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ACNR

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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

In this issue

Todd Hardy, Co-Editor.

It is a distinct pleasure to introduce this 20th anniversary edition of ACNR. Over the last 20 years the world of journal publishing has seen many changes with perhaps the biggest being the rise of pay-to-publish open access journals. We are proud at ACNR that we have remained open access while resisting article charges, and that we have been able to continue to publish quality peer reviewed articles of interest to our international readership.

The success of ACNR has been due to the support of authors who choose to publish their excellent work with us, to our advertisers who appreciate our credibility and reach, to our dedicated publishing team of Anna Phelps and Donna Earl led by the incomparable Rachael Hansford, to our editorial team including former Editors, Mike Zandi and Sian Alexander, and to my current Co-Editor, Ann Donnelly. Last but not least, ACNR is indebted to the vision of founding editor, Roger Barker, who along with Rachael Hansford conceived of ACNR as a journal dedicated to short reviews of the latest in clinical neuroscience so that specialists and non-specialists could keep abreast of the latest developments.

The last 20 years have also seen relentless progress in clinical neurology, and ACNR thought it pertinent to publish a series of articles over the next few issues which summarise the most significant advances in different subspecialty areas to highlight the progress that has been made during ACNR's lifetime.

In this issue, former ACNR editor, Roger Barker from Cambridge has returned with a distillation of the last 20 years of progress in Parkinson's disease. In his article, he anticipates that new insights into pathophysiology may lead to disease modifying therapies. Mark Manford from Bristol has similarly taken on the challenge of summarising 20 years of advances in epilepsy from changes in diagnostic criteria through to improved understanding of drug therapies. The 20 years of changes in the Association of British Neurologists since John Newsome Davies was President in 2000 are reviewed by David Burn from Newcastle.

Also in this issue, Clare Bolton and Sleep Editor Kirstie Anderson, from Newcastle, opine on the importance of asking our patients about daytime somnolence and provide practical advice regarding sleepy drivers.

Mary Galea, Aurora Messina, Bridget Hill, Catherine Cooper, Jodie Hahn and Natasha van Zyl from Melbourne examine the latest in restoring hand function using peripheral nerve transfer surgery in spinal cord injury.

Eminent Australian Neurologist, John Pollard, reflects on his career in neurology in an interview with foundation trainees Johnny Tam from Edinburgh and Leah Mercer from Oxford. Professor Pollard, among many achievements, pioneered the use of intravenous immunoglobulin and plasma exchange in Australia for neurological diseases such as myasthenia gravis, and he reminisces about his professional life and close ties with British neurology.

Regular and valued ACNR contributor, Andrew Larner from Liverpool seizes on the anniversary of ACNR to address the topic of exceptional memory or hypermnesia. Another valued, regular contributor JMS Pearce from Hull writes a biography of John Russell Reynolds, a giant in the nascent field of epileptology in the 19th century, and one of the first Neurologists appointed to what is now the National Hospital for Neurology and Neurosurgery in London.

Our case report is from Eva Bunting, Andrew Barritt, Nigel Leigh, David Wright and Waqar Rashid from Brighton on the topic of giant cell arteritis without headache. Our conference reports are by Charly Billaud from Birmingham reviewing Encephalitis 2020 and Georgina Hill reviewing the UK Stroke Forum 2020. Andrew Larner also contributes a book review. We hope you enjoy this historic edition of ACNR.

Todd Hardy, Co-Editor
E. Rachael@acnr.co.uk

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Volume 1 issue 1 of ACNR

Rachael Hansford, Publisher

Twenty years ago this month we published the first issue of ACNR, with Roger Barker as Editor. A lot has changed since then, but I'm pleased that ACNR remains true to its original concept.

In 1999 I was living in Edinburgh and working for a small publisher of medical magazines. Though it was a small company, the women I worked with were incredibly inspiring and there was a real sense that we could achieve anything we set our minds to. By this point, one of my siblings had already sustained two serious brain injuries – a third followed in 2013. The idea of branching out on my own to launch a free publication for specialists working in neurology and rehabilitation didn't seem that far-fetched.

I was lucky that my research quickly led me to Roger, who was also keen on the concept of a free publication and the opportunity to bring neuroscience to the wider neurology community. He didn't see any issue with launching a publication with an unknown young woman who had no obvious backing. Thankfully, neither did Stephen Kirker who agreed to join us as Rehabilitation Editor.

Podcast

If you're interested to hear the story of how ACNR started, please do listen to our first ever podcast, coming very soon. Roger and I sat down recently with Srikirti Kodali to discuss our first meeting, the early days and the ten years that Roger was Editor. A second podcast focusing on Roger's career will follow shortly.

ACNR isn't affiliated with any societies or organisations, and publication has only been possible thanks to our many contributors and advertisers.

So I would just like to say a huge personal thank you to everyone who has been a part of ACNR's journey over the past 20 years: to our Co-Editors Todd Hardy and Ann Donnelly, who somehow manage to squeeze ACNR into their already busy lives; Mike Zandi who steered us through our second decade; the many specialists who have so generously joined our editorial team, written or peer reviewed articles; and the advertisers whose support has made our free journal model sustainable.

Thanks also to our designer Donna who has been alongside me since those Edinburgh days, Anna who has co-ordinated the editorial for the past 15 years – and you the reader of course, without whom the whole exercise would be pointless!

Rachael Hansford

ACNR

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C19-YRS

COVID-19 Yorkshire Rehabilitation Scale

A digital assessment and monitoring tool to help manage individuals with Long COVID

- C19-YRS screens for the most common symptoms in Long-COVID.
- Grades the severity of symptoms to provide a score of burden.
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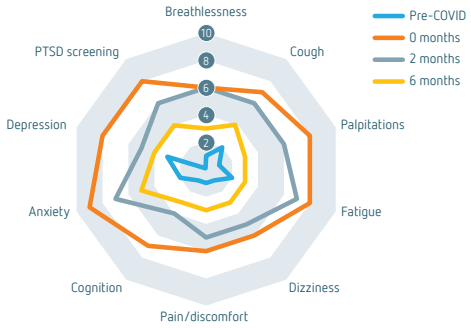
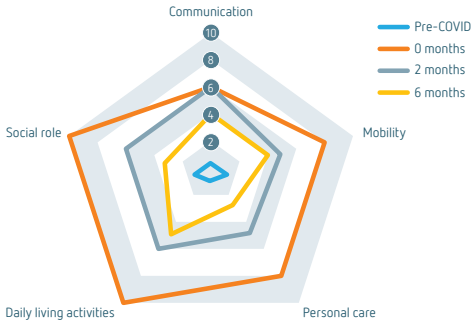
- Allows patients to track the condition with time and provides them with a quantitative assessment of improvement or deterioration which is important in the long-term management.
- Allows healthcare professionals to evaluate the treatment programmes of patients.

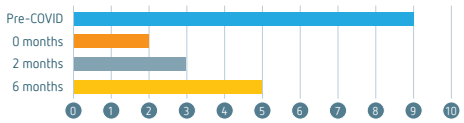
Symptoms severity score



Functional disability score



Overall health score



FEATURES

- C19-YRS questionnaire **recommended by NHS England and NICE**
- Dedicated profile for patients
- Discrete, secure, easy-to use data recording
- Online web portal to oversee patients for continuous monitoring and rehabilitation
- Report of symptoms severity score and functional disability scores
- Extensive reporting tools to support organisations better deploy, evidence and account for use of resources

BENEFITS

- **Free at the point of use for all NHS Organisations**
- Multiple patients managed in one place
- Helps clinicians capture symptoms and guide rehabilitation interventions
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C19-YRS is a clinically relevant outcome tool developed at the University of Leeds to assess persistent COVID-19 symptoms. The tool has been adopted by NHS Trusts across the UK.

DEVELOPED WITH NHS TRUSTS

C19-YRS was developed with support from Leeds Teaching Hospitals and Leeds Community Healthcare NHS Trusts.

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RECOMMENDED BY NHS ENGLAND AND NICE

NHS England has suggested routine use of C19-YRS at first assessment, 6 weeks and 6 months to monitor Long COVID.

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Reflections in the rear-view mirror. Two decades of epilepsy

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For the first series of ACNR in 2001, I wrote a series of articles covering key areas in the management of epilepsy: diagnosis; first line treatment; refractory epilepsy; status epilepticus; women and epilepsy; social effects of epilepsy. Now, 20 years on, it is interesting to review progress. The differential diagnosis of epilepsy has not changed. The tools to aid diagnosis have improved in other areas but not for epilepsy itself. For the everyday management of cases, undoubtedly the most significant advance since 2001 is the mobile phone with video capability. This enables the differentiation of dissociative from epileptic events with more than 90% sensitivity and specificity.[1] Cardiologists have helped us by developing implantable new recorders, to detect cardiac arrhythmia. EEG is working on similar long-term monitoring but is not yet there. Once epilepsy has been diagnosed, we now have a new classification.[2] Every owner of a new house feels the need to stamp its identity by redecorating the property and so it is with each generation of epilepsy specialists and classification. The new classification does have some merit in recognising that seizures are a symptom of a complex disorder in which there may be a range of different causes and different associated characteristics. Since 2001, there has been an explosion of genetic diagnosis and some of these are starting to lead to greater understanding in treatments e.g. why Dravet syndrome might be exacerbated by sodium channel blocking medications. The identification that the mammalian target of rapamycin (mTOR) was upregulated in tuberous sclerosis has led to the first anti-epileptogenic (rather than anti-seizure) drug[3] and potentially represents a paradigm shift in epilepsy management. It remains to be seen if an analagous approach is more broadly applicable, but evaluation in patients with high risk pathologies e.g. severe brain injury, haemorrhagic stroke or encephalitis would need complex, long term longitudinal study in large numbers.

In 2001, I wrote that lamotrigine was gaining ground as a first line treatment in focal epilepsy, as a result of a favourable adverse effect profile compared to carbamazepine. That position was consolidated after SANAD 1 in 2007.[4] It was also gaining popularity in generalised epilepsy because of valproate side effects and teratogenicity. Equally SANAD and other studies[5] showed it is less effective than valproate in generalised epilepsies and the choices are therefore more complex in women of reproductive age. We knew about major teratogenicity of valproate long before 2001 although the structurally undetectable consequences of foetal exposure (autism ADHD and learning disability) were not fully established until more recently.[6,7] We have had the recent government response to a Europe-wide legal case, with a frankly clumsy and coercive system of regulation and it is to the profession's credit that this has been moderated to a more sensible monitoring system. At the core of the debate are some truly profound questions which have not yet been answered: Who is responsible for balancing the risks and choosing treatment of a medically serious condition? Does a woman have the right to choose to take a risk of having a disabled child, if they feel that valproate is their best option, or does society via its government, who may have to help fund the consequences have the right to enforce a choice? At the start of this process, the answer from government was women may not choose. Now it is a grudging acknowledgment of a partial right to choose, which is in marked distinction to conversations that might be had, for example in a genetics clinic, around other disorders affecting offspring. Clinicians have responsibilities here. The first is to identify risk, and the profession has been proactive with epilepsy and pregnancy registers, starting in the UK and adopted around the world, which may give early warning of risks. The second, in which we have been less good with valproate, as it was a staple of the armamentarium for so long before this process, is to keep track of our patients on these drugs, so that we can recall them if and when information becomes available. Finally, the lesson is clear that we have to be advocates of patient choice in the face of big government. Our current knowledge is that some drugs are fairly safe in pregnancy; levetiracetam, also lamotrigine, carbamazepine and oxcarbazepine (in dose dependent fashion), some are unsafe; valproate, topiramate and phenytoin for example and others are too new to know, but presumed unsafe. Hopefully more information will emerge from our registers.

Those born in 2001 are part of Generation Z, but epilepsy specialists might call it generation K. Keppra® (Levetiracetam) has been the commercial success story of the last twenty years. With a novel mechanism of action, (SV2A protein binding) no interactions, simple kinetics, low teratogenicity and rapid dose titration, it has found a role in focal epilepsies,

generalised epilepsies and status epilepticus. For many clinicians it has become the go to first line drug, although studies suggest it is less efficacious than valproate in generalised epilepsy and there is little evidence to compare it to lamotrigine in focal epilepsy. It also has a unique and not that uncommon tendency to cause irritability, often distressing to those around the patient and not always recognised by themselves "Keppra rage". Despite levetiracetam and the explosion in the numbers of new anti-epileptic drugs since 2001, the number of seizure-free patients remains stuck stubbornly at around 70%. The drug treatment of refractory epilepsy therefore becomes the balance of epilepsy and adverse effects in the maintenance of the best possible quality of life. The best we can say is we have slightly reduced adverse effects compared to old AEDs. Principles of combining AEDs largely centre around complementarity of adverse effect profiles and pharmacokinetics and that has not changed since 2001. Epilepsy surgery remains an option for a small number of those whose epilepsy does not respond to medication and the ability to identify them accurately increases over time but no step-change here. Vagus nerve stimulation has become a widely used treatment with significant benefits and none of the neurocognitive side effects of medication. We still don't really know how or why it works but then willow bark was used widely for centuries before we understood it.

Our appreciation of psychological and social comorbidities of epilepsy has deepened. Accelerated forgetting has been identified as a common and recognisable association and, much as in many other complex neurological disorders, behavioural and cognitive changes are recognised as organic associations, for example with the identification that these neurobehavioural disorders may affect siblings of those with generalised epilepsy.[8] Epilepsy is therefore a complex neurological disorder with seizures as one manifestation, hence the new classification. In my decades managing patients with epilepsy, sadly I have not discerned any significant change in prejudice towards them, especially from employers and my heart still sinks at the struggles I fear my patients frequently face, whose tribulations are often disproportionate to the occasional hours of inability to work that their seizures may cause. With additional tragic irony, my experience is that nurses and teachers with epilepsy have particular difficulties.

In the management of status epilepticus, the greatest advance has again come from outside epilepsy, with the identification of immune mediated encephalitides, which respond to immunotherapy, rather than to AED. What did we think was going on before we knew about them? Drug treatment of status remained without new good quality evidence from 1998 until very recently, with studies now showing that Levetiracetam, Valproate and Phenytoin are not significantly different in managing status epilepticus in children and adults;[9] research following practice in the move to levetiracetam as an easier drug to manage and one that the clinician does not have to change when leaving the acute setting to long term management. We have also learned how in status epilepticus, GABA receptors are rapidly down-regulated and glutamate receptors up-regulated, explaining the loss of efficacy of benzodiazepines soon after the onset of status.[10] Buccal midazolam in the community is a major advance in reducing the risk of hospital admission and refractory status in those with recurrent episodes. In 2001, we had already started to understand the frequency and some of the risk factors for Sudden Unexplained Death in Epilepsy (SUDEP). The U remains stubbornly refractory to detailed analysis although autonomic mechanisms affecting the heart and respiration seem likely. SUDEP has risen up the priorities for clinicians, driven by patient groups and the hope is seizure detection technologies, which are becoming more reliable, will further reduce risk and give patients and their parents more control over their condition.

My wish-list for the next 20 years. Long term EEG at home; utilising AI for diagnosis and to deliver drugs, including by vector driven drug delivery for refractory epilepsy; anti-epileptogenic medicines for high-risk brain pathologies; better recognition and management of comorbidities; technologies to help prevent SUDEP; softening of social attitudes to epilepsy; World Peace and never to hear about Coronavirus or Brexit ever again. My best wishes to the next generation. It will be an exciting time as new technologies mature and others emerge.

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Clinical utility of Ongentys®▼ (opicapone) 50 mg confirmed by real-world data in Parkinson's disease patients with motor fluctuations

Clinical insights from principle investigator and lead author Prof. Dr. med. Heinz Reichmann, Department of Neurology, Technische Universitaet Dresden, Fetscherstrasse 74, 01307 Dresden, Germany

Heinz Reichmann is a member of the German Neurological Society, The European Neurological Society and is a fellow of the American Academy of Neurology. His major research interests cover etiopathogenesis and treatment in Parkinson's disease, premotor symptoms in Parkinson's disease, and neuroprotection.

OPTIPARK, a Phase IV, open-label study conducted in the UK and Germany under clinical practice conditions, supports the efficacy of Ongentys® 50 mg observed in the pivotal Phase III studies.[1]

Ongentys® 50 mg, as an adjunct to levodopa in patients with motor fluctuations, significantly improved perception of patients' global Parkinson's disease (PD) condition (≥70% as judged by clinicians and the patients themselves) 3 months after they started treatment with Ongentys® 50 mg.[1] Ongentys® is a once-daily catechol-O-methyltransferase (COMT) inhibitor. COMT inhibitor treatment is appropriate for PD patients taking levodopa/dopa decarboxylase inhibitor (DDCI) therapy where there is evidence of motor fluctuations.[1]

OPTIPARK: real-world clinical data in adult PD patients with motor fluctuations

Rationale for OPTIPARK

Findings from two pivotal Phase III studies, BIPARK I and II,[2,3] highlighted that global assessments using Clinician's Global Impression of Change (CGI-C) and Patient's Global Impression of Change (PGI-C) showed clinical improvements for Ongentys® 50 mg versus placebo[2,3] and entacapone[2] (CGI-C: p=0.0005 versus placebo, and p=0.007 versus entacapone; PCI-C: p=0.0091 versus entacapone).[2] The OPTIPARK open-label, prospective study set out to confirm these results in a real-life setting,[1] with CGI-C selected as the primary endpoint, and PGI-C as one of the secondary endpoints.

