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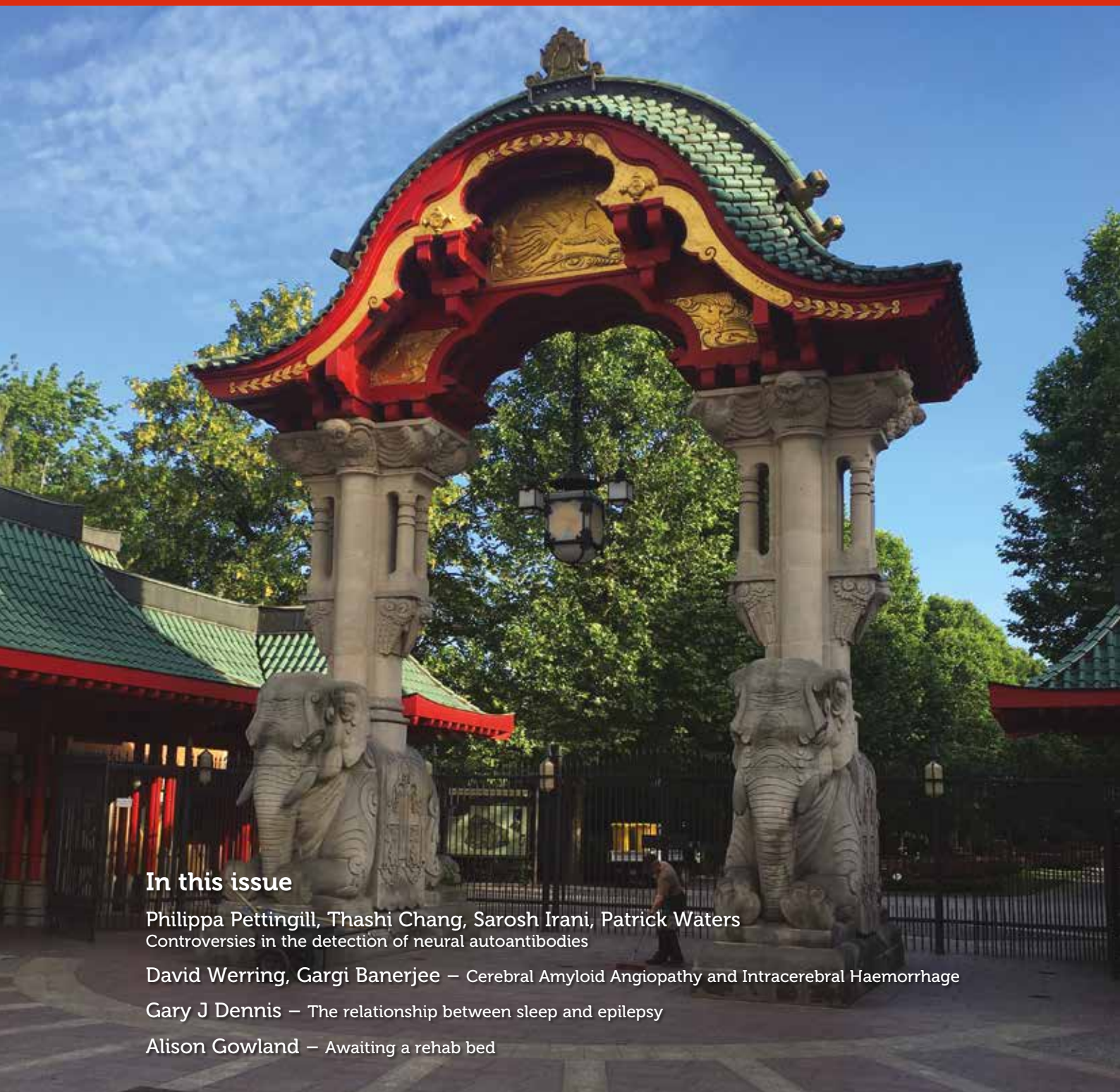
ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION



In this issue

Extending Choice in Parkinson's Disease

Xadago is indicated as adjunctive therapy for the treatment of adult patients with idiopathic Parkinson's disease (PD) as add-on to a stable dose of levodopa alone or in combination with other PD medications in mid-to-late-stage fluctuating patients.

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Consult Summary of Product Characteristics before prescribing.

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Marketing Authorisation number and basic NHS cost: EU/1/14/984/001-005, EU/1/14/984/006. NHS list price: £69.00 x 30 tablets for both 50/100mg.

Presentation: Each film-coated tablet contains safinamide methansulfonate equivalent to 50 or 100mg safinamide.

Uses: Xadago is indicated for the treatment of adult patients with idiopathic Parkinson's disease (PD) as add-on therapy to a stable dose of Levodopa (L-dopa) alone or in combination with other PD medicinal products in mid-to late-stage fluctuating patients.

Dosage and administration: Treatment with Xadago should be started at 50 mg per day. This daily dose may be increased to 100 mg/day on the basis of individual clinical need. If a dose is missed the next dose should be taken at the usual time the next day.

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Xadago may be used with selective serotonin re-uptake inhibitors (SSRIs) at the lowest effective dose, with caution for serotoninergic symptoms. The concomitant use of Xadago and fluoxetine or fluvoxamine should be avoided, or if concomitant treatment is necessary these medicinal products should be used at low doses. A washout period corresponding to 5 half-lives of the SSRI used previously should be considered prior to initiating treatment with Xadago.

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Safinamide used as an adjunct to levodopa may potentiate the side effects of levodopa, and pre-existing dyskinesia may be exacerbated, requiring a decrease of levodopa.

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Interactions:

Concomitant administration of dextromethorphan or sympathomimetics such as ephedrine or pseudoephedrine, requires caution.

Serious adverse reactions have been reported with the concomitant use of selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic/tetracyclic antidepressants and MAO inhibitors. In view of the selective and reversible MAO-B inhibitory activity of safinamide, antidepressants may be administered but used at the lowest doses necessary.

Xadago can be used safely without any dietary tyramine restrictions.

Side Effects:

Consult the summary of product characteristics for other side effects.

Serious adverse reactions are known to occur with the concomitant use of SSRIs, SNRIs, tricyclic/tetracyclic antidepressants and MAO inhibitors, such as hypertensive crisis, neuroleptic malignant syndrome, serotonin syndrome, and hypotension. Impulse control disorders; can occur in patients treated with dopamine agonists and/or other dopaminergic treatments. Other serious adverse reactions include bronchopneumonia, basal cell carcinoma, leukopenia, delirium, suicidal ideation, glaucoma, diabetic retinopathy, eye haemorrhage, keratitis, papilloedema, hallucination, depression, compulsions, delirium, suicidal ideation, impulse disorders, myocardial infarction, hyperkalaemia, peptic ulcer, upper gastrointestinal haemorrhage, hyperbilirubinaemia, ankylosing spondylitis, electrocardiogram QT prolonged and fat embolism, photosensitivity.

Common undesirable effects include insomnia, dyskinesia, somnolence, dizziness, headache, Parkinson's Disease, cataract, orthostatic hypotension, nausea and fall.

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Reporting forms and information can be found at www.mhra.gov.uk/yellowcard

Adverse events should also be reported to Profile Pharma Ltd. at profile.drugsafety@ZambonGroup.com

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Front cover picture: The cover picture this issue is of Berlin Zoo. See Tom Foltynie and James Gratwicke's report on page 27 from the 20th International Parkinson's Disease and Movement Disorders Society Meeting in Berlin.

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Sian Alexander, Co-Editor.

Welcome to another edition of ACNR – the first of the post-Brexit era, and in a time of economic and political turmoil in the UK and across Europe.

As a trainee neurologist, I am particularly appreciative when experts in a particular area present an expert opinion or summarise weighty trials in a way that I can use in everyday practice. Several of the articles in ACNR are good examples of this. Cerebral Amyloid Angiopathy, a diagnosis often made only by the availability of MRI technology, is discussed by Gargi Banerjee and David Werring; Philippa Pettingill and colleagues discuss the current techniques and limitations of autoantibody assays used in clinical practice; and Gary Dennis discusses the complex relationship between epilepsy and sleep in the second of our Sleep Series.

We also have articles reflecting our patients' experiences of neurological illness. This includes one optimistic article about an individual's experience of living with epilepsy, the support she's received in managing her condition including from charity Young Epilepsy and her surprise at the difficult adjustment to life without seizures.

Alison Gowland contributes her thoughtful British Society of Rehabilitation Medicine Student's Prize Essay Waiting for a Rehab Bed on the frustrating mismatch between patient, doctor and therapists' aspirations of early and effective rehabilitation, and service availability for many patients; a theme that is likely to resonate with many.

Our conference section includes a comprehensive report on the Movement Disorders Society meeting in Berlin by Tom Foltynie and James Gratwicke, and from Tom Jenkins on the ABN in Brighton.

We also have a report on the Festschrift of Peter Sandercock in Edinburgh, celebrating his career, his achievements and his contribution to stroke research. We at ACNR have appreciated Peter's contributions and support over the years and wish him all the best in his retirement.

Sian Alexander, Co-Editor.
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Editorial board and contributors

Philippa Pettingill

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Conflict of interest statement:
PP, SRI and PW are named inventors on patents for antibody assays. SRI and PW have received royalties. PW has received speaker honoraria from Biogen Idec and Euroimmun AG, and travel grants from the Guthy-Jackson Charitable Foundation. TC has no disclosures.

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Controversies in the detection of neural autoantibodies

Abstract
The last 15 years has seen the discovery of treatable antibody-mediated CNS diseases. The accurate detection of specific antibodies helps support patient diagnosis, treatment and predict prognosis. Here we discuss some of the limitations of different antibody detection technologies, caveats in study designs that impacts on the interpretation of assays for routine clinical use and highlight a lack of data on serum versus CSF testing in this new field of neuroimmunology.

Introduction
In the last 15 years, multiple central nervous system disease-associated and likely disease-causing antibodies have been discovered.[1-5] These autoantibodies bind the extracellular portion of proteins expressed in the central nervous system and lead to a loss of protein function, typically either by cross-linking and internalisation, or complement-mediated destruction of the cell expressing the antibody target. The detection of these antibodies is important for patient diagnosis, prognosis and management.

Pathogenic antibodies versus biomarkers
Indirect immunohistochemistry (IHC) on frozen tissue sections and immunoprecipitation of radiolabelled brain extracts have been the mainstay of diagnostic laboratories for decades, and have been a part of the process of antibody target discovery.[1,6] These methods do not distinguish between antibodies that bind cytosolic or nuclear targets that are considered epiphenomena, but are useful biomarkers often of paraneoplastic disease, and antibodies that bind native, surface-expressed glycoproteins that have pathogenic potential. Biomarker antibodies most often bind denatured protein and are routinely detected by line blot assays, whereas pathogenic antibodies require native three-dimensional structures as their assay substrate. Understanding this important difference has led to the development of new ways to detect these recently-discovered neuronal surface autoantibodies (NSAbs; Figure 1). Known NSAb targets include the N-methyl-d-aspartate receptor (NMDAR), aquaporin-4 (AQP4), myelin oligodendrocyte glycoprotein (MOG), leucine-rich, glioma-inactivated 1 (LGI1), gamma aminobutyric acid receptor B ($GABA_BR$), gamma aminobutyric acid receptor A ($GABA_AR$) and contactin-associated receptor protein 2 (CASPR2).[1-3]

The more recently developed assays use live primary cultures or transfected mammalian cells as their substrates (highlighted in blue in Figure 1). Primary cultures, which are still predominantly research tools, are used to demonstrate the presence of antibodies in serum or CSF which are likely to impact on live cell function. The cultures are often hippocampal neurons, astrocytes or oligodendrocytes. These are low throughput tests requiring two to three weeks in culture before antibody testing is possible, and are not antigen-specific. In addition, the lack of any architecture in this system can impact on protein expression and antibody binding. For example, astrocytes express low levels of membrane AQP4 in culture, whereas dense arrays of AQP4 are seen on the astrocyte end-feet that abut blood vessels in tissue.

When the antibody target is known, the wide availability of cDNA encoding human genes has enabled the development of antigen-specific cell based assays.[2,6] Mammalian cells transiently or stably transfected with a specific target express native protein on the cell surface that is most often detected with fluorescent secondary antibodies. The binding is visualised by microscopy or quantified by flow cytometry. This has become the method of choice in recent years to detect these newly identified pathogenic antibodies, and can be modified for high-throughput.[6] Controls include observing serum binding to cells transfected with a different protein or use of untransfected cells to confirm specific binding to the target protein and for quantitative assays determination of cut-offs using healthy control sera are important.

Assessment of assays: developing a paradigm?
CNS diseases associated with NSAbs are important as they often respond to immunotherapies, but they are rare. It

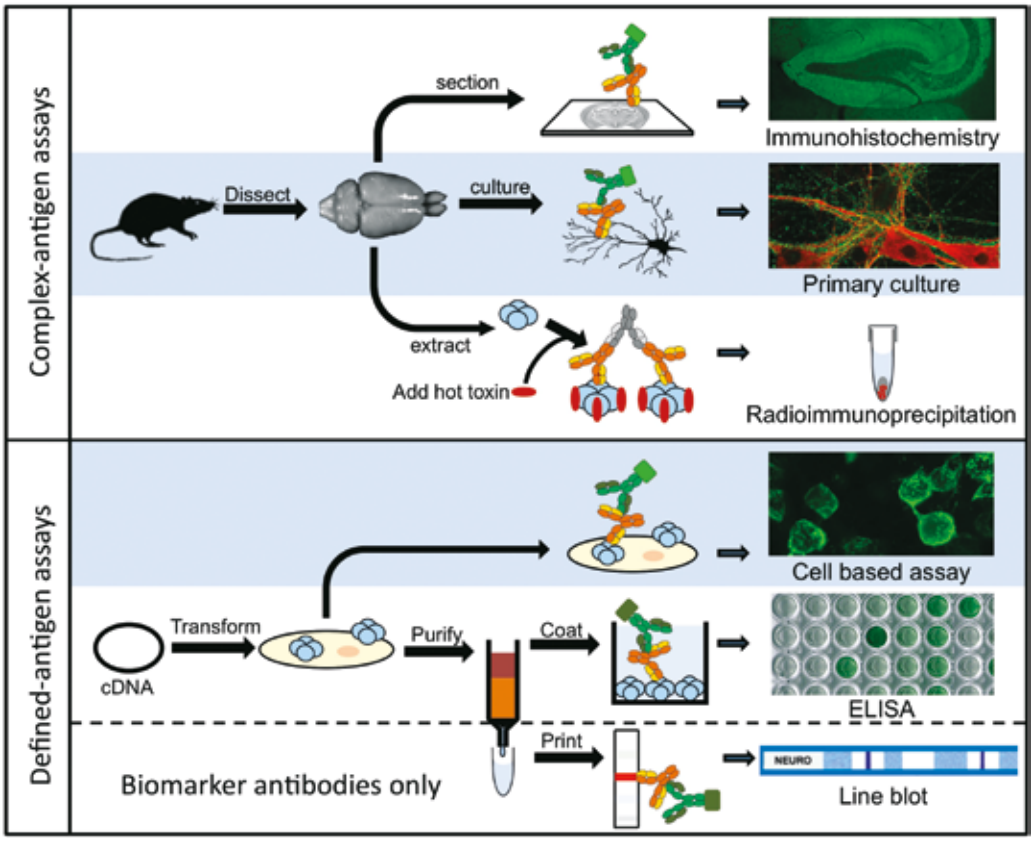

Figure 1. Assays used to detect antibodies are based on different substrates. Non-human tissue is often used to provide a complex substrate for immunohistochemistry, primary cultures and radioimmunoprecipitation assays, where the presence of antibody binding does not indicate a specific antibody target. Plasmids that express an individual protein are used in antigen specific assays such as cell based assays, ELISA and line blots. Assays on a blue background specifically identify antibodies to native protein expressed on the cell surface, all other assays can identify non-surface determinants. The orange antibodies represent patient antibody that binds the target, the green antibody represents the secondary antibody fluorescently or enzymatically labelled and the grey antibodies are anti-human IgG secondary antibodies used to immunoprecipitate the antibody-antigen complex.

is impractical to determine the true sensitivity or specificity of these assays when the prevalence is a few patients per 100,000. Hence, in the field of NSAb detection, the term 'sensitivity' is often used to describe the number of positives identified in a cohort of clinically-defined patients. For example, in AQP4-antibody assays, patients with clinically definite NMO are often used to determine assay sensitivity. The most useful controls to define assay specificity are often patients with a clinical overlap that are pathologically different, such as patients with multiple sclerosis in the case of NMO. Be aware that there is a risk of misdiagnosis in patients with clinical overlap. Importantly, double-blinding of assay interpretation should be part of the study design: no antibody information is available to the clinicians and no clinical details are available to the laboratory scientists. This seems a reasonable study set-up,[7] but it has caveats.[8] The small cohort size, often less than 100 patients per group, means that a few samples can have a large effect on the final assay sensitivity and specificity. This makes it difficult to draw conclusions about the metrics of an assay from different studies even when identical clinical criteria are used to define the patient cohorts (see ref 8 for discussion). To circumvent this issue, the same samples should be tested on different assays for the same antigen. Also, as seen in patients with NMO, there are clinically indistinguishable patients that are likely to be truly seronegative who have different treatment requirements. Separating these patients is an important aspect of diagnostic assays that is subsumed within the clinically-definite cohort in this study design, so not examined.

