ISSN 1473-9348 VOLUME 14 ISSUE 2 MAY/JUNE 2014

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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

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David Booth – The Clinical Implications from the First Hundred Known MS Susceptibility Genes

Fiona Kennedy, Marc Randall and Martin Brown – What to do about Extracranial and Intracranial Stenosis

Donna Malley, Jacqui Wheatcroft and Fergus Gracey – Fatigue after Acquired Brain Injury: a model to guide clinical management

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Significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia. Severe active infection until resolution. Severe renal impairment undergoing dialysis, because insufficient clinical experience is available in this patient group. Severe hypoproteinaemia, e.g. in nephrotic syndrome. **EDUCATIONAL GUIDANCE**: Prior to prescribing AUBAGIO, physicians must familiarise themselves with educational materials which consist of a *Healthcare Professional Education/Discussion guide* and they should provide their patients with a *Patient Card* and *Patient Leaflet*. **WARNINGS AND PRECAUTIONS:** ***Monitoring***: Before starting treatment the following should be assessed: blood pressure, alanine aminotransferase (ALT/SGPT), complete blood cell count (CBC) including differential white blood cell (WBC) and platelet count. Exclude pregnancy. During treatment the following should be monitored: blood pressure, ALT/SGPT. A CBC should be performed based on signs and symptoms. ***Accelerated elimination procedure:*** Without an accelerated elimination procedure, it takes an average of 8 months to reach plasma concentrations less than 0.02 mg/l, although due to individual variation in substance clearance it may take up to 2 years. An accelerated elimination procedure can be used at any time after discontinuation of teriflunomide. (For further information, please refer to the SmPC). ***Hepatic effects:*** Assess liver enzymes before initiation of teriflunomide therapy - every two weeks during the first 6 months of treatment, and every 8 weeks thereafter or as indicated by clinical signs and symptoms. For ALT (SGPT) elevations between 2- and 3-fold the upper limit of normal, monitoring must be performed weekly. Teriflunomide therapy should be discontinued if liver injury is suspected and discontinuation should be considered if liver enzymes are confirmed as >3x ULN. 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In cases of severe haematological reactions, including pancytopenia, AUBAGIO and all concomitant myelosuppressive treatment must be discontinued and the accelerated elimination procedure be considered. ***Respiratory reactions***: Due to the potential risk of interstitial lung disease, pulmonary symptoms, such as persistent cough and dyspnoea, may be a reason for discontinuation of the therapy and for further investigation, as appropriate. ***Skin reactions:*** In case of ulcerative stomatitis, or if skin and /or mucosal reactions are observed which raise the suspicion of severe generalised major skin reactions, teriflunomide must be discontinued and an accelerated procedure initiated immediately. ***Immunosuppressive/Immunomodulating therapies:*** Co-administration with leflunomide is not recommended. Co-administration with antineoplastic or immunosuppressive therapies has not been evaluated. ***Peripheral neuropathy***: Confirmed peripheral neuropathy, consider discontinuing AUBAGIO therapy and performing the accelerated elimination procedure. ***Vaccination***: Live attenuated vaccines should be avoided. **SWITCHING to or from AUBAGIO:** No waiting period is required when initiating teriflunomide after interferon beta or glatiramer acetate. Due to the risk of concomitant immune effects for up to 2-3 months, caution is required when switching patients immediately from natalizumab to teriflunomide. To avoid concomitant immune effects when switching from fingolimod, 10-14 weeks is needed for lymphocytes to return to the normal range. If a decision is made to stop treatment with AUBAGIO, during the interval of 5 half-lives (approximately 3.5 months, although may be longer in some patients), starting other therapies will result in concomitant exposure to AUBAGIO. This may lead to an additive effect on the immune system and caution is, therefore, indicated. **CONCOMITANT USE AND DRUG INTERACTION:** Co-administration of teriflunomide with leflunomide is not recommended. Co-administration with antineoplastic or immunosuppressive therapies has not been evaluated. Rifampicin and other known potent CYP and transporter inducers, medicinal products metabolised by CYP2C8, oral contraceptives, medicinal products metabolised by CYP1A2, OAT3 substrates, BCRP substrates and OATP substrates should be used with caution during treatment with teriflunomide. For patients receiving teriflunomide treatment with cholestyramine or activated charcoal is not recommended. For co-administration of warfarin with teriflunomide, close INR follow-up and monitoring is recommended. **PREGNANCY AND LACTATION:** ***Pregnancy:*** Women of childbearing potential have to use effective contraception during treatment and after treatment as long as teriflunomide plasma concentration is above 0.02 mg/l. In case of suspicion of pregnancy, patient must notify the physician. In case of pregnancy, the physician and patient must discuss the risk to the pregnancy and the accelerated elimination procedure. In women wishing to become pregnant, teriflunomide should be stopped and an accelerated elimination procedure is recommended (Please refer to the SmPC for further information). Both cholestyramine and activated powdered charcoal may influence the absorption of oestrogens and progestogens during the accelerated elimination procedure. Use of alternative contraceptive methods is recommended. ***Lactation***: Breast-feeding women must not receive teriflunomide. **UNDESIRABLE EFFECTS:** Based on placebo-controlled studies the most commonly reported adverse reactions in the teriflunomide treated patients were: influenza, upper respiratory tract infection, urinary tract infection, paraesthesia, diarrhoea, increased ALT, nausea, and alopecia. ***Very common (≥ 1/10)*** Influenza, upper respiratory tract infection, urinary tract infection, paresthesia, diarrhoea, nausea, alopecia, ALT increase. ***Common (≥ 1/100 to < 1/10):*** Bronchitis, sinusitis, pharyngitis, cystitis, gastroenteritis viral, oral herpes, tooth infection, laryngitis, tinea pedis, neutropenia, mild allergic reactions, anxiety, sciatica, carpal tunnel syndrome, hyperaesthesia, neuralgia, peripheral neuropathy, hypertension, vomiting, toothache, rash, acne, musculoskeletal pain, myalgia, pollakiuria, menorrhagia, pain, GGT increase, AST increase, weight decrease, neutrophil count decrease, WBC decrease, post-traumatic pain. For listings and further information on adverse reactions, please refer to the SmPC. **Legal Classification:** POM (Prescription Only Medicine). **List Price:** £1037.84 per 28 day pack. **MARKETING AUTHORISATION NUMBER:** EU/1/13/838/001-005. **MARKETING AUTHORISATION HOLDER:** Sanofi-Aventis Groupe. 54, Rue La Boétie. F-75008 Paris. France. **FULL PRESCRIBING INFORMATION AVAILABLE FROM** Genzyme Therapeutics Ltd, 4620 Kingsgate, Cascade Way, Oxford Business Park South, Oxford OX4 2SU. **DATE OF PREPARATION:** October 2013.