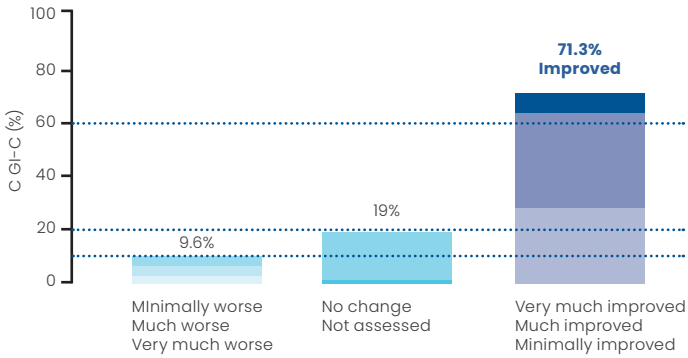
Study protocol and methodology for OPTIPARK (n=506 patients)[1]

- Key inclusion criteria: Men or women (≥30 years) with idiopathic PD reporting ≥1 symptom on the 9-symptom Wearing-off Questionnaire (WOQ-9), Hoehn and Yahr Stages I–IV (during ON), and treated with 3–7 daily doses of levodopa/DOPA decarboxylase inhibitor (DDCI)
- Treatment protocol: Ongentys® 50 mg once daily for 3 months (German sites) or 6 months (UK sites) in addition to current treatment with levodopa/DDCI. Total daily levodopa/DDCI dose could be adjusted according to the individual's condition throughout the study (except on Day 1)
- Primary endpoint: CGI-C after 3 months
- Secondary endpoints: PGI-C, the Unified PD Rating Scale (UPDRS), PD Questionnaire 8 items (PDQ-8), Non-Motor Symptoms Assessment Scale (NMSS)

Primary endpoint: OPTIPARK confirms the clinical utility of Ongentys® 50 mg

After 3 months treatment with Ongentys® 50 mg in a clinical setting of fluctuating PD patients, there were improvements in global PD condition: 71.3% of patients showed clinical improvement as rated by the CGI-C, with 43% reported as much or very much improved.[1]

Clinical Global Impression of Change (CGI-C) n=477

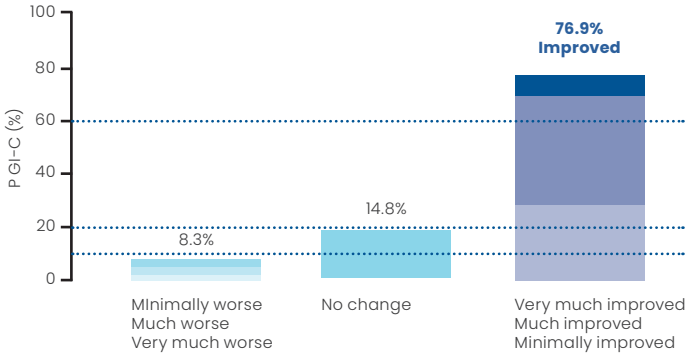


Source: Adapted from Reichmann H *et al. Transl Neurodegner* 2020[1]

Secondary endpoints: Ongentys® significantly improved motor scores, quality of life and non-motor symptoms

After 3 months treatment with Ongentys® 50 mg in UK and German PD patients, 76.9% self-reported a clinical improvement (PGI-C), with 48.1% of patients reporting they were much or very much improved.[1,4]

Patient's Global Impression of Change (PGI-C) (n=393)



Adapted from Reichmann H *et al. Transl Neurodegner* 2020[1,4]

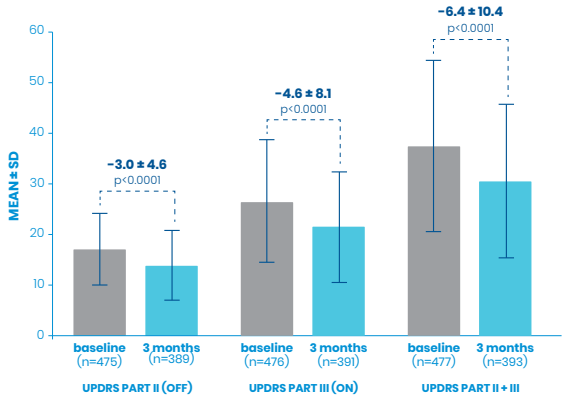
"In routine clinical practice, once-daily Ongentys® 50 mg as an adjunct to levodopa-treated PD patients with motor fluctuations significantly improved patients' perceptions about their global PD condition", ***Heinz Reichmann***

Both clinical and statistical improvements were evident for activities of daily living (ADL) and motor scores after 3 months. UPDRS scores showed a statistically significant improvement from baseline for ADL (UPDRS Part II) during OFF periods: mean±SD, −3.0±4.6 (p<0.0001), and motor scores (UPDRS Part III) during ON periods (−4.6±8.1, p<0.0001), as well as total scores (UPDRS Parts II + III), −6.4±10.4, p<0.0001.[1,4]

Prescribing information can be found on the following page

Motor scores in OPTIPARK[1,4]

Significant improvements in activites of daily living and motor scores (UPDRS II and III)

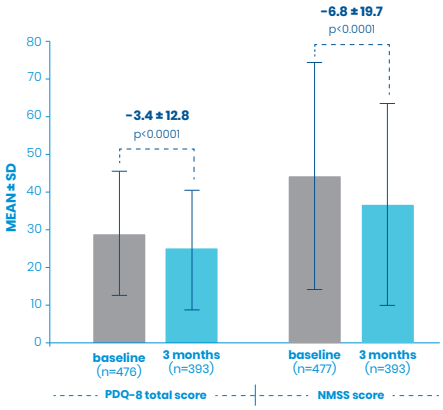


SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale.

There was also a statistically significant improvement in quality of life (PDQ-8) and non-motor symptoms (NMSS) versus baseline: PDQ-8 (mean±SD) −3.4±12.8 (p<0.0001); NMSS, −6.8±19.7(p<0.0001).[1]

Quality of life and non-motor symptoms[1]

Significant improvememts in quality of life (PDQ-39) and non-motor symptoms (NMSS)



NMSS, Non-Motor Symptom Scale; PDQ-8, Parkinson's Disease Questionnaire, 8 items; SD, standard deviation

Safety profile: The majority of drug-related treatment-emergent adverse events (TEAEs) were reported during the first week[5]

The safety profile in this large-open label study was comparable to adverse event data from the two pivotal studies.[2,3] In the 74.9% of patients who experienced TEAEs, the majority were mild or moderate in severity. Dyskinesia was the most common treatment-related TEAE (11.5%), leading to discontinuation in 1% of patients. The most common TEAE leading to withdrawal was nausea (2%).[1]

Clinical practice points:[1]

- This large real-life study in 495 patients treated with Ongentys® 50 mg mirrored a clinical setting through the inclusion of a broad population of fluctuating PD patients (Hoehn and Yahr I-III) compared to the two Phase III studies
- Despite optimised PD therapy (according to clinician's judgement), and most patients in OPTIPARK (78.8%) receiving levodopa/DDCI plus another PD medication, clinically significant improvements were reported for UPDRS motor and ADL scores
- More patients were judged by the clinician to have shown an improvement in OPTIPARK than reported in the pivotal Phase III studies (71.3% vs 59.6%)[6]

OPTIPARK confirms the clinical utility of Ongentys® 50 mg as an effective and generally well-tolerated adjunct option in patients with Parkinson's disease with motor fluctuations[1]

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Prescribing information

Ongentys® (opicapone) ▼

Please refer to the SPC before prescribing. **Presentation:** Capsules containing 50 mg of opicapone. **Indication:** Adjunctive therapy to preparations of levodopa/DOPA decarboxylase inhibitors (DDCI) in adult patients with Parkinson's disease and end-of-dose motor fluctuations who cannot be stabilised on those combinations. **Dosage and administration:** The recommended dose of opicapone is 50 mg. It should be taken once-daily at bedtime at least one hour before or after levodopa combinations. Opicapone enhances the effects of levodopa. Hence, it is often necessary to adjust levodopa dosage within the first days to first weeks after initiating the treatment with opicapone. **Elderly patients:** No dose adjustment is needed for elderly patients. Caution must be exercised in patients ≥ 85 years of age as there is limited experience in this age group. **Patients with renal impairment:** No dose adjustment is necessary in patients with renal impairment, as opicapone is not excreted by the kidney. **Patients with hepatic impairment:** No dose adjustment is necessary in patients with mild hepatic impairment (Child- Pugh Class A). There is limited clinical experience in patients with moderate hepatic impairment (Child- Pugh Class B). Caution must be exercised in these patients and dose adjustment may be necessary. There is no clinical experience in patients with severe hepatic impairment (Child-Pugh Class C), therefore, Ongentys is not recommended in these patients. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Phaeochromocytoma, paraganglioma, or other catecholamine secreting neoplasms. History of neuroleptic malignant syndrome and/or non-traumatic rhabdomyolysis. Concomitant use with monoamine oxidase (MAO-A and MAO-B) inhibitors (e.g. phenelzine, tranylcypromine and moclobemide) other than those for the treatment of Parkinson's disease. **Pregnancy:** Ongentys is not recommended during pregnancy and in women of childbearing potential not using contraception. **Lactation:** Breast-feeding should be discontinued during treatment with Ongentys. **Warnings and precautions:** Opicapone enhances the effects of levodopa. To reduce levodopa-related dopaminergic adverse reactions (e.g. dyskinesia, hallucinations, nausea, vomiting and orthostatic hypotension), it is often necessary to adjust the daily dose of levodopa by extending the dosing intervals and/or reducing the amount of levodopa per dose within the first days to first weeks after initiating treatment with Ongentys, according to the clinical condition of the patient. Ongentys contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Ongentys. Patients and care- givers should be made aware that impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments. Patients should be monitored regularly for the development of impulse control disorders and review of treatment is recommended if such symptoms develop. Increases in liver enzymes were reported in studies with nitrocatechol inhibitors of catechol-O-methyltransferase (COMT). For patients who experience progressive anorexia, asthenia and weight decrease within a relatively short period of time, a general medical evaluation including liver function should be considered. **Drug interactions:** Concomitant use of opicapone with MAO inhibitors (e.g. phenelzine, tranylcypromine and moclobemide) other than those for the treatment of Parkinson's disease is contraindicated. Concomitant use of opicapone and MAO inhibitors for the treatment of Parkinson's disease, e.g. rasagiline (up to 1 mg/day) and selegiline (up to 10 mg/day in oral formulation or 1.25 mg/day in buccal absorption formulation), is permissible. Opicapone may interfere with the metabolism of medicinal products containing a catechol group that are metabolised by COMT, e.g. rimiterole, isoprenaline, adrenaline, noradrenaline, dopamine, dopexamine or dobutamine, leading to potentiated effects of these medicinal products. Careful monitoring of patients being treated with these medicinal products is advised when opicapone is used. Concomitant use with tricyclic antidepressants and noradrenaline re-uptake inhibitors (e.g. venlafaxine, maprotiline and desipramine) should be considered with appropriate caution. Particular consideration should be given to medicinal products metabolised by CYP2C8 and their co-administration must be avoided. Particular consideration should be given to medicinal products transported by OATP1B1 and their concomitant use should be considered with appropriate caution. **Adverse events:** Refer to the SPC for all side effects. Very common side effects (≥ 1/10): Dyskinesia. Common side effects (≥ 1/100 to < 1/10): Abnormal dreams, Hallucination, Hallucination visual, Insomnia, Dizziness, Headache, Somnolence, Orthostatic hypotension, Constipation, Dry mouth, Vomiting, Muscle spasms, Blood creatine phosphokinase increased. Uncommon side effects (≥ 1/1,000 to < 1/100): Decreased appetite, Hypertriglyceridaemia, Anxiety, Depression, Hallucination auditory, Nightmares, Sleep disorder, Dysgeusia, Hyperkinesia, Syncope, Dry eye, Ear congestion, Palpitations, Hypertension, Hypotension, Dyspnoea, Abdominal distention, Abdominal pain, Abdominal pain upper, Dyspepsia, Muscle twitching, Musculoskeletal stiffness, Myalgia, Pain in extremity, Chromaturia, Nocturia, Weight decreased. **Legal Category:** POM. **Basic UK NHS cost:** Ongentys pack of 30: £93.90. **Marketing authorisation numbers:** EU/1/15/1066/003. Marketing authorisation holder: Bial-Portela & Ca., S.A., A Avenida da Siderurgia nacional 4745-457 Coronado (S. Romao e S. Mamede) – Portugal. **Further Information from:** Bial Pharma UK Ltd., Admiral House, St. Leonards Road, Windsor, SL4 3BL, UK. **Job code:** UK/ON/2020/006. **Date of preparation:** January 2020.

Adverse events should be reported. For UK healthcare professionals: reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Bial on +44 (0)1628 531171 or bial@pharmalex.com

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Sleepy drivers

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Abstract
Driving while sleepy can have devastating consequences, but it is an under-recognised problem often associated with behavioural factors, medical conditions or medications. All drivers have a responsibility not to drive if sleepy and there are DVLA regulations restricting driving for patients with certain sleep disorders who are at risk of excessive sleepiness at the wheel. However, sleepiness can be difficult for patient and doctor to assess and guidelines open to interpretation. As doctors it is important we give consistent and reliable advice to patients who may be at risk when driving. This review suggests how to assess driving risk, educate patients about risk reduction, and clarifies DVLA guidelines in this area.

Sleepiness at the wheel (SATW) is a common but under recognised problem. In the UK, anonymous voluntary surveys indicate 37% of drivers admit sleepiness at the wheel, and 13% admit falling asleep.[1] Worldwide, up to 58% admit driving while sleepy.[2]

Tiredness at the wheel increases the risk of road traffic accidents (odds ratio 2.51),[2] with studies suggesting worldwide, between 15-20% of accidents are sleep related.[3]

As doctors our role is to assess and advise patients about how sleepiness may affect driving ability. This can be difficult since sleepiness is an inherently subjective and variable feeling, and reliable tests to predict or objectively measure levels of sleepiness at any given time are lacking. Driver and Vehicle Licensing Agency (DVLA) guidelines can seem open to interpretation with limited guidance on assessing patients in clinic. We discuss assessment of patients' risk of sleepiness at the wheel, the responsibilities of patients, doctors and the DVLA and treatment strategies to reduce risk and improve symptoms.

Assessing risk of sleepiness while driving

The aim is to identify drivers who are excessively sleepy at the wheel such that it impairs driving. Taking a detailed history is key. If they feel sleepy while driving enquire how often, and under what circumstances, for example does it depend on duration or time of the journey.

Ask specifically about 'red flag' symptoms which, if occurring frequently suggest a patient is at high risk of excessive SATW:

1. Have they nodded off or had instances of 'head bobbing' at the wheel?
2. Any near misses including lane crossings, or driving onto rumble strips?
3. Any driving accidents or claims on insurance in the last three years?
4. Using behaviours aiming to increase alertness such as winding windows down or playing loud music.
5. If applicable, for older patients, asking whether they are allowed to drive with grandchildren in the car.

Next it is important to enquire about risk factors that may help to explain patients' symptoms. Discussing these factors can help patients and clinicians understand driving risk and ways to mitigate future problems. Risk factors for SATW are shown in Box 1.

A collateral history regarding driving and a description from a bed partner of any overnight sleep phenomena are useful.

Tests of sleepiness

Ideally, any test should accurately predict individual risk of accidents, provide a 'real time' measure of sleepiness, and assess response to treatment. Unfortunately current tests lack reliability and show only limited associations at best, with driving risk.[1,2] They should not be used as a sole measure of driving safety. However, assessments are often used to quantify sleepiness and sleep disorder severity. These include:

1. The Epworth Sleepiness Scale (ESS): a routinely used questionnaire assessing daytime sleepiness. Although does have driving related questions, was not designed as a driving safety tool. Scores of >10 are abnormal.
2. The Apnoea Hypopnoea Index (AHI): used for diagnosis and classification of OSA. Those with severe OSA (AHI>30) are more likely to be sleepy.
3. The Maintenance of Wakefulness Test (MWT) measures the ability to stay awake. However the testing environment, a quiet, dimly lit room is far from real life driving situations.
4. Devices which monitor behavioural and physiological variables during simulated or real life 'in vehicle' driving have been used in research studies to investigate sleepiness and driving abilities but are not yet reliable enough to predict real life driving safety.[1,2]

What advice can I give patients?

First it is important to clarify the patient's perspective on their symptoms. Patients may need an explanation of how their condition can affect driving. Risks should not be exaggerated but patients need to appreciate that driving while sleepy can have devastating consequences. Drivers should understand that it remains their duty to be alert behind the wheel regardless of whether they are on treatment. Although there is no UK law prohibiting driving while sleepy, if sleepiness is found to contribute to a driving accident, drivers can face imprisonment for dangerous driving.

Educating patients about strategies to reduce SATW can enable patients to feel safer on the road. For example, avoiding driving at night, mid- afternoon or when sleep deprived. If feeling tired on longer journeys, stopping to have a caffeinated drink and a nap does reduce

Box 1: Risk factors for sleepiness at the wheel

Lifestyle factors:

- Behavioural causes of acute[4] or chronic[5] sleep deprivation from late nights or early mornings due to social, family or work commitments. Worryingly, patients who are chronically sleep deprived may lose insight into their degree of sleepiness and continue to drive despite being excessively sleepy.[6]
- Driving at times corresponding to circadian dips in alertness, for example overnight or mid afternoon.[3,4]
- Shift workers[7]. Driving home after working an overnight shift is a particular danger since night shift workers are often sleep deprived. Additionally, drivers have built up a large sleep debt by the end of their shift. Driving in for early morning shifts can be risky especially for younger drivers who may have a natural tendency to a delayed sleep phase.
- Driving long distances, alone, on monotonous roads.[4]

Medical conditions:

Many medical conditions affect sleep and so doctors from a variety of specialties will see patients who may be at risk of sleepiness at the wheel.

Sleep disorders

- Obstructive sleep apnoea[8] (OSA). Underdiagnosed and rates are increasing due to rising levels of obesity.[9] Obstructive sleep apnoea syndrome (OSAS) describes OSA associated systemic features including daytime sleepiness. Also associated with craniofacial structural abnormalities which impair ventilation.
- Central hypersomnias[10]
  - o Narcolepsy (may have comorbid OSA)
  - o Idiopathic hypersomnia
- Sleep deprivation secondary to restless legs and insomnia is often a patient concern but with less evidence for increased crash risk.[11]

Neurological conditions

- Parkinson's disease (may have comorbid OSA, and dopaminergic drugs can cause sleepiness).
- Stroke is commonly associated with OSA.
- Lesions affecting diencephalon and brainstem structures.

Medications and drugs:

- Always review medications as drugs are an extremely common cause of sleepiness. Sedative medications, including opiates, benzodiazepines, antipsychotics, antihistamines and gabapentinoids, are often taken in combination.

sleepiness, but playing loud music, opening windows, and getting out to stretch does not.[4] The DVLA and road safety charity websites provide useful information for patients.[13,14]

Encourage patients that sleepiness typically improves with treatment. For some, sleep hygiene advice and avoiding risky situations will resolve the problem. Patients with OSA who have daytime sleepiness (Obstructive Sleep Apnoea Syndrome: OSAS) usually need CPAP. Patients with central hypersomnias will need stimulants and treatment of any cataplexy. Scheduled naps for narcolepsy can be helpful.

Do they need to stop driving?

Context is important: excessive sleepiness occurring frequently without an avoidable cause is more concerning than a single episode of sleepiness at the wheel while driving at night which the patient has then avoided doing. Concern from a friend or relative is also worrying.

For patients who have concerning SATW, as part of our duty of care, doctors should advise patients that they should stop driving. As always, the medical board of the DVLA ultimately decide whether a licence should be revoked. Patients need to be aware of the insurance and potential legal consequences of driving against medical advice.

Rarely, a patient continues to drive against medical advice. In this situation, we have support from the GMC to inform the DVLA without patients' consent although we must inform the patient of our intentions beforehand.[15]

Occasionally patients with markedly abnormal sleep study results deny SATW. Some patients genuinely do not feel tired when driving, but in other cases, patients under-report symptoms while admitting easily falling asleep in other situations, because of concern about losing their licence. This discrepancy raises suspicion that the patient could be at risk while driving. A collateral history from a partner can be helpful. Ultimately the patient's story should be taken at face value but regulations on driving and sleepiness should be discussed and documented.

What are the DVLA guidelines on sleep conditions and driving?

Patients are legally responsible for informing the DVLA if they have certain sleep related conditions (see below) or if they are excessively sleepy at the wheel for three months because of another medical condition. The DVLA will ask them to complete an SL1 (Group I licence holders) or a SL1V form (Group 2 licence holders). Full guidance can be found on the DVLA website.[16,17]

Obstructive sleep apnoea[16]

Which patients need to inform the DVLA? Those with moderate or severe OSAS with excessive sleepiness while driving need to inform the DVLA immediately, while those with mild or suspected OSAS causing excessive sleepiness while driving, only need inform the DVLA if symptom control cannot be achieved in three months.

Will the DVLA stop them driving? The DVLA only restrict driving if sleepiness is, or is likely to impair driving, regardless of the AHI.

When can patients return to driving? Patients can resume once there is control of their condition and symptoms have improved. In addition, certainly for those with moderate/severe OSAS, the DVLA needs evidence that patients are compliant with treatment and agree to be reviewed by their medical team annually (lorry or bus drivers), or every three years (car and motorcyclists).

The advice regarding symptom control can seem ambiguous, but in practice, patients need to feel more awake during the day, with improvements documented by their sleep service.

Patients who start CPAP often feel a benefit almost immediately but most services suggest using it for ≥2 weeks, and ≥70% of the night before considering driving again. The DVLA need to be informed that they are no longer sleepy, but drivers can return to driving before a DVLA decision if supported by their medical team. The British Thoracic Society provides guidance in this area.[18]

Central hypersomnia[17]

Which patients need to inform the DVLA? All patients diagnosed with narcolepsy or idiopathic hypersomnia need to inform the DVLA at diagnosis.

