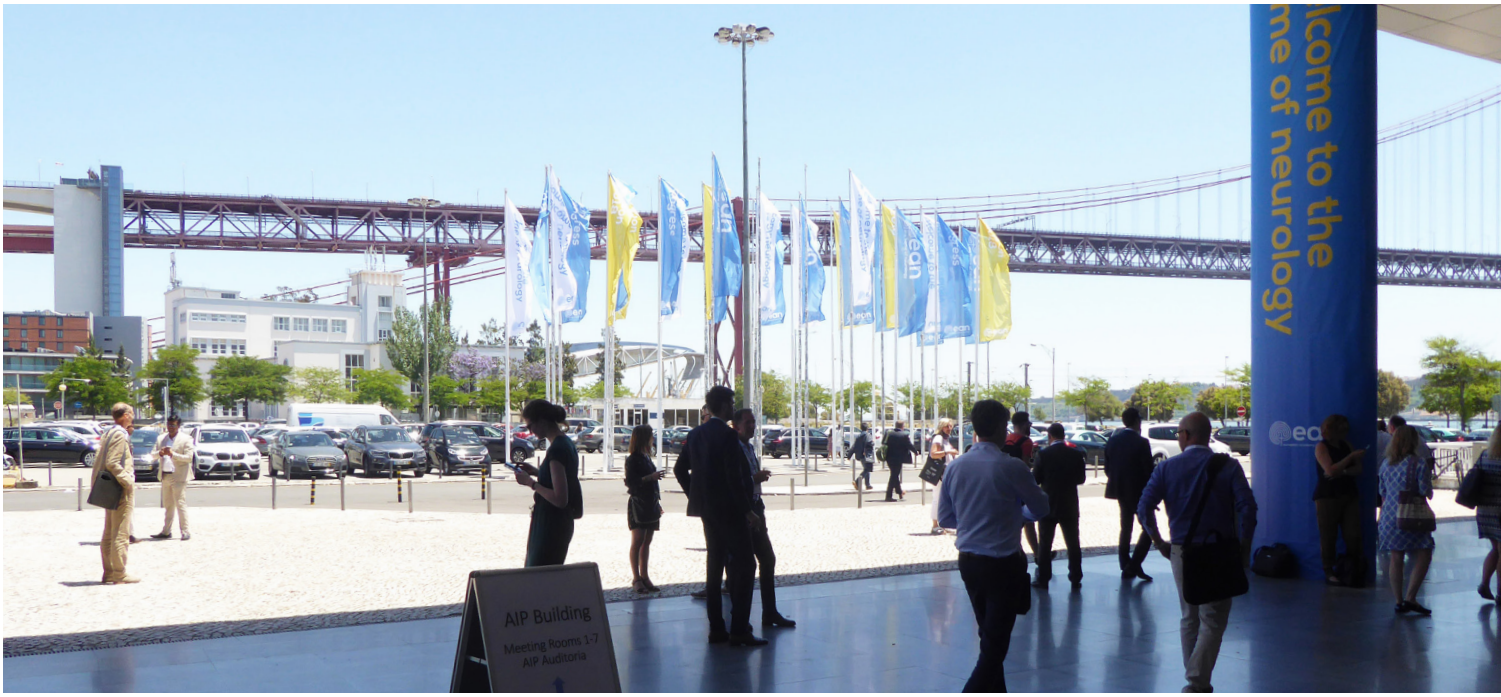
Prof Joaquim Ferreira, Chair of the local organising committee, welcomed attendees to the Opening Ceremony and encouraged everybody to learn from the numerous sessions, share experiences and knowledge, meet new people, and explore the Portuguese capital. Prof Günther Deuschl then took to the stage for his last presentation as EAN President and gave a thought-provoking reflection on some of the major advances in neurology. Innovations in neurology were the cornerstone of Prof Deuschl's presentation, including the approval of the first drug to treat secondary multiple sclerosis, which is highlighted later in this Congress Review. The 2018 Brain Prize winners were also celebrated by the EAN President for their outstanding work in the field of Alzheimer's disease pathology and their identification of blood biomarkers and imaging techniques, allowing early diagnosis of this debilitating disease.

Prof Deuschl proceeded to highlight the importance of identifying and actioning new diagnosis and treatment programmes and their direct impact on the burden of neurological disease in Europe. Neurological diseases have been ranked the third highest cause of disability adjusted life years and death in Europe following a continent-wide assessment of major diseases. Prof Deuschl used Alzheimer's disease and stroke, despite increased prevalence of the conditions, as examples of how disability adjusted life years have drastically reduced, highlighting the impact of treatment progress and early diagnosis on this ever-progressing field.

"The 2018 Brain Prize winners were also celebrated by the EAN President for their outstanding work in the field of Alzheimer's disease pathology..."

Prof Deuschl concluded his last presidential presentation by stressing the important role neurologists play in ageing European societies, with just under 6,000 neurological diagnoses per neurologist. He called for a collaborative approach between all neurologists to work together to achieve common goals. As a final act, Prof Deuschl presented Prof Alistair Compaston (UK) and Prof Mark Hallett (National Institute of Neurological Disorders and Stroke [NINDS]) with honorary membership for their contribution to multiple sclerosis and human motor control disorders research, respectively.

With EAN 2018 fresh in our minds, the EMJ team is already looking forward to the 5th EAN congress, to be held in one of Europe's fastest growing cities: Oslo, Norway, from the 29th June–2nd July 2019. The EAN congress 2018 will be the first ever congress not to be presided over by Prof Deuschl and will mark the first congress under the presidency of Prof Franz Fazekas. We look forward to witnessing the new era Prof Fazekas will bring to the EAN congresses, as we finish celebrating Prof Deuschl's esteemed contributions to the event.



Cost Burden Analysis of Brain Disorder Treatment

BRAIN disorders currently affect approximately one-third of European citizens. With up to 8 out of 10 patients with a brain disorder either remaining untreated or inadequately treated despite the existence of effective therapies; these statistics represent a significant number of patients. In response to this, the European Brain Council (EBC) initiated the Value of Treatment (VoT) study to examine the treatment gap and deliver recommendations. This study was one of the topics of discussion at the EAN congress, as reported on in an EAN press release, dated 18th June 2018.

The Vice President of the EBC, Prof Wolfgang Oertel, explained: "The VoT puts a valuable resource in the hands of political decision-makers that contains the background information they need to reach conclusions on and analyse the return on investment for various treatments, as well as pinpointing cost-effective policy recommendations for treating brain disorders in their countries."

The VoT involved an assessment of the health, social, and economic costs of the best possible treatment compared to standard treatment or non-treatment. It contains nine case studies assessing costs and providing recommendations for care, including Alzheimer's disease, epilepsy, headache, Parkinson's disease, restless leg syndrome, multiple sclerosis, normal pressure hydrocephalus, schizophrenia, and stroke.

"That said, in overall economic terms, it is still more cost-effective than early retirement and permanent incapacity at the age of 45."

One of the cornerstone recommendations of the study was that optimal care and an early start to treatment was the most cost-effective long-term policy. An example provided to highlight this was that of a stroke patient who had felt abandoned after acute therapy. After the treatment had taken place, there were no further steps in place, such as a course of rehabilitation or discussing the patient's work situation. Prof Oertel noted that while it would have been a significant time investment to provide the patient with maximum support to get back on their feet, it would still have been worthwhile. He commented: "That said, in overall economic terms, it is still more cost-effective than early retirement and permanent incapacity at the age of 45." It is hoped that the VoT study's recommendations will provide inspiration for ensuring an improved standard of care for patients with brain conditions.

Thrombectomy in Elderly Acute Stroke Patients: A Risky but Promising Therapy

A LIFE free from stroke-related disability may be available for a select group of older patients in the future using mechanical thrombectomy, suggests research presented in a EAN press release dated 18th June 2018. In numerous studies, endovascular thrombectomy has been shown to be more beneficial than drug-based therapy alone, but it is not without considerable risks; as a result, identifying those patients for whom this procedure is appropriate is of utmost importance.

"More and more study results show the high effectiveness of mechanical removal of blood clots after a stroke. But researchers are still trying to determine the type of patient for whom this relatively new procedure is the best treatment option."

"More and more study results show the effectiveness of mechanical removal of blood clots after a stroke. But researchers are still trying to determine the type of patient for whom this relatively new procedure is the best treatment option," explained Dr Ary Lopes de Sousa, Centro Hospitalar de Lisboa Central, Lisbon, Portugal.

Following this, Dr de Sousa and colleagues reviewed >200 patients who had experienced an anterior acute ischaemic stroke and had either no or slight disability prior to the event. The patients were categorised into two groups, the former containing patients <80 years old and the latter containing those ≥80 years old. These patients had all received thrombectomy and the treatment did not differ between groups (e.g., the time to revascularisation).

Findings showed that hypertension and transitory ischaemic attacks were both more frequent in the older group, but no differences in death rates were recorded between the groups. Additionally, a poor functional outcome was exhibited 3 months post-treatment in two-thirds of the older group (i.e., moderate-to-severe limitation at performing daily tasks), compared to 46% in the younger group. However, in contrast to these poor outcomes, one third of the older group was shown to have mild or no impairment to their everyday lives at 3 months follow-up. Thus, while thrombectomy is clearly a risky treatment in some regards, it can also be highly beneficial. The challenge now is to identify those in the very elderly patient population for whom mechanical thrombectomy may be a beneficial treatment option, and for this, more research is needed. "For patients over 80, thrombectomy appears to be riskier than for younger patients. But one third of the patients over 80 can be fully functional in their everyday lives after the procedure, so we must identify the factors associated with this favourable outcome," concluded Dr de Sousa.

A Focus on Stroke Treatment and Prevention

THE LATEST developments in stroke treatment were a hot topic at this year's EAN congress, including reducing the risk of recurrent stroke and the use of thrombolysis in acute stroke treatment. Detailed in a EAN press release dated 17th June 2018, these latest results will make a significant contribution to improving stroke management.

"We now have clues how MRI may identify those patients in whom thrombolysis is beneficial even if we do not know the exact time of stroke onset."

Although stroke-related death rates have steadily declined in recent years due to improved treatment and rehabilitation, further progress is still required to prevent the 600,000 newly reported cases in Europe each year. In addition, one study has highlighted the high risk of recurrent stroke; therefore, researchers have recently been addressing these issues in a number of studies presented at the EAN 2018 congress. For example, one study demonstrated the suitability of combined clopidogrel and aspirin treatment as a preventative measure of stroke recurrence. Around 4,900 post-minor cerebral infarction or transitory ischaemic attack patients were given either placebo, aspirin only, or the combined regimen. Although a heightened risk of major haemorrhage was associated with the clopidogrel-aspirin patients, this group experienced fewer cerebral infarctions, heart attacks, and deaths following the monitoring period.

Furthermore, the results of an investigation into embolic strokes of unknown cause showed that oral rivaroxaban, an inhibitor of factor Xa, was not more effective than aspirin, with the number of ischaemic events in both treatment groups being very similar (158 and 156 for rivaroxaban and aspirin, respectively). The study also showed an increased risk of haemorrhage with rivaroxaban therapy. "Before initiating any anticoagulation therapy, we still need to determine if there really exists a cardioembolic source," commented Prof Franz Fazekas, Medical University of Graz, Graz, Austria.

With a more positive outcome, another study presented evidence of the effective use of thrombolysis when time of stroke onset is unknown. The WAKE UP study involved patients who had evidence of ischaemic lesions on diffusion-weighted MRI only, suggesting stroke occurred ≤4.5 hours prior. A total of 53.3% of participants had favourable treatment outcomes alter intravenous alteplase compared to 41.8% with placebo. In addition, on a scale of 0 (no symptoms) to 6 (death), the thrombolysis group scored an average of 1 and the placebo group averaged 2; however, a higher incidence of intracranial bleeding and increased mortality rates were associated with alteplase treatment. "We now have clues how MRI may identify those patients in whom thrombolysis is beneficial even if we do not know the exact time of stroke onset," stated Prof Fazekas. The results provide hope for improving the risk of permanent stroke-related injury and preventing stroke altogether.

Improving Migraine Treatment and Prevention Could Save The Global Economy Billions

MIGRAINES seriously burden patients' work and social lives, but also impact on the wider economy. Results from a French and a second Swiss study, presented in a EAN press release dated 17th June 2018, highlight the pressing need to increase investment in research into the prevention of migraine, which is believed will benefit society as a whole. A French study of 7,700 migraine patients and a Swiss study of 700 working migraine patients both set out to assess the true cost of migraine, from individual patient costs to society and business costs as a whole.

Of those included in the French study, 3.8% had experienced severe migraines on at least 8 days each month. Of those, the average age was 41 years, meaning that migraines are affecting

individuals of prime working age, who are likely to have families to support. The study results also revealed that migraine patients reported missing an average of 33 working days a year due to the condition, costing the economy roughly €3.8 billion. The study also highlighted that patients also spent >€30 per month for non-reimbursed medicines, and 14% reported that family members had to adjust their working hours as a result of the patients' migraines.

"...experts at the EAN Congress 2018 issued a call for increased investment in migraine research into the prevention of migraine..."

The 700 Swiss patients reported losing an average of 32 days a year as a result of migraine, which is not dissimilar from the French study. However, there were differences depending on the type of headache the patient experienced: patients with chronic migraine, episodic migraine, and low-frequency episodic migraine missed an average of >56, 33, and 15 working days per year, respectively. Results also highlighted that the number of sick days taken were not constant, the total steadily increased along with the amount of medication taken.

Migraines impact all aspects of the patient's life and as a result, the quality of life for migraine patients remains far from satisfactory. As a consequence of these eye-opening study results and the burden migraines place on individuals, experts at the EAN Congress 2018 issued a call for increased investment in migraine research and prevention which would benefit not only those who experience migraines, but also society as a whole.

New Developments in Dementia Research

DEMENTIA: a disease that 47 million people across the globe currently present with, which already results in a notable social and economic burden. This number is currently predicted to increase to 131 million by 2050, with the social and economic burden set to increase accordingly.[1] Therefore, dementia research was a key talking point at the EAN congress, as reported in a EAN press release, dated 17th June 2018. Two of the topics highlighted were the use of big data and an ongoing study into the impact of physical activity.

While previous observational studies have suggested that individuals who regularly partake in physical activity tend to have a better cognitive status, there is the need to more closely examine this potential association. As Prof Ana Isabel Verdelho, EAN Scientific Panel on Dementia and Cognitive Disorders, explained at the EAN congress: "If individuals who have been physically active throughout their life do not develop dementia, you cannot necessarily conclude that physical activity is the reason. These persons may have taken other good decisions as well, for example, a healthy diet or regular checks for vascular risk factors."

"If individuals who have been physically active throughout their life do not develop dementia, you cannot necessarily conclude that physical activity is the reason."

Therefore, a study has been designed to determine if physical activity is specifically associated with superior cognitive outcomes. Participants have been identified who all share common signs of a vascular disease in the brain. These participants have been randomised into two groups: one group undertakes supervised physical activity and the other group does not. The results of this study are eagerly anticipated.

One of the reasons more of these studies have not been conducted is that it is very challenging to identify patients for randomised studies because symptoms of the disease are not perceived until they cause noticeable impairment. This is where researchers are hoping big data will play a role. Using data such as molecular biomarkers and electronic health records, it might be possible for researchers to obtain a better understanding of the development of dementia and its course. Prof Verdelho added: "Moreover, resource distribution could be optimised and tailored treatments could be made available to patients exhibiting special courses of the disease." She also added a note of caution: "Precision and critical analysis will be the keys for making optimum use of this data. Although we assume that big data is one of the correct paths to new findings, this approach has not yet arrived at a point where it affects actual practices of prevention or treatment."

References

1. Alzheimer's Disease International. Dementia statistics. Available at: https://www.alz.co.uk/research/statistics. Last accessed: 02 July 2018.

Sleep Disorders: A Diagnostic Aid?

ARE your patients presenting with sleep disorders? If so, the work of Dr Konstanze Philipp, Universitätsklinikum Münster, Münster, Germany, presented at EAN, and reported in an EAN press release dated 16th June 2018, is of paramount importance. Sleep disorders are often harbingers of serious neurological disorders. Sleep disorders to pay attention to include insomnia, excessive sleepiness, or abnormal sleep behaviours such as active sleep.

"Asking questions, listening, and documenting are the least expensive and easiest ways of diagnosing these complex diseases."

Dr Philipp explained: "Two-thirds of the population suffering from REM sleep disorders later develop Parkinson's disease, Lewy body dementia, or multiple system atrophy." He noted that a patient's history of sleep disorders, when used in combination with certain biological markers, could enable the diagnosis of neurodegenerative diseases many years before the first consciously perceived symptoms arose. Diagnosing such conditions as early as possible is currently believed to be a key step in improving patient outcomes. One example is Parkinson's disease, for which it is believed that the latest therapeutic approaches, if begun early enough, could delay or perhaps prevent the development of the disease. Therefore, any insights that lead to an earlier diagnosis could have a significant impact on patients with neurological disorders. Dr Philipp used three case studies to illustrate the importance of paying attention to these early warning signs.

However, there is a significant stumbling block faced by neurologists in this regard: a patient's sleep history is often not documented in their medical records, making an early diagnosis in this manner somewhat challenging. Dr Philipp urged: "We have to raise awareness on this matter." She went on to note: "Asking questions, listening, and documenting are the least expensive and easiest ways of diagnosing these complex diseases. We should use them. The therapeutic approaches are still expandable. Nonetheless, early detection is essential, especially for neurodegenerative disorders."

Sex Differences in Early Parkinson's Disease Progression

PARKINSON'S disease pathophysiology shows sex differences in untreated patients, according to the results of a Slovenian study. Reported in a EAN press release dated 16th June 2018, this study presents the first neurophysiological evidence supporting the theory that Parkinson's disease progression is different in men and women, suggesting sex is an important factor in treatment and management of the disease.

Previous studies have shown that women appear to be better protected from Parkinson's disease than men, with nearly twice as many males diagnosed with the condition than females; however, there has been uncertainty as to whether sex-specific pathophysiology is responsible for this observation. Since functional changes in the primary motor cortex can be detected in early Parkinson's disease using transcranial magnetic stimulation (TMS), the Slovenian-based research team focussed on this technique to investigate sex-specific differences in disease progression.

"The detected gender differences in corticospinal and intracortical excitability in patients with early untreated Parkinson's disease represent differences in disease pathophysiology..."

The Parkinson's Disease Rating Scale (UPDRS) was used to assess disease-related impairments in 39 untreated, newly diagnosed patients with Parkinson's disease (16 females and 23 males). TMS was then performed on the patients and a control group to investigate parameters such as motor thresholds of the brain, input and output curve, and short interval intracortical inhibition. Paired associative stimulation was also used to measure brain plasticity.

Although the UPDRS test did not show any sex-specific differences in motor scores, the input and output curves were less steep for females on the side of the brain most affected by Parkinson's disease. Furthermore, the female patients displayed more preserved short interval intracortical inhibition in both brain hemispheres compared to the male patients, and responded better to the paired associative stimulation protocol. No sex-related differences for any parameter was found following TMS in the control group. "The detected gender differences in corticospinal and intracortical excitability in patients with early untreated Parkinson's disease represent differences in disease pathophysiology," summarised Dr Maja Kojovic, Ljubljana University Medical Centre, Ljubljana, Slovenia. With reference to the significance of these sex-specific findings in enhancing early Parkinson's disease patient care, Dr Kojovic added: "Gender may also prove to be a relevant factor when choosing appropriate treatment."

Multiple Sclerosis Patients and Caregivers Contribute to New European Academy of Neurology Guidelines

PALLIATIVE care guidelines for people with multiple sclerosis (MS) have been developed in collaboration with those they most directly affect: MS patients themselves and their caregivers. As reported in a press release from the EAN congress dated 17th June 2018, 934 individuals directly related to the condition contributed to the creation of these new guidelines.

To allow those most affected by the disease to contribute, two methods of gathering data were used: an international online survey, supported by national MS societies; and targeted focus group meetings. The data gathered showed that most patients agree with the topics suggested by the EAN experts, with around 98% approving of the incorporation of multidisciplinary rehabilitation into the guideline. In the online survey, 569 free comments were recorded, with 182 (32%) relating to specific topics. Furthermore, 227 comments (40%) pertained to additional topics, 16 of which were suitable for inclusion within the guideline. Data gathered from five focus groups (three with MS patients and two with caregivers; a total of 35 people) supported the findings of the online survey. Thus, this collaboration between patient, physician, and caregiver helped to raise a number of important topics that may otherwise have been missing from the guideline.

"It was resource and time intensive to include consumers in the guideline process, but also highly rewarding. Patients and caregivers really helped us to formulate the guideline in a way that was in line with actual practice and their own needs," explained Prof Sascha Köpke, Institute of Social Medicine and Epidemiology, University of Lübeck, Lübeck, Germany.

This development marks a huge success for shared decision-making and is a promising step towards patient-centric, personalised medicine, an approach that the EAN has long supported. "The involvement of patients and caregivers increases the reliability and relevance of the guideline for clinical practice," concluded Prof Köpke. Just as personalised medicine is taking root in disciplines throughout the medical profession, so too is it hoped that this collaborative form of guideline development will become more widespread.

Lisbon Congress Centre

Venue of the EAN 2018 Congress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Multiple Sclerosis: New Drugs and European Treatment Guidelines

TWO novel multiple sclerosis (MS) drugs have recently been approved for use in the prevention of disease progression, coinciding with the publication of new MS treatment guidelines. A EAN press release, dated the 16th June 2018, presented the first drug approved for the treatment of primary chronic progressive MS, along with the timely release of treatment guidelines conceptualised by 13 European countries in combination with the EAN and the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS).

"Promising new drugs and the treatment guideline published this year by the ECTRIMS and the EAN will further refine and improve the treatment of MS in substantial ways."

The focus of MS treatment is to avoid relapse and halt the progression of this debilitating chronic inflammatory disease. By suppressing the chronic inflammation, appropriate and effective treatment has been able to attain disease control in 80–85% of patients. Two new MS approved drugs are hoped to further control disease for MS patients: cladribine, originally an anticancer drug, offering a convenient treatment option, and ocrelizumab, a monoclonal antibody targeting B cells involved in the inflammation.

The most common neurological disease in young adults, MS affects 2.3 million people worldwide, and as such, continuing to strive to prevent disease progression and its severe impact on quality of life is vital; these drug approvals could not have come soon enough.

In accordance with these drug approvals, new MS treatment guidelines building on analysis from clinical studies presented 21 recommendations to support physicians' decision making. Commissioning these guidelines is part of the EAN guideline programme in which all important neurological diseases will be reassessed, with roughly 20 guidelines currently being drawn up. Prof Günther Deuschl, EAN President, commented on the new guidelines and the EAN influential stand point: "These efforts underscore the major significance of the EAN, which is working through overarching topics of this kind and thus providing important principles not only to medical practitioners but also for healthcare policy."

Prof Deuschl summarised the importance of both guideline releases and new drug approvals for the treatment of MS, and stated: "Promising new drugs and the treatment guideline published this year by the ECTRIMS and the EAN will further refine and improve the treatment of MS in substantial ways."

Improving Assessment of Consciousness Disorders

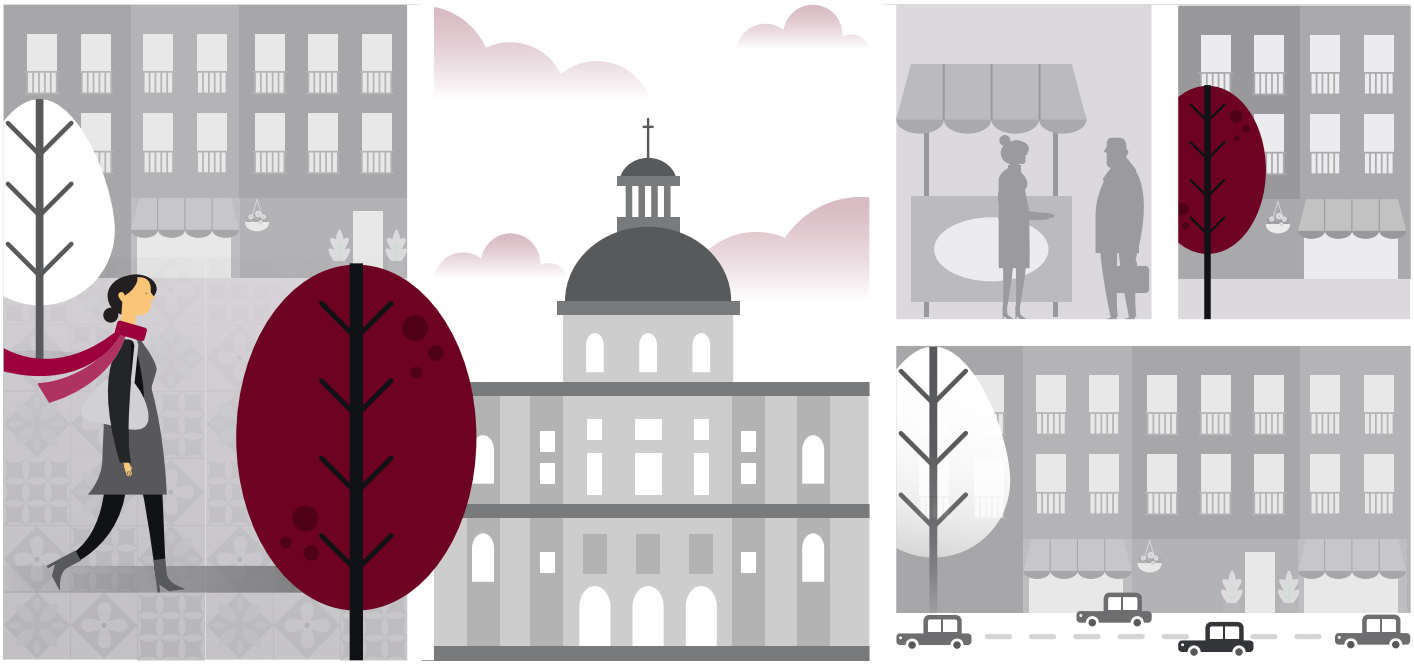
SEVERE brain injury diagnoses, which require evaluation of consciousness at various timepoints, could be improved using novel assessment and examination methods presented by Prof Steven Laureys, Coma Science Group, University of Liège, Liège, Belgium, at the EAN Congress 2018. Reported in a EAN press release dated 18th June 2018, these advances provide hope for the one in three Europeans affected by brain injury or disease during their lifetimes, as well as enhancing progress in this under-researched, relatively small field of neurology.

"This finding supports the recommendation to test patients multiple times within a short time period to establish a reliable diagnosis."

Although the number of individuals who survive comas following brain injuries is increasing, disorders of consciousness still present a great challenge for neurologists, whose decisions have a large impact on patient survival. To build on the current gold standard neurobehavioural tool, the Coma Recovery Scale (CRS)-Revised, which is not applicable to all patients, the SECONDs scale was developed and tested in severe brain injury patients. This tool was found to determine the conscious state of a patient to 99% accuracy by applying the five most frequently observed criteria and will be particularly useful in time-limited cases. Recent research has also revealed the importance of fluctuations in consciousness; for example, a study examined severe brain injury patients four times a day using CRS scores and showed that consciousness state varied throughout the day. "This finding supports the recommendation to test patients multiple times within a short time period to establish a reliable diagnosis," commented Prof Laureys.

Technological advances have also been reported in the field of consciousness disorders, such as the refinement of high-tech imaging during diagnosis. Diffusion tensor imaging, which uses MRI to record motion and directional dependence of water diffusion in the body, can aid clinicians to eliminate uncertainties during diagnosis. Novel therapeutic options are also being investigated in clinical studies, such as noninvasive transcranial direct current stimulation. It has been shown that 20 minutes of this treatment applied to the prefrontal cortex transiently improved state of consciousness after brain injury, and treatment repetition prolonged this behavioural change for up to 1 week after the end of therapy.

During his presentation, Prof Laureys stressed the importance of not providing false hope to patients and their families due to these new treatment advances, and explained how future challenges will involve implementing these high-tech methods and scientific findings in clinical practice across Europe. However, since research on brain damage and coma is relatively limited compared to other major neurological diseases, these long-awaited advances are welcomed by clinicians and their patients.