▼AUBAGIO is subject to additional monitoring. This will allow quick identification of new safety information. 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 Genzyme Tel: 01865 405 200

References: 1. AUBAGIO (teriflunomide) Summary of Product Characteristics. November 2013. **2.** Confavreux C, O'Connor P, Comi G et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol* January 2014 [Published online]. DOI: 10.1016/ S1474-4422(13)70308-9. **3.** O'Connor P, Wolinsky JS, Confavreux C, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med.* 2011; 365(14): 1293-1303. **4.** Confavreux C, Li DK, Freedman MS, et al. Teriflunomide Multiple Sclerosis Trial Group. Long-term follow-up of a phase 2 study of oral teriflunomide in relapsing multiple sclerosis: safety and efficacy results up to 8.5 years. *Mult Scler.* 2012 Sep; 18(9): 1278-89.

Date of preparation: April 2014. AUBA-UK-2/14-4844a.

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Cover image by Andrey Kuzmin

ACNR

Published by Whitehouse Publishing,
1 The Lynch, Mere, Wiltshire, BA12 6DQ.
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PRINTED BY
Buxton Press T. 01298 21 2000

Mike Zandi, Editor.

One of the biggest challenges in treating neurological disease, and neurodegenerative disease in particular, is treating it early enough – before damage and a downstream cascade of further damaging events set in. The challenge then is in identifying the disease reliably early enough, and tracking changes with time. Natalie Ryan and Nick Fox from UCL review their pioneering work in identifying early and presymptomatic Alzheimer's disease using MRI and PET, with insights from familial forms of the disease, in our first review article in this issue.

In our second review, David Booth, from Sydney, interprets the results from the genome wide association studies in multiple sclerosis. He describes how the first 100 identified genetic associations have enabled a story to be built covering aspects of pathogenesis and likely beneficial early therapies, and helps make some predictions from the most recently discovered genes.

A symptomatic carotid or vertebral stenosis is found after an ischaemic cerebral event – what should be done? And what should be done for an intracranial stenosis, or asymptomatic stenosis? Fiona Kennedy (UCL), Marc Randall (Sheffield) and Martin Brown (UCL), in our Stroke article, take us through the evidence for management in these situations, and give an update on the state of play of current trials, including ECST-2.

The neglected and challenging symptom and issue of fatigue often comes up in the clinical consultation. Donna Malley, Jacqui Wheatcroft, and Fergus Gracey from the Oliver Zangwill Centre, Ely, in our rehabilitation article, provide a helpful neuropsychological model to help assess and guide therapy of this symptom with diverse causes.

Which 19th Century American author offered an analysis of headache disorders in one family over 20 years? Andrew Larner provides the answer on page 20. We have our usual book, conference and journal reviews, the latter including papers describing membranes, baselines, pigments, families and decompression.

Mike Zandi, Editor.
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Adverse events should be reported to the local regulatory authority. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Amdipharm Mercury Medical Information via telephone on 08700 70 30 33 or via e-mail at medicalinformation@amcolimited.com.