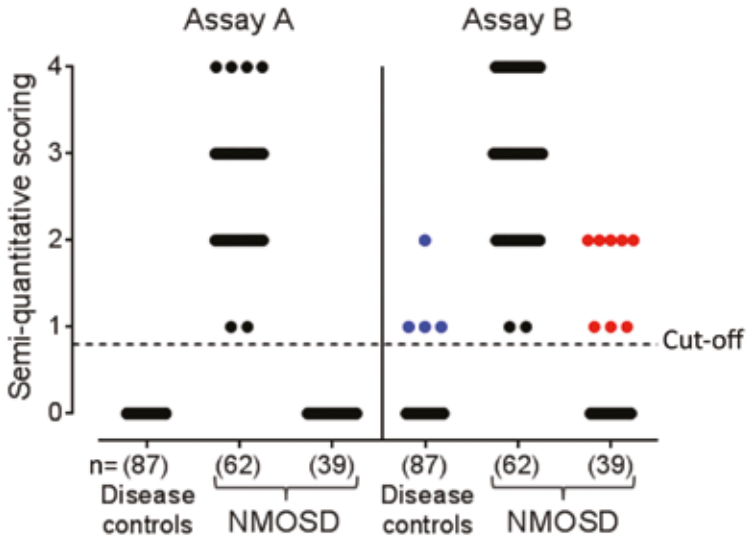

Figure 2: Two assays (A and B), performed on the same cohort of samples, 87 disease control s and 101 clinically defined NMOSD. The y-axis displays a semi-quantitative scoring system with strong positives scoring 4 and weakly positive samples scoring 1. The assay cut-off is shown as a dotted line. Assay A is 100% specific and identifies 62/101 samples from NMOSD patients as positive which are displayed in column 2. The 39/101 clinically defined NMOSD samples negative on this assay are displayed in column 3. The samples are grouped identically for Assay B. It is less specific with 4/87 disease controls positive (blue dots). All 62/101 positive samples on assay A are positive on assay B, but an additional 8/39 samples from the clinically defined NMOSD cohort are now positive (red dots) giving Assay B a higher sensitivity.

The dichotomy: sensitivity versus specificity

Which assay is clinically most useful: a highly-specific assay that may miss some samples with perhaps low antibody titres, or a highly-sensitive assay that identifies extra positive samples in the clinically-defined relevant patients (shown as red dots above the cut-off in Figure 2) but which also shows positivity in clinically irrelevant or control individuals (blue dots in Figure 2)? The implication is that the value of the antibody in unrelated diseases can be ignored on clinical grounds, and the increase in sensitivity in the correct clinical context is diagnostically useful. However,

it is likely that an assay with 'false-positive' results in irrelevant individuals will also have a similar proportion of 'false-positive' results in the clinically relevant group.

Serum versus CSF for neural antibody testing

Should we test serum or CSF? CSF is cleaner than serum containing much less protein and immunoglobulin. It can be tested at higher concentrations, often neat, and produces less background staining which leads to fewer clinically-irrelevant results in NMDAR-antibody assays for example.[9] However, the total amount and concentration of antigen-specific antibody is higher in the serum. This provides a more sensitive source of antibodies, and multiple studies have demonstrated that patients with low AQP4 antibody titres in their serum (end-point dilution of 1:250 or less) are not identified in the CSF.[10,11] Further research using paired serum and CSF samples is required to determine if the best sample to test will be individual to each assay or will be broadly applicable to all assays for NSAbs. Currently, we and others recommend simultaneous testing of paired serum and CSF samples.

Evolution of diagnostic criteria sans antibody testing

Identification of disease-specific antibodies has enabled the development of diagnostic criteria. Appreciation of these clinical features has then allowed clinicians to make a diagnosis without antibody results.[12,13] This is especially useful either early in the disease course when the results are not yet available, or at centres without access to testing. However, the antibody status often guides prognosis and long-term treatment, so world-wide access to these assays is an important goal.

Conclusions

Antibody assays are useful tools in the diagnosis and management of patients with treatable antibody-mediated CNS diseases. Future studies should address and optimise paradigms to evaluate NSAb-detection methods.

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Cerebral Amyloid Angiopathy and Intracerebral Haemorrhage

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is Professor of Clinical Neurology and Honorary Consultant Neurologist at the Stroke Research Centre, UCL Institute of Neurology, Queen Square, and the National Hospital for Neurology and Neurosurgery (NHNN), University College Hospitals (UCH) NHS Foundation Trust. Professor Werring contributes to delivering hyperacute and acute stroke care, and runs a specialist clinical service and research programme in intracerebral haemorrhage and small vessel disease. His projects include observational and neuroimaging studies of intracerebral haemorrhage, subarachnoid haemorrhage, and cerebral amyloid angiopathy. He is a member of the Association of British Neurologists Stroke Advisory Group, Stroke Specialty Lead for the NIHR North Thames Clinical Research Network, Chair of the European Stroke Organisation Education Committee, Member of the Board of Directors of the European Stroke Organisation, and member of the Editorial Board of the recently launched European Journal of Stroke.

Gargi Banerjee, MA, BMBCh, MRCP
is a Clinical Research Associate at the Stroke Research Centre, UCL Institute of Neurology, London. She is in the second year of her PhD, which is funded by the Rosetrees Trust, and is co-ordinating a study called "BOCAA" (Biomarkers and Outcomes in Cerebral Amyloid Angiopathy). This project aims to identify novel PET-MR, CSF, blood and neuropsychological markers for cerebral amyloid angiopathy, as well as providing more data on the natural history of the disease. She is particularly interested in the mechanisms by which cerebral small vessel diseases result in cognitive impairment.

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Abstract
Cerebral amyloid angiopathy (CAA) is increasingly recognised, particularly as a cause of intracerebral haemorrhage and dementia. CAA may present to the clinical neurologist in a range of circumstances, including inpatient or outpatient general neurology (with the subacute encephalopathy of CAA-related inflammation, or transient focal neurological episodes), dementia clinics (in particular in association with Alzheimer's disease) and, of course, in the context of acute stroke (intracerebral haemorrhage). This clinical review article presents an overview of the key clinical, neuropathological and imaging findings in CAA, as well as a practical review of the challenging management aspects relevant to CAA-related intracerebral haemorrhage.

Introduction

Our concept of cerebral amyloid angiopathy (CAA) has radically evolved over time: considered a rare pathological curiosity in the early 20th century, CAA is now an increasingly recognised cause of cerebral haemorrhage and dementia, with important diagnostic and mechanistic implications.[1] This development in our understanding was greatly facilitated by an improved ability to diagnose CAA *in vivo*, thanks to significant advances in neuroimaging.[2-4] CAA usually presents to clinicians in one of four ways: lobar intracerebral haemorrhage (ICH); dementia or cognitive decline; transient focal neurological episodes; and the encephalopathy seen in acute CAA-related inflammation (Table 1).[1,5] The neuropathological coexistence of CAA and Alzheimer's disease (AD) is well recognised[5] with pathological evidence of CAA in 80 – 98% of AD brains, but these processes can also occur independently of one another: only 50% of those with CAA meet the pathological criteria for AD, and moderate-to-severe CAA is seen in only 25% of those with AD.[6,7] There is also a growing appreciation that the amyloid related imaging abnormalities (ARIA) seen in those with AD receiving amyloid beta (Aβ) immunotherapy bears a striking resemblance to inflammatory CAA, and that the extent of the response may be related to pre-treatment CAA severity, suggesting a role beyond that of innocent bystander in AD pathophysiology.[8-11] The fact that non-Aβ amyloid proteins can also form comparable vascular deposits with similar clinical manifestations[1] has led to a hypothesis that these conditions are all due to failures of normal perivascular protein elimination pathways,[12] which may have therapeutic relevance in the future.

The first half of this short summary aims to introduce CAA by describing its characteristic neuropathological and imaging findings. The second half will explore the role of CAA in ICH, in particular our current diagnostic criteria and the potential management implications CAA has in the context of ICH.

What is Cerebral Amyloid Angiopathy?

Neuropathology

CAA is one of the cerebral small vessel diseases, a broad term that describes any vascular pathology affecting the small (usually <2mm) arterioles, capillaries and venules of the brain.[5,13] CAA particularly affects the cortical and leptomeningeal vessels of the cerebrum and cerebellum, frequently sparing deeper structures such as the basal ganglia, thalamus and brainstem.[1,5] This progressive vascular deposition of amyloid protein has been described for eight types of amyloid protein, most of which have been identified because they cause inherited forms of CAA that tend to present with dementia or ICH.[1,14] As the CAA secondary to Aβ is by far the most common,[1,11] the remainder of this article will focus upon this subtype; subsequent references to CAA are to Aβ CAA.

Aβ protein is formed from the Amyloid Precursor Protein (APP), with the 42 amino acid fragment found mainly in the parenchymal amyloid deposits characteristic of Alzheimer's disease, and the 40 amino acid form tending to be deposited in the vasculature.[5] Progressive accumulation of perivascular Aβ results in smooth muscle loss and eventual "double barrelling" (Figure 1).[5]

CAA can be subdivided based upon which type of vessel is affected, with type 1 CAA affecting capillaries as well as arterioles and venules, and type 2 being "capillary-sparing", whilst affecting all other vessel types.[1,5] Interestingly, these subtypes appear to be associated with specific alleles of Apolipoprotein E (ApoE) and may have discrete clinical manifestations.[5] ApoEε2 seems to be associated with type 2 CAA,[5] and is also seen more frequently in those with CAA and ICH, as well as those with disseminated cortical superficial siderosis[15] (a haemorrhagic imaging marker of CAA[2]). ApoEε4, on the other hand, has been described as "the most prevalent genetic risk factor for sporadic AD"[16] and is also associated with the cognitive decline observed

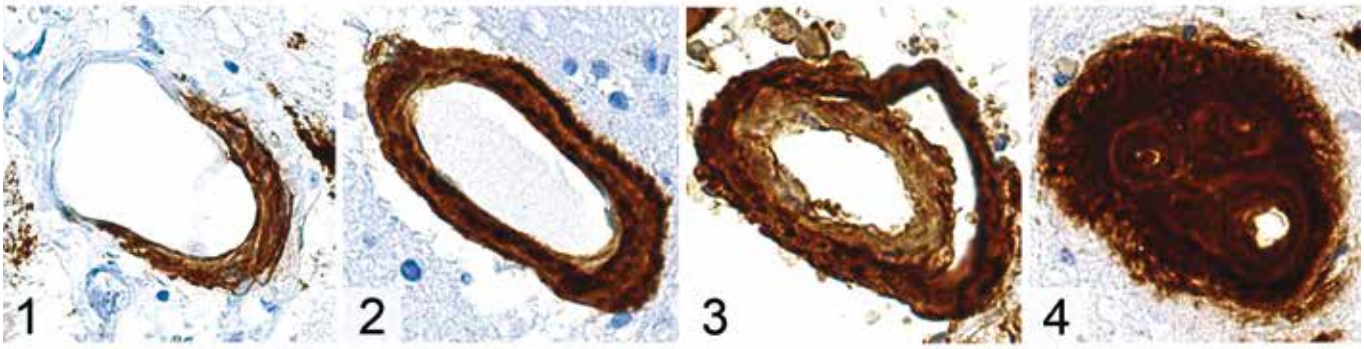

Figure 1: Neuropathological changes observed in CAA: the Vonsattel grading scheme for CAA severity.
In mild (grade 1) CAA, Aβ deposits are present in a proportion of the vessel wall. In moderately severe (grade 2) CAA Aβ is deposited circumferentially in the media. In severe (grade 3) CAA, in addition to concentric Aβ deposition, there is splitting and double-barrelling of the vessel wall. Very severe (grade 4) CAA is associated with marked obliteration of the lumen often associated with vascular necrosis, recanalisation and scarring.
Figure and legend courtesy of Zane Jaunmuktane, Division of Neuropathology, UCL Institute of Neurology.

Table 1: The four characteristic clinical presentations of CAA

Presentation	Clinical Features
• Lobar intracerebral haemorrhage (ICH)	Acute stroke syndrome – may range from mild or asymptomatic to life-threatening.
• Dementia or cognitive decline	Processing speed and executive function appear to be particularly affected [50]; note also overlap with Alzheimer's disease.
• Transient focal neurological episodes (TFNE: previously termed "amyloid spells")[51,52]	Recurrent, stereotyped, spreading symptoms (usually paraesthesia, numbness or weakness); spreading over seconds to minutes with resolution over a similar timeframe.
	Differential diagnosis includes TIA, migrainous aura or seizure, but the presence of positive symptoms, the "march" of symptoms and the time period over which this occurs should direct the clinician towards the correct diagnosis.
	TFNE may be a manifestation of acute convexity subarachnoid haemorrhage (which on imaging evolves into cortical superficial siderosis).
• CAA-related inflammation[53-56]	Subacute cognitive decline and/or seizures.
	Imaging typically shows asymmetrical confluent white matter abnormalities; microbleeds may be seen acutely or subacutely.
	There is some evidence that anti-Aβ autoantibodies in the CSF may correlate with disease activity.
	Management is with immunosuppressive therapy (although some patients recover spontaneously). Recurrence is rare but has been described.

Table 2: Useful diagnostic MRI markers in CAA

Marker	MRI sequence	Description
Strictly Lobar Cerebral Microbleeds (MBs) Adapted from references [57-59]	Paramagnetic sequences e.g. T2*-GRE, SWI	"Haemorrhagic" marker of CAA, thought to represent small self-limiting parenchymal haemorrhages. Black (hypointense) round or ovoid lesions (maximum diameter 10mm), with associated "blooming effect". Lobar location (rating scales include MARS and BOMBS).
Cortical Superficial Siderosis (cSS) Adapted from reference [51]	Paramagnetic sequences e.g. T2*-GRE, SWI	"Haemorrhagic" marker of CAA, believed to be the result of evolution of previous convexity subarachnoid haemorrhage. Dark (hypointense) bilinear 'track-like' rim around convexities of the cerebral hemisphere; restricted to supratentorial compartment in CAA.
Enlarged Perivascular Spaces (or Virchow-Robin Spaces) in the Centrum Semi Ovale (CSO-PVS) Adapted from references [60, 61]	T2	"Non-haemorrhagic" marker of CAA, demonstrating enlargement of the interstitial fluid channels that surround small arterioles Small white (hyperintense/high signal) round or linear lesions (CSF isointense).

in normal ageing.[17] It seems to be associated with type 1 CAA pathologically, and CAA without ICH clinically.[5,15] Mechanistically, this raises the possibility that the size of the affected vessel dictates clinical presentation, with capillary level disease tending to result in cognitive impairment and arteriolar level involvement resulting in ICH; further work is necessary in order to establish whether or not this is the case.

Imaging Markers

The recent advances in our understanding of CAA have been made possible by the identification of new neuroimaging measures that allow a diagnosis to be made without pathological material.[2] Although a number of novel imaging techniques, including diffusion tensor imaging, visual functional MRI and amyloid-PET, have diagnostic potential in CAA,[2] these are not always widely available in clinical practice. Table 2 describes imaging markers of CAA that may be easily identified on standard clinical MR sequences, examples of which are shown in Figure 2.