Will the DVLA stop them driving? Yes; all patients need to stop driving at diagnosis for at least three months.

When can patients return to driving? They can drive if symptoms remain satisfactorily controlled for at least three months. Advice on assessing this is vague, but patients should be free of excessive sleepiness that is likely to impair driving, and should not drive if they have little or no warning about falling asleep (so called 'sleep attacks'). Formal criteria regarding disabling cataplexy are lacking and this is usually based on clinical impression, but several attacks a day would be concerning.

Other requirements: Patients should adhere to medical advice regarding treatment of their condition and remain under regular medical review.

Patients prescribed amphetamines should be aware these are on the DVLA's list of 'prescription' drugs that police can test for if suspecting driving is affected by medications (see below). Patients may wish to carry medical documentation about their condition when driving.

Drugs and driving

In the UK drivers can face prosecution if driving is impaired by legal (prescribed or 'over the counter'), or illegal drugs.[19] Even if driving is not impaired, it is an offence to drive haven taken illegal drugs or certain 'legal' drugs (listed by the DVLA including amphetamines, certain benzodiazepines

and opioids) without a valid prescription. For patients prescribed amphetamines and opioids, the upper legal limit is higher than would be expected if these drugs were taken at a medically prescribed dose. However, for benzodiazepines and some 'z' drugs, patients may pose a driving risk with therapeutic plasma drug levels. This risk is magnified if drugs are taken in combination or with alcohol.[20]

Summary and conclusion

SATW is a common symptom with potentially tragic consequences. Public health campaigns have helped highlight risks, but it remains an under-appreciated problem. As healthcare professionals, it should be a routine question in clinic with anyone who might be sleepy during the day. We need to understand legislation in the area to provide clear and consistent advice to patients. Encouraging patients to seek help in the knowledge that once treated they will be able to return to driving is key.

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Parkinson's disease over the last 20 years

– new concepts and developments

ACNR came into existence in 2000 following discussions between myself and Rachael Hansford in 2000 and so we thought we would use this 20th anniversary to review advances in certain fields over this same time frame, including one of my main research areas- Parkinson's disease (PD).

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In the time it has taken Cambridge University to realise that it has lost two priceless original notebooks belonging to Charles Darwin (https://www.bbc.co.uk/news/entertainment-arts-55044129) much has changed in our understanding and approach to Parkinson's Disease (PD). This in part is because of new scientific methods such as the discovery of how to make induced pluripotent stem cells (iPSCs);[1] the development of improved gene editing techniques such as CRISPR/Cas9[2] and the ability to undertake single cell RNA analyses.[3] However, much of our new understanding comes directly from observations made in the clinic and related biomaterials. In this short review I will highlight some of this.

The alpha synuclein prion hypothesis

In 2008 it was reported that patients in receipt of human fetal ventral mesencephalic allografts for their PD had, at post-mortem, evidence of alpha synuclein pathology within the transplant.[4,5] Given that these dopaminergic cells were at most only 10 or more years old this raised intriguing questions as to how these cells could have "got PD". One theory was that these grafted cells were placed into a stressful environment with low grade inflammation and that this upregulated alpha synuclein expression leading to Lewy body pathology. An alternative theory, and one that has generated much interest, was that pathological forms of alpha synuclein from the host PD brain had spread into the grafted tissue and seeded pathology there (reviewed in Volpicelli-Daley et al, 2018).[6] Subsequently many experiments have been done showing that certain forms of alpha synuclein (most notably pre-formed fibrils) can spread and seed pathology in the adult CNS. This coupled to the description of the pathological stages of PD by Braak and colleagues[7] has led to the concept that PD begins in the gut/olfactory system and then spreads along the connecting nerves into the brain seeding pathology as it does so. This means that over time problems ascend up through the brainstem (eventually reaching the dopaminergic cells of the nigra) and then across the cortex. This has two major implications; (i) that there is a prodromal stage with PD before the nigral dopaminergic cells acquire pathology and express this through the early motor features of tremor, bradykinesia and rigidity and (ii) targeting this abnormal species of alpha synuclein as it spreads using immunotherapy may slow down or even stop the disease process.

The concept of prodromal PD

It has long been thought that a premotor state for PD must exist given that it only starts to express itself motorically when 50% of the dopaminergic nigral neurons are lost and 80% of its fibres in the striatum. However, the problems were: What would that look like clinically and how could we detect it – and does it matter given we have no disease modifying therapies? However, this has now been revisited given the Braak hypothesis on the pathological evolution of PD and the intense interest in trialling new disease modifying therapies based in part on the possible prion like behaviour of alpha synuclein.

Given that the earliest pathology in the Braak staging in PD targets the lower brainstem (and especially its connections to the gut) and olfactory system, one would predict that prodromal PD would be characterised by alterations in olfaction, changes in gut function and other behaviours linked to the networks of cells affected in the lower brainstem-namely sleep and mood. This has now been shown to be true for many patients as they report such symptoms ahead of developing overt motor PD. In addition, retrospective studies have shown there is alpha synuclein pathology in the gut years ahead of developing overt PD[8] and prospective studies showing that patients with hyposmia and/or a REM sleep behavioural disorder (RBD) have a high rate of conversion to PD or similar alpha synucleinopathy.[9] This concept has now been formally recognised through the establishment of research criteria for prodromal PD[10] and the move towards thinking about disease modifying therapies targeting this stage of disease.

The stratification of PD and the basis of its heterogeneity

It has been known since PD was first described in 1817 by James Parkinson that not all patients look the same and follow the same clinical course and this has also been used to argue against the Braak hypothesis, in that not all patients show this temporal pattern of pathology. In this respect, a new alternative classification has been proposed around whether the disease starts in the PNS and spreads centrally or starts within the CNS itself and then out to more peripheral sites. This has gained some traction with recent imaging studies supporting this concept of PD falling into these two subtypes.[11]

Over the last twenty years, though, hetero-

geneity of disease has been studied in two major ways; (i) clinically using non motor features of PD as much as motor problems and (ii) mechanistically using genetic and biofluid analyses to explain differences between patient groups – all of which has implications for more targeted therapies in subgroups of PD in clinical trials.

A number of different methodologies have been taken in attempts to define the subgroups of PD of which the most powerful are those using community based epidemiological studies following patients over time to death.[12] These studies are not without challenges but do capture PD as it exists in the real world and avoids some of the biases that exist when such studies are done using selective patient groups such as those signing up on web based platforms or attending hospital clinics. Nevertheless, all these studies have essentially shown that younger patients tend to do better than older patients and that those with more PD related symptoms and signs at diagnosis do less well. The reason for this clearly relates in part to: ageing processes (whatever they are!); genetic variants (such as possession of a glucocerebrosidase (GBA) mutation for example);[13] other general medical problems (such as risk factors for cardiovascular disease)[14] and possibly the patient's immune system and its response to the disease process.[15]

The importance of all this is that disease modifying or restorative therapies can now better be targeted not only to certain patient groups (e.g. younger less advanced patients for cell based dopamine therapies[16]) but specific pathogenic pathways – e.g. ambroxol for patients with PD and GBA mutations.[17] Although interestingly low GBA activity may be a feature of PD even in patients without a GBA mutation.[18]

Inflammation and the microbiome

The brain pathology of PD has long been known to show a level of inflammation but this has for many years been assumed to be secondary to the loss of cells and thus of minor relevance to the disease process. However, a number of observations have changed this perception. Firstly, the discovery that genes relating to the immune system were associated with the risk of getting PD in several GWAS. Secondly, epidemiological studies showing that patients taking certain anti-inflammatories or immune suppressants had a reduced risk of getting PD. Finally, evidence that immune activation happened early on in the disease course and may even be driving the disease process as evidenced by the fact that patients with more immune activation at diagnosis tended to do less well (all reviewed in Greenland et al, 2020).[19]

At the same time as this data was emerging, there was a realisation that the gut microbiome was a major determinant of disease states more generally. Given that PD has a major GI pathology attention naturally moved to whether the gut microbiome was different in PD and could contribute to the disease state and clinical course for which there is now some convincing evidence.[20] As such the idea of treating PD using agents that target this system are now being trialled as well as anti-inflammatory/immune suppressing agents.

The rise of drug repurposing and advanced experimental therapeutics

All of these new concepts have clearly impacted on how we can now consider treating PD using agents that may actually slow down the disease process. This has involved two strategies – one involving developing new small molecules or experimental therapies (such as AntiSense Oligonucleotides (ASOs) and immune therapies targeting alpha synuclein) and the other drug repurposing – including agents thought to act on critical pathogenic nodes in the development of PD. These latter approaches have now evolved and include recently completed phase 2 and some phase 3 trials with drugs such as ambroxol,[17] exenatide,[21] isradipine,[22] nilotinib[23] and simvastatin (Carroll et al 2019 and https://www.cureparkinsons.org.uk/news/the-pd-statsimvastatin-study-results).[24] Both of these approaches are set to increase in the coming years especially given the initiative now being championed by the Cure Parkinson's Trust and their Linked Clinical Trials.[25] Ultimately, though, it may be that these agents can best be employed as combination therapies targeting different parts of the pathogenic cascade, in much the same way as agents have been successfully used to treat other medical and infective conditions (e.g. HIV, TB and ischaemic heart disease).

Finally, advances in gene and cell therapy are now also impacting on PD with trials being undertaken or about to start using a range of different dopaminergic therapeutic approaches. This includes stem cell based dopamine cell transplants that have now just entered early clinical trials in Japan[26] and which will soon be trialled in Europe and the USA[27] and have also been the subject of a recent case report using autologous cells.[28] In addition, different gene therapies have also been trialled that transfect cells in the striatum with either some[29] or the majority of synthetic enzymes for making dopamine.[30] As to whether these therapies will prove effective or competitive is still to be decided.

In conclusion, the last 20 years has seen major changes in the way we think about PD and with this how we might now consider better treating it with an aim to cure it. Hopefully in the next 20 years we will see some of these approaches being converted into proven disease modifying therapies for PD.

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Association of British Neurologists *by David Burn*

Being asked to write an article looking back at the Association of British Neurologists (ABN) over the last 20 years was an interesting Christmas present. Since the COVID-19 pandemic is currently dominating our lives, it led me to reflect on how, by building on the achievements of the previous decades, the ABN is now so well equipped to contribute towards overcoming the challenges of the pandemic. So why do I say this?

The Association of British Neurologists (ABN) has evolved significantly since it was founded in the London drawing room of Professor Gordon Holmes in 1932, and never more so than over the last 20 years. Importantly, the Association is inclusive of the devolved nations, which provides a more rounded view of UK practice and ensures that we are essential to all Neurologists, regardless of location.

The President in 2000 was the late and highly respected clinical academic Professor John Newsom-Davis. The number of Consultant Neurologists at that time was around 400. By the time of submission this number has expanded to over 950, of which 800 are ABN Ordinary members. Data provided by the ABN has shown how relatively under-provisioned the UK is for Neurologists, when compared with other developed countries. Despite the continuing growth in numbers, this remains the case. The ABN has consistently helped to shape training and provide advice regarding job planning for Neurologists across the UK. The former was brought into sharp focus recently with the introduction of Shape of Training. With a strong track-record in promoting the benefits of research experience and academic careers, the ABN will continue to monitor the effects of Shape of Training upon the ability of neurological trainees to undertake periods of research and pursue academic careers.

2021 marks the 20th anniversary of the London World Congress of Neurology, which was hosted by the ABN. The Association has maintained and grown its international links over the past 20 years in different ways, including the appointment of many consultant colleagues from overseas, joint meetings, invited high profile overseas speakers to our annual meetings and the involvement of ABN members in a multitude of specialist societies, often in key leadership roles. With the UK now outside the European Union (EU), having an international profile, and being outward facing has never been more important. A refreshed website (https://www.theabn.org) has raised the profile of the Association, and modernised communication with members.

A major development over the last 20 years has been the development and expansion of the ABN Committees. The Services Committee advises the Association, via Council, on all matters relating to standards of neurological care as well as the staffing, organisation and distribution of neurological services in the United Kingdom and Ireland. The Research Committee concentrates on issues relating to research and academic matters; its flagship project in recent years has been the development of the highly prestigious ABN Clinical Research Training Fellowship scheme. The Fellowship scheme was first launched in 2010 and attracts candidates of the highest calibre. It has progressively expanded the annual number of awards, thanks to generous support from several sources. The Education Committee focuses on undergraduate education, postgraduate training, and continuing professional development in neurology. It supports an annual undergraduate essay competition as well as an Australasian fellowship. The ABN Quality Committee advises the Association, through Council, on all issues relating to quality improvement in neurology within the United Kingdom and Ireland. During the COVID-19 pandemic this committee structure has served the Association and its members well (in addition to the Royal College of Physicians and colleagues from other specialties), by rapidly providing practical advice in myriad areas, from the use of Personal Protective Equipment, the management of patients with neurological disorders on immunomodulatory agents, to rebooting neurology services.

Over the last two decades, ABN council representation has diversified quite considerably, but the events of 2020 and Black Lives Matter acutely raised equality, diversity and inclusion issues in all aspects of neurological practice. The ABN has therefore set up an Equality, Diversity and Inclusion Committee, reporting to Council, which

aims to address a range of topics, including encouraging the widespread availability of excellent and equitable neurological services and promoting an inclusive neurological community and equal opportunity for all neurologists and trainees.

There is, historically, a strong commitment to training and drawing the cream of the younger medical community into neurology. ABN Neurological Trainees Committee (ABNT) has developed and expanded to represent the views of all trainees in neurology on issues including training and education, career issues and research. With 420 trainees and 115 Junior doctors as members of the Association, the ABNT input was particularly important during the evolution of Shape of Training.

A significant development in 2011 was the constitution of ABN Advisory Groups (AG), which provide a ready source of expertise for media queries, government and other consultations in different sub-specialties. In 2019 the AGs collectively handled 150 consultations, many from NICE. The AGs have provided a major and effective bridge between the expertise that resides within the UK Neurology community and external bodies. In 2015, the ABN entered into a co-publishing agreement with the *BMJ* and *Practical Neurology*, which has proved to be highly successful. The chairs of each AG now sit on the editorial board of *Practical Neurology* and AG members also represent the ABN on the European Academy of Neurology's scientific panels.

It was only in 1995 that the term of the ABN President increased to two years. The scope of the ABN Executive positions is now better defined, with, dare one say it, the most recent development of "role descriptions". Most recently, we have separated out the role of Honorary and Meeting Secretaries, and the transition between these positions, as the two are quite different.

Perhaps the single most important change in the ABN over the past 20 years, and one that most definitely brought the Association into the 21st Century, was the development in 2013 of the ABN office under an Executive Director. The secretariat that reports to the Executive Director have clearly defined roles and have brought transformational changes in efficiency and agility to all aspects of ABN business. The ABN office has largely functioned virtually during the COVID-19 pandemic, but such is the resilience of the organisation that its efficacy has remained undiminished.

It is daunting to try to represent changes in the ABN over 20 years, and no doubt significant developments may have been omitted from the above account, for which I apologise in advance to those with superior institutional memories. However, no colleague could dispute that the Association actively developed and evolved over the last two decades, and remains as important and relevant in 2021 as it ever did.

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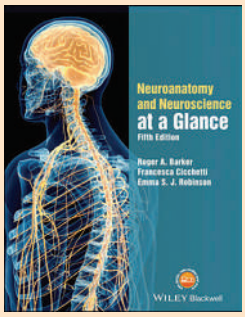
Neuroanatomy and Neuroscience at a Glance



Authors: Roger A Barker, Francesca Cicchetti, Emma SJ Robinson
Published by: Wiley Blackwell
Price: £28.00
Pages: 168
ISBN: 978-1-119-16841-6
Reviewed by: Janet M Dube, 4th Year Student Doctor, University of Liverpool.

This book is part of a series of books, providing a quick review of numerous medical science topics including Anatomy, Cardiology, Obstetrics and Urology 'at a glance'. This one covers basic, or fundamental, Neuroanatomy and Neuroscience, as well as giving a brief overview of some common clinical conditions as they relate to the biological systems covered.

As with the rest of the books in the 'at a glance' series, this book is well organised into parts, which are further subdivided into chapters. Each chapter is laid out in only two pages, with the first page containing useful cartoon illustrations of the organisation or pathways important to that chapter, and the second page briefly explaining the main concepts. I found the illustrations particularly useful; they helped me to summarise the main ideas and therefore make it easier to digest the text, as well as other resources offered.

Each page finishes with a very short 'did you know' section which describes an interesting fact that relates to that section. For example, one fact which I found particularly interesting was that eating chocolate causes the release of endorphins, which reduce pain and may cause people to get addicted to eating chocolate, much like opioids. I wonder if I suffer from this addiction myself!

The book comes with a subscription to online resources which contain multiple-choice questions and key revision points. Some questions and answers are also found at the end of the book which I found to be a useful way periodically to check my understanding.

I think this book offers a great foundation, upon which further knowledge can be built. As an undergraduate student, I have found using this book an effective signposting exercise as to unfamiliar concepts, before exploring further into the detail by using other more in-depth books or other resources.

This book covers the most important topics in Neuroanatomy and Neuroscience, but only really touches the surface, and so I recommend that the reader does not solely rely on this resource, but rather, use it as an addition to other more in-depth resources.

Although aimed at medical students, I believe this book can also benefit postgraduates and even senior clinicians, who may have moved on from the fundamental neurosciences a while ago but who also may be involved in undergraduate education. This book gives a great backbone of topic areas to cover for students.

Christmas has just passed and maybe this book is a bit serious for a Festive Season present. However, it could be a nice, reasonably priced, New Year gift from senior clinicians working in the neurosciences, to relations of theirs going through medical school, or undertaking similar studies.

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Reanimating hand function after spinal cord injury using nerve transfer surgery

Key Take Home Messages

- Loss of hand and arm function is a devastating consequence of cervical spinal cord injury
- Surgical approaches to reconstruct arm and hand function in people with tetraplegia include tendon transfer and nerve transfer surgery
- Nerve transfer surgery can be used in combination with tendon transfer surgery to increase the options for upper limb reconstruction and the number of functions that can be restored
- Nerve transfer surgery results in a softer more pliable hand, which facilitates use of electronic devices
- Further investigations of longer-term outcomes, patient selection, and optimal timing of surgery are needed

Abstract

Loss of arm and hand function is a devastating consequence of cervical spinal cord injury. Tendon transfer surgery has traditionally been used to restore key functions including elbow extension, wrist extension and grasp and pinch. The more recent development of nerve transfer surgery enables direct restoration of voluntary control of these functions. While both types of surgery are safe and effective, nerve transfer surgery results in a more open, flexible and natural hand, with more subtle control for a range of activities of daily living.

Spinal cord injury (SCI) leads to severe lifelong impairment of sensorimotor function. The annual crude incidence rates of traumatic SCI vary from 12.1 per million to 57.8 per million, with leading causes being motor vehicle accidents, falls, violence and sports activities.[1] There is a bimodal distribution, with one peak in the age group 15 to 29 years, and the second in the age group above 40 years of age. Age at injury, and injuries caused by falls have increased over time.[2] Over half of the injuries affect the cervical spinal cord,[1] leading to tetraplegia, that is, some degree of paralysis in all four limbs as well as the trunk. In tetraplegia, the degree of impairment of the upper limb, including the hand, will vary depending on the level and completeness of injury.

