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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION



In this issue

Ashley Park and Bruce Campbell – The frontiers of acute stroke management

Adrian Williams – Pellagra: 4 D's and 8 Points

Siobhan Leary, Joanne Hurford and Niamh Shanahan – An expert opinion: Vocational rehabilitation after stroke

Madhuri Khilari and Niranjana Panigrahi – Tacrolimus induced diffuse pontine hyperintensity in status epilepticus: a rare entity

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References:

1. AJOVY[®] SmPC. Teva UK Limited.
2. Ferrari MD et al. *Lancet* 2019; 394(10203):1030-1040.
3. Teva UK Limited. Data on File. Fremanezumab DOF 196. 2019.

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CONTENTS

AUTUMN 2020

STROKE ARTICLE

- 04 The frontiers of acute stroke management
Ashley Park and Bruce Campbell

NUTRITION AND STEM CELLS INTRODUCTION

- 10 Nutrition and stem cells as emerging therapies for neurodegenerative disease
Rosemary Fricker

NUTRITION AND STEM CELLS ARTICLE

- 11 Pellagra: 4 D's and 8 Points
Adrian Williams

REHABILITATION ARTICLE

- 13 An expert opinion: Vocational rehabilitation after stroke
Siobhan Leary, Joanne Hurford and Niamh Shanahan

CASE REPORT

- 16 Tacrolimus induced diffuse pontine hyperintensity in status epilepticus: a rare entity
Madhuri Khilari and Niranjana Panigrahi

SPECIAL FEATURES

- 27 Supernumerary phantom limbs
Andrew Larner
- 28 Association of British Neurologists: UK neurology workforce survey
Arani Nitkunan, Joanne Lawrence and Mary Reilly
- 32 Working less than full time – trainee experience, and top tips
Amy Ross Russell and Rhian Raftopoulos
- 34 Personal Perspectives – Tuberous Sclerosis Complex
Philippa Ward
- 36 History of Neurology – John Zachariah Laurence: 'forgotten luminary'
JMS Pearce

REGULARS

- 38 Book reviews
- 39 conference news
- 43 events diary

Well, Goodbye 2020, I cannot say that it has been an easy year, but it has certainly been memorable. Who could have predicted last year that the world would be swept up in a global pandemic, and who really believed we would have a vaccine, available by the end of the year in the UK? I look forward to seeing the published data on all the vaccines.



Ann Donnelly, Co-Editor.

Our strengths as a profession have emerged: finding solutions, adapting quickly, and continual reassessment of our situations, all under pressure of time and resources. Galvanising resolve in the face of overwhelm and despair. Many COVID response articles were submitted to ACNR, demonstrating the attitude of continual improvement and propagation of good practice.

In this issue we look back at the origins of neurology, with a tribute to one of the founding doctors of the National Hospital for Neurology and Neurosurgery, the ophthalmologist John Zachariah Laurence. Looking forward, the ABN survey results are published, giving us a look at the future, more consultants, more diversity, and more less than full time (LTFT) consultants like myself. What this approach to work life balance means for future workforce planning remains to be seen and it is certainly food for thought. The ABN trainees Amy Ross Russell and Rhian Raftopoulos have also provided a balanced view on training LTFT with practical tips for how to navigate this wisely.

Professor Bruce Campbell and Dr Ashley Park review The Frontiers of Acute Stroke management, while Dr Siobhan Leary et al. outline what vocational rehabilitation can do, and what it should look like. This is likely to be an essential part of our post COVID-19 rehabilitation.

Rosemary Fricker introduces a series looking at nutrition and stem cells, while Professor Adrian Williams reminds us of the treatable condition Pellagra, resulting from Vitamin B3-deficiency. On another rare note, Dr Andrew Larner looks historically and clinically at supplementary limb syndrome, while Dr Khilari and Dr Niranjana Panigrahi present a case of probable central posterior reversible encephalopathy syndrome.

It has been 20 years since Professor Roger Barker launched ACNR with Rachael Hansford our publisher and in 2021 we will be celebrating this in our issues throughout the year. Thank you to all of our contributors, and everyone involved with this labour of love for neurology that ACNR represents.

All I can do now is send my best wishes to every reader, and hope for a better 2021.

Ann Donnelly, Co-Editor
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The frontiers of acute stroke management

Abstract

The field of stroke has rapidly advanced in recent years with more effective reperfusion therapies (thrombolysis and endovascular thrombectomy) applied to a broader range of patients, including using imaging-based selection to treat beyond standard time windows. Recent trials have provided signals that neuroprotection and specific treatments for intracerebral haemorrhage may be achievable. The range of targeted secondary prevention strategies has also expanded, particularly with direct oral anticoagulants, more potent lipid lowering agents and patent foramen ovale closure.

Key learning points

- Endovascular thrombectomy offers improved reperfusion and revascularisation rates as well as leading to increased functional independence at 90 days compared with standard medical treatment. Patient factors and imaging findings determine the magnitude of benefit and the risk of adverse effects.
- Advanced imaging with CT perfusion or MR diffusion-perfusion can improve diagnostic confidence and inform the use of thrombolysis >4.5h and thrombectomy >6 h post-onset. CT perfusion may be more accessible compared with MRI in most stroke centres.
- Tenecteplase is a genetically engineered form of tissue plasminogen activator that has a longer half-life, higher specificity for fibrin and increased resistance to plasminogen activator inhibitor-1. It can be administered as a single bolus (without the subsequent infusion required with alteplase). This may be more convenient and effective, especially in centres that do not have endovascular thrombectomy on site.
- Short term use of combined aspirin and clopidogrel for 3 weeks reduces the risk of recurrent stroke after minor stroke and high risk transient ischaemic attack. A low density lipoprotein target <1.8mmol/L also reduces the risk of recurrent stroke.
- Percutaneous closure of patent foramen ovale is now recognised as effective in reducing recurrent stroke in younger patients with no other cause for stroke identified.

The patient journey for acute stroke patients has substantially evolved in recent years. Community recognition of stroke remains suboptimal with further education required to immediately activate emergency services.

Prehospital care

Due to the time sensitive nature of reperfusion therapy, early community recognition of stroke is crucial to rapidly activate emergency services. The FAST (Face, Arm, Speech, Time) mnemonic is used in many English-speaking countries and captures the majority of treatable stroke patients. Paramedic triage tools to identify likely large vessel occlusion (LVO) and transport to an endovascular-capable centre are increasingly used and reduce delays incurred by inter-hospital transfers.¹ In some cities, mobile stroke units equipped with computed tomography (CT) permit rapid assessment of stroke symptoms, exclusion of intracerebral haemorrhage and early thrombolysis with increasing evidence of faster treatment, improved outcomes and cost effectiveness.²

Emergency department care

Prehospital notification of suspected stroke patients can activate the stroke team and radiology staff to clear the CT scanner, facilitating direct transport from emergency department triage to CT.³ These are key elements in reducing door-to-needle time which improves patient outcomes. In regional and rural centres without onsite stroke physician expertise, telestroke consultations provide cost-effective specialist advice and thrombolysis with a safety profile comparable to major metropolitan hospitals.⁴ Telemedicine also allows selection of patients suitable for transfer to an endovascular-capable hospital for thrombectomy.

Brain imaging to diagnose and determine management

The non-contrast CT brain remains essential to identify intracerebral haemorrhage (ICH), hypodensity and more subtle signs of ischaemic stroke such as a hyperdense artery (acute thrombus in an artery) and loss of grey-white differentiation.^{5,6} CT angiography (in the same imaging session) should also be routine to identify large vessel occlusion suitable for endovascular thrombectomy as clinical severity is insensitive. CT perfusion (CTP) is useful to confirm the diagnosis of ischaemic stroke versus mimics and assists clinicians to select thrombolysis and endovascular thrombectomy candidates, particularly beyond standard time windows.^{7,9} The mismatch between a large area of critically delayed flow and a smaller area of severely reduced flow estimates the region of ischaemic penumbra that

is salvageable with rapid reperfusion. MRI is often not immediately available in the emergency department but is more sensitive for the diagnosis of ischaemic stroke and very useful to confirm the diagnosis.

Intravenous thrombolysis

Intravenous thrombolysis with alteplase, a recombinant tissue plasminogen activator (tPA), has been widely used as reperfusion therapy for acute ischaemic stroke presenting within 4.5 hours of symptom onset.¹⁰ The treatment benefit is preserved across the spectrum of age and a wide range of clinical severity but reduces rapidly with elapsed time from stroke onset. Non-disabling stroke patients may not benefit¹¹ but this does not apply to patients with mild but potentially disabling symptoms. Recent trials have indicated benefit of thrombolysis up to 9 hours after onset (or within 9 hours of the midpoint of sleep in wake-up onset stroke) if perfusion imaging is favourable.¹² However, patients with large vessel occlusions of the internal carotid, basilar or middle cerebral artery have relatively early low recanalisation rates.^{13,14}

Tenecteplase is a genetically modified tPA with a longer half-life, higher specificity to fibrin and increased resistance to plasminogen activator inhibitor-1. It is the standard thrombolytic for ST-elevation myocardial infarctions at a dose of 0.5 mg/kg. Recent trials suggest that 0.25mg/kg tenecteplase is more effective than alteplase in large vessel ischaemic stroke with similar safety profile.^{14,15} Single bolus administration of tenecteplase and lower cost in many countries have practical advantages.

Endovascular thrombectomy

Multiple trials published in 2015 established endovascular thrombectomy as a highly effective treatment to reduce disability in patients with ischaemic stroke due to large vessel occlusion, across the spectrum of age and clinical severity. Trials in patients with basilar artery occlusion have been challenging to execute and results equivocal, although most guidelines recommend thrombectomy given the dire natural history.^{16,17}

Endovascular thrombectomy is beneficial in a broad range of patients selected on the basis of large vessel occlusion within 6 hours of stroke onset. Patients also benefit in the 6-24h time window if there is evidence of salvageable brain tissue on more advanced imaging (CT perfusion or MRI).^{8,9} However, the proportion of patients with favourable imaging profiles reduces rapidly over time so treatment should still occur as fast as possible. Ongoing trials are investigating the benefit of thrombectomy in patients with a large area of

irreversibly injured brain and those with mild clinical deficits.

Secondary prevention

There is a 3-15% risk of recurrent stroke within 90 days of an acute ischaemic event or transient ischaemic attack (TIA).¹⁸ Specialist driven management and intervention within a stroke unit has been found to reduce the rate of recurrent stroke and achieve better outcomes.¹⁹ A combination of lifestyle modifications (smoking cessation, diet, exercise) with pharmacological secondary prevention should be used to minimise the risk of recurrent stroke.²⁰

Antiplatelet therapy is key to preventing ischaemic stroke, unless the patient has atrial fibrillation in which case anticoagulation is required. The addition of clopidogrel to aspirin for the first 21 days after onset of mild stroke or high risk TIA reduces the rate of recurrent events compared with aspirin alone.^{18,21} Ticagrelor and aspirin also reduces recurrent stroke versus aspirin alone.²² Unlike clopidogrel, which is a prodrug, ticagrelor does not rely on enzymatic activation for its effect. However, it is currently more expensive than clopidogrel and there are no data comparing its effectiveness for stroke prevention and bleeding risk to clopidogrel.

In patients with atrial fibrillation, direct oral anticoagulants are now generally used in preference to warfarin unless there is renal failure, mechanical prosthetic valve or rheumatic mitral stenosis.²³ Limited data are available to inform timing of anticoagulation after stroke with the volume of stroke generally considered when attempting to balance the risk of haemorrhagic transformation against early recurrent stroke.¹⁹ Dabigatran can be reversed using idarucizumab (including prior to thrombolysis)²⁴ andandexanet alfa has been approved in some countries for reversal of anti-Xa inhibitors.²⁵ For those with genuine contraindication to anticoagulation, left atrial appendage occlusion may be an option.²⁰

Statins have long been part of guidelines to reduce the risk of cardiovascular events including stroke. Recent data indicate that an LDL target of less than 1.8 mmol/L reduces recurrent stroke.²⁶ The new class of proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors may have an increasing role either in combination with a statin or in statin-intolerant patients.

Paradoxical embolism via a patent foramen ovale (PFO) has been a controversial cause of cryptogenic stroke. However, recent trials have established benefit of percutaneous closure, especially in patients aged <60 with no other identifiable cause for stroke.²⁷

Future Directions

Intracerebral haemorrhage remains a therapeutic challenge with no specific therapies other than intensive blood pressure reduction and stroke unit care. A recent minimally invasive surgery trial was neutral overall but patients who had successful removal of haematoma to <15mL appeared to benefit.²⁸ Further trials of haemostatic agents and minimally invasive surgery are ongoing.

Neuroprotection has been a disappointing field for decades. Although neutral overall, a recent trial of nerinetide, as an adjunct to endovascular thrombectomy, showed promise in patients who did not receive alteplase,²⁹ and further trials are ongoing.

Conclusion

Stroke management has dramatically evolved over recent years with high quality evidence for reperfusion with thrombolysis and endovascular thrombectomy, improved secondary prevention strategies targeted to stroke aetiology and streamlined systems of care to accelerate treatment. Ongoing systems evolution, particularly in pre-hospital care, and future strategies for intracerebral haemorrhage, neuroprotection and recovery are the frontiers for further advancement.

REFERENCES

- Suzuki K, et al. *Emergent Large Vessel Occlusion Screen Is an Ideal Prehospital Scale to Avoid Missing Endovascular Therapy in Acute Stroke*. Stroke. 2018;49(9):2096-2101. <https://doi.org/10.1161/STROKEAHA.118.022107>
- Zhao H, et al. *Melbourne Mobile Stroke Unit and Reperfusion Therapy: Greater Clinical Impact of Thrombectomy Than Thrombolysis*. Stroke. 2020;51(3):922-930. <https://doi.org/10.1161/STROKEAHA.119.027843>
- Kim J, et al. *Treatment With Tissue Plasminogen Activator in the Golden Hour and the Shape of the 4.5-Hour Time-Benefit Curve in the National United States Get With The Guidelines-Stroke Population*. Circulation. 2017;135(2):128-139. <https://doi.org/10.1161/CIRCULATIONAHA.116.023336>
- Bagot K, et al. *Integrating acute stroke telemedicine consultations into specialists' usual practice: a qualitative analysis comparing the experience of Australia and the United Kingdom*. BMC Health Serv Res. 2017;17(1):751. <https://doi.org/10.1186/s12913-017-2694-1>
- Guberina N, et al. *Detection of early infarction signs with machine learning-based diagnosis by means of the Alberta Stroke Program Early CT score (ASPECTS) in the clinical routine*. Neuroradiology. 2018;60(9):889-901. <https://doi.org/10.1007/s00234-018-2066-5>
- Vilela P, Rowley H. *Brain ischemia: CT and MRI techniques in acute ischemic stroke*. Eur J Radiol. 2017;96:162-172. <https://doi.org/10.1016/j.ejrad.2017.08.014>
- Campbell B, et al. *Endovascular therapy for ischemic stroke with perfusion-imaging selection*. N Engl J Med. 2015;372(11):1009-18. <https://doi.org/10.1056/NEJMoa1414792>
- Albers G, et al. *Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging*. N Engl J Med. 2018;378(8):708-718. <https://doi.org/10.1056/NEJMoa1713973>
- Nogueira R, et al. *Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct*. N Engl J Med. 2018;378(1):11-21. <https://doi.org/10.1056/NEJMoa1706442>

Multiple trials published in 2015 established endovascular thrombectomy as a highly effective treatment to reduce disability in patients with ischaemic stroke due to large vessel occlusion, across the spectrum of age

10. Emberson J, et al. *Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials.* *Lancet.* 2014;384(9958):1929-35. [https://doi.org/10.1016/S0140-6736\(14\)60584-5](https://doi.org/10.1016/S0140-6736(14)60584-5)
11. Khatri P, et al. *Effect of Alteplase vs Aspirin on Functional Outcome for Patients With Acute Ischemic Stroke and Minor Nondisabling Neurologic Deficits: The PRISMS Randomized Clinical Trial.* *JAMA.* 2018;320(2):156-166. <https://doi.org/10.1001/jama.2018.8496>
12. Campbell BCV, et al. *Extending thrombolysis to 4-5-9 hours and wake-up stroke using perfusion imaging: a meta-analysis of individual patient data from EXTEND, ECASS4-EXTEND and EPITHET.* *Lancet.* 2019;394(10193):139-147. [https://doi.org/10.1016/S0140-6736\(19\)31053-0](https://doi.org/10.1016/S0140-6736(19)31053-0)
13. Bhatia R, et al. *Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action.* *Stroke.* 2010; 41(10):2254-8. <https://doi.org/10.1161/STROKEAHA.110.592535>
14. Campbell BCV, et al. *Tenecteplase Versus Alteplase Before Thrombectomy for Ischemic Stroke.* *N Engl J Med.* 2018;378(17):1573-1582. <https://doi.org/10.1056/NEJMoa1716405>
15. Logallo N, et al. *Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial.* *The Lancet Neurology.* 2017;16(10):781-788. [https://doi.org/10.1016/S1474-4422\(17\)30253-3](https://doi.org/10.1016/S1474-4422(17)30253-3)
16. Liu X, et al. *Endovascular treatment versus standard medical treatment for vertebrobasilar artery occlusion (BEST): an open-label, randomised controlled trial.* *Lancet Neurol.* 2020;19(2):115-122. [https://doi.org/10.1016/S1474-4422\(19\)30395-3](https://doi.org/10.1016/S1474-4422(19)30395-3)
17. Schonewille W and BASICS Investigators. *A Randomized Acute Stroke Trial of Endovascular Therapy in Acute Basilar Artery Occlusion.* 2020 [accessed 2020 June 11]; Available from: <https://eso-wso-conference.org/eso-wso-may-webinar/>
18. Johnston S, et al. *Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA.* *N Engl J Med.* 2018;379(3):215-225. <https://doi.org/10.1056/NEJMoa1800410>
19. Hankey G. *Secondary stroke prevention.* *The Lancet Neurology.* 2014;13(2):178-194. [https://doi.org/10.1016/S1474-4422\(13\)70255-2](https://doi.org/10.1016/S1474-4422(13)70255-2)
20. Esenwa C, Gutierrez J. *Secondary stroke prevention: challenges and solutions.* *Vasc Health Risk Manag.* 2015;11:437-50. <https://doi.org/10.2147/VHRM.S63791>
21. Wang Y, et al. *Clopidogrel with aspirin in acute minor stroke or transient ischemic attack.* *N Engl J Med.* 2013;369(1):11-9. <https://doi.org/10.1056/NEJMoa1215340>
22. Johnston SC, et al. *Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA.* *N Engl J Med.* 2020;383(3):207-217. <https://doi.org/10.1056/NEJMoa1916870>
23. Kirchhof P, et al. *2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS.* *Eur Heart J.* 2016;37(38):2893-2962. <https://doi.org/10.1093/eurheartj/ehw210>
24. Van der Wall S, et al. *Idarucizumab for Dabigatran Reversal in the Management of Patients With Gastrointestinal Bleeding.* *Circulation.* 2019;139(6):748-756. <https://doi.org/10.1161/CIRCULATIONAHA.118.036710>
25. Connolly S, et al. *Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors.* *N Engl J Med.* 2016;375(12):1131-41. <https://doi.org/10.1056/NEJMoa1607887>
26. Amarenco P, et al. *A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke.* *N Engl J Med.* 2020;382(1):9. <https://doi.org/10.1056/NEJMoa1910355>
27. Turc G, et al. *Closure, Anticoagulation, or Antiplatelet Therapy for Cryptogenic Stroke With Patent Foramen Ovale: Systematic Review of Randomized Trials, Sequential Meta-Analysis, and New Insights from the CLOSE Study.* *J Am Heart Assoc.* 2018;7(12). <https://doi.org/10.1161/JAHA.117.008356>
28. Hanley D, et al. *Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): a randomised, controlled, open-label, blinded endpoint phase 3 trial.* *The Lancet.* 2019;393(10175):1021-1032. [https://doi.org/10.1016/S0140-6736\(19\)30195-3](https://doi.org/10.1016/S0140-6736(19)30195-3)
29. Hill M, et al. *Efficacy and safety of nerinetide for the treatment of acute ischaemic stroke (ESCAPE-NA1): a multicentre, double-blind, randomised controlled trial.* *The Lancet.* 2020; 395(10227):878-887. [https://doi.org/10.1016/S0140-6736\(20\)30258-0](https://doi.org/10.1016/S0140-6736(20)30258-0)



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New Study: BrainXpert Energy Complex demonstrates efficacy as alternative fuel source to the brain in patients with Mild Cognitive Impairment

New research from the University of Sherbrooke in Canada, in partnership with the Nestlé Health Science and published in *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, shows that regular consumption of Nestlé Health Science's BrainXpert, a specialised ketogenic drink, could significantly improve cognitive function in people diagnosed with Mild Cognitive Impairment (MCI).

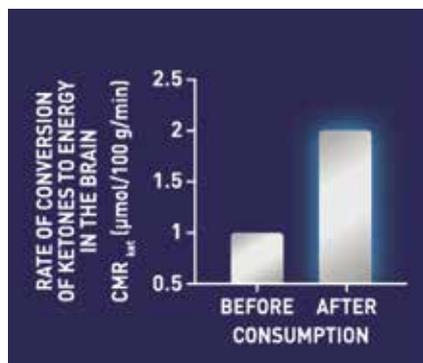
The results show that BrainXpert Energy Complex, a compound contained within BrainXpert, provides an alternative fuel source to glucose in the brain through the use of ketones and could reduce the symptoms experienced by people with MCI, such as forgetfulness and a decline in decision-making ability.

Despite affecting 15-20% of people aged 65+¹ and being twice as prevalent as dementia,² MCI is still a largely unknown condition, with more than half (58%) of the UK having little or no knowledge of it.³ BrainXpert is the first available product which has been clinically proven to have a positive effect on memory and cognitive function for people diagnosed with MCI.

Methodology

The new six-month randomised controlled BENEFIC (Brain ENERGY, Functional Imaging and Cognition) trial investigated the role of ketones, which can be used by the brain as an alternative fuel source to glucose, in the treatment of MCI.

In the randomised controlled BENEFIC trial, the intervention group was given the specialised ketogenic drink (BrainXpert Energy Complex) in a portion of 30g/day of ketogenic medium chain triglycerides (kMCT) that increased blood ketones. In comparison, the placebo group was provided a drink with an equivalent amount of energy that did not produce ketones – both drinks were taken



twice a day for six months.

During the trial, episodic memory was evaluated using the French version of the 16-item free and cued word learning and recall test⁴ and the Brief Visual Memory Test-Revised (BVMT-R).⁵ For executive function, attention and processing speed, the Trail Making test, Stroop Colour and Word Interference test (Stroop), and the Verbal Fluency (VF) tests from the Delis-Kaplan Executive Function System were used respectively. In addition, the Boston Naming Test (TNT)⁶ was used for the assessment of language ability.

Trial results

The trial results confirmed that an intervention with the BrainXpert specialised ketogenic drink clinically demonstrated a doubling of the ketones used by the brain, thereby significantly reducing the brain energy deficit caused by impaired brain glucose metabolism. Participants also showed a statistically significant reduction in MCI symptoms – they had improved memory, improved word recall, were able to think quicker, and were more able to multi-task versus participants that were given the placebo drink.

These ground-breaking results established for the first time that a specialised drink

containing a compound rich in kMCT and milk protein is an effective alternative brain energy source for people living with MCI. This research signals a major breakthrough for the MCI community that, until now, has had no available treatments.⁷

BENEFIC trial principal investigator Professor Stephen Cunnane, from the University of Sherbrooke, Canada said: "Identifying significant improvement in cognitive function in patients with MCI is an exciting development that gives us great motivation to stay on this research track. This is only the beginning and the hope is that further ketogenic innovations can be found to not just boost brain function, but to slow down progression to Alzheimer's disease and other forms of cognitive decline linked to ageing. These results should significantly improve the quality of life for people living with Mild Cognitive Impairment."

Phase one of the BENEFIC trial was published in *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* in 2019, and the cognitive results of Phases 1 and 2 combined were published in the same journal in October 2020.⁸

BrainXpert is now available online at <http://www.brainxpert.com/>. For more information on the study, or BrainXpert, please visit www.nestlehealthscience.com/BrainXpert.

BrainXpert is intended for special medical purposes for the dietary management of patients suffering from Mild Cognitive Impairment. To be used under medical supervision.



References

- Fortier M, et al. *A ketogenic drink improves brain energy and some measures of cognition in mild cognitive impairment*. *Alzheimer's & Dementia* 2019;15:625-634. <https://doi.org/10.1016/j.jalz.2018.12.017>
- World Health Organisation (2019). 'Dementia'. Available at <https://www.who.int/news-room/fact-sheets/detail/dementia>.
- Research conducted amongst 2,000 adults 18+ between 5th October and 8th October 2020.
- Van der Linden M, et al. *L'épreuve de Rappel Libre/Rappel Indiqué à 16 items (RL/RI-16)*. In: M. Van der Linden SA, & A Agniel, editor. *L'évaluation des troubles de la mémoire épisodique (avec leur étalonnage)*. Marseille (France): Solal;2004;p25-47.
- Benedict R. *Brief Visuospatial Memory Test-Revised professional manual*. Odessa, FL: Psychological Assessment Resources; 1997.
- Kaplan E, Goodglass H, Weintraub S. *The Boston Naming Test*. Philadelphia: Lea & Febiger; 1983.
- Fortier M, et al. *A ketogenic drink improves cognition in Mild Cognitive Impairment: results of a 6-month RCT*. In press *Alzheimer's & Dementia* 2020 <https://doi.org/10.1002/alz.12206>.
- Fortier, M, et al. *A ketogenic drink improves cognition in Mild Cognitive Impairment: results of a 6-month RCT*. In press *Alzheimer's & Dementia* 2020 <https://doi.org/10.1002/alz.12206>.

