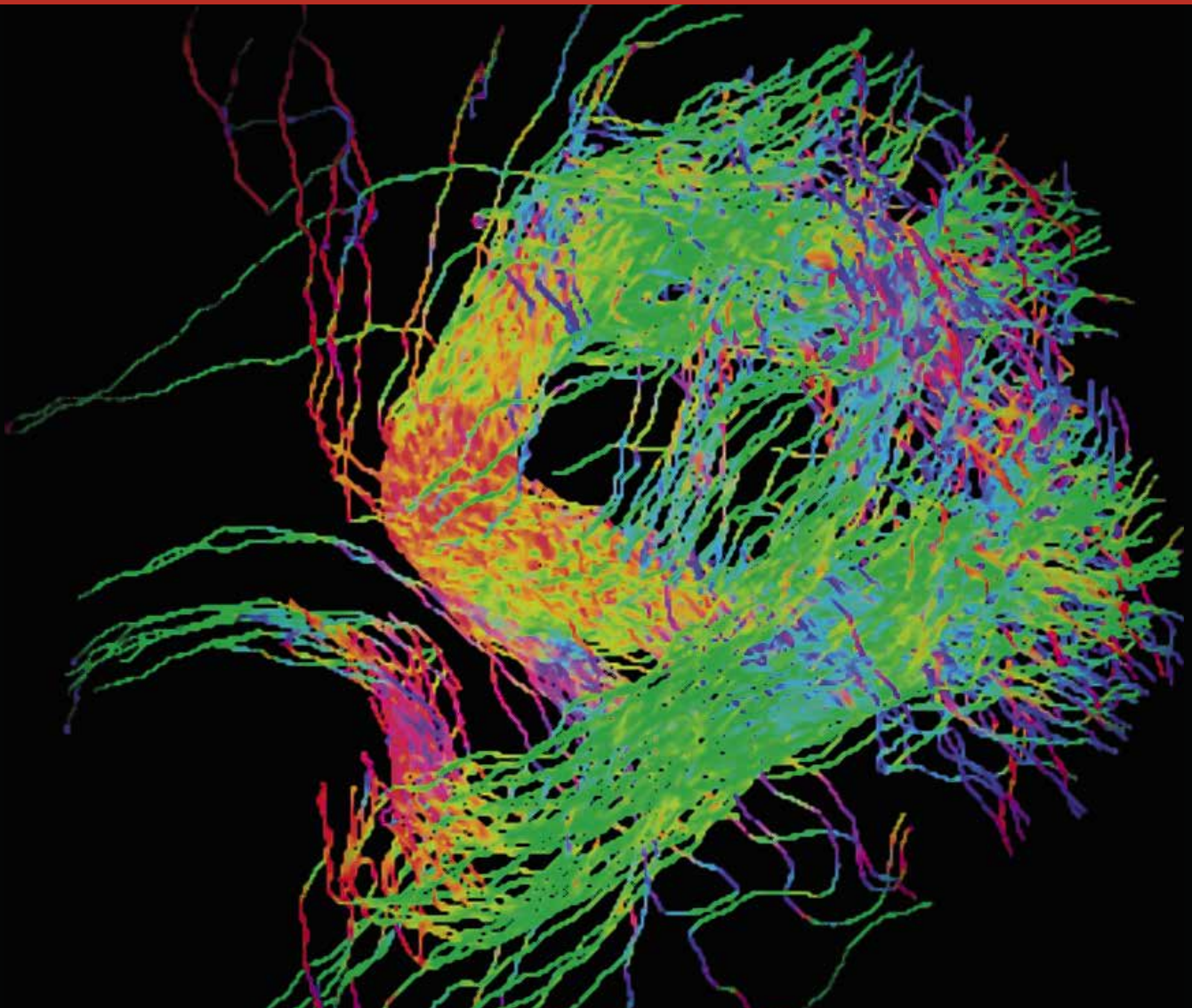


ACNR

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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION



In this issue

Gavin Giovannoni, Rhys Thomas, Stephen Halpin and Alice Jundi – Clinical Viewpoints on COVID-19

Felix Marsh-Wakefield, Scott Byrne, Simon Hawke and Georges Grau – Mass cytometry provides unprecedented insight into the role of B cells during the pathogenesis of multiple sclerosis

Ruth Dobson and Charmaine Yam – Pregnancy in multiple sclerosis

Roula Ghaoui and Merrilee Needham – Investigation of hereditary muscle disorders in the genomic era

Claire Farrington-Douglas and Alex Leff – An expert opinion in speech and language therapy

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This cover image was taken by Angelika Zarkali, our Conference News Editor. The image was entered into the ARUK 2020 Photo Competition. The image shows the connections between brain regions (or tracts) that are affected in people with Parkinson's who experience hallucinations. The colours show the direction of these connections (red: right to left, green: front to back, blue: top to bottom). The image was obtained using a technique called tractography.

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Ann Donnelly Co-Editor.

Universally, like many writers, I can only begin by expressing my deep shock at the worldwide impact of COVID-19 and also by offering deep gratitude to the healthcare responders.

Medical teams worldwide have met unprecedented challenges with bravery and flexibility, many lives have been lost, and there is no clear end in sight. Yet, there is a great focus on gathering and sharing information, and a powerful drive to find solutions.

This issue of ACNR is a reflection of what this type of thinking can achieve, with Gavin Giovannoni interrogating the relationship between COVID and immunosuppression, and Ruth Dobson, as part of the review of multiple sclerosis and Pregnancy, giving us a view on COVID in multiple sclerosis and pregnancy. Using the clinical frailty scale in patient escalation plans is imperfect, as discussed by Stephen Halpin and Alice Jundi at the University of Leeds.

Rhys Davies looks back on the first 100 days of COVID and introduces CoroNerve, (links on the ABN RaDAR page) an initiative to gather information on the neurological impact of coronavirus. This is part of an international collaborative movement to gather data. More articles will follow with a more specific neuro-rehabilitation view, online first.

Turing our gaze away, there is a description of acute ataxia in the returning traveller, a rare cause, and JMS Pearce reviews early publications on diabetic amyotrophy, which reveal the exquisite skill of a detailed description which still is accurate today. It highlights how little additional knowledge we still have, 70 years later, about this often disabling condition. What is the role of the B cell in multiple sclerosis? Felix Marsh-Wakefield et al. describe how mass cytometry helps us to define the phenotype of B cell subsets in multiple sclerosis, which can help us understand their pathological or protective roles. Roula Ghaoui and Merrilee Needham both evaluate the role of next generation sequencing in the diagnosis of hereditary muscle disorders.

Claire Farrington-Douglas and Alex Leff emphasise the principle of 'more is more' in aphasia rehabilitation as they delineate the components of their Intensive Comprehensive Aphasia Programme, with innovations such as communication partner training.

For this issue we have conference reports, and it will be interesting to see how virtual conferences can work. I give special thanks to Andrew Boardman who reviewed Spasticity: early and on-going management in an insightful and humorous way.

ACNR was established almost 20 years ago, to provide succinct articles, which aim to enrich clinical practice. Now, more than ever, this communication and propagation of good ideas is vital. We will be publishing further articles on the rehabilitation, neurology and neuroscience response to COVID, and welcome submissions from our national and international audience regarding this.

I wish you all the best of health,
Stay safe,
Ann

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Manoj Sivan, MD, FRCP, is the Editor of our Pain and Rehabilitation Section and is an Associate Clinical Professor and Honorary Consultant in Rehabilitation Medicine (RM) with University of Leeds and Leeds Teaching Hospitals and a honorary senior lecturer in the Human Pain Research Group with University of Manchester. His research interests are pain medicine, rehabilitation technology, chronic conditions and outcome measurement.



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Alastair Wilkins, PhD, is our Case Report Co-ordinator and is Reader in Neurology, University of Bristol and Consultant Neurologist at Frenchay Hospital, Bristol. His research interests are the basic science of axon degeneration and developing treatments for progressive multiple sclerosis.



Angelika Zarkali, MBBS, PGDip, MRCP, is the Editor of our Conference News section. She is a Research Fellow in the Dementia Research Centre, UCL and a Specialist Registrar in Neurology in St George's hospital. She has an interest in neurodegeneration and cognitive disorders.

ACNR Journal COVID-19 News 13/04/2020

GENERAL

Guidance on COVID-19 for people with neurological conditions, their doctors and carers [PDF] – *Association of British Neurologists (updated 09/04/20)*

The Association of British Neurologists (ABN) has released their updated COVID-19 guidance for people with neurological conditions.¹ They recommend self-isolation for people with conditions designated high-risk by NHS England. They also challenge NHS England's decision not to place people with MND in the high-risk category, as in the ABN's view, weakness of swallowing and breathing muscles in MND patients puts them at high risk from the Coronavirus. This comprehensive guide also provides useful links to other resources, including a guide to interactions between potential pharmaceutical treatments for the Coronavirus and common drugs used to treat neurological conditions and symptoms.

Coronavirus – learning for the health and care workforce – *HEE e-Learning for Health*

This Health Education England (HEE) Coronavirus training resource² is freely available to all health and social care workers in the UK. It covers essential learning areas, including infection prevention/control, Personal Protective Equipment (PPE) and specialised resources for workers in different professions and health and social care settings. There is a selection of off-site links to other more specialised learning resources at the bottom of the e-learning page.

Neurologic Symptoms and COVID-19: What's Known, What Isn't – *Medscape*

There have been preliminary, anecdotal reports of neurological symptoms in a small minority of patients with COVID-19, according to this Medscape article from 5th April.³ While most patients have a normal neurological presentation, there have been some unconfirmed reports of seizures, potential brain stem dysfunction and one presumptive case of Guillain-Barré syndrome associated with COVID-19. However, these reports ought to be treated with caution as the relationship between the virus and the nervous system is not yet known. Further study is required to elucidate any link between the symptoms and the virus.

Neurologists in Italy to colleagues in US: Look for poorly-defined neurologic conditions in patients with the Coronavirus – *NeurologyToday*

Doctors in Brescia, northern Italy, have set up a separate neuro-COVID-19 unit to treat patients with acute neurological complaints who are also fighting the Coronavirus.⁴ While no causative link has been established between the virus and the nervous system, doctors in Brescia are warning the international medical community to be alert to possible exacerbations of neurological symptoms in patients with COVID-19. The Brescian unit was established due to a high number of acute neurology patients testing positive for the Coronavirus.

PARTICIPATE IN RESEARCH

RaDAR COVID-19: Track suspected neurological complications of COVID-19 infection – ABN

The Association of British Neurologists (ABN) are asking all their members to track suspected neurological complications of COVID-19 infection.⁵ This can be done by using the form at the link in the references. This forms part of their wider RaDAR project to track short-, medium- and longer-term neurological symptoms and conditions.

NIHR: Be Part of COVID-19 Research

The National Institute for Health Research (NIHR) is pausing all new or ongoing NHS studies apart from nationally-prioritised COVID-19 studies. This site contains information for patients interested in enrolling with COVID-19 studies and research.⁶ The NIHR's general information page about their response to the Coronavirus can be found here.

MND

Coronavirus and MND: Advice from the MND Association

The MND Association has put together a webpage for FAQs about MND and COVID-19.⁷ The advice they provide is largely similar to the general Coronavirus advice from the government and NHS England, but will likely become more specialised as the virus becomes better-understood, so keep checking this page for updates.

HUNTINGTON'S DISEASE

What does COVID-19 mean for Huntington's disease families and HD research – *HDBuzz*

People with Huntington's Disease may be at higher risk from COVID-19 due to issues with their swallowing and ability to clear their lungs, says this article from HDBuzz.⁸ The article contains links to Coronavirus advice from global Huntington's Disease associations.

EPILEPSY

Epilepsia journal suspending print publication, making digital version available to all subscribers

Wiley has suspended publication of the International League Against Epilepsy's journal *Epilepsia* along with all printing and distribution of other Wiley titles.⁹ The ILAE is working with Wiley to allow subscribers to easily access the digital version, so keep an eye on their website for updates.

REHABILITATION

We need a Nightingale model for rehab after COVID-19 – *HSJ*

With the Coronavirus response currently focused on emergent patients, the writers of this article in the *HSJ* argue that we need to start thinking about a major new model for rehabilitation and discharge post-infection to improve outcomes.¹⁰ Reduced pulmonary function, physical function, quality of life and emotional well-being may turn out to be features of the post-COVID-19 patient experience, based on evidence from the SARS, MERS and H1N1 epidemics. To stop these factors from affecting long-

term health outcomes and increasing strain on healthcare resources, an effective strategy for rehabilitation needs to be formulated as early as possible.

Managing breathlessness at home during the COVID-19 outbreak—South East London Commissioning Alliance

This adapted guidance sheet for those experiencing breathlessness as a result of COVID-19 infection covers a few techniques to lessen the impact of breathing difficulties.¹¹ It also offers advice for living with breathlessness in the home.

PARKINSON'S DISEASE

Parkinson's Academy alumni provide Italy with unique way to remotely manage patients during the COVID-19 crisis – Parkinson's Academy

Parkinson's Academy has supported the ParkinsonCare initiative to bring telehealth to people with Parkinson's in Italy.¹² The service will be offered free of charge throughout Italy and hopes to alleviate patient support disruptions arising from the COVID-19 lockdown.

STROKE

Guidance on Stroke Management during COVID-19 Pandemic – American Heart Association (AHA)

Recently released guidance on stroke management during the current COVID-19 pandemic emphasises carefully managed triage, importance of appropriate personal protective equipment, and crisis resource management.¹³

MULTIPLE SCLEROSIS

Assessing and managing relapses remotely – BartsMS Blog

A major concern for people with MS is what will happen if they have a relapse during the COVID-19 lockdown. This blog post deals with the remote assessment and management of relapses and the potential impact of steroids on COVID-19.¹⁴

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Essex collaboration to focus on impact of people living with neurological conditions

Tackling the challenges faced by people living with neurological conditions is the focus of new research by the University of Essex and Healthwatch Essex. The new partnership's project is one of 53 innovative projects across the UK, to be funded by the government. The Community Research and Engagement Project (COURAGE) will focus on supporting those people living with neurological conditions and over the next few months will develop a co-designed research strategy to address needs through active engagement in research design and delivery.

To launch the six-month initiative, a collaborative workshop took place bringing together over 50 researchers, academics, practitioners, support workers and those living with brain conditions.

Project leader Dr Andrew Bateman, from the University's School of Health and Social

Care, said: "Building a research programme to tackle the challenges experienced by people living with a neurological condition is a great opportunity that can potentially involve many academics at Essex. I am really looking forward to seeing what we can achieve together to create innovative solutions."

Dr David Sollis, CEO of Healthwatch Essex, added: "Through the Essex Neurology Network, Healthwatch Essex has been promoting the understanding of neurological conditions by sharing the voices of those with lived experience. We are excited to work in partnership with the University of Essex to develop this platform and co-design the COURAGE Network's research and engagement strategy."

Nationally, the 53 projects will enable members of the public to contribute actively to research and innovation projects that affect

their lives. The projects will target communities who would not normally engage with research and innovation, so they can shape research and innovation that is relevant to their lives and their local areas.

UK Research and Innovation's Head of Public Engagement, Tom Saunders, said: "The 53 projects that we have funded represent an exciting range of ways that researchers and innovators can involve the public in their work."

"In 2020 and beyond, we will build on the lessons we learn through funding these pilot projects to help us achieve our ambition of making research and innovation responsive to the knowledge, priorities and values of society and open to participation by people from all backgrounds."

www.essex.ac.uk/hhs

Topline results of Phase 1-2 CDNF trial

Herantis Pharma Plc has announced the topline results from the ongoing Phase 1-2 clinical trial examining Herantis' proprietary neuroprotective factor and novel drug candidate, CDNF, in patients with Parkinson's disease. Herantis is developing CDNF as a disease-modifying treatment with the objective of introducing a significant breakthrough to current standard-of-care therapies for Parkinson's disease. As a novel neuroprotective and neurorestorative factor, CDNF acts on several mechanisms relevant to Parkinson's disease and has been shown to protect neurons from degeneration and to restore the function of already degenerating neurons in preclinical studies.

All patients who completed the first part of the trial volunteered to participate in the extension study in which every patient will receive one of the two dose levels of CDNF on a monthly basis. Herantis expects to announce the next set of results in Q3/2020.

"This first set of topline data provides a solid basis for the next part of the study and confirms the positive safety and tolerability profile of CDNF," commented Pekka Simula, CEO of Herantis.

"Building on the established safety profile and encouraging observations, we have initiated the planning for a Phase 2 study with a longer treatment period that will assess the efficacy of CDNF in earlier-stage, well-characterised Parkinson's patients. We currently expect to initiate patient enrolment in 2021."

Read more at <https://www.acnr.co.uk/2020/03/cdnf-trial-results/>

Licence update for BOTOX® increases involvement of MDT

Allergan has announced that the United Kingdom's Medicines and Healthcare Products Regulatory Agency has granted a licence update for BOTOX® across all of its approved indications in the UK. The product licence update makes clear that appropriately trained and qualified healthcare professionals are able to administer the product to patients, removing any barriers that may have been experienced by nurses and other therapists involved with the use of the product – ensuring easier access to treatment for these patients.

"The decision to increase the pool of healthcare professionals that can administer the product is positive, not only for the patient but also for us as healthcare practitioners. This announcement acknowledges the significant role that nurses, as part of a multidisciplinary team, play in treating chronic migraine patients, while also making it easier for patients to receive this important therapy", said Susie Lagrata, Headache and Neuromodulation Lead Nurse, The National Hospital for Neurology and Neurosurgery.

"The management and care of patients with muscle spasticity after stroke is complex, with physiotherapists playing an integral role in rehabilitation," said Dr Rhoda Allison, Consultant Stroke Physiotherapist, Torbay and South Devon NHS Foundation Trust. "Ensuring that we are included as healthcare practitioners who can administer the product will allow us to more effectively treat patients who can benefit from treatment, and improve access to treatment."

www.allergan.co.uk

First anti-CGRP preventive therapy approved by NICE

Positive Recommendation by NICE for first anti-CGRP migraine therapy: AJOVY® (fremanezumab) – Teva Pharmaceutical Europe BV announced on 12th March that the National Institute for Health and Care Excellence (NICE) has recommended AJOVY (fremanezumab) in its Final Appraisal Document (FAD) for the prevention of migraine in adults with chronic migraine. NICE recommends AJOVY® for chronic migraine patients who have not responded to at least three prior preventive drug treatments.

AJOVY® is one of several monoclonal antibodies specifically designed to target the CGRP (calcitonin gene-related peptide) pathway, a key contributor to migraine and is the first anti-CGRP preventive therapy approved by NICE. AJOVY® is a long-acting treatment that offers monthly or quarterly dosing options and can be self-injected.¹

"NICE's decision to approve the use of AJOVY® on the NHS in England and Wales for patients with chronic migraine is fantastic news," comments Dr Mark Weatherall, President of the British Association for the Study of Headache. "Anyone who looks after people with chronic migraine understands just how debilitating this neurological disorder can be. We have waited a long time for this new class of drug to be made available in the NHS, but now that we can prescribe fremanezumab, I am excited to see what a difference it will make to the lives of many of my worst affected patients."