Immigration and New Insights for Neurologists

IMMIGRANT populations have been found to offer neurologists a wealth of information regarding possible risk factors for neurological diseases. According to international studies presented at EAN and reported in a EAN press release dated 16th June 2018, both stroke and multiple sclerosis (MS) have been strongly linked to environmental factor risks, as opposed to genetic predisposition, when analysing the health status of immigrant populations.

"The study authors concluded that the risk of suffering a stroke was less a question of genetics, but more down to environmental factors, such as diet."

A Canadian study compared 1 million new arrivals to the country with roughly 3 million immigrants who had lived in Canada for ≥5 years. Despite lower income and limited access to healthcare systems, first-generation immigrants were found to have a much lower risk of stroke than those who had been in Canada for ≥5 years. Prof Antonio Federico, University of Siena, Siena, Italy, and one of *EMJ Neurology's* esteemed Editorial Board members, explained: "The study authors concluded that the risk of suffering a stroke was less a question of genetics, but more down to environmental factors, such as diet."

A separate study assessed MS prevalence in immigrant populations in Norway. MS was found to be most widespread among immigrants from Europe and North America, whereas those affected by MS from Africa and Asia were limited, showing an uneven worldwide MS prevalence. A sharp increase in MS cases in second-generation immigrants from Pakistan was identified. "This lends additional weight to the theory that strong environmental factors raise the risk of MS," commented Prof Federico.

Despite immigrant-based studies providing an untapped source of nature versus nurture data, there are a few issues host nation neurologists and physicians should be aware of. One of these is the prevalence of rare diseases in the host country that may be of greater prevalence in the immigrant population, such as Bahçet's disease (extremely rare in Europe, but relatively common in Asian countries). Other obstacles may include difficulty accessing medical records, language barriers and thus longer hospital stays waiting for translators, and stigma surrounding brain disorders in different cultures.

Despite the potential issues, these population studies will no doubt offer unique data and should be utilised by researchers. Prof Federico concluded that: "We definitely have to make sure that our healthcare systems provide sufficient medical care for all people, no matter whether they are from the original population or have only just arrived."

Influence of Deep Brain Stimulation on Parkinson's Disease Over the Long-Term

HAS deep brain stimulation changed the natural history of Parkinson's disease? This was the question posed by the authors of a comparative long-term observational study that was presented at the EAN congress and reported in an EAN press release, dated 19th June 2018.

Deep brain stimulation is a therapeutic option that involves the positioning of electrodes in specific areas of the brain. These electrodes are connected to a stimulator that has been subcutaneously implanted into either the thorax or abdomen. This allows the generation and delivery of electrical impulses that affect the function of the areas of the brain the electrodes innervate. While numerous randomised controlled trials have demonstrated the positive impact of subthalamic deep brain stimulation in regard to motor functioning in patients with Parkinson's disease, there are many other elements of the condition that the impact of deep brain stimulation has not been evaluated.

Consequently, this study was designed to investigate the impact of deep brain electrical stimulation on further long-term complications that are typically associated with Parkinson's disease. Over 50 patients with Parkinson's disease who had not been treated with deep brain stimulation were compared with over 50 patients with Parkinson's disease who had been treated with deep brain stimulation.

While deep brain stimulation was not shown to have an effect on the long-term development of dementia throughout the progression of Parkinson's disease, longevity, or when an individual had to be placed in a nursing home, it did show a positive effect on several other long-term complications. As one of the study authors, Dr Philipp Mahlknecht, Innsbruck Medical University, Innsbruck, Austria, commented: "Deep brain stimulation was associated with a decreased risk for recurrent falls in our cohort of Parkinson's disease patients under long-term subthalamic stimulation when compared with patients under conservative treatments. The onset of psychotic symptoms was also found to be delayed through this treatment." In the future, further studies need to be conducted to examine these results further.

"Deep brain stimulation was associated with a decreased risk for recurrent falls in our cohort of Parkinson's disease patients under long-term subthalamic stimulation when compared with patients under conservative treatments."

Congress Feature

Summary of the EAN 2018 Presidential Symposium

During this year's EAN Congress, the EMJ team attended the much-anticipated final presidential symposium chaired by Prof Günther Deuschl as President of the EAN, and we bring to you our own summary of the pioneering findings presented during this thought-provoking symposium on 17th June 2018. Greeted by a rousing applause from a packed auditorium, Prof Deuschl welcomed the audience and commented on the astonishing findings about to be shown in a series of presentations encompassing hot topics at the pinnacle of neurology research, including multiple sclerosis (MS) and its link with gut microbiota, the impact of biomarkers on Alzheimer's disease (AD), and drug development in migraine treatment.

Immune Pathogenesis of Multiple Sclerosis: Degeneration, Inflammation, and Gut Microbiota

Setting out to educate the audience on the link between MS and gut microbiota, Dr Hartmut Wekerle, Max Planck Institute of Neurobiology, Munich, Germany, began by explaining that the link between neurodegeneration and inflammation has long been established, first described 140 years ago during studies of MS plaques. The more poignant question now is one similar to that of the chicken and the egg: what comes first? Is inflammation caused by neurodegeneration or vice versa?

Dr Wekerle explained that inflammation in the brain is somewhat of a paradox. The healthy brain environment is a hostile place for inflammatory molecules, deficient of all components necessary for inflammatory cells to proliferate. However, this is drastically altered when observing neurodegenerative disease lesions, including AD, Parkinson's disease, and amyotrophic lateral sclerosis, in which the brain becomes a more hospitable environment for such molecules. Dr Wekerle highlighted that microglia are the crux to this change. Microglia are always present in the brain and under normal circumstances they are dormant; however, when neurons lose their suppressive effect, the microglia become active. This can occur when mitochondria are released during necrosis, due to misfolded proteins commonly seen in neurodegenerative diseases, or as a result of the microbiota.

Bringing us to the cornerstone of the presentation, Dr Wekerle presented many cases linking gut microbiota to neurodegenerative diseases from 2015 until more recently in 2018. One of which involved the study of

a transgenic murine model that had cloned myelin autoimmune T cell receptors incorporated into the genome.[1] These mice showed axonal destruction with spontaneous relapsing remitting disease, similar to that experienced by early-stage MS patients, highlighting the strong link between gut microbiota and the onset of neurological-like symptoms.

Dr Wekerle addressed the concerns of some researchers regarding the translation of these murine model studies to the clinic by highlighting a study of monozygotic twins,[2] one of whom had MS and the other was unaffected. Faecal transplants from each twin were transplanted into germ-free mice. The results were remarkable; a faecal transplant from the MS twin triggered spontaneous relapsing remitting MS-like disease in the mice, while the transplant from the unaffected twin had no effect. This study shows just how interlinked the onset of MS and gut microbiota are, potentially offering a new line of treatment for MS patients.

The closing address of Dr Wekerle's presentation focussed on the future of these therapeutic options. He suggested that antibiotic or phage therapies could be used to remove the bacteria causing inflammation in the brain and reduce the subsequent neurodegeneration, as could dietary modifications or faecal transplants. He did, however, advise against these therapies at present until further clinical studies are conducted, noting that more research is needed to ascertain whether these therapies will have a safe and efficacious effect for those living with MS.

The Evolution of Alzheimer's Disease and Dementia

The spotlight was then placed on Prof Philip Scheltens, Alzheimer's Center, Amsterdam, Netherlands, whose presentation focussed on how biomarkers have changed the field of dementia. He began by expressing what an honour it was to present to such a varied neurological audience on a topic that he believes is so important to the progression of AD research and treatment, as well as dementia as a whole. Prof Scheltens described dementia as an illogical disease and emphasised the pivotal role biomarkers continue to play in the development of this field.

The 2018 Brain Prize winners, John Hardy, Bart de Strooper, Christian Haass, and Michel Goert, were all highly praised by Prof Scheltens for their work on dementia genetics, secretases, and tau genetics and proteins. Prof Scheltens noted that this area of research is fully deserving of such highly prestigious accolades due to the relatively infantile stage that research is currently at in regard to understanding these complex diseases. He reminded the audience that we are only at the beginning of this exciting and momentous journey and there is still much to learn.

Prof Scheltens continued his presentation by highlighting how far neurology research into dementia has progressed; only 30 years ago fludeoxyglucose positron emission tomography (FDG-PET) was used to diagnose dementia, but now biomarkers have changed the whole concept of disease management. Prof Scheltens took the audience through the evolution of biomarkers in dementia and AD: from the 1980s using FDG-PET scans to identify AD brains to 1986 with the introduction of hippocampus CT imaging, fast forwarding to 1992 with the evolution of the coronal MRI slices, and then to more recently in 2004 with the first amyloid imaging used to show amyloid proteins with PET scans. Prof Scheltens highlighted that tau images are also unique between AD patients and commented that their future use in clinical trials as an outcome measurement in AD is bright.

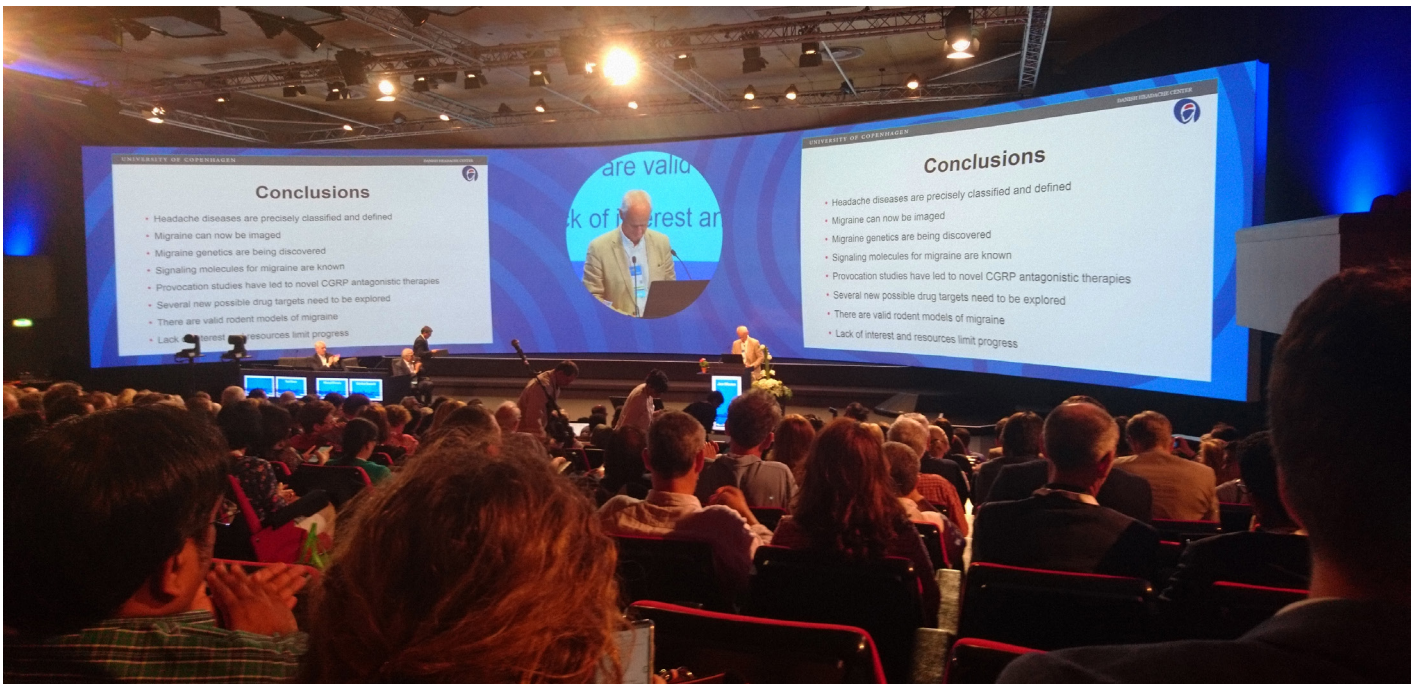
Prof Scheltens then walked the audience through the development of AD diagnosis

and the concept change surrounding this development. Decades ago, the only way to diagnose AD was during a post-mortem when a clinician could view the amyloid plaques in the brain. Of course, this was very unhelpful in the development of diagnosis and treatment methods. Then, in 1984, only 34 years ago, criteria were released that allowed AD diagnosis *in vivo*.[3] Listing symptoms and enabling exclusion of other disorders, such as tumours, was undoubtedly a step in the right direction for AD diagnosis. However, Prof Scheltens did note that there was no other basis of diagnosis, such as biomarkers, which made diagnosis subjective and did not help extend the understanding of the biological basis of the disease or allow prediction of AD.

These criteria were built upon by incorporating biomarkers, allowing for a more specific diagnosis and enabling the clinician to distinguish between dementia syndromes.[4] In 2014, further refining was executed to separate typical and atypical phenotypes.[5] Furthermore, a 2018 collaboration between the European Union (EU) and USA was based on pathological hallmarks of AD (amyloid and tau), allowing biomarkers rather than symptoms to direct diagnosis.

Prof Scheltens closed his presentation by commenting on the clinical impact of biomarkers, including how to use them effectively and how they will impact on drug development. Diagnostic impact was a cornerstone of the clinical impact of biomarkers. Results of a study presented showed that 7% of clinicians changed their original diagnosis once they were given access to pathological biomarker tests of AD.[6] This may seem a small percentage, but the impact this would have on a patient's treatment and prognosis is staggering. It is not only diagnosis that biomarkers can impact; they can also be informative of disease progression and prognosis, allowing patients to be better informed and prepared for what their disease decline is likely to entail in the years to come. Prof Scheltens also mentioned the development of an app that takes into account specific patient information and biomarkers to aid clinicians in deciding whether a test would be worth conducting.

Lastly, Prof Scheltens commented on what still needs to be addressed in the ever-evolving field of biomarkers in dementia, including analytical issues, ethical issues, and education. There is an enormous window of opportunity for the development of personalised treatment of AD patients and Prof Scheltens emphasised the imperative need to detect dementia early, ideally >20 years before symptom onset, to properly tackle this debilitating and life-changing disease. In his closing remarks, Prof Scheltens addressed his colleagues directly, stressing the importance of investing in young researchers and nurturing their development in this fast-paced, pioneering field.



Migraine: From Basic Research to New Drugs

During the final presentation of this engaging and thought-provoking presidential symposium, Prof Jes Olesen, University of Copenhagen, Copenhagen, Denmark, took to the stage. He highlighted the importance of migraine research, with a recent global burden of disease study ranking migraine the second most burdensome disease, and noted the difficulty in studying the disorder due to no neurological changes being visible during examination.[7] Prof Olesen referred back to Prof Scheltens's presentation on the importance of biomarkers, commenting that there are no biomarkers for migraine, making it particularly difficult to diagnose early.

Prof Olesen discussed the current understanding of migraine genetics and its impact, or lack of, on the advancement of migraine treatment. He used familial hemiplegic migraine as an example of how the identification of three genes (*FHMI 1*, *2*, and *3*), known to be dominantly inherited and associated with calcium channels, the potassium-sodium ADPase, and sodium channels, led to no new treatments for this form of migraine. This is echoed by many migraine disorders; 42 genome-wide significant loci have previously been identified but, despite giving a deeper understanding into the mechanism of migraine, they have not identified any novel drug targets. Ongoing studies are underway assessing polygenic risk score in relation to patient responses to drugs; however, Prof Olesen reiterated that while these studies will no doubt help advance the treatment of migraine towards the era of personalised medicine, they are unlikely to identify new drug targets.

Prof Olesen then proceeded by explaining how researchers are attempting to identify new drug targets through a number of different models. The first model presented was the very old cortical spreading depression (CSD) model,[8] which allowed researchers to identify that migraine with aura was caused by CSD. This model is now used in animal models and has allowed the development of tonabersat, which reduced attacks of migraine with aura by 75% in patients. With such promising results, why did this apparently effective drug not progress to patents? Prof Olesen answered his own question: tonabersat had a very short patent and, coupled with the fact that there are so few patients effected by migraine with aura frequent enough that they required this type of treatment, no pharmaceutical company thought the drug was worthy of developing.

The second model described to the audience was the human provocation model, which Prof Olesen described as an interesting and exciting model due to its totally unique utility in migraine research. The model induces a migraine attack in a volunteer that allowed researchers to observe physiological effects of migraine, particularly in the major arteries. This type of induction of a condition would have never been ethically viable in other neurological disorders but, due to the repressible nature of migraine, it has allowed a truly unique research angle to be explored. Using the human provocation model, 20 years ago nitroglycerin infusion was found to induce a migraine attack 5–7 hours later.[9] Nonselective inhibition of nitric oxide production by inhibiting nitric oxide synthase enzymes was found to effectively treat mild migraine; however, such nonselective inhibition would never be tolerated in a real-word environment because the side effects would be too numerous, and, as such, the development of a selective nitric oxide synthase inhibitor is still urgently needed.

The much more productive calcitonin gene-related peptide (CGRP) model identified the vasodilator molecule CGRP, located in the sensory nerves, which has strong vasodilating effects on cranial circulation. As such, this molecule is of great interest to researchers and has since been found to induce migraine attack, offering a potential novel drug target. Studies found that CGRP-induced artery diameter increase was fully blocked by the CGRP receptor antagonist olcegepant.[10] During clinical trials, olcegepant was also shown to be effective at preventing acute migraine attacks, with a 60–70% efficacy at a dose range of 2.5–10.0 mg.[10] Despite olcegepant not reaching patients, Prof Olesen was optimistic, stating that olcegepant has shown proof of concept that a CGRP receptor inhibitor could offer effective and safe preventative treatment for migraine patients. Indeed, patients who had received olcegepant and were then infused with CGRP exhibited no

vasodilating effects and no migraine was induced. Prof Olesen further demonstrated his optimism for CGRP receptor inhibitors by noting the development of four monoclonal humanised antibodies, three of which bind to CGRP itself and one binds to the CGRP receptor to prevent its effect. He stated that the most exciting and promising drug, erenumab, is already on the market in the USA and is expected to be marketed throughout Europe by the end of 2018, offering a novel treatment for those affected by migraine.

The fourth and final model presented by Prof Olesen was the pituitary adenylate cyclase activating peptide (PACAP) molecule model. PACAP has been shown to induce an immediate headache along with a delayed migraine, allowing the identification of the PAC1 receptor that is solely activated by PACAP, another potential drug target. As of yet, there are no data regarding PAC1 receptor inhibitors and their effect on migraine patients; however, there is an ongoing monoclonal antibody trial, the results of which are hotly anticipated by the migraine community.

Prof Olesen acknowledged the wonderful and effective results monoclonal antibodies can have as a therapeutic option due to their selectiveness and minimal side effects; however, he highlighted that there are still gaps to be filled. Addressing the gaps in migraine therapy, Prof Olesen hinted that one of his colleagues, Prof Messoud Ashina, University of Copenhagen, Copenhagen, Denmark, is working on an incredibly exciting therapeutic target that could rival the importance of PAC1; however, he stopped himself from further explaining the much-anticipated results because they are still unpublished. Here at the EMJ we are definitely looking forward to reading these stimulating results when they are available.

As the session was beginning to draw to a close, Prof Olesen emphasised the importance of animal models for drug discovery and development because companies considering investing in and developing a drug need to be presented with *in vivo* results. Migraine research has a well-researched rat model: STA rats. STA rats have a very low pain threshold in their head, which allows drugs to be tested to assess whether their pain threshold changes. Both sumatriptan, which acts on 5C1β receptors, and olcegepant have been shown to improve a STA rat's pain threshold in their head compared to their hind paw.[11] These rats present opportunities to test new drugs in animal models before presenting them to pharmaceutical companies, hopefully allowing the more successful development of novel drugs that will reach patients in the real-world environment.

Concluding the presidential symposium at the 4th EAN Congress, Prof Olesen stated that although headache disorders are well classified and defined, and there is a greater understanding of the genetics and signalling that underpins migraine disorders than ever before, the lack of interest and resources are the biggest hindrance to the advancement of migraine therapy.

The EMJ team thoroughly enjoyed attending this presidential symposium and eagerly await the exciting new results that will be presented at next year's EAN Congress in Oslo, Norway.

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Interviews

Discover neurological insights from across Europe in these fascinating interviews with *EMJ Neurology* Editorial Board members

Featuring: Prof Nils Erik Gilhus, Prof Antonio Federico, Dr Giuseppe Lanza, and Dr Alexandr Merkin

Prof Nils Erik Gilhus

University of Bergen, Norway

What first inspired you to pursue a career in medicine and, more specifically, in neurology?

I came as a fresh, young doctor to the active and expanding department of neurology in Bergen, Norway. The ambitions of the department were high, particularly for new treatment, improved diagnostics, and active translational research, combining clinical, laboratory, and registry projects. The department had close links with leading international neurologists. Forty years ago, this was exceptional for a clinical department in Norway. Neurology as a discipline was challenging, as it will always be, but the working environment with both young and established colleagues completing research and daily clinical work was, for me, equally important.

"Clinicians need to take part in both health and research programmes."

The study of the brain, along with its potential diseases and disorders, is quite different from other medical disciplines. What do you enjoy most about this sensitive and complex speciality?

I do not agree that neurology is so different from other medical disciplines. Neurologists should be at the forefront of active therapeutic and diagnostic work, co-operating with all other specialists and subspecialists. Neurologists are in the emergency room, the acute wards, and prehospital medicine, as well as in rehabilitation institutions and nursing homes. Neurology care should cover both children and the very old. We see the patients, listen to them, and examine them. This input is combined with results from complex investigations. From this, we have a large number of treatment possibilities, where timing, dose, and combinations are crucial. We need to follow strict and updated guidelines and treatment protocols, and be stricter than we often are, but there is still time for individual assessment.

Your research is both clinical and laboratory-based, and also makes use of registry data. What aspect of your research do you enjoy the most and why?

I love the combination. I find it a privilege to be allowed to do research, to teach, to be a clinical neurologist seeing patients every day, and to take part in administrative tasks and leadership roles. I feel the same for research, starting with the clinical questions, from what we see in the patients, and then to find an answer by combining clinical data, laboratory parameters, and information from national health and disease registries. That is what I enjoy most.

You have been the leader of national initiatives including neuroscientific research (NevroNor, Norwegian Brain Council, Research Council of the Norwegian Medical Association, etc) and programmes that provide co-ordination and support for Norwegian neuroscience. Could you explain your role in these activities and why you think such activities are important?

Clinicians need to take part in both health and research programmes. An increasing proportion of the resources for our work come from programmes and projects, while the basic funding is reduced. Doctors with our insight need to show the society what is needed and tell them repeatedly. We also have the responsibility to ensure that what is granted is used in an optimal way, for projects that have the potential to make a difference for patients in the short or the long-term. The concepts of brain disease and brain health are important to prioritise, in line with cancer, infections, and cardiovascular disease. Neurologists need to build partnerships with other groups of health workers, as well as with patients and user organisations.

You founded the Norwegian Brain Council in 2007, a subset of the European Brain Council (EBC). The EBC's mission is to promote brain research in order to improve the quality of life of those living with brain disorders in Europe. How much progress has been made to achieve these goals since the EBC was founded, and what has been done to attain better quality of life for these people?

Treatment of brain disorders is dramatically improving. Characterisation and understanding of disorders of the nervous system are excellent and this is generating extra interest for research to further improve the life of patients with brain disease. NBC and EBC have been met with great interest from the neurology society. The participation of neurologists with the NBC and EBC has, in my opinion, been a key factor for success, as well as the organised and formal partnership with patients. There are differences between countries, so we should learn from each other's experiences. There are always some setbacks, but the field of neurology and neuroscience overall is undergoing steady and rapid progression, with expansion and new treatment opportunities.

What neurological condition do you find the most interesting to research or study and why?

Myasthenia gravis is my special interest. The patients do well and we understand the disease mechanisms, but we are still missing a specific, targeted therapy, and we do not know which environmental factors cause the disease. Research is needed and in many directions.

Epilepsy is my other main research topic, particularly examining long-term effects of therapy and seizures using national disease and health registries. Both epilepsy and the drug treatments for the disorder have effects on the brain, and these could be of long-term significance. Registry studies represent an important tool to define optimal treatment, especially in vulnerable cases such as during pregnancy and early childhood. We are now building a Nordic consortium to examine this in a sufficiently large population.

"I find it a privilege to be allowed to do research, to teach, to be a clinical neurologist seeing patients every day, and to take part in administrative tasks and leadership roles."

Both the EBC and NevroNor promote brain and neurological research. Do you think more people need to be made more aware of the current developments in neuroscience research and, if so, how would you like to see societies improve the communication between physicians and the wider public?

Yes. We have a responsibility to inform society through all available channels. This includes fundamental information about what is correct and what is wrong regarding brain disorders and their treatment, but also about new and exciting possibilities, the fantastic potential of the brain, and ambitions for the future.

The European Academy of Neurology (EAN) covers a broad range of diseases, therapeutics, and innovations, but what disorder, technique, or medication do you feel deserves more attention from the medical community?

This is a difficult one; dementia and stroke are the two most important brain disorders from a public health perspective. However, I think that every society has a special responsibility to care for the young, to shape a community where children and their carers are stimulated and feel welcome. Regarding treatment, we should remember our patients with chronic disease. We see them for perhaps 1 hour a year, but they have their disease for 8,760 hours a year. We see them for a fragment of time, but we have a responsibility for their total treatment, including comorbidities.

Finally, if you could give any advice to aspiring neurologists, what would it be?

Take an active part in all aspects of what is ongoing in your department. Combine clinical work with your projects in research or systematic quality improvement, projects that at the same time are yours and involve an attractive research group. Take part in the international neurological community. Have fun, be curious, and work hard.

Prof Antonio Federico

University of Siena, Italy

You have pursued neurological medicine ever since you specialised during your medical studies. What was it that interested you about neurology and encouraged you to commit to this therapeutic field?

I was stimulated to be a neurologist because, ever since I was a student, I was very much interested in clinical research. I realised that neurology was the speciality in which there is a very high link between the clinic and research to give solutions for many major disorders. In fact, during my lifetime, very important new data have been applied to clinical practice, derived by interaction with basic research in neuroscience and neurogenetics.

You have recently described a form of Parkinson's disease that involves an atypical accumulation of manganese within the brain. How does this differ from other forms of Parkinson's disease and what implications does this research have for the clinical setting?

This was a very nice example of a good clinical approach and how from patient observation we can also gain new knowledge. A colleague referred two brothers to our unit who had a parkinsonism not responding very well to L-DOPA therapy. Brain magnetic resonance imaging (MRI) showed mineral accumulation in the basal ganglia in both cases. This condition was associated in both patients with thrombocytopenia and liver steatosis. We started

to screen for blood mineral accumulation and found a very high level of blood manganese. We could see from the literature that children with dystonia and manganese accumulation in the brain had previously been reported.

In collaboration with Prof Vincenzo Bonifati and his group from the Department of Medical Genetics, Erasmus University of Rotterdam, Rotterdam, Netherlands, we identified a mutation in the not very well-known manganese carrier protein SLC30A10C. When mutated this protein is unable to efflux manganese out of the cell. This finding was almost simultaneously reported by Dr Karin Tuschl's group from University College London, London, UK. Once the disease and the mutation were discovered, we started to treat patients via EDTA chelation, which led to an improvement of all extrapyramidal symptoms. The articles of both groups have been published and received a commentary that designated this disease as a 'new Wilson's disease'.

You have stated that chelation therapy may be a possible treatment method for this unusual form of parkinsonism. What does this kind of therapy involve, and how does it differ from other therapeutic techniques?

EDTA is able to link with manganese facilitating its transport outside the body; therefore, EDTA is used in cases of manganese poisoning or other cases of metal accumulation in the brain. Since we know that the increase of manganese, in our case, has a direct influence on many proteins' metabolism, including synuclein and prions, it is logical that the normalisation of minerals in the brain may improve the metabolic cell pattern and consequently the neurologic symptoms. This was confirmed by a 2-year follow-up. To date, we have followed the patient for >6 years and are continuing to follow them.

"Ever since I began my neurological studies, I have been fascinated by rare neurologic diseases, particularly late-onset neurometabolic diseases..."

You have a particular interest in rare neurogenetic diseases, particularly cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebrotendinous xanthomatosis, and leukoencephalopathies. Can you briefly describe these disorders and explain what it is that draws you to this line of work?