CAA is diagnosed using either the Classical or Modified Boston Criteria (Table 3).[3,4] Given the increasing evidence for a "non-haemorrhagic" CAA phenotype, these criteria may require amendments so that those who may be "cognitive-predominant" (i.e. without

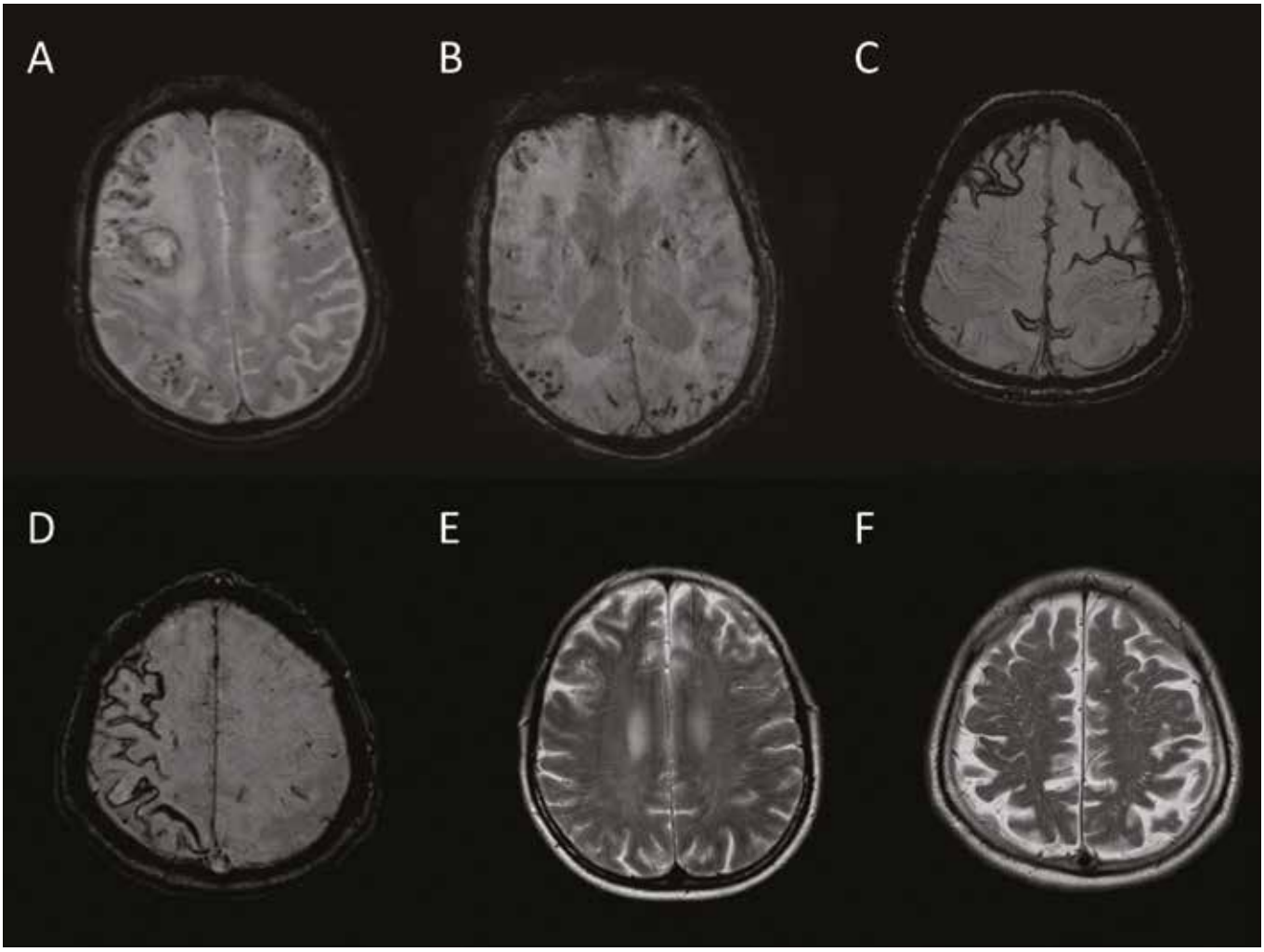

Figure 2: Commonly encountered MRI markers in CAA. Examples of lobar MBs (A, B), cSS (C, D), and CSO-PVS (E,F).

macro- or microhaemorrhage) can still be accurately diagnosed.

CAA and ICH – what do we know, and what can be done?

The association between CAA and ICH, in particular lobar ICH, has been recognised for some time; a recent meta-analysis found a significant association between CAA and lobar ICH (OR 2.21, 95% CI 1.09 to 4.45).[18] The fact that CAA is associated with lobar ICH in particular has significance, as lobar ICH appear to be more likely to recur, with an annual recurrence rate of between 2.5 – 14.3% compared with 1.3 – 2.9% for non-lobar ICH.[19] Given that the estimated one year survival rate in those with ICH is 46%,[19] and CAA may be responsible for up to 50% of lobar ICH,[20] modifying this risk could have a dramatic effect on ICH rates.

The risk factors for CAA-related ICH can be considered as modifiable or non-modifiable. Non-modifiable risk factors include increasing age, Alzheimer's disease, and any predisposing genetic factors (for example, inherited forms of CAA, or particular ApoE variants).[1,21] The presence of CAA itself, perhaps the most obvious risk factor for CAA-related haemorrhage, has always been thought of as non-modifiable; the hope is that, with the development of new therapeutic strategies for CAA such as the anti Aβ-40 monoclonal antibody ponezumab,[22] this will change.

The modifiable risk factors for CAA-related ICH are hypertension and the use of drugs that increase overall bleeding risk, for example antiplatelet agents, anticoagulants and thrombolytic strategies.[1] Statin use may also be a modifiable risk factor in this situation. These factors will now be considered in turn.

The main evidence for blood pressure (BP) lowering in CAA comes from a sub-analysis of the PROGRESS trial.[23] This study demonstrated that, even though those with CAA-related ICH tended to have lower BP than those with hypertension-related ICH (137/81mmHg vs 157/88mmHg respectively), it was the CAA group that seemed to benefit the most from BP reduction, with a 77% reduction in CAA-related ICH.[23] Although PROGRESS did not have a target BP, the trials demonstrated reductions in stroke risk for both hypertensive (>160/90mmHg at baseline) and non-hypertensive groups; the latter group had a mean entry BP of 136/79mmHg and the average BP reduction in the treatment group was 9/4mmHg.[24] Based on this, it seems reasonable to aim for a BP target of ~125/75mmHg, which is also in keeping with the results from SPS3, which showed a significant reduction in ICH in those with a BP less than 130/80mmHg.[25] However, further randomised data in ICH survivors with an aggressive BP treatment target are needed to confirm safety and efficacy in this ICH population. A trial of telemetry-guided intensive BP control is in set up in the UK to address this (Prevention Of Hypertensive Injury to the Brain by Intensive Treatment–ICH – PROHIBIT-ICH, D Werring, personal communication).

As those with CAA are at increased risk of ICH, medications that impair normal haemostasis (antiplatelet drugs, anticoagulants, intravenous thrombolysis) are best avoided, although this is not always possible and presents a difficult clinical dilemma,[26] especially as patients with CAA also appear to be at increased risk of ischaemic events.[27] There is observational evidence in favour of avoiding anticoagulation with warfarin in CAA,[28,29] and there are case reports of ICH in CAA following treatment with intravenous thrombolysis.[30-32] Presence of the ApoEε2 allele seems to particularly be associated with warfarin related ICH.[29,33,34] However, there are no randomised trial data to inform the use of warfarin in CAA. The role of non-vitamin K

Table 3: Classical and Modified Boston Criteria, table from [4]. Key differences between the Classical and Modified Criteria are highlighted in bold.

	Classical Boston Criteria	**Modified Boston Criteria**
Definite CAA	Full post-mortem examination demonstrating: • Lobar, cortical or cortico-subcortical haemorrhage • Severe CAA with vasculopathy • Absence of other diagnostic lesion	–
Probable CAA with supporting pathology	Clinical data and pathological tissue (either evacuated haematoma or cortical biopsy) demonstrating: • Lobar, cortical or cortico-subcortical haemorrhage • CAA within the specimen (any degree) • Absence of another diagnostic lesion	–
Probable CAA	Clinical data and MRI / CT demonstrating: • Multiple haemorrhages restricted to lobar, cortical or cortico-subcortical regions (including cerebellar haemorrhage) • Age ≥ 55 years • Absence of other cause of haemorrhage	Clinical data and MRI / CT demonstrating: • Multiple haemorrhages restricted to lobar, cortical or cortico-subcortical regions (including cerebellar haemorrhage) **-or-** **Single lobar, cortical or cortico-subcortical haemorrhage AND superficial siderosis (either focal or disseminated)** • Age ≥ 55 years • Absence of other cause of haemorrhage
Possible CAA	Clinical data and MRI / CT demonstrating: • Single lobar, cortical or cortico-subcortical haemorrhage • Age ≥ 55 years • Absence of other cause of haemorrhage	Clinical data and MRI / CT demonstrating: • Single lobar, cortical or cortico-subcortical haemorrhage • **Superficial siderosis** (either focal or disseminated) • Age ≥ 55 years • Absence of other cause of haemorrhage

oral anticoagulants (with about half of the ICH risk of warfarin) in those with CAA and an indication for anticoagulation (e.g. atrial fibrillation) remains to be defined, but our practice at present is to avoid long term oral anticoagulants in CAA unless there is a clear unavoidable need to give them (e.g. metallic heart valves, life-threatening venous thromboembolism). For patients with atrial fibrillation, left atrial appendage occlusion (LAAO) may have a role in patients with CAA as it has similar efficacy to oral anticoagulation with warfarin, but without the need for long anticoagulation exposure.[35-37] The case for antiplatelet agents as a clear risk factor for future ICH in CAA is less clear cut – aspirin has been the most widely studied, and has been suggested as both increasing the risk of ICH in CAA[38] and as having no effect.[28] In patients with vaso-occlusive disease and a clear ongoing indication for antiplatelet use (e.g. severe ischaemic heart disease) inclusion in the randomised trial RESTART (http://www.restarttrial.org/default.html) should be considered; however, clinicians may not have equipoise about possible benefit if patients have imaging evidence of severe CAA and a history of recurrent ICH. Further studies are required, but meanwhile care must be taken in how CAA is diagnosed; in particular, with regard to the use of cerebral microbleeds in diagnostic criteria, as these may be a consequence of antiplatelet or anticoagulant treatments in those with and without CAA.[39,40]

Whether statins increase the risk of future ICH in those with CAA remains uncertain. There is, however, some evidence that they are associated with an increase in microbleed frequency[41,42]. The evidence is conflicting:[43-46] although there is observational evidence of an association between intracranial haemorrhage (macro- and micro-) with reduced LDL-cholesterol, convincing randomised evidence that lipid lowering can increase ICH risk remains scarce.[43,47] A decision analysis suggested that in CAA-related ICH the risks of statins for future ICH might outweigh the benefit for prevention of vaso-occlusive disease, but that statins may be less hazardous in deep, non-CAA related ICH.[48,49] It seems reasonable to avoid statins after CAA-related ICH unless there is a clear and compelling indication for benefit on overall vascular risk. Randomised trials are ideally needed, with ICH subtyping as CAA- or non-CAA, to resolve this controversial therapeutic dilemma.

Summary

- CAA is a small vessel disease that occurs as a consequence of vascular amyloid deposition
- CAA has a spectrum of disease, with haemorrhage-predominant and cognitive-predominant subtypes, which may be related to ApoE genotype
- New MRI markers greatly facilitate the diagnosis of CAA from standard MRI sequences
- Key management strategies are avoidance of anti-coagulant medications and aggressive blood pressure control; the hazard of antiplatelet drugs and statins in those with CAA remains unclear

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Professor Sir Douglas Turnbull receives knighthood

Congratulations to Professor Sir Douglas Turnbull, Director of the Wellcome Trust Centre for Mitochondrial Research who was knighted in the Queen's Birthday Honours. He developed and leads the NHS National Highly Specialised Services for Rare Mitochondrial Diseases of Children and Adults and is Director of the Newcastle University Centre for Brain Ageing and Vitality, supported by the MRC and BBSRC. This knighthood is in recognition of his huge contribution to the field of mitochondrial disease which has been so publicly acknowledged.

The relationship between sleep and epilepsy

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Abstract
Epilepsy and sleep have a close association and a two way interaction. Recognising this allows for a greater awareness of the importance of good quality sleep in epilepsy patients with potential benefits on seizure control and quality of life. This article reviews this complicated but fascinating area addressing diagnostic issues, the effects of epilepsy and its treatments on sleep, the effects of sleep disorders on epilepsy concluding with some practical advice on assessment.

Introduction

Sleep and epilepsy are intimate bedfellows, having an impact on each other and adversely affecting quality of life and daytime performance.[1] Sleep has an important role in memory consolidation.[2] Sleep deprivation impairs this process[3] and epilepsy can upset this delicate balance.[4] Sleep disorders are up to three times as common in epilepsy[5] and can be a major contributor to refractory seizures,[6] poorer quality of life[7] and possibly SUDEP.[8] Recognition of the comorbid sleep disorder and successful treatment can lead to significant improvements in seizure control.[9] Many patients with epilepsy have seizures in sleep, some exclusively so. Often diagnosis is difficult due to incomplete histories from sleep partners. Even when telemetry facilities are available, data can be difficult to interpret and EEG is not always diagnostic.[10] To add to this complexity, epilepsy treatments often have impact on sleep. Understanding this complex relationship can lead to better treatment outcomes for patients. This review will begin with diagnostic issues, moving on to the effects of epilepsy and its treatments on sleep, the effects of sleep disorders on epilepsy and concludes with practical advice on assessment.

Epilepsy Syndromes Closely Associated with Sleep

There are a small number of epilepsy syndromes which are predominantly or exclusively associated with sleep (Table 1). Seizures arising from sleep are almost always of focal onset. These include the childhood onset syndromes of benign childhood epilepsy with centrotemporal spikes (BCECTS, Rolandic epilepsy), benign childhood epilepsy with occipital paroxsysms (Panayiotopoulos syndrome) and the frontal lobe epilepsy syndromes (including autosomal dominant nocturnal frontal lobe epilepsy ADNFLE). Idiopathic generalised epilepsy syndromes (IGE) such as juvenile myoclonic epilepsy (JME) and generalised tonic clonic seizures on waking arise shortly before or after sleep onset but not from a sleep state.

Diagnosing Paroxysmal Nocturnal Events

Table 2 summarises clinically important details which help in differentiating epilepsy from other sleep disorders. Derry et al (2006 & 2009) have produced very useful clinical tools to help differentiate nocturnal seizures from other sleep disorders with diagnostic accuracy up to 94%[11,12,8] however comorbidity is common[13] and an awareness of the characteristic features of the more common conditions enhances the history taking process. During nocturnal seizures patients rarely leave the bed space, episodes are often brief and stereotyped and can cluster throughout the night (Figure 1). Incontinence, tongue trauma and seizures during daytime wakefulness are strong pointers. Postictal symptoms on waking such as generalised aching, headache and amnesia of the preceding day's events are strongly associated.

Parasomnia episodes are seen in either rapid eye movement (REM) or non-REM (nREM) sleep. REM parasomnia (REM behaviour disorder (RBD) is almost exclusively seen in elderly subjects with a male predominance, often associated with alpha synucleonopathies.[14] Dream enactment occurs due to a lack of muscle atonia during REM sleep. Episodes occur late in the sleeping period where a higher concentration of REM sleep is seen. Patients often recall their dreams, behaviour is often violent and episodes are repeated each night. The American Academy of Sleep Medicine suggests RBD is diagnosed with polysomnography (PSG) as it can sometimes be difficult to differentiate it from epilepsy on the history alone.[15]

Table 1: Epilepsy Syndromes Closely Associated with Sleep

Focal Onset Syndromes	Idiopathic Generalised Epilepsy Syndromes	Epilepsy syndromes of uncertain origin
Benign childhood epilepsy with centrotemporal spikes (BCECTS, Rolandic epilepsy)	Juvenile myoclonic epilepsy (JME)	Continuous spike and wave during slow wave sleep
Benign childhood epilepsy with occipital paroxysms (Panayiotopoulos syndrome)	Generalised tonic clonic seizures on waking	Landau – Klefner syndrome
Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)		
Nocturnal frontal lobe epilepsy		
Nocturnal temporal lobe epilepsy		

Figure 1: A video EEG image of a nocturnal seizure showing short lived dystonic posturing of the right hand seen immediately on waking. 30 stereotyped attacks were recorded over 2 nights. The EEG was normal throughout. Awareness was reported for most attacks although the hand posturing was not recalled by the patient.

nREM parasomnias generally arise in childhood, they are less frequent and usually singular during the early part of a sleeping period. Patients are more often amnesic to the event however, some recollection of the later stages of events is often reported due to awakening, often in a confused state. Injury is rare, behaviour is often complex and episodes can be prolonged but usually not more than 30 minutes. Excessive daytime somnolence (EDS) is generally not a direct consequence of nREM parasomnias but if severe one should consider comorbid sleep disorders such as obstructive sleep apnoea (OSA) and periodic limb movements in sleep (PLMS).

Night terrors and confusional arousals

Differentiating between these two types of common nREM parasomnias often causes difficulty. Night terrors are exclusively a paediatric condition and don't persist into adulthood. Although deeply asleep, the child appears awake and is inconsolably terrified, often screaming loudly. Events can last up to one hour but they are not remembered. Confusional arousals occur in adulthood when an abrupt but incomplete awakening occurs from slow wave sleep (SWS), often associated with distressing dreams which can be recalled, leading to confusion and sometimes injury.[16] Diagnostic difficulty can arise when the arousal is due to a short seizure and the confusion due to postictal phenomena.

The effects of epilepsy on sleep

The effects and consequences of epilepsy on the sleep EEG

Objective PSG assessments show that interictal epileptiform discharges (IEDs), increase in sleep[17] especially in N3 nREM sleep, although seizures seem to predominate in lighter nREM sleep.[18] Nocturnal seizures lead to reductions in REM sleep and increases in nREM sleep. These changes are also seen when a wakeful seizure has occurred the previous day.[19] Seizure types have differing relationships with sleep with focal epilepsies being more likely to disrupt sleep than IGE. Even in seizure free states, interictal temporal lobe epileptic discharges seem to disrupt sleep when compared with frontal lobe epilepsy (FLE) and IGE. Temporal lobe epilepsy (TLE) correlates with worse sleep efficiency and increased stage shifts and awakenings. Despite this, frontal lobe seizures are seen more commonly in sleep than temporal lobe seizures.[20] Uncontrolled epilepsy in sleep can lead to memory impairments[4] and excessive daytime somnolence (EDS).[5]

The effect of epilepsy treatments on sleep

AEDs (Table 3) and epilepsy surgery can affect sleep however the particular effects can be unpredictable.