NICE recommends AJOVY® for chronic migraine patients who have not responded to at least three prior preventive drug treatments. This decision is based on a dossier submitted to NICE for a Single Technology Appraisal (STA). Following issuance of the FAD, NICE will provide its formal guidance to the NHS in England. The full NICE recommendations and conditions can be viewed on their website.

Reference

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Fampyra® (fampridine) becomes first treatment funded by NHS Scotland to improve walking difficulties in adult patients with all types of MS

Biogen has announced that Fampyra® (fampridine) has been accepted by the Scottish Medicines Consortium (SMC) for use within NHS Scotland. The SMC has approved its use for the improvement of walking in adult patients with multiple sclerosis with walking disability (Expanded Disability Status Scale [EDSS] 4 to 7). This advice applies only in circumstances where the approved NHS Scotland Patient Access Scheme (PAS) is utilised or where the list/contract price is equivalent or lower than the PAS price.¹

Fampridine is recommended for use in all subtypes of MS, including relapsing remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and progressive relapsing MS (PRMS) that have either very limited or no treatment options, depending on disease severity.² Two out of every three patients with MS will develop a degree of disability and walking impairment.²

"Walking problems affect most people with MS and losing independence as a result of reduced mobility is one of their greatest fears," said Dr. Simon Beck, Medical Director, Biogen UK & Ireland. "Fampridine is the only treatment shown to improve walking ability in people living with MS-related walking disability, so today's SMC decision could make a real difference to those with mobility challenges in Scotland and their carers, many of whom have been funding their own treatment until now."

Fampridine received a positive funding recommendation from the All Wales Medicine Strategy Group (AWMSG) in December 2019.³ Ireland granted reimbursement of fampridine in September 2015 along with 12 other countries in Europe.

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Immunosuppression and COVID-19



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Conflict of interest statement:

None declared

Disclosures: In the last five years, Gavin Giovannoni has received compensation for serving as a consultant or speaker for or has received research support from AbbVie, Actelion, Atara Bio, Biogen, Canbex, Celgene, EMD Serono, Japanese Tobacco, Sanofi-Genzyme, Genentech, GlaxoSmithKline, GW Pharma, Merck, Novartis, Roche, Synthon BV and Teva.

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It is clear that the COVID-19 pandemic is a global health crisis with the potential to kill millions of people, particularly the elderly and people with comorbidities such as hypertension, smoking and cardiovascular and lung disease. It has also been assumed that people who are immunocompromised, for example people with multiple sclerosis (MS) on immunosuppressive disease-modifying therapies (DMTs) are also at increased risk of developing COVID-19 and severe COVID-19. But are they?

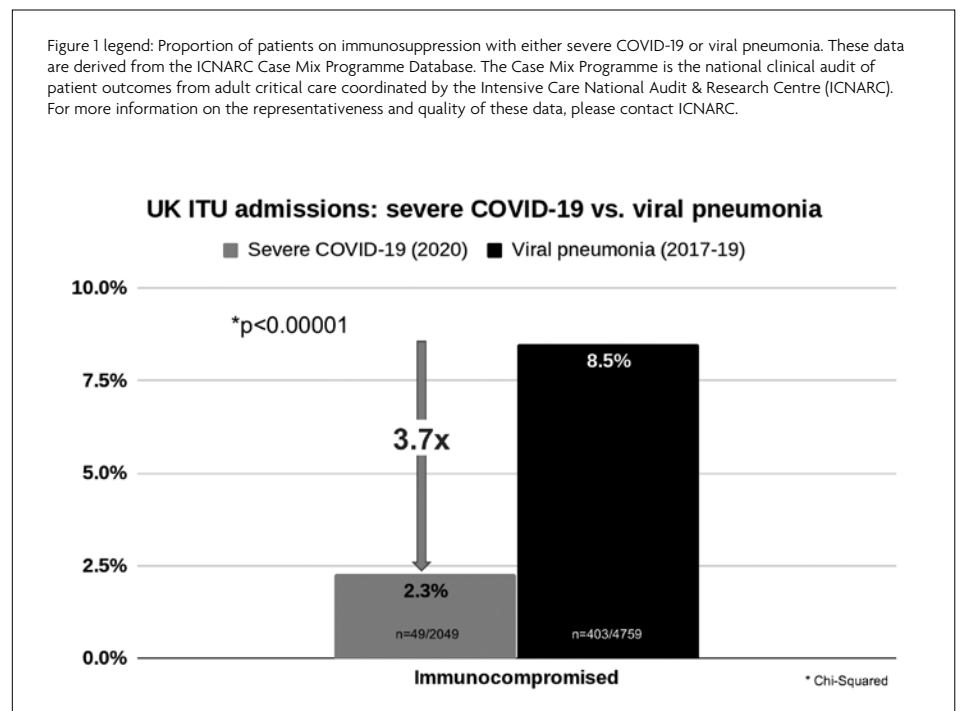
An important hypothesis being considered is that moderate immunosuppression may prevent severe complications associated with COVID-19 infection. The severe pulmonary complications of COVID-19 infection are consistent with ARDS (acute respiratory distress syndrome) caused by an over-exuberant immune response to the virus.¹ As a result, several exploratory trials are being undertaken using various immunosuppressive therapies to try and dampen the immune response to the virus. Fingolimod (ClinicalTrials.gov Identifier: NCT04280588), a S1P modulator licensed for MS, and tocilizumab (ClinicalTrials.gov Identifier: NCT04331795), an anti-IL6-receptor antagonist licensed for rheumatoid arthritis, are currently being tested as a treatment for COVID-19 associated ARDS.

New data released on the 4th April 2020 from the UK's Intensive Care National Audit & Research Centre suggests immunosuppression may protect against severe COVID.² When comparing 2249 patients admitted to ITU in

the UK with severe COVID-19 the proportion of immunocompromised patients was 3.7x lower than the proportion of immunocompromised patients admitted to ITU with viral pneumonia (the comparator) between 2017 and 2019 (2.3% vs. 8.5%, $p < 0.00001$; Figure 1).² This clearly supports the current research strategy to test if immunosuppressive therapies may improve disease outcome in patients with COVID-19.

Does this mean we can now assume that immunosuppression protects against severe COVID-19 and COVID-19-related ARDS? Not yet. The UK's ITU cohort of severe COVID-19² is almost certainly biased in that those patients who are deemed too frail and/or disabled with COVID-19 may never get to ITU, which may include a disproportionate number of immunosuppressed patients. This specific bias is unlikely to apply to ITU admissions between 2017 and 2019 (viral pneumonia cohort) when there was no such pressure on resources. Despite this caveat, this is an important bit of information that will be reassuring to people with MS on immunosuppression and their healthcare professionals.

I sincerely hope the wider MS community will reconsider their advice about not giving MS DMTs that are if anything mildly immunosuppressive to patients with active MS. By not treating our patients we may unintentionally be increasing their chances of developing severe COVID-19. Could our guidelines³ be another example of the law of unintended consequences? Let's hope



the real-world data that is currently being collected will answer this question.

Another factor to be considered is that immunosuppression may not only affect the clinical manifestation of COVID-19, but the natural history of SARS-CoV-2. A particular concern is whether or not patients on immunosuppression who are infected with SARS-CoV-2 will have increased viral replication and shedding, i.e. will they become superspreaders? I suspect yes. A recent case report of a woman with systemic lupus erythematosus (SLE) on long-term glucocorticoids and her familial cluster of COVID-19, suggest that the long-term use of glucocorticoids might cause atypical SARS-CoV-2 infections; i.e. a longer incubation period before developing COVID-19 and extra transmission of SARS-CoV-2.⁴

In light of the above the theoretical hazards posed by each DMT differ and, rather than imposing a blanket rule, decisions regarding treatment should be individualised and discussed with patients.⁵ For some patients having their active MS treated may be more important than the potential danger of being exposed to and acquiring a more severe COVID-19 infection. Any decision to start or continue an MS DMT during the COVID-19 pandemic will need to be taken carefully and will depend on the state of the COVID-19 pandemic and local circumstances.

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COVID-19 – ABN Update

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It is just over 100 days, as I write this now, since the World Health Organisation was first alerted to an outbreak of a novel respiratory virus. We are all familiar with the subsequent spread of the coronavirus, COVID-19 and the upheaval to our personal and professional lives. What has captured the headlines, inevitably so, is the number of deaths. The public health, epidemiology, and infectious disease specialists had the unenviable task of plotting national strategy based on incomplete data. Parallel to this clinicians have been desperately trying to learn about clinical course and complications of this virus, as different regions are affected at varying rates and times.

A pre-print on bioRxiv, now published in *JAMA Neurology* was the first major source of information that there were neurological features at presentation from Wuhan, China (Mao et al 2020). Some presenting features were nonspecific such as headache (13%) or dizziness (17%) however 2.8% had an acute cerebrovascular accident at presentation and 8.9% presented with peripheral nervous system symptoms – most notably impaired taste and smell. Outside of medical journals, (*Neurology Today*) there were reports from Northern Italy that neurological COVID-19 wards were opening, quoting Alessandro Pezzini as saying "... on the 18-bed unit, patients are being treated for stroke, delirium, epileptic seizures, and non-specific neurologic syndromes that look very much like encephalitis". Alessandro Padovini of Brescia noted that for some the neurological symptoms preceded the respiratory disease "... many of the patients on the neuro-COVID-19 unit initially presented with stroke, delirium, or encephalitis, and then developed respiratory distress." The most recent case series comes from the neuro-intensive care in France, who report 14% of those who are sick enough to need ICU have neurological features before intubation (Helms et al. 2020).

Severe neurological complications of COVID-19 have been reported. Haemorrhagic necrotising encephalopathy in a woman in her fifties (Poyiadji et al. 2020) and meningitis/encephalitis from Japan (with COVID-19 detected via PCR in CSF) (Moriguchi et al. 2020) are notable such cases. It is very hard to learn from anecdotes, which is why we need a national collaboration to identify the pattern and scope of these presentations; preferably rapidly.

In the UK we have set up CoroNerve, a collaborative initiative to describe the rare and severe neurological features of COVID-19. This initiative is led by Benedict Michael, Liverpool, Ian Galea, Southampton, Rhys Thomas, Newcastle, Rachel Kneen, Liverpool and Sarah Pett, UCL – with a great number of multi-disciplinary study group members. We are very fortunate to have partnered

with the ABN (Association of British Neurologists), BPNA (British Paediatric Neurological Association), BASP (British Association of Stroke Physicians), BNPA (British Neuro Psychiatry Association), and the NACCS (Neuro Anaesthesia and Critical Care Society). This is essential so that in the UK we have a coordinated response, we can rapidly compare cases that may present to different clinicians and so that there is no dual reporting of cases.

Although each of the five of us are seeing cases coming through our centres, we cannot do this alone and are really grateful for the support that we have received from the individual members of these societies to notify us of their cases. We then contact the clinicians and our admin support and clinical fellows help lessen the burden of reporting cases by helping them through the clinical reporting template. It has become clear from colleagues in the UK and overseas that we are seeing a number of unusual parainfectious features; but we also want to be well positioned to capture any post infectious consequences of COVID-19.

CoroNerve is a growing collaboration with international teams – but we can't do this without you. Thanks to all who have notified us so far! If you want to report a case, please either do so via the appropriate national society; such as RaDAR for the ABN – www.theabn.org/page/radar_7 There are two short forms that really only take a couple of minutes to complete.

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More than a number: the limitations of the Clinical Frailty Scale for patient escalation decision making in COVID-19



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Abstract

The Clinical Frailty Scale (CFS) has been suggested as a tool to aid treatment escalation decisions for frontline clinicians during the COVID-19 pandemic. We discuss the concept of frailty and role of the CFS. We explore the limitations of the CFS in people with stable long term health conditions and suggest organisations implement the new guidance with caution. Training and guidance are available to help avoid poor decisions where the CFS is not appropriate.

Clinicians are used to making decisions around admission to ICU and cardiopulmonary resuscitation (CPR) based on the likelihood of patient recovery or survival, to an outcome that is acceptable to them. On the 20th March 2020, National Institute for Health and Care Excellence (NICE) released guidance advising clinicians to use the clinical frailty scale (CFS) to guide these decisions (Figure 1 below).⁴

Frailty is a term commonly used in geriatric medicine to describe the accumulation of deficits across several physiological systems that lead to a state of increased vulnerability to adverse health outcomes and poor recovery after a stressor event, such as infection.⁵ There are a number of models of frailty and tools to measure frailty. The CFS was devised as a simple clinical measure able to predict death and institutionalisation in older people.⁶ Its use has been validated in people over 65 years and helps identify those who would most benefit from comprehensive geriatric assessment. With time it has been adopted by other specialities to help guide decision making about complex interventions such as renal replacement therapy, transcatheter aortic valve implantation and emergency laparotomy. In the ICU setting, large observational studies have shown associations between high CFS scores and increased risk of extubation

The COVID-19 pandemic that emerged from China in December 2019 has now exceeded two million cases and caused over 140,000 deaths worldwide.¹ A severe complication of the SARS-CoV-2 infection is viral pneumonia, with 2.4% of patients requiring respiratory support in an intensive care unit (ICU).² Early data from the UK suggests there is a 66% mortality associated with mechanical ventilation.³ There is an increasing focus on early decision making regarding the most appropriate level of care for individuals. This is driven by the need to achieve the best outcome for individual patients, but also may be informed by concerns over limited critical care resources.

Clinical Frailty Scale*

1 Very Fit – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 Well – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 Managing Well – People whose **medical problems are well controlled**, but are **not regularly active** beyond routine walking.

4 Vulnerable – While **not dependent** on others for daily help, often **symptoms limit activities**. A common complaint is being “slowed up”, and/or being tired during the day.

5 Mildly Frail – These people often have **more evident slowing**, and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 Moderately Frail – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 Severely Frail – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 Very Severely Frail – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9 Terminally Ill – Approaching the end of life. This category applies to people with a **life expectancy <6 months**, who are **not otherwise evidently frail**.

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging. Revised 2008.
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failure, early mortality and discharge to long term care.^{7,9}

The widespread application of CFS at the front door for assessment of patients with COVID-19 led to concerns from patients and an outcry from disability advocacy groups.^{10,11} These concerns primarily centred around the risk that clinicians may be influenced by the value that society places on disabled individuals' lives. A misapplication of the CFS in patients with stable disability may lead to snap judgments based on high social care or support needs an individual may have.

NICE amended the guideline on 25th March 2020 to include the statement: "The CFS should not be used in younger people, people with stable long-term disabilities (for example, cerebral palsy), learning disability or autism. An individualised assessment is recommended in all cases where the CFS is not appropriate."

We believe there may still be a dilemma for doctors, and risk of harm to patients. Does this brief caveat give new users of the CFS enough information to judge when its use is not appropriate? It is amply clear that the CFS is inappropriate for people with learning disabilities and autism. However, clinicians may be falsely reassured that outside of these stated examples, the CFS can be applied with confidence, even in those as young as 65 years.

Interpretation of the NICE amendment is hampered by the lack of a consistent concept of disability. Cerebral palsy is a health condition. Those who score highly on the CFS are almost certain to have disability. The CFS descriptors draw heavily on activities of daily living, and activity limitation is a key aspect of what constitutes disability, according to the International Classification of Functioning, Disability and Health (ICF) model.¹² Indeed there has been found to be a very high degree of overlap between frailty and disability (when defined as dependency in at least one basic ADL).¹³

Perhaps the emphasis should be with the word stable. However, the CFS captures only a single point in time, suggested to be two weeks prior to the acute presentation. The presence or absence of an underlying trend to increased dependency consistent with frailty will not be apparent. In short, despite the appearance of this disclaimer, invalid use of the CFS may continue. If this happens it would not only be discriminatory, it would be ineffective and would result in making the wrong decisions about best use of limited healthcare resources.

The CFS is not a direct measure of frailty, which is a physiological state. It is a series of roughly ordinal descriptions based mostly in the 'activity' domain. Its use is intuitive for clinicians as the descriptions are neatly described and are of recognisable phenotypes. Although the CFS functions well in older people as a surrogate for the likelihood of frailty, the score and the frailty are two different things. The assumption being made

when a CFS score is used to predict a health outcome is that the interaction is mediated by frailty. When applied to younger people, or those for whom measuring activity would be confounded, the assumption is not valid. Many health conditions cause limitations in activity, such as arthritis, COPD or anxiety, not necessarily via frailty. This is especially true in younger people and when the disease process is largely confined to a single body system. In someone with a previous traumatic brain injury, the link between needing assistance with finances, and chance of surviving an ICU admission may not be present at all, or may be present via another causal mechanism.

This highlights the risk of over-medicalising our decision making. Learning from the social model of disability, and recognising the significance of social determinants of health, we should accept that 'physiological vulnerability' is not the only plausible causal link between activity limitation and health outcomes. This is important because if younger disabled people experience worse outcomes from hospitalisation, this may be for reasons other than physiological frailty. These reasons need to be exposed and challenged, not made into a self-fulfilling prophecy.

We also risk losing the trust of disabled people and those with long term conditions, especially in the climate of an unprecedented pandemic. A policy for blanket administration of the CFS on admission may lead to an anchoring bias in subsequent decision making, even by clinicians aware of its limitations. This must be consciously resisted. Some people with activity limitations associated with a longstanding stable health condition may indeed be less likely to benefit from ICU admission. Ideally, this requires an individualised assessment by a clinician experienced in that particular patient group, in partnership with the individual. Availability of ideally experienced clinicians may be difficult to achieve during this pandemic. The use of a patient passport can ensure relevant information is available to all hospital clinicians to aid decision making. Effective advanced care planning reduces the need for decisions to be made in an emergency and enables the values and priorities of the individual to be incorporated fully into decision making.

As a way forward we suggest that to apply the CFS appropriately requires an understanding of its underlying premise. Geriatricians are already familiar with this, but this new guidance may see staff groups who are not well versed in frailty concepts using the CFS under pressure. The team behind the CFS have recently published a helpful one page 'top tips' guide which should be available in all clinical areas where the CFS is being used.¹⁴ The NHS Clinical Frailty Network provides training in the use of the CFS.¹⁵ Where Trusts have incorporated CFS into their local guidelines or documentation, the caveats to its use must be clearly indicated.

In conclusion, we suggest that in addition to the recent amendments to NICE guidance

on use of the CFS in making treatment escalation decisions, where there is doubt as to the applicability of the frailty concept, the CFS should not be used. There is no substitute for an individualised assessment by an experienced clinician.

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Mass cytometry provides unprecedented insight into the role of B cells during the pathogenesis of multiple sclerosis

Key take-home messages

- B cells can play a detrimental and protective role in the pathogenesis of multiple sclerosis
- Mass cytometry provides insight into the multitude of B cell subsets
- Interrogating B cell subsets will provide further insight into the pathogenesis of multiple sclerosis

Abstract

In recent years, it has become clear that B cells play a prominent role in the pathogenesis of multiple sclerosis (MS). This is most evident when considering the effectiveness of anti-CD20 monoclonal therapeutics including rituximab and ocrelizumab. In fact many successful therapeutics alter the level of switched memory B cells. It is however unlikely all switched memory B cells are detrimental in the context of MS. The ability to distinguish between various B cell subsets is hence important if we are to more specifically target detrimental from potentially beneficial B cells. Mass cytometry provides the ability to interrogate a larger number of markers in a single experiment, allowing unprecedented insight into B cell subsets and how they contribute to MS disease progression. This review highlights the importance of investigating B cells in the context of MS, and how mass cytometry provides the ability to interrogate a large number of subsets for an in-depth characterisation.