Ever since I began my neurological studies, I have been fascinated by rare neurologic diseases, particularly late-onset neurometabolic diseases; I think this area of research requires important interaction between clinical, scientific, and also social treatment approaches because rare neurologic disorders are orphan diseases with few people involved in patient care and, until the onset of the 21st century, of very low political interest. I think, however, rare neurologic diseases represent a Pandora's box for neurology and neurosciences regarding research perspectives as well as a model of common diseases.

We focussed our interest on cerebrotendinous xanthomatosis, starting to investigate a family and, after collecting >60 cases from across Italy, investigating the biochemical, molecular, clinical aspects, and finally the therapeutic approach with chenodeoxycholic acid therapy, a substance that is not produced by cerebrotendinous xanthomatosis patients' livers. Twenty-five years ago, we published a review considering this condition as a reversible aging process. Many clinical aspects leading to premature ageing (e.g., cataracts, osteoporosis, dementia, and peripheral neuropathy) may be prevented if a diagnosis and a treatment is started as soon as possible, most optimally in infancy before the brain degeneration is irreversible.

CADASIL, a disease related to *NOTCH3* mutation, is another interesting model of inherited small vessel disease, characterised by migraine, stroke, and vascular dementia. We identified >250 families with this disorder and investigated the genotype–phenotype relationship, the clinical heterogeneity, and the neuroimaging aspects of the disease.

Finally, leukoencephalopathies are a heterogeneous group of disorders, mainly characterised by central white matter changes

and a progressive neurologic impairment. MRI is an important technique to classify the different forms, but only biochemical and genetic tests are able to give the final diagnosis. We have investigated the first European family with cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy, a leukoencephalopathy similar to CADASIL, with autosomal recessive inheritance of the *HTRA1* gene mutation. Similarly to reports from Tournier–Lasserve and colleagues, we have recently found that heterozygosity for this mutation may be associated with clinical symptoms of small vessel disease. We have also been involved in many neurometabolic leukodystrophies, like metachromatic leukodystrophy, Krabbe disease, adrenoleukodystrophy, Alexander disease, and Pelizaeus–Merzbacher disease, mainly describing the adult phenotypes.

What is the present management strategy for patient with CADASIL and what challenges are currently hindering the development of disease-modifying drugs for the disease?

With all the best European experts in the field, I have co-ordinated a consensus article on CADASIL; no data are present from the literature about the general therapeutic approach to CADASIL. In this review we conclude that:

"In the absence of specific data for CADASIL, most neurologists use aspirin in secondary prevention after ischaemic strokes in older patients, for example, those aged over 40, but there is no evidence for or against its use. Whether this strategy is appropriate in CADASIL is undetermined and will require further investigation, given the possible increased haemorrhagic risk. Patients that need to undergo anticoagulation for a clear indication such as high risk atrial fibrillation should be carefully followed given the reported risk of intracerebral haemorrhage. A multicentre randomised controlled trial using donepezil to improve cognitive dysfunction showed no benefit on the primary endpoint and only improvements of uncertain clinical significance on several measures of executive function. New, rational therapeutic interventions for CADASIL are in early phases of pre-clinical development."

Where do you feel neurological therapies are currently lacking? Is there a particular disorder that you believe requires better therapeutic options?

Many neurodegenerative diseases, like Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, different forms of spinocerebellar ataxia, genetic polyneuropathies, and even Parkinson's disease, need better pathogenetic therapeutic approaches. I hope that the new era of gene therapy (similarly to what is now possible in spinal muscle atrophy!) and cell therapies will offer new possibilities of therapeutic interaction with the intimate pathogenetic mechanisms.

How would you like to see neurological therapeutics advance in the next 10 years? In your opinion, what needs to be done to achieve these goals?

It is important to learn more about the natural history of the disorders and to learn more about their mechanisms on the basis of clinical heterogeneity. Since we have, in neurodegenerative genetic disorders, a large clinical heterogeneity of patients with the same mutations presenting with severe or less severe phenotypic findings, it is possible that many genes are responsible for these different clinical presentation. It is possible that there are some endogenous factors that can protect the patient and modulate the severity of the symptoms. If we learn more about the pathogenesis of the neurodegenerative processes and about the apoptotic cascade, it is possible that we will find some protective factors that may be used as therapeutic agent.

You have been involved with many societies and held many substantial positions within different neurological societies. How important are national and international societies for the development of neurological medicine?

I have been President of the Italian Society of Neurology since 2014 and I am the Chairman on the Scientific Committee of the European Academy of Neurology, Chairman of the EAN Task Force for Rare Neurologic Diseases, and

I had several positions in the World Federation of Neurology, including Co-Chair of a Research Committee on Migration and Neurology.

I think that both national and international scientific societies have a very important role in the development of neurologic medicine and stimulating and organising neurologic care and research in clinical neurosciences, either at a political level or by stimulating the networking of people. Finally, they have a very important role in the education of not only the new generations, but all members about the field, and societies are crucial for providing their members with objective information on new approaches to neurologic disorders.

You have >500 published articles listed on PubMed, as well as having authored and edited several medical books. What drives you to continue research and share your findings with the medical world and how important do you feel accurate communication of science is to a field's progression?

This continuous scientific activity is a basic mechanism for remaining mentally young and maintaining my enthusiasm for the field; this is only possible if you have contact with young collaborators, as they often stimulate you to continue. The professor–student relationship is a bidirectional equation that is very important for both subjects and leads to mutual growth.

What advice do you have for aspiring medical students who wish to become accomplished neurological researchers?

To find a good mentor, to have the economic possibility to spend time on research, and to have the capacity to pursue a research and a life project. Furthermore, you must preserve your enthusiasm for scientific progress as well as maintaining your competence.

"It is important to learn more about the natural history of the disorders and to learn more about their mechanisms on the basis of clinical heterogeneity."

Dr Giuseppe Lanza @LinkedIn

Oasi Institute for Research on Mental Retardation and Brain Aging (I.R.C.C.S.), Italy

Firstly, why did you choose to pursue a medical career? Was there a particular person or event that inspired you?

Firstly, I chose to become a doctor because of how keen I was to know the enigmatic functioning of the human body and, in particular, the nervous system. Secondly, I like to deal with intriguing and challenging cases, manage the unmet needs of people for their diseases, and try to relieve the suffering of patients and their families. In addition, I chose to become a doctor to have the opportunity to conduct clinical research within the exciting field of neuroscience. There was not a particular event that inspired me in this choice, although an emotional aspect behind this was that my mother wanted me to be a doctor when I grew up!

Your medical training was based in both Italy and the UK. Were there any differences between neurology practice in these countries?

They both provide an excellent theoretical background and a high level of professional skills. Neurology training appears to be generally longer in the UK, but the fully-trained specialists

seem to enjoy a higher independence and better job opportunities than in Italy. The interaction between preclinical and clinical neurological research is probably more powerful in the UK, although, from a strictly clinical point of view, the opportunities for university staff to become involved in the organisation and delivery of neurology health care appear to be greater in Italy.

You currently work at the Oasi Institute for Research on Mental Retardation and Brain Aging (I.R.C.C.S.). Can you describe your role and responsibilities during a normal day at the institute?

As a clinician, my daily routine involves examining patients, suggesting diagnostic tests, and interpreting the results of these tests to determine the best treatment. I work in a team with medical staff and other health professionals, and I also take part in multidisciplinary meetings involving specialists from other departments. As a researcher, I participate in clinical studies and other research projects, write or revise articles for medical journals, and give presentations at local and external meetings, courses, and seminars.

As a consultant neurologist and clinical researcher, what part of your job do you enjoy the most?

As a consultant neurologist, I always keep in mind that a career in neurology will suit you if you love complex problem-solving, the diagnostic process, and the idea of working with a diverse range of patients. At the same time, I also love to couple clinical duties with research interests, although I am aware that this field is highly competitive. Moreover, research in neurology allows for the discovery of new diagnostic markers and the ability to keep up to date with advances in diagnosis and treatments; this often has crucial translational implications in the daily management of neurological patients.

"TMS was originally introduced for evaluating the excitability in the primary motor cortex and the conductivity along the cortical-spinal tract."

The I.R.C.C.S. is a collaborating centre of the World Health Organization (WHO). What does this relationship with the WHO entail and why, in your opinion, is it important to collaborate with large international healthcare organisations?

The I.R.C.C.S. is a long-lasting collaborating centre of the WHO, specialising in research and training in neuroscience. More recently, the institute has also been invited to contribute to the update and revision of the International Classification of Diseases 11th revision (ICD-11), the most important manual of international classification of diseases and related problems. A multidisciplinary working group, including myself, is actively working on this exciting project, especially in the field of intellectual disability, brain ageing, and neuromuscular disorders. In my opinion, the final goal of any collaboration with large international healthcare organisations, such as the WHO, is to offer the best healthcare system and scientific research in co-operation with other international groups; indeed, we are promoting a number of clinical and scientific events involving operators, patients, families, associations, and other institutions, particularly focussing on the needs of patients and their families.

One of your key interests concerns the application of noninvasive neurophysiological techniques during the diagnosis of neurological disorders, particularly transcranial magnetic stimulation (TMS). Can you briefly explain the science behind this technique?

TMS was originally introduced for evaluating the excitability in the primary motor cortex and the conductivity along the cortical-spinal tract. Nevertheless, today, the applications go well beyond the simple assessment of the pyramidal tract. Indeed, TMS can be used to provide novel insights into the pathophysiology of the circuitries underlying neurological and psychiatric diseases, to probe the *in vivo* excitability and plasticity of the human brain, and to assess the functional integrity of intracortical neuronal and callosal fibres. TMS is well-suited for studies aimed at exploring and monitoring motor system impairment during the preclinical

phase of several neurological disorders or systemic diseases involving the central nervous system. Moreover, when integrated with other electrophysiological techniques (e.g., electroencephalography [EEG]) or structural and functional neuroimaging, TMS also allows the exploration of connectivity across motor and nonmotor areas. Finally, because it can be used to evaluate the effects of drugs that are agonists or antagonists for specific neurotransmitters, TMS can selectively test the activity of glutamatergic, GABAergic, monoaminergic, and cholinergic central circuits (e.g., so called pharmaco-TMS). Briefly, TMS is based on Faraday's law of electromagnetic induction to activate cortical neurons: a transducing coil attached to a high-voltage, high-current discharge system produces a strong time-varying and short-lasting magnetic field at right angles to the stimulation coil. When the stimulation coil is placed tangential to the head, the magnetic field penetrates the scalp and skull with minimal attenuation and induces a secondary eddy current in conductive intracranial tissue.

TMS has also been shown to be an effective treatment for some neurological conditions, such as neuropathic pain and depression. What further studies need to be performed to evaluate the long-term safety and frequent use of TMS?

The feasible application of TMS in restoring altered excitability and disrupted plasticity may lead to the development of specific stimulation protocols as a potential therapeutic and rehabilitation tool in patients with drug-resistant pain or major depression. However, longer follow-up studies and larger cohorts of patients are needed to explore the length of remission produced by the TMS. Moreover, studies combining TMS with other investigations, such as the EEG, will provide direct measures of the synaptic plasticity and functional connectivity, as well as how neural network changes occur in different disorders. Finally, the long-term benefits favoured by metaplastic phenomena induced by chronic drug exposure should be further explored.

"The feasible application of TMS in restoring altered excitability and disrupted plasticity may lead to the development of specific stimulation protocols as a potential therapeutic and rehabilitation tool..."

You have recently published research that investigated the connection between the brain and conditions of the gut, including coeliac disease (CD). Can you explain the reasons behind the intriguing findings of neurophysiological involvement in gastrointestinal diseases?

We have recently reviewed that the majority of electrophysiological changes in CD are often subclinical (the so-called 'coeliac iceberg'), and these need to be strictly monitored because of the possibility of progression into clinically visible neurological syndrome, in both young and adult patients. From a purely neurophysiological perspective, findings from different techniques (EEG, TMS, and other evoked potentials) seem to converge on an overall profile of the 'hyperexcitable coeliac brain'. In particular, regarding humoral autoimmunity to neuronal antigens, CD-related antibody deposits have been found not only in the small intestine but also in different central nervous system sites. Furthermore, a possible blood–brain barrier lesion, secondary to diffuse infiltration of T lymphocytes and inflammatory cells within the perivascular cuffing, might expose cerebral tissues to antibodies. The result may be a vicious cycle that eventually leads to a prevailing synaptic hyperexcitation and a weaker inhibition at the cortical level. The increased excitability may also be the correlate of a glutamate-induced cortical rearrangement or a dysfunctional control of GABAergic inhibitory interneurons. In particular, because glutamate is of pivotal importance in synaptic plasticity, it is speculated that immune system dysregulation triggered by gluten ingestion might result in a long-standing activation of postsynaptic glutamate receptors, which would account for the enhanced hyperexcitability. The eventual

identification of neurophysiological markers might be useful in the diagnosis and monitoring of CD, aiming to improve the healthcare of both single subject and global communities.

What advances would you like to see in the next 5 years for the management of patients with neurological conditions?

The amount of scientific research in neuroscience has recently increased, providing a greater understanding of several disorders, especially those based on the neuroinflammation and disruption of the neurovascular unit. However, this was not paralleled by a similar growth of pharmacological strategies, which currently do not change the course of dementing processes or Parkinsonian syndromes but do manage to slow down progression. In my opinion, promising evidence has come from investigations on new neuroprotective agents and innovative disease-modifying drugs. In addition, a crucial contribution is given by neurogenetics: the identification of genetic markers allows the discovery of novel therapeutic targets, as well as the development of more personalised treatments. Finally, the possibility to noninvasively and painlessly modulate specific cortical–subcortical circuits implicated in vascular, degenerative, and sleep disorders opens new fascinating windows in the field of translational neurosciences and nonpharmacological options for neurological disorders.

Finally, can you tell us what your career plans are for the next 10 years? What do you hope to achieve during this time?

In the near future, I would like to carry forward investigations based on integration of different neurophysiological methods for the experimental study of the processes underlying neurotransmission and cortical plasticity specifically involved in the regulation of sleep and cognitive functions, in both normal and pathological conditions. I will also be involved in another research project aiming to identify any preclinical markers of disease process and progress in patients with vascular or neurodegenerative dementia and late-life depression, trying to correlate clinical changes with neurotrophic factors and imaging findings. These studies will both disclose relevant clinical insights on the management and treatment of neurological patients. During this time, I will keep studying to learn and continuously ask 'why', question neurobiological phenomena, attend different laboratories and institutes, and share exciting ideas with other colleagues with different areas of interest. The take-home message can be the following: "never give up and always look for cultural growth!"

Dr Alexandr Merkin

Auckland University of Technology, Auckland, New Zealand

Firstly, what first inspired you to pursue your current career in research and, more specifically, in stroke, dementia, and traumatic brain injury (TBI)?

I always had an interest in biomedical science and mental health in particular. I started reading the literature on this topic during the fifth or sixth year of secondary school and also from reading my grandfather's books and materials. My grandfather was a medical doctor and lecturer in clinical psychology, so I did not have to look far for an example of a career in this area. Studying biology throughout high school was very rewarding and enjoyable for me. Several years later, I started studying at a medical university and willingly helped out several of my friends at the institute with revising before tests; I felt I had identified a strength that could well be worth pursuing in the future. My experiences led me to a career in teaching. I always loved helping and explaining things to others, and I

have never regretted that choice. Working in the borderline area between neurology and psychiatry, which encompasses dementia, as well as consequences of stroke and TBI, provides me with a sound ability to undertake studies for the prediction and possible prevention of both neurological and psychiatric disorders.

"My experiences led me to a career in teaching. I always loved helping and explaining things to others..."

Alongside your work researching stroke and dementia, you are also an experienced psychiatrist. What led you to cospecialise in these two areas?

One of the key moments at the medical university that further supported my interest and enthusiasm for psychiatry and neurology was studying a course of electroencephalography and neuroimaging where I became fascinated by the way the brain works. I have since encountered amazing neurologists from whom I have learnt a lot along the way. I studied neurophysiological tools and related areas before moving into psychiatry, hoping to find neurophysiological mechanisms of mental disorders. I was very lucky to learn from Professors Mark and Antony Burno, Peter Baranov, and Vladimir Rotstein, who are not only brilliant psychiatrists but also wonderful people. Prof Igor Nikiforov, a remarkable professional in psychiatry and addictions with whom I have worked for a long time, highlighted that neurological conditions often underlie many psychiatric disorders. Prof Lubov Romasenko, my PhD supervisor, who is an amazing psychiatrist and has a profound interest in psycho-neurology, has shown me that it is necessary to dive into neighbouring specialities that complement psychiatry to pursue a successful career in biomedical science. She was incredibly helpful in discussing potential topics and supervising my work. During my PhD, I collaborated with medical professionals from different areas, mostly neurologists. They gave me the support I needed to grasp the comprehensive understanding of how to embed and implement psychiatric knowledge into general medicine.

How has your grounding in psychiatry supported your research and career in neurology?

My research topics are marginal between neurology and psychiatry; therefore, as a science communicator, I feel knowledge in both of these areas support ideas and studies in each of them. There are also a number of psychiatric conditions that may interfere with individuals' psychological state and affect results in research. So, understanding psychopathology and decision-making in psychiatry supports me in better understanding of results and ensures the creation of new research questions that bring fresh ideas to the field; furthermore, with my background, I can bring together research methods. Therefore, I am happy to further expand my knowledge in this direction and push the borders of our understanding.

"...I became fascinated by the way the brain works. I have since encountered amazing neurologists from whom I have learnt a lot along the way."

You manage a number of studies that are investigating the possibility of predicting health and cognitive outcomes in patients. Could you outline for us what this work entails and what you would like to achieve?

This is complex and collaborative work. We are working together at the National Institute for Stroke and Applied Neurosciences (NISAN), Auckland University of Technology (AUT), with Prof Valery Feigin and his professional team in co-operation with the Knowledge Engineering and Discovery Research Institute and other AUT institutions along with external organisations including international collaborators. Our goal is the development of machine-learning systems with the potential to be used for early and personalised disease prediction based on an individual's particular risk factors and outcomes. This approach could lead to a delay in the development, or even possible prevention, of such conditions, including stroke and dementia, as well as proper management of TBI outcomes.

It would allow patients and families to receive care at an earlier stage of disease progression; support the individual and healthcare providers in changing risky behaviours, which ultimately leads to improved prognosis and decreased morbidity; and allow health resource allocation planning by the health system. Prediction of cognitive outcomes will also facilitate discussions on legal issues with those at higher risk of developing such conditions.

Researchers from Arizona State University, Tempe, Arizona, USA, have presented new evidence proposing that oligomeric amyloid β accelerates natural mitochondrial decline; consequently, pretreating mitochondria may offer an exciting, novel avenue for the treatment of Alzheimer's disease. What do you make of these findings?

As mentioned in the recent research paper written by the team from Arizona State University, pretreatment with a novel CoQ10 analogue protects neuronal mitochondria from oligomeric amyloid β-induced mitochondrial changes, which suggests a pretreatment option to prevent oligomeric amyloid β toxicity long before the damage is apparent. These are quite promising results broadening our understanding of mechanisms of Alzheimer's disease and leading to possibly delaying, or even preventing, its onset.

With your focus on machine learning in stroke, dementia, and TBI, how important do you believe artificial intelligence will be for the future of neurology?

An enormously growing amount of information has been recorded in clinics and hospitals, which cannot be quickly processed using existing technologies. The advantage of machine learning is the speed at which it consumes data as well as the automated analytical model building, removing the need to specify rules explicitly. Using algorithms that continuously assess and learn from data, machine learning enables computers to access hidden insights. In the clinical setting, machine learning allows prediction of whether it might be an imminent risk for a clinical event or outcome (e.g., risk of stroke). This approach also enables the development of individualised predictions for patients based on their unique histories, habits, and trajectories of life. Therefore, from my perspective, novel state-of-the-art artificial intelligence technologies provide a promising ability to build sustainable predictive algorithms for stroke, dementia, TBI, and comorbid diseases.

The European Academy of Neurology (EAN) put together a spectacular scientific programme for the 2018 meeting, which promoted a wide range of neurological disorders, but what do you believe the focus of the neurological community should be for the next 5 years?

Mental and neurological disorders have become the leading causes of disability worldwide, and the burden of these diseases is constantly increasing. Dementia and stroke are two of the most severe cerebral disorders. The diseases represent two of the most significant health challenges. They dramatically change the lives of people and will have major personal, societal, and economic impacts in the years ahead. It is widely agreed that progress in dementia and stroke prevention and management can be greatly enhanced using a personalised approach. Therefore, I think that the application of artificial intelligence will be a primary focus for the next few years, and this approach would be able to address both prevention and management of diseases like dementia and stroke. Artificial intelligence represents a personalised medicine approach that maximises health outcomes for people and optimises healthcare resource utilisation.

If you could cure one neurological condition, what would it be and why?

I would choose dementia and stroke, which is what I am working on currently. Curing these conditions would allow us to live longer and keep our minds clearer for longer, as the mind is the thing that makes us something special. As Stephen Hawking said, "We are just an advanced breed of monkeys on a minor planet of a very average star. But we can understand the Universe. That makes us something very

special." I could not agree more, although I would like to add the caveat that we can try to understand the universe.

"I would advise being persistent and always having goals in mind. Once your mind is set on something, work towards that goal."

Other than EAN, are you planning on attending any congresses this year? If so, which meetings? Why do you think national and international congresses are so important?

In my opinion, attending local and international conferences is an important thing for both junior and senior researchers because it allows the exchange of the latest knowledge and learning from colleagues, and it is also a great place for networking and developing new research collaborations. I am planning to attend The German Association for Psychiatry, Psychotherapy and Psychosomatics (DGPPN) Congress 2018, which is a really exciting all-European event gathering together psychiatrists, psychotherapists, and neurologists from the across the globe. I try to attend this congress every year.

What advice would you give a young medical student or scientist looking to start a career in neurology?

I would advise being persistent and always having goals in mind. Once your mind is set on something, work towards that goal. Second, continuously try to broaden your knowledge in different areas, not only medical but also legal and sociocultural; do not avoid communication with other medical professionals, make efforts to understand their needs and intentions as well as the needs of patients; and get involved in everything possible, including public engagement and conferences. Lastly, define your own work–life balance to prevent burnout, which is quite common in the clinical area.

"We are just an advanced breed of monkeys on a minor planet of a very average star. But we can understand the Universe. That makes us something very special."

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Abstract Reviews

A collection of the very latest research findings presented at this year's EAN Congress

Neuropsychological and Brain Grey Matter Volume Changes After Computer-Assisted Cognitive Treatment in Patients with Multiple Sclerosis

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Keywords: Biomarkers, computer-assisted cognitive treatment, functional MRI, multiple sclerosis (MS), neuropsychological rehabilitation, resting functional MRI.

Citation: EMJ Neurol. 2018;6[1]:46-48. Abstract Review No. AR1.

BACKGROUND

Cognitive impairment is a common disorder in multiple sclerosis (MS), present in >65% of patients both in the early and advanced phases of the disease, and progresses over time.[1] This condition can have a significant impact on the quality of life, employment, daily functioning, and independence of patients. Results regarding cognitive treatment are contradictory, which is probably because the interventions and the outcome measures are heterogeneous. Despite this, different studies have showed that neuropsychological intervention can have favourable effects on the cognitive performance of patients.[2-4] Specifically, there is evidence that computer-assisted cognitive rehabilitation improves performance in neuropsychological tests; we therefore designed a study to evaluate the effectiveness of the application of a computer-assisted cognitive rehabilitation therapy in MS patients.

METHODS

We included 12 patients in the study. All patients had a diagnosis of relapsing-remitting clinically stable MS; mild-to-moderate cognitive impairment, as established by the

Brief Repeatable Battery of Neuropsychological Tests (Rao battery); an adequate level of visual acuity; and were aged >18 years. The patients were evaluated three times: at the beginning of the study, at Week 8, and at Week 16. Patients were randomised to receive treatment after the first evaluation (Group 1) or after the second evaluation (Group 2). The evaluation consisted of a neuropsychological assessment (using alternative versions of the same battery to reduce the practice-related effects), a functional magnetic resonance study (including a resting functional MRI, a diffusion tensor image, and a Voxel-based morphometry), and a blood sample to identify plasma changes associated with the brain-derived neurotrophic factor protein, which is involved in neuronal plasticity processes. These measures were taken to identify potential biomarkers of therapeutic efficacy. All patients received 24 sessions of computer-assisted cognitive treatment using the NeuronUP platform. NeuronUP is a cognitive neurorehabilitation online platform that has activities covering 40 neuropsychological processes.[5] The rehabilitation sessions were 45 minutes long and were performed three times a week for 8 weeks at the patient's home.

RESULTS

Preliminary results showed significant improvements in verbal memory, delayed visual memory, working memory, and semantic fluency. Structural MRI analysis (Voxel-based morphometry) showed an increase of 0.7% in the global grey matter volume in most patients. Furthermore, resting-state functional MRI studies showed a decrease in fractional amplitude of low-frequency fluctuations in the cingulate cortex, which is involved in learning and memory processes, and in the middle frontal area (Figure 1), suggesting that cognitive therapy improves cognitive performance and may induce structural and functional changes in the brains of MS patients.

CONCLUSION

These findings suggest that cognitive treatment may favour neuroplasticity-inducing changes in the cortical reorganisation, which will help to improve either cognitive or brain reserve.

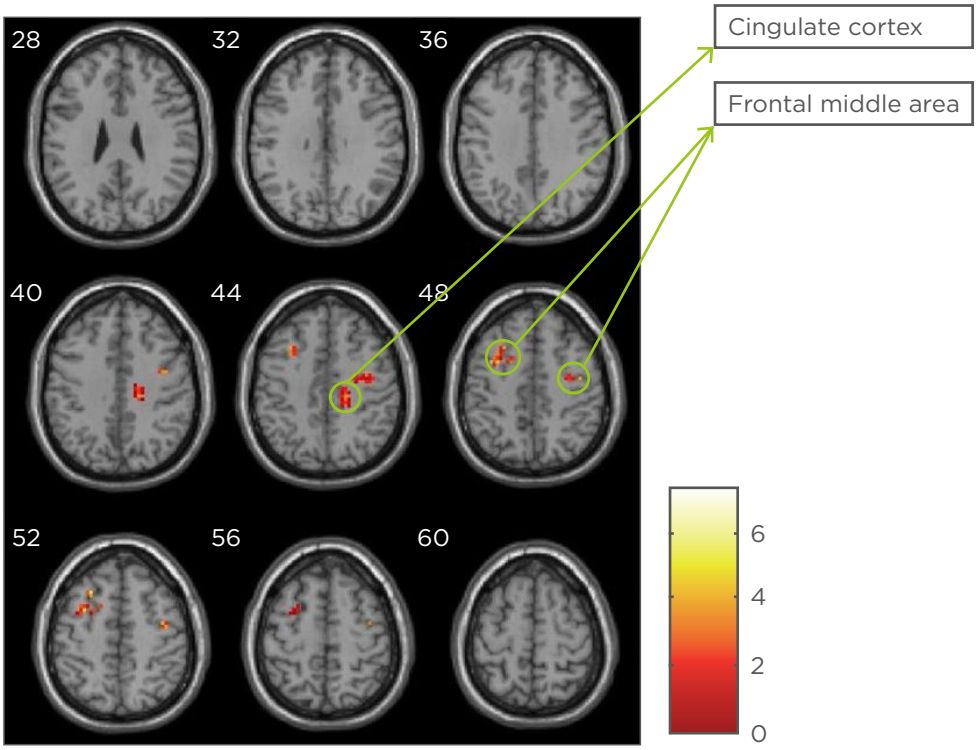

Figure 1: Decrease of fractional amplitude of low-frequency fluctuations in the cingulate cortex and middle frontal area after treatment.

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Pilot Study of Balance Training Using Visual Biofeedback in People with Multiple Sclerosis with Balance Impairment

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Keywords: Balance, balance training, Homebalance®, multiple sclerosis (MS), rehabilitation.

Citation: EMJ Neurol. 2018;6[1]:48-50. Abstract Review No. AR2.

BACKGROUND

Impaired balance is common in people with multiple sclerosis (MS) and can be present even in persons with a mild disability level.[1] With increasing disability level, gait and balance impairment increases, leading to an increased risk of falls. In recent studies, interactive commercial video games, such as Wii Fit (Nintendo, Kyoto, Japan) and Xbox Kinect (Microsoft, Redmond, Washington, USA), were used for improving balance, but these studies were limited due to a lack of individual training parameters.[2-9] Therefore, a small portable system that includes a stabilometric platform with visual biofeedback (Homebalance) that enables individual settings for exercise parameters was developed. The aim of this study was to evaluate the feasibility of balance exercise in the home setting using the Homebalance system in a group of people with MS and subjective perceived balance impairment.