UK/OLE/AD/105/2013 Date of preparation: December 2013

Imaging Presymptomatic Alzheimer's Disease

Natalie Ryan
is an MRC Clinical Research Fellow at the Dementia Research Centre, UCL Institute of Neurology, with a clinical and research interest in young onset and inherited dementias. Her research focuses on the use of MRI, and in particular diffusion tensor imaging, to investigate early pathological change and phenotypic heterogeneity in familial and sporadic Alzheimer's disease.

Nick Fox
is Professor of Clinical Neurology at the Institute of Neurology, UCL and visiting Professor at the Vrije University Amsterdam. He is Consultant Neurologist to The National Hospital for Neurology and Neurosurgery London. His research has focused on using MRI in Alzheimer's disease and related disorders to improve diagnosis and to measure progression. He has developed techniques for registration-based atrophy measurements that are now widely used in clinical trials. In addition he has a longstanding interest in longitudinal clinical and imaging studies of familial dementias.

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Acknowledgements / Conflict of interest statement:
This work was supported by the Medical Research Council (Clinical Research Training Fellowship G0900421 to NSR, Senior Clinical Fellowship G116/143 to NCF). The Dementia Research Centre is supported by Alzheimer's Research UK, the Brain Research Trust, the Wolfson Foundation and the NIHR Queen Square Dementia Biomedical Research Unit. NCF holds an NIHR Senior Investigator Award. The authors have no other conflicts of interest to declare.

Provenance and peer review:
Commissioned and externally reviewed.

To cite:
Ryan NS, Fox NC, ACNR;2014;V14(2);6-9

Summary

- The symptoms of Alzheimer's disease are preceded by a long period of gradual accrual of pathological change. Familial Alzheimer's disease, due to autosomal dominantly inherited mutations in the Presenilin 1 (PSEN1), PSEN2 and amyloid precursor protein (APP) genes, has provided important insights into the trajectory of imaging changes during this preclinical phase of disease.
- Studies of presymptomatic mutation carriers using a variety of imaging modalities have demonstrated that amyloid deposition, hypometabolism, atrophy and altered structural and functional connectivity are evident at different points in the years before expected age at symptom onset.
- Longitudinal imaging will be particularly important for further investigating the variable vulnerability of different brain regions to amyloid accumulation and the dynamics of change in different biomarkers through the presymptomatic phase.
- Presymptomatic prevention trials for familial Alzheimer's disease using amyloid-modifying therapies are now being launched, in which imaging will play a central role.

It is now well established that the pathophysiological process of Alzheimer's disease (AD) begins many years, even decades, before symptoms develop and there is currently great interest in defining and characterising the preclinical stages of the disease.[1] This interest has been driven in part by the disappointing results of trials of amyloid-modifying therapies in patients with so-called "mild to moderate" AD, with at least one trial (of Solanezumab) showing in a post-hoc analysis that milder subjects appeared to do better than more affected individuals.[2,3] The suggestion being that treatment in the majority of trials may have been "too little, too late" with the implication that treating earlier in the disease would have had greater chances of slowing progression. The observation from some previous trials, of apparent treatment-related reductions in amyloid-beta (Aβ) burden at autopsy or on amyloid imaging, have encouraged the view that disease-modification may be possible, but perhaps with only limited benefit if downstream neurodegeneration is already well established. 20-40% of cognitively normal older individuals show evidence of Aβ accumulation in both positron emission tomography (PET) imaging and cerebrospinal fluid studies and a similar proportion of healthy elderly people have been found to have AD pathology at post-mortem[1] – the percentage who are "amyloid-positive" is very age-related and is also higher in those who carry an *ApoE4* allele. The proportion of these individuals who will or would have gone on to develop AD dementia is currently unknown, so research recommendations have proposed the term 'asymptomatic at risk state for AD' to refer to this particular preclinical stage.[4] The other proposed preclinical stage of AD is 'presymptomatic AD, a term reserved for individuals with autosomal dominantly inherited mutations in the Presenilin 1 (*PSEN1*), *PSEN2* and amyloid precursor protein (*APP*) genes who will inevitably develop symptoms of familial AD (FAD). In this review, we describe the insights into presymptomatic AD that have been gained through imaging studies of FAD mutation carriers and discuss some of the uncertainties and future challenges that remain as we enter an era of prevention trials for AD.

Understanding the timing and temporal order by which different imaging biomarkers become abnormal in presymptomatic AD is a fundamental issue for the field. The longitudinal study of healthy FAD mutation carriers with multi-modal imaging provides a unique opportunity to address this question. In recent years a number of large initiatives have been gathering such data: the Dominantly Inherited Alzheimer Network (DIAN) study, a multicentre project established with clinical sites across the USA, Australia and in the UK; and the Alzheimer's Prevention Initiative (API), which studies a large Colombian kindred affected by the *PSEN1* E280A mutation. So far, the results reported from these studies have largely been cross-sectional but as symptoms tend to arise at a similar age within a family, the ages at which an individual's relatives became clinically affected have been used to predict how far from symptom onset a presymptomatic participant may be. On this basis, amyloid imaging with Pittsburgh compound B (PIB)-PET in DIAN and Florbetapir-PET in API have demonstrated accumulation of Aβ in mutation carriers who are as far as 15 years below their expected age at symptom onset.[5-7] This confirms findings from earlier smaller studies, that Aβ deposition on PET is an early event in presymptomatic FAD. A striking observation from the initial FAD PIB-PET studies was that Aβ deposition was most intense in the striatum (Figure 1); a pattern reported for a variety of *PSEN1* mutations and