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Nutrition and stem cells as emerging therapies for neurodegenerative disease

Neurodegenerative disease represents an ever-increasing burden to the UK, measured both in decrease in the length and quality of life for patients, and in rising economic cost to the NHS and social care. For example, the prevalence of Parkinson's disease (PD) in the UK is predicted to almost double between 2018 and 2065, from approximately 145,000 to over 256,000 cases. Like PD, dementia (including Alzheimer's disease), Huntington's disease (HD), multiple sclerosis (MS) and other neurodegenerative disorders continue to challenge researchers and clinicians alike; with little in the way of curative therapies in the pipeline.

Research into the treatment of neurodegenerative disorders is currently focusing on key areas: prevention of onset, neuroprotection, delaying or halting disease progression, and cell replacement. The role of nutrition, both during neural development and throughout life, is now being widely investigated; and nutritional supplementation is being evaluated as a neuroprotective therapy. With the discovery of stem cells, cell replacement therapies are now more widely considered to be a realistic option for patients with specific neurodegenerative diseases.

Nutrition

Essential nutrients, and in particular vitamins, have been linked widely with neurodegenerative disease. For example, it is well established that levels of vitamin D decline in older individuals and are generally lower in populations living in northern latitudes. Vitamin D deficiency has been linked with multiple sclerosis and more recently PD, and this vitamin is currently being tested as a neuroprotective therapy in clinical trials for MS.

Conversely excess nutrients might also be damaging to the central nervous system and there are emerging theories that modern diets may expose neurons to toxic levels of metab-

olites. Nicotinamide is one such compound. Found in large quantities in red meat, nicotinamide is a precursor to NAD⁺ the metabolite, integral to the production of energy (ATP) within mitochondria. NAD⁺ levels need to be tightly regulated for normal cellular function, and mitochondrial dysfunction is a key hallmark in multiple neurodegenerative diseases.

There is a plethora of evidence that nutrients and vitamins play a critical role in neural development. For example: retinoic acid (vitamin A), ascorbic acid (vitamin C) and 2 nicotinamide can all influence the conversion of stem cells to neural cells and subsequently neurons.

Thus, there is a clear need to balance nutrient levels both in the developing brain and throughout life. Working at the subcellular level, essential nutrients influence energy supply to neurons, mitochondrial function, and many other cellular processes. There is evidence to suggest that these nutrients may also act on non-neuronal cells within the CNS, including astroglia and immunomodulatory microglia. Therefore, adapting the nutritional balance of those suffering from a neurodegenerative disease may provide a simple yet effective therapy, potentially to slow disease progression or enhance quality of life.

Stem cells and cell replacement therapies

More than four decades of research has been conducted on identifying a suitable cell source for replacement therapies for neurodegenerative disorders, particularly for PD and HD. Indeed, founding editor of ACNR, Professor Roger Barker, currently leads an EU consortium conducting clinical trials in foetal tissue transplants for PD.

Since the early 1990s stem cells have been proposed as a sustainable, reliable and safe source for neuronal replacement. Following extensive laboratory research across the globe,

this work is reaching a critical juncture with the launch of two clinical trials involving transplantation of neural progenitors derived from human pluripotent stem cells: at Kyoto University, Japan; and through the New York Stem Cell Consortia, USA.

Key to success in converting stem cells to functional mature neurons that could be used for cell replacement is the recreation of an optimal environment for stem cell differentiation in the laboratory, i.e. mimicking the developing brain in the culture dish.

This creates the unique opportunity to merge nutritional neuroscience and stem cell technology.

The "nutrition and stem cells" series for ACNR will explore key issues and latest research into nutritional neuroscience and stem cells, as emerging therapies for neurodegenerative disease. Focus will be on current research, including: nicotinamide, vitamin D and other essential nutrients; their roles in neuronal development, stem cell differentiation, immune modulation, neuroprotection and potential for clinical application.

The series will also feature updates from ongoing clinical trials using stem cell transplants and will explore the future of this emerging therapy for neurodegenerative disease.

Rosemary Fricker, PhD HFEA,

is Editor of ACNR's Nutrition and Stem Cells series. She is visiting Professor of Neurobiology at Keele University, and formerly Director of Medical Science, at Keele Medical School.



Cancer anti-sickness drug could offer hope for hallucinations in Parkinson's

Parkinson's UK is partnering with UCL, and investing £1 million in a pioneering phase II clinical trial to explore if the drug ondansetron is safe and effective against hallucinations.

Visual hallucinations are when people see things that aren't there and may affect up to 75% of people with Parkinson's at some point during the condition.

The 12-week trial is set to recruit 216 people over two years in 20-25 NHS clinics across England, Scotland and Wales. Participants will either receive drug or placebo tablets, to take at home for 12 weeks.

<https://bit.ly/2VJBDtQ>

Pellagra: 4 D's and 8 Points



Adrian Williams, MD MSc, is Professor of Neurology in Birmingham, UK. He has a long-standing interest in Nicotinamide metabolism originally in the context of Parkinson's disease, proposing that nicotinamide is a "double edged sword" with toxicity at either end of the dosage range. Later after a MSc sabbatical, he proposed that a higher nicotinamide dietary dose from eating more meat had been an important part of our evolution with a buffer from symbionts in the gut microbiome or more surprisingly TB that excrete nicotinic acid. Such microorganisms when relied upon too heavily can become dysbiotic causing diarrhoea and clinical tuberculosis.

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Abstract

Pellagra has largely been forgotten. This is unfortunate as important lessons are to be learnt for the diseases and social consequences of poverty (and of affluence) that often involve dietary nicotinamide and nicotinamide adenine dinucleotide (NAD) homeostasis. NAD disruption can occur not only from poor diet but from increased consumption of NAD from genotoxic and other stresses. High doses of nicotinamide lead to inhibition of NAD-consuming enzymes and excessive induction of nicotinamide-n-methyl transferase (NNMT) with consequent effects on the methylome giving a mechanism for a new hypervitaminosis-B3.

The history of Pellagra has been largely forgotten even if the 4 'D's' of Dementia, Dermatitis, Diarrhoea and Death are still taught to medical students.^{1,2}

Few realise that a festinating gait, fasciculation of the tongue or myoclonic encephalopathy were first described in the pellagra epidemics and other close mimics of many neurodegenerative and neuropsychiatric diseases were seen.

Pellagrins were prone to both dysbiotic and acute infections explaining the gut manifestations and the high incidence of TB. It was widely believed to be hereditary and certainly ran in families.

The original 18th century European epidemics affected poor peasants on monophagic maize based polenta diets. The early 20th century American epidemic predominantly affected poor blacks (and whites) often working as semi-slave sharecroppers thrown into poverty with the collapse of the cotton market and eating maize, molasses and small quantities of low quality pork.

Pellagra was believed to be degenerative in the dehumanising and atavistic sense of the term. Homo sapiens evolved on a high meat high nicotinamide diet so pellagra can now be seen as an example of human evolution in reverse. Inferior cognition and antisocial and addictive behaviours led to discrimination as the degenerate "Butterfly caste" contrasting with most societies that have ruling "meat elites". Pellagrins were seen as a different race having a different physiognomy that crossed colour lines, even though it was, as it turned out, an archetypal disease of poverty, rather like TB. Pellagrins were at times subject to and used as an exemplar to justify eugenic thinking.

Pellagra was a systems failure causing premature ageing with evidence of mitochondrial failure, oxidative stress and proteinopathy. Pellagra was curable particularly after the discovery of nicotinamide in the 1940s and is normally sourced from animal products such as Vitamin B3. There were many undiagnosed and untreated cases as the exaggerated sunburn rash (Casal's necklace) was often not present ("pellagra sine pellagra") particularly in those with pigmented skin.

Point 1

A disorder that mimicked many neurodegenerative conditions as now classified can have a single and simple dietary cause even when there is evidence for (epi-) genetic involvement, dysbiotic microbiomes, mitochondrial and oxidative stress, and proteinopathy. Dietary nicotinamide with back-up from the degradation of tryptophan on the kynurenine pathway are the precursors to NAD critical to mitochondrial energetics as NADH (and other dehydrogenase reactions), anabolism as NADP(H), and NAD consumer pathways in a "NAD" world.³ Stress from toxins, whether chemical or microbial, requiring DNA or tissue repair by NAD consuming enzymes such as poly ADP ribose polymerases (PARPs) and Sirtuins could have the same pathological result if the dose of nicotinamide is not increased.

Point 2

Pellagra may be being missed. The better known clinical manifestations were recognised as being the "tip of the iceberg" in the epidemics in Europe and the south-eastern confederate states of the USA. Pellagra may be endemic in the millions in poverty who are meat and milk deprived masquerading as Kwashiorkor ("juvenile pellagra") or "environmental enteropathy" or as poor cognition particularly in black populations who are resistant to the sunburn rash. A community screening test that would not be difficult to develop should be a priority.⁴

Point 3

Tuberculosis (TB), dysbiotic diarrhoeal illnesses and high death rates from acute infections, such as smallpox and measles, disappear as societies increase their meat and nicotinamide intake. This is no mystery as nicotinamide and its analogues, such as Isoniazid, are TB antibiotics and many bacterial toxins interact with NAD-consumer pathways – so being NAD replete would improve host resistance.^{5,6} Topically, COVID-19 interferes with the

tryptophan uptake pathway and therefore NAD levels and T cell and Interferon responses through the Angiotensin-converting enzyme (ACE2) receptor through which it enters cells (that also malfunctions with mutations that lead to Hartnup disease that includes a pellagra-like syndrome). Some clinical manifestations, such as on gut and on cognition or long COVID, could be “formes frustes” or new versions of pellagra.⁷

Point 4

Reduction in many infections coincided with “meat transitions” and triggered demographic and epidemiological switches toward infertility and auto-immune, allergic and other diseases of modernity. Immune intolerance with changes in T cell subset ratios come about from less use of Indoleamine 2,3-dioxygenase (IDO) and the tryptophan to kynurenine “immune tolerance” pathway as in house production of nicotinamide is no longer necessary.⁸ Dietary modification of nicotinamide or tryptophan in diet, perhaps in concert with other vitamins such as Vitamin D, could affect the incidence of auto-immune conditions such as Multiple Sclerosis.⁹

Point 5

Meat transitions and “modernity” have, as if by magic, reduced the incidence of premature ageing, dementia, and death. Stunted lives were features of pellagra and in all species there are well described links between NAD metabolism, stem cell health and ageing, alongside resistance to infection, so no magic or much medicine is required. NAD levels fall with age and even further with many diseases of ageing and could respond to supplementation.¹⁰⁻¹²

Point 6

Early pellagra-ologists, such as Lombroso, may have been right in sensing that pellagrins were atavistic examples of degeneration in the 19th century sense of the term given that increasing meat intake was an important step in our evolution. For most of our evolution as hunter-gatherers we shared meat so the non-egalitarian meat variances that later developed are surprising and are now extreme with 100 fold variances across the globe between rich and poor. As a result, the poor particularly in poor countries face an adverse metabolic and transgenerational NAD headwind.¹³

Point 7

Inequalities of meat intake between classes and countries need to be fairer. Such extremes can be traced back to 17th century common pastureland “enclosure” movements and 19th century colonialism with the creation of the “third world”

both channelling meat to the wealthy. Earlier extremes between the Old World and the New World that had few natural animal domesticates were corrected by the Columbian exchange enabling the rise of the West. However the global South was also unlucky in its meat supply, particularly Africa with a lack of animal domesticates and unhelpful human and veterinary infections in the tsetse fly belt with trypanosomiasis and rinderpest.

Point 8

There may be a state of hypervitaminosis-B3. Many conditions, such as some cancers and metabolic syndromes common with affluence and a high meat intake (let alone nicotinamide supplementation) are linked to induction of the enzyme NNMT. NNMT detoxifies nicotinamide but consumes valuable methyl groups and nicotinamide overload might over-inhibit NAD-consumer enzymes that are metabolic master molecules.¹⁴⁻¹⁶ Nicotinamide’s methylated derivative resembles the dopaminergic neurotoxin MPTP and may, like nicotinamide, be a “double-edged sword”.

Conclusion

Pellagra’s history is well worth remembering given that nobody systematically makes sure that it or “pellagra sine pellagra” is eliminated. Many in poverty remain at risk given that variances of meat intake are now historically extreme across countries and classes. Multi-organ pellagra was never “owned” by any one specialty but it should have remained a public health concern doubtless helped by supplementation but not helped by never being a universal policy. Nicotinamide’s potential toxicity in high meat economies was also never monitored over the long-term.

Dietary dosage or nicotinamide supplements may need to be boosted when individuals have certain mutations or are under stress, whether genotoxic or anoxic/metabolic – or restrained if there really is a hypervitaminosis B3 contributing to diseases of affluence. The environmental cost of optimising meat intake would be mitigated by affluent countries eating and wasting less but sharing more. The meat supply needs to be safe, with the poor not having to rely on “bush meat” or “wet markets” so as not to risk food poisoning or old and new zoonoses, such as COVID-19. Supplementation of nicotinamide alone may not be enough as animal products contain other helpful micronutrients such as iron and sources of methyl-groups such as choline and vitamin B12.

REFERENCES

- Rajakumar K. *Pellagra in the United States: a historical perspective*. Southern medical journal. 2000;93(3):272-7. <https://doi.org/10.1097/00007611-200093030-00005>
- Williams AC, Ramsden DB. *Pellagra. A clue as to why energy failure causes diseases?* Medical hypotheses. 2007;69(3):618-28. <https://doi.org/10.1016/j.mehy.2007.01.029>
- Imai S. *The NAD World: a new systemic regulatory network for metabolism and aging—Sirt1, systemic NAD biosynthesis, and their importance*. Cell biochemistry and biophysics. 2009;53(2):65-74. <https://doi.org/10.1007/s12013-008-9041-4>
- Williams AC, Hill LJ. *The 4 D’s of Pellagra and Progress*. International journal of tryptophan research : IJTR. 2020;13:1178646920910159. <https://doi.org/10.1177/1178646920910159>
- Pajuelo D, Gonzalez-Juarbe N, Tak U, Sun J, Orihuela Cj, Niederweis M. *NAD(+) Depletion Triggers Macrophage Necroptosis, a Cell Death Pathway Exploited by Mycobacterium tuberculosis*. Cell reports. 2018;24(2):429-40. <https://doi.org/10.1016/j.celrep.2018.06.042>
- Deng Q, Barbieri JT. *Molecular mechanisms of the cytotoxicity of ADP-ribosylating toxins*. Annual review of microbiology. 2008;62:271-88. <https://doi.org/10.1146/annurev.micro.62.081307.162848>
- Baig AM, Khaleeq A, Ali U, Syeda H. *Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms*. ACS chemical neuroscience. 2020;11(7):995-8. <https://doi.org/10.1021/acscchemneuro.0c00122>
- Williams AC, Hill LJ. *Nicotinamide and Demographic and Disease transitions: Moderation is Best*. International journal of tryptophan research: IJTR. 2019;12:1178646919855940. <https://doi.org/10.1177/1178646919855940>
- Sonner JK, Keil M, Falk-Paulsen M, Mishra N, Rehman A, Kramer M, et al. *Dietary tryptophan links encephalogenicity of autoreactive T cells with gut microbial ecology*. Nature communications. 2019;10(1):4877. <https://doi.org/10.1038/s41467-019-12776-4>
- McReynolds MR, Chellappa K, Baur JA. *Age-related NAD(+) decline*. Experimental gerontology. 2020;134:110888. <https://doi.org/10.1016/j.exger.2020.110888>
- Rajman L, Chwalek K, Sinclair DA. *Therapeutic Potential of NAD-Boosting Molecules: The In Vivo Evidence*. Cell metabolism. 2018;27(3):529-47. <https://doi.org/10.1016/j.cmet.2018.02.011>
- Zhang M, Ying W. *NAD(+) Deficiency Is a Common Central Pathological Factor of a Number of Diseases and Aging: Mechanisms and Therapeutic Implications*. Antioxidants & redox signaling. 2019;30(6):890-905 <https://doi.org/10.1089/ars.2017.7445>
- Williams AC, Hill LJ. *Nicotinamide as Independent Variable for Intelligence, Fertility, and Health: Origin of Human Creative Explosions?* International journal of tryptophan research: IJTR. 2019;12:1178646919855944. <https://doi.org/10.1177/1178646919855944>
- Pissios P. *Nicotinamide N-Methyltransferase: More Than a Vitamin B3 Clearance Enzyme*. Trends in endocrinology and metabolism: TEM. 2017;28(5):340-53. <https://doi.org/10.1016/j.tem.2017.02.004>
- Schmeisser K, Parker JA. *Nicotinamide-N-methyltransferase controls behavior, neurodegeneration and lifespan by regulating neuronal autophagy*. PLoS genetics. 2018;14(9):e1007561. <https://doi.org/10.1371/journal.pgen.1007561>
- Williams A, Ramsden D. *Nicotinamide: a double edged sword. Parkinsonism & related disorders*. 2005;11(7):413-20. <https://doi.org/10.1016/j.parkreldis.2005.05.011>



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An expert opinion: Vocational rehabilitation after stroke

Key messages

- Ask the work question and start vocational rehabilitation early after stroke.
- Invisible symptoms pose particular challenges for the return to work process.
- Increased commissioning of resources is required to provide equitable and timely access to vocational rehabilitation services.

Abstract

Less than half of people return to work following a stroke. For those who do, their return is often complicated by residual 'invisible' symptoms. It is important to ask about work and to provide intervention early in the rehabilitation process. Specialist vocational rehabilitation services can support more complex and long-term interventions, but there is a paucity of service provision which needs to be addressed.

One in four strokes occur in people of working age.¹ Return to work is often a key goal for the person with a stroke and important for maintaining quality of life and wellbeing.² However, less than half of those in employment return to work after a stroke.²

Why do so few stroke survivors return to work?

Many factors may present barriers to returning to work. These include the stroke location, severity of symptoms, skills and demands of the job role, work culture and type of industry, and employer's attitudes to disability. There are often complex relationships between these factors and understanding the impact of disease-related factors within the employment context, and the wider psychosocial situation, is key to addressing return to work. The job role may significantly influence the impact of any impairment. For example, a taxi driver may not be able to return to work with a hemianopia, whereas an office worker could.

'Invisible' symptoms pose particular challenges for the return to work process and sustaining employment. These include fatigue, cognitive changes, aphasia and visual impairment. Invisible symptoms may be difficult for employers to understand

and to make accommodations for. The person with the stroke may not anticipate their impact on their ability to work. Fatigue is a common symptom that is often underestimated. This may result in a premature return with an unsustainable work pattern, leading to further sickness absence or job loss. Cognitive impairments may have wide-ranging effects. For example, executive dysfunction can manifest in difficulties with planning and problem solving, insight and awareness and social cognition. Such symptoms can lead to diminished work performance and, if not addressed, carry risk to the person's job security and to the business.

The psychological impact of stroke also influences return to work. Psychological sequelae including post-traumatic stress, anxiety, low mood, confidence and adjustment issues, and maladaptive coping styles may all contribute to poor outcomes. Negative self-appraisals of 'being unable to perform as well as before' can activate beliefs around incompetence and failure that, without skilled intervention, can perpetuate cycles of avoidance and worsen outcome.

Employer factors, such as the size and scope of the organisation and its willingness to be flexible, can be highly influential to the outcome. There is increasing government drive for employers to support people with disability in work,³ but this may present complex issues for employers and many lack knowledge and experience.⁴ The broader social context is also relevant and lower socioeconomic status is associated with an increased incidence of stroke. Stroke survivors may be less likely to have secure job contracts and income protection insurance, increasing their risk of job loss.

What help is available to support return to work?

Some people with mild symptoms can successfully return to work unaided or with minimal signposting and advice. Many others will require vocational rehabilitation to return to and remain in work, or to leave work in a supported way. Vocational rehabilitation can be provided by post-acute and community stroke rehabilitation teams and specialist vocational rehabilitation services. However, provision of vocational rehabilitation for stroke survivors in

the UK has been disorganised and patchy.⁵ Some community teams are structured to provide vocational rehabilitation as an adjunct therapy, but others lack the resources or perceived expertise to provide this. The early supported discharge model may only be resourced to intervene for a few weeks, and this may fall short of the longer term demands of a return to work intervention. Specialist NHS vocational rehabilitation services can provide more complex and long-term interventions but are scarce and, with demand frequently out-stripping capacity, may not always be able to intervene in a timely manner.

Aside from NHS resources, help may be available through generic occupational health services or private vocational rehabilitation services, although usually only accessed through an employer or insurance company. The government provides other work support including Jobcentre Plus and Access to Work, but these do not provide comprehensive vocational rehabilitation programmes. Employment support services are available through third sector organisations both nationally, such as Attend ABI and Scope, and regionally, such as Leonard Cheshire and Shaw Trust, but these usually cannot provide complex multidisciplinary interventions. The Stroke Association also provides helpful guidance on returning to work after stroke.⁶

What is the recommended approach to vocational rehabilitation?

There is little evidence to guide best practice in vocational rehabilitation. Only one randomised controlled trial, which reported benefits from workplace interventions, has been completed,⁷ and systematic reviews have found insufficient evidence to make recommendations.^{8,9} Despite this, there is growing recognition of the need for a systematic approach to vocational rehabilitation following stroke. The NICE quality standard for stroke states that adults who have a stroke are offered active management to return to work if they wish to do so.¹⁰ The Royal College of Physicians National Clinical Guideline for Stroke recommends commissioning of specialist vocational rehabilitation services in accordance with their guidance (Table 1).¹¹

When should vocational rehabilitation start?

The importance of having the work conversation and starting vocational rehabilitation early after stroke is increasingly recognised.¹² Vocational rehabilitation should start as soon as feasible after the stroke, and not be deferred to when the person wishes to return to work. Informed discussion about disclosure and early communication with the employer should be encouraged. Key areas to be addressed in the early phase are suggested in Box 1.

The need for early and integrated vocational rehabilitation after stroke is acknowledged in the NHS Long Term Plan.¹³ An inte-

Table 1. Stroke rehabilitation: recommendations for work. Adapted from the Royal College of Physicians National Clinical Guideline for Stroke.¹¹

National clinical guideline for stroke: recommendations for work
A. People with stroke should be asked about their pre-stroke work activities.
B. People who wish to return to work after stroke (paid or unpaid employment) should: <ul style="list-style-type: none"> – have their work requirements established with their employer (provided the person with stroke agrees); – be assessed cognitively, linguistically and practically to establish their potential for return; – be advised on the most suitable time and way to return to work, if return is feasible; – be referred through the job centre to a specialist in employment for people with disability if extra support or advice is needed; – be referred to a specialist vocational rehabilitation team if the job centre specialist is unable to provide the necessary rehabilitation.
C. Vocational rehabilitation programmes for people after stroke should include: <ul style="list-style-type: none"> – assessment of potential problems in returning to work, based on the work role and demands from both the employee's and employer's perspectives; – an action plan for how problems may be overcome; – interventions specifically designed for the individual which may include: vocational counselling and coaching, emotional support, adaptation of the working environment, strategies to compensate for functional limitations in mobility and arm function, and fatigue management; – clear communication between primary and secondary care teams and including the person with stroke, to aid benefit claims or to support a return to work.

Box 1. Key areas to address with early vocational rehabilitation

- Ask the work question as part of systematic acute stroke screening
- Signpost to advice on disability and employment rights
- Manage expectations to avoid premature return to work
- Communicate with the employer to provide education and manage expectations
- Establish links between post-acute, community and specialist vocational rehabilitation services

grated post-acute stroke rehabilitation service is to be piloted and vocational rehabilitation is a key requirement, with pilot sites expected to provide support for at least six months. This early input is welcome but, for some people, it may be several months before they are ready to focus on returning to work, and so access to vocational rehabilitation must still be available in the longer term.

Which disciplines are required?

Stroke may result in a range of neurological impairments, and there may be other associated medical issues. Therefore, a multidisciplinary team is required, with core disciplines including occupational therapy, neuropsychology, speech and language therapy and neurology/stroke/rehabilitation medicine. Although there is no evidence for a multidisciplinary approach in vocational rehabilitation, there is some evidence for this approach with other rehabilitation interventions.¹⁴

The multidisciplinary vocational rehabilitation out-patient service at the National Hospital for Neurology and Neurosurgery was established in 2013. It is one of just three specialist neurological vocational rehabilitation services in London. It supports people with acute and progressive neurological conditions with return to work (paid and unpaid employment), job retention and supported exit; about one third are stroke survivors. The service has dedicated occupational therapy, neuropsychology and neurology, and direct access to other disciplines.

In our experience, multidisciplinary assessment aims to develop a thorough formulation of a person's stroke symptoms and pre-morbid factors, beliefs about work, level of occupational performance and baseline cognitive functioning, as well as job demands and the social and physical environment. This process is key to understanding the individual's unique needs and interventions required.

Which interventions are useful?