METHODS

A total of 10 participants with relapsing-remitting MS were enrolled in the study (9 women, 1 man) with an expanded disability status scale of 1.5–6.5. The mean age was 38.4 years (standard deviation [SD]: 6.7) and the mean disease duration was 14.4 years (SD: 6.8). A number of assessments were performed at baseline and after 4 weeks of the training: timed 25-foot walk test (T25-FW), Timed Up and Go test (TUG), Berg balance scale, and a short version of the Balance Evaluation Systems Test (miniBEST test).

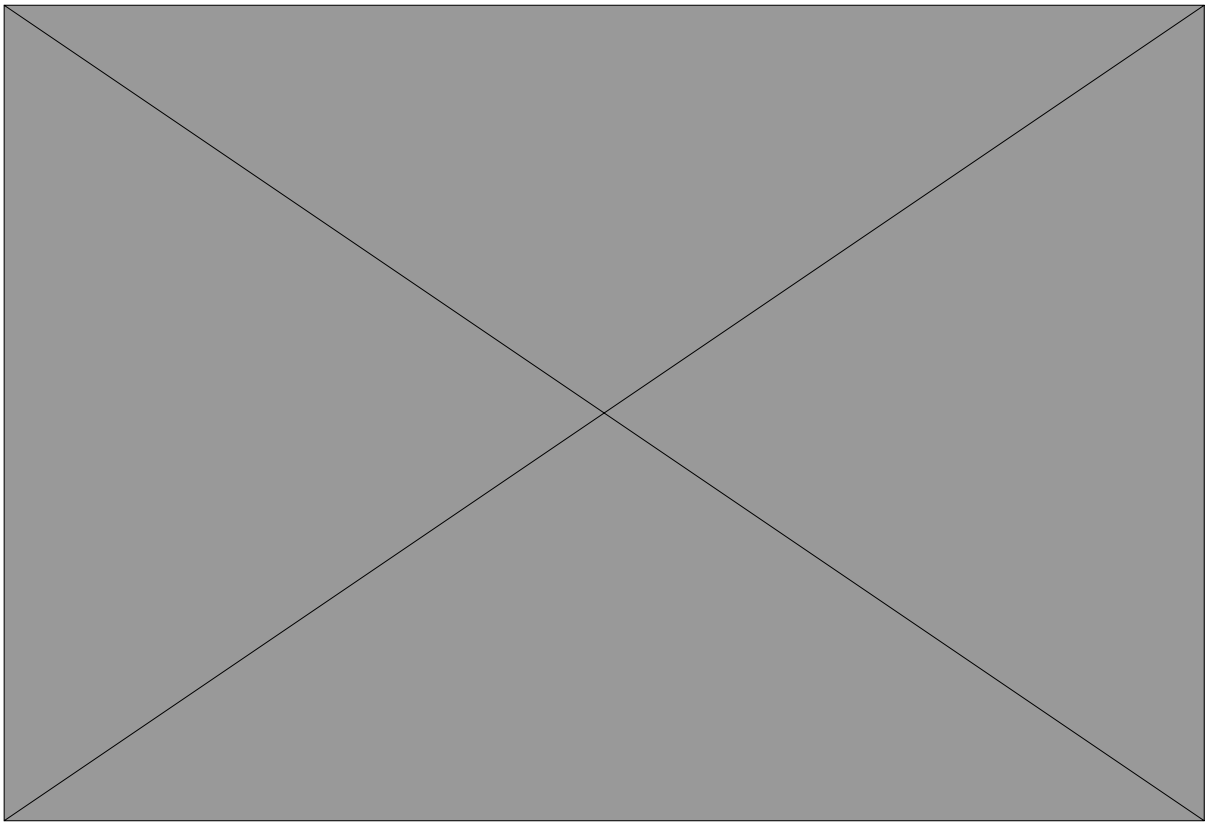

Figure 1: The components of the Homebalance system including the chess-based balance game and the stabilometric platform.

The intervention consisted of home-based balance training performed daily for 15–20 minutes for 4 weeks using the Homebalance system in a standing position. The first exercise session was supervised by a physiotherapist who set individual exercise parameters. The therapy included active repetitive game-like training. When standing on the stabilometric platform, the patient was instructed to move the avatar by shifting their centre of gravity. There were two therapeutic games available: Chessboard, where the therapeutic task can be set to different positions and directions, and Planets, where the therapeutic task increases the user's stability in combination with providing cognitive training.

RESULTS

Statistically significant improvements within the home exercise group were present for the TUG test only. An improvement was made from a mean of 16.8 seconds (SD: 15.2) at baseline to 15.1 seconds (SD: 10.2) after intervention (p=0.01). All other gait parameters, balance assessment, and patient reported outcomes did not achieve a statistically significant improvement. T25-FT went from a mean of 13.2 seconds (SD: 13.2) to a mean of 12.5 seconds (SD: 11.6), the Berg Balance test improved from a mean of 45.5 (SD: 10.3) to a mean of 47.5 (SD: 9.3) points, and the miniBEST test from a mean of 20.3 (SD: 7.2) to a mean of 21.1 (SD: 6.8) points. No adverse events were reported during the exercise period.

Several studies have shown possible benefits of this type of training using the Wii, either supervised by a physiotherapist[2-6] or at home.[7-9] However, commercial exergaming devices do not allow adjustments to individual difficulty settings that in some cases are necessary to meet the physical abilities of the individual and, therefore, the treatment goals. In contrast, in the Homebalance system, training difficulties and parameters of both therapeutic games could be set individually. Findings from our pilot study

showed that this system is safe and feasible for use in balance rehabilitation for people with MS with mild-to-severe disability.

These results could be limited due to the small sample size in this pilot study. We are now evaluating the effect of this type of home balance exercise in a larger cohort of patients with MS.

CONCLUSION

Data from our pilot study indicated that balance training using Homebalance with audio-visual biofeedback is feasible and may be an effective method for balance training in people with MS with mild-to-severe disability.

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Efficacy and Safety of Combined Open-Closed Loop Vagus Nerve Stimulation

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Keywords: Closed-loop, epilepsy, neurostimulation, vagus nerve stimulation (VNS).

Citation: EMJ Neurol. 2018;6[1]:50-52. Abstract Review No. AR3.

Vagus nerve stimulation (VNS) is a neurostimulation therapy in which the vagus nerve is stimulated in the neck region by a helical electrode that is wound around the cervical vagus fibres and connected with a lead to a subclavicularly implanted pulse generator. It represents a safe and efficacious neurostimulation treatment that is now widely available for refractory epilepsy patients. With the initial VNS devices, stimulation was delivered in an open-loop fashion with intermittent stimulation of the vagus nerve in on and off cycles. On top of this standard stimulation, a

magnet feature enables delivery of an extra stimulation at the time of a perceived seizure onset by passing a magnet across the implanted generator.[1,2] Studies have proven the added benefit of this magnetic stimulation,[2-6] but manual application of the magnet may not be possible due to clinical seizure symptoms, a physical or cognitive impairment, unawareness of the seizure occurrence, or nocturnal seizures.[1,2] Therefore, the development of an automated seizure detection feature that triggers stimulation has gained interest. Since electroencephalogram and electrocardiogram studies have shown that ictal heart rate increases occur in approximately 82% of epilepsy patients,[7] detection of these ictal heart rate changes could serve as a trigger to automated stimulation delivery. The combined open-closed loop VNS system is the first VNS device with a cardiac-based seizure detection algorithm, providing automatic stimulation triggered by ictal heart rate increases. This novel feature functions in addition to the traditional VNS system modes (normal and magnet mode), resulting in a potential therapy combination for patients using both open and closed-loop stimulation.[1,2]

In our study, we evaluated the performance and safety of this new device in a cohort of 16 refractory epilepsy patients with a minimum follow-up of 6 months. We retrospectively assessed the change in mean monthly seizure frequency (MMSF), responder rate, and adverse events at maximum follow-up. Five patients had a maximum follow-up of 15 months with a change in MMSF from 11 to 5 and a 60% response rate at 15 months. Two patients had a maximum follow-up of 12 months with a change in MMSF from 17 to 15 and a 50% response rate at 12 months. Seven patients completed a maximum follow-up of 9 months and showed a reduction in MMSF from 17 to 6 and a response rate of 43%. Finally, two patients had a maximum follow-up of 6 months with a change in MMSF from 38 to 5 and a 50% response rate. The total response rate at maximum follow-up was 50%. Less severe seizures at maximum follow-up were reported by 44% of patients. Regarding safety, the most frequently reported adverse event was hoarseness, while other adverse events were rarely reported (Figure 1). In half of the patients, the stimulation parameters had to be adjusted due to adverse events.

We can conclude that the response rate with the combined open-closed loop VNS system in this study was comparable with previous short-term VNS studies. In accordance with a previous study, we found in this small group of patients a trend towards higher response rates earlier in the course of follow-up. The safety profile was comparable to the traditional open-loop VNS devices.

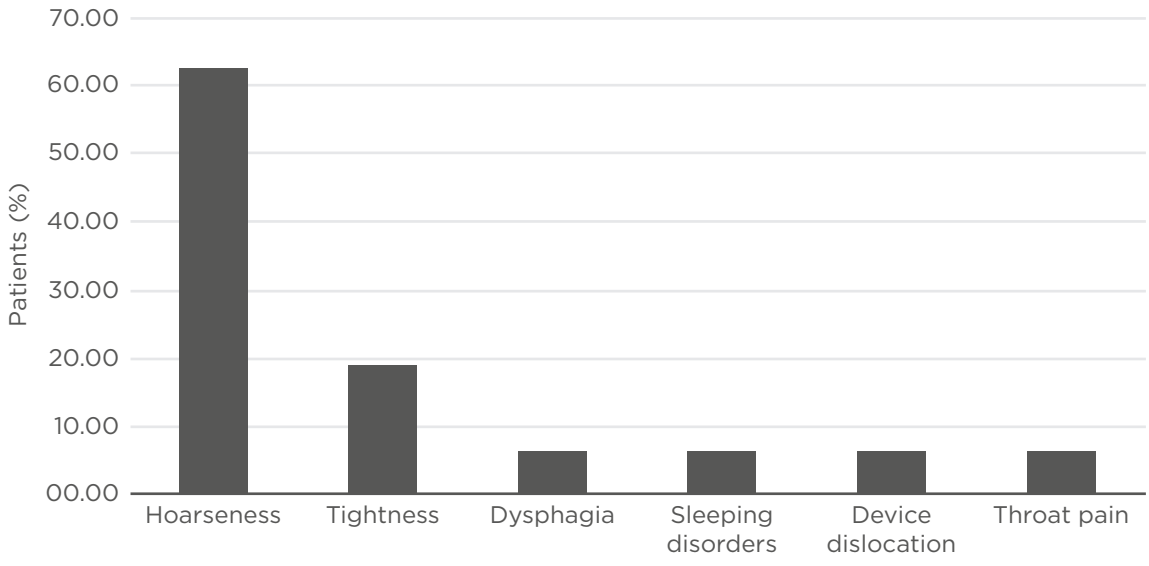

Figure 1: Adverse events at maximum follow-up.

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Disease-Modifying Treatment in Paediatric-Onset Multiple Sclerosis: A Danish Nationwide Population-Based Observational Study

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Keywords: Disease-modifying therapy (DMT), multiple sclerosis (MS), observational study, paediatric-onset, real-world data.

Citation: EMJ Neurol. 2018;6[1]:52-53. Abstract Review No. AR4.

INTRODUCTION

Multiple sclerosis (MS) with onset before the age of 18 years is characterised by higher relapse rates and more severe MRI evidence of inflammation compared to adult-onset MS. Only persons older than 18 years have been included in randomised placebo-controlled trials; however, previous observational studies have shown that early initiation of disease-modifying therapy (DMT) may be beneficial for children with MS. No official international treatment guidelines are available for paediatric-onset MS (POMS), and there is limited evidence of DMT in children with MS.

AIMS

The aim of this study was to describe DMT in POMS in Denmark from 1996, when DMT became available, until data were sourced in May 2017.

METHOD

We conducted a nationwide population-based cohort study using prospectively collected real-world data derived from the Danish Multiple Sclerosis Registry. We identified a cohort of 195 children diagnosed with MS before 18 years of age. Since recording of all patients treated with DMT is mandatory in Denmark, the cohort is considered effectively complete.

RESULTS

Out of 195 patients, 123 (63%) started DMT before turning 18 years of age. The group of treated patients had a mean age at diagnosis of 14.9 years and a mean age at treatment initiation of 15.9 years (median: 16 years; range: 4–17 years). Most of the children received a first-line DMT, with IFN-β being the most common choice (85%). IFN-β1a administered subcutaneously was the most commonly used treatment from 1996–2005 (53%), while IFN-β1a administered intramuscularly was more common from 2006–2015 (59%). From 2011–2015, only 1 (2%) patient started treatment with dimethyl fumarate and 5 (9%) patients with teriflunomide. Two patients received induction therapy with mitoxantrone (in 2005). Natalizumab was the only second-line agent used as a primary treatment and was given to 6 children after 2011.

During the 20 years follow-up, a total of 107 (87%) children switched DMT or discontinued treatment, either due to adverse events or disease breakthrough. Of the 123 treated POMS cases, 39 children (32%) received >1 DMT before turning 18 years of age. The mean number of DMT per child, initiated before the age of 18 years, was 1.4. Natalizumab and fingolimod were used as second-line DMT in 18 out of 39 subjects. Fingolimod was prescribed more frequently than natalizumab when escalation of therapy was indicated, and three patients switched from natalizumab to fingolimod. IFN were used in 10 children (26%) after the first switch.

CONCLUSION

In conclusion, this study based on real-world data provides an insight into the patterns of use of DMT in POMS in Danish clinics.

Clinical Characteristics of Intracranial Haemorrhages by Direct-Acting Anticoagulants in Secondary Prevention

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Apixaban, dabigatran, direct-acting oral intracranial anticoagulants (DOAC), haemorrhage, intraparenchymal haemorrhages, secondary prevention, rivaroxaban.

Citation: EMJ Neurol. 2018;6[1]:53-55.
Abstract Review No. AR5.

INTRODUCTION

The risk of systemic or intracranial haemorrhagic complications in patients with anticoagulated

cardioembolic stroke is double that in primary prevention.[1,2] In the literature, direct-acting oral anticoagulants (DOAC) induce a reduction in the risk of intracranial haemorrhage (ICH) versus anti-vitamin K of almost 50%, but patients with ICH present with similar rates of mortality.[1-3] In this study, we present our clinical experience of ICH secondary to DOAC in secondary prevention of ischaemic stroke and search differences in clinical characteristics.

MATERIAL AND METHODS

This observational, retrospective study included patients receiving DOAC for secondary prevention of ischaemic stroke in our tertiary hospital from October 2010 to June 2015. Clinical and radiological characteristics of these patients were obtained and both groups (events in patients both with and without ICH) were compared to determine functional outcome and a long-term strategy of anticoagulation.

RESULTS

A total of 425 patients (57.7% receiving dabigatran, 24.7% receiving rivaroxaban, and 17.6% receiving apixaban) were included in the study, with a mean follow-up of 20.0±18.1 months. Of these patients, 53.4% were women, mean age was 77.1±10.2 years, median CHA_2DS_2-VASc score was 5 (range: 2–8), and the median HAS-BLED score was 2 (range: 1–4). During the follow-up there were 10 (2.3%) cases of ICH, a median of 36 months (range: 7–78) from the beginning of treatment, with an incidence rate of 0.015 cases per person-year. These patients had no differences in age, vascular risk factors, renal function (measured by glomerular filtration rate), or percentage of previous ICH. Patients with ICH had the same embolic and haemorrhagic risk as patients without ICH. Of the patients who had experienced ICH, 8 were treated with dabigatran (7 with dabigatran 110 mg twice daily and 1 with dabigatran 150 mg), 1 with apixaban 5 mg twice daily, and 1 with rivaroxaban 20 mg. Dose of DOAC was adequate on the date of the event in all patients. There were five spontaneous intraparenchymal haematomas (median of volume 20.6 mL [2.4–149.1 mL]) and a median National Institutes of Health (NIH) Stroke Scale score of 10 (1–17), three post-traumatic subarachnoid haemorrhages, an intraventricular haemorrhage, and a subdural haematoma. At 3 months, 70% presented a modified rank scale value of ≤2. Two patients died due to massive haemorrhage (volume >100 mL). In 3 patients the same DOAC was restarted and in 1 of them the DOAC was changed. Anticoagulation was discontinued in 4 patients as a result of intraparenchymal haemorrhages. A percutaneous closure of the left atrial appendage was performed.

DISCUSSION

Direct anticoagulants are the treatment of choice in patients with atrial fibrillation.[3-5] These drugs have been shown to be just as effective as anti-vitamin K drugs, but with a lower incidence of intracranial bleeding.

In this real-life study, in line with most published studies,[2,6] patients with intracranial bleeding had lower bleeding volume and lower mortality, as well as a better functional outcome. In patients treated with dabigatran, reversal with idarucizumab should be considered.[5,6] In patients undergoing treatment with anti-factor Xa drugs, treatment with prothrombinic complex should be considered until approval of andexanet alpha by the European Medicines Agency (EMA).[6]

CONCLUSION

The rate of ICH in patients with DOAC in secondary stroke prevention was similar to the pivotal studies, and patients presented with fewer disabilities. The secondary prevention strategy in these patients should be assessed in future studies.

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Resistance to Eye Opening in Patients with Disorders of Consciousness

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Keywords: Diagnosis, disorders of consciousness (DOC), minimally conscious state (MCS), resistance to eye opening (REO), sign of consciousness, unresponsive wakefulness syndrome (UWS).

Citation: EMJ Neurol. 2018;6[1]:55-56. Abstract Review No. AR6.

Resistance to eye opening (REO) is defined as strong closure of already closed eyelids by a patient when they are touched by an examiner during ophthalmological examination. REO has been described in many different disorders, such as psychiatric coma, non-epileptic attacks, stroke, anoxia, and demyelinating illness.[1-3] Explanations for this symptom range from wilful to reflexive. As empirical data regarding REO in severe brain-injury patients with chronic disorders of consciousness (DOC) are missing, a trial was set up to investigate whether REO is a sign of consciousness or a reflex.

We selected 79 patients out of 150 consecutive patients in our centre with chronic unresponsive wakefulness syndrome (UWS), where the patients are awake but unaware, or patients who were in a minimally conscious state (MCS), during which the patients are awake with reproducible signs of consciousness, with (MCS+) or without (MSC-) language processing. Patients were behaviourally assessed daily for 1 week. We assessed a) the level of consciousness using the Coma Recovery Scale-Revised (CRS-R),[4] which is currently considered to be the most accurate clinical measure of consciousness in patients with chronic DOC, b) the presence of REO, and c) the number of times that REO was seen in each patient (repeatability). Furthermore, most patients underwent positron emission tomography (PET)-CT scanning to measure cerebral metabolism. Brain images were then compared to healthy controls.[5] A few patients also underwent MRI scanning, during which they were instructed to perform mental imagery tasks.

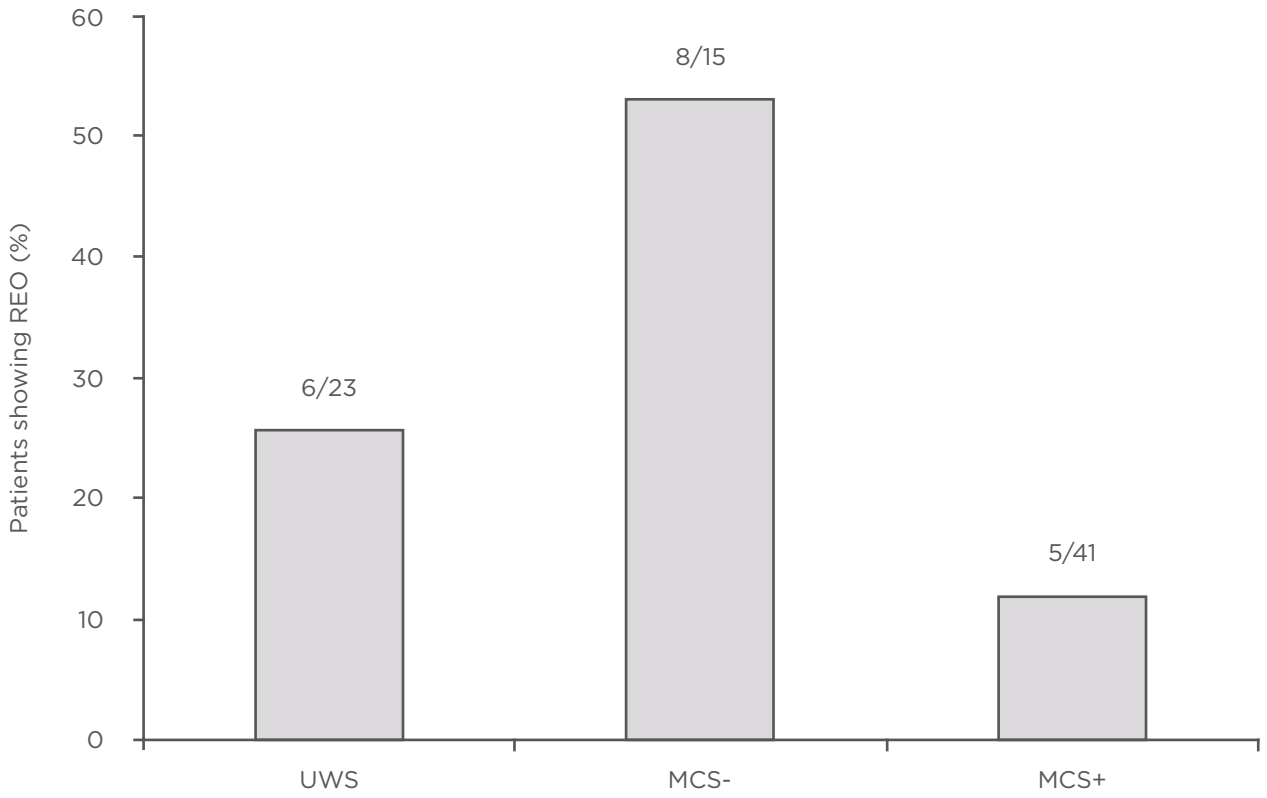

Figure 1: Percentage of unresponsive wakefulness syndrome patients and minimally conscious state patients with and without language processing who showed signs of resistance to eye opening.

MCS+: minimally conscious state with language processing; MCS-: minimally conscious state without language processing; REO: resistance to eye opening; UWS: unresponsive wakefulness syndrome.

REO was observed in 19 out of 79 patients (Figure 1). There was a significant relationship between the presence of REO and the level of consciousness. There was also a significant relationship between repeatability of REO between patients in UWS, MCS-, and MCS+. Five out of six patients with UWS that showed REO displayed neuroimaging results more compatible with the diagnosis of MCS. This atypical brain metabolism was seen more often in UWS patients with REO than without REO.

In conclusion, in our patient population, REO was observed in one in four patients with chronic DOC. As REO was noted in UWS and MCS patients, identification of REO in a single patient cannot reliably distinguish between voluntary or reflex behaviour. However, at a group level, repeatability of REO was highest in patients in MCS+, suggesting a link between repeatability and the level of consciousness. Our findings therefore suggest a voluntary basis for REO when seen multiple times in a single patient, which stresses the need for multiple assessments in DOC patients.[6]

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The Effect of Corticosteroid Therapy on Oxidative Status During Relapse in Multiple Sclerosis Patients

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Keywords: Corticosteroids (CS), multiple sclerosis (MS), oxidative stress (OS), relapse.

Citation: EMJ Neurol. 2018;6[1]:57-58. Abstract Review No. AR7.

Multiple sclerosis (MS) is a chronic, inflammatory, immune-mediated disease of the central nervous system.[1] Various mechanisms, such as inflammation, axonal damage, oxidative injury, excitotoxicity, demyelination, and remyelination, are implicated in the pathophysiology of MS.[2] Several studies have found increased levels of oxidative stress (OS) biomarkers and/or decreased levels of antioxidants in the blood and cerebrospinal fluid of MS patients.[3] The mode of action of some disease-modifying therapies in MS is mediated by their antioxidant properties.[4]

The aim of our study was to analyse the OS parameters during MS relapse and investigate the effect of corticosteroid (CS) therapy on oxidative status. Sixty relapsing-remitting MS patients, consisting of 36 females and 24 males with an average age of 39.97 years and MS duration of 7.33 years, were enrolled in the study. The control group consisted of 60 healthy individuals matched for age and sex. Levels of pro-oxidative–antioxidative balance (PAB), nitrates and nitrites, total antioxidative status (TAS), paraoxonase, transferrin, bilirubin, and uric acid were measured in the control group and in the MS patient group before (MS1) and 1 day after CS therapy (MS2). While PAB, nitrites, and nitrates are pro-oxidants, TAS, paraoxonase, transferrin, bilirubin, and uric acid are antioxidants. All measurements were completed spectrophotometrically in peripheral blood samples.

In heparinised plasma, PAB, nitrates, and nitrites were significantly higher in patients at baseline with respect to the control group ($p<0.0001$). Plasma levels of TAS and paraoxonase and serum levels of transferrin, bilirubin, and uric acid showed significantly lower values in MS patients before treatment compared to controls ($p<0.0001$). After CS treatment, PAB, nitrites, and nitrates were still significantly higher ($p<0.0001$) in the MS group versus the control group, while TAS, paraoxonase, transferrin, bilirubin, and uric acid were significantly lower ($p<0.005$) in MS2 versus the control group. When comparing MS1 versus MS2, we found significantly lower values of PAB ($p<0.0001$), nitrates and nitrites ($p<0.005$), TAS ($p<0.005$), paraoxonase ($p<0.05$), transferrin ($p<0.05$), bilirubin ($p<0.0001$), uric acid ($p<0.0001$), and Expanded Disability Status Scale score ($p<0.0001$) in MS2. However, we found no correlation between OS parameters and Expanded Disability Status Scale score or between oxidative status and MS duration. CS treatment caused a significant decrease of pro-oxidants and antioxidants in the MS patient group, which correlated with clinical improvement. As it has potent anti-inflammatory and immunosuppressive properties,[5] a beneficial effect of CS in relieving OS and lowering pro-oxidants is expected. However, at the same time, CS decreases the cellular antioxidant capacity by suppressing nuclear factor erythroid 2-related factor 2,[6] which regulates the antioxidant defence system by inducing expression of antioxidant response element-dependent genes.[7]

Our findings show the presence of persistent OS in MS patients compared to controls, before and after CS therapy (i.e., unrelated to clinical status). However, CS treatment resulted in the decrease of pro-oxidants, which might be one of the mechanisms underlying clinical improvement. We also found decreased antioxidant activity in MS patients compared

to controls and further decrease after CS therapy, unrelated to clinical improvement.

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The Italian Institutes for Research and Care (IRCCS) Network of Neuroscience and Neurorehabilitation: The Italian Platform for Care and Research About Neurodegenerative Disorders

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Disclosure: The authors have created this abstract review on behalf of the Genomic and Proteomic Network of the Italian Institutes for Research and Care (IRCCS).

Keywords: Genomic platform, neurodegenerative disorders, neurogenetics, neuromuscular diseases, neurosciences, precision medicine.

Citation: EMJ Neurol. 2018;6[1]:58-59. Abstract Review No. AR8.