Loss of function is greater the higher the level of injury. For example, individuals with C6 level of injury are able to move their arms and extend their wrists, but have little or no voluntary use of their hands. Injuries above C6 result in the inability to actively extend the elbow to reach for objects. Loss of hand and arm function is one of the most devastating consequences of spinal cord injury because of the severe impact on activities of daily living (ADL) and subsequent dependence on others, loss of privacy and loss of vocational opportunities. Loss of the use of one's hand results in the inability to grasp and manipulate objects of different sizes, heaviness and textures, inability to point and gesture, and inability to use common everyday implements (e.g. toothbrush, cutlery, pens). Therefore, people with tetraplegia report that limited hand and arm function is often more profoundly disabling and of greater importance than their inability to walk.[3,4]

The key movements for improving independence in tetraplegia are elbow extension for reach and pushing a manual wheelchair, wrist extension, and hand opening and closing for grasp, pinch and release. Different treatment strategies have been directed to improving or restoring these movements, as even modest improvements in arm and hand function can have a substantial impact on potential for employment, independence and quality of life.

Rehabilitation has traditionally involved strengthening muscles above the level of injury and, in recovering muscle groups, maintaining range of movement in the upper limb joints, providing assistive technology, adaptive

Table 1: Nerve transfers commonly used by the authors for upper limb re-animation in mid-cervical spinal cord injury (C5, 6, 7)

Function restored	Donor nerve(s)	Recipient nerve(s)
Elbow extension	Teres minor	Triceps
	Teres minor and motor portion of posterior division of axillary nerve	Triceps
	Motor portion of posterior division of axillary nerve	Triceps
	Fascicle of anterior division of axillary nerve	Triceps
Wrist extension	Supinator	ECRB
Finger/thumb extension and thumb abduction	Supinator	PIN
Finger/thumb flexion	Brachialis	AIN
	ECRB	AIN
	Supinator	AIN
	Fascicle to pronator teres	FDS

ECRB: Extensor carpi radialis brevis; PIN: Posterior interosseous nerve; AIN: anterior interosseous nerve; FDS: Flexor digitorum superficialis.

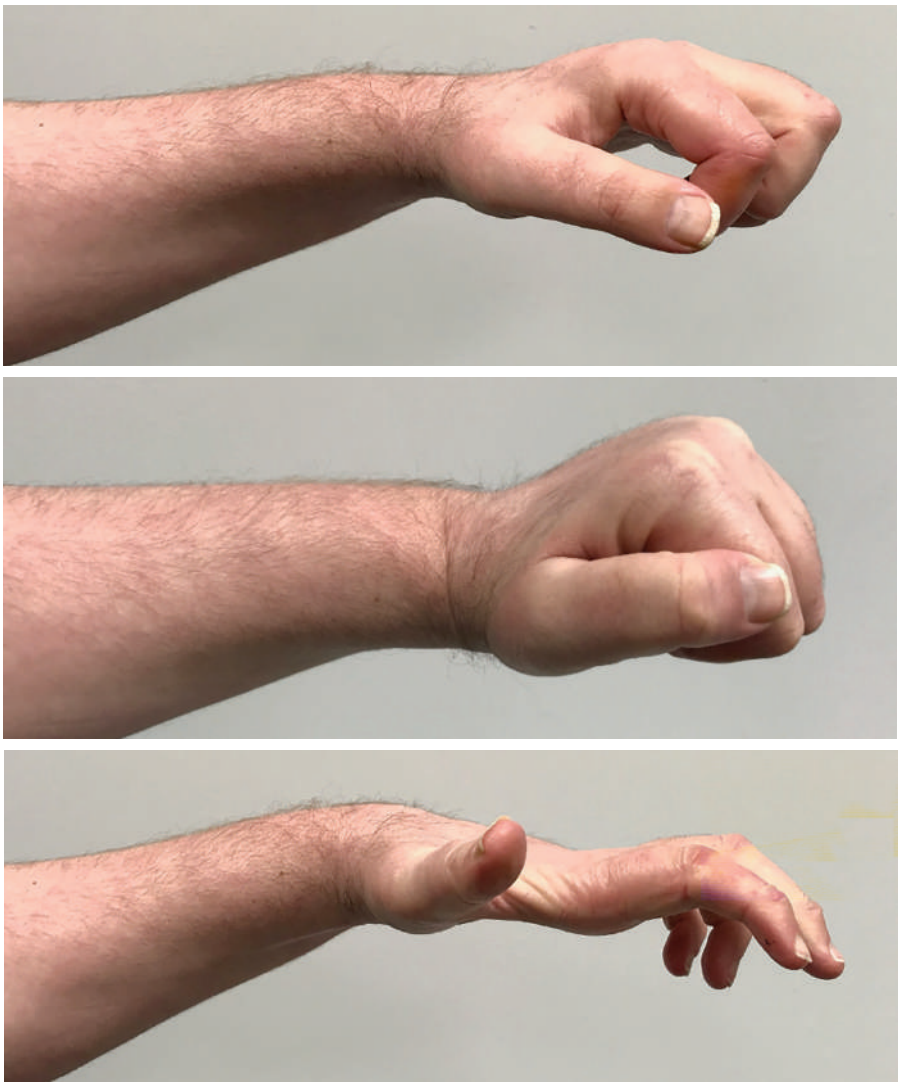

Figure 1. Hand function in a 35 y.o. male, spinal cord injury level C6, AIS B, 22 months after ECRB to AIN transfer and supinator to PIN transfer. (A) Hand at rest. (B) Hand closed in active grasp and key pinch. (C) hand open in active thumb and finger extension and thumb abduction
AIS: American Spinal Injury Association (ASIA) Impairment Scale

equipment and tools where appropriate, and training a repertoire of compensatory strategies to accomplish tasks. Among the compensatory strategies is the tenodesis grasp, which, in individuals who have voluntary wrist extension, provides a means of hand opening and closing through passive forces developed in the long finger and thumb flexors during wrist flexion and extension. Encouraging a tenodesis grasp involves improving or supporting active wrist extension, and reducing the resting length of the long flexors of the fingers and thumb, so that the fingers passively flex and the thumb approximates the fingers when the wrist is extended. An effective tenodesis grasp only enables the picking up of light objects as no power is generated.

Tendon transfer surgery to reconstruct arm and hand function in people with tetraplegia has a long and successful history. This type of surgery involves the transfer of the tendon from a functioning muscle to a new site, with the goal of reproducing lost movement at a specific joint, and reducing reliance on adaptive equipment.[5] Tendon transfers redistribute expendable, non-paralysed muscle function to that of paralysed muscles to restore a number of key functions including elbow extension, wrist extension and grasp and pinch.[6]

More recent surgical developments include nerve transfer surgery.[7,8] First developed as a surgical technique to reconstruct the brachial plexus or peripheral nerves after injury, nerve transfer surgery is now being applied to reanimate hand function in people with tetraplegia. Where a single tendon transfer can only be used to restore one function and is essentially a compensatory strategy, nerve transfers can allow for direct reanimation (restoration of voluntary control) of more than one muscle. The process involves taking working "donor" nerves from expendable muscles not affected by the spinal injury and coapting them to the "recipient" nerves of paralysed muscles. For example, to restore finger and thumb extension, the nerve(s) to the supinator muscle can be transferred to the posterior interosseous nerve. Supination of the forearm is still possible as it is one of the functions of the biceps muscle. Nerve transfer surgery can be used in combination with tendon transfer surgery to increase the options for upper limb reconstruction and the number of functions that can be restored. However, there are nerve transfer options for people with higher levels of SCI where tendon transfers are not possible.

Identifying the most appropriate candidates for such procedures requires a thorough knowledge of the functional anatomy of the upper limb and a detailed pre-operative assessment preferably by an interdisciplinary team. Evaluation of the range of movement, muscle strength and presence of spasticity are important components in determining the surgical procedure most appropriate for a specific patient, along with hand

dominance and tailored functional goals. The pattern of recovery post-injury and time since injury also influence decision making. Potential candidates for surgery should be re-assessed at appropriate intervals up to the day of surgery to track recovery, and potential surgical procedures should be delayed or reconsidered if significant natural recovery is apparent.

As there may be direct damage to the motor neurons within the injury zone resulting in a lower motor neuron injury, characterising the pattern of upper and lower motor neuron injury has implications for nerve transfer surgery. Lower motor neuron injury in the donor nerve may compromise its utility and, in the recipient nerve, it has implications for the timing of nerve transfer surgery, with surgery preferable before 12 months post-SCI to maximise outcomes. Assessing the relative proportions of upper and lower motor neuron injury in recipient nerves is not straightforward and the degree of lower motor neuron injury may vary considerably. In general, a muscle's response to surface electrical stimulation provides a good indication of the health of the peripheral nerve. Traditional motor and sensory nerve conduction studies combined with electromyography can demonstrate characteristics of impaired motor neuron function such as slowed motor conduction, reduced amplitude of compound action potentials, and fibrillations.[9] Intraoperative stimulation can more directly examine the conduction along the nerve. However, neurophysiological techniques do not provide a complete picture of peripheral nerve health. Direct assessment of peripheral nerves after SCI, through biopsies taken intraoperatively, has shown that the majority of both donor and recipient nerves sampled had morphological abnormalities. The most common abnormalities were myelin thickening and folding, demyelination, inflammation and a reduction in density of large myelinated axons. Other changes noted were a thickened perineurium, oedematous endoneurium and Renaut bodies.[10]

Numerous single case reports describing new surgical procedures or small retrospective case series have shown that nerve transfer surgery is feasible, safe, and effective. However, the reporting quality of these studies is not high, with lack of clarity regarding inclusion and exclusion criteria and consecutive recruitment. The Medical Research Council strength grading,[11] with videotapes included as supplementary material, has been the major approach used for measurement of outcomes rather than standardised functional outcome measures of hand function (e.g. the Grasp-Release Test[12]) or of independence. Rigorous prospective studies of nerve transfer surgery using standardised outcome measures in this population are lacking, as are reports of outcomes for combinations of multiple nerve and tendon transfer surgeries.

Our research group recently published the largest prospective, consecutive case series of nerve transfers (total of 59 procedures in 27 limbs) undertaken at a single centre in the tetraplegic population to date.[13] In ten of the participants, nerve transfers were performed in one hand to restore grasp and pinch while tendon transfers were performed on the other. Assessments of muscle power, grasp and pinch strength, upper limb function, independence in activities of daily living, and hand opening ability, were undertaken before surgery, and at 12 and 24 months post-surgery. Where prior to surgery none of the participants were able to register forces in grasp and pinch dynamometry tests, at the 24 month time-point there were significant improvements in their grasp and pinch strength, ability to pick up and release objects of different sizes in tests of hand function, and in their independence.

The outcomes in hands where grasp and pinch had been reconstructed with nerve transfers were similar to those reconstructed with tendon transfers, however the appearance of the hands was different. Using nerve transfers to re-animate grasp and pinch results in a more open, flexible and natural hand, with more subtle control for finer tasks and social interactions.

While nerve transfer surgery has been shown to be safe and effective and to have results comparable to those of tendon transfers, further research is needed. Areas requiring further investigation include: the longer-term outcomes of surgery, both functionally and from the individual's perspective; how to maximise an individual's use of the improved function in daily activities; and how an understanding of the health of donor and recipient nerves can be used in patient selection, predicting outcomes and determining the optimal timing of surgery.

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Professor John Pollard

Half-Century of Australian Neurology

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Figure 1: Professor Pollard in his consulting room.

With a career in medicine and academia spanning over five decades, Professor John Pollard has devoted much of his life to the development of Australian neurology. His fascinating career has been punctuated with numerous achievements, particularly in the field of inflammatory neuropathies. Now at the age of 79, he continues to work as an active Consultant Neurologist and Co-Director at Sydney's Brain and Mind Centre, seeing and treating patients.

In May 2019 we caught up with Professor Pollard after a busy afternoon list of clinics, in his seemingly ordinary consulting room set in the middle of the leafy Sydney suburb of Camperdown. As two medical students from London universities, we were visiting Sydney to learn about the way that clinical neurology is practised in a different environment from home. Part of this experience afforded us the opportunity to interview Professor Pollard. He recounted stories from his illustrious life, from his time as a young medical student and junior Doctor, to his career as a practising clinician and academic. A story that spans over half a century, Professor Pollard's experience reflects the changing practice of neurology in Australia, and holds many inspiring elements for future generations of aspiring researchers and clinicians.

Beginning of a Passion

Since an early age Professor Pollard harboured an interest in the natural sciences. This eventually led him to the University of Sydney, where he started his studies as a medical student. He had his first memorable encounter with neuroscience that was to influence the rest of his career.

'After fourth year of medical school I decided to take a year off and do a science degree. In those days the chemical neurotransmission in the CNS was largely unknown. At that point Feldberg and Gaddum[1] had produced evidence for acetylcholine as a neurotransmitter in the autonomic nervous system, and Eccles et al.[2] had shown its involvement in the synapses between the anterior horn cell and Renshaw cells of the spinal cord. However the neurotransmitter for the lateral geniculate bodies and optic nerves was not known.'

'The project I took on was to take lateral geniculate bodies in optic nerves of sheep, and see if we could extract them to find pharmacologically active materials. This involved going

Figure 2: The Brain & Mind Centre, Sydney NSW.

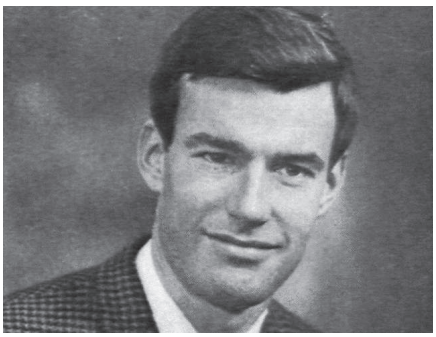

Figure 3 – John Pollard, 1965 (University of Sydney Faculty of Medicine Senior Year Book 1965).

out into the countryside, to the abattoirs, and I'd spent the most horrendous day in that rather unpleasant situation – dissecting the optic nerve and lateral geniculate from sheep that had been recently slaughtered. We had to get the nerves out within forty seconds and have them in liquid nitrogen to stop the autolytic processes from destroying what we were looking for. We had to dissect out around fifty nerves, and it was very hard work.'

'What this experience taught me was great reverence for every line of a textbook. I realised how much hard work went into every line, so in my medical studies it gave me a great respect for the knowledge within those books. It was also wonderful, I think, to take some time off from the rigours of clinical slog and book learning. It gave me time to read poetry and novels, and it gave me time to go to courses on the philosophy of science.'

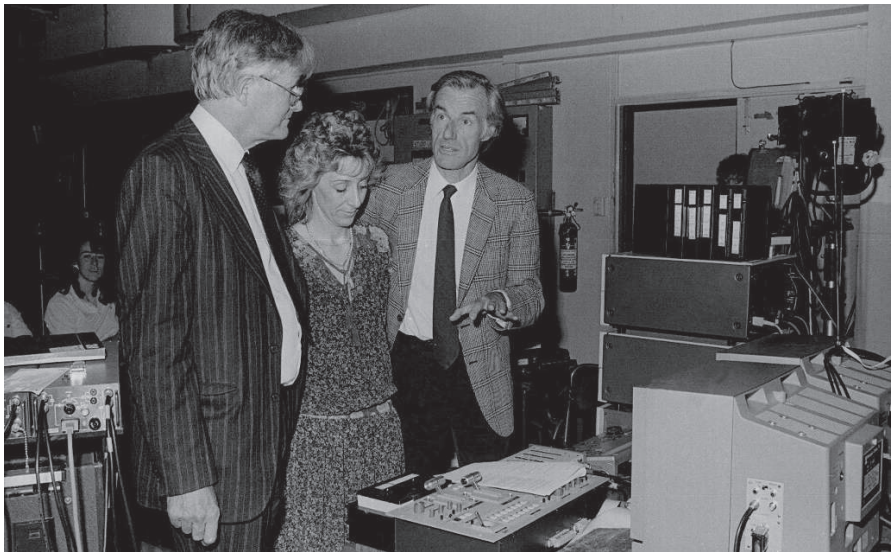

Figure 4: (left to right) Professor Jim McLeod, Dr Patsy Armati & Professor Pollard in a 1985 video on peripheral nerve disease (from the University of Sydney Archives ref: G77_2_0298).

Broadening Horizons

After graduating from the University of Sydney Medical School in 1966 and completing his houseman years, Professor Pollard embarked on specialty training to become a Neurologist. His training as a Neurology Registrar eventually led him to travel abroad to the United Kingdom, where he worked and trained at the Royal Free Hospital and the National Hospital for Neurology and Neurosurgery in London, commonly known as Queen Square.

'Now, at Queen Square, there were many wonderful teachers, and some leading world figures, like PK Thomas in peripheral nerve disease, and John Newsom-Davies in diseases of the neuromuscular junction, and Ian McDonald who was the world leader in the field of multiple sclerosis. Apart from these wonderful teachers and outstanding clinical scientists there were many interesting and delightfully eccentric people.'

'I first met John Newsom-Davies who was a visiting Neurologist at the Royal Free and at Queen Square. John in those days was studying the neurophysiology of the neuromuscular junction. Now they were the days when the underlying cause of myasthenia was uncertain – understanding that mechanism was John's major interest.'

'But in 1973, DM Fambrough et al published a paper[3] showing that the fundamental abnormality in myasthenia gravis was a lack of bungarotoxin binding sites – in other words acetylcholine receptors in the post synaptic membrane. In 1976, Lindstrom et al,[4] from the United States, demonstrated that in fact in 95-100% of patients with myasthenia there were raised levels of antibodies to the acetyl choline receptor, suggesting this was an antibody mediated disease. John Newsom-Davies, in 1977, the year after I returned from London, treated three severely weak myasthenic patients with plasmapheresis and demonstrated this miraculous recovery of strength, and that was the study which convinced Neurologists of my generation that this really was an antibody mediated autoimmune disease.'

Pioneering Therapies

His encounters with these eminent and eccentric figures in the UK inspired Professor Pollard's own clinical and academic work. On the back of these breakthroughs, he would go on to develop therapies for the many patients suffering from these debilitating diseases.

Plasmapheresis

'When I came back to Australia I began to look after patients with multiple sclerosis, autoimmune neuropathies, and myasthenia gravis. I was aghast at the number of myasthenic patients disabled with chronic disease. The treatments then available were anticholinesterases, thymectomy, and corticosteroids, and many suffered the ravages of long-term steroids. After multiple admissions to intensive care units requiring tracheostomies, many of them were institutionalised.'

'I rang John Newsom-Davies about this, and he told me about these results from the plasmapheresis, and I applied that to some of these patients. I found, as he did, that in the short term it was miraculous in its effect.'

'Then I introduced an immunotherapy in the form of azathioprine and decremental doses of steroids. Patients who had been institutionalised did so well that they were able to go out and live a free and normal life. That was a most gratifying experience.'

Professor Pollard was impressed by the degree to which his patients responded to these therapies, and his thoughts turned to their potential use in other neuroinflammatory diseases.

'I thought about applying plasmapheresis [as John Newsom-Davies had for myasthenic patients] to the immune neuropathy situation. I set up an animal model of plasmapheresis in a rabbit model of chronic immune neuropathy. We were able to demonstrate that in rabbits with severe paralysis and high levels of anti-myelin IgG, their disease stabilised and improved with plasma exchange.'

'I then introduced plasma exchange as treatment to patients with Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) in Australia, and some patients who hadn't responded to any other treatment, in those days which was steroid, did remarkably well. One of the most satisfying experiences in my life was seeing people who had been confined to a wheelchair with severe paralysis, recover their mobility and return to a normal life.'

Intravenous Immunoglobulin

It became apparent that these new immunotherapies could provide much more effective treatment for a number of debilitating diseases which clearly had an autoimmune basis. But with these new opportunities came new challenges.