B cells can play a detrimental and protective role in the pathogenesis of multiple sclerosis

In recent years, it has become clear that B cells play a prominent role in the pathogenesis of multiple sclerosis (MS). This is most evident when considering the effectiveness of anti-CD20 monoclonal therapeutics including rituximab¹ and ocrelizumab.² The majority of successful disease-modifying therapeutics (DMTs) including monoclonal antibodies, are incapable of crossing the blood-brain barrier, cladribine^{3,4} and fingolimod⁵ being exceptions. The mechanism of action of successful therapeutics such as cladribine,⁶ anti-CD19 (inebilizumab), anti-CD52 (alemtuzumab), S1P agonist (fingolimod), anti-VLA-4 (natalizumab) and dimethyl fumarate,⁷ appears

to involve modulating the level of circulating B cells within peripheral blood. More specifically, these studies have found CD27⁺ memory B cells to be particularly affected, with efficacy correlating with large numbers of memory B cells being removed from circulation. It has therefore been proposed that memory B cells play a key role in MS pathogenesis.⁸ As part of the adaptive immune response, memory B cells provide defence against previously encountered pathogens. In people with MS, the majority of B cells found within white matter lesions are CD27⁺ memory B cells.⁹ Although the exact role of memory B cells in the context of MS is yet to be fully understood, recent work by Jelcic et al.¹⁰ found memory B cells were capable of activating brain-homing T cells that may contribute to disease pathogenesis. However, it is unlikely all circulating memory B cells contribute to disease pathogenesis, meaning that more work is needed to differentiate pathogenic from non-pathogenic subsets of memory B cells.

There is growing evidence not all B cells are detrimental in the context of MS, with some playing a protective role. These so called “regulatory B cells” or B_{Regs} are capable of suppressing an immune response and many studies have investigated B_{Regs} in experimental autoimmune encephalomyelitis (EAE), an animal model of MS. Mice deficient in IL-10-producing B cells are incapable of recovering from EAE.¹¹ While depleting B cells with anti-CD20 prior to EAE induction worsens disease, removal of B cells *after* signs of clinical disease reduces disease severity.¹² Thus, B cells are important for preventing the development of CNS-autoimmunity and limiting disease severity, but once disease has developed, different B cells subsets are pathogenic. Novel DMTs such as exposure of the skin to ultraviolet (UV) radiation which can protect mice from EAE¹³ and delay the onset of MS¹⁴, work in part by activating EAE-protecting B cells.¹⁵

In contrast to regulatory T cells, which are routinely defined by their high expression of CD25 and FoxP3 and low levels of CD127¹⁶ there is no defined phenotype that enables the reliable identification of B_{Regs}. This has led to the hypothesis that any B cell has the potential to become regulatory, and that it depends on the environment in which it finds itself as to whether the B cell exerts immune regulation.¹⁷ In fact, many subsets of B cells

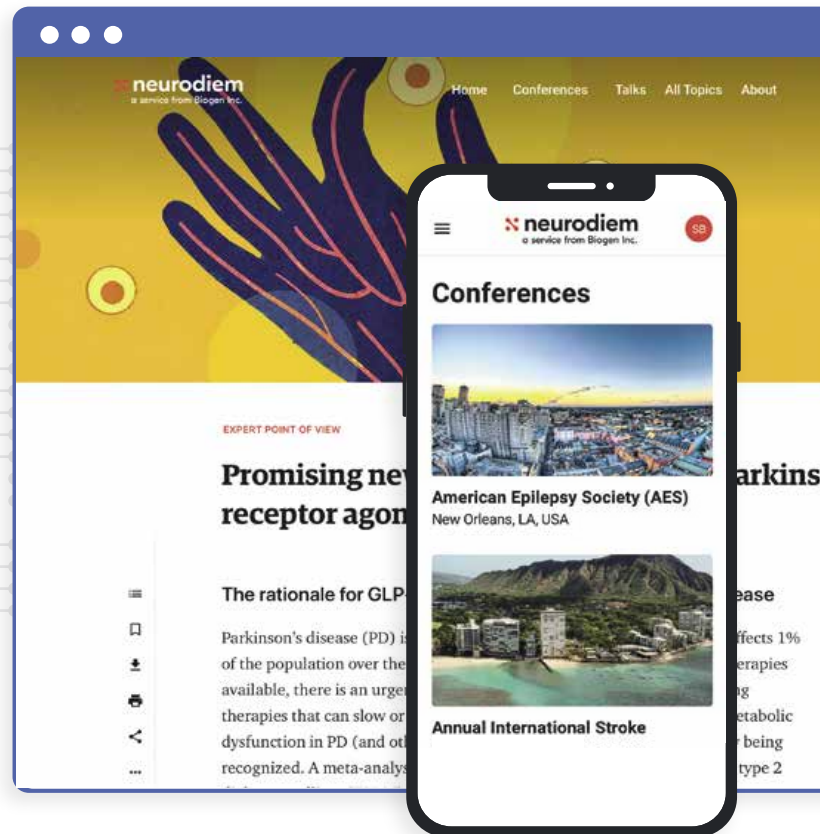
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have been found to produce immunoregulatory IL-10, including transitional B cells, naïve B cells, plasma cells, plasmablasts and even memory B cells.⁷ Furthermore, B cells can suppress the immune response in IL-10-independent mechanisms, including through TGF- β or IL-35 production, or via expression of co-inhibitory molecules such as PD-L1 or GITRL.⁷ Although IL-10 is most well-known for its suppressive capabilities, IL-10 can act as a B cell stimulant to promote immunoglobulin production.¹⁸ The success and failure of some DMTs provide clinical clues as to which B cells in MS patients are likely to be pathogenic and which are potentially protective. The success of CD20-targeting monoclonal antibodies suggest that in the context of MS, pathogenic B cells may express high levels of CD20. Alternatively, MS-protective B cells may reside in the plasma cell lineage which express low or negligible amounts of CD20 on their surface. The results from a trial of atacept (a fusion protein of immunoglobulin and TACI that blocks signals from BAFF and APRIL) showed that this DMT exacerbates disease in MS patients.¹⁹ This failure suggests that either atacept fails to deplete potentially pathogenic memory B cells,⁸ or may starve regulatory B cells of the cytokines they need to survive.

Mass cytometry provides insight into the multitude of B cell subsets

Recent advancements in flow cytometry, particularly mass cytometry, have enabled

examination of more than 40 markers in a single panel. Mass cytometry is similar to conventional fluorescence flow cytometry in that cells are stained with antibodies, but rather than antibodies being conjugated to fluorochromes they are instead conjugated to Lanthanide heavy metal isotopes.²⁰ The use of heavy metal isotopes that are not naturally found in cells, rather than fluorochromes, avoids problems of spectral overlap enabling many more markers to be investigated in a single panel. Stained cells will then be run through a flow cytometer coupled with a mass spectrometer. Following incineration, only the heavy metal isotopes remain which are then subjected to time-of-flight mass spectrometry to differentiate between the metals based on their molecular mass. Computational extrapolation to the cellular flow event allows for the identification of specific markers on (and within) individual cells.

Mass cytometry has recently been used to identify 25 subsets of regulatory T cells within the bone marrow of multiple myeloma patients,²¹ whilst Christophersen et al.²² used a tetramer to identify and phenotype T cells that recognise the gluten antigen in coeliac disease patients. It is hence possible to not only identify a range of cell subsets, but also provide unparalleled insight into the potential function of these cells. In contrast to T cells, not nearly as much work has been done to identify B cell subsets to the same extent. In fact many immunophenotyping studies simply use CD19 to identify total B cells rather than individual

subsets. Sundling et al.²³ utilised mass cytometry to identify 10 subsets of B cells within malaria patients. In our own studies, mass cytometry has identified 9 individual subsets of IgG3⁺ B cells.²⁴ In this study, we found the proportion of circulating IgG3⁺ B cells to increase as clinically-isolated syndrome patients convert to MS, whilst MS patients with active disease had a greater level compared to those with inactive MS. It is evident there are many more subsets of B cells in circulation than fairly represented in current studies, so it is important to differentiate between them at a phenotypic level to better understand their role in MS pathogenesis.

Concluding remarks

There is no longer any doubt that B cells contribute to disease pathogenesis in MS. Differentiating between detrimental and protective B cells is challenging but essential if we are to target these immune cells more specifically and effectively in the prevention and treatment of MS. Advancements in cytometry that allow for the evaluation of an increased number of parameters for a single cell provide greater power for interrogating B cell subsets. Mass cytometry allows more defined phenotyping of individual B cell subsets and revelation of their potential function. More work remains to be done, and mass cytometry will continue to provide important insight into the pathogenesis of MS, and how B cells may both contribute to and protect from such a disease.

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Pregnancy in multiple sclerosis: influence on disease trajectory

Abstract

The implications of pregnancy on multiple sclerosis (MS), and vice versa, is of great concern to female MS patients of child-bearing age. There is no evidence of worsening of MS-related long-term disability associated with pregnancy and breast-feeding, and there may even be some long-term benefits, although reverse causation remains an important confounder. Patients with more active disease have more to consider in terms of continuing disease-modifying treatment during pregnancy and immediately postpartum. Furthermore, tailored breastfeeding advice is recommended.

Multiple Sclerosis (MS) is more common in females than males, and tends to first present in early to mid-adulthood, meaning that many people with MS are women of child-bearing age. Evidence suggests that the disease itself has no negative impact on pregnancy outcomes or fertility.¹ There is, however, increasing interest in the impact of pregnancy on short and long-term disease outcomes in terms of relapse rates and disability. The mechanisms linking pregnancy and MS disease outcomes are relatively poorly understood, but likely result from a complex interplay between hormonal, immune and genetic factors. Understanding the implications of MS and its treatment on pregnancy and vice versa is an area of great concern to patients.

Pregnancy results in a reduction in MS relapse rate, followed by a transient increased risk in the immediate postpartum period. The reduction in relapse risk is most marked in the third trimester with a risk reduction of approximately 70%.² Large claims database studies have confirmed this finding; demonstrating that the risk of MS relapse declines during pregnancy (OR 0.62) and increases markedly three months postpartum to a higher level than pre-pregnancy (OR 1.71) before declining over the ensuing 12 months postpartum (OR=1.22).³ Predictors of postpartum relapses include the number of pre-pregnancy relapses indicating highly-active disease, relapse rate during pregnancy and a higher disability score at conception (Kurtzke's Expanded Disability Status Score).²

Not all MS patients experience a disease rebound postpartum; approximately 28% of women experience a relapse in the 3 months postpartum.² A greater proportion of patients show radiological evidence of active MS in the postpartum period, with new or enlarging lesions present in 14/28 of

patients on postpartum MRI and gadolinium-enhancing-lesions in 8/13 in a small case series.⁴ However, the consequence of these observed changes on longer term MS outcomes beyond the pregnancy year remains uncertain.

Several mechanisms have been proposed to explain the improved MS relapse rate in pregnancy. Oestrogen and progesterone levels increase in pregnancy, which may have both anti-inflammatory and neuroprotective effects based on animal models of experimental allergic encephalomyelitis.⁵ Oestrogen is thought to aid remyelination through mediating oestrogen receptors alpha and beta, expressed on T cells, regulatory B cells and dendritic cells through ligands in astrocytes and microglia.⁶ Progesterone is involved in axonal protection and remyelination. There is believed to be suppression of the maternal immune system in pregnancy to prevent rejection of the foetus reflected by an increased anti-inflammatory Th2 response, reduced Th1 and Th17 responses. Furthermore, there are increases in the levels of regulatory T cells, as reflected by increased FoxP3 expression; as well as increased regulatory B cells.^{7,8} In the postpartum period there are increased proinflammatory cytokines including IFN-gamma, IL-12 and TNF-alpha,⁶ which may be associated with the precipitous decline in oestrogen and progesterone levels after birth.

In the last decade, there have been an increasing number of pregnant women exposed to disease modifying therapies (DMTs) early in their pregnancy (27% in 2006 vs 62% in 2016); additionally, a significant number of DMTs have rapidly become available over this period. A study using MSBase data demonstrated that pre-conception DMT exposure appears to protect against postpartum relapses.⁹ However, managing patients who fall pregnant on newer high-efficacy treatments such as Natalizumab, which clinicians may consider using during pregnancy, particularly in the first and second trimesters, presents challenges due to pharmacodynamic considerations and the potential for rebound on cessation, particularly if no alternative DMT is commenced. The "protective effect of pregnancy" is not sufficient in at least some of these patients, who may suffer disabling relapses during pregnancy if therapy is withdrawn;¹ drug withdrawal may result in long term disability in at least some.¹⁰

Breastfeeding itself has neutral or potentially even protective effects on the risk of multiple sclerosis relapse post-partum.¹¹ Exclusive breastfeeding results in a rise in prolactin and its role in neurogenesis is controversial. Data suggests that prolactin is both neuroprotective supporting remyelination

and neurogenesis, and proinflammatory by stimulating T and B lymphocytes and macrophage cytokine release, thereby promoting the autoimmune process.¹² There have been some studies suggesting that earlier return of menses postpartum is associated with higher rates of disease relapse and lactational amenorrhoea can reduce this risk. Breastfeeding for greater than 15 months has been associated with a reduced risk of a recent diagnosis of MS/CIS compared to age matched controls (OR 0.47).¹² More recent data from population-based studies show that even breastfeeding for at least two months results in an over 60% reduction in the relapse risk in the early postpartum period, and this applies for women with more active MS prior or during pregnancy.¹²

However, population-based studies cannot fully overcome the role of individual choice as a potential confounder. The observation that breastfeeding protects against postpartum relapses is potentially confounded by the likelihood that patients with less active disease pre-pregnancy may be more likely to choose to delay restarting DMT for breastfeeding. Currently Beta-interferon and Copaxone can safely be resumed during breastfeeding; however, it takes three months following commencement of these therapies to reach peak efficacy. Corticosteroids for relapses are also safe in breastfeeding. Natalizumab, rituximab and ocrelizumab do cross into breast milk, but at low concentrations into the GI tract of the infant, resulting in very low maternal-infant transfer of these drugs.^{13,14} Despite this, and understandably, due to the limited safety data available, many women choose not to recommence DMT during lactation. As it stands currently, there is no evidence that breastfeeding negatively impacts MS disease course aside from the potential of delaying highly active DMT commencement.¹

The effect of pregnancy on modulating MS course in the long term has been a topic of intense interest. A Danish MS register study¹⁵ showed that in both men and women, parent-

hood correlates with a lower risk of MS implying it is a protective factor. In the AusImmune Study,¹⁶ higher offspring number was associated with a lower risk of a first clinical demyelinating event risk among women but not in men, although this finding is not consistent.⁸ Interestingly, one retrospective cohort showed that women with one or two pregnancies had earlier MS onset compared to nulliparous women or women with three or more children.¹⁷ MS risk may be inversely associated with parity, age at first childbirth and proximity in time since most recent birth,⁸ although reverse causality may be a cause for these observations as patients with established and more active MS may choose not to have children or to have less children, and the impact of an “MS prodrome” may change reproductive behaviour for some time prior to clinical MS development. It has been speculated that societal trends towards older maternal age and reduced offspring number may account for the increasing female incidence of MS over time.

Data from MSBase has suggested that pregnancy is independently associated with lower EDSS scores over 10 years of observation, and may be up to 4.5 times more potent than first-line DMTs (interferon- beta and glatiramer acetate).¹⁸ These findings may imply that parenthood or pregnancy itself could be protective through epigenetic changes. There is mounting evidence that environmental factors, including hormonal factors associated with pregnancy, could lead to epigenetic changes influencing DNA methylation. This may account for the cumulative effects of pregnancy process on MS disease course in the long-term. It has been found that Th17 and Treg cells in pregnant MS patients have a particular epigenetic profile (cell-type-specific regulatory regions) that is regulated by the oestrogen receptor.⁷

Current guidelines do not support routinely deferring DMT in women with MS who wish to start a family due to the risk of early myelin, white matter, neuronal and axonal damage and progressive brain atrophy from untreated

neuroinflammation, which is largely irreversible. Pre-pregnancy disease activity can aid clinicians to decide whether complete cessation of DMT or selecting either induction treatment, or highly active treatment with relative safety in pregnancy is appropriate. These decisions must always be taken in conjunction with individual patients, and with a thorough evaluation of risks and benefits associated with possible approaches. The introduction of new DMTs is rapidly changing the landscape for MS disease trajectory and needs to be taken into account in pregnancy. Some highly active DMTs, namely Natalizumab, are now deemed to be compatible with pregnancy.¹ Thus, women living with MS can be relatively assured their disease can be safely managed during pregnancy in most cases, under suitable expert advice.

What does this mean in terms of advice for patients? Breastfeeding does not increase relapse risk and in fact may be protective, but deferring DMT in a patient with highly-active disease to allow breastfeeding may be harmful. Thus, those women with relatively mild disease can, and should, be encouraged to breastfeed if they wish to do so. Women with more active MS will require individualised advice, which should be based on their desire to breastfeed along with their prior and future DMT preferences. Overall the effects of pregnancy on MS disease trajectory is not clear, but it seems that there is no large effect in the short and long-term. We can advise women that there is no evidence of worsening of MS-related long-term disability associated with pregnancy, and there may even be some long-term benefits of pregnancy over 10 years, although reverse causation remains a major confounder. As increasing numbers of registry studies report pregnancy outcomes with and without DMT exposure, and provide longer term data, our ability to help women with MS make the best decision for their individual situation can only improve.

MS, pregnancy and COVID-19 Dr Ruth Dobson

Concerns around infection with the novel Coronavirus SARS-COV-2 causing COVID-19 are particularly marked for both people with MS and pregnant women. People with MS who are also pregnant are thus likely to be doubly concerned regarding the current global pandemic. Pregnancy affects an individual's immune system, and responses to viral infections may differ in pregnant women. Much of the limited available data around COVID-19 infection and pregnancy derives from the obstetric literature, and as such, neurologists may not be familiar with the current advice.

Previous novel Coronavirus infections (SARS, MERS) were associated with increased risks of adverse outcomes including pregnancy loss and preterm birth, with case fatality rates up to 25% in pregnant women. Fortunately, this pattern has not been replicated thus far in COVID-19, and there does not appear to be more severe disease in women who are pregnant. However - the impact of critical illness during pregnancy on pregnancy-related outcomes is not insignificant, regardless of underlying aetiology. Physiological changes during pregnancy place additional strain on the cardio-pulmonary system, in addition to increasing susceptibility to infections; as such an increased risk of respiratory failure in the context of infection in pregnancy is of significant concern.

Emerging evidence suggests that vertical transmission (i.e. transmission between mother

and baby) is possible, although the proportion of pregnancies affected and the significance for the neonate has yet to be determined. To date, viral RNA (indicating active viral infection) has not been detected in amniotic fluid, vaginal secretions, or breastmilk, although there have been case reports of SARS-COV-2 IgM detected in neonatal serum at birth. IgM is a large molecule, and does not cross the placenta, meaning that this is likely to represent a neonatal immune response to in utero infection. In addition, droplet spread between mother and baby during the neonatal period is highly plausible. COVID-19 appears to be a relatively mild illness in young infants, who may be asymptomatic. However, this may not be the case in preterm or immune compromised infants, and the longer-term implications of neonatal infection with COVID-19 are currently unknown.