The Network of Neuroscience and Neurorehabilitation involves 24 highly specialised Italian Institutes for Research and Care (IRCCS) and is focussed on the sharing of knowledge, protocols, and data to promote the standardisation and optimisation of patients' clinical care and therapeutic strategies. The network comprises clinicians and researchers who co-operate in order to create a multidisciplinary platform that can improve the medical care of patients. The main purpose is to promote the use of genomic knowledge in clinical practice. In addition, the Network allows the centralisation of genetic analyses, the sharing of analytical and instrumental data, the development of standardised protocols, the creation of standardised informed consent procedures, the creation of a genomic variants database, the evaluation of variants of uncertain significance, the sharing of guidelines for the management of genetic data and the characterisation of different sub-phenotypes. In particular, the overall data will be utilised for increasing the effectiveness of prevention, diagnosis, and treatment of diseases. Furthermore, the collected information will be analysed, taking into account genetic features, lifestyles, and the environment of patients. The overall data will be employed for the development of a disease-specific atlas characterised by genomic variations related to the onset, complications, or outcomes of neurological diseases. The disease-specific atlas will be updated by the recording of dynamic data, collected not only at the time of

enrolment, but also during follow-up evaluations. Moreover, the development of web-based platforms will facilitate the sharing and analysis of clinical and genomic data. Additionally, the information sharing among the network will enable the interpretation of genomic variants with unknown significance.

This approach is used to improve the genotype–phenotype correlation in neurological disorders, as well as to disclose novel pharmacogenomic biomarkers. The Network allows the integration of clinical and genomic data ('clinomic'), leading to better characterisation of patients. Indeed, the clinomic provided by the IRCCS Institutes will be used to improve the medical care of patients in the field of neuroimages, genomics, proteomics, and tele-neurorehabilitation. Furthermore, this approach will allow the collection and dissemination of evidence of effectiveness and the costs and benefits for the main technologies in the field of diagnosis and prevention based on genomics. Specific proposals and guidelines will be published regarding the development and selection of more appropriate healthcare services for precision medicine applied to neurodegenerative disorders.

The collaboration among the IRCCS Network currently supports innovative research programmes on neurodegenerative disorders, stimulating and promoting the genomic and epigenomic translational studies.

Aura and Important Prodrome Symptoms of Migraine: A Study in a Greek Population

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Keywords: Aura, migraine, premonitory symptoms.

Citation: EMJ Neurol. 2018;6[1]:59-60. Abstract Review No. AR9.

Migraine is a common disabling primary headache disorder with two major types: with or without aura. Migraine without aura is a clinical syndrome characterised by headache with specific features and associated symptoms, while migraine with aura is primarily characterised by the transient focal neurological symptoms that usually precede, or sometimes accompany, headache.[1,2] The International Classification of Headache Disorders 3rd Edition (beta version)[1] defines prodrome or premonitory symptoms as non-headache symptoms occurring 2–48 hours before the onset of headache or aura. However, the diagnostic criteria for migraine with and without aura do not include prodromal symptoms.[1,2]

Premonitory symptoms include a heterogeneous range of cognitive, psychological, and physical changes, such as hyperactivity, hypoactivity, depression, food cravings, repetitive yawning, muscle pain or tenderness, irritability, confusion, extreme drowsiness, and impaired speech or memory.[3] Additional autonomic symptoms, for example, horripilation (gooseflesh or piloerection), have also been reported.[4] These symptoms may not be recognised by the patient as part of the attack and are probably the most neglected aspect of migraine. Prevalence rates of premonitory symptoms vary, ranging from 7–88%, likely reflecting the different methodologies used to identify these symptoms.[5,6]

The distinction between aura and premonitory symptoms is still a matter of debate. It is based on the timing at which these symptoms occur prior to the headache pain and on their clinical characteristics. Aura does not last >60 minutes, is always related to focal cortical activity, and cortical spreading depression might represent its underlying pathophysiological mechanism.[1,2]

On the contrary, premonitory symptoms are more likely to derive from different areas of the central nervous system. Specifically, recent neuroimaging studies have demonstrated early brain activation in the posterolateral hypothalamus, midbrain tegmental area, periaqueductal grey, dorsal pons, and various cortical areas during the premonitory stage of migraine, alluding to the early role of the hypothalamus and brainstem in mediating an attack.[7,8]

Using a semi-structured interview, we studied the prevalence of major premonitory symptoms and aura in a population of migraine patients in a tertiary neurology department of the University of Athens, Athens, Greece. Of the 206 migraine patients who participated in the study, 176 were women and the mean age was 48.5 years, with a range between 18 and 80 years. A total of 54 patients (26%) reported aura, including visual (72%), sensory (27%), monitory (9%), and language disturbances (15%); 56 patients (27%) reported various prodrome symptoms. The most frequently reported premonitory symptoms were yawning (36%), mood changes (39%), or both (11%). Of the 206 patients, 19 reported both prodrome symptoms and aura, most frequently yawning and language disturbances (26%). The presence of premonitory symptoms is therefore important for the diagnosis of migraine. In addition, accurate recording of these symptoms may predict the headache phase of migraine and provide an opportunity for early treatment to prevent disability of the patient during this phase.

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Efficacy of Training in a Virtual Environment for Patients with Balance Disturbances

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Abstract Review No. AR10.

For many years, force platforms and centre of pressure biofeedback were used as tools for static balance training. However, thanks to motion tracking systems based on depth cameras, in recent years it has become possible to track not only the pressure centre but also the entire body and centre of mass. The most well-known of these sensors is the Microsoft Kinect™ (Redmond, Washington, USA), which, according to many studies, has sufficient accuracy of recording movements for clinical use.[1] Additionally, for successful correction of any movement, there must be an external focus of attention.[2] Virtual reality training can provide task-oriented motion training with full

body biofeedback, based on three-dimensional (3D) motion capture data, with motivating gaming exercise.

In this study, patients with chronic cardiovascular disease and moderate balance disturbances were enrolled. Our goal was to investigate the effect of 3D balance training in virtual reality environments and compare the results to conventional training, which comprised individual sessions of vestibular exercise therapy with a physical therapist. To assess the efficacy, we used clinical scales and a built-in instrumental Romberg test, based on centre of mass displacement data.

For static balance training, a darts exercise was used in which the patient could control the aim of the dart by moving their centre of mass; 5 seconds after a dot appears the dart is fired at the target. The aim of another static exercise was to avoid flying balls by translating centre of mass in the frontal plane. Training of dynamic balance aimed to improve stability by prompting the patient to perform side and forward steps. For this, three exercises were chosen: dodging flying balls by performing side steps, stepping over the crossbar and placing the foot on the emerging track, and beating the rolling balls with one foot. The preliminary data showed significant improvements in Berg balance scale ($p<0.05$) (Figure 1) and single support phase during forward stepping, as well as decreased oscillations ($p<0.05$) during the Romberg test in the study group. In the control group, significant changes were observed only in static balance measured with Berg balance scale; the Romberg test showed only a trend of improvement.

We believe that the study group showed the best outcomes due to 3D feedback. The third-person view provided full body biofeedback and helped patients learn how to better control the position of their body in space. On the other hand, in early research it was shown that both the observation and imitation of intransitive actions seen from a first-person perspective yielded increased activity of the contralateral sensory-motor cortex compared to the same actions perceived from a third-person perspective.[3] We can assume that the efficacy of the type of view in a virtual environment depends on the type of trained task. For example, for the training of hand and leg movements, the most effective perspective is the typical first-person view.

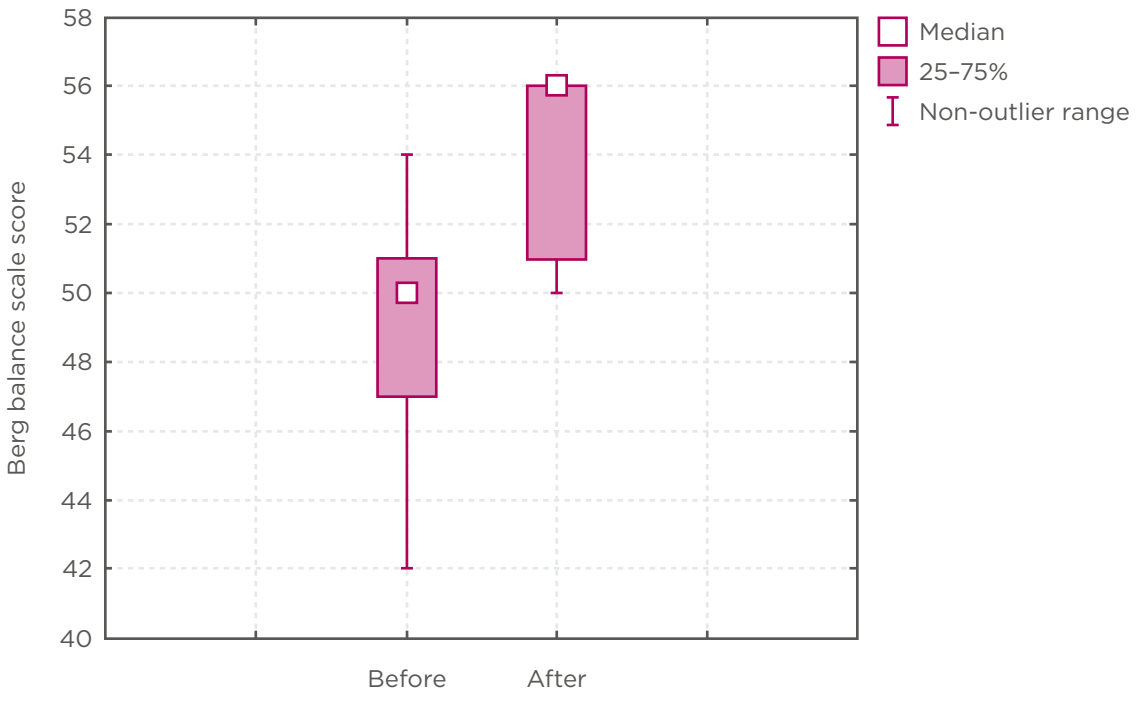

Figure 1: Berg balance scale scores in the main group before and after the treatment course.

On the other hand, for balance training, the physiological first-person view, which provides visual feedback about the position of the surroundings, may not be an informative stimulus for the patient; therefore, a third-person view can be more effective in balance training. This assumption needs further study and validation using a Kinect Romberg test. Further research is also of interest to compare the accuracy of registration and rehabilitation efficacy of separate use of the Kinect sensor and stabiloplatforms, as well as their combinations.

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Trazodone in Dravet Syndrome

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Dravet syndrome (DS) is an epileptic encephalopathy most commonly associated with *SCN1A* mutations and is typically refractory to antiepileptic drugs (AED). DS normally presents in the first year of life,[1-3] and different types of seizures may occur.[2,3] Along with epilepsy, DS is associated with developmental delay and an elevated risk of sudden death.[2]

Here we report the case of a 25-year-old woman with DS-related epilepsy (*SCN1A* mutation) with daily seizures since the age of 5 months, associated with developmental delay. Many AED combinations were tried with no apparent benefit. Seizure-free periods or a significant reduction in seizure frequency were not noted during the course of the disease. Over the years, the patient maintained daily seizures, predominantly during the night, averaging two tonic-clonic seizures a night and an uncountable number of myoclonic seizures, documented both clinically and neurophysiologically. Trazodone was started due to complaints of insomnia. Clinically, the patient's mother noted a significant improvement regarding seizure frequency, with <1 tonic-clonic seizure per month. Electroencephalogram and polysomnographic studies were repeated following 4 months of treatment with trazodone. The studies showed considerable improvement of interictal epileptiform activity and myoclonic seizures, with only subtle changes in sleep structure. This benefit persisted after 1 year of follow-up.

Recent animal studies have suggested that serotonergic pathway modulation is a potential therapeutic target for DS.[4] Clinically, there are very few cases of such evidence with the use of drugs such as lorcaserin or fenfluramine.[4-6] To the best of our knowledge, no clinical data showing that trazodone may be a useful AED in DS patients are available and our case provides this novel clinical evidence.

Despite the limitation of this report being an isolated case with possible chance factors, our data, given the outstanding and 12-month improvement, suggest a direct antiepileptic role (as opposed to indirect improvement in sleep

structure) of trazodone in DS, reinforcing the beneficial effect of serotonergic modulation in these patients; however, the need for additional investigation on this subject is clear. One must not forget that patients with DS rarely achieve seizure freedom and have a high probability of recurrent seizures, including status epilepticus.[7] Additionally, sudden unexplained death is also a risk that must be considered in these patients.[7] In the management of these patients, one tries to reduce seizure frequency but also to limit the adverse reactions.[7] Trazodone does not usually present with significant adverse effects and has a beneficial pharmacological profile.[8] If trazodone were to be found to represent an efficacious drug for these patients, it could significantly change the treatment paradigm of DS.

We hope that the presentation of this case at the EAN Congress may help disseminate this innovative concept and promote the use of serotonergic agents in DS patients, possibly to compile clinical data regarding the use of trazodone in these patients.

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Diagnosing Neuromuscular Diseases

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The field of neuromuscular diseases (NMD) has evolved at an unprecedented speed over the last two decades. Due to advances in molecular genetics, the number of identifiably different diseases has increased and a higher level of complexity has become apparent. Undoubtedly, the dizzying evolution in genetic knowledge has had a profound impact on this area of medicine. Indeed, the impact of genetics has generated a new classification that is often contrary to classical clinical definitions in many diseases.

The gene table of NMD in its online form (http://musclegenetable.fr), prepared by Jean Claude Kaplan and published every year, classifies NMD into 16 groups, lists 884 diseases involving 492 genes and as many proteins, and includes 71 loci that await identification of the corresponding genes.[1]

At the time of writing this article, the 2017 version of this table included 840 genes and 465 diseases and proteins; these numbers give an idea of the growing knowledge in this field. At present, a variety of diagnostic tools can be used in NMD but it is the physician who must wisely select which is the most useful in each case and for each individual patient. To do this, the physician must know exactly what type of information each of the examinations can provide.

CLINICAL EVALUATION: INTERROGATION AND EXAMINATION

Despite the sophistication of available diagnostic tools, the first approach to managing a neuromuscular patient is clinical; it begins with an appropriate interrogation and is followed by a complete neuromuscular examination. Procurement of a precise family history; accurate starting time of the symptomatology, in turn revealing time of evolution; presence of pain, neuropathic or otherwise; and cramps or sensory symptoms and their distribution are of great value. As most of these diseases are of genetic origin, identification of inheritance pattern (e.g., recessive, dominant, or X-linked) is of key importance.

Observation of the patient can reveal the presence and location of atrophies or muscular hypertrophies, and facial appearance can be very informative and even typical in certain cases. The classical example of this is myotonic dystrophy type I, for which the mere recognition of a facial expression is often enough for diagnosis.

The presence of scoliosis, rigid spine, and contractures in the elbows and ankles point to specific forms of muscular dystrophy (e.g., laminin alpha deficiency, collagen VI syndromes) and is detected only by careful clinical evaluation. Gait is also very important

because it may vary; waddling gait is associated with proximal weakness and foot drop or steppage with distal weakness.

In NMD, the common underlying symptom is muscle weakness. As part of the neuromuscular examination, the manual muscle test (MMT) is the physician's most important tool and performing it correctly requires practice, training, and familiarity with the scales used to assess muscle strength. In fact, MMT is to the neuromuscular neurologist what the stethoscope is to the cardiologist. The MMT allows identification of weakness patterns (e.g., proximal, distal, axial) as well as combinations of individual muscle group involvement, thus constituting the first diagnostic step. However, there are numerous diseases with patterns of involvement that are very similar or indistinguishable from each other, so this part of the examination is necessary but not sufficient. One of the most frequent patterns is that of proximal weakness, usually including axial weakness (e.g., limb girdle muscular dystrophies), which may or may not be accompanied by periscapular atrophies and scapular winging. These patients often exhibit typical waddling gait. Manoeuvres such as standing from sitting on the floor, climbing stairs, and standing up from a chair are very useful in identifying weakness patterns. Distal patterns are classically associated with peripheral neuropathies, which exhibit sensory involvement. However, many primary muscle diseases (e.g., myotonic dystrophy, distal myopathies, inclusion body myositis) present with distal weakness, steppage, and hand and forearm atrophies that result in difficulty performing tasks, such as opening bottles, handling keys, using tools, or fastening buttons. The combination of a distal pattern in the upper limbs with proximal weakness in the lower limbs and vice versa is also possible (e.g., inclusion body myositis). In addition, weakness may even be asymmetrical.

Examination of neck flexor and extensor muscles may uncover axial weakness that should be evaluated alongside abdominal and paravertebral muscles. Axial muscles are affected early in Pompe disease as well as in other myopathies (e.g., myotonic dystrophy, polymyositis, and facioscapulohumeral muscular dystrophy). The neuromuscular examination should also be used to look for muscular hyperactivity phenomena, such as myotonia, be it spontaneous (making a fist with consequent difficulty in relaxation) or provoked with percussion. Myotonia is the common denominator of various myotonic syndromes (e.g., myotonic muscular dystrophy type I and II). The presence of fasciculations and their distribution is particularly relevant in motor neurone diseases (e.g., amyotrophic lateral sclerosis); however, there are many causes of fasciculations and not all of them should be considered malignant.

A large group of diseases present involvement of the facial muscles (e.g., facioscapulohumeral muscular dystrophy and congenital myopathies) or of the ocular muscles producing eyelid ptosis (e.g., myotonic dystrophy, mitochondrial myopathies, and myasthenia gravis) and/or extraocular muscle paresis (e.g., mitochondrial myopathies). Weakness of the tongue can be observed in several NMD and in some conditions (e.g., Pompe disease) it is of early onset.

Evaluation of the respiratory muscles (diaphragm and accessory muscles) plays a very important role in pattern identification. Respiratory failure may manifest as morning headaches, daytime sleepiness, and sleep disturbances, and these symptoms should be recognised in the interrogation. It is important to stress that these conditions are not only seen in wheelchair-bound patients but can also be observed early in the disease course and even be the first symptom in ambulatory patients (e.g., Pompe disease, myasthenia gravis, and motor neurone disease).

Assessment of tendon reflexes is useful in the evaluation of patients with NMD. Both motor fibres and sensory fibre afferences are involved in these reflexes and they reveal the influence of the central nervous system at the spinal cord level. Reflex hyperactivity can also be seen among NMD (e.g., amyotrophic lateral sclerosis).

Pulmonary function tests (forced vital capacity and maximum inspiratory and expiratory pressures) are part of the neuromuscular patient assessment, as are cardiac function tests. Follow-up of these parameters is of fundamental importance because they may indicate the need for early intervention with noninvasive ventilation or the placement of a pacemaker or defibrillator in some forms of muscular dystrophy (e.g., Emery–Dreifuss muscular dystrophy).

We have seen that evaluation of inheritance mode, age of onset, weakness patterns, presence or absence of sensory disturbances, and existence of respiratory and/or cardiological involvement are key considerations in the diagnostic process of NMD. Thus, the process must begin with a differential diagnosis to distinguish between a primary disease of the muscle, the motor neurons, the neuromuscular junction, or the peripheral nerves.

ELECTROPHYSIOLOGY

In expert hands, electrophysiology can be decisive in elucidating such differences when the clinical examination is inconclusive. For peripheral nerve disorders, electrophysiology is able to differentiate axonal versus demyelinating disease. It is also capable of accurately diagnosing different types of neuromuscular junction disorders, of establishing lower motor neurone damage, and of recognising primary muscle disease. Electrophysiological studies should be performed with a clinical orientation and correlated with the patient's examination findings.

LABORATORY TESTS

Determination of creatine kinase levels is the most frequent and useful laboratory blood test in the diagnosis of NMD. These levels can point towards different diagnostic options, varying between normal values (e.g., congenital myopathies, neurogenic disorders) and thousands of units (e.g., muscular dystrophies, polymyositis, and rhabdomyolysis). Other laboratory determinations, such as lactate and pyruvate levels during ischaemic exercise, are useful in the diagnosis of metabolic myopathies.

MRI AND IMAGING

In recent years, imaging, especially muscular MRI, has become a new diagnostic tool in the field of NMD. MRI can provide information about the structure and level of involvement, the extent of fatty replacement, and fibrosis in different muscles. Muscular MRI does not attempt to replace clinical examination, such as MMT, in any way, but it does provide information that is not clinically detectable, as is the case with early paraspinal muscle involvement in Pompe disease. Visible alterations seen in MRI may precede clinical weakness. Different patterns of individual muscle involvement visible with MRI have been described in different forms of genetically distinct muscular dystrophies, even though these entities have a significant similarity in clinical phenotypes. MRI is also useful for patient follow-up.

MUSCLE AND PERIPHERAL NERVE BIOPSY

Despite advances in the use of genetics and molecular biology for the diagnosis of NMD, muscle biopsy continues to play an important and often irreplaceable role in the investigation of a large number of patients. The pathologist must have special knowledge of NMD and access to the patient's clinical information to be able to interpret the findings. Histochemical techniques as well as immunostaining lead to the accurate diagnosis of many NMD as soon as the absence or deficit of certain muscle proteins is detected (e.g., dystrophinopathies and sarcoglycanopathies). In addition, histochemical and morphological studies allow us to distinguish between multiple congenital myopathies, as well as other disorders. Peripheral nerve biopsy has more limited or restricted indications and involves the sural nerve. Nerve conduction studies provide a lot of information on nerve status and in selected cases the information obtained from nerve biopsy is of great value (e.g., vasculitis).

MOLECULAR GENETICS

The last 25 years have witnessed impressive advances in the field of genetics. Since the gene for Duchenne muscular dystrophy was recognised in 1987, hundreds of genes responsible for numerous NMD have been identified and all types of DNA mutations have been shown to be capable of resulting in a NMD. Mutations include large or small deletions, insertions, duplications, repeat expansions, and, most frequently, point mutations. Such variety of alterations requires a vast number of genetic techniques for their characterisation. These tests have changed the diagnostic algorithms in many diseases; for example, in many instances, muscle biopsies have been replaced by much less invasive blood draws.

Identifying causative mutations of different diseases has become the gold standard in the diagnosis of NMD. Nevertheless, the genetic and clinical heterogeneity in these diseases still represents a gigantic diagnostic challenge for both the clinician and geneticist. With the advent of next-generation sequencing, a large number of genes can now be sequenced in parallel. This technique makes it possible to study patients at low cost through panels of candidate genes grouped according to the phenotypic characteristics of the diseases. Whole-exon sequencing and whole-genome sequencing facilitate the examination of DNA without restriction to the candidate genes and are recommended in cases in which the panels do not permit the identification of the causative mutation.

In spite of all this diagnostic sophistication, the clinician's participation in the diagnostic process is more crucial than ever. Clinical expertise is essential for analysing the phenotype and establishing the differential diagnosis, as well as interpreting the results together with the geneticist. Nevertheless, a high number of patients in clinical practice remain undiagnosed. Rapid progress in the development and improvement of genetic techniques, as well as growing experience accumulating in joint clinical and molecular work, are expanding the diagnostic possibilities. Understanding the genetic basis of NMD has already borne fruit by yielding the first treatments derived from this knowledge. Therefore, the future is promising.

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Palliative Care in Neurology: Integrating a Palliative Approach to Amyotrophic Lateral Sclerosis Care

EDITOR'S PICK

This thoughtful, clinically relevant narrative review from Hogden et al. discusses the importance of an integrated palliative approach to care for people living with neurodegenerative conditions, using amyotrophic lateral sclerosis (ALS) as an example of the complexities involved. The importance of palliative care in the management of neurodegenerative disease is a hot topic that deserves to be more openly discussed, and specialist palliative care services need to include the full scope of health and community-based care. This review will be of interest not only to ALS specialists but also to neurology health professionals within the wider community and will allow readers to reflect on their own practices.

Samantha Warne

Editor

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Abstract

This narrative review examines connections between neurology, specialist palliative care, and an integrated palliative approach to care for people living with neurodegenerative conditions. To illustrate the complexities of including palliative care in the management of neurodegenerative conditions, amyotrophic lateral sclerosis (ALS) is used as a case study. Challenges to co-ordinated ALS care and smooth care transitions between multiple services and healthcare professionals are discussed, including the timing of palliative care delivery in ALS; the education and training needs of healthcare professionals; and misperceptions of palliative care held by healthcare professionals, patients, and families. The benefits of adopting an integrated palliative approach to care for patients, families, and healthcare professionals are clarified. To enhance this, a family perspective is given on experiences of ALS neurology and palliative services, the challenges they faced, and

aspects of care that facilitated the patient's preferences for the time they had left. This review concludes that a palliative approach integrated into the care plan of people with ALS from the time of diagnosis can optimise quality of life by relieving symptoms; providing emotional, psychological, and spiritual support pre-bereavement; minimising barriers to a comfortable end of life; and supporting the family post-bereavement. These outcomes can only be achieved if palliative care knowledge and expertise are extended beyond the domain of specialist palliative care services to include the full scope of health and community-based care. These challenges and potential actions are common for several neurodegenerative pathologies, and recommendations are made for enhancing the training of neurology health professionals within the wider community.

BACKGROUND

The World Health Organization (WHO) defines palliative care as "...an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual."[1] People living with neurodegenerative disorders receive diagnostic, therapeutic, and end-of-life care from neurology and palliative care services. While these two disciplines may seem disparate, their goals for this patient group are aligned. As the Association of British Neurologists (ABN) states, its mission is to "...improve the health and wellbeing of people with neurological disorders by advancing the knowledge and practice of neurology in the British Isles".[2] The overlapping aims of neurology and palliative care combine when teams collaborate to improve the lives and care of people with neurodegenerative conditions such as Parkinson's disease, multiple sclerosis, Huntington's disease, and amyotrophic lateral sclerosis (ALS).[3] Even so, non-malignant diseases such as these neurodegenerative conditions are under-represented in palliative care. A recent national Australian survey found that more people with cancer (64%) had received palliative care in comparison to non-malignant illnesses (4–10%),[4] echoing results of a study conducted 10 years prior.[5]

Although diagnostic, therapeutic, and palliative care services operate from different perspectives, there are synergistic relationships between the neurology and palliative care teams.[6] This narrative review uses ALS as a case study to comprehensively explore the relationship between these disciplines.[7] This style of review was selected as the optimal way to delve deeply into this issue and uncover gaps between evidence, opinion, and practice. The aims of this review were to consider how patients benefit from an integrated interdisciplinary approach and to reveal how collaboration between neurology and palliative care teams can be strengthened.

COMPLEX CARE FOR A COMPLEX DISEASE

The complexity of ALS and the subsequent impact of a diagnosis on patients and their families highlight both the interconnectedness of, and disparities between, neurological, therapeutic, and palliative care of patients throughout the disease course. As with many other neurodegenerative conditions, ALS lacks a cure or an effective disease-slowing treatment with significant benefit. Death most frequently occurs from respiratory failure 2–4 years after symptom onset, although a small proportion of patients (estimated to be around 5–10%) live for ≥10 years.[8] The presentation of the disease and the speed at which it progresses varies considerably between individuals.[9] Physical symptoms can include changes in mobility, limb strength, speech, voice, swallowing, and respiratory function, and many people will also experience mild changes of varying severity in behaviour, memory, and thinking skills.[10-12] A minority of patients will present with frontotemporal dementia,[10] with or without accompanying physical symptoms. While a small number have an inherited form of the disease,[13,14] for most, the cause is unknown.

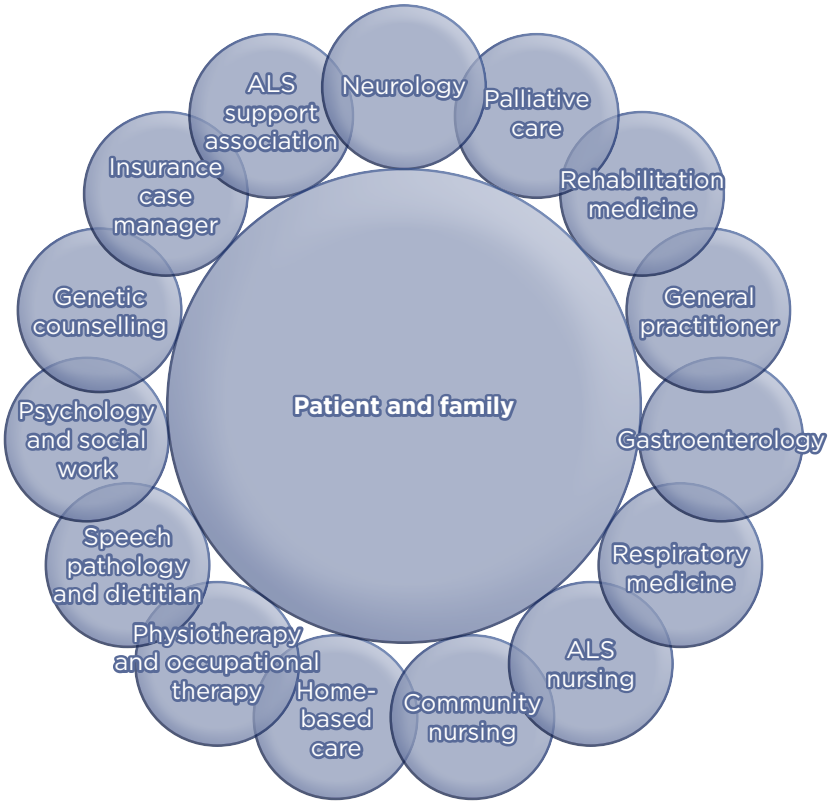

Figure 1: Interdisciplinary model of care for people living with amyotrophic lateral sclerosis.