AEDs

Few studies have been conducted in this complex area. Those which have are limited by short duration and inadequate controls for seizure types and polypharmacy. It appears that AEDs can improve sleep, however it is uncertain if this is due to improved seizure control or independent sleep consolidation.[8] Unfortunately, AEDs commonly produce daytime fatigue and at higher doses excessive daytime somnolence (EDS).[23] This can be an advantage in patients with insomnia. Some AEDs are associated with significant weight gain which can lead to OSA. Care must be taken when using sedating drugs such as the benzodiazepines (BZPs) in patients who may be prone to sleep disordered breathing as apnoeic episodes may increase.[24] Care should be taken when labeling EDS as a side-effect of AEDs as this risks under interpreting the disruptive effects of unrecognised nocturnal seizures or co-morbid sleep disorders. Polysomnography (PSG) may be required to differentiate between the two.

The effects of AED withdrawal on sleep must also not be overlooked. Withdrawal of a sedating drug may lead to reductions in sleep,[25] withdrawal of mood stabilising

Table 2: Clinical features of disorders commonly producing sleep attacks

Disorder	Age of onset	Patient Awareness	Leaves the bed	Stereotyped behaviour	Complex behaviours	Incontinence / tongue bites / injury	Daytime somnolence	No. of attacks per night	Typical duration of attack	Typical time of night
Epilepsy[8]	Any	Variable but usually poor	No	Yes (posturing, head version)	No	Yes	Variable	Often multiple	Seconds - minutes	Any
Non REM Parasomnia[8]	Childhood	None or very limited	Common	No	Yes (talking, walking, eating, intercourse)	No (rarely sustain injury)	Variable (if severe consider comorbid sleep disorders, OSA, PLMS etc)	Singular	< 30 minutes	Within 2 hrs of sleep onset
REM Behaviour Disorder (RBD)[12]	Middle age to elderly (mostly male)	Variable but can be significant (distressing dreams etc)	No	No	No	No (but injury sustained in violent acts)	No	Can be multiple	Seconds	> 4 hrs after sleep onset
Non -Epileptic / Functional attacks[8]	Young adult	Poor	Variable	No	Variable	Variable	Variable	Variable	Usually prolonged	Any
Periodic Limb Movements in Sleep	Elderly	Poor	Never	Yes (small amplitude flexion of legs)	Never	Never	Common	Numerous 10s – 100s)	Seconds	Any

Table 3: Common Effects of AEDs on Sleep Symptoms / Disorders		
AED	**Improves**	**Worsens**
Lamotrigine (LTG)	–	Insomnia
Levetiracetam (LEV)	–	Fatigue / Somnolence OSA [a]
Carbamazepine (CBZ)[8,21]	Insomnia[22]	Fatigue / Somnolence
Sodium Valproate (VPA)[21]	Insomnia	Fatigue / Somnolence
Phenytoin (PHT)[8,21]	–	Fatigue / Somnolence Insomnia
Topiramate (TPM)	OSA [b]	-
Pregabalin (PGB)	Insomnia[22,41]	Fatigue / Somnolence OSA [a]
Gabapentin (GBP)[21]	Insomnia[22]	Fatigue / Somnolence OSA [a]
Phenobarbitone (PHB)[21]	Insomnia	Fatigue / Somnolence OSA [a]
Lacosamide (LAC)	–	Fatigue / Somnolence
Zonisamide (ZON)	OSA [b]	Fatigue / Somnolence
Perampanel (PER)	–	Fatigue / Somnolence OSA [a]
Oxcarbazepine (OXC)	–	Fatigue / Somnolence
Ethosuxamide (ETH)[21]	OSA [b]	–
Benzodiazepines (BZP)[21]	Insomnia	Fatigue / Somnolence OSA
(a) – due to weight gain (b) – due to weight loss		

Table 4: Comorbid Sleep Disorders in Epilepsy Patients			
Sleep disorder	**Prevalence Rates**	**Reference**	**Commonly used non-AEDs which may worsen the disorder**
Insomnia	52% (vs 38% controls)	Khatami et al 2006[37]	Caffeine Stimulants (methylphenidate, modafinil, amantadine) Alpha-blockers Beta-blockers Corticosteroids SSRI antidepressants ACE inhibitors Angiotensin Receptor II Blockers Cholinesterase inhibitors H1 antagonists Statins
OSA	30%	Malow et al 2000[33,1]	BZPs
CSA	3.7%	Vendrame et al 2013[32]	BZPs
PLMD	17%	Malow et al 1997[40]	Antidepressants (except buproprion) Neuroleptics Antihistamines
RLS	18% (vs 12% controls) ns	Khatami et al 2006[37]	Antidepressants (except buproprion) Neuroleptics Antihistamines
EDS (>10 on Epworth Sleepiness Scale)	19% (vs 14% controls)	Khatami et al 2006[37]	BZPs Mirtazepine Tricyclic antidepressants Neuroleptics Dopaminergics
ns = non significant			

Table 5: Practical tips for the evaluation of sleep problems in epilepsy patients	
Diagnosis	FLEP scale,[11] CHIAD Tree analysis[12]
Clues regarding the onset of symptoms	Drug commencement, Drug withdrawal, Weight gain, Epilepsy surgery / VNS
Assess for comorbidity	RLS (IRLS scale),[42] OSA (Berlin questionnaire,[43] STOP BANG questionnaire), EDS (ESS)[44]
Optimise sleep hygiene	Regular bed and wake up times, Remove bedroom technology Avoid caffeine after 1800 hrs, Avoid large meals after 1800 hrs, Reduce evening fluid intake, No daytime naps

AEDs (i.e. VPA, CBZ, LTG, TPM) may lead to worsening depression and anxiety all of which can precipitate insomnia and nREM parasomnias. Withdrawal of TPM can lead to weight gain which may precipitate OSA.

Chronopharmacology

Chronopharmacology holds great potential when applied to the management of epilepsy; it recognises that circadian rhythms exist in absorption and metabolism of drugs. For example, it has been recognised that without changing the total daily dose of PHT and CBZ in epilepsy patients, serum levels increase and seizure control improves by administering proportionally higher doses at 2000 hrs compared with the morning.[26] This suggests that great benefits can be achieved by prescribing higher doses of AEDs later in the day.

Epilepsy surgery

Resective epilepsy surgery is now widely used to treat refractory epilepsy. However, only one study of 17 patients has evaluated sleep pre and post operatively using PSG. Although no overall benefit was seen, patients who attained better post operative seizure control had greater improvements in total sleep times and arousals.[27] Vagal nerve stimulation (VNS) has shown increases in SWS and nocturnal sleep latency in a study of 15 children with refractory epilepsy.[28] However, in adult populations it can lead to deterioration in sleep disordered breathing in up to 31% of patients[29] thus changes in snoring and EDS should be closely monitored post VNS insertion. Deep brain stimulation (DBS) is now a recognised epilepsy surgery technique however it may have deleterious effects on sleep as there is a small amount of evidence to suggest that anterior thalamic nucleus DBS has been found to increase electroclinical arousals on average 3.3 times more frequently during stimulation periods compared to non-stimulation periods in a study of 9 patients.[30]

The effects of sleep disorders on epilepsy

Sleep disorders are up to three times as common in patients with epilepsy compared with controls.[5]

Sleep deprivation is often associated with an increase in IEDs and poorer epilepsy control[31] with 77% of JME patients reporting more seizures when sleep deprived.[32] AEDs are associated with weight gain,[33] and mental health disorders[34] and both of these conditions predispose to sleep disorders. OSA is often caused or worsened by increases in the BMI and is known to have prevalence rates up to 30% in epilepsy populations[33] and is associated with worsening seizure control.[6] TLE has a greater association with OSA than extra temporal seizures.[35] Management of OSA with continuous positive airway pressure (CPAP) produces improvements in epilepsy control with seizure freedom seen in almost 20% in a randomised controlled trial of 68 using therapeutic vs sham CPAP.[7] Impressive responder rates (>50 % seizure reduction) have also been reported in trials of CPAP for OSA in epilepsy subjects (OR 32.2).[36] Mood disturbance is also very prevalent in epilepsy patients.[34] Sleep disorders are commonly associated with these mental health problems. Concurrent use of antidepressants is common, thus an awareness of the effects of these drugs is required when evaluating

sleep complaints in epilepsy patients to ensure their contribution is not overlooked (Table 4), in particular an awareness of the potential for precipitation of RBD, RLS and PLMD. RBD can be mistaken for epilepsy and can be effectively treated with removal of the antidepressant or the use of melatonin. RBD, restless leg syndrome (RLS) and periodic limb movement disorder of sleep (PLMD) are also commonly precipitated by antidepressant and neuroleptic drugs however RLS and PLMD occur in a primary form in the absence of pharmacological triggers and can significantly disrupt the quality of sleep although the evidence available suggests they are no more common in epilepsy subjects compared with controls.[37,38] There is no published evidence on the impact of treating RLS / PLMD on seizure control however this should be considered good practice.

Conclusions

Epilepsy and sleep and its disorders are very closely associated and improvements in the recognition and management of either will have beneficial effects on the other (see Table 5 for practical tips on clinical assessment). Research in this field is still in its infancy compared with other neurological conditions, however greater awareness and investment promises much for epilepsy patients.

Table 6: Abbreviations

ADNFLE – Autosomal dominant nocturnal frontal lobe epilepsy
AED – Anti epileptic drug
BCECTS – Benign childhood epilepsy with centrotemporal spikes
BMI – Basal metabolic rate
BZP – Benzodiazepine
CBZ – Carbamazepine
CPAP – Continuous positive airway pressure
CSA – Central sleep apnoea
DBS – Deep brain stimulation
EDS – Excessive daytime somnolence
ETH – Ethosuximide
FLE – Frontal lobe epilepsy
GBP – Gabapentin
IED – Interictal epileptiform discharges
IGE - Idiopathic generalised epilepsy
JME – Juvenile myoclonic epilepsy
LAC – Lacosamide
LEV – Levetiracetam
LTG – Lamotrigine
nREM – Non rapid eye movement sleep
OR – Odds ratio
OSA – Obstructive sleep apnoea
OXC – Oxcarbazepine
PER – Perampanel
PGB – Pregabalin
PHB – Phenobarbitone
PHT – Phenytoin
PLMD – Periodic limb movement disorder of sleep
PSG – Polysomnography
RBD – REM behaviour disorder
REM – Rapid eye movement sleep
RLS – Restless leg syndrome
SUDEP – Sudden death in epilepsy
TLE – Temporal lobe epilepsy
SWS – Slow wave sleep
VNS – Vagal nerve stimulation

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Neurological Literature: Headache Part 9

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It is some years since the previous article in this series presenting accounts of headache encountered in literary or biographical material,[1] and, astonishingly, almost a decade since the first[2] I hope readers will indulge me by accepting this further offering.

As neurologists, we now draw a clear clinical distinction between "headache" and "neuralgia", as enshrined in diagnostic criteria.[3] However, our clinical experience indicates that this distinction may not be evident to patients (or even sometimes primary care physicians) who may use the terms interchangeably.

The author W Somerset Maugham (1874-1965) was a medical student at St Thomas' Hospital, London, in the 1890s,[4] during which time he attended, according to his own account, 63 confinements in 3 weeks in houses in Lambeth. This experience of the labouring poor provided the source material for his first novel, *Liza of Lambeth* (1897). First hand observation may underlie Maugham's accounts of the headaches suffered by the heroine's mother, Mrs Kemp, who says to her daughter:

> *'Oo, my 'ead!' she was saying, as she pressed her hands on each side of her forehead. 'I've got the neuralgy again; wot shall I do? I dunno 'ow it is, but it always comes on Sunday mornings'.*

Later in the novel, apparently neglected by her daughter one day, she complains on her return:

> *'I've 'ad the neuralgy all the mornin', and my 'ead's been simply splittin', so thet [sic] I thought the bones 'ud come apart and all my brains go streamin' on the floor.'*

The good lady's drinking habits may give us an all too transparent clue to the timing of her headaches.[5]

The use of the term "neuralgia" as a description of head pains, sometimes apparently interchangeably with headache and even migraine, may be encountered elsewhere, for example in the writings of Elizabeth Gaskell (1810-1865),[6] Louisa May Alcott (1832-1888),[7] and Francis Kilvert (1840-1879),[8] all of whom suffered from headaches. I suppose it may be possible that this reflects the usage of these terms in the nineteenth century.

In none of these individuals, Mrs Kemp excepted, did headache appear to stifle creativity, although it might interrupt for a time social and occupational function. Hence it is unsurprising to note that the possessors of very disparate talents may also be afflicted by headache, ranging from the levity of the comedian Peter Kay, who reports:

> *Nowadays I get a blinding migraine if I stay up until the end of News at Ten and I have to have a siesta the following day.*[9]

to the gravitas of Thomas Henry Huxley (1825-1895), Darwin's "bulldog". In Adrian Desmond's biography, Huxley is reported to be "crushed by headaches after lecturing". Developing his interests in fossils, he "started another course for his students but it took the inevitable toll. Headaches plagued him". Both these references relate to the mid-1850s, when Huxley was in his late 20s or early 30s, and still trying to establish himself, this being in the midst of what Desmond chooses to call the "Lost in Wilderness Years (1850-1858)".[10] One might wonder whether Huxley's "dyspepsia", accounted one of his "Town afflictions", might also be ultimately migrainous in origin.

Although a "plague", might headaches ever enhance, facilitate or stimulate creativity, perhaps by affording new insights, or granting different mind states, which may then be translated to the non-headache state? On the extremely rare occasions that I have had a migraine-type headache I have been subjectively aware that I am seeing things or thinking about things differently from my usual non-headache state.

There is of course a considerable literature addressing these possibilities. One article relates to the suggestion that Pablo Picasso may have been a migraineur, the cubist style being in part a response to the fragmentation and distortion of visual images experienced in migraine aura. It is a fascinating idea, but one currently still without any definite evidence to prove or refute.[11]

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Mentored By A Madman – The William Burroughs Experiment

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One of the most distinguished British Neurologists of the last 40 years is Andrew Lees, who is recognised as being a world authority on Parkinson's disease with a publication record to match. Andrew is also well known for the slightly different way he has of seeing the world of research and clinical practice and in his latest book this is revealed in a new, entertaining and apposite way. In this new book Andrew discusses the influences that the late William Burroughs (a well known drug addict who wrote extensively about this in his many books, essays and articles) had on his career, in particular on his quest to find the treatment that would ultimately free patients with Parkinson's disease (PD) from many of their problems and/or complications of their oral dopaminergic treatments. The book therefore interweaves stories and episodes from Andrew's scientific career with advice from Burroughs, and as such makes for a fascinating read.

First and foremost what comes out of this book is Andrew's pioneering spirit. This involved him trying out therapies on himself first – selegiline to see if it truly did not evoke a cheese reaction with tyramine stimulation. This led to him being amongst the first to trial MAO-A inhibitors for PD which also led to him establishing the UK PD study group. In addition, he undertook the very first work on apomorphine in PD which began with him trying it in the privacy of his own home having had it specially made at the Royal Marsden Hospital in London. An injection that produced some interesting effects! This work followed on from his research that began in the 1970s on dopamine agonists. All of these treatments he saw through from anecdotal open label studies to mainline therapeutic interventions with an inventiveness and tenacity that is sadly hard to find in the modern day landscape of regulatory oversight. Indeed this is one of the major issues explored in this short book – namely has the research landscape changed for the better with the development of more rigorous review and regulation? He thinks not, as many breakthroughs in medicine come about by careful observation and serendipity, and then judicious experimentation. Andrew has been a great exponent of all this, often observing and noting much that goes unnoticed by others while also looking to find new empirical approaches to treatment that owe as much to intuition and reasoning – a reasoning that does not necessarily come from dry scientific articles, but the writings of others such as William Burroughs.

Overall this is a delightfully refreshing book that shows just how much Andrew has brought to this field over his career – therapies that he has championed and which we take for granted without knowing how they came to be tried in the first place. Side effects that we now all know about but which he first noticed and helped define – most notably the abnormal behaviours with dopamine agonists that he first observed with the initial patients he treated with bromocriptine in 1976! This corpus of work which he has delivered over the years has helped many careers and many patients, and in this new book the inspiration for it is laid bare. In particular this book shows that the way to do pioneering clinical research relies critically on mentors with imagination and the writings of those who may not immediately spring to the standard neurologist's mind. So when you are next pondering what to do with your research career, read this book and consider carefully where to look for your inspiration!

Please mind the gap

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The ABN meeting in Brighton this year was based on the theme of the 'Seven Ages of Man'. This phrase, describing a monologue from Shakespeare's 'As You Like It', poetically portrays moving between the formative eras of life. Robert Smirke (1796) based his matched paintings on this: the infant; the schoolboy; the lover; the soldier; the justice; the pantaloons; and the old age.

Figure: Sidney Harris, Published in the New Yorker April 11, 1994

A football club is said to be in 'transition' often when there has been a run of poor form, a change in manager, and the jury is still out on the sweeping changes at the club. It clearly describes the uncertainty, the flux, and suggests progression from one state to another. Within sporting parlance, it is used euphemistically – and that club may remain in the doldrums fighting a relegation battle before another manager is proffered that poisoned chalice and the 'transition' starts again. Transition is a time of uncertainty.