There is insufficient evidence to definitively recommend specific interventions. In our opinion, interventions should be individually tailored and focused on functional goals identified collaboratively with the stroke survivor. The primary goal is usually returning to work with adjustments. Therefore, establishing and maintaining relationships with the employer is key to the process,⁴ and interventions may need to continue after the point of return to facilitate a sustained outcome. Some may achieve their goals with short-term uni-disciplinary interventions such as implementation of strategies to self-manage symptoms. Others,

Box 2. Common vocational rehabilitation interventions

- Job demand analysis: leading to work hardening and task simulations, to help build insight and highlight any difficulties prior to returning to work.
- Establishing the right timing for return to work.
- Developing a plan for graded return to work, working hours and duties, and reasonable adjustments.
- Neurological fatigue assessment and education: to pro-actively manage symptoms through behavioural change and attitudes to rest.
- Providing emotional support to address adjustment issues, anxiety and the impact of the stroke on the individual's sense of identity and ability to work in the same way as before.
- Understanding cognitive strengths and weaknesses and developing compensatory strategies specific to the individual's working role.
- Exploring difficult work relationships and promoting psychological strategies to manage these.
- Educating the employer regarding the condition, invisible symptoms and stroke recovery.
- Empowering the individual to communicate about their stroke and changing needs with their employer.
- Meeting with the individual and employer to establish expectations and the employer's willingness to support the return to work and explain rationale for reasonable adjustments.
- Monitoring return to work and exploring alternatives where current work is not feasible or cannot be sustained.

particularly those with complex invisible symptoms and reduced insight, may require various facets of multi-disciplinary intervention over the longer-term (Box 2). Managing the person's expectations and supporting the evolving adjustment to their situation is a central aspect throughout the process. If job demands outweigh the person's new capabilities, the goal may change to a supported work exit with interventions focused on exploring meaningful activities to replace work and ascertaining financial stability.

How should outcome be measured?

It is important to measure outcome to assess efficacy of interventions and support development of services. Vocational rehabilitation is a difficult area to measure and there is a lack of robust outcome measures. Even return to work is heterogeneous in nature and not a defined outcome.¹⁵ Some employment programmes focus on return to work as the main outcome and cease intervention when the person starts back at work. In our experience, this is not helpful and may lead to premature return to work, breakdown in the process and risk of sickness absence or job loss.

What are the future priorities?

The priority for stroke vocational rehabilitation is to increase commissioning of resources to provide equitable and timely access to services. Research into the most effective service models, interventions and outcome measures is also essential. A multicentre randomised controlled trial to assess the effectiveness of early stroke specific vocational rehabilitation is currently underway in the UK,¹⁶ and it is hoped that there will be further such robust trials. In the meantime, stroke services should adapt their clinical practice to raise the work question early and to establish pathways with existing vocational rehabilitation services.

REFERENCES

1. Stroke Association. *State of the nation 2018*. https://www.stroke.org.uk/sites/default/files/state_of_the_nation_2018.pdf
2. Daniel K, Wolfe C, Busch M, McKevitt C. *What are the social consequences of stroke for working-aged adults? A systematic review*. *Stroke* 2009;40:431-40. <https://doi.org/10.1161/STROKEAHA.108.534487>
3. Department for Work & Pensions, Department of Health. *Improving lives. The future of work, health and disability*. Her Majesty's Stationery Office 2017. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/663399/improving-lives-the-future-of-work-health-and-disability.PDF
4. Coole C, Radford K, Grant M, Terry J. *Returning to work after stroke: perspectives of employer stakeholders, a qualitative study*. *J Occup Rehabil* 2013;23:406-18. <https://doi.org/10.1007/s10926-012-9401-1>
5. Sinclair E, Radford K, Grant M, Terry J. *Developing stroke-specific vocational rehabilitation: a soft systems analysis of current service provision*. *Disabil Rehabil* 2014;36:409-17. <https://doi.org/10.3109/09638288.2013.793410>
6. Stroke Association. *A complete guide to work and stroke*. 2018 <https://www.stroke.org.uk/resources/complete-guide-work-and-stroke>
7. Ntsiea M, Van Aswegen H, Lord S, Olorunju SS. *The effect of a workplace intervention programme on return to work after stroke: A randomised controlled trial*. *Clin Rehabil* 2015;29:663-73. <https://doi.org/10.1177/0269215514554241>
8. Baldwin C, Brusco N. *The effect of vocational rehabilitation on return to work rates post stroke: A systematic review*. *Topics in Stroke Rehabilitation* 2005;18:562-72. <https://doi.org/10.1310/tsr1805-562>
9. Brouns R, Valenzuela A, Goudman E, Moens M, Verlooy J. *Interventions to promote work participation after ischaemic stroke: A systematic review*. *Clin Neurol Neurosurg* 2019;185:105458. <https://doi.org/10.1016/j.clineuro.2019.105458>
10. National Institute for Health and Care Excellence. *Stroke in adults. Quality standard*. 2016 <https://www.nice.org.uk/guidance/qs2/resources/stroke-in-adults-pdf-58292707525>
11. Intercollegiate Stroke Working Party. *Royal College of Physicians National Clinical Guideline for Stroke*. 2016 [https://www.strokeaudit.org/SupportFiles/Documents/Guidelines/2016-National-Clinical-Guideline-for-Stroke-5t-\(1\).aspx](https://www.strokeaudit.org/SupportFiles/Documents/Guidelines/2016-National-Clinical-Guideline-for-Stroke-5t-(1).aspx)
12. Dworzynski K, Ritchie, G, Fenu E, MacDermott K, Playford D. *Rehabilitation after stroke: summary of NICE guidance*. *BMJ* 2013;346:f3615. <https://doi.org/10.1136/bmj.f3615>
13. National Health Service. *The NHS Long Term Plan*. 2019 <https://www.longtermplan.nhs.uk/wp-content/uploads/2019/08/nhs-long-term-plan-version-1.2.pdf>
14. Turner-Stokes L, Pick A, Nair A, Disler PB, Wade DT. *Multi-disciplinary rehabilitation for acquired brain injury in adults of working age*. *Cochrane Database Syst Rev* 2015;CD004170. <https://doi.org/10.1002/14651858.CD004170.pub3>
15. Radford K, Grant MI, Sinclair EJ, Kettlewell J, Watkin C. *Describing Return to Work after Stroke: A Feasibility Trial of 12-month Outcomes*. *J Rehabil Med* 2020;52:jrm00048.
16. Radford K. *RETurn to work After stroKE. Pragmatic, multicentre RCT with internal pilot, cost effectiveness evaluation and embedded process evaluation, comparing Early Stroke Specialist Vocational Rehabilitation (ESSVR) in addition to usual NHS Rehabilitation to usual NHS rehabilitation alone*. <https://www.nottingham.ac.uk/research/groups/strokerehabilitation/documents/retake-study-summary-v1.0.pdf>

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Tacrolimus induced diffuse pontine hyperintensity in status epilepticus: a rare entity

Key learning points

1. Diffuse non-restricted pontine Hyperintensity is a significant clue towards the rare central Posterior Reversible Encephalopathy Syndrome.
2. Tacrolimus, Hypertension, chronic kidney disease are a few of the underlying factors to be looked for and corrected.
3. Serum tacrolimus levels may not correlate with the clinical picture of neurotoxicity. Stopping it might be beneficial despite normal serum drug levels.

Abstract

Posterior reversible encephalopathy syndrome resulting from the hypertension-induced failure of cerebral autoregulation, is a well-described neuro-imaging finding resulting from vasogenic oedema. Pontine Hyperintensities resulting from this condition need recognition to prognosticate and avoid unnecessary investigations. We report a 48-year-old male with chronic diabetes mellitus, hypertension and chronic kidney disease, and history of liver transplantation who presented with established status epilepticus. He was on Tacrolimus for prophylaxis for graft rejection. His MRI brain showed diffuse pontine and predominantly left thalamic hyperintensity, which suggested the diagnosis of central PRES. His evaluation for CNS infections and autoimmune encephalitis was negative. On stopping Tacrolimus, the imputed drug, and control of hypertension, along with dialysis, and symptomatic management for seizures, a complete recovery was observed over one week. Repeat MRI also showed partial regression of the pontine hyperintensity. This report documents the importance of this less described neuroradiological finding that can change management significantly and have a bearing on the prognosis.

Tacrolimus induced brain white matter abnormalities have long been described.¹ Posterior reversible encephalopathy syndrome (PRES), a clinico-radiological syndrome that can occur following tacrolimus administration

or other aetiologies, is also characterised in the literature. However, the typical description of PRES imaging is occipito-parietal white matter abnormality. There has been a flurry of literature recently dwelling on the atypical or central variant of PRES. This finding constitutes variable involvement of the brainstem and the basal ganglia. As this condition carries a good prognosis timely recognition is paramount. This case report emphasises recognising atypical brainstem involvement in patients who present with neurological complications while being on Tacrolimus.

Case Presentation

A 48-year-old male presented to the casualty unit with status epilepticus. Seizures started the morning of admission, and he was brought to the hospital within about half an hour of onset. Seizures persisted despite the administration of phenytoin, Levetiracetam. He was a post-liver-transplantation patient (post alcoholic liver cirrhosis), with chronic renal failure, on Tacrolimus 0.5mg twice a day, and mycophenolate mofetil 750mg twice a day for the last four years. He also had diabetes mellitus, hypertension, and chronic kidney disease (CKD).

He was afebrile, comatose on admission, with no motor response on deep painful stimulation. There were no meningeal signs. His blood pressure at presentation was 190/100mmHg (Mean arterial pressure 130mmHg), the baseline being around 160/90mmHg. Pupils were symmetrical and reacting to light, and the doll's eye response was preserved. Fundus evaluation revealed severe diabetic retinopathy, but no disc oedema.

Seizures subsequently were controlled after administration of lorazepam and loading dose of sodium valproate. Blood pressure was promptly controlled with intravenous labetalol infusion. Serum magnesium levels were 1.5mEq/L, while the other electrolytes were normal on admission. Liver function tests were normal. Serum creatinine was 3.5mEq/L, which was his baseline value. He had a haemoglobin of 7.7gm/dL on admission. MRI brain and CSF evaluation were subsequently done.

On day three after admission, he developed reduced urine output, necessitating daily haemodialysis for about a week. Gradually his sensorium improved. On regaining consciousness, he did recol-

lect a headache on the morning of the day of seizures; however, he was amnesic about the events that followed. There were no focal neurological deficits on recovery.

Clinically, two diagnostic possibilities were considered initially: encephalitis, considering his immunosuppressed status; and hypertensive encephalopathy, considering the high blood pressure. He was evaluated for infectious and autoimmune encephalitis. CSF pressure was normal (20cc of H₂O), and CSF was acellular with mildly elevated proteins (49mEq/L). Workup for CNS infections and autoimmune encephalitis was negative (Table 1).

MRI brain helped us nail the diagnosis. It showed findings suggestive of non-restricted pontine and thalamic hyperintensity in the FLAIR and T2 weighted images. The clinical picture along with the imaging findings favoured the diagnosis of PRES.

Diagnosis of PRES in this patient was confirmed by expression of central PRES pattern, as shown in Figure 1. a, b, and c with vasogenic oedema, reversibility on follow up (partial reversal after ten days in our case), as shown in Figure 2. a and b, along with the typical clinical presentation of PRES.

We considered Tacrolimus as an added imputing factor, in addition to hypertension and CKD. It was deemed an added attributing element, in addition to hypertension and CKD, and was, therefore, stopped. The patient discussed here had slightly low serum magnesium levels that were corrected after admission.

Discussion

Reversible Posterior Leukoencephalopathy Syndrome was initially described by Hinchey et al. back in 1996. They had noted patients with headache, altered sensorium, seizures, and visual deficits that completely reversed with treatment, along with the reversal of parieto-occipital white matter changes that correlated with the clinical picture.² The clinical and radiological findings are attributed to subcortical vasogenic oedema resulting from a capillary leak from endothelial damage and disruption of the blood-brain barrier.³ A myriad of causes and multiple comorbidities have been stated behind this disorder. These include hypertension, immunosuppressive drugs like calcineurin inhibitors, CKD, dialysis

Table 1: Investigations:		
Serum Tacrolimus levels	2.54	Therapeutic range 5-20 ng/ml
Liver Function tests	Direct Bilirubin	0.41
	Indirect Bilirubin	0.11
	AST	42
	ALT	20
	Alkaline Phosphatase	270 U/L
Renal Function Tests	Albumin	2.26
	Urea	48.65mg/L
	Creatinine	3.36 mg/dL
	Calcium (Total)	7.92
Cerebrospinal Fluid	Phosphorous	6.95
	Cells	2cells/cu mm (lymphocytes)
	Protein	49 mg/dL
	Glucose	80 mg/dL
Gene expert TB	Gene expert TB	Negative
	Biofire PCR	Negative
	Bacteria:	
	E. coli	
	H. influenzae	
	L. monocytogenes	
	N. meningitidis	
	S. agalactiae	
	S. pneumoniae	
	Viruses	
	CMV	
	Parvovirus	
	HSV 1,2	
	HHV6	
	VZV	
Paraechovirus		
C. neoformans, gatti		
M. Tb complex		
India ink	Negative	
Complete Blood Count	Hb	7.7
	TLC	8.9 (N: 91%)
S. Sodium	143 mEq/L	
S. Magnesium	1.5 mEq/L	
Auto-immune Encephalitis panel:		
	NMDA, AMPA, GABA B, LGI1, CASPR2 (VGKC type)	Negative
Anti Thyroid Antibodies		Negative



Figure 1a: Axial FLAIR showing diffuse pontine hyperintensity.

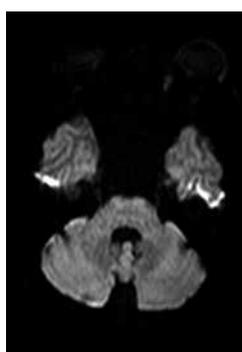


Figure 1b: showing corresponding DWI with lack of restriction.

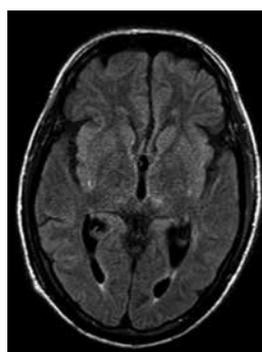


Figure 1c: showing left thalamic subtle hyperintensity.

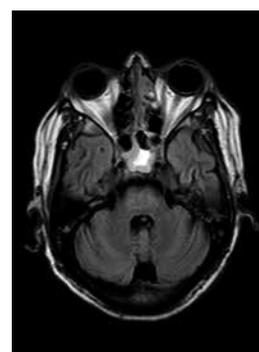


Figure 2a: showing subtle reduction in the diffuse pontine hyperintensity in FLAIR at day 10.

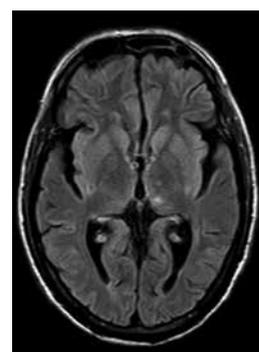


Figure 2b: shows the left thalamus hyperintensity at day 10.

dependency, malignancy, and hypertension.^{2,3} Some studies describe an association of renal insufficiency and PRES; however, the mean arterial pressure in one study was 150mmHg.⁴ Hence, the real underlying cause could still be hypertension. Three patients in the case series by Hinchey et al., who developed PRES while being on Tacrolimus, had normal blood pressure. However, hypertension and nephropathy are known with Tacrolimus as well as cyclosporine related CNS symptoms.^{2,4} Indeed, these side effects are more common than its neurotoxicity.⁵ Wong et al. noted hypertension in 2/10 patients on Tacrolimus who had developed PRES.⁶ According to a systematic review, hypertension was noted in 69% of calcineurin inhibitor-associated PRES.⁷ However, some authors state that more than 50% of the PRES induced by calcineurin inhibitors are not clinically hypertensive.⁸ There are; however, other calcineurin inhibitor mediated mechanisms that could result in this reversible vasogenic oedema. These include endothelial toxicity, resultant endothelial mediated vasoconstriction, micro thrombosis, and haemolytic uremic syndrome.²

Chen et al. describe a common immunogenic mechanism for PRES mediated by all causes like hypertension, immunomodulators, eclampsia, sepsis, and autoimmunity; this mechanism incites endothelial injury and involves cytokine release (IL 2, IL-1, TNF alpha, INF gamma), that result in T cell activation and upregulation of adhesion molecules like ICAM-1, VCAM-1, P and E selectins, and macrophage activation. Ultimately microcirculatory dysfunction, altered vascular tone, and impaired vascular permeability result.⁹ Both the cytotoxic (immunogenic) and vasogenic mechanisms could result in this condition.⁸ In the described patient there is also a possibility of an immunogenic mechanism with an exacerbation induced by moderate hypertension (MAP 130mmHg).

Both these theories have been described in the pathogenesis of PRES, with the vasogenic theory supporting the MAP rise of beyond 150-160mmHg that contributes to PRES.^{8,3} There is another neuropeptide theory that explains the vasoconstriction resulting in cerebral oedema.³ Other mechanisms could also have contributed in our case. For example, the association of hypomagnesemia and PRES is not proven with Tacrolimus, however is known to contribute to cyclosporine-induced PRES; it could have been an undetermined inciting factor in the reported patient.^{10,11}

Tacrolimus is a calcineurin inhibitor (FK506), an effective immunosuppressor for the prevention of graft rejection in solid organ and bone marrow transplantation. Most of the Tacrolimus induced PRES patients described in the literature had normal serum tacrolimus levels, and these levels failed to correlate with the

degree of neurological symptoms.⁷ This could be explained by the variable half-life (3.5-40.5hr) of Tacrolimus and active metabolites of Tacrolimus.¹ Variability in Tacrolimus levels and lack of association of Tacrolimus levels with PRES has been described by other authors as well.^{12,13} One of these patients had renal insufficiency, possibly Tacrolimus induced.¹³ In a study, the incidence of Tacrolimus associated PRES was 1.6%.⁶ However, pontine PRES resulting from Tacrolimus has fewer reports. We could only find two case reports, one with reversible expressive aphasia, and the other one with diplopia and bilateral sixth nerve palsy.^{12,14}

Posterior circulation predilection has been attributed to less sympathetic innervation that has a protective effect against unbridled cerebral vasodilation.¹⁵ The pons may be prone to vasogenic oedema, particularly in CKD patients, as in our case, owing to albuminuria.¹⁶ Although brainstem findings have been noted in about 13% of PRES patients, this condition's identification becomes easier because of co-existent hemispheric features. Although an equal expression (20-30%) of the three described primary imaging patterns in PRES with patchy/confluent or linear involvement (holo-hemispheric, superior sulcus pattern, dominant parietal-occipital pattern, and partial/asymmetric pattern) is described,⁹ an isolated pontine involvement is quite rare. McKinney et al. had initially described this isolated finding as central PRES, in a patient with cocaine toxicity who lacked the classical parietooccipital hyperintensity, but had brainstem, thalamic and deep white matter oedema.³ They subsequently reported about 4% of all PRES patients with similar findings.⁹

Although brainstem findings have been noted in about 13% of PRES patients, identification becomes easier because of co-existent hemispheric features. Although all the three described imaging patterns in PRES with patchy/confluent or linear involvement (holo-hemispheric, superior sulcus pattern, dominant parietal-occipital pattern, and partial/asymmetric expression of these primary patterns have been described in almost equal proportions [20-30%],¹⁷ isolated pontine involvement is quite rare. McKinney et al. had initially described this isolated finding as central PRES and reported about 4% of all PRES patients with that finding.¹⁸

Conclusion

To conclude, Central PRES is a rare condition that otherwise presents with symptoms concordant with the commonly described PRES. People with organ transplantation receiving calcineurin inhibitors like Tacrolimus should be suspected with this diagnosis when they present with neurological symptoms. It is a reversible condition, when recognised and treated in time.

REFERENCES

- Appignani BA, Bhadelia RA, Blacklow SC, Wang AK, Roland SF, Freeman RB. *Neuroimaging findings in patients on immunosuppressive therapy: experience with tacrolimus toxicity*. American Journal of Roentgenology 1996 Mar;166(3):683-8. <https://doi.org/10.2214/ajr.166.3.8623651>
- Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al. *A Reversible Posterior Leukoencephalopathy Syndrome*. New England Journal of Medicine. [Internet]. 1996;334(8):494-500. <https://doi.org/10.1056/NEJM19960223340803>
- Granata G, Greco A, Iannella G, Granata M, Manno A, Savastano E, et al. *Posterior reversible encephalopathy syndrome-insight into pathogenesis, clinical variants, and treatment approaches*. Autoimmunity Reviews. 2015;14(9):830-6. <https://doi.org/10.1016/j.autrev.2015.05.006>
- Gao B, Liang H, Liu F, Lv C. *Isolated Pons Involvement in Posterior Reversible Encephalopathy Syndrome in a Patient with Chronic Renal Insufficiency: Case Report and Literature Review*. Clinical Neuroradiology. 2012 Dec <https://doi.org/10.1016/j.ensci.2016.11.008>
- Bechstein WO. *Neurotoxicity of calcineurin inhibitors: impact and clinical management*. Transplant International. 2000;13(5):313-26. <https://doi.org/10.1007/s001470050708>
- Wong R, Beguelin GZ, Lima MD, Giralat SA, Hosing C, Ippoliti C, et al. *Tacrolimus-associated posterior reversible encephalopathy syndrome after allogeneic haematopoietic stem cell transplantation*. British Journal of Haematology [Internet]. 2003;122(1):128-34. <https://doi.org/10.1046/j.1365-2141.2003.04447.x>
- Song T, Rao Z, Tan Q, Qiu Y, Liu J, Huang Z, et al. *Calcineurin Inhibitors Associated Posterior Reversible Encephalopathy Syndrome in Solid Organ Transplantation*. Medicine (Baltimore) [Internet]. 2016 Apr 8 [cited 2020 Jun 9];95(14). <https://doi.org/10.1097/MD.00000000000003173>
- Gao B, Lyu C, Lerner A, McKinney AM. *Controversy of posterior reversible encephalopathy syndrome: what have we learnt in the last 20 years?* Journal of Neurology, Neurosurgery & Psychiatry. 2018;89(1):14-20. <https://doi.org/10.1136/jnnp-2017-316225>
- Chen Z, Shen G-Q, Lerner A, Gao B. *Immune system activation in the pathogenesis of posterior reversible encephalopathy syndrome*. Brain Research Bulletin 2017 May [cited 2020 Jun 17];131:93-9. <https://doi.org/10.1016/j.brainresbull.2017.03.012>
- Almoussa M, Goertzen A, Brauckmann S, Fauser B, Zimmermann C. *Posterior Reversible Encephalopathy Syndrome due to Hypomagnesemia: A Case Report and Literature Review*. Case Reports in Medicine. 2018;29:2018:1-6. <https://doi.org/10.1155/2018/1980638>
- Thompson CB, Sullivan KM, June CH, Thomas ED. *Association between cyclosporin neurotoxicity and hypomagnesaemia*. The Lancet. 1984 Nov;1116-20. [https://doi.org/10.1016/S0140-6736\(84\)91556-3](https://doi.org/10.1016/S0140-6736(84)91556-3)
- Oliverio PJ, Restrepo L, Mitchell SA, Tornatore CS, Frankel SR. *Reversible Tacrolimus-induced Neurotoxicity Isolated to the Brain Stem*. American Journal of Neurology. 2000 Aug 1;21(7):1251-4. <https://pubmed.ncbi.nlm.nih.gov/10954277/>
- Small SL, Bramblett GT, Edelman BH, Fukui MB. *Immunosuppression-induced leukoencephalopathy from Tacrolimus (FK506)*. Annals of Neurology. 1996;40(4):575-80. <https://doi.org/10.1002/ana.410400406>
- Jorge R, Gayowski T, Fung J, Todo S, Alessiani M, Starzl TE. *Expressive Dysphasia Possibly Related to FK506 in Two Liver Transplant Recipients*. Transplantation. 1990;50(6):1043-81. <https://doi.org/10.1097/00007890-199012000-00028>
- Beausang-Linder M, Bill A. *Cerebral circulation in acute arterial hypertension-protective Hypertension effects of sympathetic nervous activity*. Acta Physiologica Scandinavica [Internet]. 1981;111(2):193-9. <https://doi.org/10.1111/j.1748-1716.1981.tb06724.x>
- Gowan JM, Liu A. *Isolated pan-pontine posterior reversible encephalopathy syndrome in a patient with uncontrolled hypertension*. Clinical Case Reports 2019;7(1):32-6. <https://doi.org/10.1002/ccr3.1888>
- Bartynski WS, Boardman JF. *Distinct Imaging Patterns and Lesion Distribution in Posterior Reversible Encephalopathy Syndrome*. American Journal of Neuroradiology [Internet]. 2007 Aug 1;28(7):1320-7. <https://doi.org/10.3174/ajnr.A0549>
- McKinney AM, Jagadeesan BD, Truwit CL. *Central-Variant Posterior Reversible Encephalopathy Syndrome: Brainstem or Basal Ganglia Involvement Lacking Cortical or Subcortical Cerebral Edema*. American Journal of Roentgenology. 2013 Aug 23;201(3):631-8. <https://doi.org/10.2214/ajr.166.3.8623651>

SIGNALS OF CHANGE

RECOGNISING THE EARLY SIGNS
OF PROGRESSION TO SPMS



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FOREWORD

By Dr David Paling

Multiple sclerosis (MS) is a progressive autoimmune neurological condition which affects the central nervous system (CNS), leading to the development of increasingly debilitating symptoms¹.

This long-term condition, often striking at the prime of people's lives, progressively worsens as damage and scarring to the nervous system builds¹. It is therefore essential to provide people with MS (PwMS) and healthcare professionals (HCPs) with support and education to identify progression early, and initiate interventions to prevent or forestall the gradual worsening of physical and cognitive functions over time.

The majority of PwMS (85%) are initially diagnosed with relapsing remitting multiple sclerosis (RRMS) characterised by clinical acute attacks or, relapses, typically accompanied by periods of partial or complete recovery². These relapses are defined by the subacute development of new or worsening neurological symptoms caused by inflammation to the CNS and vary in type and degree of severity^{1,2}.