The number of currently pregnant women with MS is relatively small, and so clinical experience with this group is limited, but gradually increasing. Pregnant women do not appear to be more likely to contract COVID-19 than the general population. In general, women with MS who are also pregnant should be advised to follow appropriate social distancing measures and/or shielding measures depending on their immunosuppressant exposure and additional clinical co-morbidities. They should be reassured that obstetric services are continuing to operate, with appropriate efforts to minimise the risk of infection for women under their care.

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Investigation of hereditary muscle disorders in the genomic era

By Roula Ghaoui and Merrilee Needham

Full author details on page 20

Abstract

Identifying the genetic basis of inherited muscle disease is the single most important step to accurately guide patient care. A timely and accurate diagnosis is crucial for patients with neuromuscular disorders and their families. Advances in genomics are transforming the way we diagnose and treat many inherited diseases and their integration into clinical practice has reduced the diagnostic odyssey for patients with limb-girdle muscular dystrophies and myopathies. This review proposes a new, less invasive diagnostic algorithm that incorporates next generation sequencing (NGS) into neuromuscular clinics, reserving muscle biopsies for the “difficult to diagnose” patients. We discuss the importance of accurate history taking and detailed phenotyping, followed by initial screening investigations and exclusion of the common neuromuscular disorders. Once sufficient clinical and screening information has been obtained, NGS would be considered an appropriate next step, with a targeted neuromuscular panel usually favoured in view of the lower cost and less difficulties with variant data compared to whole exome and whole genome sequencing. Using this diagnostic paradigm will enable a greater number of patients to achieve an accurate and timely diagnosis, receive appropriate disease-specific treatments and gain access to informed family planning.

Introduction

Many patients with limb-girdle muscular dystrophies and inherited myopathies often remain undiagnosed or are misdiagnosed for long periods of time due to the phenotypic heterogeneity of these disorders. The traditional diagnostic pathway has relied on a stepwise process of clinical assessment and multiple investigations that are performed prior to proceeding to a muscle biopsy. Histologic and biochemical assessment of a muscle biopsy has remained the historical “gold-standard” for diagnosing the muscular dystrophies and myopathies.^{1,2} Based on the muscle biopsy findings and the clinical phenotype, Sanger sequencing of candidate genes would be subsequently performed, usually one gene at a time. A lack of clear genotype-phenotype correlation meant many genes often needed to be sequenced to identify the causative gene and pathogenic variants. Sanger sequencing a large number of individual genes is time consuming, laborious and prohibitively expensive. Moreover, often large genes such

as titin (*TTN*) with 363 exons, were not entirely Sanger sequenced routinely due to its size and complexity. Thus, only a few *TTN* mutations were reported prior to the advent of next generation sequencing (NGS).³

Using this traditional sequential pathway, the diagnostic rate for the limb-girdle muscular dystrophies remained low as reported in a review of a large Australasian limb-girdle muscular dystrophy (LGMD) cohort for whom 65% of families remained without a genetic diagnosis, despite numerous investigations at an expert neuromuscular centre.⁴

Integration of NGS technology into clinical practice for the diagnosis of Neuromuscular Disorders: Benefits and Ongoing Challenges

Implementation of NGS into clinical practice has transformed how we investigate and deliver health care to myopathy and muscular dystrophy patients. NGS, also known as massively parallel sequencing, enables high-throughput DNA sequencing of large numbers of genes simultaneously. There are three methods of DNA sequencing technologies available; Neurogenetic Subexomic Supercapture (NSES), also known as targeted neuromuscular panel, whole exome sequencing (WES) and whole genome sequencing (WGS).^{5,6}

NGS has been shown to be efficacious^{4,7,8} and also cost-effective.⁹ NGS has also facilitated the discovery of novel disease genes¹⁰ and allowed us to expand the phenotype of known disease genes.¹¹⁻¹³ In a cohort of Australasian LGMD patients that had been previously extensively investigated, the use of NSES or WES had enabled a diagnosis to be achieved in 45% of these families. Other studies have shown a similar diagnostic rate for the limb-girdle muscular dystrophies, myopathies and the congenital myopathies.^{7,14} The inclusion of family members or “trios” for WES yielded a better diagnostic rate of 60% compared to 40% diagnosis in cases where the proband was only included for WES.⁴ The inclusion of “trios” allows filtering and stratifying identified variants based on familial segregation with disease. Moreover, including family members highlights variants that might have been interpreted as unlikely candidates or simply overlooked when a large amount of data is generated with the initial bioinformatics analysis.⁴

Despite our best efforts to improve the diagnostic yield of neuromuscular patients using

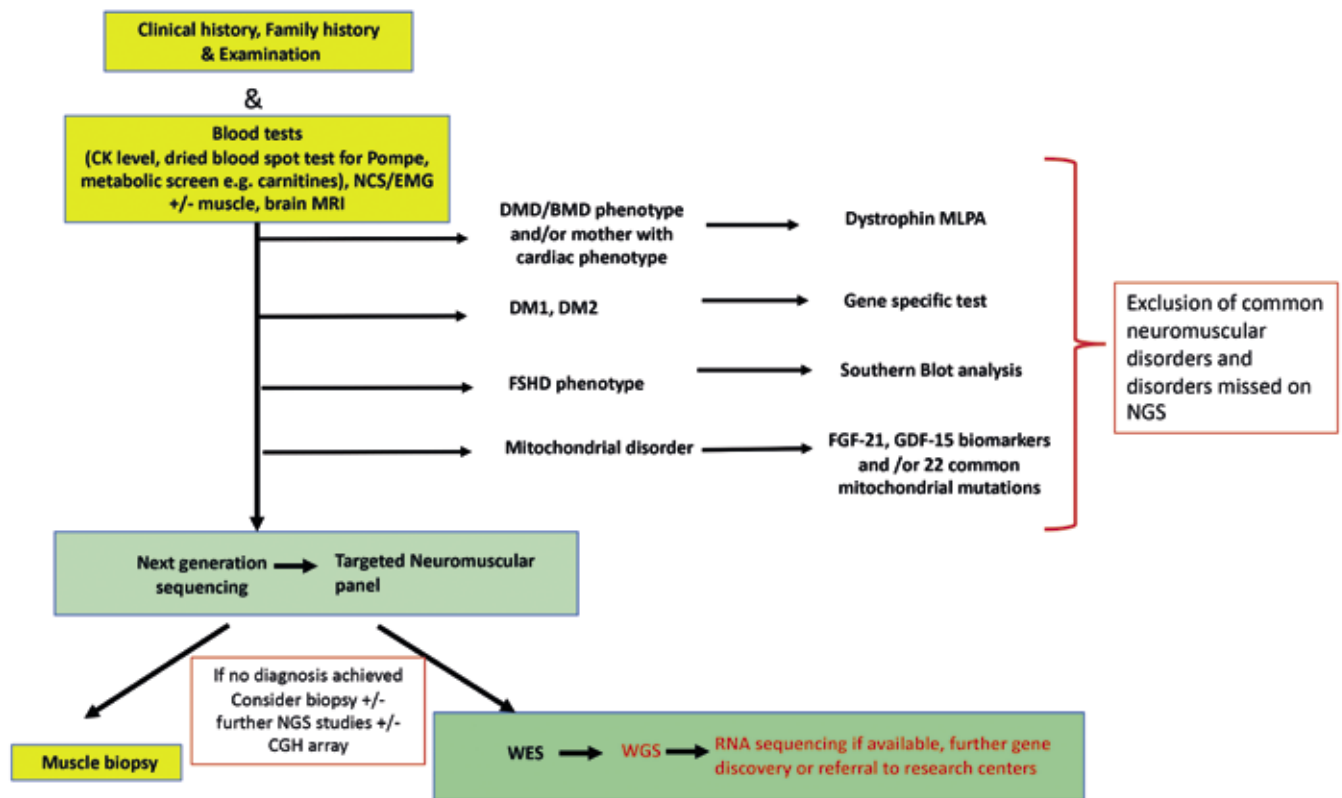


Figure 1: Proposed diagnostic algorithm for limb-girdle muscular dystrophy and myopathy. CK=creatinase kinase, NCS=nerve conduction studies, EMG= electromyography, MRI=magnetic resonance imaging, DMD=Duchenne muscular dystrophy, BMD=Becker’s muscular dystrophy, MLPA= Multiplex Ligation-dependent Probe Amplification, DM1=myotonic dystrophy type 1, DM2=myotonic dystrophy type 2, FSHD=facioscapulohumeral muscular dystrophy, FGF-21=Fibroblast growth factor 21, GDF15=growth and differentiation factor 15, WES=whole exome sequencing, WGS=whole genome sequencing, NGS=next generation sequencing, CGH=comparative genomic hybridisation microarray.

NGS technology, the diagnostic rate for the adult dystrophies and myopathies remains under 50%.⁴ This may in part be due to the large number of challenges and limitations relating to the use of NGS technology that we need to be aware of when utilising this technology.

Limitations of NGS

1. Common neuromuscular disorders are missed by NGS

Not all coding regions are well covered with NGS platforms potentially missing variants in those regions. On average 10% of the entire exome lacks the required 20x coverage or reads. This can occur in large genes with repetitive regions such as titin (*TTN*) and nebulin (*NEB*), in genomic regions with high GC-content,¹⁵⁻¹⁷ in the promoter region and the 5’ untranslated region (5’UTR) regions which are also poorly covered with targeted capture and WES.¹⁸

Standard NGS technology such as targeted panels and WES will not detect disorders that arise from repeat expansions. Detection of repeat expansions is currently performed with polymerase chain reaction–based assays¹⁹ or with Southern blots for large expansions and repetitive sequences such as the D4Z4 repeats in facioscapulohumeral muscular dystrophy (FSHD) type 1.²⁰ The most common neuromuscular disorders such as the myotonic dystrophies are also due to repeat expansions.

These genetic changes represent a potential pitfall of using NGS and may possibly account for a proportion of our undiagnosed myopathy patients, especially if clinicians are not suspecting these disorders and thus have not ordered the correct gene-specific assay.

Other complex genetic abnormalities such as structural variants (insertions/deletion) and copy number variations (CNVs) are also poorly detected by NGS.¹⁷ To detect these variants, comparative genomic hybridisation (CGH) microarrays need to be performed as an ancillary test. CGH microarray may also be performed in individuals suspected to have recessive inheritance but exome or targeted panel sequencing only found one causative mutation.^{14,21} Recently, several CNV analysis tools for NGS data have been developed and are in use for routine diagnosis.^{22,23}

2. Challenges in analysis of the variant data generated by NGS

NGS produces a large amount of variant data which requires analysis and correlation with clinical phenotype to accurately interpret their significance.^{4,7,24} Assigning pathogenicity to variants and our ability to interpret their functional and clinical impact is also a challenge.^{24,25} Moreover, proving genetic variants are pathogenic can be a long and difficult process. In particular, this applies when variants are in non-essential splice sites or missense variants not previously linked to disease. There can also be many “variants of uncertain signifi-

cance” (VUS) that are identified. Any rare variant has the potential to be pathogenic even if bioinformatics tools predict that the variant is benign. Functional studies are often critical to prioritise and follow up candidate variants. These functional studies are often done under research activities, rather than as part of standard diagnostic laboratory practices. Abnormal splicing events in disease genes, for example, deep intronic variants which create novel splice sites or activate a cryptic splice sites, are increasingly becoming recognised as an important mechanism of disease.²⁶⁻²⁸ The reliance on additional investigations such as a CGH array and RNA sequencing to detect variants missed by NGS is becoming a necessary step to increase our diagnostic rate.

3. Other disorders that may be missed with NGS; Mitochondrial and Methylation

There is also poor coverage of the mitochondrial genome through targeted capture and in standard whole-exome capture kit to either provide accurate variant data of the complete mitochondrial DNA (mtDNA) genome sequence, or reliably detect low levels of heteroplasmy.²⁹ Modified exome kits have been developed and together with WGS are likely to improve the diagnosis of mitochondrial disorders. WGS can sequence both nuclear DNA (nDNA) and mtDNA simultaneously and provides high levels of mtDNA coverage (>30, 000 reads), allowing even low

levels of heteroplasmic mtDNA mutations (<1%) to be detected and reliably quantitated.²⁹ If a clinician is suspecting a mitochondrial disorder, WGS should be considered as the preferred diagnostic test.

DNA methylation changes are also not picked up by NGS¹⁷ and further research is required to further understand whether such changes can be pathogenic and how to effectively screen for them.

A Proposed Diagnostic Pathway

A stepwise process is required for investigating patients with suspected hereditary muscle disorders taking into account the limitations of NGS technology. It remains essential for the initial patient evaluation and non-invasive investigations to be implemented as previously described.³⁰ We propose the following diagnostic paradigm to investigate patients with inherited muscle disorders (Figure 1). Our paradigm emphasises the importance of accurate history taking and accurate phenotyping. Physicians need to look for clues on examination of a patient presenting with muscle weakness to direct them towards specific disorders. These may include contractures, skin changes, pattern of muscle weakness and/or wasting and other organ involvement, (such as cardiomyopathy).

A detailed family and past medical history may provide clues about inheritance patterns, involvement of other organs, or the presence of diabetes or deafness which may point to a mitochondrial disorder. Following initial assessment, the appropriate screening investigations are recommended to be undertaken including a CK level, dried blood spot test for Pompe disease, Thyroid function tests, neurophysiology studies (nerve conduction studies [NCS] and electromyography) and lower limb muscle MRI. In particular clinical circumstances, other blood tests may be required for example to help rule out an autoimmune muscle condition, or if the history points towards a metabolic muscle disease (such as a fasting carnitine profile).

The next step is to exclude common neuromuscular disorders that are missed by NGS such as FSHD type 1, myotonic dystrophy type 1 (DM1) and type II (DM2), spinal muscular atrophy (SMA which should be clear on NCS) and Duchenne and Becker's muscular dystrophy. For suspected female Duchenne carriers or Becker's muscular dystrophy, a dystrophin MLPA would be required. In cases where a mitochondrial disorder is suspected, the clinician may consider requesting mitochondrial biomarkers on serum tests³¹ such as FGF21 or GDF15, and/or screening for the common mitochondrial disorders prior to proceeding to WGS.

Once the common neuromuscular disorders are excluded, then requesting NGS testing would be considered an appropriate next step and deferring invasive investigations such as a muscle biopsy for the "difficult to diagnose cases", and where a candidate gene has not been identified. NSES is usually favoured in

view of the lower cost to WES and WGS. Moreover with NSES, there are less variant data generated in addition to VUS's and incidental findings.³² In cases where a diagnosis is not achieved despite NSES, then referral for WES for the affected proband and preferably the parents (trio) may further aid the diagnostic process.^{4,10} A trio exome however may be costly and discussion with a local genetics service would be recommended.

Should a diagnosis remain elusive despite NSES or WES, a clinician may at this point consider liaising with a neuromuscular centre or research laboratory regarding further diagnostic or research testing. A muscle biopsy may be considered or alternatively WGS, and/or RNA sequencing (RNA-seq), which requires access to muscle tissue (as the preferred tissue).

WGS has increasingly been used where a diagnosis had not been achieved with NSES or WES. WGS has the added advantage of improved identification of disease-causing copy number and structural variations, repeat expansions, non-exonic regulatory and splicing variations and better coverage of the mitochondrial genome. Evidence for an added diagnostic benefit for WGS over WES in paediatric childhood diseases has been conflicting.^{33,35} One of the main challenges of using WGS is the vast amount of genomic data that is generated and also difficulties in variant interpretation of the genomic data. There is often difficulty in the validation of non-coding variants or coding changes that impact RNA expression.³² Previous studies have shown that RNA-seq is valuable for the interpretation of coding as well as non-coding variants, and can provide a substantial diagnosis rate in patients for whom exome or whole genome analysis has not yielded a molecular diagnosis. RNA-seq has the potential to detect structural variants such as inversions or translocations in known genes that have likely inferred pathogenicity.^{26,27,36} RNA-seq has also been shown to identify splice altering variants in both exonic and deep intronic regions that may be missed on WES and WGS thereby improving our diagnostic rate.³⁷ In two cohorts of rare, undiagnosed muscle disorders, RNA-seq analysis from muscle biopsies achieved a diagnosis in 35% and 36% of cases.^{26,36} The application of WGS combined with RNA-seq may further increase the diagnostic rate in these patients by improving our ability to interpret variants²⁶ and potentially identify new disease genes. A significant challenge with the study of RNA-seq in neuromuscular disease is its limited availability as a diagnostic test, as currently it is mainly accessible on a research basis.

Finally, it is important to note that WES, WGS and RNA sequencing are not accredited in all laboratories around Australia and liaising with the local genetics service, research labs and neuromuscular centres may offer guidance on further testing or research inclusion if available in the "difficult to diagnose case." The Australasian Neuromuscular Network (ANN) website provides information on the

neuromuscular gene tests that are available in NATA accredited laboratories in addition to other resource information for health professionals (<https://www.ann.org.au/>).

Conclusions and Recommendations

Identifying the genetic basis of muscle disorders is the single most important step to accurately guide patient care. A timely and accurate diagnosis is crucial for patients with neuromuscular disorders and their families. It enables us to provide them with better and more accurate prognostic information, as well as predict and prevent associated complications, such as heart involvement. We cannot yet cure these families or treat most inherited myopathies and dystrophies, but we can prevent the family from having further affected children as they are able to access pre-implantation genetic testing. Moreover, entry criteria for clinical trials are often dependent on the genotype being known, especially now with the emergence of gene therapies for various muscular disorders.³⁸⁻⁴¹

Implementation of NGS technologies into clinical practice has transformed the diagnostic pathway, replacing sets of multiple and invasive investigations with a simple blood test and ensuring appropriate use of genetic testing to allow earlier interventions and personalised medical management. Integration of NGS in our neuromuscular clinics has paved the way for a new, less invasive and more cost-effective diagnostic algorithm to be incorporated into neuromuscular clinics worldwide. NGS has enabled a greater number of patients to achieve accurate and timely diagnosis, receive appropriate disease-specific treatments and gain access to informed family planning.

Ongoing improvements in sequencing coverage of DNA and RNA sequencing are likely to further improve the diagnostic yield for our patients and also identify new disease genes. This, in turn, can lead to insights into disease pathogenesis and the potential for identification of new targets for future therapies, which can have a lasting impact on the quality of life and improving morbidity and mortality of patients.

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Photograph by Josh Wells

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An expert opinion in speech and language therapy: The Queen Square Intensive Comprehensive Aphasia Programme

Abstract

Less is more, right? Wrong: more is more. Here we make the case that the total dose of speech and language therapy (SLT) is a key factor in improving persons with aphasia's (PWA) outcomes. The challenge is: how can we deliver high-dose therapy when resources are stretched? We review the recent evidence for dose and timing of SLT and then describe one solution to the problem of dose that we are trialing at Queen Square, an Intensive Comprehensive Aphasia Programme (ICAP).