The World Bank identified the key adolescent transitions as: from dependent child to autonomous adult; from primary to secondary and later education; from education into the workforce; transition into responsible and productive citizenship; transitions in health from dependent recipients of children's healthcare to adults responsible for their own healthcare. Within a healthcare setting a transition clinic is normally a one of or series of joint clinics where the paediatrician and adult physician meet with the patient and their family. This provides an opportunity to reassess diagnosis, treatment aims and to get a timely second opinion. A double handed Consultant clinic allows one to speak to the family (alone) and another to speak to the young adult (also on their own).

There are a whole host of neurological disorders that span childhood-adulthood and yet in the UK the transition clinic is most likely to be in place to help people with epilepsy. So, is there a crisis in transitional neurology clinics in the UK? What is the state of play?

"In XXX, [attending transition clinics] does not happen. Trainees would have to actively seek this experience. A formal transition clinic has only recently been established in XXX although historically the XXX specialist did it for his clinic."
(Anonymous feedback from an ABN Trainee Regional Rep)

When representatives for adult neurology trainees in each region were asked to identify their experiences of transition clinics and the training opportunities available to them locally there were some singular comments. At best trainees either attended transition clinics when attending epilepsy clinics, or on an ad hoc basis – perhaps because the trainee was motivated. One region was also able to offer a transitional headache clinic. There was a general feeling that the Consultants were happy for trainees to attend and were often supportive, but that opportunities were limited to a clinic or two every three months only during selected blocks of training. There was a region where a service existed but no one could ever remember a trainee attending. Some trainees were using an elective block to attend paediatric clinics and used this experience to meet their training needs. There was also a concern that people thought they were getting transitional clinic experiences, but they were not. 'We just see paediatric cases as new cases in the epilepsy clinic' for example. Furthermore there are some practical barriers to trainees' attendance at transition clinics. A frustrated trainee working adjacent to a major paediatric centre was prevented from accessing opportunities there by the bureaucratic burden of a mountain of paperwork.

"Generally, like many places there is a lot of pressure on neurology trainees for service commitment and stroke rotas and in this sort of climate the opportunity to do innovative useful stuff can be limited."
(Anonymous feedback from an ABN Trainee Regional Rep)

Why is this important? Younger adults reported greater dissatisfaction with NHS services than older adults. The risks are greater than poor service configuration: a BMJ study found that 35% of young renal transplant recipients had lost their transplants by 36 months after transfer to adult renal care.[1] Recognising this problem, the Royal College of Physicians in 2015 as part of the 'Future Hospitals Programme' put together the 'Young adults and adolescents transition project.' This project aims to "improve the quality of care for young adults and adolescents with long-term and complex conditions as they transition from paediatric to adult services." The first stage is a review of current services (as above) and the second is a platform to showcase the best of current practice. Examples of good practice can be gleaned from the RCP acute care toolkit.[2]

Do we need standards for what determines a transition clinic? What is the minimum involvement we need as trainees? The next time we need to think about transition may be as a junior Consultant when we are helping to shape services. The best way to 'mind the gap' between paediatric and adult services is by ensuring that trainees from both backgrounds get sufficient exposure to transition clinics. We have a lot to learn from each other and it is time to shine the spotlight of adolescent services to ensure that young adults get the support they need to navigate the next stage in the NHS.

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Young Person's Health Special Interest Group – www.yphsig.org.uk

Acute Care Toolkit – www.rcplondon.ac.uk/guidelines-policy/acute-care-toolkit-13-acute-care-adolescents-and-young-adults

Living with epilepsy – my invisible shadow

Yasmin Belgrave
Yasmin was diagnosed with epilepsy in 2004 and until recently, her tonic-clonic seizures were uncontrolled. She is currently looking for work in the not-for-profit sector and hopes to one day return to university to do a Master's degree in Art Psychotherapy.

Young Epilepsy is the national charity working exclusively for the 112,000 children and young people aged 25 and under with epilepsy and associated conditions. The charity exists to improve the lives of children and young people with the condition to enable them to fulfil their potential and ensure they have the best quality of life. Young Epilepsy provides world-class diagnosis, assessment and rehabilitation for children and young people with epilepsy. Young Epilepsy's campus is also home to St Piers School and College as well as The Neville Childhood Epilepsy Centre, the only rehabilitation unit in the UK that specialises in young people with epilepsy.

How Young Epilepsy works with healthcare professionals

It is important for professionals to understand the many issues that epilepsy can cause families including diagnosis, treatment, emotional impact and living with epilepsy.

For families whose child has complex epilepsy there will be many other issues to deal with. Certain co-morbidities quite commonly occur and families may need help managing behaviour, language and communication, and other multisensory impairments. Young Epilepsy provides training to all professionals as well as organising conferences and workshops to further understanding around epilepsy and associated conditions. We also offer bespoke packages for individual organisations.

Training courses cover topics including:

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- Complex childhood epilepsy and managing challenging behaviour
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- Intro into epilepsy

Please call 01342 832243 ext 296 or email epilepsytraining@youngepilepsy.org.uk for more information.

Twelve years ago, at the age of thirteen, I was formally diagnosed with epilepsy. I had been having quite severe headaches for about a year, when I had my first seizure at a friend's birthday party. We'd been doing karaoke and whilst I was in the middle of a song, I fell backwards and began to convulse. Unlike other seizures that I have had since then, I maintained some level of consciousness that meant I could hear my friends' screams. My mother has since said that she didn't believe them when she got their panicked phone call that night. In fact, it wasn't until she actually witnessed me having a seizure a few months later that she could truly accept what was going on.

Unlike everyone else around me, I adjusted to having epilepsy fairly quickly. As teenagers, most of us are quite malleable and I suppose it was this that allowed me to wake up, bruised and confused, and wholly accept that this was now a part of me. It is however very important to note the difference between having a seizure and witnessing one. I've only ever seen one other person have a seizure before and it terrified me. It was whilst I was in Sixth Form – without warning, a friend of mine dropped to the ground in our crowded common room and began fitting. I stood frozen, just watching over her before running away. The helplessness that I felt in that moment was magnified by the knowledge that that was how it felt for my friends and family. Although it was jarring, the experience of watching someone else have a seizure gave me a fresh perspective on my condition which was something I really benefited from.

Since my diagnosis, I've had well over 100 seizures – the vast majority of which have been tonic-clonic (although I've also had partial and myoclonic). Whilst they are undeniably disruptive and dangerous, it is indirect aspects of the condition such as medication side effects, headaches, lethargy and memory loss that I have found to be most challenging. I think it is easy for people to forget about the multi-faceted nature of epilepsy, and unfortunately this lack of awareness can sometimes leave you feeling misunderstood.

As with most things, I have found being able to talk about epilepsy and how it has affected (and continues to affect) my life to be one of the most important and effective therapies. I am very lucky to have an extremely strong support system in my family and friends. However, due to the subjective nature of the condition, attempting to explain epilepsy to new acquaintances can be particularly difficult. Many people who are unfamiliar with it often default to 'flashing lights' as photosensitivity does tend to dominate the public understanding of the condition. Others react with fear (which can sometimes read as aversion), worried that I'm going to start fitting right then and there. When this happens, rather than get offended I try to openly inform people of the complexities and diversities present within epilepsy.

At the beginning of 2015, my epilepsy nurse recommended that I get in contact with Janine Palm from the charity Young Epilepsy. Initially, my meetings with her were one-on-one: we would meet for a coffee in central London and discuss my admittedly turbulent transition from student to working adult. Despite having a close network of family and friends, I found it surprisingly comforting and helpful to have someone who was removed from my personal life to be able to talk to. I suppose it afforded me a level of honesty that, as a proud and independent person, came as a great relief.

Since meeting Janine, I have been introduced to lots of young people coping with epilepsy through volunteering at various focus groups and events run by the charity – something that I have found to be therapeutic, educational and inspiring. Volunteering has allowed me to share my experiences of living with epilepsy whilst simultaneously learning from others about theirs. The scope of disability and the way in which different individuals experience it cannot be underestimated, and I think this is only something I truly realised having spent more time with other disabled people.

Schemes such as those run by Young Epilepsy are unfortunately rare due to a lack of funding. However, I feel that there is a great deal to be gained from encouraging communal activities within disability – particularly for younger people. It is all too easy to become isolated when you are labelled by society as being different, so time spent socialising with others who have an acute understanding of your circumstance can provide great respite.

Thankfully, after over a decade of more medications than I'm able to remember, I finally found a combination that seemingly controls my condition in September 2015. Prior to that, I'd had my worst year ever seizure-wise so it's hard to overstate the relief this bought not only to my body, but to my mind also. Despite this, I initially struggled when the 'what if' of epilepsy became 'what now'. After living with it for so long and growing accustomed to the unpredictability of it, factoring epilepsy out of my life seemed to be a much harder task than factoring it in had been. For a while, I felt like I was in epilepsy limbo – it was almost as if I was waiting to have another seizure. Although I'm a natural optimist, I suppose I just wanted to manage my expectations and prevent any disappointment further down the line. Having had some time to adjust, I've finally allowed myself to feel excited about a seizure-free future and all of the possibilities that that entails.

Essentially, I see my condition as a mark of strength, not one of weakness. I am proud to count myself as one of the millions of disabled people living in this country, for the resilience that I have discovered within myself and witnessed in countless others along the way has given me motivation and a level of awareness that I wouldn't otherwise have. I only hope that in time this attitude will become a universal one, for the existing stigmas surrounding disability are harmful not only to the affected individuals but ultimately to society too.

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'Awaiting a rehab bed'
the implications of delayed admission to rehabilitation after neurological injury

The British Society of Rehabilitation Medicine (BSRM) Medical Student's Essay Prize is awarded annually on a competitive basis. This year's winning entry was particularly interesting in considering the interface between specialist rehabilitation and acute hospital care and, we thought, worthy of a wider audience. While elements of inpatient rehabilitation become increasingly specialised and remote, the wait for transfer to such services can be frustrating for clinicians and patients alike. The appropriate multi-disciplinary management of acquired neurological disability should occur regardless of where in the health service a patient happens to be. The essay eloquently frames a different perspective on this issue.

The Essay Prize is worth £250 and is open to all medical students in the UK. The submission should be up to 2,500 words in length on a subject pertinent to Rehabilitation Medicine from a medical, biological or sociological point of view and include a review of relevant literature. Entries are judged by the education sub-committee of the BSRM executive. Further information and details of the other prizes awarded by the BSRM are available at www.bsrm.org.uk.

Winning entry by Alison Gowland

Alison is a final year medical student at GKT Medical School in London. Previously she worked as a Research Assistant in neuropsychology at the University of New South Wales. After graduating this summer she will take up an Academic Foundation Programme post at King's College Hospital, London.

Last summer I spent four weeks of my medical elective working with the neuro-rehabilitation team attached to a major trauma centre. I divided my time between the acute setting and one of its associated specialist neuro-rehabilitation units, with the intention of following some patients through this early part of their rehabilitation.

Only two patients made the transition from the acute hospital into inpatient neuro-rehabilitation during my period of observation, one of whom (patient L) I followed during part of their stay in the rehabilitation unit. The two main issues I identified during my involvement in this patient's case (which is presented briefly below) were i. the delay in their admission to the rehabilitation unit, and ii. the continuity of their care during this delay. These issues will be explored in terms of their possible effects on patients with neurological injuries, with reference to the relevant literature as well as to patient L's own experience.

Patient L

The patient I met in the acute setting had been admitted with a spontaneous right basal ganglia haemorrhage, complicated by intraventricular extension and raised intracranial pressure. This was treated neurosurgically with an external ventricular drain. They were accepted onto the waiting list of a specialist inpatient neuro-rehabilitation unit a little over three weeks after their initial admission, and remained on the waiting list for a further five weeks before a bed became available. In the interim, they were transferred between different wards three times, with associated changes in their therapeutic team (for example, during their time on a trauma ward they were treated by the peripatetic neuro-rehabilitation therapy team, whereas during their time on neurosurgical wards they were treated by the ward-based therapists). The question of whether their care should have been managed under the integrated stroke pathway was formally raised on two occasions, yet they remained under the care of the neurosurgical team until their discharge to the rehabilitation unit. They were medically stable during their five-week waiting period and the main action point on their medical care plan was to await the availability of a rehabilitation bed.

Delayed access to rehabilitation?

Delays in the appropriate care and management of patients with acquired brain injury are strongly contraindicated in the hyper-acute phase, where the concept of 'time is brain' (as coined by Gomez[7]) has become well embedded in the relevant clinical guidelines (e.g. those for stroke[5,9] and head injury[11]). The imperative for timely diagnosis and management of patients with brain injury is driven by the goal of minimising secondary insult and thereby, over the longer-term, reducing disability. But there has perhaps been less emphasis on the possible impact of delays later in the process on patients' rehabilitation potential (and by extension, their long-term morbidity and disability).

The unfortunate (if inevitable) existence of such delays is widely apparent anecdotally, and obvious from even the briefest encounter with rehabilitation unit waiting lists. Published data on actual waiting times for transfer to rehabilitation in the UK could not be found, though this information is routinely collated in the UK Rehabilitation Outcomes Collaborative (UKROC) dataset. UKROC data supplied by my neuro-rehabilitation unit for the 2014/2015 period show that the average wait between assessment (of the patient's suitability for this unit) and eventual admission to the unit was 31 days. The current standards[3] for transition into rehabilitation services suggest that this should happen within two weeks of assessment, for transfer into a Level 2 rehabilitation unit (local specialist rehabilitation services, such as the unit I attended), and within six weeks for Level 1 care (tertiary specialised rehabilitation services). However, the standards document itself notes that 'the majority of rehabilitation services are not adequately staffed and resourced to meet the proposed response times, and...the standards given are aspirational'.

This problem is not limited to the UK, nor is it attributable solely to limitations in the capacity of rehabilitation services as alluded to above. A study by Poulos and colleagues in Australia[14] that used utilisation review technology to assess appropriateness of patient bed days in acute care found that, for a group of stroke patients, only 49% of days spent in acute care actually met the criteria for this level of care. The commonest cause of the inappropriate occupation of acute care beds was delay due to awaiting an inpatient investigation or procedure, followed by delay due to awaiting review by a healthcare professional, though a significant proportion of patients were, like patient L, awaiting transfer to a rehabilitation bed (6.6%) or other discharge location (10.4%).

The impact of rehabilitation delay

What are the possible consequences of this delay for patients' rehabilitation? The idea that timely initiation of rehabilitation affects longer-term outcomes has been validated in animal studies of post-stroke recovery (e.g. by Biernaskie and colleagues[2]), as well as in cohort studies of stroke patients that suggest a critical time window of 'spontaneous neurological recovery' in the early days to weeks after stroke (see for example the work of Langhorne and colleagues, 2011[8]). Clearly, randomised controlled trials in this field are unachievable for ethical reasons, therefore the literature mostly relies upon retrospective comparisons to investigate this putative association. For example, a study by Salter and colleagues in 2006[15] conducted retrospective medical record reviews to examine the effects of early (i.e. within 30 days) versus delayed admission to rehabilitation after stroke, using FIM™[20] scores (Functional Independence Measure) to compare progress between groups. The FIM™ is a well-validated measure of the degree of assistance required by a patient across a range of domains that are important for activities of daily living, and is commonly used to assess patients' progress in rehabilitation. This study found that patients in the early admission group had higher FIM™ scores at admission and discharge, as well as shorter lengths of stay in the rehabilitation unit. Both groups made functional gains (as represented by change in FIM™ score) during their rehabilitation, but when the analysis was adjusted to take account of their higher FIM™ scores at the time of admission, it was apparent that the early admission group demonstrated greater gains. Both groups were similar in terms of age, gender, and side of lesion, though those in the delayed admission group were significantly more likely to have experienced haemorrhagic stroke than ischaemic stroke (and it is not clear that the authors conducted any further analyses to check whether this group difference was independently associated with the FIM™ outcome measures). It should also be noted that no information was available to the researchers about the initial stroke severity or acute medical complications experienced by the patients (both of which could interact with the purported association between rehabilitation admission delay and rehabilitation outcome). Nevertheless, these findings have been supported in similar retrospective cohort studies such as those by Wang and colleagues[17,18] and these studies appear to have been more careful to acknowledge and control for the myriad factors that contribute to delayed rehabilitation admission over and above logistical and capacity issues (such as characteristics of the stroke, the patient's age, and the patient's co-morbidities).

This association has also been reported for other neurological patient groups, such as those with traumatic brain injury (TBI), though this body of work is not yet as substantial as that for stroke. A retrospective study of paediatric cases of moderate and severe TBI (as defined by initial Glasgow Coma Scale score)[16] found an association between delay in commencing rehabilitation and rehabilitation outcomes (measured using FIM™), which was significant for children with moderate TBI, though did not quite reach significance for severe TBI (reflecting the greater potential for rehabilitation and recovery in those whose initial injuries are less destructive). For adult patients with severe TBI, a Norwegian study[1] demonstrated better functional outcomes at twelve months (as measured by the Glasgow Outcome Scale Extended) for patients who were allocated to early intensive rehabilitation, compared to patients who followed a standard pathway to sub-acute inpatient rehabilitation. The latter study highlights an interesting question over what specific characteristics of early access to rehabilitation might be most important for generating a better rehabilitation outcome. In the study, early intensive rehabilitation was initiated in a dedicated suite of beds in the Intensive Care Unit (ICU), the 'Early Rehabilitation Section of the ICU' (ERSICU), as opposed to the traditional model of transferring neurological patients to a separate, specialised inpatient unit to commence rehabilitation (which is the model employed in most of the research into the inverse association between delay to rehabilitation admission and rehabilitation outcomes).