'Later on, after 1985, the Dutch published the fact that CIDP, and later Guillain-Barré syndrome (GBS), would respond to intravenous immunoglobulin(IVIg); a much safer treatment than steroid and immune suppression and simpler to administer than plasmapheresis. When I attempted to obtain intravenous immunoglobulin for my patients, I discovered that this precious resource was strictly controlled; for the haematologists for use in the patients with Immune Thrombocytopenic Purpura (ITP), and the immunology patients with immunoglobulin subclass deficiency. It was impossible to get for neurological use.'

'I travelled around Australia attending meetings of Haematology and Immunology, describing how effective this therapy was for people with chronic neuropathies who were severely paralysed, showing videos I had taken of severely weak people recovering their strength and mobility.'

'I used to go and visit sporting clubs – if I had a patient in an area surrounded by a sporting club, I would go out and ask those fit young people to donate blood to the blood banks so that we could extract immunoglobulin for the patient from their area.'

'Eventually a National Body was established to control the use of IVIg for therapeutic purposes. This body decided that IVIg should be given only to those conditions for which

class 1 evidence for efficacy from controlled clinical trials was available and fortunately there was plentiful such evidence in the neurological literature. IVIg then became available in Australia for the treatment of autoimmune neuropathies. A contemporary of mine from Queen Square in the 1970s, now Professor Richard Hughes from Guys Hospital, made a major contribution to this literature, particularly in the form of influential Cochrane reviews.'

Today, immunotherapy, plasmapheresis and intravenous immunoglobulin have become mainstays in the treatment of immune-mediated neurological conditions. Professor Pollard's contribution in this field improved the lives of many patients who suffered from these debilitating conditions, both in Australia and around the world.

The Neurologist

After working as a Neurologist over the span of five decades, Professor Pollard continues to be inspired and humbled by his patient's experiences, reminding him of why he chose to become a Neurologist all those years ago.

'I think of a young lady that I saw in clinic down in South Sydney, who was only nineteen. She came to me complaining that she had no memory.'

'I said to her "really, what do you forget, where you lose your keys? Or do you forget what you've come down the shops to buy?'

'But she replied "no, Doctor, a year ago I had a baby, and I can't remember giving birth to that baby', and I thought "goodness – this is significant memory loss.'

'Her neurological examination was normal, and she was bright and lively. But I thought of the things that might affect memory in a young woman, and as I talked to her it was obvious that she was having mild, but multiple absences. She obviously had mild partial complex seizures, and she was wiping the memory circuits in her temporal lobe.'

'When we put her on sodium valproate, these eventually ceased, and her memory returned over months – it was life changing for her.'

'In these days when computers are playing such a role in medicine, we still need the importance of history and examination because the computers do not give us the whole answer. There are often clues in the history and examination.'

The Future

'I think that people planning to come into medicine should recognise it is a wonderful, interesting, and exciting field. You should enjoy it. It is a great privilege helping people, and contributing in small measures to their wellbeing.'

'I think contributing to medicine means keeping up to date, at least in your field with scientific advances. I would suggest that every medical practitioner should do their best to contribute in some small measure to science and science advancement at least in their field. Every small addition to knowledge can give satisfaction.'

'Participating in the international research community and attending national and international conferences facilitates meeting colleagues who share your ideas and interests. Many of these colleagues will become collaborators and wonderful friends and this is one of the great privileges of working in the sciences and clinical sciences.'

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An atypical presentation of giant cell arteritis without headache

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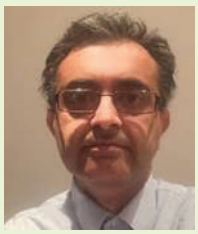
Waqar Rashid



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Abstract

We describe an unusual case of giant cell arteritis initially manifesting as insidiously progressive spastic quadriparesis, widespread muscle wasting and fasciculations in the absence of headache, followed by a complete left pupil-involving 3rd nerve palsy 10 months later. MRI and CSF analysis revealed evidence of intracranial involvement with established white matter lesions and intrathecal oligoclonal bands, respectively, whilst whole body FDG-PET demonstrated isolated uptake within the descending aorta. The temporal arteries were clinically and radiologically unremarkable but biopsy showed transmural inflammation and multinucleate giant cells. A rapid, complete and sustained improvement followed steroid therapy.

Case Presentation

A 69-year-old male ex-smoker with well-managed hypertension presented with painless diplopia on right gaze 15 minutes after waking, followed by progressive left-sided ptosis which completed over four hours. Over the preceding 10 months he also reported increasing pain and weakness in both legs, with particular difficulty rising from his car seat and a significant limitation in walking distance. Four months previously similar symptoms had begun in the arms and the patient had noticed generalised loss of muscle bulk and that occasionally muscles would 'twitch'. Appetite had become poor and body weight had fallen by 10kg, with sporadic episodes of nocturnal sweating. Bowel, bladder and cognitive functions were normal. Medications included Amlodipine 5mg daily and occasional Ibuprofen for osteoarthritis.

Examination revealed a weakly reactive dilated left pupil, with globe exotropia and abduction, but normal visual acuity and fields, anterior and posterior chambers, and fundoscopy. The remaining cranial nerves were normal, apart from a brisk jaw jerk. Forward neck flexion was MRC 4/5 in the context of myalgia. However, there was generalised loss of muscle bulk, fasciculations in the limbs and upper trunk, and a spastic quadriparesis with MRC power 4/5 at elbow extension, hip flexion and knee flexion. Reflexes were globally brisk including finger jerks, Hoffman signs and crossed adductors, in addition to ankle clonus and extensor plantars bilaterally. Sensation to all modalities and co-ordination were normal. Cardiorespiratory and abdominal systems examined normally without rashes, ulcers or palpable masses.

Blood results (Table 1) included mild

Table 1: Blood test and lumbar puncture results.

Blood Analyses	CSF Analyses	Presentation	Post treatment
Haemoglobin 133g/L	RBC	<1	<1
MCV 84.9fL	WCC	3	<1
Platelets 508x10^9/L	Protein	282 mg/L	294 mg/L
ESR 60mm/hr	Glucose (serum)	3.8 (6.0)	6.8 (8.9)
CRP 22.2mg/L	Intrathecal OCBs	+ve	+ve
CK 35 iu/L	Viral PCR	-ve	-ve
HbA1c 40mmol/mol	ACE (serum)	1.4 (17)	1.2 (15)

Normal were: renal, liver thyroid function; serum protein electrophoresis; ANA; ANCA; ACE; anti-neuronal, anti-MOG, anti-Aquaporin4; and anti-ganglioside antibodies; HIV, Syphilis, Hepatitides A-C and Lyme serology.

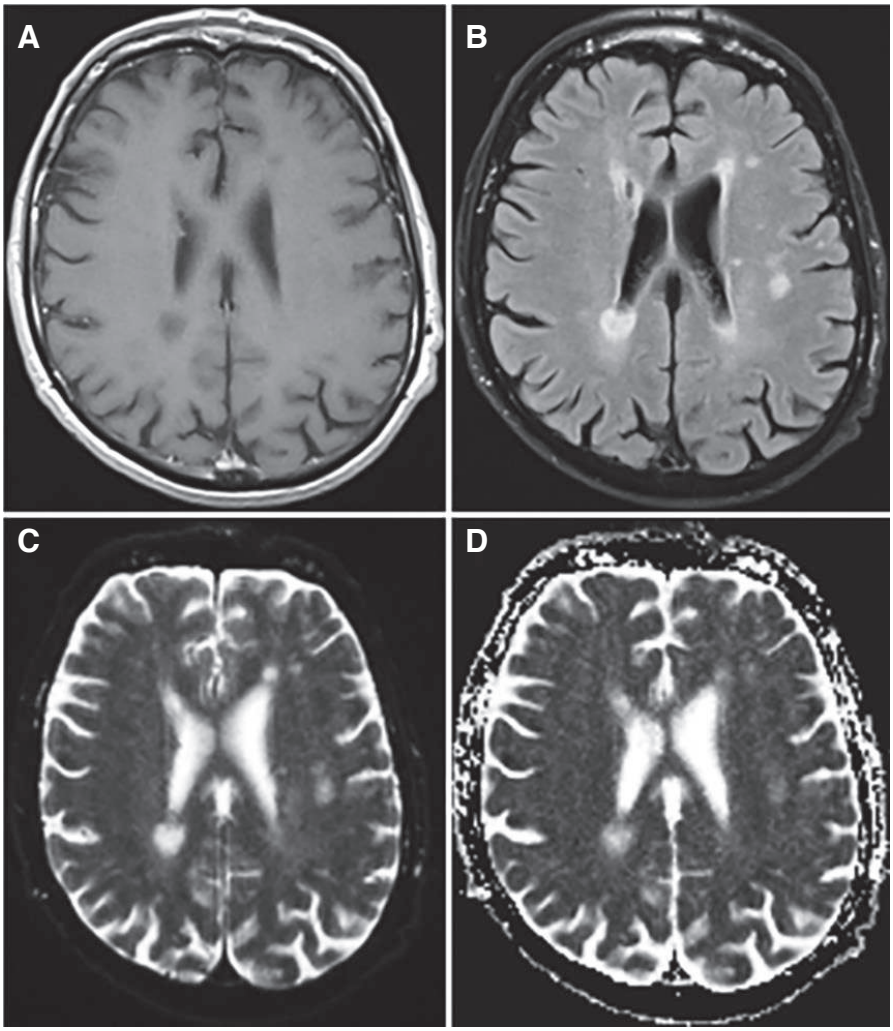

Figure 1. MRI Brain at the presentation showing multiple areas of hypointensity within the subcortical white matter on T1 (A; without gadolinium enhancement), hyperinstensity on T2 (B) and only T2 shine-through on diffusion-weighted imaging (C) and no true abnormally-restricted diffusion on ADC (D) at this stage. The appearances raised the suspicion of an underlying ischaemic or inflammatory process. Spinal cord imaging was unremarkable.

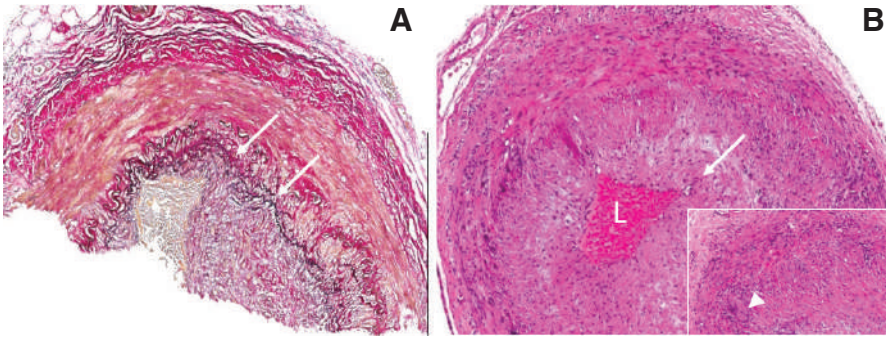

Figure 2. Histology of temporal artery biopsy. Elastic van Gieson staining clearly shows disruption of the internal elastic lamina (A; arrows), whereas haematoxylin and eosin staining confirms trans-mural infiltration of inflammatory cells with occasional multinucleate giant cells (B inset; arrowhead), marked fibrointimal thickening (B; arrow) and reduction in luminal diameter ("L").

normocytic anaemia, elevated platelets and raised ESR (peak 63mm/hr) and CRP (peak 70) in the absence of infection or autoantibodies. MRI brain and whole spine showed multiple areas of signal hyperintensity within the white matter and basal ganglia of both hemispheres without contrast enhancement or restricted diffusion (Figure 1), raising the possibility of inflammation or ischaemia. Initial CSF analysis was essentially unremarkable but an intrathecal pattern of oligoclonal bands synthesis was detected (Table 1). Neurophysiology confirmed widespread fasciculation potentials in the limbs, without polyphasic sharp waves or fibrillations and the tongue appeared normal. Mild neurogenic changes in the limbs were noted upon voluntary activation, with polyphasic waves and reduced recruitment. Normal motor and sensory conduction was otherwise seen with no evidence of myopathic discharges. CT with contrast of the chest, abdomen and pelvis was normal and whole body PET-CT was unremarkable, apart from a mild non-specific uptake along the left wall of the descending thoracic aorta considered at first to be a radiological artifact, given that it was not circumferential.

The patient continued to deteriorate with fluctuating low grade pyrexia, myalgia and drenching night sweats. Nutritional supplements in addition to regular meals were only maintaining his already decreased body weight and limb weakness worsened such that he required a wheelchair for distances beyond a few meters. Interestingly, prior to steroid therapy his 3rd nerve palsy began to spontaneously improve over six to eight weeks.

Consideration of the Differential Diagnoses

The evolution of motor symptoms might have initially been suggestive of amyotrophic lateral sclerosis (ALS) or one of its mimic syndromes,[1] although the progressive systemic symptoms and abrupt onset diplopia by the time of his presentation became inconsistent with these. The acute, unilateral, pupil-involving left oculomotor nerve palsy arising in the absence of contralateral ptosis, superior rectus paresis or concurrent hemiparesis pointed away from respective nuclear IIIrd, Benedikt's fascicular or Weber's fascicular midbrain syndromes and instead to a peripheral lesion outside the brainstem and proximal to its division within the superior orbital fissure. Accounting for pupil involvement, an external compressive cause would still have been a reasonable consideration over a microvascular phenomenon, although additional cranial nerve palsies and meningism were not present to suggest pathology within the cavernous sinus or basal meninges, where the imaging was unremarkable.

Clinical examination implicated bilateral pyramidal tract and spinal motor neuron involvement at multiple levels, as corroborated by central nervous system lesions on MRI and widespread neurogenic change on neurophysiology, respectively. Although no neuromyotonic discharges were seen on EMG, the predominantly proximal pattern of weakness with myalgia and systemic features prompted consideration of underlying endocrinological, infective, neoplastic, drug-induced, inflammatory muscle and neuromuscular junction disorders[2] for which no clear evidence was found. However, given the equivocally abnormal FGD-PET findings, negative autoantibody screen (including anti-neuronal antibodies) and lack of organ involvement anticipated in other vasculitides, a large vessel vasculitis was suspected as the most plausible diagnosis to unify malaise, fever, night sweats, weight loss, myalgia, normocytic anaemia, raised ESR and CRP, clinically progressive CNS lesions and complete 3rd nerve palsy. Intra- and extracranial MR angiography were normal

and the temporal arteries prominent but not pulseless or tender. Nevertheless, temporal artery biopsy demonstrated a mainly lymphocytic transmural inflammation, with occasional multinucleate giant cells (Figure 2). Of note, well formed non-necrotising granulomas were not present.

A diagnosis of Giant Cell Arteritis (GCA) was made in accordance with The American College of Rheumatologists Classification (age >50, ESR >50mm/hr and abnormal artery biopsy).[3] Intravenous Methylprednisolone 1g daily for three days was commenced immediately, followed by Prednisolone at 1mg/kg/day and Aspirin 75mg daily. Within 72 hours the patient reported cessation of myalgia and night sweats. Weight and walking distance improved over the next month, muscle twitching ceased and the ESR, CRP and haemoglobin normalised.

Patient outcome

After four weeks, Prednisolone was gradually tapered over eight months. Reducing the dose below 10mg/day on two occasions unmasked increasing leg discomfort, weakness, poor concentration, and swelling at the temporal biopsy site, which responded rapidly to dose restoration and a much more gradual reduction. Repeat neurophysiology at nine months was normal and serial MR neuraxis imaging has remained unchanged for 34 months.

Discussion

Giant cell arteritis (GCA) is a granulomatous autoimmune vasculitis typically affecting medium and large diameter vessels in proportionally more female patients over the age of 50 (peak incidence 70-79).[3-6] Suspicion is classically raised by new onset headache or localised head pain in this demographic, and is the only heraldic symptom defined within currently accepted diagnostic criteria.[3] Prompt initiation of glucocorticoids is obliged to prevent the feared complication of permanent visual loss secondary to anterior ischaemic optic neuropathy. Superficial temporal artery specimens are often used to confirm GCA pathologically, although up to 40% are unrevealing due to characteristically inhomogeneous segmental involvement with so-called 'skip lesions'.[7] Diagnosis can be made on clinical grounds but the condition's alternative designations of "temporal arteritis" or "cranial arteritis" shouldn't detract from the extracranial manifestations such as limb claudication. Indeed, headache may be conspicuously absent, as in this case, despite a positive tissue diagnosis. Furthermore, aching and stiffness in the pelvic and/or shoulder girdles distinctive for polymyalgia rheumatica (PMR) is seen in roughly 50% of patients with GCA at diagnosis and, conversely, around a fifth of patients with PMR develop GCA,[8] with 'constitutional' symptoms of weight loss, fever and night sweats frequently encountered in both conditions.[6]

Histopathologically, the immune-mediated assault of arterial walls in GCA is believed to evolve from the outside in although which factors may initiate the whole cascade are unknown. Antigen-presenting dendritic cells within the adventitia enter a 'mature' activated state which enables recruitment of T cells via endothelium in the vasa vasorum followed by macrophages which may eventually coalesce into multinucleated giant cells.[5,6,9] Pro-inflammatory cytokines including inter-leukin-6 (IL-6), IL-1 and interferon gamma sustain what becomes a transmural inflammatory process and are implicated in mediating the constitutional and myalgic symptoms in association with increased CRP, prolongation of the ESR, elevation of platelets and activated circulating monocytes.[9,10] Arterial biopsies in PMR are rarely undertaken, but dendritic cell activation without a T cell response has been described, as have isolated clumps of mononuclear inflammatory cells surrounding capillaries proximal to the adventitia.[11,12] For these reasons, large vessel imaging modalities such as axillary ultrasound, CT/MR angiography and FDG-PET are able to demonstrate increased arterial wall echogenicity, thickness or glucose uptake, respectively, supportive of a (perhaps subclinical) vasculitic process in patients with 'PMR' or in lieu of arterial biopsy,[5,6] accepting that a less than overwhelming 'artefactual' or 'equivocal' anomaly might need to be interpreted in context, as here. Accordingly, it has been proposed that the diagnostic criteria for GCA as a syndrome be expanded to include affirmative imaging findings and the spectrum of cranial and extracranial features.[6]

This particular patient is unusual for several reasons. Extraocular paresis in GCA, albeit on the rarer side, is well recognised and almost always involves the oculomotor and/or abducens nerves. However, pupil involvement is not common.[13,14] Despite one case previously incriminating extraocular muscle necrosis,[15] occlusive arteritis affecting branches of the ophthalmic artery within the globe are considered responsible for paresis of eye movement[14] and would certainly seem most plausible in our case. Indeed, diplopia is often reported in the days to weeks leading up to frank visual loss.[14]

The brain parenchymal lesions and the unmatched oligoclonal bands (OCBs) in the CSF are unusual. In a known hypertensive and ex-smoker it is possible that the subcortical lesions reflected accelerated microvascular damage. There was no evidence of abnormally restricted diffusion or contrast enhancement and, without a pre-morbid comparator, the changes are impossible to age. However, the progressive motor symptoms and signs in context of the diplopia and PMR suggest active central pathology related to GCA and might provide an explanation for the OCBs which are not unusual in CNS vasculitides. It is unclear how often positive OCBs are reported specifically in GCA even with cerebral involvement, although B-cell involvement is increasingly recognised.[5,16] An incidental second diagnosis, such as late onset primary neuroinflammatory disease, would be unlikely given there has been sustained clinical improvement without radiological progression and we would prefer to apply Occam's Razor here. An alternative diagnosis of neurosarcoid is worth consideration, however serum and CSF ACE were normal, there was no suggestion of systemic involvement on CT or PET imaging, there was no haemorrhagic component or enhancement of the CNS lesions or meninges and the ophthalmology assessment was not supportive of this diagnosis and as such we think a systemic vasculitic process remains most likely.