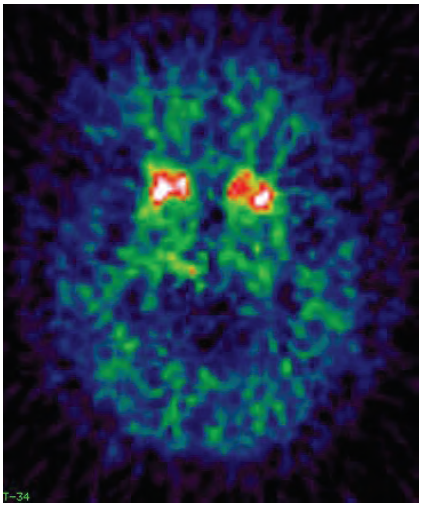

Figure 1: Prominent striatal amyloid deposition in a presymptomatic PSEN1 mutation carrier approximately three years prior to anticipated age at onset. Reprinted from 'Neuroimaging in Dementia', published by Springer.

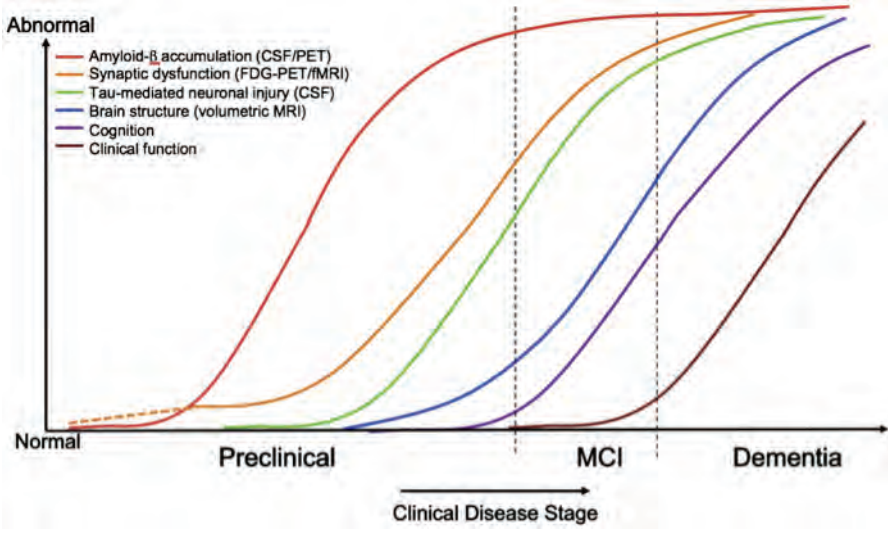

Figure 2: Hypothetical model of dynamic biomarkers of the AD expanded to explicate the preclinical phase, reprinted from Sperling et al.[1]

Aβ as identified by cerebrospinal fluid Aβ42 assay or PET amyloid imaging. Synaptic dysfunction evidenced by fluorodeoxyglucose (F18) positron emission tomography (FDG-PET) or functional magnetic resonance imaging (fMRI), with a dashed line to indicate that synaptic dysfunction may be detectable in carriers of the E4 allele of the apolipoprotein E gene before detectable Aβ deposition. Neuronal injury is evidenced by cerebrospinal fluid tau or phospho-tau, brain structure is evidenced by structural magnetic resonance imaging. Biomarkers change from normal to maximally abnormal (y-axis) as a function of disease stage (x-axis). The temporal trajectory of two key indicators used to stage the disease clinically, cognitive and behavioural measures, and clinical function are also illustrated. Figure adapted with permission from Jack et al.[14]

for APP mutation and duplication cases.[8-10] This striatal predominance does not appear to be seen with the Colombian kindred *PSEN1* mutation, and other *PSEN1* mutations have subsequently been found to be associated with more prominent thalamic PIB uptake.[11] The topography of early amyloid deposition in FAD caused by different mutations therefore appears to be more heterogeneous than was once thought.