As MS progresses, there is a gradual worsening of neurologic function, independent of relapses, caused by permanent nerve damage or loss^{3,4}. This leads to an accumulation of disability over time³, marking the transition to secondary progressive multiple sclerosis (SPMS). Over 75% of people with RRMS transition to SPMS within 30 years of diagnosis⁶. Both inflammatory activity and neurodegeneration are integral components of SPMS, with immune reactions compartmentalised within the CNS being more evident in SPMS than in RRMS^{7,8}.

Since the majority of PwMS eventually transition to SPMS, monitoring and tracking the course of progression is critical to providing timely intervention and improving patient outcomes⁶. However, SPMS is currently diagnosed retrospectively, with a significant delay of up to three years, and is often associated with a period of diagnostic uncertainty⁴. Challenges in the early identification of SPMS are caused by the difficulty in recognising the subtle signs and symptoms that characterise progression, due to their gradual and variable nature. This is also combined with the lack of treatment options available for SPMS to date and anxiety from PwMS regarding a 'new' diagnosis and what this may mean for their future⁴.

This report explores four diverse perspectives from across the multidisciplinary team and a person with MS – and discusses the landscape and challenges in SPMS diagnosis within the clinical and community setting. These insights challenge our thinking around our current approach to clinic appointments and coordinated multidisciplinary care, and outline the need to strive for more urgent, curious and honest conversations with PwMS about the reality of their future. From investigative consultations, coordinating multidisciplinary team care, educational tools and keeping PwMS at the centre of their management, we suggest that the MS community continues to strive towards being as proactive as possible in recognising the signals of change that characterise progression.

These signals of change will help raise awareness and urgency to drive towards an earlier recognition of SPMS, improve consultations and provide PwMS with early access to the vital information they require to navigate the changing course of their disease.



STAYING CURIOUS

The Consultant Neurologist perspective

Dr David Paling is a Consultant Neurologist at the Royal Hallamshire Hospital, Sheffield, visiting Consultant Neurologist at Doncaster Royal Infirmary, Honorary Senior Lecturer at the University of Sheffield and Clinical Lead for the MS Centre, Sheffield.

David approaches his consultations for people with SPMS with curiosity, vigilance and honesty and encourages them to come prepared to maximise the short time they are able to spend in clinic. As the SPMS landscape continues to evolve, David emphasises that people recently diagnosed with SPMS should leave their consultations with **"a feeling they have been listened to, an explanation of their symptoms, an understanding of what might help and an action plan of what they and their Consultant feel is the best way forward"**.

CONFRONT THE STIGMA OF SPMS

"The Lublin criteria are challenging our diagnostic structure, and these fit much more intuitively with what PwMS are telling us."

Taking action in SPMS first requires addressing the challenges surrounding diagnosis. One challenge is the stigma associated with SPMS, which may cause Consultant Neurologists to delay providing a formal diagnosis⁹. This delay can be accompanied by the doctor's belief that this is beneficial for PwMS, as discussing progression without providing a treatment isn't perceived as valuable. However, delaying the conversation leaves PwMS without an explanation for what they are experiencing. Furthermore, with additional SPMS treatments on the horizon, identifying progressive disease and approaching the conversation with PwMS may be highly valuable.

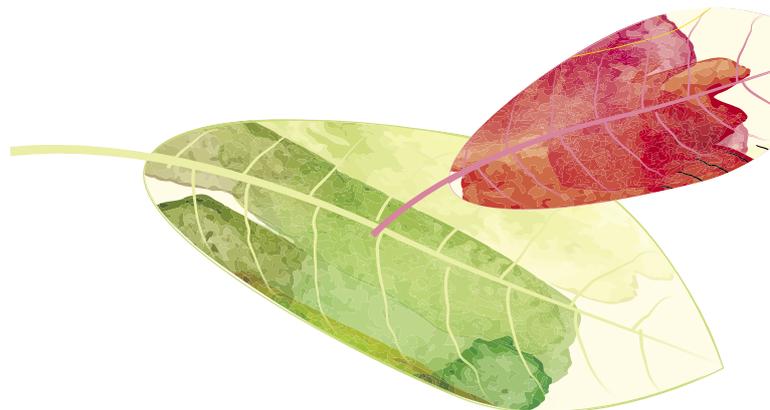
The updated Lublin criteria have been a great step forward for characterising SPMS and have questioned the diagnostic structure beyond RRMS^{10,11}. They provide criteria beyond the simple dichotomy of 'relapsing remitting' vs 'secondary progressive' MS and discuss attributes that parallel the experiences of PwMS. In David's experience, PwMS are less interested in the label of their MS, than they are in getting a really clear understanding of what is happening to them and why, if what they are experiencing is normal for MS and what it means for their future.



CURRENT SPMS DIAGNOSTIC CHALLENGES⁴

Supplemented with the opinion of Dr David Paling

- Lack of treatment options to date
- Stigma of formal diagnosis of SPMS and its psychological impact
- Reduced amount of time with PwMS
- Impact of comorbidities



THE UPDATED LUBLIN CRITERIA¹¹

Defining SPMS

The Committee urges clinicians, investigators, and regulators to consistently and fully use the 2013 phenotype:

1. Using the full definition of activity, that is, the occurrence of a relapse or new activity on an MRI scan (a gadolinium-enhancing lesion or a new/unequivocally enlarging T2 lesion)
2. Framing activity and progression in time
3. Using the terms ‘worsening’ and ‘progressing’ or ‘disease progression’ more precisely when describing MS course

Definitions and time frames

Term	Definition	Recommended time frame for evaluation
Active disease	Clinical: relapses, acute or subacute episodes of new or increasing neurologic dysfunction, followed by full or partial recovery, in the absence of fever or infection	Annually (but can be another time frame, as long as it is specified)
	And/or	
	Imaging: gadolinium-enhancing lesions or new or unequivocally enlarging T2 lesions	Annually (but can be another time frame, as long as it is specified)
Progressing disease or disease progression	Accrual of disability, independent of any relapse activity, during the progressive phase of MS (PPMS or SPMS)	Annually by clinical assessment (but can be another time frame, as long as it is specified)
Worsening disease	Any increase in impairment/disability irrespective of whether it has resulted from residual deficits following a relapse or (increasing) progressive disability during the progressive phase of the illness	Not required

MAXIMISE TIME DURING CONSULTATIONS

“One useful thing about the waiting room was that PwMS had undisturbed time where they could think about what has changed over the past year.”

During clinical appointments, symptoms remain the focus of conversation for PwMS. David advises that to maximise their short 15-minute annual consultations, PwMS should try to spend some time thinking about what they feel has changed for them in the last year, what they are worried about, and what they want to get out of their appointment. This organisation of thoughts provides the basis for strong conversations to figure out what support PwMS need and identify any signals of progression. David also notes that the COVID-19 pandemic has sometimes made this harder for PwMS as when they have teleconsultations, rather than clinic appointments, they have not had their journey and time in the waiting room to reflect. Therefore, it is really important for PwMS to try to schedule this time of reflection in a different way.

Once in the appointment, the Consultant Neurologist should ask open questions and be attentive to signals of progression. When suspicions are aroused, investigations should promptly occur to confirm whether the signals point to progression, a relapse or another disease. Forestalling addressing changes means losing the opportunity to focus on the holistic treatment of SPMS with the help of the multidisciplinary care team; a benefit that could provide real support, empower PwMS to engage in their care, and alleviate some of their concerns.

“It’s important to ask open questions. I ask PwMS if anything has changed recently. I often ask about their holidays as these tend to stick in the mind.”

MS progression is different from relapses – it is slow and hard to discern on a day to day basis. PwMS may discuss urinary tract issues and cognitive impairment, yet not necessarily associate them with their MS or progression, but rather a sign of ageing. It is important that the Consultant Neurologist, as well as the multidisciplinary care team, uncover such symptoms, especially if they can be treated, and not delay in offering practical support. For example, PwMS who have balance problems can be referred to physiotherapy and bladder symptoms can be seen by an continence service. By identifying these signals early, it is possible to both provide practical support and address the topic of MS progression.

“If you deny the presence of SPMS, your label of what is happening is discordant with that of the person with MS and because of that, you may damage the relationship you have built together because they’re telling you things that you’re minimising or ignoring.”

Once it is clear that a person is transitioning to SPMS, it is key to discuss progression openly. Avoiding honest communication may inadvertently establish a relationship where the person with MS doesn’t feel listened to and may discourage them from discussing their symptoms and how they’re feeling in future meetings. It is important to plan forwards and come to an agreement on next steps, as well as offer an idea of the prognosis and review disease modifying therapy (DMT) eligibility. This will help people with MS leave their appointment with an understanding of what is happening, a feeling that they have been listened to, an awareness of the things that might help their progression and an action plan for the best way forward.

Looking to the future, David urges Consultant Neurologists to continue to be curious during consultations to enable the earlier detection of the subtle signs and symptoms of progression to SPMS. This vigilance and honesty in approach will help identify the signals of change that mark progression, and improve SPMS diagnosis and management as we navigate the changing landscape of SPMS.



TOPICS FOR OPEN DISCUSSION DURING CONSULTATIONS FOR PWMS

- A list of anything that has changed in the past year
- Worries and/or concerns
- Review of key time points, such as holidays
- Needs from their appointment



AN HONEST ASSESSMENT

The MS Clinical Nurse Specialist perspective

Sarah White is a MS Clinical Nurse Specialist based at St George's University Hospital in South West London. An important part of her role is establishing and building relationships with PwMS, providing them the support they need and coordinating their holistic care with other members of the multidisciplinary team.

MS nurses tend to stay in their role for a long time, and Sarah is no exception, having spent 17 years supporting PwMS. Through this experience, Sarah believes that building trusting relationships with PwMS can lead to more honest assessments and open conversations that can help facilitate the identification of the signals that mark MS progression. ***"The nurse and the person with MS often have this trusting relationship, as we have known each other for a long time. PwMS will open up to you more, and part of our role is to do that more intricate assessment."***

SUPPORT HONEST CONVERSATIONS

"It's important to go at the pace of the person with MS. I often bounce questions back at them and ask what they're thinking, getting them to voice it first. We can then have a gentle conversation about what it then means."

Approaching the conversation about transitioning to SPMS can be difficult, but Sarah finds honesty to be an important asset. She is keen to point out that it can be a difficult time for PwMS as the news is almost akin to being diagnosed again, and often tied to personal and professional difficulties they may be managing, as well as big decisions about the next steps in their life.

Unlike with RRMS, there are no diagnostic tests to denote a person has SPMS¹⁰. A key role of the MS Clinical Nurse Specialist is to look for the hidden symptoms that signal change, and where appropriate, approach the discussion with the Consultant Neurologist. Where possible, it is the aim for PwMS to be seen every six months, either by their Consultant Neurologist or Clinical Nurse Specialist. However, it is also important that PwMS have easy access to the service if new or worsening symptoms arise, allowing for flexibility in care, rather than having to wait for their routine review. An essential part of care is to ensure that adequate time is spent with PwMS at each appointment; a point that Sarah notes can be a challenge in most clinics due to limited capacity. This time in clinic is especially important for people transitioning to SPMS to allow for accurate documentation of their progression – a key aspect in identifying signals of change.

After PwMS have been gradually worsening over six to nine months, Sarah starts to open the conversation around progression. After a year of suspected progression, Sarah will address the topic more directly if it has not been raised by the person with MS. During these conversations, she believes it is important to go at the pace of the person with MS as they may be fearful, and ask them what they are thinking, as well as keep the conversation positive and talk about what they are able to achieve.

PARTNER TO NAVIGATE TRANSITION

"My role is to give PwMS the support they need at each stage, asking them what they want to know and then answering their questions."

To ascertain how MS is progressing, Sarah relies on PwMS to speak about changes they have encountered. This is achieved through asking questions about daily activities – for example how far they can walk, how far they can move without taking a rest and whether they are able to feed themselves and clean their teeth. To support PwMS during these conversations, Sarah will often ask them to problem solve what would make their experience easier. Her past experiences have helped her to see that when she encourages PwMS to come up with solutions themselves, it leads to better adherence to the activity. As PwMS progress, it is important that they are provided with written information and it may be helpful to bring someone to an appointment or record the conversation on their phone. This will aid them in remembering what was discussed, allowing them to recall the conversation, especially as cognitive function may start to decline.



SPMS "HIDDEN" SYMPTOMS: BEYOND MOBILITY^{3,12,13}

- Increased fatigue has a large impact on day to day life
- Bladder and bowel dysfunction can take precedent and PwMS often have to plan around the availability of the nearest toilets
- Changes in cognition includes impaired concentration, trouble forming words and slower information processing

A key aspect to getting the most out of their visits is providing PwMS with the tools to self-manage and keep track of symptoms. This not only supports PwMS' emotional well-being, it also provides them with a measure of control in the management of their MS.

"I give PwMS the tools they need to self-manage as much as possible. This in itself supports well-being and helps them maintain a level of control."

ADVOCATE FOR IMPROVED SPMS CARE

"Going forward – as clinicians we should be open and curious to signs of progression and relapses."

Sarah explains that there are still many challenges that need to be addressed to aid in an accurate and timely SPMS diagnosis. As DMTs for SPMS become available, there will need to be a consensus on how the Lublin criteria are implemented, as HCPs will be more actively looking for, and diagnosing, SPMS.

Additionally, there also needs to be more time for HCPs to support PwMS, not only during transition, but afterwards as well, as clinical appointments for people with SPMS are often more complex due to their increased symptom burden and intricate management¹⁴. This includes improving access to specialists, such as social care and psychologists, as well as recognising disparities in PwMS' support networks and access to resources.

Finally, implementing better care for people with SPMS may include changes in technology and more digital self-assessment in order to accurately reflect what they are experiencing. Centralisation of information from each of the different disciplines would also be helpful to provide the overall picture for each person with MS. All these tools will help build a future where people with SPMS are supported and changing signals can be recognised and managed earlier.



MANAGING HOLISTIC CARE – A ROLE FOR AN MS CLINICAL NURSE SPECIALIST

People with SPMS often need coordinated care, and an MS Clinical Nurse Specialist can have an important role in building relationships with the community teams (local services) and hospital teams to maximise coordinated care.

- Know where a patient can be referred, and the capacity within those teams
- Provide advice on what specific services are offered to help join up care
- Provide tips whilst PwMS are waiting to see a Specialist to help them prepare (i.e. tips for swallowing before seeing the Speech and Language Therapist)



COORDINATING CARE

The Allied Healthcare Professional perspective

Tania Burge, a Specialist MS Physiotherapist based at North Bristol NHS Trust, started in the role of an Advanced MS Champion in 2020 as part of a 15-month pilot programme which is across six sites in the UK and funded by the MS Trust. The full evaluation of this phase one Advanced MS Champion pilot will be shared at their flagship conference in November 2021.

As part of this new role, Tania evaluates the needs of people with progressive MS, delivering and sharing best practices and improving standards of care across the multidisciplinary team. **“This is an exciting role because people with progressive MS often do not receive the dedicated time they need. This role is instrumental in organising the services involved in an individual’s management, following an informed approach to care.”**

KEEP PWMS AT THE CENTRE OF THEIR CARE

“Coordinating care is an essential part of establishing and following a treatment plan – but the plan is only as good as everyone knowing it exists. This is one of the most important parts of SPMS diagnosis and management; establishing good communication and ensuring the person with MS remains at the centre.”

In the complicated landscape of MS management, people with SPMS are most often managed outside of the hospital setting across different community teams¹⁵. This can make it difficult to connect care and recognise all the signals of change that may indicate progression to SPMS. This congregation of a wide range of disciplines opens up a role for coordinating care amongst multidisciplinary teams; a collaboration that is central for the holistic management to support the needs of PwMS. However, as time spent in a clinic appointment can be limited, and many people with more advanced MS are unable to physically access a clinic appointment, it may be beneficial to supplement PwMS’ care with home visits to ascertain all their requirements. Additional protected time spent with PwMS in their living environment, can provide the opportunity for more open conversations about their preferences and facilitate stronger decision-making abilities based on a deeper understanding of their needs.

Tania’s role as an Advanced MS Champion allows her to provide support, education and an access route to lead PwMS back into the healthcare system. Through investigating notes, assessments and recommendations across the multidisciplinary team, as well as from carers and PwMS themselves, Tania evaluates the wider picture of MS care, subsequently implementing and communicating a coordinated management plan that works across all teams.

USE DATA TO GUIDE CONVERSATIONS

“If everyone starts to talk about progression early, it doesn’t have to be the elephant in the room. There are a lot of processes that can be put in place to support PwMS through their SPMS diagnosis. As a multidisciplinary team, it is really important to take time, listen and support PwMS.”

In a landscape where there is a drive towards drug management and ‘stopping’ MS progression, discussing SPMS and progression can be complex. As a person with MS progresses, it can be difficult for them to grasp that there is no clear dividing line between RRMS and SPMS. In order to manage this complexity, one way to facilitate early conversations about progression is through reviewing neurological assessments used to closely monitor their course of disease. To track progression, outcome measures are used to investigate the level of improvement and rehabilitation-potential a person with MS requires to return to their baselines following a relapse. Using these measures, residual damage can be assessed to closely monitor signs of progression and correlated with findings on an MRI scan¹⁶.

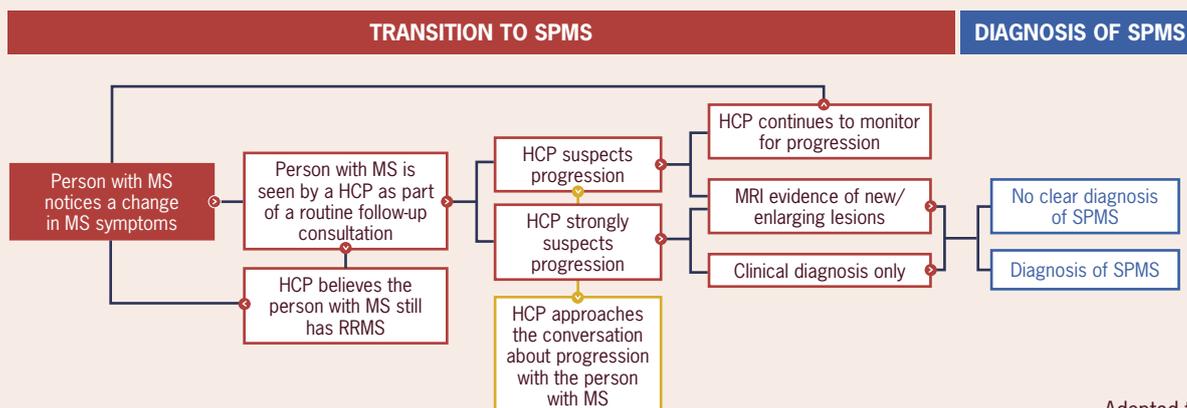
Through this process, the team can have open and honest conversations about MS progression and signals of change with PwMS, providing measurements that illustrate the transition to SPMS through tangible evidence. This information ensures the reality of progression is understood and empowers PwMS to engage with their care, as well as work in partnership with their multidisciplinary team.

SUPPORT THE DIAGNOSIS

“The realisation that despite managing factors within their control, including exercise and diet, they cannot improve function, is when it often becomes difficult for PwMS to come to terms with what they can and cannot achieve following SPMS diagnosis.”

The psychological impact of SPMS diagnosis can vary between PwMS from relief to devastation. For some, each adjustment to their MS, including transition to SPMS, can often mirror the experience of their original MS diagnosis. For an SPMS diagnosis, part of the challenge PwMS face is the acceptance that some of the changes to their condition are permanent, and that a new adjustment period has to be followed whilst they come to terms with their progression and functional limitations. This stage may often be marked by a struggle to engage with rehabilitation as PwMS psychologically adjust with a new presentation. It is therefore imperative to support PwMS with the internal acceptance of progression and to help them engage with recommendations important for the management of their condition.

THE JOURNEY OF PEOPLE WITH SPMS⁹



Adapted from Oh J et al. 2019

TAKE A HOLISTIC APPROACH

“As part of the multidisciplinary team we all work together to help open new doors for PwMS after SPMS diagnosis; they may not have chosen this, but there is so much we can do to show them what is available to them and this can improve their quality of life.”

With most DMTs licensed for RRMS only, it is essential that people with SPMS realise the importance of supplemental care, such as physical therapy and psychological support. From a physical therapy standpoint, early intervention and regular exercise can significantly improve quality of life and symptom management, providing a greater level of independence⁹.

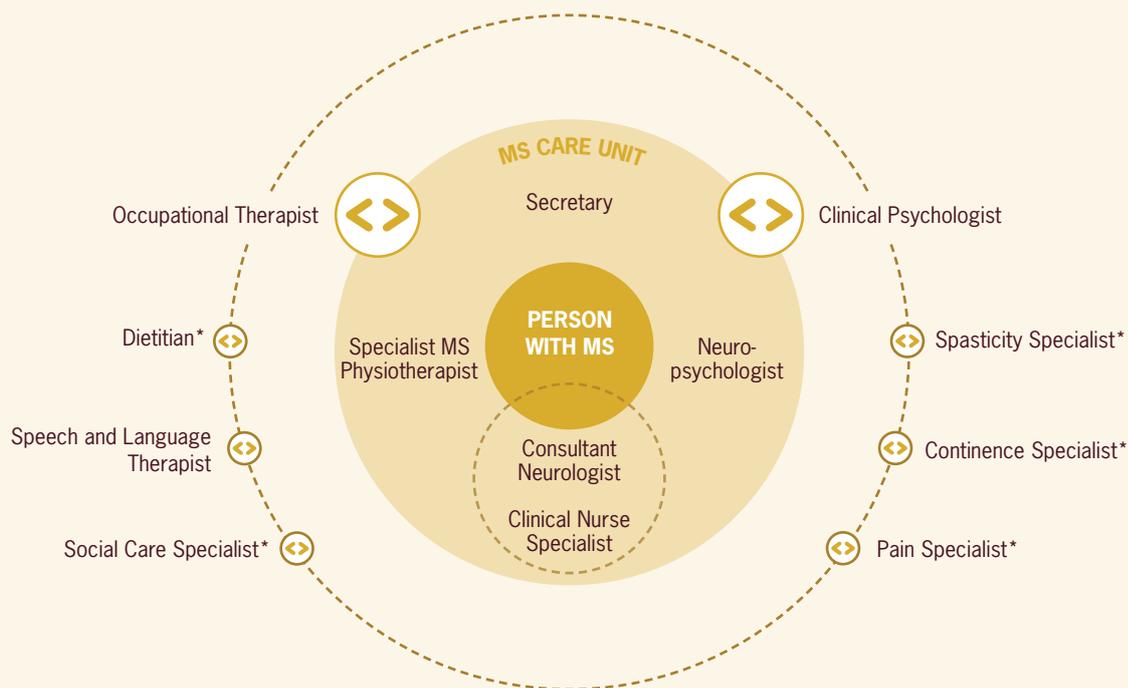
The outcome and success of treatment plans for PwMS are difficult to predict due to the variability in MS disease and manifestation, therefore is important that MS multidisciplinary teams form a partnership with PwMS to find the best way to implement a management plan. In this regard, the open and honest communication will need to be both from the care team and the person with MS in order to optimise the management plan. Tania advises to balance the unknowns with the knowns of MS treatment and to support discussions with clinical insight, and the latest research that is evidence-based.

EMPOWER PWMS TO BECOME EXPERTS IN THEIR OWN CARE

“In the landscape of separate community and hospital healthcare systems that have barriers to communication (e.g. due to time constraints or different computer systems), it is essential to arm PwMS with the knowledge and information about their own treatment which allows them to remain at the centre of their own care.”

Looking to the future, and to further improve SPMS diagnosis, it is crucial that PwMS work with all their HCPs across the multidisciplinary team to truly understand their progression and have open, honest conversations early in the course of their progressive disease. Through strengthening and coordinating communication between hospital and community teams and empowering PwMS to become the experts in their own care, they can be given the toolkit to play a larger role in their proactive management plans, placing them at the centre of their treatment. Tania believes that it is this combined approach that can help facilitate multidisciplinary teams to recognise the signals of change that characterise progression and drive towards earlier SPMS diagnosis for PwMS.

THE MULTIDISCIPLINARY TEAM INVOLVED IN THE HOLISTIC CARE FOR PEOPLE WITH SPMS¹⁷



◄> collaboration with an external part-time specialist

*Service that may be provided by a Consultant Neurologist or Clinical Nurse Specialist member of the multidisciplinary team with special education or interest

Adapted from Sorensen, S et al. 2019



THREE PILLARS OF SUPPORT

The Patient Perspective

Patrick Burke, a retired IT Consultant from London, was diagnosed with RRMS in 1995 followed by SPMS in 2000 and has described his diagnoses as very different to current practice in which a landscape of DMTs, medicines and therapies are now available.

At the time of his SPMS diagnosis, Patrick was working overseas, had a busy life and would regularly take his dog for 60-mile walks. He described it as *“just an ordinary day – it was just a different type of MS, but still the same thing, I was still the same person.”*

LOOK AT PROGRESSION THROUGH THE EYES OF PWMS

“With RRMS, you constantly go between two kingdoms; one of the healthy and one of the ill. However, with SPMS you are permanently in the kingdom of the ill. The problems with walking, falling over, bladder symptoms etc are always there, they build up and don’t go away. To my mind, that’s a very significant point that identifies the transition from early to late stage MS.”

Patrick’s initial RRMS diagnosis was led by a very slow and gradual progression. First experiencing bladder symptoms in the 1970s and 1980s and then double vision in 1995, Patrick was referred to an MS Specialist who diagnosed him with RRMS. The transition from RRMS to SPMS occurred a few years later. His description of early SPMS, with the benefit of hindsight, is *“beginning to notice that your situation is now going downhill and getting worse and realising you don’t go back to normal.”*

Patrick relays his SPMS diagnosis as being given a one-way ticket. At the time, SPMS meant that a person with MS went from a DMT to management of symptoms only, as there was nothing that could be given to stop progression¹⁴. Whilst the SPMS diagnosis felt like another ordinary day to Patrick, the resulting consequences of medical retirement in 2012 came as a huge shock. He recalls that he found the switch between working and retirement especially challenging due to the loss of motivation and support from an environment that had brought structure to his life.