Timing and dose

The evidence base for the clinical effectiveness of speech and language therapy continues to build with the latest Cochrane review (using data from 3002 participants) making it clear that, "SLT results in clinically and statistically significant benefits to patients' functional communication."¹ Cochrane reviews were not developed to evaluate complex interventions like SLT and more sophisticated meta-analyses are underway² but even in the crude Cochrane analysis, dose emerges as a powerful effect.³

Animal models of post-stroke neuroplasticity suggest that we should be going hard and early with practice-based neurological rehabilitation.⁴ There is no doubt that PWA's recovery curves are at their steepest in the first few weeks and months after stroke, but does that mean that this is the best time to intervene? The Very Early Rehabilitation for SpEech (VERSE) study is completed, a pre-print is available, but still awaiting full peer-review publication.⁵ This large, meticulously carried-out, multicentre trial randomised 246 aphasic patients to one of three groups (usual care [averaged 9.5 hours of therapy], usual care Plus [21.0 hours] and VERSE [22.4 hours]) and began SLT within two weeks of their stroke. The primary outcome was a change in the WAB-R(AQ) at 12 weeks. The main finding was that, on average, aphasic patients improved a lot on their WAB score from baseline to 12 weeks getting better by ~50% of their maximal potential recovery (the gap between baseline and ceiling score that is recovered). However, there were no significant differences between the three treatment groups, meaning that 11

hours of extra therapy in the acute phase makes little difference to medium term outcomes. The authors speculate that their trial, along with a similarly negative RATS-3 trial⁶ "...provide compelling evidence to challenge the 'more is better' mindset in early stroke and language recovery." While it is theoretically possible that there is a ceiling to what therapy can achieve in the acute phase, these sorts of conclusions cannot be made from null results, especially when the therapy dose is so small. Is it reasonable to expect clinically meaningful differences in language outcomes in patients with moderately severe aphasia based on a dose difference of only 11 hours? The landmark meta-analysis by Bhogal et al. reported that almost 100 hours of SLT were required to achieve clinically meaningful changes in communication, with negative studies weighing-in at ~40 hours.⁷ While it is heroic to carry out interventional studies in acute stroke patients, sacrificing dose to expediency leads to damagingly underdosed studies, like the ACT NoW study where patients in the intervention arm averaged only nine hours.⁸ Negative results from studies like these are frequently misinterpreted.⁹

The evidence is clearer in the chronic phase, perhaps because researchers are not battling such a radically changing baseline. Breitenstein et al. carried out a partial cross-over RCT where the intervention group received an average of 31 hours of direct therapy together with 15 hours of home (predominantly computer based) treatment over three weeks compared to 4.5 hours in the control group leading to a statistically significant improvement in language function.¹⁰ Importantly, a subgroup of patients who got at least five weeks of intensive SLT improved proportionately more, suggesting that clinically useful gains can be made when the dose is upped.

How to up the dose then? One way is to use computer-based therapies so that patients can practice in their own time. Palmer et al. did this using StepByStep software, an impairment-based therapy aimed at improving naming. Patients practiced for an average of 28 hours over six months. Comparing it to two control groups, they found a large effect on trained words (16% improvement over six months of variable practice, sustained at 12 months) which equates to a 30% improvement using the maximal potential recovery

metric.¹¹ As is often the case with these types of intervention, therapy effects were only seen on trained items which is why it was especially good to see that these had been personalised by the patients.¹²

Another approach to achieving a high-dose is to use traditional SLT but deliver it in a large dose over a short time period to those who can tolerate it, so-called Intensive Comprehensive Aphasia Programmes.¹³ We have started just such a service at Queen Square with two years' funding from The National Brain Appeal (<https://www.nationalbrainappeal.org/what-we-do/current-appeals/aphasia/>) and have been treating groups of four PWA for ~6 hours a day over 15 consecutive weekdays, to get close to the 'magic' 100 hours. The programme is embedded in a normal clinical environment (NHS), but is staffed with charity funding. The cause of aphasia is predominantly, but not exclusively, stroke. The average time since stroke/brain injury is 39 months (IQR 16:54). Outcome measures are recorded at four time points: baseline, post three-week intervention, three months, six months and 12 months. These include standardised measures of: impairment (Comprehensive Aphasia Test); function (Communicative Effectiveness Index); quality of life and mood (both patient and carer reported outcomes); and we are also collecting participant-specific, goal-based outcomes, including, where appropriate, an economic goal using the Goal Attainment Scale. Preliminary results are very promising and we will be presenting these at the upcoming European Stroke Organisation conference in November 2020: <https://eso-stroke.org/events/eso-wso-conference-2020>. We will now discuss some of the key components that make up our ICAP.

Content

Evidence-based aphasia therapy across the pathway aims to address all aspects of the international classification of functioning, disability and health (ICF) framework. Underpinning our ICAP is the rationale that addressing all aspects of the ICF simultaneously yields the best outcomes.¹³ The dose and intensity of the different types of intervention are driven by the goals negotiated between the PWA and the SLT at the start of the programme. Due to space limitations, we can only offer a brief overview of the key components here.

Brain injury education: People with aphasia and their friends and family benefit from understanding their aphasia and any other communication and cognitive changes. This is the first step to setting meaningful goals, self-management of their communication disorder and adjustment to living with aphasia. SLTs provide this at every stage across the pathway, but people living with aphasia for many years need the opportunity to develop their continual understanding of

aphasia.¹⁴ We deliver this in both 1:1 and group formats, as PWA find the sharing of their aphasia stories and questions about what has happened to them to be particularly helpful.

Meaningful goalsetting: Spending time negotiating meaningful stretching but motivating goals is an essential component of acute, inpatient specialist rehab, ICAP and community-based therapy.¹⁵ These goals may be structured using goal attainment scaling (GAS) or other similar methods and address both impairment and the impact on participation. Therapy then targets these goals, so it's essential that time is spent prioritising goalsetting at the start of therapy and continuously reviewing and updating goals throughout the rehabilitation process.¹⁶

Impairment therapy at word, sentence and conversation level: We employ a wide range of impairment-based therapies. These include verb network strengthening treatment,¹⁷ semantic feature analysis¹⁸ and gestural facilitation of naming.¹⁹

Choosing meaningful target words, phrases and topics for therapy increases motivation and likelihood of generalisation and functional use. These therapies are delivered by the SLTs, SLT assistants and via targeted computer-based therapy. The importance of embedding these target words/phrases into conversation therapy further maximises the chances of generalisation and having an impact at a participation level. Edmonds et al. demonstrated that verb network strengthening treatment (vNest) had a positive impact on trained and non-trained sentence targets and maintenance of gains and generalisation were observed, with some improvements at a discourse level.¹⁷ By delivering an adapted version of vNest for 15-30 hours through 1:1 and computer-based therapy we are observing similar levels of improvement for the PWA on the ICAP.

Communication and strategy use in a range of real-life environments:

Impairment therapy alone rarely solves the challenges faced by someone with aphasia. Using those words, phrases and sentences in real context embeds the new learning and ensures the therapy generalises into everyday conversation. Group therapy provides opportunities for PWA to practice their strategies in a conversational contact with peer support and feedback.²⁰

Taking this a step forward, "Out and about" activities provide opportunities to communicate with the general public e.g. in cafés, museums, shops, public transport with the additional challenges of background noise, unfamiliar communication partners and real-life problems to work through.

Neuropsychological interventions and support: PWA are very likely to experience low mood and depression.²¹ Until recently

they have generally been excluded from large treatment studies. Having neuropsychology integrated into our service, through 1:1 and group intervention, addresses these needs. The neuropsychologists also work jointly to provide support, education and training for friends, family and carers of PWA which helps to address some of the many adjustment and relationship changes that affect each PWA's social networks and interactions.

Communication partner training:

There is a growing body of evidence that Communication partner training (CPT) can result in improvements at conversation and relationship levels as well as at an impairment level.²² We use video as a basis for PWA and their friends/family to identify the most effective strategies to support conversation for all involved (and these will be different for different communication partners). The communication partners have capacity to take on strategies more easily and reduce the effort placed on the PWA. Including this as a component of the ICAP has been challenging logistically as people need to travel long distances to access the programme.

Future directions

The initial outcomes from the Queen square ICAP are promising. PWA, their family and friends are feeding back that some of these gains are impacting positively on their participation and quality of life. Future developments include trialing changes to the programme such as moving to four days a week over four weeks; offering remote, video call sessions to involve family and friends more consistently in therapy; closer working with therapists in the acute and community settings to ensure timing of the ICAP fits with an overall pathway for PWA; widening the interdisciplinary team so we can better address fatigue management, work based goals and physical exercise within the programme.

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The Salt Path

We don't often review best sellers in ACNR, still less travel books. But 'The Salt Path' is a bestselling travel book with a neurological twist. It is written by a woman married to a person recently diagnosed with Corticobasal degeneration. And for good measure, they have just contended with legal and financial catastrophe too.

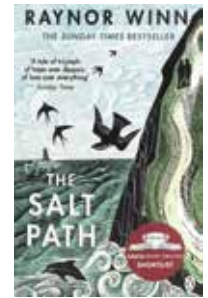
It is a medical book in the sense of showing the limitations of our profession. Perhaps the best that can be said for Medicine here, is that it comes out of the story better than the Law!

A point that's highly relevant to medical practice, however, is a recurring theme of *The Salt Path*: when you hit rock bottom, the only way is up. That's if you allow yourself to try, and are willing to risk that you might die laughing in the effort... What was that they said about the best medicine?

While Cornwall comes out better than either Medicine or the Law, the hero of the piece is an abstraction of the indomitable human spirit. It inhabits all of us from time to time, except the most unlucky. It certainly inhabits the travellers on 'The Salt Path' as they journey on; and one perceives that, having journeyed, this spirit will be all the stronger in the event of future travails.

I must say that Raynor Winn (et al!) provide a compelling (if not scientifically irrefutable) case for the benefits of positive action and of physical therapy, even for the ghostliest of neurodegenerative conditions. Of course, this is something which resonates with data presented more formally by our colleagues in Rehabilitation Science of late; that includes a paper in a very recent edition of the 'other' Clinical Neuroscience journal which comes through the door of many UK neurologists.

The Salt Path is a 'feel good' read for clinicians in Neuroscience; there can be life, even when there is no cure. I think its positivity might also benefit some of our patients, perhaps many of them.



Author: Raynor Winn
Published by: Penguin
Paperback price: £9.99
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ISBN: 9781405937184
Reviewed by: Rhys Davies

Spasticity: Early & Ongoing Management

As a fresh faced ST3 Rehabilitation Medicine trainee, I was eager to find a book to help me get to grips with the pathophysiology, assessment, and management of spasticity. Luckily, after attending a spasticity course in Liverpool (conducted by the lead author himself) I received this book; I can honestly say that I have used it every week since.

At a first flick through, the book is very pleasing to the eye with a bright, 'modern' colour scheme, lots of pictures, and an easy-to-follow layout with handy tabs (colour coded). Section 1 gives an overview of spasticity, explaining pathophysiology, diagnosis, and options for treatment. As a new trainee I found this part extremely useful, but no doubt my senior colleagues will already be familiar with this. Where the real strength of this book lies, however, is in Section 2. This section is a practical guide to ultrasound-guided localisation, injection of botulinum toxin, and post-toxin therapy measures. For example, the section on elbow flexors dedicates a page to each of the main target muscles to explain the dosing for each of the three main brands of botulinum toxin type A, with pictures and tips to help localise injection sites. The pages are uncluttered, and the logical order in which the muscles are presented means you don't have to keep flicking backwards and forwards. This is followed by the post injection management plan, with examples of exercises for the patient to perform until your next meeting.

Whilst this is all excellent, there are a few aspects to the book that could have been a bit slicker. The main thing that bothered me (and this might just be me being overly fussy) was that text is 'unjustified'. Don't worry, I just mean that the text lines vary in lengths down the the page. I have no idea why this bothered me so much; it seemed incongruous with the care taken in organising the actual content. Secondly, some of the pictures aren't as clear as they could be; this means that a few of the ultrasound pictures are a little difficult to interpret, while some pictures of the 'live' model have a greyish quality that makes it seem as if he had recently been pulled from the bottom of a lake. This aside, as already mentioned, I found and still find this book enormously helpful to my clinical practice. Since getting my hands on it, I really have used it every week to guide treatment, to help with injection dosing and localisation, and generally to give me the appearance of competence in front of my seniors!

In summary, has this book improved my management of spasticity? I'd certainly like to think so. Would I recommend this book to others? Definitely, especially for those who wish to gain confidence in the use of ultrasound for localisation. Do I pray for the health of the model? Yes, each and every night.



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Vertigo and Disequilibrium. A practical guide to diagnosis and management

Patients who experience the acute onset of vertigo and disequilibrium may have a benign condition susceptible to relatively simple interventions, many of which can then be incorporated in to an effective programme of self-management. Alternatively, they may have a potentially life-threatening arterial occlusion which requires the urgent orchestration and choreography of many professionals. Today, for people with acute dizziness it could be Cawthorne Cooksey exercises or clot retrieval. The stakes are dizzyingly high.

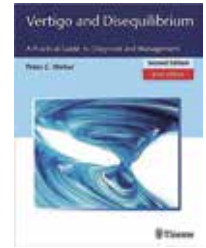
We put this book, described as a practical guide, on the main desk of the acute stroke ward in the hope that by consulting it we would develop skills and behavioural 'software' to help us manage this very important group of patients. It has 36 authors (there is some overlap of content), 21 chapters, an appendix of FAQs (with answers), and an index. A detailed review of the vestibular system proceeds from an assessment of the vertiginous patient to an in-depth overview of the relevant anatomy, biology, physiology and pathology. On the inside cover is a code which allows access to some excellent online videos, which were watched on a range of devices and were a useful supplement to the written material.

The focus is very much on vestibular conditions, to the extent that much is predicated on the patient having a disorder of the vestibular system which needs characterising, rather than on the need to work through the differential diagnosis of the presenting symptoms. The detail in chapter 3 on computerised testing of the vestibular patient conveys well just how specialised the book is: a unilateral weakness of the vestibular system is defined as $(RC+RW)-(LC+LW)/(RW+RC+LW+LC)$, an approach that made it clear that this was not a book in to which we could dip to help us sort out the 'distressed and vomiting' in the nine-bedder. But, we persevered. The chapter on Radiology was encouraging and served to remind us of the relevance of high resolution

CT in assessing the effects of trauma on the temporal bone and vestibule, and of the power of MR imaging in working through the differential diagnosis of cerebellopontine angle lesions e.g. epidermoid cysts are hypointense on T1, hyperintense on T2, and restrict on DWI. Chapter 5 was more challenging. It is described as a basic overview, but the opportunity costs of grasping the basics of the angular and linear vestibulo-ocular reflexes, and the difficulty we had incorporating this new knowledge in to our 18-bed ward rounds, put us off delving further into the relevance of the prepositus hypoglossi.

However it was in the second half of the book that we found things of a more practical nature, and the chapters on BPPV, labyrinthitis and dehiscence of the superior semicircular canal proved to be more useful and clinically relevant, if still very detailed. Mal De Debarquement syndrome, despite the weaknesses inherent in all syndromic diagnoses, is a useful label for some patients, and the description in chapter 12 is pragmatic ("treatment is still predominantly medical and is mostly ineffective") and reminds us that it occurs after all sorts of travel, not just ocean cruises. Some chapters included questions to help consolidate learning, which were very useful, more so, it has to be said, than the 1,148 references in the book, 160 of which followed the chapter about Ménière's disease.

In conclusion, we would not recommend this book for clinicians on busy wards full of patients with multiple comorbidities who need to be examined to establish the basics (like whether their problems are central or peripheral in origin, and whether brain imaging is required). Rather, this is a book for the specialist in the field of Vestibular Neurology who makes use of computerised assessment. Unfortunately, its detail could dissuade the young doctor from persevering at the bedside of the dizzy in the rough and tumble of 'messy' Medicine. However, it does deserve to be kept in the Audiovestibular clinic, within easy reach.



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REGULARS — AWARDS AND APPOINTMENTS

Professor Mary Galea awarded WFNR Franz Gerstenbrand Award

Professor Mary Galea, Professorial Fellow from the University of Melbourne in Australia and her team have won the 2019 World Federation for NeuroRehabilitation (WFNR) Franz Gerstenbrand Award for their research. The team were awarded £3000 for their project showing how nerve transplantation can improve spinal cord injury causing weakness of the upper extremity.

Professor Galea led the research group from the Department of Medicine at the Royal Melbourne Hospital and the Victorian Spinal Cord Service at Austin Health, together with Dr Natasha van Zyl, a plastic and reconstructive surgeon at Austin Health, in the largest prospective, consecutive case series of nerve transfers undertaken to date at a single centre in the tetraplegic population.

Their research found that at the two-year time-point, significant improvements were observed in the participants' ability to pick up and release objects of different sizes within a specified time and also in their independence.

The 2020 WFNR Franz Gerstenbrand Award is now open for entries – visit <http://wfnr.co.uk/education-and-research/wfnr-award/> for further information and an application form.

Dr Tilo Kunath wins the Tom Isaacs Award

The Cure Parkinson's Trust (CPT) and the Van Andel Research Institute (VARI) have announced Dr Tilo Kunath as this year's deserving winner of the 'Tom Isaacs Award'. This award is presented to a researcher who has had the greatest impact on the lives of people living with Parkinson's (PD) and/or has involved people with Parkinson's in a participatory way in their work.

Dr Kunath is one of the world's leading stem cell researchers and it is his compassion and enthusiastic engagement with the PD community, and his willingness to share his expert research knowledge that particularly impressed both those who nominated him and the panel of judges.

The award was announced during the annual Grand Challenges in Parkinson's Disease symposium and Rallying to the Challenge meeting at Van Andel Institute in Grand Rapids.

Nominations are now open for the 2020 Tom Isaacs Award.

Diabetic amyotrophy (Bruns-Garland syndrome)

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Abstract

Garland and Taverner first fully described diabetic amyotrophy as a clinical entity in 1950. Its distinctive features were a painful, markedly asymmetrical proximal weakness and wasting of the thighs and legs often with diminished or absent tendon reflexes. Motor signs dominated the picture, but autonomic and sensory nerves could be involved. Characteristically it occurred in poorly controlled diabetics in whom substantial if not always complete recovery was generally observed. A lumbosacral plexus neuropathy, associated with microvasculitis with secondary inflammatory perivascular mononuclear cell infiltrates is the underlying pathology.

The inelegantly named diabetic lumbosacral radiculoplexus neuropathy (DLSRPN) was first highlighted after a clinical observation in 1950 by my erstwhile teachers, Hugh Garland (1903-1967) (Figure 1) and Deryck Taverner (1914-1998). They found only one earlier account, by Bruns in 1890 which 'had been overlooked or dismissed as irrelevant'.¹ The condition has similar clinical features to non-diabetic lumbosacral radiculoplexus neuropathy (LSRPN).^{2,3}

Ludwig Bruns of Göttingen (1858-1916) had described three patients, aged 58, 59, and 70, suffering from diabetes mellitus of short duration; all three developed severe pain in the hip and thigh followed by weakness and wasting of leg muscles without objective sensory loss, and each recovered fairly quickly following dietary restriction.^{1,4} But the condition was largely unrecognised and received no mention in neurological texts until Garland and Taverner's report⁵ of 1953, which has not been bettered:

Attention is drawn to a form of diabetic neuropathy previously described 60 years ago but forgotten. The syndrome consists of asymmetrical pain, weakness, muscle wasting, and areflexia in the legs, without objective sensory disturbance, in middle-aged patients (ages 56 to 73) with diabetes mellitus of relatively short duration. Three had unequivocal extensor plantar responses. In none was there any objective sensory disturbance. None had been treated with insulin. The protein content of the C.S.F. was raised in four subjects. Electromyographic changes in the affected muscles showed denervation with decreased pattern of motor-unit activity on voluntary contraction compatible but not diagnostic of a cord lesion. Five new examples of the syndrome are described and the literature reviewed.