Finally, the widespread fasciculations are most intriguing. The authors are unable to find mention of these in conjunction with GCA but they clearly arose in the context of the myalgia and weakness, and evaporated quickly following steroid therapy. Neurophysiology additionally demonstrated minimal neurogenic changes and mildly reduced recruitment which is similar to that seen in partial compressive root lesions with proximally-generated fasciculations.[17] We propose that the fasciculations were generated peripherally representing a multilevel radicular arteritis of the vasa nervora, albeit without evidence of significant axonal loss.

Learning Points

1. Giant Cell Arteritis (GCA) can present with intra- or extracranial manifestations in the absence of headache.
2. GCA is a vascular cause of pupil-involving complete 3rd nerve palsy.
3. Large vessel imaging modalities, such as CT or MR angiography and FDG-PET, may support diagnosis of GCA.
4. Positive oligoclonal bands may be seen with intracranial vessel involvement.
5. Widespread fasciculations in GCA is highly unusual and may represent multilevel proximal radiculopathy.

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- Authors EB and AWB contributed equally to this work.
- EB and AWB performed a review of the literature and drafted the article.
- DW contributed to the figure panels and histological information.
- WR and PNL provided clinical expertise and critical appraisal of the article for submission.

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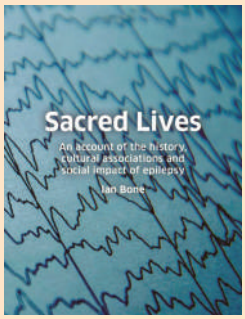
Sacred Lives. An account of the history, cultural associations and social impact of epilepsy



Author: Ian Bone
Published by: Amazon, 2020.
Price: £12.00
Pages: 363
ISBN: 9781838036713
Reviewed by: AJ Larner, WCNN, Liverpool.

A recent ABN Newsletter drew my attention to this book by Ian Bone, a long serving (now retired) Consultant Neurologist in Glasgow. Prompted by the experience of caring for a son with epilepsy, this book has been written as an awareness raiser for a general audience, hence it is lightly rather than exhaustively referenced, although there is much here for Neurologists to learn from.

Whereas standard epilepsy texts focus on diagnosis, classification, investigation, and treatment (all briefly touched upon here), this book has more to say about epilepsy in the arts, the media, and society, as well as including a personal account of living with epilepsy. The book thus may be said to complement standard neurology texts, seamlessly bridging the gap between expert text and patient narrative. Only a brief flavour of the rich resulting melange can be given here.

With the benefit of the author's personal perspective, the sections on stigma and social isolation are particularly informative. Some of the history of this ostracism is also given, for example relating to the eugenics movement and to the "epilepsy colony" movement, both originating in the nineteenth century. The author's clinical experience is to the fore in discussing legal ramifications of epilepsy. The legal subdivision of automatisms into sane and insane is indicative of the gulf that may exist between medical and legal thinking (p.263).

The many examples of the portrayal of individuals with epilepsy in books bespeaks an immense amount of reading. In addition, examples are also given from film, television, and other of the arts, resulting in a broad frame of cultural reference ranging from Dostoevsky to East Enders! The many inaccuracies in such portrayals are highlighted. Amongst the historical figures alleged to have had epilepsy who are discussed, I would have been intrigued to hear Dr Bone's thoughts on the claim that St Paul suffered from epilepsy.

Proceeds from the book will go to the William Quarrier Scottish Epilepsy Centre, in light of which I hope it will not seem churlish or mean-spirited to voice some minor criticisms. For example, it is not the case (p.29) that Chalfont St Peter was the first colony for people with epilepsy in the UK ("first patient admitted 1894"), since it was predated by the Maghull Home for Epileptics on the outskirts of Liverpool (first patient admitted 1888). Indeed, Maghull's founding clinician, William Alexander (p.30), was asked for advice by the directors of the Chalfont colony, both at its foundation and some years later.

I'm also in disagreement with Ian Bone in his analysis of Shakespeare's Othello, where he seems ready to follow convention in diagnosing Othello with epilepsy (p.66-7), but all the eye witness evidence is from Iago, hardly a reliable informant. I'm also sceptical that Dickens's character Walter Wilding, from the play No Thoroughfare (1867), has epilepsy (p.77).

There are a few typographical errors, the most egregious of which is "San Michael" for San Michele" in the title of Axel Munthe's celebrated autobiography (p.171; an autocorrect?). The index is commendably thorough, a cut above the perfunctory apparatus one encounters in most textbooks.

There is a wealth of information in this book, evidently a labour of love. I highly recommend it to anyone involved in or interested in the care of people with epilepsy. At just £12, it's a steal!

Neurological signs: hypermnesia

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Anniversaries are times for remembering, if not always for celebrating. However, the chances are that few readers will be able to recall any of the contents of the very first issue of ACNR, published 20 years ago (or maybe even the most recent issue!). After some pondering, I did eventually recollect that the inaugural ACNR issue included an excellent piece by Alasdair Coles on the oculomotor nerve.

Awareness of failure to recall may prompt a complaint of poor memory function without there necessarily being any pathological substrate, and certainly this kind of functional disorder is the bread-and-butter work in the cognitive function clinic. Amnesia in its various forms is less frequently encountered. Some literary accounts of impaired memory have already been presented in the journal.[1] Indeed there are many more, so much so that "the amnesia story" has been claimed as a specific genre of literature.[2]

Conversely, I do not recall ever encountering in clinical practice a complaint of memory being too good, or hypermnesia. This general term, like amnesia, may be further qualified, dependent upon the particular nature of exceptional memory or functional excellence. Hyperthymesia, or the hyperthymestic syndrome, is the ability to remember an abnormally large number of life experiences in vivid detail, and is also known as highly superior autobiographical memory (HSAM).[3] Eidetic, or "photographic", memory is the ability to recall precisely images from memory after a brief or single viewing. Some definitions of eidetic memory exclude use of mnemonic devices, as used by trained mnemonists. However, synaesthesia may be linked to eidetic memory, with synaesthetic experience possibly being used as a mnemonic aid.

The classic account of hypermnesia is that of AR Luria (1902-77), who in *The mind of a mnemonist* described his patient, Solomon Shereshevsky, a journalist with fivefold synaesthesia whose memory was apparently "for all practical purposes … inexhaustible". Studied over a period of thirty years beginning in the 1920s, Luria noted that Shereshevsky was able to convert information into visual images. In his introduction to the 1968 reprint, Jerome Bruner credited Luria with founding a new literary genre with this book.[4]

Another noted hypermnesic was the Hungarian-US mathematician John von Neumann (1903-57), said by his wife to have an "almost photographic memory",[5] a report corroborated by his colleagues: he could apparently memorise names, addresses, and telephone numbers from a phone book on sight.[6] His work on computers was initially justified by means of biological analogy with the working of neurones (only latterly did the analogy reverse to "brain as computer") although subsequently he came to doubt the parallel, as shown in his posthumously published Silliman lectures of 1957.[7] I do not know whether or not von Neumann's own prodigious memory stimulated his interest in the potential similarities and differences between computers and brains,

The "photographic memory" is also, of course, a trope much resorted to in film and TV. Examples, conjured fairly randomly from my memory, include the film *Carry on Spying* (1964) in which Barbara Windsor (1937-2020), who later developed dementia, plays Agent Daphne Honeybutt; and Sheldon Lee Cooper in the long running TV serial *The Big Bang Theory* (2007-2019).

There are also some literary accounts suggestive of hypermnesia. Perhaps the most notable is that by the Argentine author Jorge Luis Borges (1899-1986) in his short story, *Funes el memorioso*, usually translated as *Funes, the memorious* but also as *Funes, his memory*, which appeared in a collection entitled *Artifices* first published in 1944. In his foreword to this collection, the author calls this story "one long metaphor for insomnia".[8] Set in Uruguay in the 1880s, it describes Ireneo Funes who, having been "hopelessly crippled" after being knocked unconscious when bucked by a half-broken horse, finds that now, in his late teenage years, "his perception and his memory were perfect". However there is evidence that his perception of time and memory for proper names was "precise" even before the injury. Now "the most trivial of his memories was more detailed, more vivid than our own perception of a physical pleasure or a physical torment".

> He had effortlessly learned English, French, Portuguese, Latin. I suspect nevertheless that he was not very good at thinking. To think is to ignore (or forget) differences, to generalize, to abstract. In the teeming world of Ireneo Funes there was nothing but particulars – and they were virtually immediate particulars.

Oddly enough, given these exceptional memory faculties, Funes also crops up in the aforementioned anthology devoted to amnesia.[2] Oliver Sacks made several references to Funes, finding him to be "uncannily similar" to Luria's patient, and wondering whether he may have been based on a personal encounter between the author and a mnemonist.[9] Unlike the situation of Funes and of Shereshevsky, for von Neumann "the trees did not conceal the forest from him".[6]

The history of prodigious feats of memory is, in fact, ancient. One of the books which Funes reads is the *Naturalis Historia* of Pliny the Elder (AD 23-79) which catalogues (in Book VII, Chapter XXIV) cases of prodigious memory, for example (in the translation of Philemon Holland, 1601):

> One Charmidas or Carmadas, a Grecian, was of so singular a memorie, that he was able to deliver by heart the contents word for word of all the bookes that a man would call for out of any librarie, as if he read the same presently within a booke.

A more recent example is to be found in Pascal Mercier's novel *Night train to Lisbon*, set partially in the time of the Portuguese dictatorship in the early 1970s. Estefania Espinhosa "had this unbelievable memory. Forgot nothing, neither what she had seen nor what she had heard. Addresses, phone numbers, faces. We used to joke that she knew the phone directory by heart" (shades of von Neumann?). This "phenomenal memory" is used to retain all the secrets of the *Resistência*: "We didn't have to write anything down, didn't have to leave a paper trail. The whole network was in her head" (in the film version, which differs in many details from the book, Estefania is shown reciting names and telephone numbers of supporters of the resistance). However, the possession of these abilities renders Estefania a liability when the secret police seek to track her down, necessitating her flight from Portugal. As she recalls: "it was about keeping me safe … but it wasn't only me, it was mainly my memory".[10]

Detrimental effects of these exceptional memory functions are reported. For example, Shereshevsky appeared unable to hold down any job for a prolonged period. There is a quote attributed to Friedrich Nietzsche (1844-1900) to the effect that "Many a man [*sic*] fails as an original thinker simply because his memory is too good". So, perhaps we should not be too harsh on our own memory lapses!

References are overleaf

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Abstract
When neurology began to develop as a specialty, Russell Reynolds was one of the first Neurologists appointed to the Hospital for the Paralysed and Epileptic, Queen Square.

Of many contributions his work on epilepsy was influential, espousing many new concepts. He followed and developed Hughlings Jackson's original ideas about positive and negative neurological symptoms. His approach to patients was holistic at a time when more objectively defined notions of illness dominated medicine. He wrote on vertigo, and about criminal lunacy, and his book *The Diagnosis of Diseases of the Brain, Spinal Cord, Nerves and their appendages* was a major text of the period.

Well versed in poetry, philosophy, art, and music, he was widely admired. He became President of the Royal College of Physicians.

Like the great Sir Jonathan Hutchinson and other Victorians of privileged stock, Sir John Russell Reynolds (1828–1896) (Figure 1) never attended school. His father, a nonconformist minister at Romsey in Hampshire, educated him personally. His grandfather Henry Revell Reynolds (1745-1811), FRS, was an illustrious physician at the Middlesex and St Thomas's Hospitals and physician to George III.

Figure 1: Sir J. Russell Reynolds. [Published in British Medical Journal, 6 June 1896].

As a nonconformist he was excluded from Oxford and Cambridge* and read Medicine at University College London, graduating with a gold medal in physiology, comparative anatomy, and medicine in 1851.[1] An impecunious young Doctor, he sought a living, practising in Leeds where his brother was a Minister of the East Parade Mission Chapel, and his brother-in-law a journalist on the Leeds Mercury.

A year later his former teacher Marshall Hall, FRS (1790-1857), a Physician and brilliant experimental Physiologist, persuaded him to return to London,[2] where at modest cost Hall let him live in his home at 38, Grosvenor Street and join his consultant practice, mainly in nervous diseases.

Only four years after graduating Russell Reynolds' outstanding ability led to his appointment as Assistant Physician at the Hospital for Sick Children and to the Westminster and University College Hospitals. There he became Holme Professor of Clinical Medicine in 1862, and in 1867 succeeded Sir William Jenner as Professor of Medicine. Just five years after the opening of the National Hospital for the Relief and Cure of Paralysis and Epilepsy, Russell Reynolds showed his interest in neurology and was appointed to its staff. He was elected FRS on 3rd June 1869.

At this time neurology began to flourish; he worked with many distinguished early Neurologists. They included Hughlings Jackson (1835-1911), Jabez Ramskill (1825-1897), Charles Bland Radcliffe (1822-1889) who succeeded Brown–Séquard in 1863, and published *Lectures on Epilepsy, Pain, Paralysis, and certain other disorders of the Nervous System*, 1864, and articles in Reynolds's *System of Medicine*. His brother John Netten Radcliffe (c. 1830-1884), a pioneering epidemiologist, was also Medical Superintendent of the Hospital for the Paralysed and Epileptic.

No man works in a vacuum. Marshall Hall, (who in spite of his acknowledged distinction[3] surprisingly had failed to get an academic post in London) inspired and encouraged Reynolds. Amongst contemporary and subsequent notable physicians he influenced were: the erudite Charlton Bastian (1837-1915); Charles Edward Beevor, (1854-1908); Howard Tooth (1856-1925); James Taylor, (1859-1946) editor of Jackson's Selected Writings; and the punctilious Thomas Buzzard (1831-1919), his neighbour in Grosvenor Street, and friend of both Hughlings Jackson and David Ferrier (1843-1928).

Such was Reynolds's reputation that he was rewarded with both the Lumleian and the Harveian lectures at the Royal College of Physicians of London, becoming President from 1893-1895. Like his grandfather, he was physician to the royal household in 1879 and was made a baronet in 1895. He was President of the BMA until his death.

A popular and fluent lecturer, he was shy and serious but had a quiet humour and a 'directness of speech that was no respecter of persons.' Described as courteous, shrewd and kind, his approach was holistic—long before it became fashionable:

> Not to merely make a diagnosis, much less to write a prescription, but to advise the individual patient what he or she should best do to regain their health… and what changes in the environment, mental, emotional, or physical were most likely to achieve this end.[2]

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Medical works

Russell Reynolds is often remembered for his descriptions of epilepsy, eclamptic convulsions, and febrile convulsions in children.[4,5] He also used electrotherapy in various nervous diseases.[6]

Interestingly, he is widely quoted for commending the "great value of Cannabis indica" in migraine, epileptic conditions, depression, and asthma. In 1890 he prescribed a cannabis tincture for the menstrual cramps suffered by Queen Victoria. He noted in *The Lancet*:

> When pure and administered carefully, [cannabis] is one of the most valuable medicines we possess.[7]

Of greater import was his 1861 paper (Figure 2) that espoused the concept of positive and negative neurological symptoms.[5,8] Positive symptoms were abnormal behaviours that included not only clonic jerking and abnormal movements but also hallucinations and paranoid delusions.

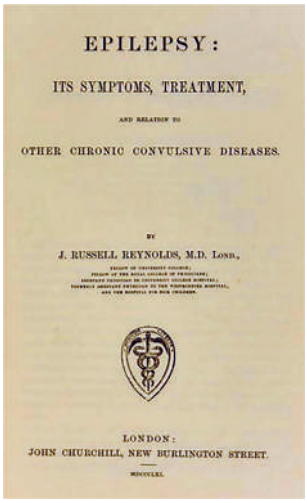
> Some symptoms are negative, i.e. they consist in the negation of vital properties. Of this kind are paralysis, anaesthesia, and the like…Other symptoms are positive, i.e. they consist in excess or alteration of vital properties. Of this kind are spasms, pain, convulsions and the like… (p.9-12, 28)

Unfortunately he failed to write further on this theme. Like Jackson, Russell Reynolds shrewdly noted that the lesion did not directly cause the symptoms observed.

The origins of positive and negative symptoms were inextricably intertwined with Herbert Spencer's ideas of dissolution and evolution of the nervous system.[9] Hughlings Jackson extended Spencer's idea to patients' symptoms, both positive and negative. Jackson believed that negative symptoms related to dissolution of neural function while positive symptoms resulted from excitation or the release of lower levels from higher inhibitory control:

> Speaking of the physical side, there are degrees of loss of function of the least organised nervous arrangements with conservation of function of the more organised. There is in each reduction to a more automatic condition; in each there is dissolution, using this term as Spencer does, as the opposite of evolution.[10]

Russell Reynolds wrote his first book on *Vertigo*. In 1856 he examined legal pleas for insanity in his *Criminal Lunatics: are they Responsible?* He believed that epilepsy could be a distinct or 'idiopathic' disease, a controversial view well expressed in *The Diagnosis of Diseases of the Brain, Spinal Cord, Nerves and their appendages* in 1855 (dedicated to Marshall Hall),


EPILEPSY:

ITS SYMPTOMS, TREATMENT,

AND RELATION TO

OTHER CHRONIC CONVULSIVE DISEASES.

BY

J. RUSSELL REYNOLDS, M.D. Lond.,

LONDON:
JOHN CHURCHILL, NEW BURLINGTON STREET.

Figure 2. Reynolds: Epilepsy, its symptoms, treatment and relation to other chronic convulsive diseases. 1861

This was later contradicted by Kinnier Wilson who stated that all epileptic events were symptoms, whether or not any underlying pathology could be demonstrated.[11]

Always inclined to a broad approach he described the interictal symptoms of 62 patients with idiopathic epilepsy. He found about one third had mild impairment of recent memory and a similar proportion had moderate to severe psychopathological findings. His interpretation of epileptic activity (well described by Eadie[12]) was in large measure approved by Hughlings Jackson.

He edited and wrote many chapters in *A system of medicine* (London: Macmillan, in five volumes from 1866 to 1879), a major text rivalled only by John Cooke's *Treatise in Nervous Diseases*, published in two volumes, in 1820 and 1823, the second volume of Bright's *Reports of Medical Cases* 1831, and Romberg's *Manual of the Nervous Diseases of Man* 1840.[13]

Russell Reynolds practised at a time when neurology was in its infancy. It relied on clinical description and elementary pathology. In this morass of evolving knowledge Reynolds formulated a classification of neurological diseases that remains the kernel of modern systems. His work in neurology linked the highly original physiological and clinical works of his mentor Marshall Hall to Hughlings Jackson's intellectual explorations of the brain's complex functions and hierarchies, and to the more systematic descriptive neurology of William Gowers.[12] His students included Charlton Bastian (1837-1915) and Sir William Gowers (1845-1915), whose writings often reflect his influence.

Legacy

He was well versed in poetry, philosophy, art, and music. He was married, first, to Margaret Ainslie, and, secondly, to Frances Crespigny, but left no children. He died aged 68 of 'pulmonary congestion' at his home in 1896.

The scholarship and clinical advances made by Reynolds can be seen as important influences on contemporary and also later notable Neurologists at the National Hospital. He bridged the eras of Victorian neurology with that of the dawning 20th century. He was noted as:

> A man of scholarship and wisdom, in his Presidential address in 1894, in a spirit of prophecy he warned the subject-ridden student of to day of the danger of becoming entangled in the net of an ill-considered and misunderstood technical phraseology, and of juggling with words when he ought to be dealing with concrete things.[2]

And Eadie characterised him as:

> A most eminent, scholarly and influential physician who was greatly respected and admired by his contemporaries… the sort of man whose ideas would not readily be discarded because it might almost seem disrespectful to do so unless a better alternative could be clearly demonstrated to exist.[12]

* So-called dissenters (Catholics, Jews, and Quakers) were denied admission because their religious beliefs prevented their taking an oath to adhere to the 39 articles of the Anglican Church. This was abolished by the Universities Tests Act in 1871.