ALS: amyotrophic lateral sclerosis.

RECEIVING A DIAGNOSIS

The complexity of ALS care begins with obtaining a diagnosis, and a timely and definitive diagnosis is an ongoing concern for patients and clinicians.[15] It is important for neurologists to make a definite diagnosis rather than an early but tentative diagnosis. Establishing the diagnosis with certainty often requires periods of observation of symptom development and evolution of the clinical signs. Making an ALS diagnosis too early can cause enormous anxiety for patients and families, especially if a tentative diagnosis is incorrect. On the other hand, delays in obtaining a diagnosis can put patients at risk of depression,[16] unnecessary interventions such as spinal surgery,[15] and unnecessary clinical consultations.[15,17]

COMMUNICATING THE DIAGNOSIS

Many neurologists report being uncomfortable and inadequately trained to sensitively communicate an ALS diagnosis,[18] adding to patient and carer anxiety.[19-21] Moreover, in a recent Australian study, nearly 40% of patients and family carers were dissatisfied with the way they received the diagnosis.[19,20] Greater adherence to effective communication techniques when delivering bad news, particularly displaying empathy, may improve the way neurologists perform this difficult task. Targeted educational programmes and the development of best practice protocols may go a long way to making these improvements attainable. Additionally, the diagnosis of ALS is frequently given by a neurologist outside of a multidisciplinary clinic (MDC) environment and without the involvement of specialised ALS services. Referral to specialised ALS and palliative care services can then be delayed until after a second opinion has been received.

Once a diagnosis is obtained, the continual progression of ALS creates further challenges to the delivery of co-ordinated patient care. Issues include timely provision of treatment and equipment[22] and assessment of end-of-life care in line with patients' preferences.[23] Disruptions

to service delivery can lead to fragmented care and put patient quality of care and quality of life at risk; this is a frequent concern raised by patients,[24] family members,[25-27] and health professionals.[28]

MODELS OF CO-ORDINATED CARE

In response to these challenges, specialised ALS care requires co-ordinated and multifaceted service delivery to address the variability of clinical presentations and patients' continually changing needs. The multidisciplinary model of care (i.e., teams remaining within their boundaries to work with the patient), developed to provide comprehensive and evidence-informed patient care,[29,30] has evolved into an interdisciplinary model (i.e., care teams working in an interactive, co-ordinated, and coherent way to provide patient care)[31] as the spectrum of care for patients with ALS has broadened.[32] Furthermore, the focus of care has become more patient-centric and the team that assembles around the patient and their family to provide care may be individualised to reflect the patient's preferences. Thus, ALS patient teams can now include clinical care from medical, nursing, and allied health professionals from neurology, palliative care, rehabilitation, gastroenterology, respiratory medicine, and psychiatry, working alongside support services such as ALS support associations,[33] genetic counselling,[13] and pastoral care (Figure 1). Patients and families may also access assistance from government agencies, community services, and national ALS information and support services, and patients may integrate complementary therapies, such as massage, to assist their wellbeing. Guidelines recommend that clinical care is delivered through specialised ALS MDC to ensure care is well co-ordinated between healthcare disciplines and ALS support organisations where available.[29] Specialised ALS MDC have been shown to provide effective care that can prolong patient survival time.[34]

INTEGRATING PALLIATIVE CARE INTO MULTIDISCIPLINARY CLINICS

There is increasing evidence that incorporating palliative care in MDC care, as shown in Figure 1, leads to improved symptoms and quality of life of people with ALS and their families.[3,35,36] Even so, the timing of discussions of the concept of palliative care with ALS patients and when they are referred to and receive palliative care services is contentious. Introducing newly diagnosed patients to the concept of palliative care is a challenge for health professionals and can create tension between ALS therapeutic and palliative services that is often unresolved.[37] Guidelines recommend that ALS patients are referred to palliative services early in the disease course to improve the patient's quality of life,[36,38,39] but patients, families, and health professionals may not be ready to discuss this type of care for some time.

Another view is that patients should be referred to palliative care once particular ALS disease milestones have been reached. However, referrals to palliative care are often triggered by crisis situations,[40,41] resulting in care that is too little and too late.[28] There is disparity between patient, carer, and health professional views on when and how end-of-life discussions should be conducted.[42] Patients and family members may become distressed when end-of-life issues are raised,[24,25] equating the topic with the end of hope. Many diagnostic and therapeutic health professionals feel unprepared to discuss end-of-life care, particularly with newly diagnosed patients.[40,42] The potential consequences of avoiding palliative interventions also conflict with patient wishes for a peaceful death,[43] as patients who are unable to access well-timed palliative interventions risk an uncomfortable death through poorly controlled respiratory problems, pain, and anxiety.[44] The authors consider that a better way to integrate palliative care services into ALS care is to adopt a palliative approach to care, and this approach is elaborated below.

ADOPTING A PALLIATIVE APPROACH TO AMYOTROPHIC LATERAL SCLEROSIS CARE

The original intent of palliative care was as a philosophy of and approach to care; however, palliative care has now become more equated with service provision that focusses on the last months and weeks of life. A palliative approach to care begins at the time of diagnosis and does not link care provision too closely with prognosis, instead promoting early interventions

for patients and their family members, aligned to their goals of care, comfort measures, and needs and wishes.[45,46] The Worldwide Palliative Care Alliance (WPCA)[47] has also suggested that a palliative care approach be adopted by all, not just specialist healthcare professionals, and that general palliative care be provided by primary care professionals who have an understanding of palliative care principles.

It is important to delineate the palliative care approach from specialist services since both operate at different stages of the disease trajectory. A palliative approach[45] in ALS emphasises patient and family-centred care that focusses on the person and not just the disease, the importance of therapeutic relationships between care providers and the patient and their family, and clear communication throughout the illness trajectory; in particular, the approach is based on the goals of care and advance care plans (ACP) (Box 1).[48]

There is increasing evidence that a palliative approach integrated into ALS multidisciplinary care leads to improved symptoms and quality of life of people with ALS and their families.[3] Integrated into the care plan for people with ALS from the time of diagnosis, a palliative approach can optimise quality of life by relieving symptoms; providing emotional, psychological, and spiritual support pre-bereavement; minimising barriers to a comfortable death; and supporting the family post-bereavement. These outcomes can only be achieved if palliative care knowledge and expertise are extended beyond the domain of specialist palliative care services to include the full scope of health and community-based care services, mostly at home, to meet the extensive range of needs of people living with ALS and their families. In most instances, a palliative approach to care can be provided in the community, supported by knowledgeable health professionals, and lasts for the duration of the disease.

Admission to a specialised palliative care inpatient facility may only occur during brief episodes of care, such as respite, symptom management, or terminal phase of illness,[49] or may be required for intractable symptoms or in a crisis.[45] However, the home is the preferred place of care for many patients.[50,51] The palliative approach supports this by offering care delivered in the environment of the patient's choice; control of symptoms, including medication for sleep, depression, anxiety, and distress; patient choice and control over management; holistic care; support for both the patient and their family throughout caregiving;[26] and ongoing bereavement support for the family as needed.[52]

Barriers to Integrating a Palliative Approach

Barriers to integrating a palliative approach into ALS care arise from limited understanding of what palliative care offers, the availability of care beyond the hospice, and the effectiveness of palliative interventions for ALS.[37,50] They include the belief that a palliative approach is only appropriate for end-of-life, lack of recognition that a person is terminally ill, health professionals' lack of knowledge or interest in a new approach, discomfort with discussing the need for palliative care,[45] and concern about resource and funding issues.

Overcoming these barriers involves educating health professionals, patients, and families (and the wider community) about the benefits of a palliative approach integrated into neurodegenerative disease care. As discussions about using a palliative approach can begin at any time, it can be gradually adopted so that changes to care are not abrupt. Health professionals can ensure that patients and families understand that other services, including neurology and rehabilitation, will continue alongside palliative services. In ALS, care transitions may be confusing and frightening[53] because they often signal deterioration in the patient's condition, from which there is no improvement. To fully integrate a palliative approach and to ensure transitions are seamless, education and training in integrating palliative care need to be provided to all health and community service providers involved in ALS care; education and training in the care needs of people with ALS should also be given to palliative care service providers. Educational programmes to improve the knowledge of health professionals about a palliative approach in ALS care have been recently implemented.[54]

Alongside a palliative approach to care, another integrated model of care for people with ALS has emerged.[55] Neuropalliative rehabilitation is a speciality that recognises the intersection

between neurology, rehabilitation, and palliative care services. The aims of this approach are to promote quality of life through proactive symptom management and may involve a broad range of health disciplines, such as music therapy.[56] The objectives of neuropalliative rehabilitation are to prevent secondary complications, provide an environment for promoting patient health, allow treatment and modification of the disease (where possible), help the patient adapt to their altered circumstances, modify the patient's environment to promote safety and quality of life, and support the family.[55] Neuropalliative rehabilitation is particularly appropriate for people with rapidly progressive disease and those with distressing symptoms.[55] While neuropalliative rehabilitation shares many of the benefits of a palliative approach, it is less easily integrated into non-specialist ALS services in the wider community, where many patients who are unable to attend MDC receive their care.

Box 1: Essential characteristics of a palliative approach.[48]

- An upstream orientation to care: early on in the illness trajectory, even as soon as the time of diagnosis.
- An emphasis on anticipatory planning and open conversations about goals of care.
- An adaptation of palliative care knowledge and expertise by primary care professionals.
- An operationalisation of a palliative approach through integration and contextualisation within healthcare systems.
- Promote better service planning, better care, and better outcomes for patients and their family members.

Table 1: A family's perspectives on integrated care from diagnosis to bereavement.

Disease stage	Aims	Challenges	Enablers
Early	• Focussing on making the most of the time remaining. • Leaving a lasting legacy. • Being able to die at home.	• Health system constraints restricting HP to immediate issues. • Transition to palliative care should have begun at this point, rather than at end stage.	• Direct and honest communication with neurologist. • Equipping and adapting the home to meet patient's long-term needs. • Information to prepare the family for what was to come. • Strong relationships with HP and ALS support association. • HP anticipating future issues. • Advance care planning.
Mid	No specific aims.	• Delayed acquisition of equipment. • Fatigue and overload attending ALS clinic; need for real-time information sharing. • Care and respite workers' lack of understanding of ALS and training in palliative care approaches. • System constraints for service provision.	• Information, resources, and support from ALS support association.
End	• Receive all services at home.	• Establishing new relationships with palliative home-based care team. • Self-care for carers. • Accessing information on palliative sedation.	• Family providing personal and overnight care. • HP working across ALS MDC and palliative care teams. • Direct and honest information from ALS and palliative care team.

ALS: amyotrophic lateral sclerosis; HP: healthcare providers; MDC: multidisciplinary clinics.

Adapted from Warren et al. in Oliver et al.[59]

FAMILY CARERS AS PARTNERS IN A PALLIATIVE APPROACH TO AMYOTROPHIC LATERAL SCLEROSIS CARE

Family carers are vital partners in a palliative approach to care. As the patient becomes more physically dependent, family members provide logistical and hands-on care, as well as emotional support.[25] A range of health professionals work closely with the patient and family to ensure effective care from diagnosis to the end of life.[57] ALS service experiences of people living with ALS and their carers have provided insight into how quality of care is perceived.[24,25,27,51,58] A published example from one family revealed how a palliative approach to care was perceived through the care aims, challenges, and enabling aspects encountered during their family member's ALS journey.[51] Their story, summarised in Table 1, reveals the benefits of an integrated palliative approach and how planning for a comfortable death can co-exist with living each day to the fullest.[59]

A second example has highlighted the ongoing support and education for family carers as a further benefit of integrated approaches to care. The family, and in particular the primary family carer (most often the spouse who may act as a substitute decision maker), should be informed about all options throughout the disease course and be prepared for the impending loss of their loved one. This aims to minimise their psychological burden when they are asked to make existential decisions they are rarely well-equipped to make, and, as a consequence, reduce adverse outcomes such as complicated grief, which can continue through the bereavement stage.[27,52] To this end, an Australian ALS support association has trialled the use of a person-centred international validated tool, the Carer Support Needs Assessment Tool (CSNAT), which creates the opportunity for systematically holding conversations about the practical, psychological, spiritual, and existential needs of carers in supporting their care recipients and helping themselves.[60] Like the family account given in Table 1, the highest support priorities of ALS family carers were knowing what to expect in the future, knowing who to contact if concerned, equipment to help care, and dealing with feelings and worries. For the priority of knowing what to expect in the future, discussions with service providers covered end-of-life issues, advance health directives, future care, and the role of palliative care.[59] This demonstrates an integrated palliative approach to care and its focus on patient and family needs.

Around the time of end of life, it is common for people with ALS to refuse life-sustaining treatment. Decisions for end-of-life care, including the use and withdrawal of ventilation and nutrition, need to be discussed with the patient and family proactively in advance of deterioration. It is important that patients and families determine their preferences and that these decisions are documented in an advance health directive or an ACP. However, the uptake of such documents is still low worldwide, ranging from 10–25%, though those who received palliative care were two to three-times more likely to have an advance health directive or ACP in place.[4]

Despite the inevitability of death associated with an ALS diagnosis, many families do not receive bereavement support. For example, an Australian study of ALS family carers reported that half of participants did not recall receiving offers of bereavement support and over one-third of the sample met criteria for prolonged grief disorder, a much higher proportion than the general population estimate of 10%.[22] On average, palliative care services were received <2 months before patient death.[22] The benefits gained by family carers in being engaged in early and direct assessment of their support needs before bereavement[53] reinforce the need for palliative care services to effectively support carers well before the patient's death.[4,45] A continuum of support between caregiving and bereavement lends itself well to palliative care services that have the opportunity to investigate grief and bereavement support in the lead up to the patient's death.[4,45] This is more achievable with a palliative approach that can be initiated earlier in the disease journey, allowing a rapport to develop between the family carers and the relevant professionals within the interdisciplinary care team.

CONCLUSION

Every person with a life-limiting illness has a fundamental right to a palliative approach

to care. To enable this right to be met, issues regarding palliative care, specifically equity, access, affordability, and integration in care plans, need to be considered for both current and future populations. While much research has tended to focus on specialist palliative care, there is a limit to the resources available for providing specialist palliative care to all life-limiting illnesses. Hence, the authors advocate for a more realistic palliative approach to care that is more achievable from diagnosis through to bereavement, particularly for conditions like ALS for which there is no cure or effective treatment. More improvements are still needed and these can be achieved through the strategies highlighted in this review, including those that have been trialled by ALS support associations based on research evidence. However, these can only be effective if integrated in routine practice, allowing improvements in patient and family carer outcomes and aiming for seamless patient care.

The challenges cited for ALS are common to other neurodegenerative conditions that are progressive, disabling, and lacking in curative options. Therefore, implementable actions for these conditions should target recognition of the needs of patients and their families before and after bereavement; the empathetic delivery of the diagnosis; and the essential collaboration between neurology, palliative care, primary care, and rehabilitation medicine in physical and psychological symptom management and integration of care. Generic triggers and decision points for end-of-life care include a request from the patient or their family, dysphagia, cognitive decline, dyspnoea, repeated infection, weight loss, and a marked decline in condition. Throughout this journey, open communication about disease progression, effectiveness of interventions, preparation for dying, and advance care planning should be maintained.

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Behçet's Disease and Neuro-Behçet's Syndrome

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Abstract

Behçet's disease is an idiopathic chronic relapsing multisystem vascular-inflammatory disease of unknown origin, which usually presents with orogenital ulceration and uveitis and is identified as the triple-symptom complex. Primary neurological involvement in Behçet's disease is known as neuro-Behçet's syndrome (NBS). Clinical findings and neuroimaging demonstrate that there are two major forms of NBS: a central nervous system inflammatory parenchymal disease, and a less common nonparenchymal form that involves the large extraparenchymal vascular structures, mainly the venous dural sinuses. Cranial magnetic resonance imaging (MRI) typically reveals brainstem lesions with parenchymal involvement and an occluded dural sinus may be seen in the extraparenchymal type. Cerebrospinal fluid studies typically indicate inflammatory changes in the parenchyma and increased pressure with extraparenchymal involvement. Drugs used for the preventive treatment of NBS include azathioprine, cyclophosphamide, and anti-TNF agents.

INTRODUCTION

Behçet's disease (BD), originally described in 1937 by the Turkish dermatologist Hulusi Behçet[1] as a distinct disease with orogenital ulceration and uveitis known as the triple-symptom complex, is an idiopathic chronic relapsing multisystem vascular-inflammatory disease of unknown origin. The disease affects many organs and systems, causing mucocutaneous lesions, eye inflammation, musculoskeletal problems, and major vessel vasculopathy. There can also be cardiac, pulmonary, and gastrointestinal involvement alongside nervous system involvement.[2]

Due to the lack of specific laboratory, radiological, or histological findings for BD, accurate diagnosis of BD depends on clinical features. Various sets of diagnostic criteria have been published, with general agreement on the importance of mucocutaneous and ocular manifestations. The diagnostic criteria may not be met in many patients upon initial assessment because symptoms do not all appear at the same time. According to the International Study Group for Behçet's Disease classification criteria,[3] a diagnosis of BD requires recurrent oral aphthous ulcerations in combination with two of the following: genital ulcerations, skin lesions, eye lesions, or a positive pathergy test (Table 1). The International Study Group for Behçet's Disease criteria for classification of BD has a reliable diagnostic value, reaching a sensitivity of 92% and a specificity of 97%. Minor diagnostic criteria include arthritis or arthralgia, deep vein thrombosis, subcutaneous thrombophlebitis,

epididymitis, and family history, along with gastrointestinal, central nervous system (CNS), or vascular involvement.[3]

The epidemiology of BD varies geographically, with a higher prevalence along the ancient Silk Road countries, extending from the Mediterranean region to Japan. This is coupled by a similar variation in the human leukocyte antigen (HLA)-B51, which is strongly associated with the disease in high-prevalence areas.[4] The *HLA-B51* allele, which is accepted as a genetic risk factor strongly associated with BD, is seen in 50–80% of BD patients and has a prevalence of 20–25% in the general populations of Silk Road countries.[5]

The usual onset of BD is in the third or fourth decade of life; however, although rare, onset in children has also been reported.[6] While BD shows equal frequency between each sex, males have a more severe disease course.[7]

The aetiology of BD is unknown but clinical and laboratory data suggest that there is dysfunction of both the innate and adaptive immune systems, resulting in an exaggerated response to viral or bacterial insults.[8] Debate is ongoing as to whether this hyper-reactivity is an autoimmune phenomenon or, as suggested by more recent data, an autoinflammatory phenomenon.[7] The core histopathologic phenomenon in some cases is vasculitis, and a low-grade, chronic, nonspecific inflammation in others.[9]

NEURO-BEHÇET'S SYNDROME

The primary neurological involvement in BD is named neuro-Behçet's syndrome (NBS). Neurologic manifestations have been reported in 4–49% of cases; however, when large series are studied, their prevalence remains between 3% and 9% of all patients with BD.[10]

The age of onset of NBS, when excluding paediatric cases, is usually late within the third decade of life, with the mean duration between the onset of BD and NBS being approximately 5 years. NBS is almost three times more frequent in men than women, with up to 6% of patients presenting with neurological involvement without fulfilling the International Study Group for Behçet's Disease classification criteria for BD.[11]

The suggested Cerrahpaşa School of Medicine diagnostic criteria for NBS in a patient that fulfils the International Diagnostic Criteria for BD is the occurrence of neurological symptoms not otherwise explained by any other known systemic or neurological disease or treatment, and in whom objective abnormalities consistent with NBS are detected either on neurological examination and/or with neuroimaging studies, including magnetic resonance imaging (MRI) and/or abnormal cerebrospinal fluid examination.[12] In 2014, Kalra et al.[13] suggested NBS diagnostic criteria were adapted and modified by the International Neuro Behçet's Advisory Group and recommended for the diagnosis of NBS (Box 1); however, neither of these criteria have been validated. Although definite vasculitis is rarely observed, it has been considered that CNS involvement is caused by vaso-occlusive angiitis with venous predominance.[9,14]

Patients with BD may present with different neurological problems, related either directly or indirectly to the disease. Primary neurological involvement or neurological involvements directly related to BD include headache (migraine-like, non-structural), cerebral venous sinus thrombosis (CVST) (extra-axial NBS), CNS involvement (intra-axial NBS), arterial NBS, neuro-psycho-Behçet's syndrome, peripheral nervous system (PNS) involvement, and subclinical NBS. Secondary neurological involvement or neurological involvement indirectly related to BD encompass neurologic complications secondary to systemic involvement of BD (e.g., cerebral emboli from cardiac complications of BD, increased intracranial pressure secondary to superior vena cava syndrome) and neurologic complications related to BD treatments (e.g., CNS neurotoxicity with cyclosporine, peripheral neuropathy secondary to thalidomide or colchicine).[15]

Although NBS may occur with variable neurological problems, clinical findings and neuroimaging demonstrate that there are two major forms of NBS: a CNS inflammatory parenchymal disease and a less common nonparenchymal form that involves the large extraparenchymal vascular structures, mainly the venous dural sinuses. These two types of involvement very rarely occur in the same individual and it is assumed that they have a different pathogenic mechanisms.[15]

Table 1: Criteria for diagnosis of Behçet's disease.*

Finding	Definition
Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulcers observed by the physician or reliably described by the patient which recurred at least three times over a 12-month period.
Recurrent genital ulceration	Aphthous ulceration or scarring observed by the physician or reliably described by the patient.
Eye lesions	Anterior or posterior uveitis or cells in the vitreous body on slit-lamp examination, or retinal vasculitis detected by an ophthalmologist.
Skin lesions	Erythema nodosum, pseudofolliculitis, papulopustular lesions, or acneiform nodules not related to glucocorticoid treatment or adolescence.
Positive pathergy test†	Interpreted as positive by the physician at 24–48 hours.

*For a definite clinical diagnosis of Behçet's disease, the patient must have recurrent oral ulceration plus at least two of the other findings in the absence of any other clinical explanations; †The pathergy phenomenon is a nonspecific skin hypersensitivity that is almost specific for Behçet's disease. It is performed by inserting an 18-g needle into the dermis of the forearm. The reaction is considered positive if either a papule, a pustule, or an ulcer forms at the puncture site within 48 hours. Presence of erythema only is considered negative.

Box 1: International consensus recommendation criteria for neuro-Behçet's syndrome diagnosis.

Definite NBS meeting all of the following three criteria:

a) Satisfy the ISG criteria for BD;

b) Neurological syndrome (with objective neurological signs) recognised to be caused by BD and supported by relevant and characteristic abnormalities seen on either or both:

i) Neuroimaging; ii) CSF;

c) No better explanation for the neurological findings.

Probable NBS meeting one of the following two criteria in the absence of a better explanation for the neurological findings:

a) Neurological syndrome as in definite NBS, with systemic BD features but not satisfying the ISG criteria;

b) A non-characteristic neurological syndrome occurring in the context of ISG criteria-supported BD.

BD: Behçet's disease; CSF: cerebrospinal fluid; ISG: International Study Group; NBS: neuro-Behçet's syndrome.
Adapted from Kalra et al.[13]

PARENCHYMAL NEURO-BEHÇET'S SYNDROME AND INTRA-AXIAL NEURO-BEHÇET'S SYNDROME

The majority of patients (70–80%) with neurologic involvement due to BD present with parenchymal CNS involvement. This form is termed parenchymal NBS (p-NBS) or intra-axial NBS and commonly affects the brainstem-diencephalicregion.[16] p-NBS typically follows a subacute clinical course and the presentation can be headache, cranial neuropathies, dysarthria, ataxia, or hemiparesis. Cognitive-behavioural changes, emotional lability, a self-limited or progressive myelopathy with urinary sphincter dysfunction, and, to a much lesser extent, other CNS manifestations, such as extrapyramidal signs and seizures, have been reported. There are also a small number of cases that have reported cerebellar degeneration, isolated optic neuritis, or recurrent peripheral facial paresis. Optic neuritis is extremely rare in BD and most visual symptoms are due to ocular involvement.[17]

Onset of p-NBS is usually associated with flaring of systemic features of BD. Some patients may only have a single attack, with or without residual neurologic deficits, but most will have recurrences with further sequelae, and some will have secondary progression. A small number of patients may have a primary, progressive course. p-NBS is usually associated with a poor prognosis; approximately 50% of p-NBS patients are severely disabled within 10 years of being diagnosed with the disease.[12] Asymptomatic p-NBS corresponds to abnormal neurological signs in a BD patient without neurological symptoms. The detection of abnormalities on neurophysiological studies, as well as by neuroimaging in asymptomatic patients, further suggests that the subgroup of patients with subclinical CNS and PNS involvement may not be so uncommon. However, the clinical and prognostic value of detecting abnormalities in such diagnostic studies in this subgroup of patients is currently still not clear.[18]

MRI is the gold-standard neuroimaging tool for the diagnosis of NBS. Parenchymal lesions are generally located within the brainstem, occasionally extending to the diencephalon, and less often are within the periventricular and subcortical white matter. Acute or subacute lesions are hypointense to isointense on T1-weighted images, commonly heterogeneously enhanced with contrast-enhanced T1-weighted images, and hyperintense on T2-weighted and fluid-attenuated inversion recovery images (Figure 1).

Chronic lesions tend to be isointense and smaller, and it is not uncommon to see brainstem atrophy and third ventricular enlargement on follow-up MRI. In some patients with residual brainstem and subcortical lesions, images may rarely mimic multiple sclerosis. All these findings support the venous onset of the lesions.[16]

There are also a number of reports of NBS cases in which MRI images have shown mass lesions that mimicked brain tumours, some necessitating histological diagnosis.[14] The presence of brainstem atrophy, particularly in the midbrain tegmentum and pons, have also been reported and correlated with a progressive form of the disease.[19] Heterogenous enhancement with gadolinium may be seen in acute parenchymal lesions. The number of lesions detected with susceptibility-weighted imaging is larger than the conventional T2* gradient-echo.[20] Most of the lesions in p-NBS were found to be haemorrhagic, supporting the proposed venous pathology.[20]

Spinal cord involvement is not common but does exist. In reported cases, the major site of involvement was the cervical spinal cord with the myelitis-like inflammatory lesions continuing for >2 segments and extending to the brainstem in some cases.[21] The authors have observed a number of NBS patients presenting with longitudinal extensive myelitis in whom neuromyelitis optica-IgG was negative, and, recently, a distinct MRI pattern was identified which was labelled as Bagel Sign, supporting the venous pathology of BD.[22,23]

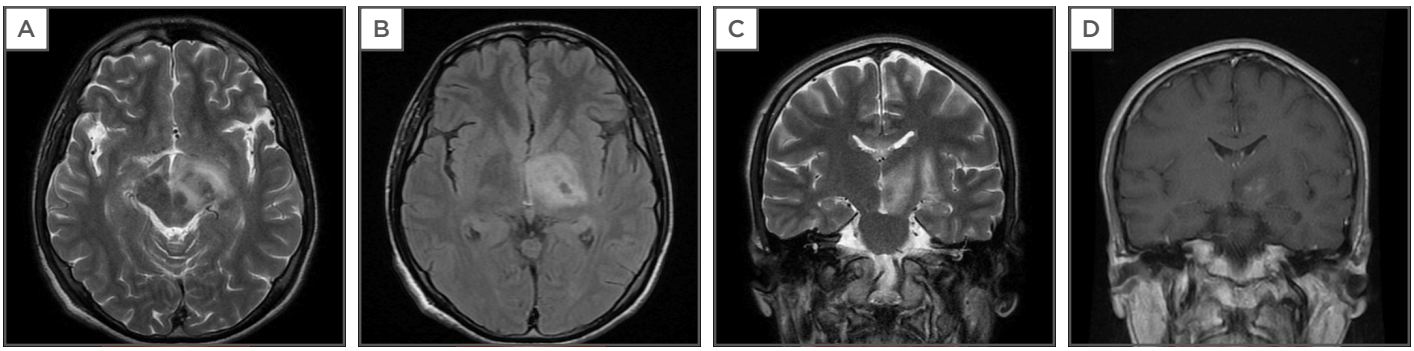

Figure 1: T1 and T2-weighted magnetic resonance imaging (MRI) of the brain.