“If I had any advice for PwMS, it’s to accept that at some point you’re going to have to slow down to the extent you retire. Once a person gets into a position where working becomes more difficult, they then need to be briefed about how they are going to accept life when they can no longer work. This is a very important part of SPMS diagnosis.”

TURN SUPPORT INTO ACTIONS

For the MS community, Patrick advises on three pillars to support PwMS in their diagnosis: education, honesty and a focus on relationships.

Patrick recalls his lack of MS knowledge at the time of his diagnosis and how in the absence of a dedicated MS Specialist Nurse, he did his research at home, finding only limited information and resources available online. Although the landscape is different today and there has been a recent drive for more MS Specialist Nurses in the UK¹⁸, it is key that support is in place for PwMS at the time of their initial diagnosis so they can adjust to life with MS and what it could potentially mean further down the road. Patrick emphasises the importance of PwMS needing to be armed with information from the beginning of their MS journey about what they can do, who they see, and how they can make sure their condition is as good as possible. This includes information about medical benefits, support groups, adaptations to the home and work environment, and honest information about the course of their progression.

‘It’s a bit brutal, but MS is a brutal disease, so you’ve got to fight it on its own terms.’

Patrick admits that he did not understand what his diagnosis of SPMS meant for his disease course. Reliable sources and a support team, especially a go-to person, should be made available for PwMS going through the same process, for education and advice on managing problems. Patrick describes the current practice of a 15-minute annual consultation with a Consultant Neurologist as not providing sufficient time for PwMS to have detailed discussions about the course of disease progression, the changing signals, or the day to day issues that affect their quality of life.

Outside of the direct clinical community, Patrick believes there are several trustworthy sources for PwMS which provide honest information and management tools to supplement knowledge and navigate SPMS diagnosis, such as the MS Trust or The MS Society^{5,19}. Not only do these reliable sources help PwMS feel less like they have been condemned, they can be a basis for connecting people or act as signposting to those who can provide further information. Patrick believes that building a MS community through WhatsApp groups, regular coffee morning, or other activities where possible, is key for PwMS to help manage their condition, share signals that may indicate change and aid in their educational outreach. Patrick emphasises that it is essential for PwMS to build a relationship with someone who can provide advice outside of consultations and act as a foundation of support, which can only develop through knowing the person with MS and the course of their condition.



THREE PILLARS OF SUPPORT

Education is about empowering PwMS with the information and tools to navigate their disease. It is important that PwMS are educated as early as possible after their initial MS diagnosis about what could happen during the course of their disease. PwMS can often feel a sense of anxiety, which needs to be managed as early as possible, with the right level of upfront transparent information.

“Education is key and this is missing in the MS community. You have to educate and make sure that the person that has got the illness has the tools to find a way around it.”

Honesty is about arming PwMS with the right information to prepare them for their future. This includes, wherever possible, complete transparency from the Consultant Neurologist and multidisciplinary team. When it comes to recognising MS progression, PwMS should be honest with themselves also, and it is beneficial to have someone who is honest with them, and that can provide perspective on what they can’t see for themselves, such as the compensations they make on a daily basis to manage.

“The Consultant Neurologist needs to be as upfront as possible so that you can prepare yourself early on for what might happen in your future”

Relationships are about building confidence in the person with MS and providing them with knowledge about their condition through a foundation of support. It is important that PwMS find their own support group that can help them, but also to have someone to point towards useful information including Shift.MS, The MS Trust, MS Society or an MS therapy centre. It is important for people to act as signposts. As MS is different for everyone, it must be recognised that there is no one size fits all approach, the template is not the same for each person.

“Sometimes you have to paddle your own canoe to find someone with whom you can work and build up a relationship with, and find ways of increasing your own knowledge about MS.”

Whilst the landscape of MS is continuously changing and important conversations are happening earlier in the course of progression, Patrick advises that following these three pillars of education, honesty and relationships will provide a more complete care package to support people with SPMS. These combined factors will help raise earlier awareness and identification of the key signals of change that characterise progression, and most importantly, help PwMS prepare for their future.

REFERENCES

1. National MS Society. Definition of MS. Available at: <https://www.nationalmssociety.org/What-is-MS/Definition-of-MS> (Last accessed: October 2020).
2. MS Trust. Relapsing Remitting MS. Available at: <https://www.mstrust.org.uk/a-z/relapsing-remitting-ms-0> (Last accessed: October 2020).
3. Gross HJ, Watson C. Characteristics, burden of illness, and physical functioning of patients with relapsing-remitting and secondary progressive multiple sclerosis: a cross-sectional US survey. *Neuropsychiatr Dis Treat*. 2017;Volume 13:1349-1357.
4. Inojosa H, Proschmann U, Akgün K, Ziemssen T. A focus on secondary progressive multiple sclerosis (SPMS): challenges in diagnosis and definition. *J Neurol*. Published online July 30, 2019. doi:10.1007/s00415-019-09489-5
5. National MS Society. Secondary Progressive MS. Available at: <https://www.nationalmssociety.org/What-is-MS/Types-of-MS/Secondary-progressive-MS> (Last accessed: October 2020).
6. Khurana V, Medin J. Time to, and rate of secondary progression in patients with multiple sclerosis: results of a systematic search. Poster session presented at: 7th Joint Congress of the European Committee for Treatment and Research in Multiple Sclerosis– Americas Committee for Treatment and Research in Multiple Sclerosis; 2017 Oct 25-28; Paris, France.
7. Ontaneda D, Fox RJ. Progressive multiple sclerosis: *Curr Opin Neurol*. 2015;28(3):237-243.
8. Correale J, Gaitán MI, Ysrraelit MC, Fiol MP. Progressive multiple sclerosis: from pathogenic mechanisms to treatment. *Brain*. 2017;140:527-546.
9. Oh J, Alikhani K, Bruno T, et al. Diagnosis and management of secondary-progressive multiple sclerosis: time for change. *Neurodegener Dis Manag*. 2019;9(6):301-317.
10. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83(3):278-286.
11. Lublin FD, Coetzee T, Cohen JA, Marrie RA, Thompson AJ, on behalf of the International Advisory Committee on Clinical Trials in MS. The 2013 clinical course descriptors for multiple sclerosis: A clarification. *Neurology*. 2020;94(24):1088-1092.
12. Amato MP, Langdon D, Montalban X, et al. Treatment of cognitive impairment in multiple sclerosis: position paper. *J Neurol*. 2013;260(6):1452-1468.
13. Achiron A. Cognitive patterns and progression in multiple sclerosis: construction and validation of percentile curves. *J Neurol Neurosurg Psychiatry*. 2005;76(5):744-749.
14. MS Trust Media Report. Is MS Care Fair? 2018. Available at: <https://www.mstrust.org.uk/sites/default/files/MS%20care%20media%20report%20a4.pdf> (Last accessed: October 2020).
15. Davies F, Wood F, Brain KE, et al. The Transition to Secondary Progressive Multiple Sclerosis. *Int J MS Care*. 2016;18(5):257-264.
16. Macaron G, Ontaneda D. Diagnosis and Management of Progressive Multiple Sclerosis. *Biomedicines*. 2019;7(3):56.
17. Soelberg Sorensen P, Giovannoni G, Montalban X, Thalheim C, Zaratin P, Comi G. The Multiple Sclerosis Care Unit. *Mult Scler J*. 2019;25(5):627-636.
18. MS Specialist Nursing in the UK 2016: Report on progress towards equitable provision. Available at: <https://support.mstrust.org.uk/file/MS-Specialist-Nursing-in-the-UK-2016.pdf> (Last accessed: October 2020).
19. MS Trust. Secondary-progressive MS. Available at: <https://www.mstrust.org.uk/a-z/secondary-progressive-ms> (Last accessed: October 2020).



Supernumerary phantom limbs

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Silas Weir Mitchell (1829-1914), justly regarded as one of the founding fathers of neurology, published accounts of phantom limbs in the 1860s and 1870s,¹ around the time that neurology was emerging as an independent clinical discipline (although earlier accounts of phantom limbs are recognised²). Phantom limbs are most often observed in the context of amputation, but reports of extra limbs occurring without amputation have also appeared. Two brief cases are presented here to illustrate the clinical heterogeneity of the supernumerary limb, the possible pathophysiology of which is briefly considered.

Case 1

A 59 year-old right-handed lady was referred to the neurology clinic with a history of three stereotyped episodes occurring over a five-month period in which she had the sensation of having two arms and two hands on the left hand side, these symptoms lasting between 30 minutes and two hours. She was not aware of any spontaneous movement of this extra limb, which was not visible to her, nor could she move it voluntarily. She had a longstanding history of anxiety and her psychiatrist thought that the symptoms might be a reflection of this. Neurological examination was normal. MR brain imaging showed some high signal white matter changes. As it was not possible to say with certainty whether these changes were ischaemic or inflammatory she underwent lumbar puncture which showed normal CSF contents with no unmatched oligoclonal bands. She was then symptom free for around 18 months, when a further cluster of similar episodes occurred. Repeat MR brain imaging showed no change from previously. In the absence of a structural or inflammatory lesion, the working neurological diagnosis was

somaesthetic migraine aura (both her children had migraine). About six months later she started getting multi-coloured flashes in her vision and was seen by an ophthalmologist who found no ocular pathology and thought that the visual symptoms were likely to be migrainous.

Case 2

A 55 year-old lady (previously reported in abstract³) with acute motor and sensory axonal neuropathy which had required ventilatory support developed the sensation of two extra arms and legs during the prolonged recovery phase. More than six months after the acute onset of neuropathy, nerve conduction studies showed uniform absence of sensory responses, and likewise absence of lower limb distal and proximal motor responses. Median and ulnar nerve motor responses were markedly reduced (<1mV) with increased latencies and reduced velocities. Awareness of the phantom limbs could be reduced by visualising her normal limbs.

The phenomenon described in these cases has been known by various names, including supernumerary phantom limb(s) (SPL), reduplication of body parts, and pseudo(poly)melia. As these cases show, the phenomenology of SPL is heterogeneous: symptoms may be transient/episodic or persistent/prolonged, and may involve single or multiple limbs, or even other body parts (such as teeth⁴). In most cases, SPL has only somaesthetic characteristics but in some cases the limb can be seen and voluntarily moved (i.e. multimodal SPL). SPL has been described in association with stroke affecting the right hemisphere^{5,6} and in episodic form in epilepsy.^{7,8} A possible migraine-related case is that of Todd and Dewhurst,⁹ although their patient also had a diagnosis of epilepsy. SPL has been described in acute inflammatory demyelinating polyneuropathy.¹⁰ Cancellation of SPL by vision of the real limb is reported.

The pathophysiology of phantom limbs has attracted much attention in recent years. They have been variously regarded as delusional beliefs or hallucinatory perceptions,¹¹ or as disorders of the body schema resulting from a failure to integrate neural impulses initiating motor action and from sensory feedback.¹² The profound deafferentation indicated by the neurophysiological findings in Case 2, along with impaired motor conduction, would be in keeping with such an explanation. Spatial distortions of body size occurring in migraine (macro- and microsomatognosia, also known as "Alice in Wonderland" syndrome) have also been attributed to "pathologies of sensory input",¹² so a similar mechanism of failure to integrate motor command and sensory feedback might be occurring in Case 1.

Whilst structural reorganisation, with reinnervation of deafferented sensory cortex from other cortical regions, may occur in persis-

tent cases of SPL associated with brain injury (e.g. after stroke), as has been suggested for phantom limbs in amputees,¹³ this may not be a necessary feature for the development of SPL, as suggested by transient forms. Functional neuroimaging (fMRI) in a patient with a poststroke (subcortical capsulolenticular haemorrhage) SPL with somaesthetic, visual and intentional motor components showed modality-specific activations in motor, visual and somaesthetic areas, interpreted as cortical deafferentation for the subcortical lesion.¹⁴ fMRI was also undertaken in Case 2 during a motor paradigm task, which showed activation within the primary motor and supplementary motor areas only,³ as might be anticipated with an exclusively somaesthetic SPL.

REFERENCES

- Nathanson M. *Phantom limbs as reported by S. Weir Mitchell*. *Neurology* 1988;38:504-505. <https://doi.org/10.1212/WNL.38.3.504>
- Finger S, Hustwit MP. *Five early accounts of phantom limb in context: Paré, Descartes, Lemos, Bell, and Mitchell*. *Neurosurgery* 2003;52:675-686. <https://doi.org/10.1227/01.NEU.0000048478.42020.97>
- Fulton J, Williamson J, Das K, Doran M. *The phantom menace*. *J Neurol Neurosurg Psychiatry* 2016;87:e1 (abstract 031). <https://doi.org/10.1136/jnnp-2016-315106.31>
- Jacome DE. *Dracula's teeth syndrome*. *Headache* 2001;41:892-894. <https://doi.org/10.1111/j.1526-4610.2001.01162.x>
- Halligan PW, Marshall JC, Wade DT. *Three arms: a case study of supernumerary phantom limb after right hemisphere stroke*. *J Neurol Neurosurg Psychiatry* 1993;56:159-166. <https://doi.org/10.1136/jnnp.56.2.159>
- Miyazawa N, Hayashi M, Komiya K, Akiyama I. *Supernumerary phantom limbs associated with left hemisphere stroke: case report and review of the literature*. *Neurosurgery* 2004;54:228-231. <https://doi.org/10.1227/01.NEU.0000097558.01639.F5>
- Weisbord A, Saver JL, Leary MC. *Episodic supernumerary phantom limb due to epileptic disruption of the neural representation of the body image*. *J Neuropsychiatry Clin Neurosci* 2002;14:109 (abstract P27).
- Millonig A, Bodner T, Donnemiller E, Wolf E, Unterberger I. *Supernumerary phantom limb as a rare symptom of epileptic seizures – case report and literature review*. *Epilepsia* 2011;52:e97-e100. <https://doi.org/10.1111/j.1528-1167.2011.03156.x>
- Todd J, Dewhurst K. *The double: its psycho-pathology and psycho-physiology*. *J Nerv Ment Dis* 1955;122:47-55. <https://doi.org/10.1097/00005053-195507000-00006>
- Melnyshyn AN, Gofton TE, Schulz V. *Supernumerary phantom limbs in ICU patients with acute inflammatory demyelinating polyneuropathy*. *Neurology* 2016;86:1726-8. <https://doi.org/10.1212/WNL.0000000000002541>
- Cipriani G, Picchi L, Vedovella M, Nuti A, Di Fiorino M. *The phantom and the supernumerary phantom limb: historical review and new case*. *Neurosci Bull* 2011;27:359-365. <https://doi.org/10.1007/s12264-011-1737-6>
- Haggard P, Wolpert DM. *Disorders of body schema*. In: Freund HJ, Jeannerod M, Hallett M, Leiguarda R (eds.). *Higher-order motor disorders. From neuroanatomy and neurobiology to clinical neurology*. Oxford University Press, 2005:261-271.
- Ramachandran VS, Rogers-Ramachandran D. *Phantom limbs and neural plasticity*. *Arch Neurol* 2000;57:317-320. <https://doi.org/10.1001/archneur.57.3.317>
- Khateb A, Simon SR, Dieguez S et al. *Seeing the phantom: a functional magnetic resonance imaging study of a supernumerary phantom limb*. *Ann Neurol* 2009;65:698-705. <https://doi.org/10.1002/ana.21647>

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Association of British Neurologists: UK neurology workforce survey

Abstract

A neurology workforce survey was conducted by the Association of British Neurologists and compared with the annual Royal College of Physicians census in November 2018-March 2019. 46% of consultants and 35% of trainees responded. Based on the clinical work contracted (excluding academic and other work), the calculated number of Consultant Neurologists was 1 per 91,175 of the population. There is significant geographical variation in the number of consultants throughout the UK. There is a gradual shift when comparing the trainee and consultant data towards better gender and ethnic representation in the former. The data highlights potential future workforce planning issues including the potential impact of the increasing number of female trainees.

also to obtain more subspecialty specific information.

Methods

A link to an electronic survey was sent out to all ABN members on November 30th 2018 with reminders sent out until close of survey in March 2019. Non-members were also encouraged to complete it. The data from this was compared to the RCP survey published in October 2019.¹ Any duplicates were removed from the dataset. It was assumed that the sample was representative and therefore the results were extrapolated.

Results**Response rate**

There were 615 respondents in the ABN survey (Tables 1a, 1b). Of these, 400 were ordinary members and 445 stated their role as consultant neurologist (Tables 1a, 1b). The RCP survey determined the total number of consultant neurologists in the country as 958. This is a robust figure derived using data from the General Medical Council (GMC), as well as contacting each trust to determine the number at an individual trust level and incorporating data from new consultant appointments compiled by the RCP during the year. Using 958 as the total number of consultant neurologists,

Determining current neurology workforce is key to planning future care of patients with neurological conditions in the UK. The Royal College of Physicians (RCP London, Edinburgh and Glasgow) run an annual census with the help of the Medical Workforce Unit. The Association of British Neurologists (ABN) wanted to triangulate the figures obtained by conducting an independent survey during 2018-2019. The secondary aim was

Table 1a – The self-declared roles of each respondent.

What is your professional role?	Total
Consultant neurologist	445
Lecturer	5
SpR	93
Research Fellow	35
Retired	6
Other	3
Blank	27
Consultant neurophysiologist	1
Grand Total	615

Table 1b – The ABN membership categories for all respondents

ABN membership category	Total
Ordinary (consultant)	400
Associate (trainee/research fellow)	123
Senior (retired consultant)	41
Not a member	38
Affiliate (post trainee but not neurology consultant)	8
Overseas (overseas consultant)	3
Honorary Foreign	1
Blank	1
Grand Total	615

Table 2: The average number for each different type of Programmed Activity for all consultant neurologists and then for those whose primary contract is with the NHS and with a University. DCC (Direct Clinical Care), SPA (Supporting Programmed Activity). This is compared to the Royal College of Physicians survey with all consultant physicians.

	ABN survey N=445	ABN survey Primary contract NHS N=351	ABN survey Primary contract University N=76	RCP survey All Physicians
Total	9.3	9.6	9.5	10.5
DCC	6.3	7.1	3.0	7.4
SPA	1.6	1.8	1.1	1.9
Academic	1.2	0.2	5.9	0.6
Other	0.5	0.5	1.4	0.7

Table 3 Geographical spread of consultant neurologists across the country as a percentage of the total. *NHNN = National Hospital for Neurology and Neurosurgery

	ABN (%)	RCP (%)	Population (%)
England	84	86	85
London & Southeast (NHNN*,Thames)	35 (13,22)	39	28
East Anglia	4	8	9
Mersey & Northwest	9	8	10
Northern	3	4	4
Oxford	5	4	4
Southwest	6	7	7
Trent	2	4	7
Wessex	6	3	4
West Midlands	7	8	9
Yorkshire	4	8	9
Wales	4	3	4
Scotland	11	8	8
Northern Ireland	1	2	3

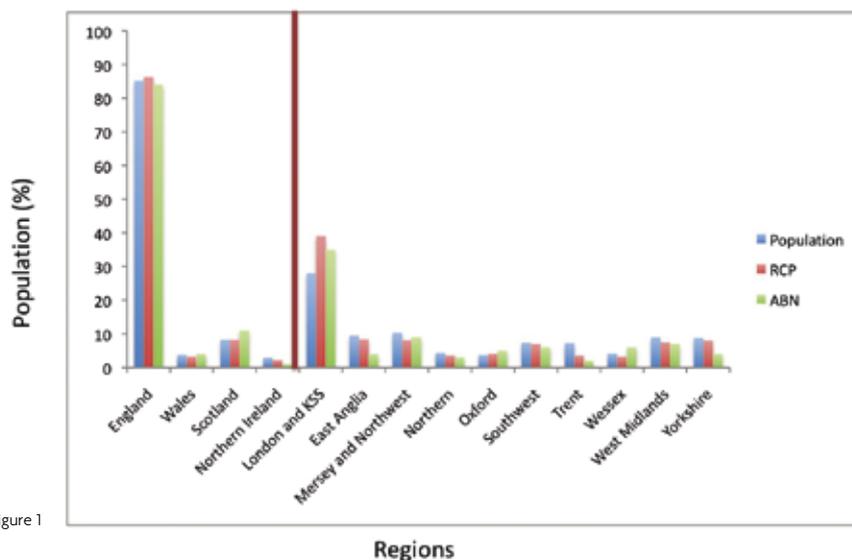


Figure 1

the respondent rate for the RCP survey was 31%. For the ABN survey, the respondent rate was 46% (445/958).

123 associate members responded to the survey (Table 1b). It is noted that 93 respondents determined their role as specialist registrars and 35 as research fellows (Table 1a). The RCP had information from the Joint Royal College of Physicians Training Board (JRCPTB) that determined the total number of neurology trainees as 362. Using this, the

respondent rate for the RCP survey was 37%. For the ABN survey, using both registrars and research fellows as a surrogate for trainees, the equivalent respondent rate would be 35%.

The role of the respondent / Membership of the ABN

Table 1a lists the self-declared role of each respondent and 1b summarises the membership category of the ABN held by the respondents.

Consultant Neurologists

This section of the report is based on consultants alone ie those who responded as their role being a consultant neurologist.

Consultant workforce

The RCP survey calculated the number of consultant neurology Full time equivalents (FTEs) for the population of 65,737,181 as 873 ie 1 per 75,292. The total number of Direct Clinical Care (DCC) and Supporting Programmed Activity (SPA) for the 445 consultant neurologists surveyed in the ABN survey was 3419. If this is extrapolated to the 958 consultants, that would equate to 721 FTEs ie 1 per 91,175 (1.1 per 100,000). If all the PAs in the ABN survey were considered together ie including university and others then this would equate to 875 FTEs, which is equivalent to the RCP estimate of 873. The similarity between the two surveys adds validity to the data but as one of the aims of the ABN survey was to identify FTEs involved in patient care (ie DCC and SPA), the figure of 1 per 91,175 (1.1 per 100,000) is the most accurate reflection of consultant neurology numbers involved in patient care and thus for workforce planning future needs.

To put this in context, in 2004, according to WHO² high, high middle, low middle, low income countries, the number of neurologists per 100,000 population was 2.96, 3.10, 0.74 and 0.03 respectively. This is despite the UK having a relatively good density of medical doctors per 10,000 of the population at 28 (WHO 2019³) where the equivalent numbers for high, high middle, low middle, low income countries are >30, 10-30, 2-10, <2 respectively. A recent survey in 2019 by the European Academy of Neurology⁵ (EAN) estimated the number of neurologists per population in the UK to be 1 per 39,059 (mean across Europe 1 per 15,799). The discrepancy in results is due to the European study including trainees and not including the impact of less than full time working. The similarity of the RCP and the ABN data suggests the ABN figure of 1 per 91,175 for FTEs is more accurate but even using the EAN number the UK was ranked 44 out of 45 European countries for number of neurologists per population with only Ireland being worse.

The number and type of Programmed Activities (PAs) for consultants was analysed and showed that neurologists were similar to physicians as a whole when considering those whose primary contract was with the NHS (79%). However, unsurprisingly those with their primary contract with a university (17%) had different job plans (Table 2).

Geographical spread of workforce

The geographical spread across the country compared to the spread of the population is outlined in Table 3 / Figure 1. Although the proportion of consultants currently based in London and the South East was greatest, the number of consultant neurologists in this region remains well below the numbers in other high income countries.

Table 4: The percentage of male and female consultant neurologists as per the ABN and RCP survey compared to the consultant physicians as a whole.

	ABN survey (%)	RCP survey neurologists (%)	RCP survey All physicians (%)
Men	61	77	63
Women	29	23	37

Gender

The RCP survey calculated the percentage ratio of men to women as 77:23 ie less gender balanced compared to the physicians as a whole (Table 4). The ABN survey found that the balance was better (10% did not answer the question) but still not on par with physicians as a whole.

Table 5: The percentage of consultant neurologists in each ethnic group compared to the consultant physicians as a whole.

	ABN survey (%)	RCP survey All physicians (%)
Data available on	91	82
White	76	65
Asian	11	28
Mixed	2	2
Black	0.9	2
Other	0.7	3

Ethnicity

The ethnic profile of consultant neurologists is currently different to that of the consultants as a whole with fewer from ethnic minorities (Table 5).

Table 6: The percentage of consultant neurologists who have graduated from either UK, Europe or otherwise compared to the physicians as a whole.

	ABN survey (%)	RCP survey
UK	71	72
Europe	14	8
Outside Europe	10	20

Country of Graduation

The proportion of neurologists from Europe and outside Europe is reversed compared to physicians as a whole (Table 6). Most consultant neurologists who trained outside the UK trained in Europe rather than outside Europe.

Less than full time working

27% of consultant neurologists reported that they worked less than full time (LTFT). 56 (47%) were women; 49 (42%) were men and 13 (11%) did not specify their sex. 8/118 consultants stated that they were part time but their PAs totalled greater than 10 and 33/327 consultants stated that they were full time but their PAs totalled less than 10. As per the RCP census, this was not taken into account and the data were analysed based on self-reporting. The equivalent for RCP census was 23% of all physicians reported that they worked LTFT.

The reason for this varied depending on gender – 84% of women worked LTFT for family commitments and 65% of men worked LTFT due to partial retirement. The percentage of male consultants increased with age (Figure 2) so most male consultants working LTFT were older.

Clinical work performed

84% of the consultants reported that they practiced general neurology. There was a spread in the number of general neurology clinics run per week with an average of 2.3 (standard deviation 1) – see Figure 3.