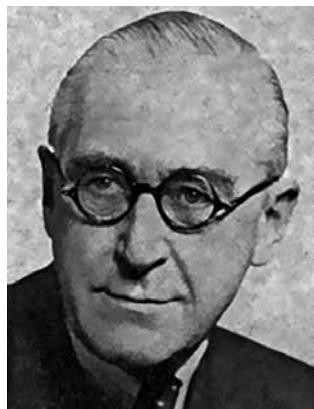


Figure 1: Hugh Garland.

Garland's subsequent paper⁶ (Figure 2) in 1955 renamed the disorder diabetic amyotrophy and described subsequent progress:

In four of the original five patients, there has been a striking recovery of power, with less obvious improvement in muscle wasting, and they all demonstrate that weakness, areflexia, and extensor plantar-responses are, in this condition reversible. Since then seven additional patients have been seen... [The total of] 12 patients showing a syndrome which includes weakness and wasting of muscles with tendon areflexia, associated with frank diabetes or at least with impaired glucose tolerance. Some may result from a myelopathy. Diabetic amyotrophy is the result of uncontrolled diabetes and is probably always reversible by full diabetic control.

Comment

Diabetic amyotrophy is much less frequent than other diabetic neuropathies, affecting approximately 1% of diabetics.² The several designations of this syndrome point to the confusion about its pathological basis and whether the exact site of the lesion lies in the cord, spinal roots, plexus, or in the nerves. Terminology includes: diabetic myelopathy, diabetic amyotrophy, Bruns-Garland syndrome, diabetic mononeuritis multiplex, diabetic lumbosacral plexopathy, diabetic polyradiculopathy and multifocal diabetic neuropathy.⁷ Both of Garland's papers disclose certain patients with extensor plantar responses, which led to the initial suspicion of a cord lesion despite lack of other evidence. The term myelopathy has however, disappeared from the title in his second report, which is couched in somewhat more cautious terms:

Because of the variable findings "amyotrophy" rather than myelopathy is perhaps the most suitable designation.

Occasional instances of upper limb involvement, and a painless form have subsequently been described,^{4,7} though they are mentioned in Garland's reports. Although proximal motor signs dominate the picture, distal segments and autonomic and sensory nerves can be involved.⁸

Recent studies report ischaemic injury from microvasculitis with secondary inflammatory perivascular mononuclear cell infiltrates⁹ as the pathophysiological basis of typical DLSRPN. A follow-up study confirmed that improvement generally begins between three and twelve months from diagnosis, facilitated by optimal control of blood glucose levels, which can result in complete reversal of muscle wasting and weakness. Significant functional disability persists in a minority.¹⁰

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Figure 2: 2nd paper
Diabetic Amyotrophy.

Dengue Cerebellitis



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Abstract

Dengue produces neurological manifestations uncommonly and acute cerebellar ataxia (ACA) is particularly rare. We describe a traveller returning to a non-endemic area who presented with rash, abdominal pain, fever and classical laboratory findings consistent with dengue fever who then developed ACA. MRI scan showed focal nodular leptomeningeal enhancement over the cortex. Other potential causes were excluded. Symptoms largely resolved within one month with supportive care. This case records a rare complication in a traveller returning to a non-endemic area and demonstrates neuroimaging abnormalities. It is important to include dengue virus infection in the differential diagnosis of ACA in returned travellers.

Learning points

- Acute cerebellar ataxia (ACA) is a rare complication of dengue
- Neuroimaging findings in dengue are variable and can include meningeal enhancement
- Consider dengue as a cause of ACA in returned travellers from endemic areas

Introduction

Dengue is a mosquito-borne arboviral infection that causes multi-systemic disease with considerable morbidity and mortality.¹ Neurological sequelae of dengue virus infection are uncommon and acute cerebellar ataxia (ACA) is particularly rare.² This infectious aetiology is an important part of the differential diagnosis of ACA in travellers returning from endemic areas.

Case report

A 73-year-old Caucasian woman presented with right-sided abdominal pain, diarrhoea and nausea. She had recently returned from Fiji.

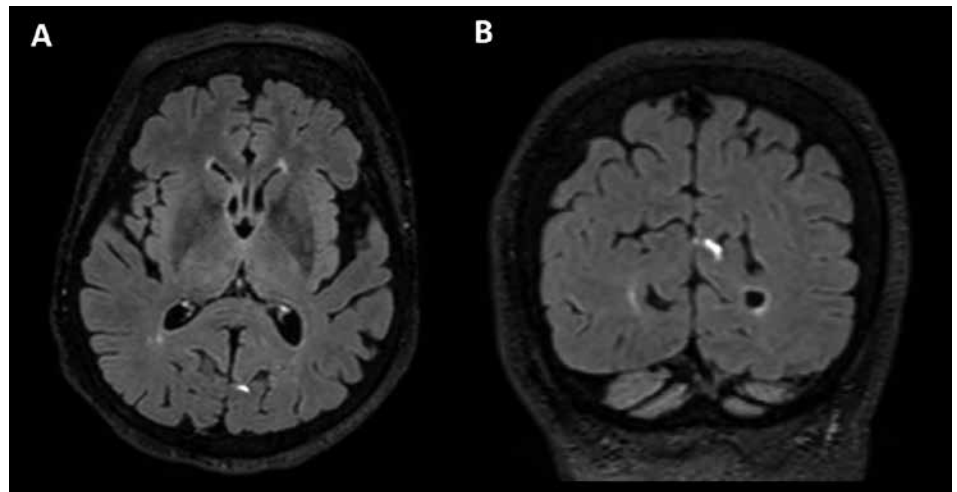
She was systemically well during her trip and had no relevant exposures or obvious bites. On return home, she was fatigued and gradually developed abdominal pain, nausea, watery diarrhoea, subjective fevers and rigors, generalised arthralgias and myalgias. She had no urinary symptoms, rashes or pruritus. Three days after her return she became unsteady on her feet with associated headache.

Her past history was significant for diverticular colitis treated with mesalazine, appendectomy, hypertension, hiatus hernia, gastro-oesophageal reflux disease, osteoarthritis with left total knee replacement, depression, previous caesarean section and tubal ligation, dyslipidaemia and drop attacks of uncertain aetiology. She had a loop recorder in situ for investigation of potential arrhythmia. Her medications included fluoxetine, ranitidine, pantoprazole, rosuvastatin, mesalazine, aspirin, celecoxib, fexofenadine, glucosamine, irbesartan, hydrochlorothiazide, paracetamol and vitamin supplements.

On examination, she was alert, orientated and haemodynamically stable with a low grade fever to 37.7 C. Her abdomen was soft and generally tender without peritonitis. Bowel sounds were normal. Eye movements and vestibulo-ocular reflexes were normal. There was no nystagmus. Speech was normal. She had mild proximal weakness, easily elicited deep tendon reflexes and flexor plantar responses. There was a slight terminal tremor on the left with mild dysdiadochokinesis but no dysmetria. There were no extrapyramidal signs. Gait was wide-based and ataxic. Tandem gait could not be attempted. Romberg's was negative. Sensory examination was normal, including proprioception. There was a subtle blanching maculopapular rash over the trunk.

Full blood count at nadir showed haemoglobin 110 g/L, leukocytes 1.8×10⁹/L, neutrophils 0.8×10⁹/L, lymphocytes 0.6×10⁹/L and platelets

Figure 1. MRI brain imaging in dengue-associated ACA. MRI T2-weighted fluid attenuated inversion recovery axial (A) and coronal (B) images showing focal areas of nodular leptomeningeal enhancement in the left occipital region.



82×10⁹/L. Electrolytes, urea and creatinine were normal. There was mild liver enzyme derangement (ALT 24 U/L, AST 43 U/L, ALP 76 U/L, GGT 37 U/L), low albumin (27 g/L) and elevated lactate dehydrogenase (259 U/L). Vitamin B12, folate and iron were replete. Haemolytic and disseminated intravascular coagulation screens were negative. Coagulation profile was normal. C reactive protein was raised to 20.8 mg/L. Blood and stool cultures were negative. Dengue virus NS1 antigen and IgM antibodies were positive. Respiratory multiplex PCR and malaria testing were negative. Cytomegalovirus serology indicated previous infection. Antineuronal antibody panel was negative. MRI brain scan showed two focal areas of nodular leptomeningeal enhancement in the left occipital region as well as over the left frontal cortex (Figure 1).

The patient received supportive care. Her symptoms had largely resolved at follow up, one month after initial presentation.

Discussion

We consider this to be a case of ACA due to dengue fever with warning signs.³ This represents an intermediate category of dengue severity that requires strict monitoring and supportive care.³ Other potential causes of ACA have been excluded and the syndrome occurred concurrently with typical clinical and laboratory features of dengue virus infection.¹ This case is important because it records this rare complication in a traveller returning to a non-endemic area and demonstrates neuroimaging abnormalities.

Neurological manifestations of dengue are uncommon and include encephalopathy, encephalomyelitis, immune-mediated phenomena, neuro-ophthalmic and neuromuscular disorders.¹ Cerebellar ataxia has been reported in endemic areas.⁴

Neuroimaging and serological testing in this case show no evidence of a vascular, neoplastic, paraneoplastic, demyelinating or toxic cause. CSF examination was not performed, however the clinical (rash, abdominal pain, fever) and laboratory (thrombocytopenia, liver enzyme derangement, positive serology) features favour the diagnosis of dengue-related ACA.

Dengue virus causes neurological sequelae via direct viral neurotropism, delayed post-infectious immunological mechanisms and systemic metabolic derangements.^{2,3,5} The former pathogenic mechanism is most likely in this case given the early development of ACA in the setting of acute dengue virus infection. Autopsy studies demonstrating dengue antigens in cerebellar tissue offer further support for this mechanism.⁵

Imaging findings in dengue virus infection are variable and can include meningeal enhancement, as seen in this case⁶ (Figure 1). The location of these changes do not correspond to the clinical picture of ACA and may reflect a more generalised meningeal inflammatory response to the virus. The absence of cerebellar changes is not uncommon.⁴

Prognosis is generally favourable,^{2,4} as seen in this case, although dengue virus infection can be fatal.¹

This case highlights the importance of including dengue virus infection in the differential diagnosis of ACA in travellers returning from endemic areas.

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Neurodiem, a new digital platform of independent, high-quality scientific content for UK neuro practitioners

With the non-stop influx of scientific data in neurology, healthcare professionals often struggle to stay up to date on the latest developments by searching through multiple journals and pouring through lengthy articles in search of new advances.

To address the challenge, Biogen Inc. established a single, online platform that aggregates high-quality scientific content in 18 neurology topics, in digestible format. The service was developed by listening to neurologists' needs through extensive desk research, interviews, prototype testing and ongoing user feedback to ensure the service is relevant and constantly improving.

Called Neurodiem, the non-promotional digital platform from Biogen Inc. is available in six languages and is now live in the United Kingdom, United States, France, Germany, Italy, Spain, Canada and Japan. The scientific information on the platform is entirely objective and independent from Biogen. It is selected, written, and published exclusively by independent scientific writers and editorial partners, who endure ongoing relationships with faculty from academic institutes, and hospitals worldwide. In 2020, the platform features over 3000 daily summaries from key publications, exclusive presentations and interviews from over 70 key medical experts on emerging topics, real-time highlights from 13 international neurology conferences, and access to over 900 full-text articles from renowned neurology journals.

"COVID-19 has forced us to use more online resources to keep ourselves up-to-date," says Rhys Davies, Consultant Neurologist, Liverpool. "I had not previously made much use of online video lectures. However, now I've discovered neurodiem.co.uk I find, in particular, its "library" of short lectures from key opinion leaders very useful, in terms of subject selection, content and format!"

More than 7,000 healthcare professionals, including over 4000 neurologists, registered to the platform worldwide in less than one year. For 2020, Biogen Inc. plans on launching the Neurodiem App in the UK to ease access of information on the go. Additionally, the digital team behind the platform is strongly focusing on improving the user experience through advanced personalisation, as a means to provide healthcare professionals in neurology with the best and most convenient service to stay up-to-date in their ever-evolving field.

Learn more on www.neurodiem.co.uk. Neurodiem is free and exclusive to healthcare professionals.

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BI-00027



The British Neurotoxin Network



Queens College, Oxford – 24th-25th September 2020

The BNN is an independent network of neurotoxin injectors (mainly consultants neurologists, but also ophthalmologists, maxillofacial, ENT) in the UK and its aim is to share and promote best practice.

Meeting programme

- Extending the therapeutic field of Botulinum toxin covering the indications of Botulinum toxin in neuropathic pain, in ophthalmology beyond blepharospasm, in dermatology beyond cosmetic, and in gastroenterology.
- Exploring the physiopathology of dystonia and its relation to Dopamine.
- Talking to a patient just diagnosed with cervical dystonia adjusting expectations and giving him the keys for self management.

Who is the meeting for?

The meeting is reserved to UK Botulinum toxin injectors, who are BNN members. To become a member, you need to register for free on the website www.neurotoxinnetwork.org.

Booking and fees

Thursday 24th from 2pm until Friday 25th at 1pm.

Book at <https://mondale-events.co.uk/event/british-neurotoxin-network-2020-annual-meeting/>

Fees: £80.00 per person for Consultants and Associate Specialists. £50.00 per person for Nurses, Physiotherapists, Speech Therapists and Orthoptists. *Accommodation is available on a first come, first served basis for those delegates attending the two days.*



The British Neurotoxin Network 2nd October 2020



**The Wellcome Collection – London
The Meige syndrome**

The BNN is an independent network of neurotoxin injectors (mainly consultants neurologists, but also ophthalmologist, maxillofacial, ENT) in the UK and its aim is to share and promote best practice.

Meeting programme

Clinical phenotypes, physiopathology and therapeutic management of Meige syndrome or craniocervical dystonia will be presented.

Who is the meeting for?

BNN members with experience in treating dystonia, who want to learn more about the complexity of the clinical syndrome and its management.

Booking and fees

One day meeting, 9.30 am - 4.30 pm

Book at <https://mondale-events.co.uk/>

Workshop fees: £125 including lunch and coffee break
Clinical CPD points: 5



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Insomnia and Alzheimer's disease roundtable event

Conference details: 3 December 2019, European Parliament, Brussels, Belgium. **Report by:** Dr Jina Swartz: MSD (known as Merck and Co, in the USA and Canada), Dr Chantal Van Audenhove, LUCAS KU Leuven, Professor Markku Partinen, Helsinki Sleep Clinic, Tineke Mollema, Board member of GAMIAN-Europe, MEP Tomislav Sokol, Joke Jaarsma, President, European Federation of Neurological Associations [EFNA] and European Brain Council [EBC]. **Conflict of interest statement:** Dr Jina Swartz is a full-time employee of MSD (known as Merck and Co, in the USA and Canada). Professor Markku Partinen, has received funding from UCB Pharma, GSK, Takeda and Orion and has been involved in Clinical Trials for Bioprojet, Jazz Pharmaceuticals, MSD and Flamel. The other authors report no conflict of interest.

At an event held at the European Parliament on 3rd December 2019, patients, policy makers, clinicians, and researchers met to raise awareness about the significant impact of sleep disorders in persons with Alzheimer's disease and their families.

The "Tackling Insomnia in Alzheimer's disease: A Wake-Up Call" event, held under the auspices of Tomislav Sokol MEP (EPP, HR), was the fourth in a series of "What if?" policy roundtables on Alzheimer's disease, supported by MSD.

Alzheimer's disease is recognised as a major societal challenge. Around 10.5 million people in Europe are living with dementia¹ and global costs are estimated at US\$600 billion.² However, the link between Alzheimer's disease and sleep disturbances is not well known or acknowledged. In fact, more than 70% of people with Alzheimer's disease have disturbed sleep or insomnia.^{3,4} Evidence also shows that poor sleep may be amongst the strongest risk factors for neurodegenerative diseases, including Alzheimer's disease.⁵ Public health officials and healthcare providers thus need to realise the significant impact that insomnia has on the onset and progression of Alzheimer's disease, as well as on the life and health of both patients and their carers.

The event at the European Parliament featured Tomislav Sokol MEP, Joke Jaarsma (European Federation of Neurological Associations / European Brain Council), Dr Jina Swartz (MSD), Tineke Mollema (GAMIAN-Europe), Prof Chantal Van Audenhove (LUCAS KU Leuven) and Prof Markku Partinen (Helsinki Sleep Clinic). Bringing together different perspectives on the topic under discussion, the speakers shed light on the heavy burden which sleep disturbances cause on people living with Alzheimer's disease, as well as on their families, carers, healthcare professionals and healthcare systems as a whole.

Event host MEP Tomislav Sokol stressed that Alzheimer's disease is one of the most important healthcare issues facing Europe.

People suffering from Alzheimer's disease also face critical co-morbidities, including sleep disorders. Crucially, the EU has regulatory and financial instruments to help address both Alzheimer's disease and such co-morbidities. For instance, the Horizon 2020 and future Horizon Europe programme should be used to increase research, which would help improve the assessment and treatment of insomnia and Alzheimer's disease. Also, MEP Tomislav Sokol encouraged putting insomnia in Alzheimer's disease higher up the EU's health policy initiatives, as this would further raise awareness of the difficulties which these people and their families face.

As explained by Professor Van Audenhove and Tineke Mollema, "The nights can feel very long," both for the patients and the carers. "Sleep is the 'washing machine' of the brain, it cleanses it from accumulated toxins. Lack of sleep can be comparable to living in the same clothes for years!", said Prof Markku Partinen, Research Director at the Helsinki Sleep Clinic. Insomnia among patients also disrupts the sleep of family members providing care at home, which then impacts their health status. In addition, the depth of impact on the quality of patients and caregivers' lives extends well beyond day to day care and the emotional/mental toll often pushes people to institutionalise their loved one.

Dr Jina Swartz and Prof Markku Partinen highlighted that insomnia is not only a burdensome complication of Alzheimer's disease – it is also a major risk factor for cognitive decline, which in turn can lead to Alzheimer's disease.

An interactive Q&A session, moderated by EFNA President and EBC Treasurer, Ms Joke Jaarsma, raised critical policy actions – notably the need for:

- Promoting the funding of patient- and carer-centred research to help improve the assessment and management of insomnia in people with Alzheimer's disease;
- Inclusion of insomnia in Alzheimer's disease and dementia as a priority issue in upcoming EU health research initiatives;
- Raising awareness of the environmental and life risk factors for Alzheimer's disease,

including sleep disturbances;

- Developing initiatives to further support family members who care for people living with Alzheimer's disease;
- Developing pharmacological and non-pharmacological solutions to empower and support patients and carers.

A direct outcome of the event was the coordinated development of a Science Policy Paper, which builds on the discussion and conclusions of the roundtable and creates a bridge between the scientific evidence, real-life accounts from patients and carers, and the policy recommendations to help address this important issue.

This latest paper complements the White Paper "Driving Policy to Optimise Care", resulting from the previous "What If" Policy Roundtables. This White Paper covers the issues of stigma, discrimination and inequalities faced by people with Alzheimer's disease, ethical challenges of early detection and diagnosis, and the economic implications of the disease in Europe.