A,B,C: Axial T2-FLAIR and coronal T2 images reveal hyperintense lesion mainly in the midbrain extending to diencephalon; D: Axial coronal T1 gadolinium sequence shows gadolinium enhancement at diencephalon.

NON-PARENCHYMAL MANIFESTATIONS OF NEURO-BEHÇET'S SYNDROME

Cerebral Venous Sinus Thrombosis (Nonparenchymal Syndrome): Extra-Axial Neuro-Behçet's Syndrome

The second most common form of neurologic involvement is cerebral venous sinus thrombosis (CVST), which may be seen in up to 12–20% of the patients with BD who have primary neurological involvement.[12] This form is also termed vascular-NBS or extra-axial NBS. Clinical manifestations resulting from thrombosis of the intracranial venous system vary according to the site and rate of venous occlusion and its extent.

Our observation is suggestive that CVST in BD evolves gradually, so that a fulminating syndrome with violent headache, convulsions, paralysis, and coma is uncommon. Papilloedema and sixth nerve paresis are the most common clinical signs reported related to intracranial increased pressure.[18]

Cranial MRI usually shows an occluded dural sinus but otherwise normal parenchymal findings. In some cases, parenchymal lesions occur secondary to CSVT. MR venography might confirm the diagnosis and the extent of the CVST. According to the involvement, the superior sagittal sinus is the most common site of thrombosis, followed by transverse sinuses, deep cerebral veins, and cavernous sinuses, respectively.[18] Venous haemorrhagic infarcts are not expected to occur constantly in people with CVST due to BD, in comparison to CVST caused by other aetiologies.

Arterial Neuro-Behçet's Syndrome

Arterial involvement resulting in CNS vascular disease is rare, consistent with the systemic arterial involvement that is also uncommon in systemic BD. Arterial involvement affects mostly large arteries located at the extracerebral sites of the craniocervical arterial tree, suggesting that an extra-axial arterial pattern of NBS may exist, as well as an intra-axial arterial NBS pattern related to intracranial arteritis and intra-axial small arterial occlusions similar to the venous involvement seen in NBS. Aneurysm formation is common in the visceral arteries in BD but extremely rare in the intracranial or extracranial arteries.[24]

PSYCHIATRIC AND COGNITIVE DISORDERS

Anxiety and depression are the most common psychosomatic symptoms in BD. However, some patients with BD develop a neurobehavioural syndrome, which consists of euphoria, loss of insight or disinhibition, indifference to their disease, psychomotor agitation or retardation, paranoid attitudes, and obsessive concerns. The authors observed the development of these psychiatric symptoms either at the onset of other neurological symptoms of NBS or independently and unrelated to the use of glucocorticosteroids or any other therapy, and subsequently named this syndrome neuro-psycho-Behçet's syndrome.[25]

HEADACHE

Headache is the most common neurologic symptom and occurs in 70% of BD patients. Headaches can result from different causes, including the nonstructural headache of BD, p-NBS, CVST, in association with ocular inflammation, and co-existing primary headaches (e.g., migraine or tension-type headache).

In a case series,[26] it was observed that paroxysmal migraine-like pain occurred with exacerbation of BD systemic features. It may be explained by a vascular headache triggered by the immunomediated disease activity in susceptible individuals and may be seen in up to 18% of BD patients. This type of headache is not specific for migraine and similar headaches have been described in some other systemic inflammatory disorders, such as systemic lupus erythematosus.[26]

PERIPHERAL NERVOUS SYSTEM INVOLVEMENT

PNS involvement with clinical manifestations is extremely rare in BD. Mononeuritis multiplex, a peripheral neuropathy prominent in the lower extremities; polyradiculoneuritis, a sensorimotor axonal neuropathy; and an axonal sensory neuropathy with recurrent episodes of myositis

have been reported. Although primary involvement of PNS is rare in BD, it should be kept in mind that polyneuropathy may occur secondary to thalidomide or colchicine treatment as a side effect.[18]

SECONDARY NEUROLOGIC INVOLVEMENT

Neurologic complications secondary to systemic involvement of BD, such as cerebral emboli from cardiac complications of BD or increased intracranial pressure secondary to superior vena cava syndrome, are indirect neurologic problems seen in BD. CNS neurotoxicity with cyclosporine and peripheral neuropathy secondary to thalidomide or colchicine use are neurologic complications related to BD treatments.[11]

DIAGNOSTIC STUDIES

Blood Tests

No laboratory tests provide a definite diagnosis of BD. Although erythrocyte sedimentation rate has been reported to be associated with BD activity, there is no defined relationship between elevated erythrocyte sedimentation rate or C-reactive protein and NBS activity. HLA testing can support the diagnosis in populations in which the disease is associated with the HLA-B51 phenotype and may help in the differential diagnosis. Despite being one of the diagnostic criteria, the pathergy test has a low sensitivity. According to the International Neuro Behçet's Advisory Group's consensus recommendations, a positive pathergy test in a patient with suspected BD and systemic BD features contributes significantly towards the diagnosis; however, a negative test does not exclude NBS.[13]

Cerebrospinal Fluid

Cerebrospinal fluid (CSF) pathology is found in 70–80% of patients with CNS involvement in NBS. If performed during the acute stage, CSF studies usually show inflammatory changes in most cases of NBS with parenchymal involvement. An increased number of cells, up to 100/mL or more, with modestly elevated protein levels are expected in most parenchymal cases. When the spinal tap is performed in the acute stage, the increased cells are likely to show a neutrophilic predominance, but this is not always the rule and a lymphocytic prominence may also be seen. In later stages, cell numbers decrease and lymphocytes are almost always the prominent cell type.[10]

Oligoclonal bands are usually absent, not exceeding 15–20%.[27] Elevated concentrations of IL-6 in the CSF of patients with both acute and chronic progressive NBS in relation to disease activity have also been reported.[28]

DIFFERENTIAL DIAGNOSIS

In countries with a high incidence of BD, all chronic recurrent uveal inflammations, especially panuveal inflammations, must be differentiated from BD. Patients should be examined and followed-up for other manifestations of this symptom complex. In patients who present with symptoms of intracranial hypertension and in whom neuroimaging reveals thrombosis in one or more of the cerebral venous sinuses, BD needs to be included in the differential diagnosis. The differential diagnosis of p-NBS contains multiple sclerosis, stroke in young adults, CNS vasculitis, neurosarcoidosis, CNS tuberculosis, brainstem glioma, high-grade astrocytoma, and primary CNS lymphoma.[29]

MANAGEMENT OF NEURO-BEHÇET'S SYNDROME

Treatment of Parenchymal Neuro-Behçet's Syndrome

There are no controlled trials for the management of vascular, gastrointestinal, and neurologic involvement of BD.[30] Treatment strategies for NBS mostly depend on the clinical experience of the neurologists involved. Treatment options include high-dose intravenous methylprednisolone pulses for 5–10 days, followed by a taper of oral prednisolone (1 mg/kg for up to 4 weeks, or until improvement is observed), and should be followed with an oral tapering dose of glucocorticoids over 2–3 months in order to prevent early relapses.[18]

After remission is induced, long-term treatment with immunosuppressive agents should be

considered in patients with parenchymal CNS involvement because this form in most patients can be followed by a relapse or secondary progressive course and may result in significant physical and cognitive deficits leading to neurologic disability.

Colchicine, azathioprine, cyclosporine, cyclophosphamide, methotrexate, chlorambucil, thalidomide, IFN-alpha, and anti-TNF agents are among the drugs used for the preventive treatment of the systemic features of BD and have also been trialled for CNS involvement.

In neurologic involvement, azathioprine has shown a tendency to improve the long-term outcome of neurologic involvement in a large uncontrolled series. Cyclosporine is an effective treatment in BD patients who have eye involvement; however, physicians should be mindful of the higher risk of developing CNS disease under cyclosporine treatment and it should be avoided in patients with established NBS.

It has been shown that in patients with NBS who had ongoing clinical relapses on single or multiple immunosuppressants, a switch to infliximab prevented further relapses and stabilised disability.[31] Seventy-four BD patients without NBS were put on infliximab for either arterial or eye involvement because of failure of other immunosuppressants, none of whom had developed NBS at the time of last follow-up.[31] The efficacy of TNF blockades for patients with severe NBS and resistance to standard immunosuppressive regimens was also shown in another recent case series.[32]

The authors' current approach in the treatment of NBS depends on the severity of the initial neurologic event, as well as the systemic manifestations of BD. Treatment is decided in consultation with the patient's treating rheumatologist. If the patient has poor prognostic factors and frequent systemic symptoms, it is usual to start infliximab in the first-line, otherwise azathioprine 2.5 mg/kg per day is started with tapering oral steroids.

Treatment of Cerebral Venous Sinus Thrombosis

Venous thrombosis of BD is usually treated with either high or medium-dose steroids because it is accepted that clot formation in veins is caused by a low-grade endothelial inflammation, rather than hypercoagulability; however, anticoagulation is the primary treatment in systemic venous thrombosis and CVST of any aetiology. In CVST this approach still remains controversial as BD patients with CVST are more likely to have systemic large vessel disease, including pulmonary and peripheral aneurysms that carry a high risk of bleeding.

Table 2: The neurologic spectrum of Behçet's disease.

Primary neurologic involvement (neurologic involvement directly related to BD)	Secondary neurologic involvement (neurologic involvement indirectly related to BD)	Coincidental: unrelated (non-BD) neurologic involvement
› Cerebral venous sinus thrombosis (extra-axial NBS). › CNS involvement (intra-axial NBS). › Arterial NBS. › Neuro-psycho-Behçet's syndrome. › Isolated headache syndrome (migraine-like, nonstructural). › Peripheral nervous system involvement. › Subclinical NBS.	› Neurologic complications secondary to systemic involvement of BD (e.g., cerebral emboli from cardiac complications of BD; increased intracranial pressure secondary to superior vena cava syndrome). › Neurologic complications related to BD treatments (e.g., CNS neurotoxicity with cyclosporine; peripheral neuropathy secondary to thalidomide or colchicine). › Somatoform neurologic symptoms associated with having a chronic disease.	› Primary headaches and any other coincidental neurologic disorders.

BD: Behçet's disease; CNS: central nervous system; NBS: neuro-Behçet's syndrome.

Adapted from Siva and Saip.[11]

The use of anticoagulation should be considered only after such possibilities have been ruled out. Recurrences of CVST, although uncommon, are possible in BD and, as these patients are also at a higher risk of developing other types of vascular involvement, long-term azathioprine is also recommended in some of these patients with CVST.[29]

PROGNOSIS

Brainstem or spinal cord involvement, frequent relapses, early disease progression, and high CSF pleocytosis are poor prognostic features for p-NBS. Initiation with severe disability, primary or secondary progressive course, fever at onset, relapse during steroid tapering, meningeal signs, and bladder involvement are sometimes associated with poor outcome. Sex-associated systemic features age at onset do not change the prognosis of NBS.[10,12] Although the neurologic outcome is better in patients with CVST, these patients may have significant mortality and morbidity due to more severe systemic vessel involvement.[29]

CONCLUSION

BD requires a multidisciplinary approach that involves rheumatology, dermatology, ophthalmology, and neurology departments. Neurologic involvement in BD is summarised in Table 2. Parenchymal NBS affects the telencephalic–diencephalic junction, brainstem, and spinal cord, and these patients present with a subacute onset of severe headache, dysarthria, ataxia, and hemiparesis. The prominent clinical feature of CVST in NBS is severe headache that usually develops over a few weeks. High-dose intravenous methylprednisolone pulses for 7–10 days, followed by gradual oral tapering over 3–6 months, is used for acute episodes. Although there is no randomised trial for the long-term treatment, azathioprine or infliximab initiation, depending on the relapse severity and accompanying BD symptoms, has been used.

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Spatial Patterns of the Tau-Immunoreactive Inclusions in Eight Different Tauopathies are Consistent with the Spread of Pathogenic Tau

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Abstract

Background: Tauopathies are a major group of neurodegenerative disorders characterised by the presence of tau-immunoreactive inclusions in the cytoplasm of neurons and glia. The spread of pathogenic tau along neuroanatomical pathways may play a significant role in the pathogenesis of neurodegenerative disorders. It is hypothesised that such a spread of tau along neuroanatomical pathways would give rise to a characteristic spatial pattern of the tau-immunoreactive neuronal cytoplasmic inclusions (NCI) in affected tissue.

Methods: The aim of this study was to investigate this hypothesis by comparing the spatial patterns of NCI in regions of the cerebral cortex in eight different tauopathies: Alzheimer's disease, argyrophilic grain disease, chronic traumatic encephalopathy, corticobasal degeneration, frontotemporal dementia with parkinsonism linked to chromosome 17, Guam parkinsonism-dementia complex, Pick's disease, and progressive supranuclear palsy.

Results: Regardless of disorder, tau isoform, or inclusion morphology, the NCI were most frequently aggregated into clusters, which were regularly distributed parallel to the pia mater. In many regions, the regularly distributed clusters of NCI range in size (400–800 µm) approximating to the dimension of cell columns associated with the cortico-cortical pathways.

Conclusion: The presence of regularly distributed clusters of NCI in the cortex of all eight tauopathies suggests an association between the pathology and the cortico-cortical pathways and is consistent with the pathogenic spread of tau along these connections. Hence, treatments designed to protect the cortex from this spread may be applicable across many tauopathies.

INTRODUCTION

The formation of inclusion bodies in the cytoplasm of neurons, also known as neuronal cytoplasmic inclusions (NCI), is a typical pathological feature of neurodegenerative disease.[1-5] In many disorders, the inclusion bodies contain the microtubule-associated tau protein and are therefore referred to as tauopathies.[2] Several disorders, both common and rare, are classified within this group, including the most common, Alzheimer's disease (AD),[6] as well as argyrophilic grain disease (AGD),[7-10] chronic traumatic encephalopathy (CTE),[11] corticobasal degeneration (CBD),[12-14] frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17),[15] Guam parkinsonism-dementia complex (GPDC),[16] Pick's disease (PiD),[17] and progressive supranuclear palsy (PSP).[18-20]

The molecular composition of pathogenic tau varies between the different tauopathies. Tau is encoded by the *tau* gene on chromosome 17, and alternative splicing of exons 2, 3, and 10 results in six possible isoforms.[21] Tau resulting from alternative splicing inclusion of exon 10 is known as 4-repeat (4R) tau, while tau lacking exon 10 is referred to as 3-repeat (3R) tau.[2] Individual tauopathies are characterised by inclusions containing differing proportions of 3R and 4R tau. Hence, NCI in PiD are characterised almost exclusively by 3R tau;[22] those in AGD, CBD, and PSP by 4R tau;[1,4,23,24] and in AD, CTE, and GPDC, the inclusions have a more complex composition containing both 3R and 4R tau in differing proportions.[16,25] FTDP-17 has a particularly complex tau pathology in which different individuals may predominantly exhibit either a 3R or 4R tau pathology and proportions of the two may vary. Different NCI morphologies are also present, the majority being either flame-shaped neurofibrillary tangles (NFT), predominantly found in AGD, AD, CBD, CTE, and FTDP-17, or globose, as present in the Pick bodies of PiD. By contrast, PSP may have both flame-shaped and globose NFT.[26] Hence, NCI is a collective term for all NCI in the tauopathies, but there are also specific names applied to specific inclusions in certain disorders such as NFT and Pick bodies.

It is believed that there are relatively few cellular pathways contributing to cell death in neurodegenerative disease[27,28] and, consequently, the tauopathies are likely to have pathological mechanisms in common. One common feature of these disorders may be the pathogenic spread of tau along neuro-anatomical pathways.[29] Recent research suggests that several pathogenic proteins, including tau, α-synuclein, amyloid β (Aβ), and the disease form of prion protein, can be secreted from cells, enter other cells, and seed small intracellular aggregates within these cells.[29,30] This raises the possibility, as first suggested by Hawkes et al.[31] with specific reference to the synucleinopathy Parkinson's disease,[31] that pathogenic agents may be propagated through the brain along neuro-anatomical pathways. If pathogenic tau spreads from cell to cell in tauopathies, then the resulting NCI would exhibit a spatial arrangement pattern in the tissue that reflects this spread.[32] Nonrandom distributions of the NCI have been observed previously in various tauopathies, which lends some support to this hypothesis.[33-35] The objective of the present study was, therefore, to compare the spatial patterns of the respective tau-immunoreactive NCI in the cerebral cortex of eight different tauopathies (AGD, AD, CBD, CTE, FTDP-17, GPDC, PiD, and PS) and to answer two questions:

1. Do the NCI exhibit similar patterns of spatial distribution across different tauopathies?
2. Could these spatial patterns be the consequence of cell-to-cell spread of pathogenic tau along neuroanatomical pathways?

MATERIALS AND METHODS

Cases

Cases of AD (n=6; mean age: 78 years; standard deviation [SD]: 9.2), CBD (n=12; mean age: 90 years; SD: 9.7), PiD (n=10; mean age: 65 years; SD: 11.3), and PSP (n=8; mean age: 73 years; SD: 7.4) were obtained from the Brain Bank, Department of Neuropathology, Institute of Psychiatry, King's College, London, UK.

AGD (n=25; mean age: 90 years; SD=9.7) and FTDP-17 (n=3; mean age: 77 years; SD: 4.7)

cases were obtained from the Departments of Neurology and Pathology and Immunology, Washington University School of Medicine, St. Louis, Missouri, USA.

CTE (n=11; mean age: 70 years; SD: 6.4) and GPDC (n=3; mean age: 77 years; SD: 0.71) cases were obtained from Boston University Chronic Traumatic Encephalopathy Center, Boston, Massachusetts, USA (VA-BU-CLF Brain Bank). Cases were diagnosed using current consensus criteria for AD,[36-39] AGD,[40] CBD,[41] CTE,[11] FTDP-17,[15] GPDC,[42] PiD,[15] and PSP.[43]

Tissue Preparation

All procedures performed in these studies were in accordance with the ethical standards of the Institute of Psychiatry, London, UK; Human Studies Committee of Washington University School of Medicine, St Louis, Missouri, USA; and the Institutional Review Board of Boston University, Boston, Massachusetts, USA, and were carried out according to the 1964 Declaration of Helsinki and later amendments. After death, the next-of-kin provided written consent for brain removal and retention for research studies. Brain tissue was preserved in buffered 10% formalin. Tissue blocks were taken from various cortical areas including the superior frontal gyrus (B8), the superior parietal lobule (B7), the inferior temporal gyrus (B22), the parahippocampal gyrus (B28), and the ambient gyrus (B27).

Brain material was fixed in 10% phosphate buffered formal-saline and embedded in paraffin wax. Immunohistochemistry was performed on 6–8 µm sections using various anti-tau antibodies (AT8, PHF-1, TP70). Sections were also counterstained with haematoxylin to reveal the various types of neuronal and glial cells and establish the tissue boundaries.

Morphometric Methods

In each region of the cerebral cortex the NCI were counted along a strip of tissue located parallel to the pia mater, using between 32 and 64, 50x250 µm sample fields arranged contiguously.[44] The sample fields were located both in the upper (approximating to layers II/III) and lower (approximating to layers V/VI) cortex. The short edge of the sample field was orientated to be parallel with the pia mater and aligned with guidelines marked on the slide. Where cortical sections exhibited severe atrophy, as in PiD and CTE, only the upper cortical laminae were studied. The number of NCI present in each sample field was counted. NCI were measured in alkyltransferase rather than the argyrophilic grains for consistency with the other tauopathies, such as the NCI of AGD (tangles and pre-tangles), which are also characteristic features of the disease.[7-10]

Data Analysis

Changes in density of inclusions along the tissue parallel to the tissue boundary were analysed using spatial pattern analysis.[45-47] This method uses the variance–mean ratio (V:M) to determine whether NCI were distributed randomly (V:M=1), regularly (V:M<1), or were clustered (V:M>1) along a strip of tissue. Counts of NCI in adjacent sample fields were then added together successively to provide data for increasing field sizes (e.g., 50x250 µm, 100x250 µm, and 200x250 µm) up to a size limited by the length of the strip sampled. V:M was then plotted against field size to determine whether the clusters of NCI were regularly or randomly distributed and to estimate the mean cluster size parallel to the tissue boundary. A V:M peak indicates the presence of regularly spaced clusters while an increase in V:M to an asymptotic level suggests the presence of randomly distributed clusters. The statistical significance of a peak was tested using t distribution.[45] Spatial patterns of inclusions in the various regions were classified into four categories: random, uniform or regular, regularly distributed clusters, and large-scale clusters without evidence of regular spacing. The frequency of regions in which regularly distributed clusters were in the size range 400–800 µm (i.e., the size of the columns of cells associated with the cortico-cortical pathways) was also determined. A more complex spatial pattern was evident in some regions in which smaller clusters of inclusions were aggregated into larger clusters and the frequency of this spatial pattern was also determined. Comparison of frequencies among disorders was made using chi-square contingency tables tests. Mean cluster size of the NCI was compared among disorders using a one-way analysis of variance (ANOVA) (STATISTICA™, Statsoft Inc., Tulsa, Oklahoma, USA)

followed by Tukey's honestly significant difference post-hoc test. In each disorder, the correlation between cluster size of the inclusions, disease duration, and disease stage was tested.[48-51]

RESULTS

Examples of the spatial patterns exhibited by NCI in various tauopathies are shown in Figure 1. In AGD, the NCI (NFT) exhibited a V:M peak at a field size of 50 µm suggesting the presence of clusters of NFT, 50 µm in diameter, regularly distributed parallel to the pia mater. The V:M ratio of the NCI (NFT) in AD increased with field size, without reaching a peak, suggesting the presence of a large cluster of NFT at least 1,600 µm in diameter. The V:M ratio of the NCI (NFT) in CTE exhibited two V:M peaks at 50 µm and 400 µm suggesting clustering at two scales in the tissue.

A summary of the frequencies of the four types of spatial patterns exhibited by NCI in the eight tauopathies is shown in Table 1. Most frequently, the NCI were clustered (mean cluster size in the range of 200–1,600 µm) and were regularly distributed parallel to the pia mater. This spatial pattern was present in all eight tauopathies but varied in frequency from 36% of CTE regions to 73% in AD. Larger-scale clustering of NCI, without evidence of regular spacing, was also present, especially in PiD and CBD. In some disorders, including AGD, CTE, and PSP, the NCI were also randomly distributed in a proportion of regions.

Chi-square contingency table tests (Table 1) suggested that there were significant differences in the frequency of the various spatial patterns among tauopathies (χ^2=100.69; 21 degrees of freedom [DF]; p<0.001), with AGD, CTE, and PSP having regions exhibiting a higher proportion of random distributions, and PiD and CBD a higher proportion of regions with large-scale-clustering.

The Chi-square contingency table tests also indicated that there were significant differences among disorders characterised by different tau isoforms (χ^2=32.04; 3 DF; p<0.01) with 3R tau PiD having the lowest proportion of random or regular and uniform distributions compared with the 4R tau disorders (AGD, CBD, PSP) (χ^2=12.81; 3 DF; p<0.01) and those characterised by both 3R and 4R tau (AD, CTE, and GPDC) (χ^2=19.88; 3 DF; p<0.001). In addition, the 3R/4R combination disorders had a higher frequency of uniform distributions compared with both PiD (3R tau) (χ^2=19.88; 3 DF; p<0.001) and 4R disorders (χ^2=12.54; 3 DF; p<0.01).

There were also differences in the spatial patterns in disorders with predominantly flame-shaped NFT (AGD, AD, PSP, and CBD) compared with PiD, which has predominantly round or oval inclusions (χ^2=25.19; 2 DF; p<0.001), and with PSP, which has both morphologies (χ^2=17.33; 6 DF; p<0.001), with regularly distributed clustering being more frequent in PiD.

The Chi-square contingency table tests also suggested there were similarities in spatial patterns in cases characterised by a genetic aetiology (FTDP-17) or associated with head trauma (CTE) (χ^2=1.40; 3 DF; p>0.05), but both differed from the remaining disorders which have a more uncertain aetiology in which regular-spaced clusters are less frequent. In a significant proportion of brain regions in all disorders, especially PiD and CBD, the regularly distributed clusters of inclusion were in the size range 400–800 µm (Table 1). A more complex spatial pattern, in which smaller clusters were aggregated into larger clusters, was also evident, with the exception of CTE and PSP.

Mean cluster size of NCI (Figure 2), averaged over cortical regions, varied among disorders (F=16.95; p<0.001). Post-hoc tests suggested that cluster sizes were greater in AD than in all the other tauopathies, cluster size was significantly larger in PiD than in the other disorders with the exception of AD, and that size was greater in CBD than in AGD, CTE, or GPDC. No statistically significant correlations were observed between cluster size of the NCI and either disease duration or disease stage in any disorder.

DISCUSSION

There are a number of limitations to this study that should be considered when interpreting the results. The first point to consider is that different tau antibodies were used for the various tauopathies; however, no differences in density, type, or morphology of NCI have been observed between the tau antibodies used.[33]

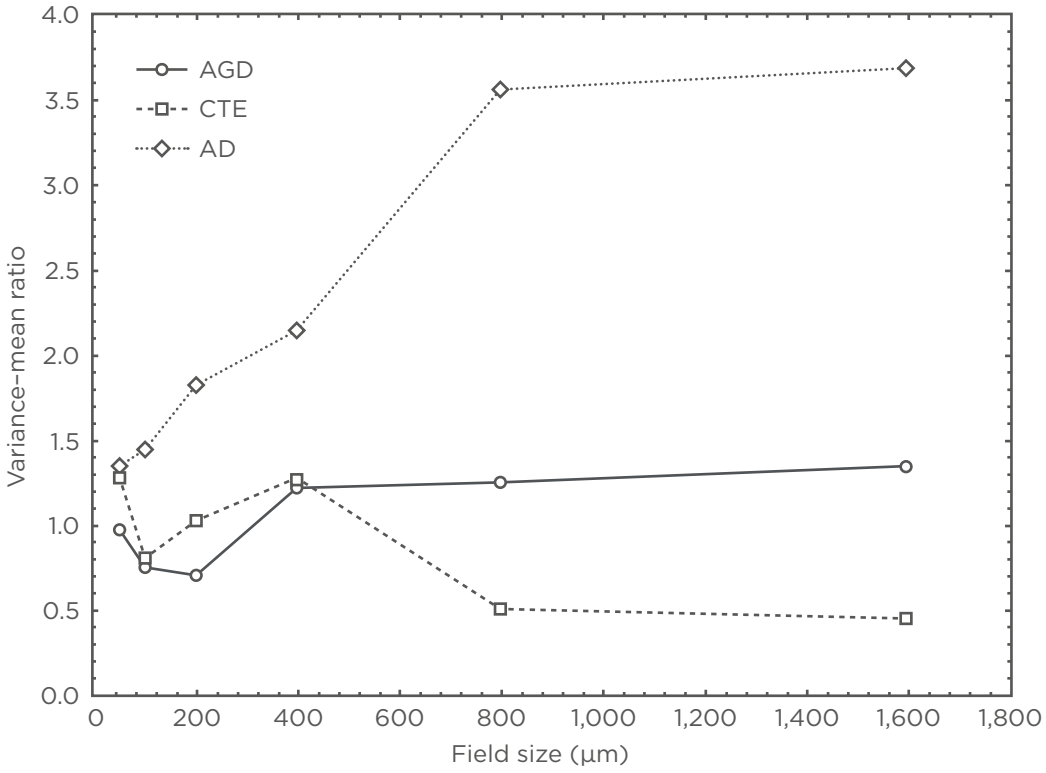

Figure 1: Pattern analysis plots showing examples of the spatial patterns exhibited by neuronal cytoplasmic inclusions in argyrophilic grain disease, chronic traumatic encephalopathy, and Alzheimer's disease.

AD: Alzheimer's disease; AGD: argyrophilic grain disease; CTE: chronic traumatic encephalopathy.