Whilst amyloid-PET imaging measures the accumulation of abnormal protein, the other imaging modalities that have been applied to presymptomatic FAD are thought to capture aspects of neurodegeneration further downstream. The most widely used of these have been FDG-PET to measure glucose metabolism and structural MRI to investigate atrophy. MR spectroscopy has also been used and found to demonstrate posterior cingulate metabolic changes in presymptomatic mutation carriers who were on average 10 years younger than the mean age at onset for their family.[12] Using FDG-PET, widespread hypometabolism has been observed in presymptomatic FAD in a pattern similar to that seen in sporadic AD.[13] In the DIAN study, parietal hypometabolism was evident from around 10 years prior to the parental age at symptom onset. Most regions appeared to show the sequence of events predicted by theoretical biomarker models of AD, with amyloid accumulation occurring first, followed by hypometabolism followed by atrophy[14] (Figure 2). However, the DIAN data also indicated that there may be more complexity to the trajectory of presymptomatic biomarker changes than such models at first suggest. Firstly, different brain regions appear to vary in their vulnerability to the presence of amyloid pathology. Whilst all subcortical regions showed elevated PIB uptake, hypometabolism was only evident in the hippocampus.[6] Secondly, the direction of biomarker change was not always as predicted. In very young mutation carriers who were ~25 years from expected age at onset, there was some suggestion that there might be a hypermetabolic phase in some regions including precuneus and posterior cingulate. The numbers in this subgroup were small, however, so replication of the results in a larger cohort will be required.

Structural MRI is the imaging modality that has been most thoroughly investigated in FAD and, importantly, it has been used to study mutation carriers longitudinally from a presymptomatic stage up to the actual age at onset of clinical symptoms. Accelerating hippocampal and whole brain atrophy rates have been observed at 5.5 and 3.5 years before symptom onset in mutation carriers.[15] Cortical thinning of precuneus and posterior cingulate cortex has been reported approximately four and three years before onset respectively.[16] In these small cohort studies, longitudinal measures were able to detect presymptomatic change earlier than when a cross-sectional approach was taken. Visual rating of hippocampal atrophy in presymptomatic FAD appears to be relatively insensitive.[17] In view of the early striatal and thalamic amyloid deposition witnessed in FAD, more recent studies have also examined whether these subcortical structures undergo presymptomatic atrophy. We reported decreased volumes of thalamus and caudate in mutation carriers who were on average 5.6 years from parental age at onset, at a stage where hippocampal atrophy was not yet evident.[18] Presymptomatic atrophy of thalamus, caudate and putamen has also been reported in a separate cohort of mutation carriers who were ~15 years younger than the median age of dementia diagnosis in their family.[19] A voxel-based morphometry analysis of DIAN data demonstrated decreasing thalamic grey matter in presymptomatic DIAN mutation carriers closer to age at onset.[20] Subsequent analysis of a larger cohort from DIAN using an automated segmentation technique to assess cortical thickness and subcortical regional volumes demonstrated atrophy of the hippocampus, putamen, thalamus, amygdala and accumbens ~10 years and cortical thinning, particularly of precuneus, ~5 years before the parental age at symptom onset.[6] The lack of caudate atrophy in the DIAN data is somewhat surprising, particularly given the high amyloid burden observed in this structure. However, the caudate has been associated with a number of unexpected results in studies of presymptomatic FAD. Lee et al. found that, although caudate volumes were reduced in young presymptomatic mutation carriers, there was a trend towards increasing caudate size in symptomatic mutation carriers during the predementia phase.[19] Another group reported increased caudate volumes and cortical thickness in precuneus and parietotemporal areas in a small number of mutation carriers who were approximately a decade younger than their family's median age at symptom onset – with the intriguing possibility that early amyloid deposition may cause volume increases perhaps due to plaque-associated inflammatory responses.[21] Like the report of

hypermetabolism in very young mutation carriers, these observations of possible increases in regional volumes require replication in larger studies to ensure that they are not artefactual but they do raise the possibility that biomarkers may change in unexpected ways during the presymptomatic stages of the disease.

Diffusion tensor imaging (DTI) is another modality that has been found to show some unexpected abnormalities in presymptomatic FAD. This advanced MRI technique provides insights into tissue microstructure by examining the magnitude and directionality of water diffusion within white matter tracts and fibre-rich grey matter regions. Diffusion in white matter is described as anisotropic as it occurs preferentially along the major axis of a fibre. The three-dimensional nature of this diffusion is characterised by a diffusion tensor, from which various metrics can be extracted. Fractional anisotropy (FA) describes the overall shape of the tensor, with axial (AxD) and radial diffusivity (RD) representing diffusion in the principal direction of the tract and in the plane perpendicular to this. Mean diffusivity (MD) describes the overall magnitude of diffusion. Early DTI studies focused on white matter FA alone and decreased FA in the fornix, interpreted as loss of structural integrity, was reported in presymptomatic mutation carriers who were on average 13 years younger than the age at dementia diagnosis in their family.[22] We recently made a different observation; symptomatic mutation carriers were found to have the expected widespread reductions in white matter FA with increased MD, RD and AxD, however presymptomatic mutation carriers demonstrated a contrasting decrease in MD and AxD in the right cingulum.[18] Reductions in AxD occur in axonal injury, which we hypothesised may be an early event in presymptomatic FAD. We also examined diffusion characteristics in grey matter regions of interest and found a corresponding reduction in MD in the right hippocampus. Reduced caudate MD has been reported in another cohort of presymptomatic PSEN1 mutation carriers and it has been suggested that reductions in MD may reflect early pathological responses to amyloid accumulation such as microglial activation and/or swelling of neurons and glia.[21] Finally, we observed increased FA in the thalamus and caudate of presymptomatic mutation carriers, which we proposed may be due to the degeneration of long-coursing white matter tracts with preservation of short interneurons within these highly connected structures. Refinement of DTI analysis methods and their application to larger cohorts, particularly those with longitudinal data, will hopefully allow these initial findings to be explored in greater depth.