For more information about the "Tackling Insomnia in Alzheimer's disease: A Wake-Up Call" event and paper, the issues covered, or the wider "What if?" advocacy initiative on Alzheimer's disease, please contact Boris Azais, Director of Public Policy at MSD at boris.azais@msd.com.

This information is provided as a professional service by MSD. The views expressed in this publication reflect the experience and opinions of the authors and not necessarily that of MSD.

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Encephalitis Conference 2019

Conference details: 2nd December 2019, Royal College of Physicians, London, UK. **Report by:** Dr Chishimba Lorraine, University of Zambia School of Medicine, Department of Internal Medicine, University Teaching Hospital, Lusaka, Zambia and edited by: Dr Ava Easton, Chief Executive, Encephalitis Society.

Conflict of interest statement: None declared.

2nd December 2019 saw a host of over 170 health care professionals descend on the prestigious Royal College of Physicians in London to attend the Encephalitis Society's 2019 conference. It was an event graced by delegates from various fields of medicine, science, and research. The speakers at this international event presented expert work in line with various fields that aligned with all things encephalitis. They included neurologists, neuroscientists, neuropsychologists, neuropsychiatrists, and sociologists. It was a packed house to the end of the day.

The first session was chaired by Professor Tom Solomon, a professor of neurology and Chair of the Society's Scientific Panel.

The opening presentation was given by Dr Kamran Zaman, from the ICMR-Regional Medical Research Centre, Gorakhpur in India: he discussed a study that looked into the aetiological agents of acute encephalitis syndrome (AES) in cases in Eastern Uttar Pradesh. The backdrop of the discussion was the long-standing presumption that Japanese encephalitis virus (JEV) was the cause of every encephalitis case in India, prior to a 2005 outbreak. With the development of newer serological and molecular diagnostics other infectious causes of encephalitis, including bacterial, could be identified. He reported that *Orientia tsutsugamushi* – the causative agent of Scrub Typhus was in fact the most common aetiological agent from the AES cases in Uttar Pradesh in the year 2018. He highlighted that despite the seasonal outbreaks over the decades which were associated with high mortality, there has been a general decline in AES in India owing to JE vaccination campaign and prophylactic use of azithromycin/ doxycycline in acute febrile illness (AFI)/ AES cases.

Dr Christopher Duncan, University of Newcastle, UK presented on the role of homozygous missense mutation in STAT2 as being responsible for the failure of regulation in interferon pathways and hence leading to unrestrained type 1 signalling in sterile encephalitis. Type I interferons (IFNs) are essential antiviral cytokines but uncontrolled activity can be harmful. Dr Duncan presented a new genetic disease associated with sterile encephalitis in two brothers carrying a homozygous missense mutation in STAT2. STAT2 is a transcription factor that functions downstream of IFN, and the pathogenic variant (STAT2-R148W) was accompanied by prolonged JAK-STAT signalling and enhanced responses to IFN α/β , due to a failure of STAT2-dependent negative regulation. These findings demonstrate a new regulatory function of STAT2, and suggest that blocking IFN signalling might offer



Dr Nicholas Davies, Professor Tom Solomon, Associate Professor Sarosh Irani.

benefit in similar neuroinflammatory diseases linked to excessive IFN activity

Dr Danielle Bastiaansen from Erasmus MC University Center, Rotterdam, the Netherlands followed with a discussion on her work showing how autoimmune encephalitis could easily be misdiagnosed as dementia syndrome because about a third of AE cases presented with symptoms of dementia. Seizures were a late feature in the disease course with subtle seizures being easily missed, while dementia was of rapid progression making its suspicion more prominent than AE. Moreover, disease progression in AE can be slower over months to years. She concluded by emphasising the need for physicians to be aware of AE, especially when patients have other symptoms such as seizures in particular because AE is a treatable condition with better outcomes. She also highlighted that abnormal ancillary tests, including CSF, MRI and EEG are red flags for AE.

Dr Audrey Daisley and Dr Rachel Tams, Consultant Clinical Neuropsychologists from the Oxford Centre of Enablement, UK talked about the use of a resilience focused approach to supporting families affected by encephalitis. They acknowledged that, despite the often devastating psychological impact of this condition, there is little research into family adjustment to it and very few interventions have been developed. Dr Daisley and Dr Tams emphasised the importance of helping all members of a family, including child relatives, to understand and find ways to live as

well as possible with the unique challenges that encephalitis can bring; in particular they noted the challenges for families to understand and cope with the "invisible" aspects of the illness (such as cognitive problems and fatigue), to help families discover their "new normal" and to talk through and grieve the complicated and ambiguous losses they experience. They also stressed the value in helping families connect with others in a similar situation and illustrated this in a short film of a "Family Resilience Day" (run in conjunction with the Encephalitis Society and the London Fire Service in 2018). They also presented their group work with children affected by Multiple Sclerosis in the family, and suggested that this one-day resilience group programme could be adapted for children living with encephalitis in the family whose parents are affected by encephalitis. They concluded by calling for more family focused research in this area

The late morning session was chaired Dr Bonnie-Kate Dewar and the first presenter was Professor Ajit Rayamajhi from the Kanti Children's Hospital, Kathmandu, Nepal. He presented on the role of fluid management in the outcome of children with Acute Encephalitis Syndrome (a group of symptoms and signs used by World Health Organization to help diagnose acute viral encephalitis). Data on optimum fluid management for patients with non-traumatic brain injury, in particular AE is limited. Low admission weights which could be malnutrition or dehydration related

in children with encephalitis has been associated with poor outcomes. He reported low admission weight-for-age and loss of weight after admission as correlates for poor outcomes. The children with bad outcome tended to have low admission weight for age and more fluid deficit with a trend for higher admission serum lactate levels which meant that they could have been dehydrated. He indicated that high serum lactate could also be harmful to the brain and thus contribute to poor outcome, hence the need for optimum and appropriate fluid management to mitigate poor outcomes.

Dr Ana Arenivas from The Institute for Rehabilitation and Research Memorial Hermann and Baylor College of Medicine Houston, USA presented that age is associated with long term adaptive behaviour after anti-NMDAR encephalitis (anti-NMDAR). She showed that in comparison to adolescent and adults, children with anti-NMDAR may experience deficits in adaptive function, despite no differences in mRS score between groups. Further, males may experience more adaptive behaviour challenges than females. Results suggest distinct consequences of the disease on the early developing brain. Findings underscore the importance of ongoing monitoring of functional outcomes to inform appropriate treatment planning and advocacy. Future longitudinal and prospective research should examine children with anti-NMDAR longitudinally to better understand the impact of other variables (e.g., pharmacological, rehabilitative, behavioural intervention) on additional cognitive and behavioural outcomes.

Dr Fabian Docagne's presentation (French Institute for Health Research, France) followed on how B-cell response mediates experimental NMDA receptor autoimmune encephalitis. He presented findings of a recent animal model which suggested that B-cell response could lead to autoimmune reaction against NMDAR that would then drive the encephalitis-like symptoms despite overt T-cell recruitment. This is unlike other autoimmune neurological diseases such as multiple sclerosis that is mediated by T cells. The autoimmune response was associated with B cell infiltration and no T cell, toward the ventricles, and depletion of B cell reduced the severity of the symptoms in the mice. These findings call for further work in encephalitogenic mechanisms in animal models and testing immune system therapeutic strategies.

Dr Ava Easton, Chief Executive of the Encephalitis Society presented on vaccine-preventable encephalitis using case studies to illustrate often-devastating patient outcomes in Rabies, Japanese encephalitis, and tick-borne encephalitis.

A keynote lecture entitled *Diagnosing infectious encephalitis including PCR multiplex panels and meta-genomics* was presented by Associate Professor Matthijs Brouwer, Academic Medical Centre, Amsterdam. His talk focused on diagnosing infectious encephalitis which can be caused by many different



Audience shot.

organisms including viruses, bacteria, parasites, and fungi. Identification of the causative aetiology is important as it improves the outcome if the correct treatment is started early during infectious encephalitis. The clinical history, physical exam and cranial imaging all help in arriving at the possible aetiology of encephalitis. Useful clues to exotic micro-organisms include a history of travel and animal contact. Cranial imaging is useful and may give a clue especially in Herpes Simplex Virus encephalitis with characteristic changes involving the temporal lobe due to swelling. CSF studies however are the gold standard to identification of the various aetiologies. Microscopic examination and culture can be done on CSF to identify various organisms. The drawback with culture is that it may take weeks to get to the offending organism, about 3-6 weeks for tuberculosis (TB) and up to 8 weeks for fungi. When checking for viruses in cerebral spinal fluid CSF there is always the chance that the virus may not be detected as it may be only in the brain parenchyma and not in the CSF. This then becomes the basis for a repeat lumbar puncture (LP) usually within a few days. Polymerase Chain Reaction (PCR) is a valuable tool to identify many viruses and several bacteria, but is less sensitive in cases such as TB and Borellia (50% and 18% respectively). PCR may be especially helpful in patients treated with antibiotics in whom bacteria no longer grow in cultures. PCR multiplex panels are relatively new modality able to identify 14 targets including 6 bacteria, 7 viruses and Cryptococci, but does not include TB. So far the additional value above culture, PCR and serology is not obvious. Next generation sequencing is an important research technique for finding new viruses but so far is not very sensitive. He explained that there appears to be clinical relevance for this mode of diagnosis in a selected population but does not replace currently used microbiological diagnostics. Other novel methods such as patterns of metabolism, proteins and lipids in the CSF may also show what the cause of encephalitis is, and are currently still subject to scientific research.

Following lunch the third session was

chaired by Dr Nicholas Davies, Chelsea and Westminster Hospital and the first presentation was given by Dr Aline de Moura Brasil Matos a neurologist from the Tropical Medicine Institute at University of São Paulo in Brazil. Her talk focused on a study on the triple arboviral epidemics in the Brazilian north-east between 2015 and 2017. Dengue virus (DENV), Zika virus (ZIKV) and Chikungunya virus (CHIKV) are endemic to Brazil and a look at the epidemics revealed an increase in Chikungunya cases over time, along with a rise in incidence of a variety of neurological syndromes observed following these epidemics. In previous reports, few describe Chikungunya neuropism and patients often manifested with non-neurological symptoms such as rash and arthralgia. The study demonstrated CHIKV as the commonest viral aetiology for encephalitis during the epidemics, and other neurological presentations such as myelitis or acute polyneuropathy could occur along with the encephalitis. The greater neuropism seen with CHIKV not seen with the other arboviral agents of the epidemics might probably be attributed to likely infection of astrocytes

Dr Luisa Diaz-Arias, from Johns Hopkins, Baltimore, USA presented research findings regarding fatigue in encephalitis survivors. Recognition and treatment of fatigue in these individual would improve quality of life. Using the modified Fatigue impact scale, they demonstrated that fatigue, in physical (86% of participants), cognitive (83%) and psychological domains was commonly reported by encephalitis survivors, with women tending to report more fatigue than their male counterparts. Sleep quality and depression were also reported with modest association to fatigue but they could not completely account for it, hence a call to further explore biological underpinnings of fatigue in survivors of encephalitis.

The second keynote address of the day was provided by Professor Emma Morris, Institute of Clinical Cell and Gene Therapy, University College London, UK. Professor Morris focused on the role of T cell immunity in autoimmune encephalitis. Professor Morris was able to

take the audience through the workings of the immune system including the selection, maturation and development of a sub-population of T cells, in the thymus, into a regulatory T cells (Treg) that is important in suppressing the immune system and maintaining immune tolerance. The regulatory T cell contain a transcription factor FoxP3 gene that determines the function of the Treg cells. Mutation to this gene can lead to deleterious effects via severe autoimmunity and immune dysregulation. Regulatory T cells have been used in cancer immunotherapy as genetically engineered T cells. The CAR T cells are Tregs engineered to have genes that encode chimeric antigen receptors (CAR) in order for them to have specific antigen targets. In haematological cancer immunotherapy the CAR T cells are designed with CD19 antigen as their target. CD19 is a surface marker expressed by all B cells including the neoplastic lineages. With the use of CAR T cell immunotherapy Professor Morris indicated observation of organ specific autoimmunity. There is an observed association between CAR T cells and autoimmune encephalitis through neurotoxicity. She indicated that patients present with seizures and slow waves on EEG and that one of the initial signs that point to autoimmune encephalitis from CAR T cell therapy is a change in handwriting. The takeaway message was that T cell immunity plays a role in autoimmune encephalitis.

Dr Frederik Bartels, University of Berlin, Germany discussed the findings of their study on failure of brain growth in children with myelin oligodendrocytes glycoprotein (MOG) antibody-associated encephalitis. The backdrop to their study was acute disseminated encephalomyelitis (ADEM) an acquired demyelinating syndrome that commonly affects children and affects brain growth over time. ADEM is characterised by encephalopathy, polyfocal neurological symptoms and predominant white matter changes on MRI scans. Over the years it has been shown that many children with ADEM are also seropositive for autoantibodies against myelin oligodendrocyte glycoprotein MOG, so that potentially this could be a separate disease entity (MOG spectrum disorder). ADEM though typically monophasic can also have a relapsing course with ADEM-Optic neuritis phenotype and studies have shown negative influence on brain growth over time. Dr Bartels research, based on MRI scans illustrated that though no differences were found in whole brain volume between MOG antibody-positive and MOG antibody-negative ADEM patients, there was significant brain volume reduction with a corresponding CSF fluid volume expansion in patients with ADEM (MOG anti-body negative and positive) compared with healthy controls. He also demonstrated that there was failure of age-expected brain growth in patients with ADEM compared to controls.

Dr Georgios PD Argyropoulos, University of Oxford, UK described a novel disorder of emotional dysregulation following auto-



Delegates from Malawi, Zambia and Harvard, USA.

immune limbic encephalitis characterised by pathological tearfulness. The acute phase of autoimmune limbic encephalitis may be characterised by psychiatric and behavioural symptoms with high T2 signal in the limbic system on MRI. Following immunosuppressive therapy many patients recover satisfactorily, though a substantial proportion develop atrophy in the limbic system and residual cognitive impairment with deficits centering on episodic memory. The study by Dr Argyropoulos and team demonstrated that half the patients in the chronic post-acute phase of autoimmune limbic encephalitis reported tearfulness that was unrelated to depression, impulsiveness, executive dysfunction, memory impairment or acute phase amygdala abnormalities. Instead the study demonstrated a correlation between pathological tearfulness with specific emotional brain networks. Abnormal resting-state functional connectivity between the hippocampus and the posteromedial cortex and right middle frontal gyrus, abnormal hemodynamic activity in the left fusiform gyrus, right inferior parietal lobule and ventral pons, and volume reduction in the right anterior hippocampus, left fusiform gyrus and cerebellum correlated with this novel phenomenon. He indicated potential of these findings to inform future pharmacological therapies.

The conference sessions concluded with a debate chaired by Professor Tom Solomon entitled "This house believes ALL patients with suspected Autoimmune Encephalitis should receive IVIG as an adjunct to corticosteroids". For and against the motion were Associate Professor Sarosh Irani, and Dr Nicholas Davies respectively. An in-house pre and post-debate poll was carried out with members of the audience participating in the voting process through an online portal. The background for the debate was the lack of consensus on IVIG as an adjunct in the first-line treatment for suspected autoimmune encephalitis, with different groups using it as such and other groups preferring plasmapheresis over IVIG, with no evidence for superiority of either approach. The audience favoured use of IVIG as an adjunct to corticosteroids in both the

pre and post-debate poll. Professor Sarosh Irani was convincing in his arguments for the motion so that more votes went to the motion after the debate.

Phillipa Chapman, Director of Services, Encephalitis Society presented a video highlighting a range of events and activities that took place in the year 2019 to mark and celebrate the 25th anniversary of the Society.

The day drew to a conclusion with awards: best oral presentation was awarded to Dr Frederik Bartels, Department of Neurology, University of Berlin for his presentation on "Failure of brain growth in children with MOG antibody-associated encephalitis". Best poster presentation was awarded to Giuliano Tomei of Oxford Health NHS Trust; Department of Psychiatry, University of Oxford (other authors: Ksenija Yeeles, Iona Cairns, Jessica Venkaya, Isobel Harrison, Alasdair Coles, Michael Zandi, Peter Jones, Belinda Lennox) for his work on "Anti-neuronal membrane antibody associated psychosis: clinical and demographic characteristics from a screening cohort". A long-standing volunteer award was presented to Rachel Tarlton for her work over the last 10 years with the Encephalitis Society.

Closing remarks were delivered by Dr Ava Easton after which there was a networking opportunity over wine and snacks.

Many thanks go to the sponsors of the event: ACNR, Aston Neuroscience Institute, Brain Infections Global, Cambridge University Press, Euroimmun, Liverpool Brain Infections Group, NIHR, Oxford University Press, Routledge, The Lancet Neurology, University of Liverpool, Valneva

To register for the Encephalitis Conference 2020 on December 8th (early bird rates available), apply for bursaries, or sponsor and exhibit, please visit: <https://www.encephalitis.info/Event/conference-2020>

Prizes will be awarded again for best Oral and Poster presentations.

Postpone, cancel, or go online with your healthcare event?

Having spent more than 14 years in the Events Industry, five of which heading up the Events delivery and strategy for an International Pharmaceutical Company, Gail set up Elementary Events, an independent Events Agency specialising in the Healthcare Sector. Gail holds the Level 3 Diploma in the promotion of medicines from the ABPI, which ensures all elements of her work is undertaken with compliance in the forefront of her mind.

Elementary Events Offers a wide variety of services such as: event strategy, event management, delegate management and in-house 'implant'. We offer bespoke packages to cover all requirements. **Email Gail at** gail@elementaryevents.co.uk



Postpone, cancel, or go online? These are the options facing the healthcare events sector currently.

This unprecedented period we are now in could never have been predicted, and the decisions the industry makes in the coming weeks and months will impact not only the events sector, but the wider industries such as travel and tourism. Most notably it is going to impact small businesses and freelancers, who contribute to the £70bn UK events industry and without whom many events would not be possible.

There is a lot of discussion on numerous professional platforms regarding the need for face to face events, and about the potential for utilising virtual meetings instead. Although I agree virtual events definitely have their place, congresses – which have seen the biggest impact – are not the same online.

A number of congresses have been offering virtual platform opportunities for a number of years now, and when I worked as an Event Manager for an international pharmaceutical company, I livestreamed a few symposia. The technology worked well and it was promoted well, but the numbers who actually logged on were not ground breaking. The virtual

element of congresses have never been well 'attended' in my experience. Maybe the fact there is no other option at present will impact this in a positive way, and it is definitely better than nothing. But with all of the HCPs currently stretched as it is dealing with the crisis, who will be logging in?

Postponing events which can't go ahead at present seems like the most sensible option if Congress organisers work together to collaborate. However, we still risk becoming saturated with events in the later part of the year. Also, there is a big question mark around NHS study days even being granted in the short term. Even when the pandemic has died down there will still be resource issues, with the day to day 'business' such as clinics trying to catch up with routine appointments, and trying once again to reduce the routine operations waiting list which has swelled with all the postponed procedures. I am sure all countries will have the same issues. Therefore cancelling may be the only option at present for some events. This leads us back to the impact this will have on the medical events industry and the domino effect thereafter. There is no easy answer to this.