The top three sub-speciality clinics run by consultant neurologists were epilepsy, multiple sclerosis (MS) and movement disorders with 15%, 14% and 13% of consultants reporting these three as their main subspecialist interest (Figure 4). The prevalence of these three conditions is epilepsy 4 per 1000 and both MS and Parkinson’s are 2 per 1000. Taking prevalence into account, there should be double the number of consultants for epilepsy compared to MS and Parkinson’s. The prevalence of stroke is 14 per 1000 but the finding that stroke is not within the top three is probably explained by other medical specialities being involved in stroke care. However Shape of Training changes with consultant neurologists being more involved in acute neurology and stroke may impact on this in the future. Figure 4 illustrates the spread of sub-specialities covered by neurologists.

Table 7: The average number for each different type of Programmed Activity for consultant neurologists who have “retired and returned” compared to consultant neurologists as a whole. DCC (Direct Clinical Care), SPA (Supporting Programmed Activity).

ABN survey		
	Retire and Return N=28	Consultants N=445
Total	7.2	9.3
DCC	5.0	6.3
SPA	1.4	1.6
Academic	0.8	1.2
Other	0.2	0.5

Retire and Return

6.3% of consultant neurologists reported that they were in a “retire and return” post. This is in comparison to the 4.9% of all consultant physicians reported in the RCP survey. The distribution of work performed by this group of consultants is shown in Table 7 as compared to the consultant neurologist group as a whole.

Neurology Trainees

This section presents the trainee data. As mentioned above, for this analysis, those respondents who self reported themselves as either a specialist registrar (93) or a research fellow (35) are considered as a trainee.

Table 8: The percentage of male and female trainees compared to consultant neurologists as per the ABN survey and also compared to the RCP survey of the trainees as a whole and for neurology trainees alone.

	ABN Survey Consultants (%)	ABN Survey Trainees (%)	RCP Trainees (%)	
			Neuro	All
Male	61	56	57	49
Female	29	40	43	51
Did not say	10	4	Not available	

Gender

Although the trend is shifting towards gender equality, this has not reached the level of medical trainees as a whole with a higher proportion of neurology trainees being male (Table 8).

Table 9: The percentage of trainees in each ethnic group compared to consultant neurologists and to the RCP survey of trainees (neurology and as a whole).

	ABN Survey Consultants (%)	ABN Survey Trainees (%)	RCP Survey All trainees (%)	
			Neuro	All
Data available on	91	94	41	
White	76	61	57	55
Asian	11	23	26	28
Mixed	2	4	3	3
Black	0.9	5	2	3
Other	0.7	1	6	5

Ethnicity

As with gender, the shift in the ethnicity of the neurology trainees is moving towards the ethnic distribution seen for trainees as a whole (Table 9).

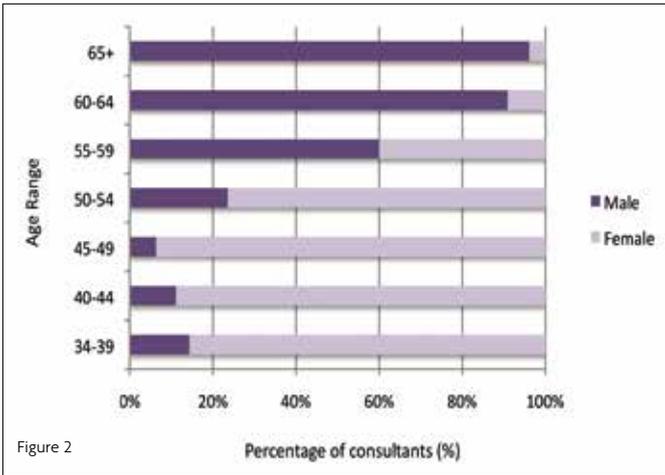


Figure 2

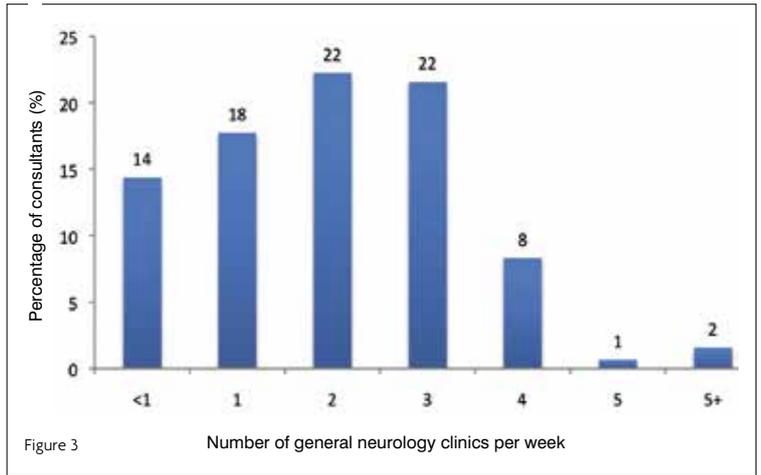


Figure 3

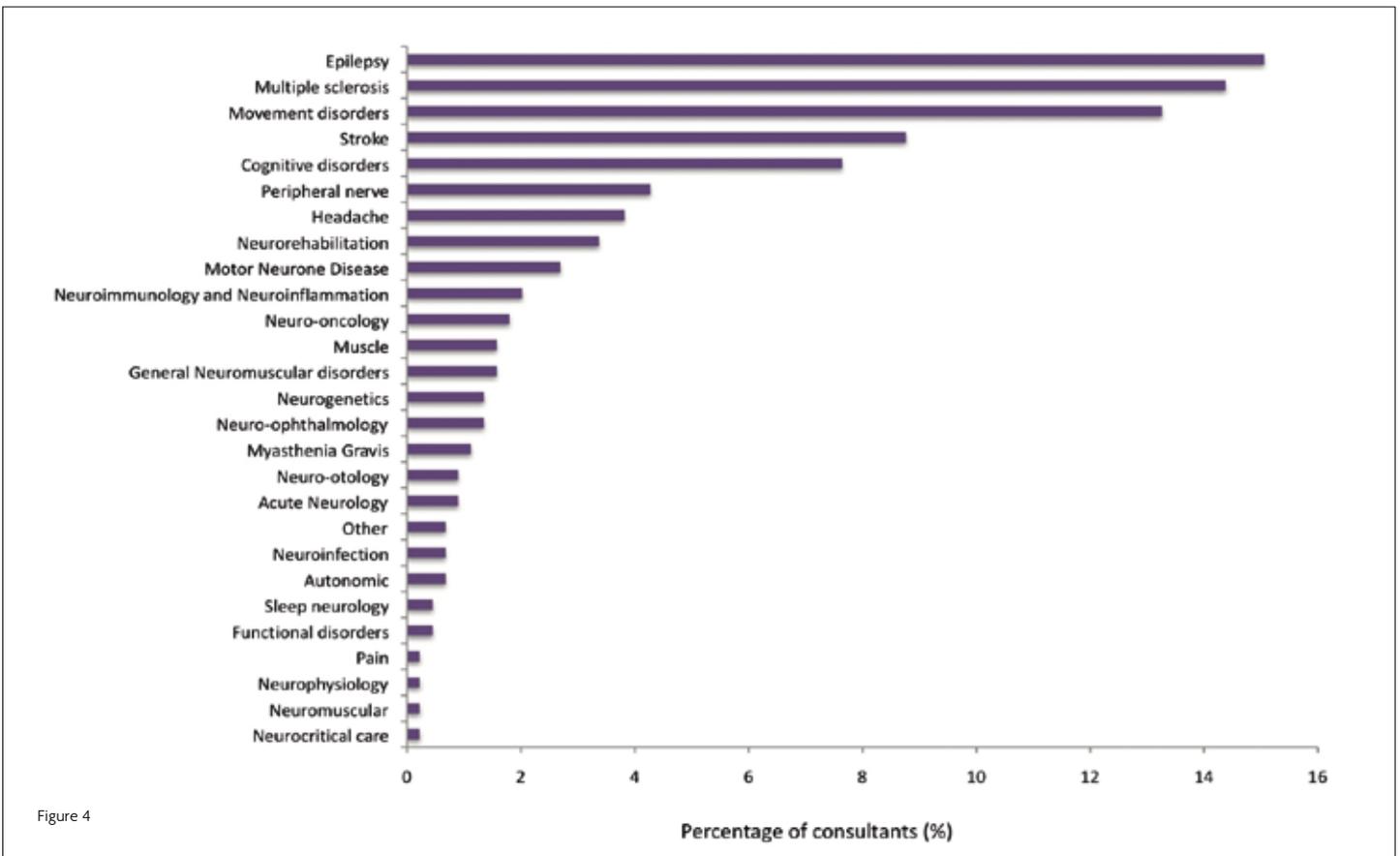


Figure 4

Table 10: The percentage of neurology trainees who have graduated from either UK, Europe or outside Europe compared to the ABN survey data of neurology consultants and RCP survey data of trainees as a whole.

	ABN Survey Consultants (%)	ABN Survey Trainees (%)	RCP survey (%)
UK	71	79	78
Europe	17	9	6
Outside Europe	10	11	16

Country of Graduation

This is similar to RCP trainees as a whole (Table 10).

Less than full time working

Fewer trainees work less than full time compared to consultants. This needs to be taken into account in workforce planning as the number of consultants who work LTFT is over double (27%) the number of trainees (12%) who do so (Table 11). Compared to trainees as a whole, more male neurology trainees work LTFT. 75% of female LTFT trainees cited family commitments as the reason for working LTFT whilst 17% of male LTFT trainees gave that reason with 83% of the men stating “other – not specified”.

Table 11: The percentage of trainees who reported Less Than Full Time (LTFT) working compared to the consultant cohort and to the RCP survey of trainees as a whole and for neurology trainees alone.

	ABN Survey Consultants (%)	ABN Survey Trainees (%)	RCP Survey All trainees (%)	
			Neuro	All
LTFT	27	12	14	14
LTFT who are women	47	53	78	88
% of total consultants / trainees working LTFT				
women	43	16	25	26
men	18	8	4	3

Discussion

The key findings of this survey conducted by the ABN are:

1. For consultant neurologists involved in patient care (DCC and SPA PAs), the number of FTEs is 1 per 91,175 (1.1 per 100,000) and not 1 per 75,292 as calculated by the Royal College of Physicians. This is much less than expected for similar high income European countries⁵ (eg. France and Germany both have 1 per less than 25,000). This inevitably has an impact on quality of care provided for patients with a neurological condition especially with regards to equitable and timely access to a consultant neurology opinion throughout the UK.
2. As per the RCP data, there is significant geographical variation in the number of consultants throughout the UK.
3. There is a gradual shift when comparing the trainee and consultant data towards better gender and ethnic representation in the former.
4. There is concern for future workforce planning in that the number of female trainees is increasing but of the 27% of consultants that work part time 47% are female and work part time mainly due to family commitments. In contrast the 42% of male consultants that work part time generally do so at the latter stage of their careers due to partial retirement. If the increasing number of female trainees continue to work part time at the same rate as the current female consultants do then this will have an impact on consultant neurologist numbers in the immediate future.
5. The type and number of sub-specialist clinics offered by consultant neurologists is appropriately centred around the three most prevalent neurological conditions (epilepsy, multiple sclerosis and Parkinsons disease) with the exception of stroke which may be explained by stroke care being traditionally shared by multiple medical specialities.

The ABN survey has provided valuable and accurate data on the number of consultant neurologists involved in patient care, the gender and ethnic breakdown of the consultant body and for the first time the breakdown of general neurology and sub speciality practise. Similar data is provided for neurology trainees.

The key limitation of this survey is the assumption that the respondents to the survey are representative of the consultant neurologist / trainee population.

Whilst it is reassuring to see the shift among neurology trainees towards a more representative gender and ethnic mix, there are worrying findings highlighted by this survey. The fact that the number of neurologists involved in patient care is

much less than comparative to European countries⁵ is particularly worrying at a time when there is a marked and welcome increase in therapies for neurological conditions which often need specialist administration and monitoring (eg. immunotherapies for multiple sclerosis, thrombectomy for stroke and the advent of novel genetic therapies for inherited neurological diseases). Although there is geographical variation in the number of neurologists in the UK with particular recruitment difficulties in certain parts of the UK that need addressing, the total number of consultant neurologists in the UK is too low and workforce planning needs to focus on increasing this number. This is particularly important as neurologists are increasingly and appropriately involved in stroke care, and the plan for neurology training in the new Shape of training curriculum is for all future neurologists to be dually trained in neurology and stroke medicine for the benefit of the patients.

Another urgent concern is the dual impact of LTFT working doubling as trainees move to consultant posts and the 6% of neurologists who have retired and returned. We appreciate there are too few doctors across all specialities in the UK⁴ and that various long term solutions are being discussed to address this. There is an urgent need to immediately address the needs of young parents to make it easier to work more if they choose to do so. Making it more attractive for consultants not to either retire early or retire and return but to stay full time longer could also be made feasible immediately by removing the financial penalties of continuing to work full time. This is an issue which affects all specialities and is under active discussion which hopefully will lead to a speedy resolution.

We would like to thank all who contributed to this survey. Having accurate information is the first step towards recognising problems and working towards solutions.

REFERENCES

1. Royal College of Physicians. *Focus on physicians: 2018-2019 census (UK consultants and higher speciality trainees)*. Accessed December 2019
2. WHO & WFN. *Atlas Country Resources for Neurological Disorders*. 2004
3. Global Health Observatory data, WHO 2019. Accessed November 2019. WHO & WFN. *Atlas Country Resources for Neurological Disorders*. 2004
4. Goddard A. *Double or Quits: calculating how many more medical students we need*. Royal College of Physicians June 2018
5. Günther Deuschl, Ettore Beghi, Tímea Varga. *The burden of neurological diseases on Europe: country profile of the UK*. European Academy of Neurology. 24.6.2019.

Working less than full time – trainee experience, and top tips

By Amy Ross Russell and Rhian Raftopoulos
Full author details on page 34

Data from the RCP 2017/2018 census demonstrates that the number of physicians training flexibly at both consultant and trainee levels is increasing. Approximately 27% of neurology consultants, and 12% of neurology trainees work Less Than Full Time (LTFT), according to the ABN workforce survey 2018, and 18% of responses to the recent ABNT census 2020 were LTFT trainees.

This perhaps reflects a changing culture within medicine and more broadly within society itself recognising the need for a better work-life balance with greater autonomy over how and when we work. There are many reasons a doctor may choose to work LTFT as well as many different ways of working flexibly and the concept and accessibility of flexible working within the NHS is still evolving.

We are two neurology trainees at different stages in our career who have chosen to work LTFT and we hope to give you the benefit of our experience so far.

We both started LTFT working on our return to work after our first maternity leave. We hoped that working flexibly would give us the best of both worlds, allowing us to spend important time at home with our children, whilst continuing to progress and thrive in our careers.

The reality is not always as simple and there are times when the two worlds compete and spill over into each other, and it can sometimes feel like we are performing neither role well. Juggling our two identities effectively without feeling a sense of disloyalty to either or both is a challenge.

However, overall LTFT working has been a positive experience for both of us and has given us the flexibility to enjoy the demands of neurology training, whilst also enjoying quality time with our family.

Eligibility (and being organised)

Recent changes to guidance mean that all junior doctors with “well founded individual reasons” should have the option of LTFT working and all applications should be viewed positively. In practice LTFT requests are mainly prioritised based on two categories. Category 1 includes disability or ill health (this can include undergoing IVF), caring for an ill or disabled partner, relative or

dependent, or caring for children. Category 2 includes unique opportunities for personal professional development as well as non-medical professional development including management courses. It is encouraging that The RCP is supportive of broadening category 3 training whereby a trainee can work LTFT without a specified reason.

If you are considering working LTFT then it is important to talk to the right people as early as possible. Getting the support of your educational supervisor and training programme director is key. There is an application form to fill in that can be obtained via your deanery LTFT administrator. Again ensure you fill in this form early to allow your deanery as much time as possible to accommodate your request.

Once your application has been approved and you have decided your percentage working hours, it is a good idea to get in contact with the department that you will be working in and identify key clinical and educational activities during the week to guide which days of the week to work. Where there is some flexibility, think carefully about which days you want to work. We prefer to work three consecutive days so as to provide some continuity of care and mindset, whereas others prefer to break the week up to avoid having all the work and time away from home in one chunk (and vice versa!)

If relevant, get your childcare organised early. Our jobs are not always predictable so take into consideration opening hours of the nursery/childminder. For example, is there any flexibility if you need to stay late? Do you have a back-up plan in case of sickness etc.?

Time (and being organised)

Most LTFT posts are slot shares where the responsibilities of one full time post are split between the two (or more) trainees, but you're employed and paid as individuals. Get in touch with your slot share partner as soon as possible. Negotiating working days and ensuring both of your needs are being met can be tricky but it is much better if you can achieve this between yourselves. A good working relationship is key as you will need to ensure good handover (especially if there are a lot of inpatient responsibilities) and trust that your job share will follow up on urgent issues that have arisen during your working days. If this relationship works well it will make both your lives easier as well as being a source of moral support.

Get a copy of your rota as soon as it is available and remember that each LTFT doctor must be given a personalised work schedule. Ensure that you know your rights and responsibilities with regards to out of hours work as some rota coordinators may not have a good understanding of this for LTFT trainees. We would recommend reading the BMA good rostering guide prior to contacting your rota coordinator. Some key recommendations we have found useful to know include:

1. You will be required to work the pro rata percentage of each type of shift on the

full time rota (in a slot share out of hours work should be split 50% and any additional hours required to meet the LTFT percentage should be made up with educationally beneficial normal working hours)

2. Unless otherwise agreed a normal, long day or twilight shift should not be rostered on a non-working day
3. Night shifts should only encroach on a maximum of one non-working day in a fixed working pattern
4. Adequate notice should be given if fixed working days need to be changed
5. Annual leave and study leave is calculated on a pro rata basis
6. Where a doctor's working hours fall below their LTFT percentage and they are required to 'make up shifts', any additional shifts should be on normal working days unless otherwise agreed

It is likely at some point that issues will arise with your rota. Be as proactive and as flexible as you can in finding a solution. Remember that you are not alone and if you are struggling to resolve rota issues get in touch with the Champion of Flexible Working (it is now mandatory for each trust to have one). Make sure you involve your educational supervisor in your discussions.

Money

Although LTFT allows greater flexibility it does have financial implications and means that your pay takes a hit. It is important to have thought carefully through your financial commitments (including childcare costs or additional costs incurred by travelling to work or being at work) before deciding on your percentage hours. When you get your first pay cheque ensure you check your pay slip is correct, as in our experience mistakes are common. This is a good resource for taking you through your payslip step by step. <https://www.bma.org.uk/features/lessthanfulltimetrainees/>

In addition remember that pension contributions for LTFT doctors are based on their full time equivalents.

If you do need to supplement your income LTFT trainees are now allowed to undertake locum work – see here for guidance. <https://www.copmed.org.uk/publications/guidance-on-undertaking-additional-work>

Some colleges and memberships, eg GMC/BMA offer reduced rates if your income is below a certain threshold.

Career progression

Remember also that working LTFT will extend your training and delay your CCT date. The JRCPTB provides this tool to help you work out your CCT date <https://www.jrcptb.org.uk/training-certification/less-full-time-training>

You will still be required to have an annual ARCP and you will be required to complete a pro rata number of assessments. There will of course be less time within a week to complete these, but the extension to your training should mean there is overall as much,

if not more opportunity to identify suitable cases. You still need admin time and time for personal development, so be careful not to let this be taken over with clinical duties to "make up for not being there other days". Again, if there are difficulties with this, involve your Champion of Flexible Working.

Training opportunities may be limited to particular times of the day or week, for example sub-specialty clinics or MDTs. It is helpful to think about these early to allow you to plan how to achieve this experience/training, and your educational supervisor should be able to help you with this. Sometimes it is possible to rearrange your working days for a couple of weeks, or to arrange to attend a different clinic/MDT as an alternative, or find a suitable course to replace this experience. Close attention to your e-portfolio, careful design of your Personal Development Plan (PDP), and close liaison with your educational supervisor will be important in ensuring smooth progression and avoiding falling behind. We would encourage you to be proactive in this, as it is easy to let it slip, and hard to find time to catch up.

Challenges

We would be lying if we said there had not been challenges along the way. Not all colleagues find it easy working with job-share trainees, and conflicting schedules make certain clinical roles or responsibilities harder. Ensuring continuity of clinical care is more challenging, and there is less time to get to know complex patients or situations. You need to rely on handover information from your colleagues, and sometimes will not be able to have the benefit of a face to face handover but need to rely on written information. This is difficult. It requires energy and enthusiasm for what you are doing, and means you sometimes feel you under-perform compared to your colleagues (or former self). Try not to think this way, but appreciate that developing the ability to become rapidly acquainted with a case is a key skill in becoming a senior trainee, and when necessary, explain that you need a little more time to get to grips with a complex case.

It can be more difficult to establish yourself within the team, especially if you start training LTFT before you are well known in a team, or around a time you change places of work. LTFT trainees often describe feeling they are not taken as seriously as their full-time counterparts and you can miss out on opportunities simply because you are not around as much. Comments such as "what are you doing on your day off?", or "don't worry – you don't have time for this" can be frustrating and reflect a misperception of LTFT working.

Arranging out of programme (OOP) opportunities, and funding for OOP may be more challenging. Again, this is mainly tackled by knowing your rights, and being organised. Trainees should not be prevented from taking time OOP (for good reasons) on the basis of working LTFT, in exactly the same way that any other trainee should not be prevented because

there are staffing issues. But, as with the latter, it is always best to plan ahead, communicate clearly with your training programme director and educational supervisor, and be as flexible as possible. This not only gets people on your side, but also means that the process will be smoother, as the necessary organisation for filling your space, and arranging funding can be sorted, and it avoids last minute disappointments. Remember that time OOP may also be LTFT and there will be implications from this on experience, opportunity, and duration of time OOP.

Benefits

Despite all the challenges mentioned, in our experience, the benefits far outweigh the challenges and it has definitely been the right decision for us. LTFT has provided us with a better work life balance – allowing us to spend more time with our young children, easing some of the pressure on family life, and avoiding this feeling “squeezed” into a weekend.

The reduced burden of on calls is significantly appreciated, especially when the reasons for LTFT working include responsibilities at home, and when sleep is at a premium!

At work, we find we have a greater appreciation and enthusiasm for our work. The ‘extreme end of week fatigue’ is much less of a problem when working a three-day week, and having less time spent at work during the week, particularly if you have previous experience of full time working, can feel liberating!

The slower pace of training can also be a real benefit, as new opportunities open up, and you may end up taking a very different route to that which you originally planned. You have more time to ‘enjoy the ride’ and reflect on what you want to get out of your training, before you are committed to a substantive consultant post.

Top Tips for LTFT working success

Be organised
Contact the right people at the right time
Know your rights and responsibilities
Know who to contact for help if problems occur
Communicate any problems early on
Be proactive and flexible in finding solutions
Seek out other LTFT for advice/support-find a mentor
Set realistic and achievable training goals
Prioritise goals/objectives in order of importance/time sensitivity
Handover is everything!
Show initiative and seek out opportunities
Be kind to yourself – accept that you cannot be all things to all people all of the time!
Always have a back-up plan in case of emergencies

Other useful resources

BMA LTFT guidance <https://www.bma.org.uk/advice/career/applying-for-training/flexible-training-and-ltft>

The BMA good rostering guide <https://www.bma.org.uk/advice/employment/contracts/junior-doctor-contract/rostering-guidance/roster-design-for-ltft-doctors>

NHS Employers Doctors in Flexible training. Equitable pay for flexible trainees

Other sources of support

BMA LTFT forum

LTFT Trainees Facebook page

The Medical Women's Federation

ABN LTFT representative



Amy Ross Russell

is an ST6 Neurology SpR in Wessex, and Chair of the Association of British Neurologists Trainees.



Rhian Raftopoulos, MbChb, MRCP, PhD

is a LTFT Neurology Trainee currently working at the National Hospital for Neurology and Neurosurgery, London. She has an interest in MS and completed her PhD in the Queen Square MS Centre. She is passionate about improving opportunities for LTFT trainees and promoting flexible working practices within the NHS.

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Tuberous Sclerosis Complex

By Philippa Ward

It's nearly nine years since I first heard the words Tuberous Sclerosis Complex. I remember the date very clearly – Friday 24th February 2012 – but most other memories from that time are cloudy and vague, to say the least. You see, I was physically and emotionally drained. I had a five-month-old baby who had spent the previous ten days behaving oddly, making strange jerky movements and crying incessantly. I had an energetic two-year-old in the mix too. You can imagine what my life was like. So, my first reaction on hearing those words was “tubular what?” I thought immediately of the Mike Oldfield

classic, Tubular Bells. That was about as much as my already-full brain could manage.

I was the kind of exhausted that every parent with a small baby and a toddler experiences at some point. But, I was also exhausted from the double-whammy of rejections I had received from two different GPs who had dismissed my concerns about my baby, Thomas, as “colic” and “teething”. One of them even said “you can't think he's having seizures”. Oh, how ironic those words seem today.

You see, on Valentine's Day, I had been getting Thomas ready for bed when I noticed he was making very subtle jerky movements

with his arms. He was five months old, so I thought he should have grown out of the startle reflex, but that was the only thing I could think of that made any sense. However, it didn't really make any sense and something just didn't seem right. Over the course of the next few days, things got worse. Thomas was doing this strange movement, which I could only describe as an exaggerated version of the startle reflex, more and more. He was also crying more than usual. I guess, looking back, I was pretty certain, deep down, that there was something terribly wrong with him. I knew from my experiences with my older son that

babies cry. But this was something different; this crying was on another level. I had spent three nights driving round the countryside near where we lived with Thomas in the back of the car, just to get us out of the house so that my husband and our other son could get some rest.