Another advanced MRI technique that is starting to be applied to the study of presymptomatic FAD is functional MRI (fMRI), which appears to be capable of detecting very early differences between mutation carriers and their mutation-negative siblings. In the Colombian kindred, altered hippocampal activation during memory encoding on fMRI and decreased right parietal volume has been reported approximately two decades before the median age at onset of mild cognitive impairment for the family.[23] Another study has found decreased left hippocampal fMRI activity during memory retrieval in mutation carriers.[24] In the DIAN study, resting state fMRI data has been analysed to look at functional connectivity in the default mode network; the set of brain regions whose coordinated activity during wakeful rest appears to be critical for successful memory function. Reduced connectivity in precuneus/posterior cingulate and right parietal cortex was observed in mutation carriers on average 12 years from parental age at onset, with decreasing functional connectivity observed in those closer to their expected age at onset.[25]

One of the challenges in comparing different imaging studies of presymptomatic AD is that different groups have used different measures to estimate how far from clinical onset the mutation carriers may be. These include years from the parental age at symptom onset, the mean or median age at symptom onset for the family or the mean/median age at diagnosis of mild cognitive impairment or dementia. The latter two of these will of course occur later than the age at symptom onset and may vary according to a range of sociocultural factors surrounding presentation to health professionals. Recollections of when a relative's symptoms began are themselves subjective and can change over time. Furthermore, although symptoms appear to manifest at broadly similar ages within families, there is variability. Our understanding is currently quite limited regarding both the degree of such variability and the potential genetic or environmental modifiers that may underpin it. All of these caveats should be considered when cross-sectional studies are used to predict the temporal evolution of imaging changes in presymptomatic FAD. Comparability between studies may also be limited by differences in image analysis techniques as variability in methods, for example the approach used to segment a structure of interest like the caudate, may have an influence on the results generated. Finally, it remains uncertain how heterogeneously different FAD mutations affect imaging biomarkers in the presymptomatic phase.

Overall, the literature to date indicates that a variety of imaging biomarker abnormalities is evident in presymptomatic FAD. The use of a range of modalities has started to provide insights into the selective vulnerability of different regions to Aβ pathology, which longitudinal data should help to clarify. Longitudinal imaging will also be important for exploring the suggestion that the direction of change in some biomarkers may be dynamic at different points during the presymptomatic stage of disease. Appreciating the possibility that imaging biomarkers may change in unpredictable ways during preclinical disease is important, particularly in light of upcoming treatment trials. Previous clinical trials have shown that treatments can also have unexpected effects on biomarkers, with the greatest volume losses in the AN1792 Aβ active immunisation trial actually seen in antibody-responders.[26] As the API and DIAN study have now both launched presymptomatic prevention trials of amyloid-modifying therapies, information about the sequence of biomarker changes during the natural history of the disease and in the context of treatment will be acquired in tandem. Study of the asymptomatic at-risk state of sporadic AD may progress in a similar fashion, with plans underway for an anti-amyloid treatment trial in healthy older people with evidence of Aβ deposition on amyloid PET scans (the A4 trial). In this context, where imaging will be used to both define and study an at-risk state, a multimodal approach will be important and insights from the study of presymptomatic FAD may be particularly valuable. ◆

Understanding the timing and temporal order by which different imaging biomarkers become abnormal in presymptomatic AD is a fundamental issue for the field. The longitudinal study of healthy familial AD mutation carriers with multi-modal imaging provides a unique opportunity to address this question

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The Clinical Implications from the First Hundred Known MS Susceptibility Genes

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Conflict of interest statement:
The author has no financial or any other conflicts of interest to declare.

Provenance and peer review:
Commissioned and externally reviewed.

To cite:
Booth R, ACNR;2014;V14(2);10-13

Summary

- The first 100 genetic loci affecting MS susceptibility have been identified
- The genes indicate susceptibility is mainly due to variation in immune response
- The gene list includes current targets for MS therapy, and so likely future targets
- The two genes regulating Vitamin D activation are risk genes
- Biomarkers, and new therapeutic targets for existing and novel molecules, should follow from these genetic discoveries.