This implies that it may not be the admission to a specialist unit that is most critical for optimising functional recovery, but the early application of a multidisciplinary rehabilitation model at a sufficient level of intensity, regardless of the actual environment in which this occurs (be it ICU, acute medical or surgical wards, or district general hospitals). Indeed, this is suggested as a reason why some studies have failed to identify an association between delay to rehabilitation admission and rehabilitation outcomes, such as the study by Gagnon and colleagues.[6] In this retrospective review of stroke patients discharged from a Canadian specialised inpatient rehabilitation programme, the researchers did not find any significant difference in outcomes (as measured by FIM™) between groups of patients with a short (less than 20 days), moderate (20-40 days) or long (more than 40 days) interval between their stroke onset and their rehabilitation admission. Groups were matched for age, gender and stroke severity (the latter characteristic is notably not controlled for in some of the studies that did find an association between delay and rehabilitation outcomes, such as that of Salter and colleagues[15]). The authors hypothesise that any negative effects of delayed admission to a rehabilitation unit were forestalled by the services offered within the acute care setting, where inpatient rehabilitation (here defined as physiotherapy, occupational therapy, and speech and language therapy) was rapidly initiated after initial stroke onset (usually within 72 hours). This is similar to the provisions for acute care in the UK, where early rehabilitation is embedded in practice and supported by the relevant clinical guidelines (such as those for stroke[5] and for rehabilitation after critical illness[10]). As yet there does not appear to have been any evaluation of the cost effectiveness of establishing rehabilitation in acute and critical care settings, nor of the ideal model for delivering this service, though a recent position paper[19] from the European Union of Medical Specialists (Section of Physical & Rehabilitation Medicine) supports a model in which dedicated rehabilitation beds, under the supervision of a specialist in rehabilitation medicine, are provided within the acute care setting.

Continuity of care

One of the advantages of such a model, which is particularly pertinent to the case of Patient L, is that it would establish a continuity of care for the patient within a dedicated rehabilitation pathway, even while they remain in the acute hospital setting. Patient L was not cared for under the remit of an integrated stroke pathway, for reasons not explicitly provided in their patient record but possibly related to the fact that the initial management of their injury was neurosurgical. Consequently, they spent the remainder of their inpatient admission being transferred between different neurosurgical and trauma wards (instead of in a dedicated stroke unit), with corresponding changes in the staff responsible for their early rehabilitation (from various disciplines including physiotherapy, occupational therapy, speech & language therapy and social work). In my visits during this period, they were often confused (with GCS of 14/15) and made frequent references to staff members who were not known on the current ward, as well as complaints about people who 'said they would come back and never did.' It is possible that their distress would have been lessened had they been cared for in a more consistent environment that took account of their cognitive and emotional needs. These are not uncommon issues after stroke: up to 75% of patients suffer some form of cognitive impairment, and mood disturbances are common, often presenting as depression or anxiety[12]. In the case of TBI, patients who remain in post-traumatic amnesia are often agitated or confused, and may be considered to be in a state resembling delirium[13] and thus could benefit from strategies commonly used to care for delirious patients, such as the establishment of a quiet and consistent ward environment, and continuity of staff care where possible. It is feasible that distress caused by inadequate management of cognitive and emotional states in the acute setting after neurological injury has some effect on the patient's rehabilitation potential in the short and long term, but no relevant literature could be found that investigates this possibility. It would be interesting to examine whether any such effects might also interact with the demonstrated association between delayed admission to rehabilitation and eventual rehabilitation outcomes. .

Conclusions

This essay has attempted to explore some of the issues arising from a prolonged stay in the acute hospital setting while waiting for a specialist neuro-rehabilitation unit bed. These issues were brought to life for me by patient L, who I was privileged to follow as they made this transition after a five-week delay. In choosing to focus on the issues from the patient's perspective, I have not given any consideration to the implications of delayed admissions for healthcare service delivery, which might pose a rather different set of problems. For example, provision of intensive rehabilitation in the acute setting during the wait for a place in a specialist neuro-rehabilitation unit could lead to functional improvements by the time such a place becomes available, compared to the functional level at which the patient was assessed when they were accepted to the unit. If patients arrive for specialist rehabilitation with a higher level of functioning than the unit is intended to cater for, this has implications for the future planning and resourcing of rehabilitation units.[4]

That said, there are some straightforward implications for healthcare services that follow from the above discussion of delayed access to rehabilitation and lack of continuity of care. Careful consideration needs to be given to the experience of patients who no longer require acute care but who do not yet have access to a place in a specialist inpatient rehabilitation unit. Integrated care pathways for stroke, incorporating dedicated stroke units, have helped to achieve a consistent rehabilitation focus for this patient group, but provision is less streamlined for patients with other neurological injuries (TBI in particular). A model that provides dedicated neuro-rehabilitation beds for such patients within the acute setting could help to avoid the situation like that of patient L, who did not appear to entirely 'belong' anywhere during their wait for a rehabilitation bed.

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The Festschrift of Peter Sandercock

Conference details: 15 April 2016, Edinburgh, Scotland. ***Report by:*** Tim Wilkinson, MBChB(hons), BMed Sci(hons), MSc MRCP(Edin), Clinical Research Fellow in Neurology, Centre for Clinical Brain Sciences, University of Edinburgh. ***Conflict of interest statement:*** The author declares that there are no conflicts of interest.

Given that Edinburgh is world-famous for its festivals (there are 12 in total), some might have considered it brave of the organisers of the Festschrift Conference in honour of Peter Sandercock to refer to the day as "a festival of epidemiology, clinical trials and evidence based medicine". Their confidence was justified however, as over 170 people from around the world came together on the 15th April 2016 to celebrate Peter's career, his achievements and his contribution to stroke research.

The day began with a look to the past, and a reminder that 30 years ago, when Peter began his research, knowledge of global stroke epidemiology was limited and there were no effective evidence-based treatments for stroke. Stefano Ricci spoke about Peter's work with the Oxford Community Stroke Project (working as Charles Warlow's first research fellow), and its influence on our understanding of the epidemiology of stroke as well as its role in introducing a practicable yet simple method of stroke classification. Bo Norrving discussed the changing global burden of stroke, and in particular how it is declining in high yet increasing in low income countries. Peter Langhorne colourfully likened the work of the Cochrane Stroke Group in looking through "long-dead clinical trials", to haruspicy, the ancient practice of predicting the future by looking through the entrails of dead animals. On a more positive note, he went on to discuss the beneficial influence the group (for whom Peter served as coordinating editor for a decade), has had on stroke practice worldwide. Zhengming Chen completed the session by reflecting on IST-1 and CAST, the first mega-trials testing treatments for acute stroke, and how they revolutionised a field that was previously lacking in high quality evidence.

The next session was entitled 'from past to present' focusing on aspects of current large scale trials in stroke and trauma in which Peter is involved. Colin Baigent discussed Peter's role as co-chief investigator of the IST-3 trial, which, with over 3000 patients, accounts for around half of the total available randomised evidence on the effect of thrombolysis in acute stroke. Next Ian Roberts spoke about the three CRASH trials in trauma and head injury, in which Peter has played a supporting role. He made a nice point that while the 'how to' of designing trials is well understood, the 'how to' of actually running these large trials is a 'craft' which is passed from 'master craftsman' to 'apprentice'. Martin Dennis spoke about the portfolio of trials he has run (Peter in a supporting role again) establishing the evidence behind interventions that may protect the rest of the body whilst the brain has time to recover after a stroke. Richard Lindley concluded the session with a talk on the nuances behind conducting stroke trials in low and middle income countries, and how interventions may need to be adapted to a given population based on affordability. Paradoxically, he also said, some low-cost interventions evaluated in low-income countries may well find application in the developed world too!

The session after lunch was centred on the future of stroke research, and Joanna Wardlaw began by discussing the process of translating an interesting clinical observation, through basic science and into clinical trials, using small vessel disease as an exemplar. Prof Wardlaw identified the 'Sandercock tool box' – a list of tips to advancing medical knowledge using Peter's pragmatic approach to science. Next up was Rustam Al-Shahi Salman who used the example of haemorrhagic stroke to discuss how randomised controlled trials need to be big, simple, and easy to do in order to be successful. He also explained the importance of understanding the local population in conducting an international trial (even if that means camel riding in Mongolia). Gillian Mead discussed the potential role of fluoxetine in recovery after stroke, and how conducting several concurrent 'sister' trials can be a useful alternative to a single multi-national trial; in this case, the FOCUS (UK), EFFECTS (Scandinavia) and AFFINITY (Australia) trials. Will Whiteley completed the look into the future with a talk on the potential value of using 'big data' to improve stroke care, and the possibilities of incorporating machine-learning technology into medical research.

In the final session of the day Shaun Treweek spoke about Trial Forge (www.trialforge.org), an initiative that intends to improve the evidence base behind the process of conducting trials and Jane Armitage discussed the need to train a new generation of experts in clinical trials, reinforcing the importance of apprenticeship in learning this trade.

Appropriately, Peter gave the last lecture of the day. He spoke about the highs and lows of his career, in what he referred to as "36 years of team science". His top tip for success? "You need to be steely in a nice way".

There were recurrent themes over the course of the conference when speakers expressed their opinions of Peter and his approach towards his work and his colleagues. "Calm" and "diplomatic" were the two most frequently used adjectives throughout the day. Many cited his diplomacy as the crucial factor in holding these mega-trials together. Several speakers regarded Peter as a "master craftsman" in clinical trials. However, Craig Anderson, from Sydney, in a typically robust antipodean fashion, characterised Peter (with a twinkle in his eye as he said it) as a "tenacious bastard". Much laughter ensued. The most evident aspect of the day was how Peter's approach to research has influenced many stroke physicians, trialists and epidemiologists. In all it was an enlightening, enjoyable day that covered the entire spectrum of stroke research whilst celebrating the role Peter has played during his illustrious 36-year career in the field.

Congratulations and happy retirement to Prof Sandercock. Edinburgh can proudly add a 13th festival to its events of 2016.

Prof Zhengming Chen (left) with Prof Peter Sandercock.

ABN 2016

Conference details: 17-19 May, 2016, Brighton, UK. ***Report by:*** Tom Jenkins, Clinical Senior Lecturer and Consultant Neurologist, Sheffield Institute for Translational Neuroscience and Royal Hallamshire Hospital, Sheffield. ***Conflict of interest statement:*** The author declares that there are no conflicts of interest.

All the world's a stage, and the stage for the 2016 ABN meeting was a sparkling spring morning in Brighton. Reflecting the shared meeting with the British Paediatric Neurology Association, the theme was the seven ages of man. Continuing the spirit of the meeting, this report will review some chosen highlights in seven stages, covering both clinical and research sessions.

At first the infant, as Shakespeare wrote, although the opening session actually preceded even this stage, with a review of issues surrounding pre-conceptual counselling, an emerging area of importance for neurologists as genetic advances continue apace; Mary Porteous took us through this complex topic, describing the IVF techniques available and also the quite stringent criteria that patients must fulfill. A discussion of anticonvulsant management in pregnancy followed with John Paul Leach arguing that sometimes less is more, when considering monitoring drug levels and dose adjustments, in inimitable Glaswegian style.

"From birth to the teens: the mewling, puking and whining years" must have been one of the more unusual lecture remits that Richard Bowman, Consultant Paediatric Ophthalmologist, has been given in his career but, together with Simon Hickman, Diego Kaski and Gordon Plant, it did not appear to faze him, as we were taken on a rapid tour of eye movement disorders, culminating in a smorgasbord of challenging spot diagnoses: look once, look twice and then look again was my slightly shameful take-home message from this important session on a difficult subject.

One of the more difficult ages of man is adolescence, as any parent of a teenager can attest, and more difficult again for adolescents with neurological disorders; this was acknowledged in the session on transition clinics, which offered practical tips on optimising history taking, for example, by using the examination as an opportunity for private discussion with both teenagers and parents. Advice was given on setting up services based on what young people actually want: opportunities to talk to other young people in similar situations are valued and boredom is anathema, according to Ros Quinlivan's studies. The neurology of young adulthood session included a masterclass on avoiding misdiagnosis of cerebral palsy from Neil Wimalasundera; essentially, determine phenotype, determine aetiology, perform imaging and be alert if the ducks don't line up, because there are treatable mimics.

Another thorny issue in practice at any age is CNS vasculitis, covered in a research presentation in the diagnostics session: unhelpfully, it appears that angiography results and brain biopsy contradict each other more often even than should occur by chance, rather like an angry toddler. In the absence of a clear gold standard test, as ever in neurology, the clinical picture must remain king.

Service organisation was addressed in a report from the Queen Square neuromuscular group in which a new clinic to streamline intravenous immunoglobulin delivery was shown to save thousands of pounds. I thought I might use this session to prove to our managers why attending the ABN represents good value for money. More food for thought in the cases session, a Sacksian collection of phantom limbs in Guillain-Barre, both PML and a germinoma mimicking neurosarcoidosis, tau imaging in frontotemporal dementia, hepatitis E related brachial neuritis and, finally, a voltage-gated potassium channel antibody-mediated spinal neuronitis resulting in head drop, spinal myoclonus and camptocormia. Of course, I may be a little biased but clinical neurology is surely the most fascinating of all medical specialties.

Professor Alistair Compston must think so, having devoted his life so successfully towards its forward progress. His ABN medallist lecture "A tale of three cities" took us on a journey through his extraordinary career, covering his achievements in advancing the field of MS genetics, the development of alemtuzumab therapy and more. The focus throughout his presentation was of the friends he made along the way and his self deprecating insistence that he had really only performed two rather lengthy experiments each lasting about 20 years. This however did not appear to convince the audience, judging by the prolonged and warm standing ovation he received. From other giants in their field, Ingrid Scheffer's Gordon Holmes lecture described the cumulative results of 20 years of productive research in epilepsy genetics and explained how results are now starting to lead to the elusive goal of personalised medicine. The Practical Neurology lecture, given by David Pencheon, warned of ecological Armageddon, had members of the audience checking their carbon footprints in real time, and made me walk to the station, instead of taking a taxi, at the end of the conference.

Professor Alistair Compston

And so into old age, a second childishness followed by mere oblivion, as Shakespeare rather depressingly put it. Aspects of the neurobiology of ageing were considered. Jonathan Schott described Macdonald Critchley's astute clinical observations in the elderly from the last century and still used today, for example, the importance of not over-interpreting absent ankle jerks and loss of distal vibration sensation in this group. He showed how many of the original observations have subsequently been revalidated by modern studies. Carol Brayne reported interesting and surprisingly positive news for ageing males worrying about dementia (your correspondent was particularly attentive here), and Paul Ince described the results of brain bank studies, from which interesting discrepancies between the presence of Alzheimer pathology and the clinical picture have emerged. As the conference entered its 7th age, the final session contrasted differing approaches to the same presenting symptom from opposite ends of the age spectrum. First, Hugh Markus took us through management of young stroke in the context of carotid arterial dissection post-CADISS (antiplatelets as good as anticoagulants and a reassuringly low recurrence risk). Examples of diagnosis of muscle weakness from Mark Roberts and James Miller followed, due to Anoctamin-5 limb girdle and myotonic dystrophy. Finally, the tricky disentanglement of ataxia, especially in children, was tackled by Peter Baxter and Mark Wardle and included pertinent comments on the diagnostic problems posed by normal levels of clumsiness in 4 year-olds.

So, a varied and fascinating conference, with the usual mix of useful and practical pointers from national and international experts, special interest groups, up-to-date research developments and a chance to catch up with neurologist friends from posts and PhD years gone by. A chance too, perhaps, to reflect on the passing of time, its influences on our patients and the diseases that afflict them, and on ourselves. And, as we shift into the lean and slippered pantaloon and bid farewell to Brighton, we look forward to the next age of the ABN in Liverpool.

The 20th International Parkinson's Disease and Movement Disorders Society Meeting

Conference details: 19-23 June, Berlin, Germany. ***Report by:*** Tom Foltynie and James Gratwicke ***Conflict of interest statement:*** The authors declare that there are no conflicts of interest.

So, this excellent meeting was back during those halcyon days (Pre-Brexit) when plans for new UK-European science collaborations were still an exciting, cross disciplinary, potential reality and England football fans were contentedly in the "phase of optimism", with every expectation of Euro2016 being their year...it all seems like such a long time ago. The MDS meeting, in contrast was an unarguable success.

Personalised Medicine

The most recurring theme throughout the week (plenary lectures by Susan Fox then Rejko Kruger) was the subject of Personalised Medicine in Parkinson's disease (PD). So many trials of neuro-protection have failed – CoQ10, Creatine, Minocycline, Pioglitazone – perhaps at least in part because we simply lump all PD patients together when recruiting.

A wealth of examples of the variability of PD were presented to underline the point;

1. COMT genetic variation predicts response to Entacapone,
2. Rasagiline response varies according to dopamine D2 receptor variants,
3. GBA mutation carriers have higher risk for dementia,
4. Alpha synuclein polymorphisms have relationship with cognitive impairment,
5. Protective effects of caffeine may depend on GRIN2A allelic status,
6. Positive outcomes from DBS relate to reduced alpha synuclein expression...