One thing is certain, and that is that

congresses are more than just symposia and workshops. They are: networking opportunities with peers; a chance to take time out of the usual 'day to day' to really focus on education, to sit in workshops and read abstracts which aren't directly linked to current clinical practice but may trigger a memory in the clinic in years to come; a chance to broaden knowledge by discovering new products and services in the exhibition halls. These things you simply can't do without being physically present.

In the meantime, this is an ideal opportunity to utilise the event professional's transferable skills for other activities. Some activities we are offering clients:

- Events Processes and Procedure writing.
- Contingency planning for when (!) something like this occurs in the future
- Developing more robust Transfer of Value (TOV) procedure and documentation.
- Reviewing meeting and event SOP's and Policies.
- Event Strategy reviews.

By utilising the events community in this way, you can ensure they are still around when you need them to deliver your next congress. This will happen – we are just not sure when that may be!

This unprecedented period we are now in could never have been predicted, and the decisions the industry makes in the coming weeks and months will impact not only the events sector, but the wider industries such as travel and tourism

These dates are correct as we go to press. Please see www.acnr.com/event, or check with the organisers for any changes due to the COVID-19 pandemic. Please send diary listings for our website and next issue to Rachael@acnr.co.uk

Courses

ONLINE – Oxford Online Programme in Sleep Medicine (MSc/PgDip)
2-year programme beginning October 2020, currently open for applications, E. sleepmedicine@ndcn.ox.ac.uk
www.ndcn.ox.ac.uk/study-with-us/online-programme-in-sleep-medicine

MAY

ONLINE – 6TH EAN Virtual Congress 2020 – FREE OF CHARGE
23-26 May, 2020; E. headoffice@ean.org – www.ean.org
Programme online at <https://ipp-ean20.netkey.at>

JULY

Unravelling Strength and Conditioning for Therapists
4-5 July, 2020; London Road Community Hospital, Derby, UK
T. 01332 254679, E. u.hdb.ncore@nhs.net
www.ncore.org.uk/events

ONLINE – Federation of European Neuroscience Societies (FENS)
11-15 July, 2020; Glasgow, UK
www.bna.org.uk/mediacentre/news/fens-2020-to-be-a-virtual-meeting/

Cognitive-Behavioural Therapy Approaches to Physical Rehabilitation
14 July, 2020; Derby, UK
T. 01332 254679, E. u.hdb.ncore@nhs.net
www.ncore.org.uk/events/event_details.aspx?mode=detailedView&mode2=screen&event_id=2777

Posture and Balance as it relates to Selective Control of the Lower Limb
14-15 July, 2020; London Road Community Hospital, Derby, UK
T. 01332 254679, E. u.hdb.ncore@nhs.net
www.ncore.org.uk/events/event_details.aspx?mode=detailedView&mode2=screen&event_id=2781

AUGUST

NSANZ 2020: Neuromodulation Society of Australia & New Zealand
7-9 August, 2020; Queensland, Australia
E. elodie@dcconferences.com.au
<https://dcconferences.eventsair.com/nsanz2020/>

SEPTEMBER

International Conference on Movement and Cognition
3-5 September, 2020; Paris, France – www.movementis.com

Neuropsychiatry 2020: Joint International Conference of Faculty of Neuropsychiatry and International Neuropsychiatry Association
17-18 September, 2020; London, UK – www.rcpsych.ac.uk

Explain Pain
8-9 September 2020; Derby, UK
T. 01332 254679, E. u.hdb.ncore@nhs.net
www.ncore.org.uk/events/event_details.aspx?mode=detailedView&mode2=screen&event_id=2816

Posture and Balance in Relation to the Upper Limb for Assistants
9 September, 2020; Derby, UK
T. 01332 254679, E. u.hdb.ncore@nhs.net
www.ncore.org.uk/events/event_details.aspx?mode=detailedView&mode2=screen&event_id=2782

Where innovation meets evidence: The cutting edge of Neurologic Music Therapy and evidence-based practice in clinical settings
September 10, 2020; 9-5pm, London, UK
<https://chilternmusictherapy.co.uk/events/conference>

VasCog 2020
9-12 September, 2020; Newcastle University, UK
E. vascogsoc@gmail.com – www.vas-cog.com/vascog-2020

Mobilisation of the Neuroimmune System
15-16 September, 2020; Derby, UK
T. 01332 254679, E. u.hdb.ncore@nhs.net
www.ncore.org.uk/events/event_details.aspx?mode=detailedView&mode2=screen&event_id=2574

Parkinson's Foundation MasterClass
17-19 September, 2020; Halifax Hall, Sheffield University Campus, UK
<https://parkinsonsacademy.co/courses/foundation-masterclass-course/>

ONLINE – Sleep Medicine: The Physiological Basis of Sleep (CPD)
23-25 September, 2020; Oxford University, UK
E. sleepmedicine@ndcn.ox.ac.uk
www.conted.ox.ac.uk/about/sleep-medicine

ONLINE – Sleep Medicine: Sleep-disordered breathing and sleep-related movement disorders (CPD)
29 September-3 November, 2020; Oxford University, UK
E. sleepmedicine@ndcn.ox.ac.uk
www.conted.ox.ac.uk/about/sleep-medicine

Parkinson's Advanced MasterClass 38A – Module 1
29-30 September, 2020; Halifax Hall, Sheffield University Campus, UK
<https://parkinsonsacademy.co/courses/advanced-masterclass-course/>

MS Leadership MasterClass – Module 2
30 September-3 October
<https://multiplesclerosisacademy.org/>

OCTOBER

Controversies in Neurology
2-5 October, 2020; London, UK – <http://cony.comtecmed.com>

British Neurotoxin Network London Workshop on Meige Syndrome
2 October, 2020; London, UK
<https://mondale-events.co.uk/event/british-neurotoxin-network-2020-annual-meeting/>

Posture and Balance in Relation to the Lower Limb for Assistants
6 October, 2020; Derby, UK
T. 01332 254679, E. u.hdb.ncore@nhs.net
www.ncore.org.uk/events/event_details.aspx?mode=detailedView&mode2=screen&event_id=2785

7th Global Medical Symposium on Medical Ketogenic Dietary Therapies
6-10 October, 2020; Brighton, UK
T. 01342 836571, E. info@globalketo.com
www.globalketo.com

MS Intermediate MasterClass 11 – Module 1
7-9 October, 2020; Sheffield, UK
<https://multiplesclerosisacademy.org/events/ms-intermediate-masterclass-11-module-1/>

4th ILAE British Branch Epilepsy Neuroimaging Course
8-10 October, 2020; Chalfont Centre for Epilepsy, UK
E. registrations@ilaebritish.org.uk – <https://bit.ly/2WR05JZ>

Posture and Balance as it relates to Selective Control of the Upper Limb
10-11 October, 2020; Dublin, Ireland – T. 01332 254679, E. u.hdb.ncore@nhs.net – www.ncore.org.uk/events

Skill Acquisition in Stroke Rehabilitation
10 October, 2020; Leamington Hospital, Warwick, UK
T. 01332 254679, E. u.hdb.ncore@nhs.net
www.ncore.org.uk/events/event_details.aspx?mode=detailedView&mode2=screen&event_id=2842

Management of Spasticity in the Upper Limb following Stroke
12 October, 2020; Derby, UK
T. 01332 254679, E. u.hdb.ncore@nhs.net
www.ncore.org.uk/events/event_details.aspx?mode=detailedView&mode2=screen&event_id=2805

ABN Annual Meeting
15-16 October, 2020; Bournemouth, UK
www.theabn.org/page/meeting_postponed

British Neurotoxin Network Paediatric Workshop on Ultrasound Guided Injection
17 October, 2020; London, UK
<https://mondale-events.co.uk/event/british-neurotoxin-network-paediatrics-ultrasound-workshop/>

Unravelling Strength and Conditioning for Therapists
17-18 October, 2020; Whittington Hospital, London, UK
T. 01332 254679, E. u.hdb.ncore@nhs.net
www.ncore.org.uk/events

Neurological Upper Limb for Occupational Therapists
19 October & 16 November, 2020; Derby, UK
T. 01332 254679, E. u.hdb.ncore@nhs.net
www.ncore.org.uk/events/event_details.aspx?mode=detailedView&mode2=screen&event_id=2786

MS Basecamp
19-20 October, 2020; Sheffield, UK
<https://multiplesclerosisacademy.org/events/ms-basecamp-1/>

Advanced Stroke Imaging Course
28 October, 2020; London, UK – E. s.gill@ucl.ac.uk
www.ucl.ac.uk/short-courses/search-courses/advanced-stroke-neuroimaging

NOVEMBER

ONLINE – Cognitive Behavioural Therapy for Insomnia Masterclass
2-3 November, 2020; Oxford, UK
E. sleepmedicine@ndcn.ox.ac.uk
www.ndcn.ox.ac.uk/study-with-us/online-programme-in-sleep-medicine/short-courses/masterclass-in-cbt-i

MS Advanced MasterClass 12 – Module 1
4-6 November, 2020; Sheffield, UK
<https://multiplesclerosisacademy.org/events/advanced-masterclass-12-module-1/>

Naidex 46
9-10 November, 2020; Birmingham, UK
www.naidex.co.uk/?PtnACNR

MS Service Provision in the UK 2020: Raising the Bar
12-13 November, 2020; Birmingham, UK
<https://multiplesclerosisacademy.org/events/ms-service-provision-in-the-uk-2020-raising-the-bar/>

Unravelling Strength and Conditioning for Therapists
14-15 November, 2020; Darlington Memorial Hospital, Darlington, UK – T. 01332 254679, E. u.hdb.ncore@nhs.net
www.ncore.org.uk/events

Posture and Balance as it relates to Selective Control of the Upper Limb
21-22 November, 2020; Darlington, UK – T. 01332 254679, E. u.hdb.ncore@nhs.net – www.ncore.org.uk/events

KetoCollege
23-25 November, 2020; East Grinstead, UK
www.mfclinics.com/keto-college/ketocollege-uk-2020

DECEMBER

Posture and Balance as it relates to Selective Control of the Upper Limb
3-4 December, 2020; Derby, UK – T. 01332 254679, E. u.hdb.ncore@nhs.net – www.ncore.org.uk/events

Alzheimer's Advanced Masterclass – Module 1
3-4 December, 2020; Sheffield, UK
<https://dementiaacademy.co/events/alzheimers-masterclass-1-module-1/>

Encephalitis Conference
8 December, 2020; Royal College of Physicians, London, UK
www.encephalitis.info/conference

Dizziness and Balance Workshop
8 December, 2020; London, UK
www.dizzinessandbalanceworkshop.co.uk

2021

JANUARY

Recognising Post Traumatic Stress Disorder
18 January, 2021; Derby, UK
T. 01332 254679, E. u.hdb.ncore@nhs.net
www.ncore.org.uk/events/event_details.aspx?mode=detailedView&mode2=screen&event_id=2790

FEBRUARY

Exploring Functional Patterns of Movement
1 February, 2021; Derby, UK
T. 01332 254679, E. u.hdb.ncore@nhs.net
www.ncore.org.uk/events/event_details.aspx?mode=detailedView&mode2=screen&event_id=2793

The Children's Trust National Paediatric Brain Injury Conference 2021
4 February, 2021; RSM, London, UK
www.thechildrenstrust.org.uk

Balance Rehabilitation
23-24 February, 2021; Derby, UK
T. 01332 254679, E. u.hdb.ncore@nhs.net
www.ncore.org.uk/events/event_details.aspx?mode=detailedView&mode2=screen&event_id=2693

Assessment and Ideas for the Treatment of Thorax in Adults with Neurological Damage
26 February, 2021; Derby, UK
T. 01332 254679, E. u.hdb.ncore@nhs.net
www.ncore.org.uk/events/event_details.aspx?mode=detailedView&mode2=screen&event_id=2795

MARCH

Palliative Care 2021
11-12 March, 2021; Sheffield, UK
<https://neurologyacademy.org/courses/palliative-care>

Management of Spasticity in the Upper Limb following Stroke

15 March, 2021; Derby, UK
 T. 01332 254679, E. uhd.ncore@nhs.net
www.ncore.org.uk/events/event_details.aspx?mode=detailedView&mode2=screen&event_id=2805

MS Foundation MasterClass 10.2

18-19 March, 2021; Sheffield, UK
<https://multiplesclerosisacademy.org/events/ms-foundation-10-module-2/>

Parkinson's Advanced MasterClass 40.1A

23-24 March, 2021; Sheffield, UK
<https://parkinsonsacademy.co/events>

UK Neuro-Ophthalmology Society (UKNOS) Annual Meeting

25 March, 2021; London, UK
Festschrift for Dr Gordon Plant
 26 March, 2021; London, UK
www.UKNOS.com

APRIL**MS Intermediate MasterClass 11.2**

21-22 April, 2021; Sheffield, UK
<https://multiplesclerosisacademy.org/events/ms-intermediate-masterclass-11-module-2/>

Neuropharmacy 2 – Mod 2

23-24 April, 2021; Sheffield, UK
<https://neurologyacademy.org/events/neuropharmacy-masterclass-2-module-2/>

MAY**MS Advanced 12 – Mod 2**

13-14 May, 2021; Sheffield, UK
<https://multiplesclerosisacademy.org/events/advanced-masterclass-12-module-2/>

Dementia MasterClass 7

18-19 May, 2021; Sheffield, UK
<https://dementiaacademy.co/events/dementia-masterclass-7/>

MS Advanced MasterClass 12 – Module 2 – PREVIOUS MODULE 1 REQUIRED

20-21 May, 2021; Sheffield, UK
<https://multiplesclerosisacademy.org/events/advanced-masterclass-12-module-2/>

2nd International Conference on Neuro-Rehabilitation (NEURAM 2021)

27-28 May, 2021; Balaclava, Mauritius
 T. 0203 238 8683, E. neuram@bcdme.com
<https://zibrant.eventsair.com/neuram-2020/neuram>

JUNE**2nd International Keto Live Conference**

7-11 June, 2021; Switzerland
www.keto-live.com

Alzheimer's Mod 2

8 June, 2021; Sheffield, UK
<https://dementiaacademy.co/events/>

MS Foundation MasterClass 13.1

9-11 June, 2021; Sheffield, UK
<https://multiplesclerosisacademy.org/events/>

8th EAN Congress 2021

19-22 June, 2021; Vienna, Austria
 E. headoffice@ean.org – www.ean.org

SEPTEMBER**MS Intermediate MasterClass 14.1**

15-17 September, 2021; Sheffield, UK
<https://multiplesclerosisacademy.org/events/>

ILAE British 2021 Annual Scientific Meeting

28-30 September, 2021; Cardiff, UK
<http://ilaebritish.org.uk/>

Parkinson's Foundation MasterClass 41F

12-13 October, 2021; Sheffield, UK
<https://parkinsonsacademy.co/events/>

NOVEMBER**MS Advanced MasterClass 15.1**

17-19 November, 2021; Sheffield, UK
<https://multiplesclerosisacademy.org/events/>

DECEMBER**Parkinson's Advanced MasterClass 40.2A**

7-8 December, 2021; Sheffield, UK
<https://parkinsonsacademy.co/events/>

Raising the bar through leadership: MS Leaders Academy

Conference details: 19-21 February, 2020, Sheffield, UK. **Report by:** Anita Chadha-Patel on behalf of the MS Academy. **Conflict of interest statement:** None declared. **First published on-line:** 19 March 2020.

Despite all the advances in available treatments, data for England in 2018/19 show that nearly one in five people living with multiple sclerosis (MS) were admitted into hospital as an emergency. With an average stay of 7.7 days, the average emergency admission cost is £2844.¹ But the most common reasons for emergency admissions are often preventable with patient risk stratification and proactive care. The MS Academy 'Raising the bar' initiative was set up in 2018 to bring all health professional stakeholders together, identify the barriers to care, and collaborate in workstreams to address practical problems in a timely fashion.

Although all involved are passionate about improving care and health outcomes in MS, it was quickly realised that leadership skills are fundamental to implementing system-wide change. However, leadership is not usually part of formal training and people are often expected to simply 'pick up the skills while on the job'. To this end, one of the key workstreams being implemented is the MS Leaders Academy which, following a robust application and vetting process, has identified 9 potential leaders for development. Course participants represent the spectrum of people working in MS services; from Consultants to Pharmacists, Nurse Specialists and Service Coordinators. The MS Leaders Academy is based on the learning model successfully run by the American Academy of Neurology (AAN), which has enabled a young generation of neurologists to take on leadership roles and has come full circle by these very leaders, newly elected to serve on Board and Committees, updating the policies of the AAN to meet the changing needs of its membership. The 6 month course is run by Professor Gabriele De Luca (University of Oxford) who is himself a graduate of the AAN leadership programme, and his leadership coach Barbara Hoesel who brings her skills and experience from the AAN and similar programmes.

The first face to face meeting of the MS Leaders Academy took place in Sheffield on the 19th-21st February. Course participants were challenged to think about the differences between leadership and management, to define the requirements for modern leadership, and to think about how they would like to lead others. Delegates noted that they hardly ever take the time to reflect on their own skill sets and the learning experiences that have shaped their approach. Discussions touched upon how good health services are

led by people who have a clear vision and who effectively match 'what they say' with 'what they do'. Many of the participants found themselves agreeing that, because of time and resources pressures, they often find themselves taking a management role (problem solving, controlling, budgeting, staffing and organising) whereas a leadership role (setting a direction, aligning and inspiring the team and having a commitment to act) is what is required.

The February meeting focused on the need for leadership, leading self and leading others. Participants were taken through a series of exercises where they considered different communication and work styles, the importance of team synergy, understanding systems and personal agility. The discussions were sometimes personal, not always comfortable, and left delegates motivated to learn. There was agreement that the course content was directly applicable to their roles but was clearly missing from their prior training. Each of the participants has been paired with a senior mentor, and both mentor and mentee have committed to a series of monthly calls where they can discuss problems, go through proven strategies to address the diverse and often unpredictable problems that people working in MS services often face and ideas for further leadership development. Alongside these mentoring calls, participants will also benefit from 1 on 1 and group coaching calls, and will also work on a group project aiming to minimise emergency admissions for people with MS. The leadership group will work together in a shared leadership model and use the resources available to them on the course to develop a detailed proposal, which will be presented first to key stakeholders, and then the wider MS community at the next Raising the bar meeting in November. This will be a key test because the MS Academy comprises members from almost every MS centre in the country, patient advocacy groups as well as NHS England.

Ultimately, the real work of leadership is to create new leaders. The goal is to develop this leadership project into an ongoing programme starting with MS and then moving into other areas of neurology.

Reference

1. Thomas et al (2020). *MS Hospital Episode Statistics Emergency Admissions 2018/19* Wilmington Healthcare London. Available at <http://www.multiplesclerosisacademy.org>

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CGRP, calcitonin gene-related peptide

*Patients with difficult-to-treat migraine were episodic and chronic migraine patients who had documented failure to 2-4 classes of migraine preventive medications²

References:

1. AJOVY[®] SmPC. Teva UK Limited.
2. Ferrari MD *et al. Lancet* 2019; doi: 10.1016/S0140-6736(19)31946-4.
3. Teva UK Limited. Data on File. Fremanezumab DOF 196. 2019.

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teva

Please refer to the Summary of Product Characteristics (SmPC) for full details of Prescribing Information

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Teva UK Limited on 0207 540 7117 or medinfo@teva.com

UK/FREM/19/0006h Date of Preparation: March 2020

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