Multiple sclerosis (MS) is one of the most common neurological diseases of young adults. It is primarily an inflammatory disorder of the brain and spinal cord in which focal lymphocytic infiltration leads to damage of myelin and axons.[1] The risk of an individual developing MS increases greatly with the relatedness to someone who has MS. Typically from 1 in a 1000 for the normal population, about 10 fold higher for a first degree relative with MS, and about 200 fold higher for an identical twin with MS.[1] This indicates genetic variants can increase MS susceptibility, and identification of the genes should enable a better understanding of MS pathogenesis, development of better therapeutics, discovery of biomarkers to predict and measure response to therapies, and so better clinical management of the disease. Excitingly, many of these genetic variants have now been identified, as described in two recent papers in Nature (2011)[2] and Nature Genetics (2013).[3]

However, it's notable that if one identical twin has MS, the other most likely will not have MS.[1] This suggests it will be unlikely that genetic variants can be used to predict MS risk accurately in the clinic, since even for those identical genetically there is less than a 25% chance of concordance. Environmental factors are clearly also of major importance in disease risk, and these include exposure to UV light, vitamin D levels, smoking, and exposure to Epstein Barr virus.[4]

Concomitant with the discovery of the genes affecting MS, has been the sudden increase in pharmaceutical options for the most common form of MS, relapsing remitting MS. These new therapies can be more effective than previous therapies in reducing relapse rates, disability, disease progression, and brain damage as assessed by changes in brain volume and increase in gadolinium enhance lesions. But drugs which have significant effects on relapse rate and progression such as alemtuzumab and nataluzimab, carry increased risk of serious side effects. MS progression is highly variable and individuals are most responsive to disease modifying therapies when in the early stages of disease.[5] Since individuals are likely to vary in their response to each therapy, the decisions of which therapy to use, and how to measure response, are now critical to MS management. Can the identification of the genetic basis for MS risk be used to advance knowledge of such biomarkers? Can it enable the development of new therapies, including for secondary and primary progressive MS? How useful in the clinic is having a list of genes affecting MS risk?

Risk gene discovery

The first MS risk gene, HLA-DRB1 1501, indicated much about pathogenesis. The protein product of this gene has only one known function, to present antigen to CD4 T cells. So CD4 T cells are important in MS, MS is at least in part an immune disease and therapies targeting this interaction between antigen presenting cells and CD4 T cells may be effective: glatiramer acetate arose out of experiments using peptides designed to bind this MHC class II molecule, and interferon beta is an immune modulator.

In 2007 two more genes were identified using a genome wide association study (GWAS),[6] and there are now (2014) more than 110 genetic regions (the MS110), plus the MHC region, associated with MS.[3] The breakthrough in identification of the MS risk genes was enabled by three major steps forward in human genetics: the sequencing of the human genome (2001), the cataloguing of the common genetic variants in the HapMap project (2005) and the 1000 genome project (2012), and the dramatic drop in the cost of genotyping, from about $50/variant to less than $0.01. This, combined with the collection of DNA samples from thousands of patients with MS and ethnically matched controls, with international collaboration mediated by the International MS Genetics Consortium, allowed the necessary genetic experiments and analysis to be done.

Many genes which affect MS risk also affect risk of other autoimmune diseases. The immunochip was designed to accelerate the discovery of the next genes in MS and other autoimmune diseases, by loading a genotyping chip with a high density of SNPS from all the genetic regions known to be associated with more than 10 autoimmune diseases from first phase GWAS. This allowed fine mapping of associations, and genotyping of more than 200,000 individuals, including 20,000 with MS, and replication or not of initial findings. This succeeded in finding another 48 MS risk genes, replicating the original Wellcome Trust GWAS find-

MS endeavour is an educational programme initiated and funded by Teva UK Limited

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Salford Royal NHS Foundation Trust
Salford

Ms Amanda Grant
Derriford Hospital
Plymouth

This meeting is open to Nurses working in Multiple Sclerosis only

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Friday 11 July 2014 19:00 – 20:30

- **Registration**
- **Chairs' welcome**
  Ms Karen Vernon & Ms Amanda Grant
- **Patient perceptions *vs* clinician perceptions**
  Prof Carolyn Young
- **Gains in neurology and TONiC**
  Prof Carolyn Young
- **Dinner**

Saturday 12 July 2014 08:30 – 15:30

- **Chair's introduction**
  Ms Amanda Grant
- **Inflammation and tissue damage in Multiple Sclerosis**
  Dr Matt Craner
- **Workshop session 1** *(Delegates can attend 3/4 workshops)*
  - Workshop 1: Selecting and monitoring Multiple Sclerosis treatments to suit your patient
    Ms Karen Vernon
  - Workshop 2: Impact of increasing disability in Multiple Sclerosis
    Dr Krystyna Walton
  - Workshop 3: The impact of pregnancy on the Multiple Sclerosis patient and the course of the disease
    Ms Pauline Shaw
  - Workshop 4: Recognising and managing social cognition
    Dr Jo Johnson
- **Workshop session 2** – (repeat of above 4 workshops)
- **Workshop session 3** – (repeat of above 4 workshops)
- **Debate:** This house believes that engaged patients perform better on Multiple Sclerosis treatments
  For: Dr Martin Duddy
  Against: Dr Ben Turner
- **Case studies:**
  - Importance of accessing physiotherapy for Multiple Sclerosis patients
    Dr Wendy Hendrie
  - Using acceptance and commitment therapy (ACT) to help manage your patients
    Dr Jo Johnson
  - Recognition and treatment of pain as a symptom
    Dr Sam Chong
- **Window of opportunity in Multiple Sclerosis treatment**
  Prof David Bates
- **Question and answer session**
  Moderator: Ms Amanda Grant
- **Chairs' comments and close**
  Ms Karen Vernon & Ms Amanda Grant