Women had studied at Oxford since the 1870s. But until 1921, they were not entitled to claim the degrees they had earned. Cambridge followed in 1947.

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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

MARCH

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/

BPNS Teaching Course on Peripheral Neuropathy
18 March, 2021; Online
www.bpns.org.uk
E. secretariat@bpns.org.uk

Leading Edge Neurology for the practising clinician 2021
18-19 March, 2021; Online
E. d.blundred@ucl.ac.uk
https://acnr.co.uk/event/leading-edge-neurology-for-the-practising-clinician-2021/

BPNS Spring Meeting
19 March, 2021; online
www.bpns.org.uk, E. secretariat@bpns.org.uk

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

ILAE British Chapter: Purple Day Epilepsy Webinar
26 March, 2021; Online
https://acnr.co.uk/event/ilae-british-chapter-purple-day-epilepsy-webinar/

APRIL

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

SBNS Spring Meeting
15-16 April, 2021; Online
https://acnr.co.uk/event/sbns-spring-meeting-2021/

Child Brain Injury Trust: Rehabilitation , now and the future
20 April, 2021; Online
https://acnr.co.uk/event/child-brain-injury-trust-rehabilitation-now-and-the-future/

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/

MS Advanced 12 - Mod 2
3-14 May, 2021; Sheffield, UK
https://multiplesclerosisacademy.org/events/advanced-masterclass-12-module-2/

Alzheimer's Advanced MasterClass
Module 1: 17-18 May 2021· Module 2: TBC, Sheffield, UK
https://dementiaacademy.co/courses/

Behavioural Therapy Training – Behavioural therapy for tics Institute
18 May, 2021; Online
https://acnr.co.uk/event/behavioural-therapy-training-behavioural-therapy-for-tics-institute/

Cancer Research UK Cambridge Centre Neuro-Oncology Conference 2021
18-19 May, 2021; Online
https://crukcambridgecentre.org.uk

Parkinson's Advanced MasterClass
Module 1: 19-20 May 2021 · Module 2: 7-8 December 2021, Sheffield University Campus
https://parkinsonsacademy.co/courses/advanced-masterclass/

MS Advanced MasterClass 12 – Module 2 - PREVIOUS MODULE 1 REQUIRED
20-21 May, 2021; Sheffield, UK
https://multiplesclerosisacademy.org/events/advanced-masterclass-12-module-2/

KetoCollege 2021
25-27 May, 2021; West Sussex, UK
www.mfclinics.com/keto-college/ketocollege-uk-2020/

2nd International Conference on Neuro-Rehabilitation (NEURAM 2021)
27-28 May, 2021; Balaclava, Mauritius
https://zibrant.eventsair.com/neuram-2020/neuram
E. neuram@bcdme.com
T. 0203 238 8683

JUNE

Alzheimer's Mod 2
8 June, 2021; Sheffield, UK
https://dementiaacademy.co/events/

MS Foundation MasterClass 13.1
9-11 June, 2021; Sheffield, UK
https://multiplesclerosisacademy.org/events/

8th EAN Congress 2021
June 19-22, 2021; Vienna, Austria
www.ean.org/
E. headoffice@ean.org

6th Pacific Rim Conference: #headstogether2021, combined INS, ASSBI, CCN Hybrid Conference
30 June – 3 July 2021, Melbourne, VIC, Australia
https://www.mersevents.com/6th-pacific-rim-conf

JULY

British Neuro-Oncology Society Annual Meeting
8-9 July; Online
https://www.bnosconference.co.uk/bnos-conference/

NR-SIG-WFNR Conference
5-6 July 2021, VIC, Australia
https://www.mersevents.com/18th-nr-sg-wfnr

2nd Targeting Therapy of Alzheimer's and Related Neurodegenerative Diseases Conference
25-28 July, 2021; Lisboa, Portugal
https://www.fusion-conferences.com/conference/128
E. emily@fusion-conferences.com

AUGUST

Edinburgh Sleep Medicine Course
23-27 August, 2021, Edinburgh
https://www.sleepconsultancyltd.co.uk/courses/edinburgh-sleep-medicine/

ESNA Annual Conference (Epilepsy Nurses)
12-13 September, 2021; Glasgow, UK
https://esna-online.org/event/esna-annual-conference

2021 Congress of the European Association of Neuro-Oncology (EANO)
23-26 September, 2021; Online
https://www.eano.eu/eano2021/

SEPTEMBER

VasCog 2021
7-11 September, 2021; Newcastle University, UK
www.vas-cog.com/vascog-2020/
vascogsoc@gmail.com

MS Intermediate MasterClass 14.1
15-17 September, 2021; Sheffield, UK
https://multiplesclerosisacademy.org/events/

MS Advanced MasterClass
Module 1: September 2021 · Module 2: March 2022, Sheffield University Campus
https://multiplesclerosisacademy.org/courses/advanced-masterclass/

ILAE Virtual Scientific Conference
23-24 September, 2021; Online
https://www.ilaebritishconference.org.uk/

The International Spinal Cord Society Annual ASM 2021
30 September-2 October, 2021; Vancouver, Canada and Online
https://www.iscosmeetings2021.org/

OCTOBER

World Congress of Neurology WCN 2021
3-7 October, 2021; Rome, Italy
https://2021.wcn-neurology.com

EAN Regional Teaching Course
4-6 October 2021, Liverpool, UK
https://www.ean.org/learn/educational-events/regional-teaching-courses/rtc-in-liverpool-uk

Parkinson's Foundation MasterClass 41F
12-13 October, 2021; Sheffield, UK
https://parkinsonsacademy.co/courses/foundation-masterclass/

7th Global Medical Symposium on Medical Ketogenic Dietary Therapies
19-23 October, 2021; Brighton, UK
www.globalketo.com
T. 01342 836571
E. info@globalketo.com

NOVEMBER

UKABIF Time for Change Summit
8 November, 2021; London, UK
https://acnr.co.uk/event/ukabif-time-for-change-summit/

MS Advanced MasterClass 15.1
17-19 November, 2021; Sheffield, UK
https://multiplesclerosisacademy.org/events/

MS Academy Basecamp
17-18 November 2021, Sheffield, UK
https://multiplesclerosisacademy.org/courses/basecamp/

***NEW DATE* 2021 Spine Society of Australia 32nd Annual Scientific Meeting**
International Convention Centre, Sydney, Australia
26-28 November 2021
www.dcconferences.com.au/ssa2021

DECEMBER

Encephalitis 2021
7 December 2021
Royal College of Physicians, London (and virtual)
www.encephalitis.info/conference

Parkinson's Advanced MasterClass 40.2A
7-8 December, 2021; Sheffield, UK
https://parkinsonsacademy.co/events/

MS Foundation MasterClass
Module 2: December 2021, Sheffield University Campus, UK
https://multiplesclerosisacademy.org/courses/foundation-masterclass/

MARCH 2022

Posterior Fossa Society – First Global Meeting
March Date to be confirmed, 2022; Liverpool, UK
www.delegate-reg.co.uk/pfs2021/

6th World Parkinson Congress
7-10 June, 2022; Barcelona, Spain
E. info@worldpdcongress.org,
www.worldpdcongress.org

Encephalitis 2020

Conference details: 8th December 2020, Royal College of Physicians, London, UK. Conference streamed virtually. ***Report by:*** Charly Billaud, Institute of Health and Neurodevelopment, Aston University, Birmingham, UK. ***Edited by:*** Dr Ava Easton, Encephalitis Society, Malton, UK.
Conflict of interest statement: None declared.

The 2020 Encephalitis Conference successfully took place during the 2020 COVID-19 pandemic. Despite these challenging circumstances the conference was delivered with a few key personnel present in-person and outside of this digitally to 257 delegates from 34 countries, welcoming researchers and healthcare professionals from around the world interested in a wide range of subjects related to encephalitis.

The Conference began with a session chaired by Dr Benedict Michael, Vice Chair of the Society's Scientific Panel; Consultant Neurologist and Senior Clinician Scientist Fellow at the University of Liverpool, UK.

Dr Cecilia Zivelonghi, from the Department of Neurosciences, Biomedicine and Movement sciences at the University of Verona, Italy, gave a first presentation on SARS-CoV-2 infection. She discussed how COVID-19, a disease that mainly causes respiratory symptoms, also involved anosmia and ageusia, which led to the question of possible central nervous system (CNS) infection. They retrospectively analysed samples referred for antibody screening for SARS-COV-2 IgA and IgG testing, from March 1st 2020 to August 31st 2020. Among 339 patients referred for antibody testing, 23 showed either SARS-CoV-2 IgA and/or IgG (IgA n=9, IgG n=1, IgA and IgG n= 13). Among 21/23 available CSF, 4 were positive (IgG n=3, IgG and IgA n=1). Clinical features, available in all 23 cases, revealed encephalopathy (n=18) and seizures (n=8) as common manifestations and, in 4 cases, myelitis, predominantly with lower limbs weakness. 17/23 patients were systemically asymptomatic. Brain MRI showed FLAIR-T2 hyperintensities in 13/18 patients. EEG showed alterations including epileptic discharges (n=5) and/or generalised slowing (n=12). CSF pleocytosis (>5 cells/μL) was reported in 9/19 investigated cases. The clinical and radiological characteristics were compared with a group of 75 seronegative patients. Autoimmune neurology screening among seropositive cases revealed one patient with serum titin autoantibodies, one with limbic encephalitis and seizures had serum and CSF amphyphisin antibodies, and one presenting with acute disseminated encephalomyelitis had serum and CSF MOG antibodies. The incidence of SARS-CoV-2 IgG/IgA positivity was higher (7.8%, 18% when considering only patients with suspected encephalitis) than that reported in the Italian population (2.5%) and the observed clinical spectrum of disorders suggest that SARS-CoV2 could trigger inflammatory CNS processes, usually not associated with well-known autoantibodies.

Dr Yvette Crijnen, from the Erasmus University Medical Center, Rotterdam, presented a study about the autoimmune aetiology of new onset status epilepticus. Only patients without a known cause were included. Status epilepticus is commonly observed in autoimmune encephalitis, and, in this case, it is best treated with early immunotherapy. Dr Crijnen presented 50 patients with new onset status epilepticus, of whom 38% had a definite or probable autoimmune aetiology. Compared to patients without an autoimmune aetiology, patients with a definite or probable autoimmune cause were younger on average. They more frequently had a super-refractory status epilepticus, a tumour, behavioural changes preceding status epilepticus, abnormal mesiotemporal hyperintensities on MRI scans, as well as increased levels of white blood cells in the cerebrospinal fluid (CSF). A strong majority of the patients with a definite or probable autoimmune cause became seizure free after one year, especially those with antibodies against extracellular antigens. Their study demonstrated that status epilepticus with unknown aetiology frequently has an autoimmune aetiology. Neuronal antibody testing, MRI and CSF assessment can help identify such aetiology in patients with status epilepticus.

Dr Nicholas Davies, Chair, Encephalitis Society Scientific Panel.


Producing a digital conference.


Prof. Tom Solomon delivering the Encephalitis 2020 Presidential Address

Dr Laura Bricio-Moreno, from the Massachusetts General Hospital and Harvard Medical School in Boston, USA, presented on the role of CXCL1 in viral encephalitis, a peptide produced by astrocytes and neurons in response to herpes simplex virus-1 infection, a disease associated with increased CSF neutrophils and inflammatory cytokines. Although treatment has shown a reduction in mortality, the morbidity of such often remains. Dr Bricio-Moreno showed that mice models with HSV encephalitis also had a majority of neurological morbidities, involving blood-brain-barrier (BBB) permeability and increased infiltration of neutrophils and inflammatory monocytes into the brain. Increased presence of CXCL1 was observed, but when deficient in CXCL1-associated receptor CXCR2, mice had reduced clinical severity, a higher rate of survival, reduced recruitment of neutrophils, decreased BBB leakage and viral morbidity. In addition, when neutrophil were depleted in WT mice, there was increased survival and reduced clinical severity, suggesting that neutrophils mediate HSV outcome and morbidity. This work shows that the CXCL1-CXCR2 axis could be a therapeutic target for limiting the morbidity linked to over-exuberant immune response in HSV-1 encephalitis. The potential of corticosteroids to help neutrophil migration was discussed.

Professor Tom Solomon, President of the Encephalitis Society and Professor of Neurology at the University of Liverpool, UK, concluded the first morning session with a presidential address entitled "Encephalitis Research in the Next 25 Years". Prof Solomon highlighted the importance of surveillance in the identification of infectious and autoimmune encephalitis, but also in those with unknown aetiology. International spread of animal or arthropod-borne viruses has increased in the past centuries in part due to the amount and speed of human travel, overcrowded cities, agricultural progress, climate change, and pathogen evolution. Creation of zoonotic research hubs and development of

machine-learning algorithms to predict viral phenomena, newer approaches to diagnosis, and more research on viral co-infections are emerging. Treatment development is also guided by the number of clinical trials which needs to be increased, especially in rare conditions. Furthermore, vaccines are being developed and more widely used with the current pandemic demonstrating how fast things can happen. The need to anticipate new pandemics in neuroscience, the importance of raising awareness of the excellent risk-benefit ratio of vaccines, the potential of neuroprotective treatments for elderly populations and the need to improve access to basic clinical protocols were discussed.

The second morning session was chaired by Dr Jessica Fish, Clinical Psychologist and Lecturer at the Institute of Health & Wellbeing, University of Glasgow, UK.

Dr Mette Scheller Nissen, from Odense University Hospital, Denmark, presented on 55 patients with anti-NMDAR encephalitis. The majority had a definite diagnosis of autoimmune anti-NMDAR encephalitis, and they could be subdivided into three categories, pure-, post-HSE or NMDAR encephalitis alongside other comorbidities (paraneoplastic and demyelinating). Memory impairment and sleep disturbances were rare in children, and abnormal movements were rare in adolescents. Cognitive decline, behavioural and psychiatric symptoms were relatively common in all age groups. The majority of the cases had abnormal CSF and EEG observations, and MRI abnormalities were found in approximately half of patients. PET revealed a majority of abnormal scans, mostly occipital and fronto-temporal, in almost half of patients with a normal MRI. Almost all of them received first line therapy and maintenance treatment, with only a quarter of patients receiving second line treatment. In an average follow up of two years and two months most patients with pure NMDAR encephalitis had a good clinical outcome, with much less among those with post-herpes simplex or other types. Awareness in paediatric patients and fast diagnosis and treatment remains important.

Dr Greta Wood, from Royal Liverpool University Hospital, UK, introduced a retrospective study on the predictors of seizures in encephalitis. Seizures affect large proportions of patients, although its effects and risk factors are unclear. Dr Wood presented a cohort of 203 patients from 24 hospitals across England, in which 121 had one or multiple episodes of seizures, or status epilepticus. The three most common aetiologies were infectious (including HSV), autoimmune (including encephalitis associated antibodies), or unknown. Most patients had seizures, focal and/or generalised: they were frequently multiple but there was also status epilepticus. Seizures were significantly associated with antibody or HSV related aetiologies. These were also associated with fever, reduced Glasgow Coma Scale (GCS, measuring levels of consciousness) on admission, and a worse clinical outcome. The aetiology, reduced presence of focal neurology signs, and lower GCS were the key predictors of seizures both during the first stage of the illness and in the inpatient period. This confirmed past research on correlates of seizures in encephalitis: the data highlighted the need to identify potential outcomes and anticipate their consequences. The discussion mentioned the lack of associations with MRI abnormalities and the possible findings of quantitative analyses, as well as the need to identify underlying mechanisms.

Vasundharaa S Nair, a PhD Researcher at the National Institute of Mental Health and Neurosciences in Bangalore, India presented factors that limited or facilitated reception of care in India, for persons with acute brain infections. Patients had diverse social and religious backgrounds, and most participants had a low socio-economic status. Ms Nair exposed two types of pathways that led to access to neurological services care. Most patients followed the medical model that directly went through General Practitioners referring to the services. A minority went through traditional methods: relatives would first refer to a traditional healer, with rituals lasting days against a perceived curse or a divine punishment. Some were also advised to meet priests in churches due to sin or possession, who then would refer them to a physician. The latter would then give referral to neurological services. The presentation also showed the costly impact of health care requests, requirement of funding schemes, concerning the need for psychoeducation, work support or follow-up therapies. Lack of awareness, cultural practices, misinformation, unaffordability or unavailability of care, and lack of adequate policy planning were the main barriers to treatment. Facilitators were the understanding of the medical model by religious referents, adequate awareness and acknowledgement of the disease, and accessibility to physicians and healthcare services.

Dr Frederik Bartels, from the Charité University Hospital at Berlin presented a study describing longitudinal changes in brain volumes of patients with anti-NMDA receptor encephalitis. Considering past reports of cases with long-term atrophy, Bartels presented quantitative analyses of MRI scans that were run over a median follow-up period of three years in a cohort of patients from the German Network for Research on Autoimmune Encephalitis. Around half of the cohort presented with abnormal MRI scans. The analyses allowed to test differences in brain volumes from the first to the last MRI. They showed that the annualised percentage of brain volume decreased over time while ventricular volumes increased. More specifically, white matter, but not grey matter, was subject to a significant decrease in the following scans. The volume reduction rate exceeded the pathological cut-off values that had been defined in multiple sclerosis with a similar age. High heterogeneity in volume trajectories and severe atrophy were also observed in individual evaluations. This led to the conclusion that brain atrophy was present in anti-NMDAR encephalitis, although with high variability in individual brains, specifically driven by white matter loss.

The morning sessions ended with the first Keynote lecture by Professor Carsten Finke, from the Berlin School of Mind and Brain and Charité University Hospital, Berlin. Professor Finke focused on the information about the cognitive deficits in the years following anti-NMDA receptor encephalitis. Although many patients have a good neurological outcome using the modified Rankin scale, the discrepancy with persisting cognitive deficits was pointed out. One explanation for this is the impact of NMDA receptors in the hippocampus, a key region for memory processing. Mostly executive functions and memory deficits are found in long-term outcome. Predictors of these deficits included delayed treatment, higher disease severity and older age. Routine MRI reported relatively rare abnormalities but was found to be a predictor of long-term deficits. Functional MRI may be more sensitive: studies show abnormal spontaneous brain activities and reduced connectivity between regions, including the hippocampus, but also large networks correlated to cognitive performance. These differences also changed over time in dynamic connectivity analyses. Volumetric analyses of MRI scans also demonstrate volume and shape alterations of the hippocampus and white matter tracts, both correlating with cognitive performance. MRI studies are also relevant in children where much higher abnormalities and alterations were found in long-term brain development. Potential functional neuroplastic improvement in younger patients was discussed.

After lunch Dr Nicholas Davies, Chair of the Encephalitis Society Scientific Panel and Consultant Neurologist at Chelsea and Westminster, Charing Cross and the Royal Marsden Hospitals, London, UK, chaired the third session.

Dr Priya Thomas, from the National Institute of Mental Health and Neurosciences, in Bangalore, India, presented an exploratory study aiming at identifying the consequences of encephalitis in young adults and their families. Patients in South India who presented in a neurology department in a tertiary referral care centre were interviewed to collect information about how remission from the disease was managed by families and healthcare services with limited resources. How the illness changed their lives and relationships, the need for accurate information about what to expect, and the need for care support of families were recurrent themes. In the weeks following discharge from acute care, patients experienced a range of symptoms including headache, fatigue, seizures, motor and language difficulties, or memory loss. Dr Thomas concluded that it is important to understand and identify the consequences of the disease and its varying aetiologies, so that

better health care and long-term support can be provided in these families and communities. The opportunity for these findings to impact institutional and regional policies in India was also raised during the discussion.