A second consideration is that different anatomical pathways are affected in the different disorders and each of the cerebral cortex regions selected for study, mainly frontal and temporal lobe regions, may not reflect the critical regions in all disorders. Thirdly, different stages of disease progression are likely to be present within the various disorders. In an attempt to address the effect of disease stage, the correlation between cluster size of inclusions and disease duration and disease stage was investigated. The data, however, provided little evidence that cluster sizes altered consistently during the disease process, which could have been due to the small number of cases studied within each disease category. Finally, rare diseases, such as FTDP-17 and GPDC, were only represented by small numbers of cases and results for these tauopathies should be regarded as provisional.

The data suggest that NCI in the eight tauopathies, regardless of disorder, tau isoforms, aetiology, or inclusion morphology, were commonly clustered in regions of the cerebral cortex and, in a significant proportion of gyri, the clusters were regularly distributed parallel to the pia mater.[34] However, the frequency of this spatial pattern varied among tauopathies, being most frequent in AD and least frequent in CTE and PSP. This spatial pattern was also present in disorders that had a prominent additional glial pathology (e.g., CBD[35] and PSP[26]) or where an additional major molecular pathology was present, such as the Aβ deposits in AD. Variations in the overall frequency of different spatial patterns were also observed, the data suggest significant differences between AD, PiD, and CBD, in which regularly distributed clusters of inclusions were common and random distributions rare compared with AGD and PSP in which random distributions were significantly more common.

A number of features of the observed spatial patterns are consistent with the development of NCI in association with the neuro-anatomical pathways of the cerebral cortex and most specifically the cortico-cortical pathways.[45,52]

In cortical regions, the cells of cortico-cortical projection origin are clustered and occur in bands that are regularly distributed along the cortex. Individual bands of cells traverse the cortical laminae and, in primate brains, vary in width in the range of 400–500 µm up to 800–1,000 µm, depending on cortical region.[53,54] Although there was considerable variation in cluster sizes among disorders, the width of the NCI clusters and their distribution along the cortex is consistent with an association with these pathways, with three exceptions. The first exception was that in some regions the NCI occurred in clusters larger than 400–1,000 µm, with some clusters being >3,200 µm in diameter, especially in AD, PiD, and CBD. In a small number of regions, clustering occurred at more than one site with smaller clusters of NCI aggregated together. The larger and more complex clusters suggest that the smaller regularly distributed clusters of inclusions could coalesce to form larger aggregations as the disease progresses, a process which appears to be a feature of AD, PiD, and CBD resulting in especially large clusters in these disorders.[45] Another exception was that NCI were randomly distributed in some gyri, especially in AGD, CTE, and PSP. Random distributions are often the result of low densities of inclusions,[34,55] which are likely to occur in the cortex in PSP, a primarily subcortical disorder.[26] In AGD, by contrast, NCI may not be the most abundant tau pathology present in these cases, which are also characterised by significant aggregations of neuropil threads and argyrophilic grains.[50,51,56]

The size and distribution of the clusters of NCI in all the tauopathies studied suggested a close relationship in the cortex between the developing pathology and neuroanatomical pathways. The most likely explanation for this association is the spread of pathogenic tau among cortical regions along the cortico-cortical connections.[29] However, differences in cluster size of the NCI were observed in different tauopathies, which suggests variation in the degree to which the cortical modules which comprise these connections were affected.

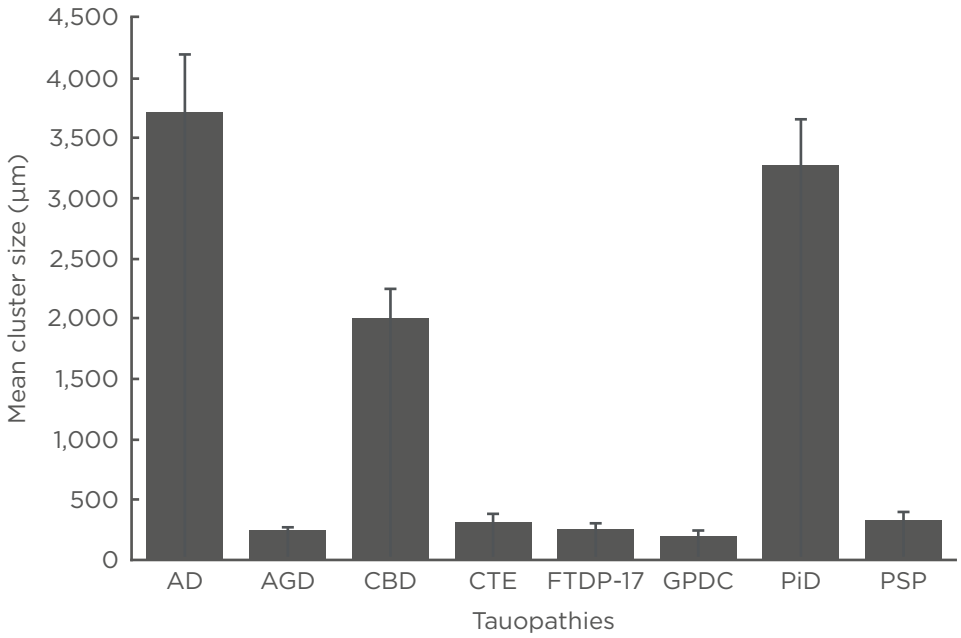

Figure 2: Mean cluster size of the neuronal cytoplasmic inclusions in the cerebral cortex of the eight tauopathies.

One-way analysis of variance (ANOVA) (with Tukey's honestly significant difference post-hoc test) analysis showed a cluster size of $F=16.95$ ($p<0.001$). Significant differences shown between groups: AD larger than all other tauopathies; PiD larger than all others except AD; and CBD larger than AGD, CTE, FTDP-17, GPDC, and PSP.

AD: Alzheimer's disease; AGD: argyrophilic grain disease; CBD: corticobasal degeneration; CTE: chronic traumatic encephalopathy; FTDP-17: frontotemporal dementia with parkinsonism linked to chromosome 17; GPDC: Guam parkinsonism-dementia complex; PiD: Pick's disease; PSP: progressive supranuclear palsy.

Table 1: Frequency of different types of spatial pattern exhibited by neuronal cytoplasmic inclusions in the upper and lower cortex in the various tauopathies.

Frequency of spatial pattern								
Disorder	NCI	N	Random	U/RG	RGC	LC	RGC (%)	RGC (400–800 µm)
AD	NFT	30	1	0	22	7	73	6
AGD	NFT	61	15	2	30	9	49	3
CBD	NCI	76	2	2	48	24	63	24
CTE	NFT	42	11	11	15	5	36	6
FTDP-17	NFT	13	3	2	5	3	38	3
GPDC	NFT	16	2	2	9	3	56	3
PiD	PB	48	1	0	27	20	53	15
PSP	NFT	23	11	0	10	2	43	2

Chi-square contingency tests comparing totals of upper and lower cortex. Comparing all taupathies: χ^2=100.69 (21DF; p<0.001); comparing 3R tauopathies with 4R tauopathies: χ^2=32.04 (6DF; p<0.001); 3R with 4R: χ^2=12.81 (3DF; p<0.01); 3R with 3R and 4R: χ^2=19.88 (3DF; p<0.001); 4R with 3R and 4R: χ^2=12.54 (3DF; p<0.01); comparing FTDP-17 and CTE with idiopathic tauopathies: χ^2=46.01 (6DF; p<0.01); FTDP-17 with CTE: χ^2=1.40 (3DF; p>0.05); FTDP-17 with idiopathic: χ^2=8.63 (3DF; p<0.05); CTE with idiopathic: χ^2=45.31 (3DF; p<0.001); Comparing different NCI morphologies: All disorders: χ^2= 36.96 (6DF; p<0.001); PiD with PSP: χ^2=25.19 (2DF; p<0.001); PSP with all other disorders: χ^2=17.33 (3DF; p<0.001); PiD with all other disorders: χ^2=15.08 (3DF; p<0.01).

AD: Alzheimer's disease; AGD: argyrophilic grain disease; CBD: corticobasal degeneration; CTE: chronic traumatic encephalopathy; DF: degrees of freedom; FTDP-17: frontotemporal dementia with parkinsonism linked to chromosome 17; GPDC: Guam parkinsonism-dementia complex; LC: large clusters; N: total number of cortical regions analysed for each disorder; NCI: neuronal cytoplasmic inclusion; NFT: neurofibrillary tangles; PB: Pick bodies; PiD: Pick's disease; PSP: progressive supranuclear palsy; RGC: regularly distributed clusters; U/RG: uniform or regular.

The largest clusters were observed in AD, PiD, and CBD, while the smallest were found in AGD, CTE, and PSP. Differences in cluster size could be attributable to:

- Difference in density of the NCI.
- Differences in the vulnerability of anatomical pathways to the spread of pathogenic tau, a more selective group of neurons being compromised in AGD, CTE, and PSP.
- Differences in the rate of spread of pathogenic tau along neuroanatomical connections.

Propagation of pathogenic tau is not the only explanation for the results as they could represent intrinsic spatio-temporal-specific neuronal vulnerability affecting clusters of neurons and that not all stages in the proposed transfer have yet been demonstrated experimentally through cellular uptake, templated seeding, secretion, and overall transfer via synaptic and non-synaptic pathways.[57]

CONCLUSION

In conclusion, neurodegenerative disorders characterised by tau-immunoreactive NCI exhibit similar spatial patterns in regions of the cerebral cortex, consistent with their association with the degeneration of specific anatomical pathways. This association could reflect cell-to-cell spread of pathogenic tau in the tauopathies consistent with a common pattern of cortical neurodegeneration across disorders. Hence, it would be useful to trace the spatial pattern of inclusions along specific anatomical pathways in various tauopathies to test this hypothesis more rigorously. In addition, the data imply that different tauopathies may be amenable to similar interventions (e.g., immunotherapy that targets extracellular pathogenic tau) that could lead to its removal, thus preventing or slowing cell-to-cell propagation.[58]

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Plasmapheresis for Neuromyelitis Optica: A Review from the Transfusion Medicine Specialist's Perspective

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Abstract

Neuromyelitis optica is characterised by severe visual impairment and neurologic dysfunction, and aggressive plasmapheresis treatment is often recommended. Medication and therapeutic interventions for acute and chronic treatment have been the subject of retrospective studies and case reports; however, the clinical improvement that follows plasmapheresis cannot be explained merely by the removal of the pathogenic antibodies. The guidelines regarding plasma volume in plasmapheresis are often not adhered to; however, treatment of lesser volume reduces complications and the cost incurred, without affecting clinical outcome. The goal of this review is to understand the biologic and clinical data supporting plasmapheresis, examine the possible role of low-volume plasma treatment, and highlight advanced apheresis techniques that may be applied as therapeutic modalities.

INTRODUCTION

Neuromyelitis optica (NMO) is an autoimmune, inflammatory, demyelinating disorder characterised by attacks within the spinal cord and optic nerve.[1] The disease is more prevalent among middle-aged women in Asian populations.[2,3] The natural history of NMO leads to a stepwise impairment without a progressive phase; however, the mortality rate has dropped dramatically since the use of immunosuppressive drugs.[4]

The purpose of this review is to understand the evidence for the effectiveness of plasmapheresis as an add-on therapy for NMO spectrum disorders (NMOSD). The technical aspects of the procedure will also be discussed from a transfusion medicine specialist's perspective and the authors will comment on the role of low-volume plasmapheresis based on their

>10-year experience at a tertiary neuroscience centre in southern India.

CLINICAL SPECTRUM

The current diagnostic criteria for NMO include optic neuritis, acute myelitis, and at least two of the following three supportive criteria: contiguous spinal cord MRI lesions extending over ≥3 vertebral segments, brain MRI not meeting diagnostic criteria for multiple sclerosis, and NMO-seropositive status.[5] Myelitis presents with paraparesis and sensory loss below the lesion, sphincter loss, dysaesthesia, and radicular pain. Optic neuritis is characterised by poor prognosis, appears in middle and older-aged women, and presents with ocular pain, visual field deficits, and positive visual phenomena.[5-7] The hypothalamus and brainstem are involved in 15% of cases. Symptoms of central nervous system (CNS) involvement include hiccups, intractable nausea, and respiratory failure. NMO can have either a monophasic or relapsing course.[8] The monophasic course is associated with younger age at disease onset, equal male and female predominance, and has a 90% 5-year survival rate; however, approximately 80% of patients with NMO have relapsing course,[3,9] which has a poor prognosis.

PATHOGENESIS

Circulating autoantibodies against aquaporin-4 (AQP4; NMO-IgG) and complement are the two main drivers of NMO pathogeny.[10] AQP4 is abundantly expressed in the CNS and is found in the spinal central grey matter, optic nerve, and hypothalamus, which can be involved in NMO.[11,12] NMO-IgG is detected in 60–80% of patients with clinically and radiologically diagnosed NMO,[13,14] and is associated with more severe and extensive disease. NMO-IgG antibodies are also involved in complement-dependent toxicity against astrocytes and regulate the expression of AQP4.[11] Altered expression of AQP4 leads to brain and spinal cord oedema by changing the water flow.[13,15]

CURRENT TREATMENT MODALITIES

The first-line treatment for NMO is high-dose intravenous methylprednisolone administered rapidly and continued for 3–5 days.[16] Steroids reduce the inflammatory cellular response by triggering apoptosis of lymphocytes; however, this is not always sufficient and NMO relapses are commonly resistant to steroids.[17] Intravenous Ig therapy can be used in acute exacerbations,[16,18] and for refractory demyelinating events and resistant cases of persistent inflammation without improvement after both steroids and plasmapheresis, escalation to cytoablative therapy is effective.[19]

Plasmapheresis is an established adjunct therapy used in severe NMO attacks according to the American Society for Apheresis (ASFA) Category 2,[8,13,17] and as a maintenance therapy (ASFA Category 3) for the prevention of NMO relapse.[8,20] As a therapeutic option, plasmapheresis is of critical importance in patients with either seropositive or seronegative NMO with acute neurological deficit affecting spinal cord function; these patients do not clinically improve with steroids alone and often have severe relapses.

PLASMAPHERESIS

Rationale for Plasmapheresis

The clinical benefit of plasmapheresis is primarily observed in monophasic acute NMO cases, and a long-term effect in relapsing NMO is less frequently achieved. By means of plasma treatment, NMO-IgG antibodies and complement are excluded from the circulating pool.[17] NMO-IgG serostatus does not affect the response rate of plasmapheresis and is not required to start treatment in a severe relapse patient.[20,21]

Studies and case series have reported significant improvement in around 44–75% of NMO patients treated with plasmapheresis,[13,17,20,22] and a 45% response rate in severe and sudden attacks.[5] Weinshenker et al.[23] considered a transition from corticosteroids to plasmapheresis in patients with myelitis. The investigators randomised NMO patients who were unresponsive to steroid therapy to active or sham plasma treatment in a double-blind study.[23] The patients experienced marked therapeutic benefit with plasmapheresis, whereas no effect was observed with sham exchange.

The pattern of demyelination is a key determinant of plasmapheresis efficiency. Keegan et al.[22] reviewed clinical data from 10 patients who received plasmapheresis and the treatment outcome was measured during the first month and monitored until late clinical outcome at 1 year. In this study, a moderate or marked improvement was reported in 60–80% of NMO patients following plasmapheresis.[14,22] Watanabe et al.[13] reported treatment in six female NMO-IgG-positive patients with 3–5 sessions of plasmapheresis. The investigators recorded significant functional improvement in two NMO-IgG-positive patients with severe myelitis and one with optic neuritis following plasmapheresis. The clinical improvement started to appear after one or two sessions and removal of the humoral factors resulted in an alleviation of the inflammatory responses and led to functional recovery.[13] In a previous study by the authors, 19 of 24 patients had clinical improvement 6 months after plasmapheresis.[14]

Favourable outcomes after plasmapheresis have also been reported in patients with severe brain attacks or posterior reversible encephalopathy syndrome.[24,25] Plasmapheresis minimises the residual impairment that follows NMO. However, judging clinical improvement is complex due to the subjective classification of mild, moderate, or marked disease instead of a quantified clinical exam;[22,26,27] therefore, the difference in expanded disability status score is taken as the main clinical outcome in various studies.[17] In two studies,[17,20] Bonnan et al. observed lower residual and mean difference in expanded disability status score in the plasmapheresis-treated group compared to the steroid-only group.

A synergistic effect of combined steroid and plasmapheresis treatment is expected due to their complementary action. Merle et al.[28] showed that plasmapheresis combined with pulsed intravenous steroids in 16 acute optic neuritis patients was more effective than pulsed intravenous steroids alone in 19 patients.[28] Wang et al.[29] reported that most patients responded to high doses of steroids in the subsequent relapses post plasmapheresis. Plasmapheresis is also useful as a rescue therapy when steroid therapy is not effective in repeat myelitic attacks.[22,29]

Timing of Plasmapheresis

Plasmapheresis efficiency depends on the timing of initiation, ranging from immediate, dramatic improvement, otherwise known as the Lazarus effect, to no effect.[30] In previous studies, the procedure has been started immediately (median: 19 days)[31] or was delayed (median: 41 days),[13,16,32] which affected residual visual acuity. In recovered patients, averaged residual visual acuity tended to be lower in patients who had delayed plasmapheresis.[17,20] Jacob et al.[33] initiated plasmapheresis 2 weeks after high-dose steroids if no recovery was seen and if deficits were severe, while Llufriu et al.[26] observed improvement in 83% of patients when plasmapheresis was given before Day 15, but improvement fell to 43% of patients after 2 months. Magaña et al.[21] found similar functional improvement in 4 days (after the third session).[21] In addition, Bonnan et al.[17] recommended early initiation (within 2 days) of plasmapheresis after clinical suspicion of acute NMO, while the authors of this review recommend plasmapheresis initiation within 1 week of an acute attack.[14,17] Patients who have preserved reflexes and receive early plasma treatment, within 20 days of an attack, have been shown to have a high likelihood of responding to plasmapheresis.[8] However, there is no evidence to support the immediate and simultaneous administration of corticosteroid therapy and plasmapheresis for NMO or other acute demyelinating relapses.[16]

Bonnan et al.[17,20] postulated a link between the staging of NMO lesion and the plasmapheresis effect on clinical and radiological outcome; a fairly good outcome was observed if plasmapheresis is performed at either Stage 1 or 2. In another study, nonresponders were enrolled late for active treatment, around Stage 3, and, due to severe, irreversible axonal injury, plasmapheresis was not found to be useful.[14,17]

Prophylactic and Maintenance Plasmapheresis

Retrospective case reviews have shown that plasmapheresis is beneficial as a chronic treatment for the prevention of NMOSD relapse;[8] for example, those who received plasma treatment had lower residual disability scores. Together with immunosuppressive

drugs, weekly plasmapheresis has been used to achieve a sustained depletion of NMO-IgG and complement, and a case series analysed the efficacy of concurrent plasmapheresis treatment in NMO relapse prevention.[34] Young age, male sex, preserved reflexes, and early initiation of treatment were associated with moderate or marked improvement.[14,16] In addition, following plasmapheresis, a sustained improvement was observed.[22] Patients with steroid-refractory optic neuritis may also benefit from weekly plasmapheresis.[9,34]

Plasmapheresis Procedure

Plasmapheresis is based on the extracorporeal blood separation technique designed to remove either plasma or its constituents from the blood's cellular elements.[35] The removal of circulating anti-AQP4 antibodies is the principal mechanism of action in NMO treatment;[10] though, the presence (or absence) of the antibody has no effect on the volume of the plasma treated.[14]

There are three different plasmapheresis methods used to treat this autoimmune disease: plasma exchange; double filtration plasmapheresis (DFPP), also known as cascade plasmapheresis; and immune adsorption (IA).[36] The process of DFPP selectively removes the antibodies and hence the substitution fluid required (albumin, fresh-frozen plasma [FFP]) is less.[37] After removal of the antibody in the intravascular space, there is rapid plasma redistribution from the extravascular space into the intravascular space, which requires repeated sessions.[38] This necessitates the combination of short-term active plasma volume treatment with long-term immunosuppression.

The therapeutic benefit of plasmapheresis cannot be attributed to the maximal removal of the antibody per session. Often, guidelines regarding volume of plasma treated per patient are not strictly adhered to, although definite clinical improvement is seen in the majority of cases. The minimum recommended plasma volume to be treated per session is equivalent to the patient's total plasma volume.[8] Both Weinshenker et al.[23] and Keegan et al.[22] recommended seven sessions of plasmapheresis, administered on alternative days for 14 days. In their study, Watanabe et al.[13] treated 2–3 L of plasma in each session; however, as per the revised 2016 ASFA guidelines, the recommended standard volume treatment in NMO is 1–1.5-times the plasma volume per session,[8,18] or 39–55 mL of plasma per kg of body weight.[39] Daily or alternate day treatment, with a duration of 10–14 days and consisting of 5–7 sessions, is recommended for cases of acute exacerbation of NMO.[8,18]

The authors of this review propose the definition of low-volume treatment as the removal of 0.6–0.8-times the plasma volume per session, or 23 mL of plasma per kg of body weight, spread over 5–7 sessions.[14] In the authors' opinion, less-than-recommended treatment of plasma is as near efficacious, if not equally so, in treating acute attacks of NMO. For example, the authors processed and treated 59% less plasma volume (22 mL/kg [0.6 plasma volume])[40] than reported by Keegan et al.[22] (55 mL/kg [1.1 plasma volume]) per session of plasmapheresis.

Complete removal of pathogenic antibodies is impossible to achieve. With the use of replacement solutions, an exchange of one plasma volume leads to the immediate clearance of the antibodies by 50–60%. Similarly, an increase in the volume exchanged by 1.4-times lowered plasma levels by 75%;[1] procedures with volumes beyond this level have shown little benefit.[17] For every extracorporeal method, coagulation variables should be closely monitored during treatment.

Plasmapheresis Technique

Plasmapheresis is carried out in either a designated suite or intensive care unit and is achieved with centrifugation devices or with permeable blood filters. The authors separate plasma by intermittent flow centrifugation, although continuous flow centrifugation has been found to be more efficacious and requires less time.[14] A plasmapheresis session is usually performed over a 2–6 hour period, depending on the patient's height, weight, haematocrit level, and other technical parameters, such as the method of separation (filtration or centrifugation, intermittent or continuous flow, single or dual venous access), volume of plasma treated, and blood flow rate.[17]

One or two peripheral or central venous accesses are mandatory. Two 16-gauge needles

are placed in both arms for peripheral access in continuous flow separation.[17] In intermittent flow separation, a single 16-gauge needle is placed. In the authors' experience, a single needle is preferred because it achieves better venous flow[14] and reduces the complications that follow double-needle venous access, and even a central venous access.[41] For patients without satisfactory peripheral access, inadequate flow rate, or high-flow plasmapheresis, a double-lumen catheter is placed in one of the major veins, either the internal jugular or femoral.[17]

Anticoagulants, specifically citrate (the authors' preferred option), heparin, or a combination of the two, are either added to the preplasma filter (in the filtration method) or infused via the outlet line (in the centrifugation method) to prevent the blood from clotting.[17] Albumin and plasma expander solutions, such as normal saline or hydroxyethyl starch, can be used as replacement solutions for plasma discarded during plasmapheresis.[42] FFP can be transfused if post-procedure coagulopathy is suspected; the authors suggest prophylactic transfusion of two units of FFP at the end of plasmapheresis session.[14]

Duration and Discontinuation of Procedures

The exact role of continued plasmapheresis during NMO attacks to ensure low impairment of the patient has not yet been addressed.[17] Most studies performed an average of five procedures for acute exacerbation, but the number of procedures ranged from 2–20.[8] In one case series, 5 out of 7 patients who received maintenance plasmapheresis (three sessions per week for 2 weeks, two per week for 2 weeks, and then once weekly for 3–5 weeks) showed varying degrees of improvement and reduction in the number of NMOSD exacerbation.[8]

Bonnan et al.[17,20] reported minor side effects in 24% of plasmapheresis-treated patients. The common reactions include hypotension, vasovagal reactions, and perioral paresthesias due to hypocalcaemia. Urticaria or allergic reactions, following plasma transfusion, and leucocytosis are uncommon, as well as complications of vascular catheters (thrombotic occlusion, pneumothorax, haemothorax, nerve injury, haemorrhage, and infection). Venous thrombosis, coagulopathy, electrolyte disturbances, and cardiac arrhythmias are very uncommon.[39] Plasmaphereses are contraindicated in cases of ongoing infectious disease, precarious haemodynamics, and active haemorrhage (heparin). Immediate side effects are related to the extracorporeal line: haemodynamic instability (hypotension or hypertension), vasovagal syndrome, perioral paresthesias, numbness or tingling due to hypocalcaemia, venous puncture hazards with excessive local bleeding, or septicaemia.[17]

Anaemia is also common but self-limiting, and thrombocytopenia is an inevitable sequela, with a >30% drop in post-procedure platelet counts. Haemostasis is affected in variable ways: first, an immediate hypocoagulation state, which rarely leads to bleeding, followed by a hypercoagulable state, which may result in venous thrombosis. Preventive anticoagulation with heparin may be required in chronic nonambulatory patients and persistently low fibrinogen levels have been described with the concomitant use of high-dose steroid infusion.[17,22]

FUTURE TREATMENT STRATEGIES

Since lesion severity depends on initial and definitive depth of the loss of AQP4 and astrocytes, future treatment strategies may be directed to AQP4 preservation[43] that may also include targeted removal of the pathogenic antibodies. DFPP and IA may be used as novel therapeutic modalities for NMOSD and other neurological illnesses when conventional plasmapheresis is otherwise indicated. Yoshida et al.[44] reported a patient who developed anaphylactic shock symptoms after FFP infusion, and DFPP led to clinical improvement without any complications. While there is no published experience of cascade plasmapheresis in the treatment of NMO, the authors believe that a reduced number of sessions would be required to achieve therapeutic benefits with cascade plasmapheresis compared to conventional plasma exchange. IA, previously described in myasthenia gravis[31] and various other neurological disorders,[45] is the most specific plasmapheresis technique. IA is especially suitable to NMO since the pathological core is anti-AQP4 IgG antibodies, which are selectively removed.[17] There has been

some experience of IA in the NMO setting.[46] The advantage of these newer techniques is removal or adsorption of the specific antibody without fluid replacement.[45]

CONCLUSION

Immunologic and clinical studies have established a definite role for plasmapheresis in the management of NMOSD. Plasmapheresis is now recommended for unusual and severe attacks of multiple sclerosis and NMO that do not improve with high-dose corticosteroid treatment in the expected timeframe.[47] Plasmapheresis-treated patients achieve a better outcome after a spinal attack, especially if treatment is given during the first attack. Together with steroids, plasmapheresis is also a major treatment for relapse, aimed at preventing cumulative disability, and is a safe, well tolerated, and efficient add-on therapy in NMO. Plasmapheresis also improves the short prognosis of NMO relapses, if given early, and is proven to be effective regardless of NMO-IgG status.[17] A European Federation of Neurological Societies (EFNS) Task Force paper underlined the importance of the positive effect of this treatment.[48]

No controlled trials of therapeutic plasmapheresis in NMO have been published. However, the authors are aware that effective trials against placebo may be difficult to perform because NMO can be an extremely debilitating disease. Studies of treatment for NMO are also made difficult by natural fluctuations in disease activity. Based on experience, plasmapheresis leads to functionally significant neurological recovery in a proportion of severely disabled patients with acute attacks of NMO in which patients do not respond to high-dose steroid therapy.

Few authors have shared these experiences, and attempts to evaluate the feasibility and safety of small (low)-volume plasmapheresis as a potential alternative low-cost treatment for patients with Guillain-Barré syndrome, especially in India, have been limited.[49,50] The authors suggest the consideration of low-volume plasmapheresis as part of the treatment of severe NMO attacks and that, considering the procedural complications seen, especially when standard volume treatment is followed, low-volume treatment could be given repeatedly, albeit less frequently, in severe relapses of NMO, extended transverse myelitis, or bilateral severe optic neuritis resistant to steroids. The authors also propose large multicentric randomised therapeutic trials to validate low plasma volume treatment compared to standard plasma volume treatment, and to determine the effectiveness based on clinical improvement and radiological assessments rather than only on absolute decrease in the antibody levels.

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