After my two failed GP visits (although, to give the second one her dues, at least she had offered to write to the paediatrician for advice), I decided to take matters into my own hands. It was my mum who had gently suggested that if I was really worried, I should think about going up to the local hospital. So, on that Friday morning, my husband went to work, I deposited our two-year old at nursery, packed a bag with some emergency supplies and headed to the A&E department. By this time, I was armed with video evidence of Thomas's unusual episodes (thank goodness for smartphones!) but even the triage nurse dismissed the footage as "definitely not seizures". Luckily, we were eventually seen by a paediatrician who took one look at the video and knew straight away that he had a classic case of infantile spasms on his hands. Rare in itself, he explained that it could be caused by an even rarer genetic condition called Tuberous Sclerosis Complex.

We spent two nights in that small, local hospital, before being moved to a paediatric neurology ward at a bigger hospital in a nearby city for an MRI scan which would determine whether Thomas did in fact have Tuberous Sclerosis Complex. I still hadn't really processed what was happening, although I finally felt as though I was being taken seriously. How I now wish it had just been a bad case of colic...

The day of the MRI came and that experience was so frightening. There was talk of sedation, but Thomas had a cluster of seizures immediately beforehand and slept for the entire 20 minutes of the scan, without moving a muscle. I, on the other hand, felt every single clang and bang of the scanner as if time were standing still. The following day we received the devastating diagnosis, which was to change our lives forever. The consultant was sensitive and had held off delivering the diagnosis until we'd had a chance to get some sleep. However, it was a diagnosis nobody wants to receive. Fortunately, I had my husband with me, but processing something like that is impossible. I still don't know to this day if I will ever come to terms with it.

I know it isn't easy for the healthcare community to deliver a diagnosis like this. However, being on the receiving end of it is shattering. It propels the entire family into a maelstrom of confusion. We were faced with countless scans and tests, regular monitoring of symptoms and medication, we had so many questions which nobody could answer; all against a backdrop of uncertainty about what the future would bring. It hasn't been easy for us and there are days when we still think "why Thomas, why us"? But, over time, we have gradually learned to come to terms with our new life and the realities of having a child like Thomas.

We were handed a leaflet, which at the

time seemed a ridiculous consolation prize for having been given such shocking news. However, in time, this leaflet became our lifeline. It was a leaflet produced by the amazing Tuberous Sclerosis Association who offer all kinds of support and information, which is invaluable once you have left the safety of the hospital environment and are back in your own home working out how to put your life back together and what your new version of "normal life" looks like.

Thomas is now nine years old and still regularly experiences seizures because of his epilepsy and where the tubers are situated in his brain, although he spent several years on a clinical trial for an epilepsy medicine which has been amazing, not just for him, but for the entire family. Happily that drug has now been made available on the NHS. Thomas' development is profoundly delayed: he is non-verbal, struggles to communicate in a conventional way and cannot do many of the daily tasks that most of us take for granted. But, he is the happiest little boy you could ever meet! He is cheeky, funny and great company. He takes everything in his stride and has developed his own little ways of letting us know what he wants and needs. He skips off when we get him up on a morning, looking for his tablet so that he can watch his beloved Barefoot Books videos on YouTube. He regularly runs away when we are trying to dress him after his evening bath, and can be usually found in his brother's room waiting for a tickle or a cuddle. He knows where the treats are kept and when he is hungry will bring us a food packet that needs unwrapping to let us know it's time for a snack – he recently upgraded to bringing us the toaster because he knows it's where he gets one of his favourite foods from, toast!

We were fortunate, in a way, to have actually received a diagnosis and that it ended up being Tuberous Sclerosis Complex. I now know countless families who have children without a diagnosis, or who have something so rare that there is no support group or community of like-minded people. With Tuberous Sclerosis Complex, there is the support and I am eternally grateful for that. I have formed a strong link with the charity and many of the other families that are in the same boat as us. I am eternally grateful for their support. I am also hugely thankful to those 50 original families affected by Tuberous Sclerosis Complex who came together in 1977 to share their experiences and ultimately establish what has since become the Tuberous Sclerosis Association.

It's not the route that any of us expected our lives would take, but Thomas brings absolute joy to everyone whose path he crosses. He has taught us so much, enriched our lives beyond expectation and given us a different lens to view the world through. We don't know what the future will bring, but let's face it, who does? What we do know is that we're as ready as we can be to face the challenges that are thrown in our path and the bumps in the road that may come our way.



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The Tuberous Sclerosis Association operates a support line for all TSC-related enquiries, including those from health and social care professionals. Contact the TSA Support Line through telephone (0808 801 0700) or email support@tuberous-sclerosis.org.

John Zachariah Laurence: 'forgotten luminary'

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Abstract

John Zachariah Laurence was one of the four medical staff appointed in 1860 to the new "Hospital for the Paralysed and Epileptic," at 24 Queen Square, London. A prize-winning graduate of UCH he was known for his high intellect and skills in general surgery and in ophthalmology. After a brief period at Queen Square he left to found the South London Ophthalmic Hospital that became the Royal Eye Hospital, and the "Ophthalmic Review", the first British journal of ophthalmology; he later served at Barts. Highly accomplished in the arts, literature and research his achievements were sadly neglected by his contemporaries.



Figure 1: John Zachariah Laurence

Since its foundation, the Hospital for the Paralysed and Epileptic at Queen Square has appointed surgeons and ophthalmologists to its staff. John Zachariah Laurence (c. 1829 – 18 July 1870) was one of the four medical staff, and a board member appointed in 1860 to the new hospital at 24 Queen Square, London.¹ It began with a small working party and a public meeting at the Mansion House on November 2, 1859. Here it was resolved to set up a special institution in the fashionable Queen Square, to be called the "Hospital for the Paralysed and Epileptic," now National Hospital for Neurology and Neurosurgery. It had been instigated by Johanna, Louisa and Edward Chandler, and the Lord Mayor, David Wire.² It was prompted by the Chandlers whose grandmother had received poor, inadequate treatment for paralysis, and David Wire, who had himself recently been afflicted with a hemiparesis.

At the outset there were only four influential

medical staff: Jabez Spence Ramskill (1824-1897) the first physician,³ Charles Edouard Brown-Séquard,⁴ William Fergusson, Surgeon Extraordinary to Queen Victoria, and John Zachariah Laurence. Two years later Hughlings Jackson was appointed assistant physician; he was intellectually outstandingly original if eccentric, admired but not well understood in his time. Renowned for both original experiments and for his frequent peregrinations Brown-Séquard left in 1863, but the others have all but vaporised into the mists of history, their names now generally unknown.

In 1860, it was decided that a visiting surgeon should be elected to the hospital, and John Zachariah Laurence (Figure 1) was appointed. We can only assume that it was his academic brilliance and skills in general surgery and in ophthalmology that were valued in a hospital for nervous diseases. Laurence had started in surgery and became an ophthalmologist. He lived and practised at 30, Devonshire Street. In 1857 he became the founder, with assistance of Carsten Holthouse, of the South London Ophthalmic Hospital that became in 1892 the highly reputed Royal Eye Hospital. It opened with two beds in a house in St George's Circus, Southwark. Laurence's biographer, Arnold Sorsby was its first full time Professor in Ophthalmology.

Laurence was born into a middle-class Jewish family, his great-grandfather was an immigrant from Bohemia. He graduated from University College London in 1854 with several gold and silver medals and prizes.⁵ He became Fellow of the Royal College of Surgeons less than a year later. He trained in general surgery and published three much credited books and many papers.

He was surgeon at the Northern and Farringdon Dispensaries in 1855, and in 1858, Surgeon to the St. Marylebone General Dispensary. As a specialist in eye diseases, in 1864 he became founder and editor of the "Ophthalmic Review", the first British journal devoted to ophthalmology. He promoted the ophthalmoscope at Queen Square. He had successfully modified the binocular instrument of Giraud-Teulon and also invented a monocular ophthalmoscope. Laurence was the first to describe disciform degeneration of the macula in 1867, a decade before von Michel. In 1860 he described himself as Surgeon [Ophthalmic Surgeon]¹ to the Hospital for Paralysis [Queen Square]. His time at Queen Square was but brief, since his commitment to eye diseases led to his leaving to found the South London Ophthalmic hospital in a house in St George's Circus, Southwark. Towards the end of his career he was Ophthalmic Surgeon

to St. Bartholomew's Hospital, Rochester (1866-69) founded in 1078, the oldest hospital in England, until it closed in 2016.

What can we discover of Laurence the man?

Critchley related:

Laurence was a man of great gifts and versatility, a philanthropist, and a pioneer of new ideas. He was also a fine linguist, and was deeply interested in the Arts.¹

For reasons uncertain his work was undervalued as Arnold Sorsby's (1900-1980) belated obituary reveals:

Laurence was well and truly interred by his contemporaries. They had come to bury Caesar not to praise him. Eleven years later the existence of an Ophthalmic Review that he had founded and edited for nearly, four years (1864-7) but which had not survived longer than that, was not mentioned by its new editors.⁵

And he was described as:

A scholarly and wise man, and his intelligence and versatility served the hospital well at its inception. He may have helped to introduce the ophthalmoscope developed by Hermann von Helmholtz (1851) at Queen Square.² (p.363)

His name remains only in the rare, eponymous Laurence-Moon-Biedl syndrome. With his colleague Robert Charles Moon, his American house surgeon, in 1866 he described the syndrome:

Marian T., a fat, flat-framed, heavy looking child' with 'want of intelligence' and retinitis pigmentosa.⁶

Inheritance was autosomal recessive. He described a similar affection in three of her seven brothers, who in addition to the eye lesion showed peculiar bodily defects; they were all stunted, possessed of a solid, heavy countenance, mentally dull, and in addition showed remarkable under-development of the external genitalia. Re-examination, a few years later showed a spastic paraparesis. This picture of familial obesity, mental retardation, hypogonadism, associated with retinitis pigmentosa was completely forgotten until Bardet in 1920, and Biedl in 1922 described a similar disorder with polydactyly. This heterogeneous disorder bearing his name is caused by compound heterozygous mutation in the PNPLA6 gene on chromosome 19p13.

Laurence wrote three highly regarded books: *The diagnosis of Surgical Cancer*. (which won the Lister Prize) London, 1855; *The optical defects of the Eye*. London, 1865; and

A Handbook of Ophthalmic Surgery. London, 1866. In addition he published numerous papers (in the *British Medical Journal*, *Lancet*, *Medical Times and Gazette*, *Royal London Ophthalmic Hospital Reports*, and *First Ophthalmic Review*) listed by Sorsby.⁵ Of neurological interest were his: *The influence of the variations of the size of the pupil on the accommodating power of the eye*. *Glasgow Medical Journal* 1861; *On encephalocele, the history of a case with a tabular analysis of 75 cases*. *Medico-Chirurgical Transactions* 1856; *Encephaloid tumour of bone*. *Medical Times and Gazette* 1858; *On a case of encephalocele*. *Lancet* 1857.

Information about the life of Laurence is sparse. Indeed Julius Hirschberg in *The History of Ophthalmology* found him:

a noteworthy figure, a learned and inventive man, and one who had aspired to great things; it was a matter for regret that nothing concerning his life was to be obtained from the usual sources of reference.⁷

He was married to Miriam Solomon, at the West London Synagogue on August 9, 1854 and had three daughters and a son who died in childhood. Miriam died in 1863. Seven years later Laurence died after a protracted



Figure 2

illness, aged only 41 at St Peter's Square, Hammersmith, leaving one son and three daughters. He was buried beside his wife in the Balls Pond Road Cemetery (N.1) (Figure 2). The renowned Arnold Sorsby described him⁵ as 'versatile to a fault; he found relaxa-

tion in singing, music, drawing and fishing, and was a fine linguist and a scholarly writer.' The *British Journal of Ophthalmology* in 1932 belatedly portrayed him as:

One of those forgotten luminaries who shone brilliantly in his own day but whose career was so brief that he has all but been forgotten today.

REFERENCES

1. Critchley M. *The Beginnings of the National Hospital, Queen Square (1859-1860)*. *Brit Med J*. 1960;2:1829-37. <https://doi.org/10.1136/bmj.1.5189.1829>
2. Shorvon S, Compston A. *Queen Square A history of the National Hospital*. Cambridge University Press 2019. <https://doi.org/10.1017/9781316181430.002>
3. Lorch MP. *The Unknown Source of John Hughlings Jackson's Early Interest in Aphasia and Epilepsy*. *Cog Behav Neurol* 2004;17:124-132). <https://doi.org/10.1177%2F096772013479758>
4. Aminoff MJ. *Brown-Séquard a visionary of science*. New York : Raven Press, 1993. <https://doi.org/10.1097/0006123-199311000-00033>
5. Sorsby A. *John Zachariah Laurence- a belated tribute*. *Brit J Ophthalm* 1932;16(11):727-40. <https://doi.org/10.1136/bjo.16.11.727>
6. Laurence, JZ, Moon RC. *Four cases of retinitis pigmentosa occurring in the same family and accompanied by general imperfection of development*. *Ophthal Rev*. 1866;2:32. <https://doi.org/10.1002/j.1550-8528.1995.tb00166.x>
7. Hirschberg J. *The History of Ophthalmology 1899 to 1917, nine volumes*. (translated by Frederick C. Blodi. Bonn, JP. Wayenborgh. 1982.

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The first chapter introduces the reader to fundamental scientific basis of Neurology and Neurosurgery by going through anatomical and physiological aspects, with anatomical regions grouped in different sections. There is even a section dedicated to embryology. As with the rest of the book, this chapter is well-suited to the visual learner, with many diagrams, tables, and clinical images used to illustrate the points made. Overall, this chapter functions as a refresher for the pre-clinical topics. A reader completely new to the subject, seeking greater understanding would probably benefit from a fuller text.

The next chapter is more directly relevant for the clinical years of medical school, as it covers neurological signs and symptoms, history-taking, and examination. There are images to help illustrate examinations that are difficult to visualise. Included at the end is a section on management options, which comprises commonly used medications in Neurology and different neurosurgical procedures, and a section on investigations, including Neuroradiology (including different types of magnetic resonance imaging and how they work) and Neurophysiology.

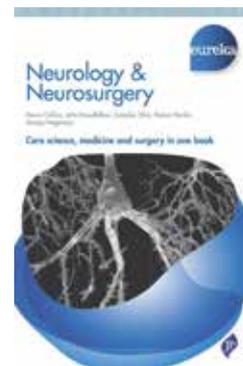
The book then transitions to chapters discussing a range

of common and important neurological and neurosurgical disorders. These fall under topic chapters on headaches, movement disorders, dementia, emergencies and others. Most of the 16 topic chapters start with one or two worked-through clinical cases featuring vivid narratives, neuroimaging, and figures to capture the reader's interest and enthuse them for the chapter ahead. With 27 cases in total, their aim is to help develop clinical reasoning and decision making. The chapter texts discuss the diseases relevant to the topic, with subdivisions to explain aetiology, clinical features, diagnostic approaches, investigations, and management.

The final chapter contains single best answer questions based on the previous chapters, and this is a great tool for reinforcing knowledge and revision. Throughout the book are text boxes highlighting important concepts which help break up the text and allow the reader to reflect on the new information before moving on.

There were a few typographical errors but, in addition, at least one factual error in the first chapter, p. 16. Here it was claimed that during depolarisation, "when a stimulus ... causes K^+ efflux to increase, the membrane potential becomes less negative." K^+ efflux should be replaced with Na^+ influx. Perhaps this is best considered as a large 'typo'. I do not think it detracted from the general reliability and authority of the text.

Overall, this book succeeded in its aim to cover the Neurology and Neurosurgery that is relevant for medical students throughout their degree and would therefore be a great resource and revision aid for any medical student.



Authors: Dawn Collins, John Goodfellow, Dulanka Silva, Ronan Dardis, and Sanjoy Nagaraja
Published by: JP Medical Ltd, 2018
Price: £25.95
Pages: 496
ISBN: 9781907816741
Reviewed by: Tamara Al Bahri, Medical Student, University of Liverpool.

Sir Charles Bell: His Life, Art, Neurological Concepts, and Controversial Legacy

The biography of Sir Charles Bell by Michael Aminoff is a win-win at least in the sense that both the subject and author may be considered to be "one of us". Although associated with the Royal College of Surgeons, Bell can be considered a Clinical Neuroscience practitioner in the modern sense (of blurred boundaries between the 'crafts' of diagnosis and intervention). Aminoff, likewise it seems, is a British Neurologist/Neuroscientist; having known his name from several North American tomes, I only now realise(-ize) that he is British born, bred and trained!

The volume benefits from a pleasing size (just over 200 pages), excellent writing and numerous well-judged illustrations. And then, of course, there is the interesting context of the subject's life, straddling the political and academic medical centres of Edinburgh and London in the late 18th century and the early to mid-19th. The first line of a book's last chapter is as good an indicator of its potential as any: 'Bell was born when America was still a British colony and France still had a king.'

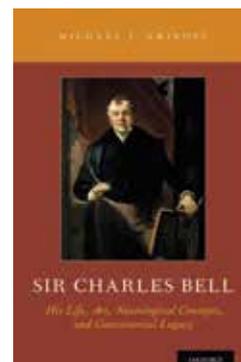
Of course I knew about Bell's palsy, and Bell's phenomenon, but I really hadn't known very much about Bell's life and general academic output before this book. I was fascinated to read that he wrote on the 'Expression of Emotions' (Chapter 4), on the relevance of the anatomy of our facial muscles for Art, which seems to resonate with such modern concepts as mirror neurons and social cognition. While I'll avoid spoiling the fun by relaying the whole list of Bell's neuroanatomical and clinical insights (Chapters 8 and 9 respectively), you should know that they're impressive. And Aminoff argues that we revere Bell less than we should,

because of the misjudgements of his later career.

But we cannot expect a fellow Neurologist to be impeccably objective in his role as an amateur historian: Aminoff is clearly in the Bell fan club. He gives a generous account of Bell's interference with his own writings to justify primacy in discovery (of the motor and sensory functions of the anterior and posterior spinal roots). I even note that Magendie, Bell's competitor, is described in the most grisly manner, conducting vivisection experiments on puppies ... which he had been given as a Christmas gift, on no less portentous a page of the book than 101.

This autumn, many of us may take the opportunity to reflect on social and economic pressures upon scientists and clinicians. Bell's self-referential approach to scientific progress and his acceptance of presenting Science in relation to Belief (Christian belief that is, in the Bridgewater treatises) seem rather familiar. In Bell's case, his misjudgements led to a retirement that was earlier and quieter than he might have wished it to be. Aminoff's generous view (which I tend to share) that Bell's mistakes were less than egregious, and less numerous than his achievements, must in part be due to the kindness that comes with the passage of time. It may also be that the truly egregious challenges of public scientific discourse in the present day make Bell a somewhat more sympathetic persona for us.

So, please go to one of Aminoff's textbooks if you want to learn Neurology. But, if looking for a stimulating Christmas read, for yourself or for the recipient of a gift, go for this. And if you also get a puppy this Christmas, please look after it better than Magendie did his.



Author: Michael J Aminoff
Published by: Oxford University Press
Price: £65.26
Pages: 265
ISBN: 9780190614966
Reviewed by: Rhys Davies, Consultant Neurologist, Liverpool

“Dementia in a changing world” – the 30th Alzheimer Europe Conference

Conference details: 20-22 October, 2020. Conference streamed virtually. **Report by:** Kate Boor Ellis, Communications Officer, Alzheimer Europe.

The 30th Alzheimer Europe Conference (#30AEC) was held online from 20-22 October 2020. Almost 800 participants from 42 countries attended, and 260 speakers and 100 poster presenters shared their research, projects and experiences in an atmosphere of collaboration and solidarity, against the backdrop of the global COVID-19 pandemic.

Iva Holmerová, Chairperson of Alzheimer Europe opened the conference, extending a special welcome to the 35 people with dementia among the delegates, as well as their supporters. Delegates were also welcomed by Helen Rochford-Brennan, outgoing Chairperson of the European Working Group of People with Dementia (EWGPWD) and Myrra Vernooij-Dassen, Chairperson of INTERDEM.

As part of this year's new conference format, Alzheimer Europe organised two plenary roundtable sessions, in lieu of keynote lectures. The first of these, “Dementia in a changing world”, saw a panel discussion including Adelina Comas Herrera, co-lead of the Strengthening Responses to Dementia in Developing Countries (STRiDE) project; Mario Possenti, general secretary of Federazione Alzheimer Italia; Helen Rochford-Brennan and Lennert Steukers, Associate Director, Janssen Neuroscience Team.

Panelist Adelina Comas-Herrera, Care Policy and Evaluation Centre, London School of Economics and Political Science, referred to an updated report she co-authored, for which data was collected regarding the impact and mortality of COVID-19 in people living with dementia in nine countries. The percentage of people with dementia in care homes, whose deaths were linked to COVID-19, ranged from 29% to 75% across those countries.

The ban on visits to care homes across the world has kept people with dementia detached from essential affective bonds and from the provision of family care, for many months. There is a pressing need, and also an opportunity for innovation. Guidelines and tools to support institutions and practitioners to respond better to the needs of people with dementia during the pandemic are needed as a matter of urgency, she stressed.

Lennert Steukers emphasised that a number of stages of research have been impacted during the ongoing pandemic: Discovery/preclinical work has suffered due to lab closures and technical unemployment of researchers; clinical work has been hit, with clinical trials being suspended or severely delayed, which may have an impact on data quality; and patient involvement has also been difficult due to travel restrictions and only limited face-to-face contact being possible.



PL2: Diagnosis and medical management

The clinical trial landscape has dramatically changed in terms of how these trials are being conducted and will continue to be conducted. He gave the examples of decentralised, remote and virtual trials, and pointed out some of the challenges this presents in the field of neurodegeneration. There has been a huge impact on the research community, he said, with a whole generation of researchers being affected, for instance due to fellowship schemes/research programmes being stopped.

The second plenary session of the conference was on “Diagnosis and post-diagnostic support” and opened with a presentation on “Improving the diagnosis of neurocognitive disorders: implementing the recommendations of the 2nd European Joint Action on Dementia”, given by Pierre Krolak-Salmon, President of the French Federation of Memory Centres. We are still facing an under-diagnosis of Alzheimer's disease and dementia in the field of primary care in Europe, he stressed, noting that the Joint Action recommends new training programmes to help in the fight against the major diagnosis gaps present in primary care. He also shared that a new graduated and personalised diagnosis strategy had been adopted by the Joint Action, which can be adapted to any and all European countries. Finally, he said that advanced practice nurses could help to better detect neurocognitive disorders in primary care.

During the next presentation, on ethical issues linked to the disclosure of diagnosis, clinical Neurologist Edo Richard, offered a different perspective, highlighting the impact of a diagnosis and the importance of considering that “timely” diagnosis may not always

be synonymous with early diagnosis. The introduction of a biomarker-based diagnosis of Alzheimer's disease blurs the boundary between health and disease, he said. Finally, he highlighted the widening gap between research and clinical practice around diagnosis of Alzheimer's disease.

In the third presentation, Simon Lovestone, Vice-President, Disease Area Leader, Neurodegeneration, Janssen, looked at the pharmacological treatment of Alzheimer's disease and at what we have learned in recent years. Developing therapies for Alzheimer's disease is particularly challenging for many reasons, he said. The brain is the least understood organ in the body and the disease is inherently complicated, so there are a number of hurdles to overcome when doing clinical trials in this population. He also noted, however, that while clinical trials have not produced a disease-modifying drug, “we have gained tremendous knowledge from years of research and promising efforts are underway that it should only be a matter of time before we see therapies that should delay onset or progression of disease.”

The final presentation was delivered by Gunhild Waldemar, Professor of Neurology and Chair of the Danish Dementia Research Centre at Rigshospitalet, University of Copenhagen. She was one of the leading forces in the establishment of the new European Academy of Neurology (EAN) and her presentation, on medical management issues in dementia, shared the new recommendations from the EAN.

She began by pointing out that people with dementia are at increased risk of infections, malnutrition, incontinence, dehydration, adverse effects of certain medications, epileptic seizures, and neuropsychiatric symptoms, and said that medical conditions may go unnoticed in some cases. A lack of treatment, or mis-management of medical conditions may worsen symptoms of dementia, and lead to pain, physical disability, psychiatric symptoms, hospitalisations or even death, she continued. The new EAN guideline, “Medical management issues in dementia”, was developed by a multidisciplinary working group with the aim of helping to guide physicians on five selected topics: The need for medical follow-up of people with dementia; when and how to treat severe psychiatric symptoms with antipsychotics; the treatment of epilepsy; of vascular risk factors; and of pain.

The third plenary explored “Building dementia-inclusive societies”. Dianne Gove, Director for Projects at Alzheimer Europe, opened with a presentation on “Patient and public involvement approaches in dementia research: the

experiences and contributions of the European Working Group of People with Dementia” (EWGPWD). Sabine Jansen, Executive Director, Deutsche Alzheimer Gesellschaft (DALzG) shared some of the experiences of her organisation, with regards to promoting dementia-inclusive hospitals. The third presentation was given by Jacqueline Hoogendam, who is the co-ordinator for dementia policy and international affairs on Long-Term Care at the Ministry of Health, Welfare and Sport in the Netherlands. She listed some of the learnings from the Dutch dementia strategy - the “Deltaplan Dementie” – with regards to making Dutch society more dementia-friendly. The final presentation of plenary three was given by John Keady, who leads the inter-disciplinary Dementia and Ageing Research Team at the Division of Nursing, Midwifery and Social Work. He was the Chief Investigator on the multi-site ESRC/NIHR Neighbourhoods and Dementia Study and it was this study and the outcomes of the project which were the main focus of his talk.