...and perhaps the most robust is the development of a cumulative genetic risk score – Using a panel of 19 Single nucleotide polymorphisms, it appears possible to accurately predict time to progression to Hoehn & Yahr stage 3 (Mike Nalls et al...)

All of this emphasises our need to focus on which aspect of PD pathophysiology is being targeted by any specific symptomatic, or disease modifying approach to have any hope of writing sensible inclusion criteria and defining appropriate outcome measures when designing trials.

The most clear demonstration of personalised/precision medicine is the use of gene silencing, now a real possibility. Small interfering RNAs, zinc finger protein repressors and anti-sense oligonucleotides (very nicely reviewed by Pedro Gonzalez – Alegre) can target genetic mutations leading to a toxic gain of function and such approaches are now a reality and are in clinical trials in Huntington's disease (led by Sarah Tabrizi). Encouraging outcomes can be expected to lead to this approach being adopted in other single gene disorders like DYT1 dystonia or the Spinocerebellar ataxias. If we can get the dose right, perhaps it might even be conceivable that targeted silencing of alpha synuclein expression might become a possibility for PD.

Susan Fox (MDS Secretary Elect) posing in front of the conference centre.

Other ways of tailoring approaches to PD genetic subtypes were also presented. Although there are concerns that the current raft of LRRK2 inhibitors may lead to excessive lung toxicity, there still remains hope that this precision medicine approach might ultimately reach the clinic as a potential solution to PD patients with the LRRK2 G2019S mutation. And at the risk of Coenzyme Q10 fatigue, there was recurrent mention of the use of this agent and/or Vitamin K2 specifically for use in patients with mitochondrial forms of PD i.e. arising as a result of parkin/Pink1 types. Indeed, Patrik Verstreken/Melissa Vos have shown improvement in mitochondrial complex 1 function in fruit flies with Pink1 mutations which (Christine Klein tells me) has already led to plans of a formal randomised trial of CoQ10 in this subgroup of patients.

In other "parkin" news, Dr Koentjoro presented a fascinating story of a young PD patient with parkin mutations whose mother turned out to be homozygous for parkin mutations (and had no active parkin detectable in skin fibroblasts) but yet had almost zero signs of parkinsonism. It turned out that she had preserved mitophagy as a result of an "alternative mitophagy protein" which can be manipulated by viral vectors or even protein inducers….

While still with relevance to the mitochondrial PD subgroup, fibroblasts from DJ1 patients seemingly have loss of mitochondrial dynamics as a result of absence of the DJ1 protein due to mis-splicing of RNA. Very neat creation of a new U1 splicing small nuclear RNA restores the splicing machinery and can enable functional DJ1 protein to be translated.

Pathway convergence

In contrast however, it was also clear from one of The Controversy sessions that we're not all (particularly Eduardo Tolosa) in agreement that Movement disorders treatment approaches are (as yet) in any way dependent on genetic results.

Indeed while we may need to look at PD subgroups for some approaches towards disease modification, other approaches may have a broader reach. These include direct targeting of alpha synuclein e.g. the vaccination trials being set up by Affiris, Prothena, Biogen which, if successful, should have relevance for a far larger pool of PD patients. In this field, Jeff Kordower is developing the use of "intrabodies" (antibody fragments engineered to target intracellular alpha synuclein) which apparently have been shown to have positive behavioural effects in rodents. Furthermore we may yet have additional "convergence" along the lines of Oliver Bandmann's work on parkin fibroblasts that confirmed a role for Ursodeoxycholic acid (UDCA) to combat mitochondrial dysfunction yet seemingly this same compound also helps neuronal dysfunction of LRRK2 origin, i.e. is precise and yet broad..?

Analagous with this, Ole Isacson and others have previously shown that GCase levels (the enzyme associated with Gaucher's disease and Glucocerebrosidase (GBA) related PD) fall in the Substantia nigra during ageing even in sporadic (non-GBA) PD patients. Targeting single gene disorders may therefore lead to therapies for many other individuals aside from those with a specific gene mutation. Indeed, gene therapy delivery of GCase can seemingly rescue alpha synuclein pathology in a wide range of animal models.

In further contrast to the emphasis on patient "subgrouping", James Surmeier explained that the pattern of PD neurodegeneration occurs according to the brain connectome albeit with some synaptic partners being resistant to spread, and other cells degenerating even in the absence of Lewy pathology. His work has shown that some aspects of neuronal vulnerability depend on calcium dependent pacemaking activity. So why do we have this energy sapping system? This is supposed to have advantageous activity on mitochondrial energy

production to help us continue to move in emergency circumstances (such as lion attacks – his example), however "This design comes at a cost" with mitochondrial and proteostatic dysfunction ultimately arising in the context of a large energy demanding axonal arbor. We will find out in a year or two whether this vulnerability can in fact be reversed by his trial of the calcium antagonist isradipine…

Another approach that was presented is to search for medications associated with slower disease progression in the data from previous cohort studies/trials. This has identified that amitriptyline (of all neurological cliches!) was associated with prolongation of time from diagnosis before needing dopaminergic treatment. This unexpected finding gains some support by observations that amitriptyline has been shown to bind to alpha synuclein in culture, and retrograde transport of preformed fibrils of alpha synuclein is markedly diminished with the related drug, nortriptyline.

Alongside this, the problem that unites most PD patients is the core dopaminergic loss that characterises the disease. Stephane Palfi presented his data on Prosavin (a gene therapy construct containing all the genes necessary for the biosynthesis of dopamine), and described the current plans for further work using a more potent vector developed by Oxford Biomedica, due to start recruitment in France and UK this year.

Other PD stuff

In more immediate, clinically relevant news; Eduardo Tolosa also discussed prodromal PD, highlighting that 91% of REM sleep behavior disorder (RBD) patients convert to PD by 14 years, and that submandibular gland biopsies from RBD patients contain alpha synuclein pathology (in 8/9 patients compared to 0/26 controls). Murat Emre also highlighted the relevance of RBD to the later development of Dementia with Lewy Bodies (DLB). Among 174 RBD patients followed up for 10 years- 90% developed a neurodegenerative synucleinopathy (DLB, PD or MSA). Murat also described how CSF measurement of A-beta42 may help distinguish DLB from AD and it seems quite reproducible that low levels of CSF A-beta42 predicts rate of cognitive decline not only in AD but also even in the Lewy body dementias.

There are also some new PD drugs available. Angelo Antonini reviewed the additional beneficial effects of the newly launched drugs Safinamide and Opicapone, both of which can improve motor OFF time by 30-60 minutes and launched in the UK in 2016. He described the additional potential for the future use of the Adenosine receptor antagonist Tozadenant, and the pros and cons of Rytary (the bead formulation of L-dopa allowing for extended release), which include the need to significantly increase the daily dose of L-dopa to achieve the same plasma levels. There is also new data on the Accordion pill (constructed from multiple layers of L-dopa) which gradually releases in the stomach for up to 12 hours. A poster presentation of the Neuroderm

(subcutaneous L-dopa) data also suggests clinically relevant reduction in OFF time alongside reduction in L-dopa induced dyskinesias.

The prospects for cell repair in PD have had mixed news; strengthened by recent post mortem evidence from a patient who died 24 years after transplant confirming extensive reinnervation but, as in previous patients, with the existence of alpha synuclein pathology within the graft. And in the 18 year follow up data from patients transplanted in the Freed trial, now with a disease duration of 28-36 years, 5/40 are still alive, 4/5 have had DBS, 2/5 are on very low meds, 2 are living independently and DATScan imaging in 3 shows survival of tissue. However graft induced dyskinesias are present in 2/3, and these individuals still accrue non-motor symptoms consistent with the progression of disease. The evidence of trans-synaptic spread of alpha synuclein grows, with recent data from Patrik Brundin's work showing that preformed fibrils of alpha synuclein injected into the olfactory bulb spreads across multiple synapses over 12 months even in wild type animals.

So what else?

In an excellent lecture by Katie Lunnon we were taught about EWAS – epigenome wide association studies. Epigenetics is all about tissue specific gene silencing – enabling necessary differential gene expression in brain, heart etc, requiring DNA methylation that occurs based on the intact presence of >450k methylation sites across the genome. In an EWAS using post mortem entorhinal cortex from Alzheimer brains, the top locus for association was ANK1, alongside a strong correlation between an increase in methylation and disease severity that is consistently reproducible. Our "Movement disorder" priority of course, is to reproduce this type of work using nigra/ striatum from brains of PD patients- and while there were posters on EWAS in peripheral blood from PD patients, I was pleased to hear from colleagues that the post mortem region-specific work is indeed underway in the UK.

The huge range of videos shown at this meeting are always an excellent clinical aid for those seeing a variety of movement disorder patients. We saw several videos of patients with: whispering dysphonia (so no excuses for forgetting that this is due to TUBB4 mutations); a lady with spasmodic dysphonia, torticollis, and jerky hand movements, the clue to the diagnosis was the presence of multiple lipomas frequently seen in MERRF; and if you see someone with ataxia, dystonia or parkinsonism with bulging eyes, might be worth testing for SCA3.

And if you like collecting genes, Rab39b is yet another cause of (X-linked) dominant, but otherwise typical dopa responsive PD. It is a regulator of vesicular trafficking and leads to alpha synuclein toxicity in yeast.

Grand Rounds

These were great – all the experts performed very well, and the diagnoses were all very get-able if you were on the ball.

1. Young onset jerky movements plus postural tremor, father was an alcoholic – all the information you need! Myoclonus Dystonia
2. Young onset dystonia parkinsonism in several members of same generation. Presenting with odd dystonic gait. Possible parental consanguinity. Homozygous Pink1 mutation.
3. Rapid onset speech disturbance, and inability to walk. Jaw dystonia (Sardonic smile), swallowing difficulty, Clear parkinsonism on examination. (Dan Healy diagnosed Rapid onset dystonia parkinsonism due to ATP1A3 mutation just by seeing his facial expression as he came on stage...)
4. Childhood onset ataxia and speech problem followed by dyskinetic type movements – lower facial movements, dystonic gait. We debated ADCY5 but this time I won – Ataxia telangiectasia. NB – If you suspect Ataxia Telangiectasia, do not do any X-rays! – This disease is characterised by DNA fragility therefore the patients are very sensitive to radiation!
5. Severe dystonic head tremor in young man, dystonic speech and some balance issues, little intention tremor and slow horizontal saccades – otherwise pretty normal examination. Family History of tremor, ataxia but also MND – Spinocerebellar ataxia type 2 (with 42 CAG repeats).

Video Olympics

James Gratwicke went to the Video sessions and scrupulously recorded the descriptions and diagnoses while I had to attend another meeting. General feedback was that these were good but perhaps too many videos crammed into one session. (Our own Huw Morris performed admirably as a panel expert).

1. A young woman with neck stiffness, loss of dexterity, slow finger taps and tongue movements, with hypomimia and poor R arm swing. She had some improvement in symptoms with Ldopa. MRI, Datscan, and PET imaging were all normal. Anti-GAD titre was > 50,000. In this lady there was no evidence of underlying malignancy and

she had some improvement with IVIG.

2. A 60 year old male with subacute short term memory impairment and agitation and a background of 20 yrs focal epilepsy controlled on carbamazepine. He had a recent increase in seizures, and unexplained collapses. Chronic smoker. He had exaggerated round the houses vertical eye movements, a cerebellar syndrome, slow downward saccades. His MRI showed cerebellar atrophy. Anti-Ma2 Antibodies were positive and were causing an encephalitis in association with Hodgkins lymphoma.
3. A 65 year old male, with 10 year history of gait dysfunction, bilateral hearing loss, dropping objects for most recent 7 years. He had a vertical supranuclear gaze palsy, and round the houses eye movements, and myoclonic jerks. He was confirmed to have Niemann Pick type C.
4. A 19 year old male, with episodic involuntary movements for 1 yr, occurring 10-100x /day lasting 30s-5min. His EEG was normal, bloods and metabolic profile were normal but he had a low Parathyroid hormone.
5. A 14 year old female with 3/12 history of Bipolar disorder found unconscious. A few days later had onset of axial tremor of neck. Her lithium levels were normal on admission. Temperature 39 degrees, WCC 27,000. MRI revealed a swollen cerebellum. CT showed no evidence of solid tumours. NMDA-Receptor antibodies were negative. Repeat Lithium levels were very high. She was plasma exchanged and improved except the axial head tremor. This was "SILENT" (syndrome of irreversible lithium induced toxicity).
6. An 8 year old with severe developmental delay who had stopped clonazepam and then developed sudden onset involuntary movements. The MRI showed a hypoplastic cerebellum, with dilatation of the ventricles. = pontocerebellar atrophy type 2.
7. This 61 year old male had slowly progressive writing difficulty and abnormal movements in his right hand. Shaking of the hand had begun as a child. In his 20s, it worsened and interfered with ADLs. Alcohol helped. It gradually worsened over 15 years. No FH. Genetic testing revealed XYY Jacob's Syndrome. Males with this condition are tall (in contrast Kleinfelter's XXY are short), postural and kinetic tremor can occur in both.
8. A 28 year old female with tremor who had iron deficiency. Many of her family members had the same condition. Her parents were consanguineous. She had bilateral postural and intention tremor and a cerebellar syndrome with axial tremor of neck. Vitamin E deficiency.
9. A 43 year old female, with an unremarkable past medical history, then a 3 year gradually progressive illness featuring dizziness, dysarthria, unsteadiness and cognitive deterioration. There was a dominant family history of similar symptoms. She had upbeat nystagmus, a bilateral cerebellar syndrome. The MRI was normal and CSF was negative for protein 14-3-3. After 7 months she had much worse ataxia. This autosomal dominant cerebellar syndrome was a genetic prion disorder due to PRNP mutation, Gerstmann-Straussler-Scheinker syndrome.
10. An 8 yr old with recent onset symmetrical choreiform movements. Hypotonic. Treated with tetrabenazine, then one year later developed a generalised mobile dystonia. Treated successfully with trihexyphenidyl. Positive for a GNA01 de novo mutation. 2 paediatric cases have responded to DBS.
11. A 72 year old male, with no past medical history. He had slowly progressive gait difficulties. After developing a Left C8 radiculopathy, he had C3-T1 laminectomies and cervical spinal fusion. 2/12 later he had neuropathic pain in the C4/5 dermatomes in arms, severe when sitting or standing, mild on lying i.e. postural symptoms. Then he developed involuntary movements of head, neck, shoulders and upper back. EMG showed grouped rhythmic ndischarged in C5-innrevated muscles on standing only (not lying), and c-spine x-rays showed a misaligned anterior plate at C4/5.
12. A 32 year old female with abnormal neck and arm movements persisting for one year after implantation of a Vagal nerve stimulator. When she turned her neck to the left, her left arm rose involuntarily. This was due to an aberrantly placed VNS lead.
13. A 62 year old female with a previous left middle cerebral artery stroke. Afterwards she developed brief episodes of painful abdominal repetitive contraction on the right side. Epilepsia partialis continua causing belly dancing on video.
14. A 78 year old with AF who was warfarinised then developed subacute onset of new R arm weakness, dysphasia, dysarthria, blepharospasm, and facial grimacing. His CT brain was normal. Bloods were normal. Ultimately diagnosed with Tetanus.
15. A 57 year old male, with past history of depression and gout. He developed transient diplopia. An MRI brain was normal, CSF was normal but, 4/12 later he had a subacute dementia, supranuclear gaze palsy, slow bilateral myoclonic movements in all four limbs. The EMG showed a myoarrythmia. The diagnosis was CNS Whipples disease (NB did not have the classical oculomasticatory myoarrythmia).

A tribute

On a more somber note, one of the plenary sessions was devoted to the memory of one of the most highly regarded movement disorder neurologists (and "mensch") Eldad Melamed, who died in 2015 and was prefaced by a very moving tribute by his friend Jeff Kordower.

The MDS meeting goes from strength to strength with evenly balanced clinical fascination and basic science discovery. Next year will be in Vancouver – see you there!