The next presentation was led by Dr Anna EM Bastiaansen, from the Erasmus University Medical Center, Rotterdam. Dr Bastiaansen presented an observational nationwide study of a Dutch cohort diagnosed with anti-NMDAR encephalitis. The cell-based assays and immunochemical analyses that were run proved to be more sensitive to the diagnosis of the disease when dealing with CSF cells rather than blood serum cells: this was an indication that CSF tests should be recommended when suspecting anti-NMDA receptor encephalitis. Patients with an onset of the disease after 45 years less frequently had behavioural symptoms, seizures and seropositivity. Furthermore, they had a higher rate of delayed improvement (in coming back to an independent lifestyle), poor outcome after 1 year, and death. Common association of the disease with cancerous carcinoma was found in elderly patients. It also showed that second line immunotherapy led to recovery in a median of 61 days. This demonstrated that late onset of anti-NMDAR encephalitis is not as uncommon as previously thought and can lead to a worse outcome and delayed remission.

The second keynote lecture was given by Dr Benedict Michael, Vice Chair of the Society's Scientific Panel, Senior Clinician Scientist Fellow at the NIHR Liverpool and Honorary Consultant Neurologist at the Walton Centre, Liverpool, UK. Dr Michael presented how the SARS-Cov2 virus affected the brain, the evidence known to date and how it can be addressed. As encephalitis involves infectious and auto-immune inflammation with direct and consequent phenomena, COVID-19 could be the cause of associated neurological disorders. Although biologically plausible, the evidence is still debated as encephalitis was found in low proportions of patients, with unspecific effects. However, there may be a neglect of symptoms resulting from cerebrovascular events like headaches and anosmia, as well as data that clinicians do not have the time to collect. Neuropsychiatric and cerebrovascular events were found in several patients with COVID-19 including delirium and inflammation in the nervous system. Cases of encephalopathy have also been found with MRI, but findings may be limited due to the difficulty of scanning ventilated patients. Dr Michael presented the COVID-Clinical Neuroscience Study that is currently investigating neurological complications, their mechanism, the role of biomarkers, and how to prevent long-term disabilities. Unresolved questions remain about the possible continuum of encephalitides across patients, including those that may have been unidentified.

Josephine Heine, a Cognitive Neuroscientist and PhD Researcher at the department of Neurology at Charité University Clinic in Berlin presented a study that looked at health-related quality of life (HRQoL) in recovering patients with anti-NMDA receptor encephalitis. The study showed that patients with anti-NMDAR encephalitis reported a lower HRQoL compared to the norm, despite good physical outcomes. Ms Heine exposed perceived burdens years after the onset of the disease, including seizures, fatigue and sleep problems, cognitive symptoms, and affective and behavioural symptoms. Additionally, higher prevalence of depression and anxiety, and reduced sleep quality was correlated negatively with HRQoL. Among subjective burdens, persisting seizures had the worst effect on HRQoL. Factors that correlated with higher HRQoL were greater day-to-day independence, fewer depressive symptoms, higher self-efficacy and higher satisfaction with one's own memory abilities. The latter was higher than the population norm, even though actual lower memory performance was found, which might reflect a bias resulting from remission. Less frequent use of negative stress coping strategies also contributed to a better HRQoL: this could benefit from behavioural intervention. The study therefore highlighted the long-term contribution of under-reported factors that affect quality of life and may require further support during recovery from anti-NMDAR encephalitis.

This first afternoon session concluded with research funded by the Encephalitis Society. The first study was presented by Dr Aline de Moura Brasil Matos, Neurologist and PhD Researcher from the Tropical Medicine Institute at the University of São Paulo, Brazil. She gave a focus on demographic and clinical data obtained in patients with Chikungunya virus (CHIKV), followed in Brazil from 2017 to 2019. CHIKV is also thought to be an aetiological agent in encephalitis: the latter was detected in the majority of patients, among whom 37.5% died. The main mortality risk factors included hypertension, diabetes, required mechanical ventilation, seizures, acute kidney injuries, male gender and an age over 60. The relation of neurobiology data and population dynamics was discussed.

The second study was presented by Charly Billaud, a PhD student from the Institute of Health and Neurodevelopment at Aston University, Birmingham, UK. He presented behavioural and emotional profiles in a cohort of children with autoimmune encephalitis, which raised concerns about the difficulties faced among peers, conduct, emotions, prosocial behaviours, and hyperactivity. Overall, these difficulties were considered slightly raised in the general population norm but showed proportions of children with specifically more difficulties in these different areas, in a similar fashion to children with general neurology disorders. Behavioural analyses are to be used in a project involving neuroimaging-guided predictions that may help clinicians anticipate these future difficulties.

The last session was chaired by Ava Easton, CEO of the Encephalitis Society and Honorary Fellow, Dept. Clinical Infection, Microbiology and Immunology at the University of Liverpool.

Dr Easton interviewed Brian Deer, an investigative journalist known for his inquiries into the drug industry, medical and social issues for The Sunday Times. He provided a reading from his new book "The Doctor who fooled the world", which explores disgraced Doctor Andrew Wakefield's controversial war against MMR vaccines. Deer exposed how clinical research was manipulated and conducted unethically, to the detriment of both the deceived public and the patients and their families, for the purpose of proving a link between the MMR vaccine and autism that in fact did not exist. The interview went into details about how Wakefield's attempt to prove that vaccines caused neurodevelopmental issues had gone through grievous biases and research misconducts, as well as cover ups and costly legal battles. This was an example of deception and fraud that needs to be dealt with in biomedical research, not only on the part of Wakefield but also the system that allowed such research to happen.

Dr Ava Easton began to close the conference with a Call to Action relating to the Encephalitis Society's situation going through the pandemic. She showed a video summarising what the Encephalitis Society has gone through during this pandemic year including how the charity has pivoted quickly and developed digitally for their beneficiaries. They have however lost significant fundraising events leading to income shortfalls, in direct contrast to a significant increased demand for help.

Dr Nicholas Davies and Dr Ava Easton then presented the awards and prizes for best poster and best oral presentations:

Best poster for "Factors predicting patient quality of life after LGI1-antibody encephalitis" to Dr Sophie NM Binks, from the Oxford Autoimmune Neurology Group, at the Nuffield Department of Clinical Neurosciences of the University of Oxford, UK, (with colleagues M Veldsman, S Jacob, P Maddison, J Coebergh, S Michael, S Ramanathan, Easton A, M Scheller Nissen, M Blaabjerg, Leite M Isabel, D Okai, M Husain, SR Irani).

Best oral presentation for "Barriers and Facilitators in seeking care for Persons with Acute Brain Infections" to Vasundharaa S Nair from the Institute of Mental Health and Neurosciences, Banglalore, India.

The conference concluded with thanks to the conference sponsors and a closing call to action from Dr Ava Easton and Dr Nicholas Davies to get involved with World Encephalitis Day on 22nd February.

Encephalitis 2021 will be held at the Royal College of Physicians, London on 7th December 2021. You will be automatically notified if you are a professional member of the Society (membership is free) or you can find out more here: www.encephalitis.info/conference

Improving Stroke Care: The UK Stroke Forum 2020

Conference details: 7-9 December, 2020. Conference streamed virtually. ***Report by:*** Georgina Hill, Research Communications Manager at the Stroke Association.
Conflict of interest statement: None declared.

The 15th UK Stroke Forum (UKSF) took place virtually for the first time ever, last December (7-9). Around 1800 delegates took part to make this the best attended Forum in its history.

The UK Stroke Forum is a coalition of over 30 organisations who are all committed to improving stroke care in the UK and is funded by the Stroke Association and the British Association of Stroke Physicians. Highlights of this years' programme are outlined below.

Day 1

Juliet Bouverie OBE, CEO of the Stroke Association, opened #UKSF20 and shared some of the biggest innovations in stroke research from the past year. She talked about positive results from a trial of Vagus nerve stimulation for upper limb rehabilitation, the launch of the UK Communication Access Symbol, which was co-ordinated by the Royal College of Speech and Language Therapists and the launch of the Getting It Right First Time National Stroke report.

Delegates saw powerful videos from stroke survivors, clinicians and researchers who shared their experiences of living and working during the COVID-19 pandemic. Juliet highlighted how the Stroke Association has adapted its services to support stroke survivors during the pandemic and the charity's influencing to ensure that stroke remains a national priority.

Dr Deb Lowe, National Clinical Director for Stroke NHSE&I spoke passionately about the new NHS People Plan 2020/21; highlighting that it is more relevant than ever, but "means nothing until we make it so." The event allowed Deb to reflect on the efforts of health and social care staff and how they'd adapted during the COVID-19 pandemic. Deb expressed that the year had "shone a light on the power of the NHS and its people" and "that we are stronger together than individuals."

Dr Richard Smith, London School of Hygiene and Tropical Medicine delivered an insightful talk on the role health services play in mitigating the climate crisis, outlining the pathway to a net zero health service.

Without a doubt, the pandemic has sparked challenges and opportunities in stroke care. This was discussed during a training session on remote rehabilitation chaired by Dr Lisa Kidd, University of Glasgow and Dr Lesley Scobbie, Glasgow Caledonian University. Speakers Dr Rebecca Fisher, University of Nottingham, Dr Nicola Hancock, University of East Anglia, and Ms Charlie Dorer, Cambridgeshire and Peterborough NHS Foundation Trust covered topics including how stroke survivors can continue to get the support they need and gain access to rapidly developing resources for health and social care professionals.

This was followed by a series of parallel sessions looking at emerging evidence that addresses key questions on COVID-19 and stroke, upper limb function and dysphagia after stroke.

To conclude, delegates were presented with a whistle stop tour of the methods and recommendations in the Getting It Right First Time stroke work stream, to improve the stroke service delivery model at all points in a stroke patient's care journey.

Day 2

Prof Avril Drummond, University of Nottingham opened Day 2 by highlighting the need for big ambitions in research and clinical practice to help support even more stroke survivors to rebuild their lives. This includes trialling new research methods and uniting the research community to increase funding for stroke research.

Parallel sessions looked at emerging evidence on thrombectomy, post-stroke fatigue and telemedicine. There was particular interest in the telemedicine session due to the rapid and significant changes in how rehabilitation has been delivered during the COVID-19 pandemic, with an increase in the use of audio and visual technologies. The general consensus was that these changes can help to reach stroke survivors over a wider geography and more quickly, however these innovations need further evaluation to make sure they are effective and accessible to all stroke survivors.

A training workshop brought together diverse perspectives on stroke

care at 10 minutes, 10 weeks and 10 years, highlighting that people affected by stroke are not getting the support they need throughout their recovery – which can be a life-long process.

Day 3

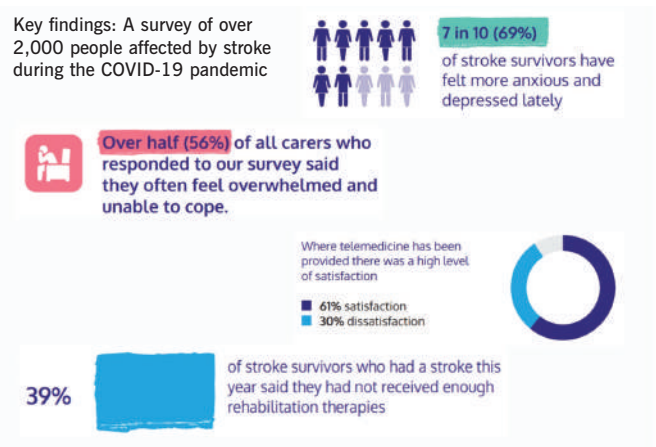
On the final day, latest research advances were presented in supported self-management and person-centred long-term care, supporting stroke survivors with aphasia and management of high blood pressure, the biggest risk factor for stroke.

The final session tied together a focus throughout the conference – inequalities in stroke risk, treatment and care – and looked at ways to tackle this.

To conclude, delegates celebrated the achievements of prize winners, including, Prof Marion Walker and Prof John Bamford who were awarded prizes for their contributions to driving improvements in stroke treatment and care.

As this year's event was virtual, it was easier than ever before to view posters and the exhibition hall. There were also virtual networking rooms and delegates have the opportunity to catch up on all the sessions – which are available online until March 2021. This year's event highlighted the huge progress that has been made in stroke research and care during a particularly challenging time, and sparked empowered discussions on how to overcome obstacles that remain, so that stroke survivors get the treatment, care and support they need to rebuild their lives.

Look out for registration and more information on UKSF 2021 conference at: www.stroke.org.uk/uksf



Stroke Recoveries at Risk, Stroke Association, September 2020

NeuroLifeNow App

The Brain & Spine Foundation and The Neurological Alliance have come together to launch a new App and website to support people with neurological conditions to more easily share their experience of healthcare.

NeuroLifeNow will encourage people with any neurological condition to report what their life has been like during this pandemic, and how they are accessing care on a monthly basis through a patient survey. In return, people will receive monthly updates about what the neurological community are experiencing, access to support services provided by the Brain & Spine Foundation, as well as have the opportunity to directly shape the future of the platform.

Experiences shared via the App will be used to influence how neurological services are funded and delivered. It is the first time a digital tool has been developed to capture patient experience data on a continuous basis across all 'neurological' conditions. It puts 'lived experience' at the heart of learning about how to deploy and develop services at a time when the NHS is under pressure to create more agile ways of working. We hope to have 1000 responses to the questionnaires by the end of March 2021.

Find out more about NeuroLifeNow: www.neurolifenow.org

NeuroLifeNow
It's time to make your story heard

Aquilion ONE GENESIS Edition CT Scanner

Photo caption: (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.

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 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.

Despite the Coronavirus pandemic, 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 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.

https://uk.medical.canon

BIAL takes the lead in Europe for the commercialisation of epilepsy treatment, Zebinix® (eslicarbazepine acetate), expanding neurology footprint

- *BIAL has announced the end of the licence agreement established in 2009.*
- *BIAL takes the lead for the marketing and distribution of Zebinix® (eslicarbazepine acetate) in Europe.*
- *Eslicarbazepine acetate is a once-daily anti-epileptic used to treat epilepsy patients with focal seizures (partial-onset seizures).*

Bial

For over a decade, BIAL and Eisai have had an agreement in place for Eisai to market, promote, and distribute eslicarbazepine acetate in Europe. Following the end of this partnership, BIAL will take the lead for the ongoing marketing, promotion and distribution in Europe. This move reinforces its continued commitment to and ongoing investment in neurological conditions.

BIAL has over 10 years of experience of delivering life-improving medicines for neurological conditions such as epilepsy and Parkinson's disease. Eslicarbazepine acetate was the first medicine discovered and developed by BIAL. Each month more than 90,000 people with epilepsy around the world benefit from eslicarbazepine acetate to meet their treatment needs.

BIAL has worked closely with the relevant organisations from around Europe to put in place all the supply, quality and pharmacovigilance processes that are needed to ensure a seamless transition for both healthcare professionals and patients. All required drug safety and medicine continuity measures have been secured to ensure an uninterrupted treatment supply for all those who need it.

Following a constructive partnership with Eisai, we are excited to be taking the lead on the commercialisation of eslicarbazepine acetate in EuropeIt was the first medicine to be developed through BIAL's own research and is a valuable part of our portfolio as we continue to expand into new territories, building on our established heritage and making life better for all those affected by epilepsy.

José Almeida Bastos, Chief Commercial Officer of BIAL

Neil West, Vice President EMEA, Global Neurology Business Unit from Eisai, also commented, "We have enjoyed working alongside BIAL, providing our extensive commercialisation experience for the marketing and distribution of this important treatment. We believe eslicarbazepine acetate has made a real difference to patients' lives during this period and are proud of our contribution."

For more information on BIAL: www.bial.com
For more information on Zebinix®: https://www.ema.europa.eu/en/medicines/human/EPAR/zebinix#product-information-section

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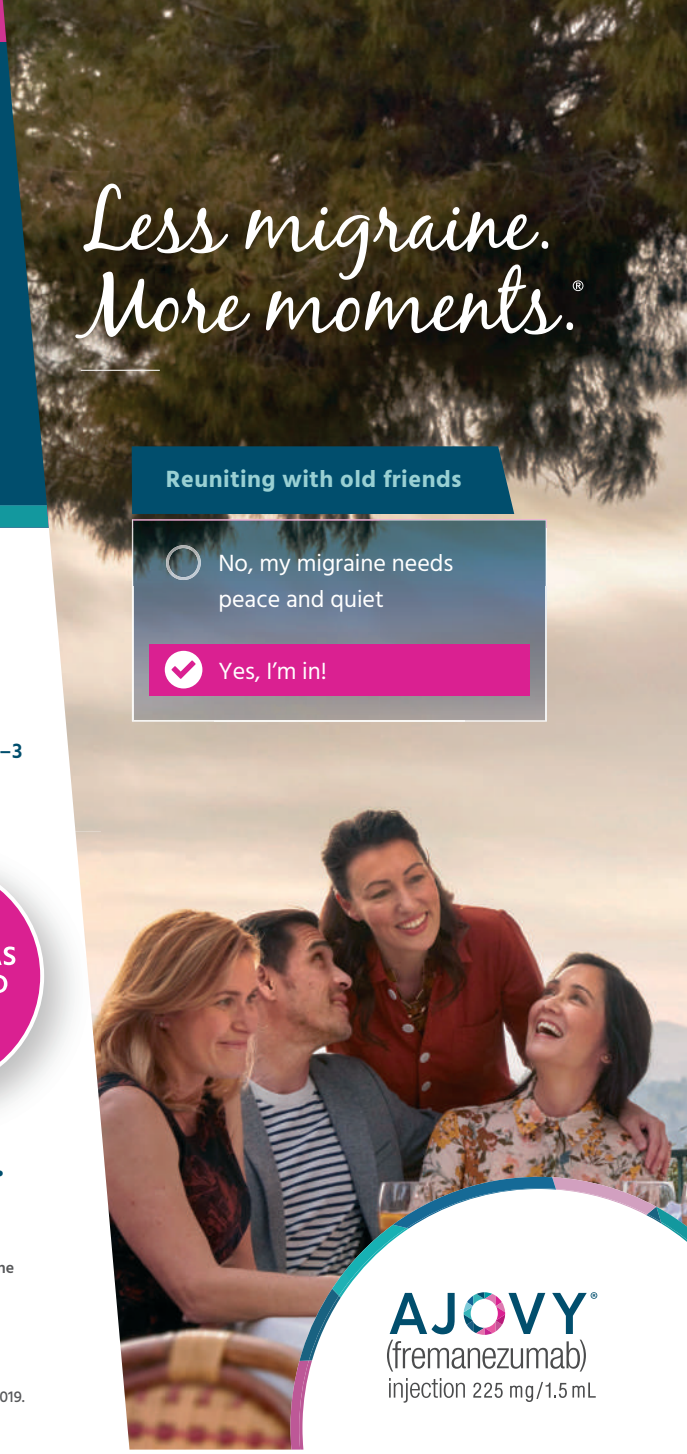

AJOVY® is indicated for prophylaxis of migraine in adults who have at least four migraine days *per* month[1]

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- **Studied with and without a concomitant oral preventive[1]**
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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 medications[2]
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.

AJOVY® (fremanezumab) injection 225 mg/1.5 mL

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@tevauk.com

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. No data in severe renal impairment. *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 biological 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 breast-feeding. **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.

AJO-GB-00023 Date of Preparation: September 2020

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