The fourth plenary began with Carol Brayne, Professor of Public Health Medicine and Co-Chair of the Cambridge Public Health Interdisciplinary Research Centre in the University of Cambridge, giving a talk on the latest trends in the prevalence of dementia and discussing whether prevention messages are having an effect.

Dementia is changing across generations and within populations, she said. The evidence on prevention clearly points to the fact that primary prevention for dementia risk profiles for whole populations, combined with effective management of existing risk

conditions in individuals, is the most effective strategy. On the other hand, she stressed that “there is no evidence that screening and early detection will be effective at present”.

Up next, Alexander Kurz, senior scientist at the Department of Psychiatry, Klinikum rechts der Isar, Technical University of Munich and Director of the university’s memory clinic, shared some of the findings of “INDEED, an inter-professional intervention in dementia education for South-Eastern European countries”. Dementia is a complex disorder that can only be tackled by several health and social care professionals working together, he said. He also stressed that inter-professional shared education is key for collaboration and networking, and can take advantage of modern digital learning formats. The INDEED project provides an online e-learning programme, addressing multiple professions simultaneously and conveys a person-centred, holistic concept of dementia care, he summarised.

In the third presentation, Dympna Casey, Professor and Head of School in the School of Nursing & Midwifery NUI Galway looked at assistive technologies and explored what the role of social robotics could be in dementia.

Carlos Diaz, CEO of Synapse Research Management Partners and Coordinator of the IMI NEURONET project, was the final speaker in plenary four. He discussed the neurodegeneration portfolio of the Innovative Medicines Initiative (IMI), and looked at ways to ensure project results are converted to sustainable assets.

Globally, society is facing several highly complex, urgent challenges, and to be able to

respond, he said, scientific research may need a paradigm change in how it is organised. A systems leadership approach is being explored in the IMI neurodegeneration portfolio and it is hoped this will help to propel scientific efforts towards the much-needed actionable results.

The fifth and final plenary session took the form of a second roundtable discussion, this time revolving around “Maintaining dementia as a European priority”. Panellists included Maria Carrillo, Chief Science Officer, Alzheimer’s Association (US) global research programme; Dan Chisholm, Programme Manager for Mental Health at the WHO Regional Office for Europe, Nils Dahl, Senior Policy Advisor at Germany’s Federal Ministry of Health; Charles Scerri, Chairperson of the Malta Dementia Society, Vice-Chairperson of Alzheimer Europe and National Focal Point on Dementia in Malta; and Nicoline Tamsma, Policy Officer at the European Commission’s DG for Health and Food Safety, Unit Health Promotion, Disease Prevention, Financial Instruments.

The three-day conference also featured 24 parallel sessions and 6 special symposia on diverse topics for delegates to choose from.

The three-day virtual conference was formally closed by Alzheimer Europe Chairperson Iva Holmerová. All delegates were invited to mark the dates of the next Alzheimer Europe Conference (#31AEC) in their calendars. “Building bridges” will take place in Bucharest, Romania from 29 November to 1 December 2021.

The 30th Alzheimer Europe Conference received funding under an operating grant from the European Union’s Health Programme (2014-2020).

CONFERENCE PREVIEW: 2nd Targeting Therapy of Alzheimer’s and Related Neurodegenerative Diseases Conference

Conference details: 25-28 July 2021, Lisbon, Portugal.

This conference will provide a unique forum for the research community focusing on translational studies geared towards therapies in AD and related neurodegenerative diseases to come together and to discuss the latest advances and the future challenges in the field.

The talks and poster presentations will include the most updated therapeutic strategies, newly discovered therapeutic targets, and recent clinical developments at various stages in the area of Alzheimer’s and related neurodegenerative diseases. Key topics of discussion will include; BACE1 inhibitors and/or -secretase modulators for reducing amyloid deposition, active and passive vaccination for enhancing clearance of amyloid

plaques, vaccines for reducing tau pathology, antisense approaches for AD, PD and ALS therapy; neural stem cell approaches for neurodegeneration, inflammatory modulators for neurodegeneration, genetic linkage study and big data approaches and novel therapeutic targets.

Call for Abstracts
Talk Submission 15 February 2021
Poster Submission 28 May 2021
Conference webpage:
<https://www.fusion-conferences.com/conference/128>

EVENT PREVIEW: Epilepsy Climate Change (EpiCC)

The newly formed consortium, Epilepsy Climate Change (EpiCC) is planning to hold a virtual event focusing on the impact of climate change on people with epilepsy, and the responsibility of clinicians to reduce their own contribution to global warming.

The conference and series of webinars will draw on expertise from around the world. As well as sharing current research into the impact of

climate change, they will look at the response of different countries to the COVID-19 pandemic.

To find out more, you can register your interest at
www.epilepsysociety.org.uk/climatechange

Nectar Conference 2020

Conference details: 19-20 March, 2020. Conference streamed virtually. **Report by:** Sophie Skidmore, Dr Venkat Pisupati and Dr Shaline Fazal, The Stem Cell Institute, Cambridge. **Conflict of interest statement:** None declared.

On the 19th and 20th November 2020, the annual NECTAR conference took place, bringing together people from all over the world to discuss the latest in the field of CNS disorders and novel treatment strategies, from pioneers in their respective fields, to students just starting their careers. The conference was held, for the first time, as an online webinar conference, due to the ongoing COVID-19 pandemic. The conference comprised of talks from expert speakers who have paved the way for both cell and gene therapies and a number of DataBlitz sessions, which gave the opportunity for students and post-docs to present their data and receive valuable feedback from a large, diverse audience. At the end of the first day, there was the opportunity to attend one of a number of breakout sessions, led by experts in the respective fields, which ranged from cell therapies in Parkinson's disease to treatment strategies for Huntington's disease. Notably, these sessions offered the opportunity for the audience to engage and learn from experts and encouraged invaluable discussion between Neurologists and basic scientists.

The conference kicked off with a talk from Professor Jun Takahashi, who delivered a fascinating overview of the recent CiRA trial, whose aim is to assess the safety and efficacy of iPSC-derived dopamine cells as a clinical option for HLA-matched Parkinson's patients. This included extensive investigation into the safety and efficacy of this potential therapy using cellular and animal models. Professor Takahashi informed us that 4 patients have been grafted with iPSC-derived dopamine cells, to date, with a view of grafting a further 3 patients by 2021. Participants will be assessed for improvements in their motor function for 2 years after grafting. Professor Takahashi finished his talk, reminding the audience "Regenerative medicine is a comprehensive art", prompting discussion into how cell therapies may be used in conjunction with other gene, rehabilitation or pharmacotherapies in the future.

As well as iPSC-based therapies, embryonic stem cell-derived (ESC) therapies are also of major interest in the field of cell therapies for Parkinson's disease. Professor Lorenz Studer was the second speaker of the day and discussed the fascinating, ESC-based trial – NYSTEM-PD, which he assured, is due to start in the very near future. This exciting trial will explore the safety and efficacy of replacing lost dopamine cells in 10 moderate to severe Parkinson's patients, with H9 embryonic stem cell-derived dopamine cells. Professor Studer also discussed the ATLAS-PD trial, which is a longitudinal 3-year study, involving moderate to severe PD patients, with the

aim of investigating the correlation between clinical biomarkers and disease progression. Alongside outlining the pipeline to clinical application, Professor Studer looked into the future and discussed the ultimate goal of an 'off-the-shelf' cell-therapy for Parkinson's disease, and the bottlenecks that lie between clinical and commercial grade cell products.

While many planned and ongoing trials are focused on treating idiopathic Parkinson's disease, some are aiming to treat specific, hereditary forms of the disorder. Dr Pablo Sardi delivered a very engaging talk about the most common genetic form of alpha synucleinopathy – GBA. The GBA gene encodes for the lysosomal hydrolase glucocerebrosidase (GCase), mutations in which lead to dysfunction and the pathogenic accumulation of lipids such as glucosylceramide. This mutation has also been implicated in the onset and progression of Parkinson's disease. Dr Sardi gave an elegant overview of ongoing AAV (adeno-associated virus) and small molecule therapies, such as Ambroxol, an activator of GCase and Venglustat an inhibitor of glucosylceramide synthase for the treatment of GBA-PD. He finished by explaining the potential for such therapies to be broadened to treat both genetic and idiopathic forms of Parkinson's disease.

The final talk of the day came from Professor Krystof Bankiewicz. Professor Bankiewicz discussed the use of the AAV-AADC viral vector, as a method of restoring aromatic L-amino acid decarboxylase (AADC). AADC has a role in the production of both serotonin and dopamine. He started by discussing a Phase I/II clinical trial investigating AAV-AADC as a means of treatment for AADC deficiency – a rare paediatric neurodevelopmental disorder, which manifests as a number of motor and non-motor symptoms. One of the most moving moments of the day came when Bankiewicz showed pre and post-operative videos of AAV-AADC treated children and the vast improvements in both their motor and non-motor function, from 5 weeks to 2 years post-operative. Professor Bankiewicz ended by discussing the progress made using a similar approach in Parkinson's patients and interestingly highlighted the difference in efficacy and the difficulties that come with treating a more elderly patient cohort. However, he was able to demonstrate that this approach could increase striatal dopamine levels, which correlated with improvements in motor function and a decrease in levodopa-equivalent dose in patients.

The second day started with a series of talks based on the recent advances in Parkinson's disease and other neurodegenerative disease. The first of such talks was

delivered by Professor Per Borghammer, who discussed his novel theory of 'Brain and Body first Parkinson's disease'. Professor Broghammer beautifully explained his theory that Parkinson's disease can start primarily in the periphery of some patients and spread to the brain, while in others, pathology appears to originate in the amygdala and spread into the periphery at later stages. This fascinating talk was supported by a plethora of clinical data, correlating data from imaging studies with post-mortem data in order to support his theory. This talk was an excellent example of how imaging modalities are essential and wonderfully useful tools for understanding disease progression and pathology onset in man.

Following on from Professor Borghammers discussion was Professor Jorgen Kjems, who delivered an excellent discussion about the recent advances in the application of nanoscience for central nervous system diseases. Professor Kjems covered a range of topics, one of which included how multi-valent tagging using nanoscaffolds can aid in allowing peptides to cross the blood-brain-barrier, which has been a problem in the field for generations. Later in his talk, he also discussed how nanoscience technology and machine learning was being used to detect novel biomarkers for central nervous system disorders, from as little as a few microlitres of blood plasma. Another highlight of the talk was on circular RNAs and their identification and function in neuronal differentiation. In this way, Professor Kjems' talk emphasised the synergy between both technological advancement and for the progression of science.

Kicking off the section on cell therapies for Huntington's disease (HD) and other Central Nervous System (CNS) disorders was Professor Anne Rosser. Professor Rosser's talk was about the next steps in cell therapies for HD where she provided solid foundations for understanding the challenges that the field of HD research currently faces, whilst highlighting new areas of ongoing research into cell therapies. Such studies and consortiums mentioned included Repair-HD which was a collaborative effort to take stem cell therapies into clinical application, TRIDENT, a trial focused on delivery of novel therapeutics and SC4HD (Stem Cells for HD) which is focused on developing a neural intra-cerebral stem cell-based therapy for HD reliant on the collaborative efforts of clinicians, scientists and patients alike. A clear message from Professor Rosser's fantastic talk was the need for authenticity of stem cells and the scope there is for advancing cell therapies in HD.

As critical as neurons are in neurodegen-

erative disorders, the glial population must not be forgotten, the importance of which was emphasised in the talk by Professor Steven Goldman. His talk focused on the use of stem cell therapies for disorders of the white matter tract, whilst demonstrating how useful animal models still are in pre-clinical research. Professor Goldman showed some very exciting and promising results using stem cells in ameliorating some features of neurodegenerative disorders and ended by high-

lighting how HD could also be considered a glial therapeutic target.

In addition to the talks discussed above, we were treated to a number of DataBlitz 10 minute talks, which largely discussed novel methods of modelling PD and HD, with a specific emphasis on the use of 3D and organoid systems, as well as methods of improving differentiation capacity and graft efficacy for cell-replacement therapies. Also discussed were novel approaches to treating

CNS disorders from neurotrophic approaches to rehabilitation with exercise.

Given the current climate we find ourselves in, the organisers did a brilliant job of putting together a selection of both topics and speakers that reached out to scientists and clinicians alike, making this a highly successful virtual event. The success of NECTAR 2020 only fuels anticipation for the next one!

ABN 2020: The virtual experience

Conference details: ABN 2020. **Date:** The meeting spread over 9 weeks with a main meeting day on Friday 16 October, preceded and succeeded by four Thursday night sessions. **Report by:** Amy Ross Russell. Amy is a LTFT Neurology Trainee in Southampton, UK. **Conflict of interest statement:** None declared.

If you look back to your copy of ACNR from early March, you will see Richard Davenport promising a spectacular and sunny meeting in Bournemouth. But as 2020 had other plans, the ABN annual meeting, like many, underwent significant revisions this year, adapting to the current restrictions and requirements for fun, virtual learning. The result? A flexible feast of neurology.

Following on from the success of the “lockdown lectures” aimed at neurology trainees earlier in the year, the ABN meetings committee adapted the programme of the planned annual meeting to fit in to a series of Thursday evening lectures, sandwiching a clinically focused day, that incorporated the firm favourites of the meeting.

On the 16th October, our main day saw Hadi Manji draw comparisons between COVID-19 and the viral pandemics of the past, with important lessons for us all. Rustam Al-Shahi Salman brought us up to speed with the syndromes we have been seeing as a consequence of COVID-19 infection, and reminded us there’s no such thing as a free school trip, and Chris Kipps took us elegantly through the changes that have been required by Neurologists through the pandemic, and the positive effects that have been seen on reported rates of burnout.

The day continued with a clinical focus, with exceptional talks from Mark Roberts and Hannah Cock, on two of the most anxiety provoking neurological presentations – acute respiratory failure, and status epilepticus – with pithy, practical, priceless advice.

The day finished on an absolute high, as

anyone who watched Lucy Kinton deliver the CPC will confirm. A devilish case, elegantly broken down so that even the most junior amongst us felt empowered to tackle the next diagnostic conundrum. And if the presentation itself hadn’t been impressive enough, she even managed to generate a cliff hanger by disconnecting her internet in the final seconds before her denouement – Genius!

The evening sessions which have sandwiched this, combine the best offerings from the planned meeting programme, and cover a broad range – from therapeutics, offering hope to those suffering with (and treating!) migraine, and a breakdown of the implications of MS therapies during current times, to advances in technology that dramatically expand the information available to us, through remote monitoring systems, and genomic sequencing, so long as we are equipped with the skills to interpret these – and find the signal in the noise.

There were excellent clinical talks, with invaluable wisdom – highlighting red flags in adult cerebral palsy, taking us through challenging cases by video, and dissecting out tremor and ataxia for the general Neurologist.

The final two weeks have been particularly enjoyable for me, seeing so many of the trainees around the country demonstrate the amazing work they have been doing. The platform and poster presentations have been exceptional, hugely varied and such a reflection of what a fascinating and varied area neurology is. Congratulations to all those who were shortlisted for these sessions, and congratulations to the winners – Edwin

Jabbari, London, (Variation at the LRRK2 locus determines the rate of disease progression in progressive supranuclear palsy), Ingrid Hoeritzauer, Edinburgh (The clinical features and prognosis of scan negative cauda equina), Hannah Glasse, Manchester (Is there a positive correlation between single breath count and forced vital capacity), Sabrina Kalam, Imperial, London (a case of bad altitude) and Rebecca Hodnett, Bristol (Quality improvement: Restructuring the neurology ‘In-hours’ on-call service at North Bristol Trust) for winning best platforms, poster, clinical case presentation, and quality improvement project prizes.

Incorporated within the conference were attempts to mitigate the detrimental effect of not being able to hold a face-to-face meeting. We hope people enjoyed the virtual fun run, morning yoga session, and the head-scratching musical quiz. Whilst this year definitely suffered for a lack of face to face, and evening refreshment, it also served as a reminder of what a great, diverse community there is within neurology, and I was amazed by the enthusiasm and energy that was retained.

I’m sure we are all hoping that it won’t be long before we can once again meet face to face. In the meantime, we are keen to gather your thoughts and feedback from the virtual meeting this year and are particularly grateful for suggestions of innovative ways to harness the energy and community which we have seen this year and breathe some life in to the next virtual meeting.

The day finished on an absolute high, as anyone who watched Lucy Kinton deliver the CPC will confirm. A devilish case, elegantly broken down so that even the most junior amongst us felt empowered to tackle the next diagnostic conundrum. And if the presentation itself hadn’t been impressive enough, she even managed to generate a cliff hanger by disconnecting her internet in the final seconds before her denouement – Genius!

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

Clinical Neuroanatomy Courses

Available all year round, virtual
<https://clinicalanatomycourses.com/courses/online-neuroanatomy-course/>

JANUARY

Queen Square Multidisciplinary Neuro-oncology Teaching Course: Benign & Malignant Tumours
 13 January 2021, London, UK
<https://www.ucl.ac.uk/ion/study/queen-square-courses/queen-square-multidisciplinary-neuro-oncology-teaching-course>

Liverpool Neurological Infectious Diseases Course
 20-21 January, Virtual
<https://www.liverpool.ac.uk/neuroidcourse/about/>

Recognising Post Traumatic Stress Disorder
 18 January, 2021; Derby, UK
https://www.ncore.org.uk/Website_Event_List
 E. uhdb.ncore@nhs.net
 T. 01332 254679

19th Annual King's Neuromuscular Disease Symposium
 29 January 2021, Virtual
<https://estore.kcl.ac.uk/conferences-and-events/academic-faculties/institute-of-psychiatry-psychology-neuroscience/department-of-basic-and-clinical-neuroscience/19th-annual-kings-neuromuscular-disease-symposium>

FEBRUARY

Exploring Functional Patterns of Movement
 1 February, 2021; Derby, UK
https://www.ncore.org.uk/Website_Event_List
 E. uhdb.ncore@nhs.net
 T. 01332 254679

Edinburgh Sleep Medicine Course
 22-25 March 2021, Edinburgh
<https://www.sleepconsultancy ltd.co.uk/courses/edinburgh-sleep-medicine/>

Balance Rehabilitation

23-24 February, 2021; Derby, UK
https://www.ncore.org.uk/Website_Event_List
 E. uhdb.ncore@nhs.net
 T. 01332 254679

Assessment and Ideas for the Treatment of Thorax in Adults with Neurological Damage
 26 February 2021; Derby, UK
https://www.ncore.org.uk/Website_Event_List
 E. uhdb.ncore@nhs.net
 T. 01332 254679

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
https://www.ncore.org.uk/Website_Event_List
 E. uhdb.ncore@nhs.net
 T. 01332 254679

MS Foundation MasterClass 10.2
 18-19 March, 2021; Sheffield, UK
<https://multiplesclerosisacademy.org/events/ms-foundation-10-module-2/>

Edinburgh Sleep Medicine Course
 22-25 March 2021, Edinburgh
<https://www.sleepconsultancy ltd.co.uk/courses/edinburgh-sleep-medicine/>

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

2021 Spine Society of Australia 32nd Annual Scientific Meeting
 International Convention Centre, Sydney
 9-11 April 2021
www.dconferences.com.au/ssa2021
 E. ssa2021@dconferences.com.au

BNA2021 Festival of Neuroscience
 12-15 April, 2021; Online and worldwide
<https://meetings.bna.org.uk/bna2021/>

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/>

2nd Academic and Clinical Symposium in Cognitive-Communication Disorders (CCDs)
 29-30 April 2021, Manchester, UK
<https://m.mersevents.com/2nd-CCD-Symposium.html>

MAY

British Society of Clinical & Academic Hypnosis (BSCAH) National Conference 2021
 7 May, 2021; Totnes, UK
<https://www.bscah.com/book-event/nationalconference2021>
 E. natoffice@bscah.co.uk

British Neurotoxin Network Paediatric Workshop on Ultrasound Guided Injection
 8 May, 2021; London, UK
<https://mondale-events.co.uk/event/british-neurotoxin-network-paediatrics-ultrasound-workshop/>

NHS Lothian selects Canon Medical for CT

Aquilion ONE GENESIS Edition takes its place inside the new Department of Clinical Neurosciences

The Department of Clinical Neurosciences (DCN) and the Royal Hospital for Children and Young People (RHCYP) at NHS Lothian have both selected Canon Medical's Aquilion ONE GENESIS Edition CT scanner to support routine and research imaging services. Both systems were chosen to replace an incumbent CT supplier and support services inside the new £150 million hospital in Edinburgh, a project that involved the re-location of the both the DCN and the Royal Hospital Sick Children from other parts of the city to under one roof at the Little France site at the Royal Infirmary of Edinburgh.

The CT scanner is now operational at the Department of Clinical Neurosciences for neurology, general imaging, CT angiography and interventional procedures with the new Royal Hospital for Children and Young People also set to bring into service its own Aquilion ONE GENESIS Edition CT when the hospital is fully open. The new building will adjoin the Royal Infirmary of Edinburgh via adult and children emergency departments.

Canon Medical was awarded the CT contract for balancing high-end medical imaging technology with value for money. It also offers low



(L to R): Iain Gray Account Manager at Canon Medical Systems UK; Lesley McKinlay, Principal Radiographer at DCN/RHCYP; Lindsey Todd, Specialist Radiographer; and Chantelle Houston, Specialist Radiographer in DCN at NHS Lothian.

dose capabilities, excellent image quality and innovative CT reconstruction through its Advanced intelligent Clear-IQ Engine (AiCE). Together this will lead to enhanced clinical confidence and an improved patient experience.

Lesley McKinlay, Principal Radiographer at DCN/RHCYP at NHS Lothian states, "Despite the Coronavirus pandemic the CT installation has been completed by Canon Medical and we are operational. We are already seeing the benefits of its wide-ranging functionality in the delivery of routine clinical work and research projects. The staff have been extremely well supported by the Canon applications and support teams."

"We are delighted to have been awarded the CT partnership at NHS Lothian and

welcome them to our stable of NHS customers across the UK. We hold great pride at Canon Medical that the end of a sale is just the start of a long term imaging partnership - we look forward to providing online and physical application and service support into the future," states Iain Gray, Account Manager at Canon Medical Systems UK.

<https://uk.medical.canon>

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*Patients with difficult-to-treat migraine were episodic and chronic migraine patients who had documented failure to 2-4 classes of migraine preventive medications²
CGRP, calcitonin gene-related peptide

References:

1. AJOVY[®] SmPC. Teva UK Limited.
2. Ferrari MD et al. *Lancet* 2019; 394(10203):1030-1040.
3. Teva UK Limited. Data on File. Fremanezumab DOF 196. 2019.

teva

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.co.uk

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

Ajovy[®] ▼ (fremanezumab) 225mg Solution for Injection in Pre-filled Syringe and Ajovy[®] (fremanezumab) 225mg Solution for Injection in Pre-filled Pen Abbreviated Prescribing Information.

Presentation: Fremanezumab 225mg solution for injection in pre-filled syringe. Fremanezumab 225mg solution for injection in pre-filled pen. **Indications:** For prophylaxis of migraine in adults who have at least 4 migraine days *per month*. **Dosage and administration:** The treatment should be initiated by a physician experienced in the diagnosis and treatment of migraine. Ajovy is for subcutaneous injection only and can be injected into areas of the abdomen, thigh, or upper

arm that are not tender, bruised, red, or indurated. For multiple injections, injection sites should be alternated. Patients may self-inject if instructed in subcutaneous self-injection technique by a healthcare professional. **Adults:** Two dosing options are available: **Monthly dosing:** 225mg once monthly. **Quarterly dosing:** 675mg every three months. When switching dosing regimens, the first dose of the new regimen should be administered on the next scheduled dosing date of the prior regimen. The treatment benefit should be assessed within 3 months after initiation of treatment. Evaluation of the need to continue treatment is recommended regularly thereafter. **Missed dose:** The indicated dose should resume as soon as possible, a double dose must not be administered to make up for a missed dose. **Children:** No data are available. **Elderly:** Limited data available. Based on the results of population pharmacokinetic analysis, no dose adjustment is required. **Renal impairment:** No dose adjustment is required. **Hepatic impairment:** No dose adjustment is required. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Precautions and warnings:** In order to improve the traceability of medicinal products, the name and the batch number of the administered product should be clearly

recorded. If a hypersensitivity reaction occurs, discontinue administration and initiate appropriate therapy. No safety data are available in patients with certain major cardiovascular diseases. **Interactions:** No formal clinical drug interaction studies have been performed. **Pregnancy and lactation:** It is preferable to avoid the use of Ajovy during pregnancy as a precautionary measure. A risk to the breastfed child cannot be excluded. A decision must be made whether to continue Ajovy therapy while breastfeeding. **Effects on ability to drive and use machines:** No influence on the ability to drive and use machines. **Adverse reactions:** Hypersensitivity reactions such as rash, pruritus, urticaria and swelling. **Very Common:** Injection site pain, injection site induration and injection site erythema. **Common:** Injection site pruritus. Consult the Summary of Product Characteristics in relation to other side effects. **Overdose:** It is recommended that the patient be monitored for any signs or symptoms of adverse effects and given appropriate symptomatic treatment if necessary. **Price:** 1 single pre-filled syringe of Ajovy: £450.00. 1 single pre-filled pen of Ajovy: £450.00. **Legal category:** POM. **Marketing Authorisation Number:** EU/1/19/1358/001. **Marketing Authorisation Holder:** Teva GmbH, Graf-Arco-Str. 3, 89079 Ulm, Germany. **Job Code:** AJO-UK-00017. **Date of Preparation:** July 2020.

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AJO-GB-00023 Date of Preparation: September 2020

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