To list your event in this diary email Rachael@acnr.co.uk by 6th Sept, 2016

September

Parkinson's Foundation MasterClass
7-8 September, 2016; Sheffield, UK. T. 0845 338 1726, @TheNeuroAcademy, E. info@neurologyacademy.org, www.neurologyacademy.org

Royal College Psychiatrists Faculty of Neuropsychiatry Conference
15-16 September, 2016; London, UK. T. Virali Shah on 020 3701 2622, www.rcpsych.ac.uk, E. virali.shah@rcpsych.ac.uk

ILAE British Chapter Specialist Registrar Epilepsy Teaching Weekend
23-24 September, 2017; Oxford, UK. E. members@ilaebritish.org.uk

Multiple Sclerosis MasterClass
26-27 September, 2016; Sheffield, UK. T. 0845 338 1726, @TheNeuroAcademy, E. info@neurologyacademy.org, www.neurologyacademy.org

Hot Topics on The Management of Children with Complex Needs Symposium
29 September, 2016; London, UK.
www.nutricia.co.uk/events/children_with_complex_needs/

OCTOBER

38th Clinical Neurology Course
3-4 October, 2016; Edinburgh, UK. E. judi.clarke@ed.ac.uk

ILAE Irish/British Chapter Annual Scientific Meeting
5-7 October, 2016; Dublin, Ireland. www.ilae-ukconf.org.uk

Neurorehabilitation in Movement Disorders
6 October, 2016; London, UK. T. 020 7501 6762,
www.mahealthcareevents.co.uk/neurorehabilitaiton2016

11th International Congress on Non-Motor Dysfunctions in PD and Related Disorders
6-9 October, 2016; Ljubljana, Slovenia. www.nmdpd2016.kenes.com

Padovan® Therapy in UK: Neuro Functional Re-Organisation
MODULE I (4 days): Sensorimotor Development
11-14 October, 2016; Brighton, UK. E. info.uk.nfrpadovan@gmail.com

Hughlings Jackson lecture by Professor Alastair Compston and President's inaugural address - Evening meeting
27 October 2016; RSM, London, UK. www.rsm.ac.uk/events/CNH01

NOVEMBER

Sleep Summit 2016
22-24 November, 2016; London, UK. T. 020 7183 82 31
www.sleepsummit2016.com, E. sales@euroscicon.com

24th Annual Meeting of the European Charcot Foundation
24-26 November, 2016; Baveno, Milan, Italy. www.charcot-ms.org

The ILAE 2016 Concise Clinical Epilepsy Course for Junior Doctors
24 November, 2016; London, UK. http://ilaebritish.org.uk/events/concise-clinical-epilepsy-course-junior-doctors

DECEMBER

The brain series: Memory and the brain - Evening meeting
1 December, 2016; RSM, London, UK. www.rsm.ac.uk/events/CNH02

BNPA Neurology & Psychiatry SpRs Teaching Weekend The Essentials of Neuropsychiatry
9, 10, 11 December, 2016; Oxford, UK. T. 0560 348 3951,
E. admin@bnpa.org.uk or jashmenall@yahoo.com

2017

JANUARY

15th Annual Kings Neuromuscular Disease Symposium
27 January, 2017; London, UK. www.kcl.ac.uk/ioppn/news/events/2017/15th-Neuromuscular-Symposium.aspx
E. samantha.smith@kcl.ac.uk

Neurology and neurosurgery - on the wards and on take
30 January; 2017; RSM, London, UK. www.rsm.ac.uk/events/CNH03

FEBRUARY

Edinburgh Stroke Winter School
20-22 February, 2017; Edinburgh, UK. http://bit.ly/1USueTl

2018

FEBRUARY

10th World Congress for NeuroRehabilitation WCNR2018
7-10 February 2018; Mumbai, India
E: traceymole@wfnr.co.uk, www.wcnr2018.com

PREVIEW: ECTRIMS 2016




Declan Chard [1] ***Wallace Brownlee*** [1] ***Karen Chung*** [1] ***David Miller*** [1,2]

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The European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) meeting is, for the first time, being held in London (14-17 September 2016). It falls during a period of rapid and exciting change in the management of MS, and so for clinicians and researchers alike this should prove to be a useful opportunity to update. As in previous years, the meeting opens with a series of core teaching sessions, followed by a scientific programme that develops focused themes with a mix of invited reviews and related abstracts, and sessions that explore rapidly evolving or controversial areas. Several themes run though this year's meeting, but two that seem particularly topical are precision (personalised) medicine, which will be the subject of the ECTRIMS lecture to be given by Xavier Montalban, and progressive MS, now the focus of an international research effort through the Progressive MS Alliance (www.progressivemsalliance.org).

Precision medicine, the tailoring of management to individual rather than groups of patients, is not a new concept. It has been the goal of not to medicine for centuries, but in an era of large scale studies and trials it has perhaps been overlooked, particularly when there are few treatment options to choose from. However, with increasing range of medications that prevent MS relapses there is greater potential to choose. To date treatments have been initiated based on past disease activity, principally relapses. However, there is growing interest in biomarkers that will not only more rapidly assess efficacy than is currently possible with clinical measures, but will also predict MS disease activity and likely responses to treatments. Two teaching courses will cover genetic factors and biomarkers relevant to precision medicine in MS, "Advanced MS genetics and immunology" and "Examination of blood and CSF in clinical practice". Patient-specific treatment choices will be considered during the "Disease modifying treatments" teaching course, and in the scientific programme a Hot Topic session will explore the early treatment of active relapsing remitting MS. The likely mid and long term course of individual people with MS is difficult to predict, especially early on, and treatment decisions are based on relatively short term goals. Parallel Session 8 will consider long-term outcomes following a clinically isolated syndrome, including recent insights from imaging. Predicting treatment responses will be reviewed in two sessions: Teaching Course 13 "MRI as [a] predictor of treatment response" and Hot Topic 7 "CSF biomarkers can predict the course of MS and response to treatment". Balanced against the possible benefits of treatments, we also need to recall potential side effects. The association between the risk of progressive multifocal leucoencephalopathy (PML) and treatment with natalizumab is well established, but there is growing evidence to suggest that other treatments may also be associated with PML, and so Hot Topic session 4 "Biomarkers associated with the development of PML" will be of particular interest.

In the face of growing success in suppressing MS relapses, the contrast with treatment options for progressive MS has become increasingly stark. For patients, progressive MS has significant implications. The withdrawal of medications to suppress relapses, without the introduction of others to slow or prevent progression, may be seen very negatively. However, with recent positive trial results (simvastatin in secondary progressive MS and ocrelizumab in primary progressive), we are now seeing that progression may be slowed in some people with MS. Given that the majority of people with MS eventually develop progression, as with the introduction of highly active drugs for relapsing-remitting MS, when effective treatments for progressive MS become available, they are likely to equally substantially change MS clinical practice. Neurodegeneration is thought to be responsible for a significant proportion of the irreversible progressive disability in MS, and there are three sessions looking at the mechanisms underlying this and strategies to prevent it. Neuroprotection in the context of an acute inflammatory lesion will be reviewed in Parallel Session 2, while Parallel Session 6 will look at methods to assess neurodegeneration in life, and the role mitochondrial deficits play in neurodegeneration will be considered in Parallel Session 7 "Mitochondrial dysfunction and energy deficits mediating neurodegeneration in MS".

This year ECTRIMS meeting will be held in conjunction with the Rehabilitation in Multiple Sclerosis (RIMS) meeting. Parallel sessions will focus on novel multidisciplinary rehabilitation strategies (RIMS Parallel Session 1) and the neurobiological basis for brain plasticity that might be influenced by physical and cognitive rehabilitation in MS (RIMS Parallel Session 3). Symptomatic treatments are essential to improve the quality of life of people living with MS, and will be discussed in RIMS Parallel Session 2 and ECTRIMS Parallel Session 5, and also in a practical teaching course covering bladder dysfunction, spasticity and mood disorders (Teaching Course 7). In the last few years there has been increasing recognition of the importance of medical co-morbidities in people with MS. Parallel Session 10 will focus on vascular and non-vascular co-morbidities and how they may influence long-term outcomes in MS. Teaching Course 4 will explore the recent concept of "MS Brain Health" considering lifestyle issues such as cigarette smoking, obesity and physical inactivity that may have a detrimental effect on neurological outcomes in people with MS. With presentations from leaders of other Treatment and Research in Multiple Sclerosis organisations, Parallel Session 1 will discuss challenges for MS care and research in several regions around the world.

While the programme comprehensively covers MS clinical practice and research, it is not limited to this, and a substantial part is devoted to diseases that can clinically overlap with MS, such as neuromyelitis optica (Teaching Course 11 "Differential diagnoses", Teaching Course 12 "Neuromyelitis optica spectrum disorders", Parallel Session 3 "NMO update"). The Late Breaking News session may also throw up some interesting parting surprises: At the 2015 meeting the first trial to demonstrate a beneficial treatment effect in primary progressive MS (ocrelizumab) was presented.

Cardiff University employs Siemens MRI to unravel the mysteries of the human brain

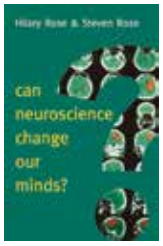
Her Majesty the Queen has officially opened the Cardiff University Brain Research Imaging Centre (CUBRIC), a unique neuroimaging research hub. The facility will seek to provide unprecedented insights into the causes of neurological and psychiatric conditions such as dementia, schizophrenia and multiple sclerosis. Four MRI systems from Siemens Healthineers will aid research by providing insights into the structure, function and chemical composition of living brain tissue, in turn helping to develop better neurology and psychiatric treatments. The research set to take place in CUBRIC will use cutting-edge methods that involve imaging and cognitive techniques. These will then be applied to key psychological and clinical questions.

It is hoped that the research will have a direct impact on the understanding of neurological and psychiatric conditions, including changes in the brain that lead to disordered cognition and mental health.

Professor Derek Jones, Director of CUBRIC, comments, "The Cardiff University Brain Research Imaging Centre is unique in Europe. This is the most exciting development in this field in the past decade and the start of a new era in neuroimaging. The technology will allow us to establish a much better picture of the make-up of the brain, including detailed measurements of the fibre-bundles that interconnect different parts of the brain. Ultimately we hope that this will help provide new targets for treatment."

www.siemens.co.uk/healthcare

New book by Steven and Hilary Rose separates the hope from the hype surrounding neuroscience



With its promise to cure physical and social ills, neuroscience has been trumpeted as a tool to increase the 'mental capital' of children. Instead of tackling intensifying poverty and inequality, claims are made that basing upbringing and education on brain science will transform both the child's and the nation's health and wealth. In Can Neuroscience Change Our Minds? neuroscientist Steven Rose and sociologist Hilary Rose take a sceptical look at these claims and the science underlying them. Examining the ways in which science is shaped by and shapes the political economy of neoliberalism, they argue that neuroscience on its own is not able to bear the weight of these hopes. This lucid, witty and incisive book makes eye-opening reading.

Can Neuroscience Change Our Minds? published by Polity Press.

http://politybooks.com/bookdetail/?isbn=9780745689319

Encephalitis Society 2016 Medical Essay and Travel Bursary competitions

The Encephalitis Society is seeking entries for its 2016 Medical Essay and Travel Bursary competitions.

The competition is a big part of its work to raise awareness and understanding of the condition, an inflammation of the brain, early in the careers of budding doctors, researchers and other clinical professionals.

Winners will be awarded £500 with an additional £250 for the runner-up in the Medical Student Essay Prize.

They will also be invited to meet leading professionals in the study of encephalitis and present their submissions at The Society's professional panel seminar in December, 2017.

For more information, visit www.encephalitis.info/awards

Neurology Academy launches MS MasterClasses

The Neurology Academy is launching a series of MasterClass courses to provide expert training for clinicians to advance understanding and confidence caring for people with multiple sclerosis (MS).

The first course this September is aimed at non-specialist MS neurologists and final year registrars. Clinicians will develop skills in both the clinical and managerial aspects of running an MS service while also gaining confidence in prescribing for patients with MS. Covering topics such as diagnosis, multidisciplinary team involvement, and relapse management, the MasterClass is delivered through taught sessions. Delegates will also receive ongoing mentorship and support provided by an experienced clinician. The programme is overseen by Professor Gavin Giovannoni, Chair of Neurology at Barts and The London School of Medicine and Dentistry, who is faculty lead for the MS Academy. Prof Giovannoni is developing the 2017 programme. The 2017 courses will be delivered in two streams. A specialist course targets trainees to become MS experts and explores how to set up and work within an MS specialist service; a more generalist course is aimed at general neurology clinicians and other health professionals, providing them with an update on developments in MS to ensure they develop the skills and competence to look after patients in the general setting. Both are focused on the knowledge and skills required in clinical practice.

www.neurologyacademy.org

SAVE THE DATE: Hot topics on the management of children with complex needs symposium

29th September 2016, 10:00 – 16:15
The Royal Society of Medicine, 1 Wimpole St, London, W1G 0AE

This symposium will provide a unique platform for discussion on the management of children with complex needs and will attract experts in paediatrics from across the country, who share a passion in paediatric nutrition.

Topics include:

- Nutritional Implications in Children with Neurodevelopmental Disabilities
- The Growing Child with Complex Needs: Practical Management and Real Case Scenario
- Feeding Team Tips and Tactics - Managing Children with Complex Needs

Presentations from:

- Dr Diane Sellers, Speech and Language Therapist (Clinical Lead Eating and Drinking Difficulties) Chailey Heritage, Clinical Services Sussex Community NHS Foundation Trust
- Professor Peter B Sullivan MA, MD, FRCP, FRCPCH, Oxford Children's Hospital, Associate Professor in Paediatrics, Associate Dean of the Medical School, University of Oxford
- Dr Veronica Kelly, Consultant in Paediatric Neurodisability, Evelina London Children's Hospital, Guy's and St Thomas' NHS Foundation Trust
- Dr Camilla Salvestrini MD,FRCPCH, Consultant Paediatric Gastroenterololgist, Centre of Paediatric Gastroenterology, Hepatology and Nutrition, Addenbrooke's Hospital, Cambridge University Hospital NHS Foundation Trust
- Sophie Audrey, Lead Paediatric Dietitian, Department of Children's Therapies, The Royal London Children's Hospital, Barts Health NHS trust
- Dr Kate Blakeley, Consultant Paediatric Clinical Psychologist, The Royal London Children's Hospital, Barts Heath NHS Trust.

Full programme to follow. To register please go to www.nutricia.co.uk/events/children_with_complex_needs

IT'S ABOUT GOOD DAYS, NOT LOST DAYS

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

COPAXONE® (glatiramer acetate) 40mg/ml Solution for Injection, Pre-filled Syringe Abbreviated Prescribing Information

Presentation: Glatiramer acetate 40mg solution for injection in 1ml Pre-filled Syringe. **Indications:** Copaxone is indicated for the treatment of relapsing forms of multiple sclerosis (MS) (see Section 5.1 of the Summary of Product Characteristics (SmPC) for important information on the population for which efficacy has been established). Copaxone is not indicated in primary or secondary progressive MS. **Dosage and administration:** Patients should be instructed in self-injection techniques and should be supervised by a healthcare professional the first time they self-inject and for 30 minutes after. A different site should be chosen for every injection. The recommended dose in adults is 40mg of Copaxone (one pre-filled syringe) subcutaneously three times a week with at least 48 hours apart. It is not known for how long the patient should be treated. A decision concerning long term treatment should be made on an individual basis by the treating physician. *Children and adolescents:* No specific studies. *Elderly:* No specific data. *Impaired renal function:* No specific studies. Monitor renal function during treatment and consider possibility of glomerular deposition of immune complexes. **Contraindications:** Known allergy to glatiramer acetate or mannitol. Pregnancy. **Precautions and warnings:** Subcutaneous use only. Initiation to be supervised by Neurologist or experienced MS physician. One or more of vasodilatation, chest pain, dyspnoea, palpitations or tachycardia may occur within minutes after injection. These generally resolve spontaneously after a short time. If severe, treat symptomatically. Caution in patients with pre-existing cardiac disorders and review such patients regularly. Convulsions and/or anaphylactic or allergic reactions can occur rarely. Rarely, serious hypersensitivity reactions may occur. If severe, treat appropriately and discontinue Copaxone. **Interactions:** No formal evaluation. Increased incidence of injection-site reactions with concurrent corticosteroids. Theoretical potential to affect distribution of protein-bound drugs, therefore concomitant use of these should be monitored. **Pregnancy and lactation:** Contraindicated in pregnancy. Consider contraceptive cover. No data on excretion in human milk. **Effects on ability to drive and use machines:** No studies have been performed. **Adverse reactions:** Serious hypersensitivity reactions have been reported rarely *e.g.* bronchospasm, anaphylaxis or urticaria. *Very Common:* Infection, influenza, anxiety, depression, headache, vasodilatation, dyspnoea, nausea, rash, arthralgia, back pain, asthenia, chest pain, injection site reactions, pain. *Common:* Bronchitis, gastroenteritis, herpes simplex, otitis media, rhinitis, tooth abscess, vaginal candidiasis, benign neoplasm of skin, neoplasm, lymphadenopathy, hypersensitivity, anorexia, weight increased, nervousness, dysgeusia, hypertonia, migraine, speech disorder, syncope, tremor, diplopia, eye disorder, ear disorder, palpitations, tachycardia, cough, seasonal rhinitis, anorectal disorder, constipation, dental caries, dyspepsia, dysphagia, faecal incontinence, vomiting, liver function test abnormal, ecchymosis, hyperhidrosis, pruritus, skin disorder, urticaria, neck pain, micturition urgency, pollakiuria, urinary retention, chills, face oedema, injection site atrophy, local reaction, oedema peripheral, oedema, pyrexia. Consult the Summary of Product Characteristics in relation to other side effects. **Overdose:** In case of overdose, patients should be monitored and the appropriate symptomatic and supportive therapy instituted. **Price:** Packs of 12 Pre-filled syringes £513.95. **Legal category:** POM. **Marketing Authorisation Number:** PL 10921/0026. **Marketing Authorisation Holder:** Teva Pharmaceuticals Ltd, Ridings Point, Whistler Drive, Castleford, West Yorkshire, WF10 5HX, United Kingdom. **Job Code:** UK/MED/15/0096. **Date of Preparation:** January 2016.

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

UK/UKCPX/16/0015b
Date of Preparation: July 2016