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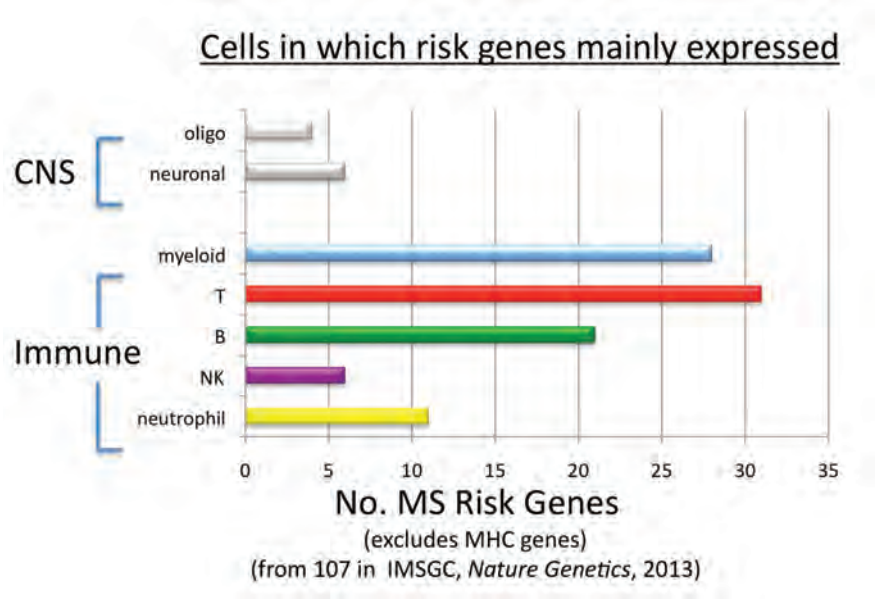

Figure 1. The cell types indicated by the genes: The number of the 110 MS risk genes[3] predominantly expressed in each cell type are shown, as identified in Parnell et al.[9]

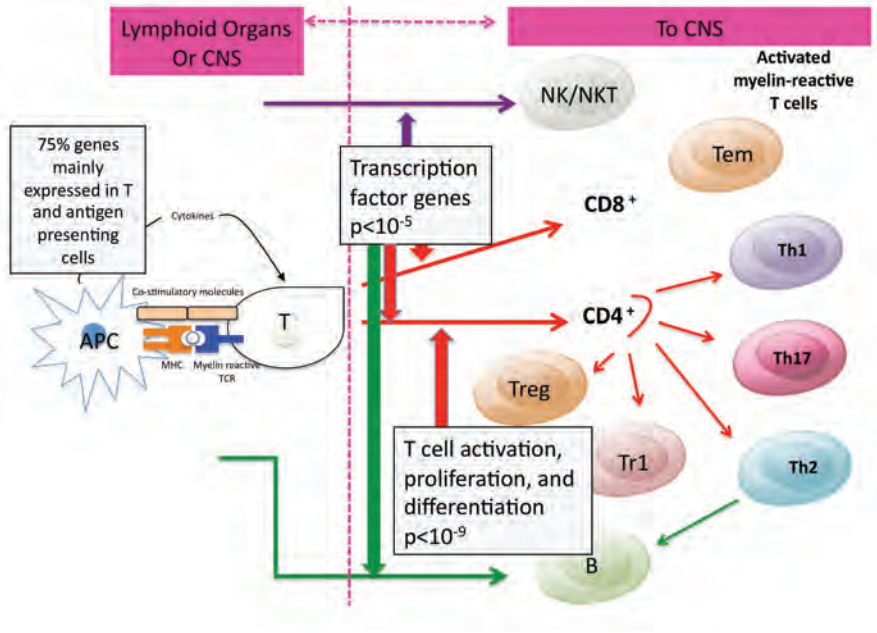

Figure 2: Metabolic pathways indicated by the risk genes: The likely net consequence of the risk variants may be to ultimately increase number and activity of myelin reactive T cells. Transcription factors regulating immune cell differentiation are over-represented in the MS110,[9] and genes encoding proteins which regulate T cells are also over-represented[2]. More details on the molecular architecture indicated by the genes are found in Hafler, 2012.[8]

ings, and more precisely identifying the regions of association.

How do the risk variants affect MS pathogenesis?

These MS risk genes are mainly expressed in immune cells,[7] especially in antigen presenting and T cells, supporting the paradigm that MS is an immunological disease driven by excessive activation of myelin reactive T cells[8] (Figures 1, 2). Strikingly, most associated SNPs are in intronic or intergenic regions.[7] This suggests the genetic variants increase risk by regulating gene expression. The over-representation of transcription factors controlling lymphocyte differentiation, suggests dysregulation of particular immune cell subsets may be driving MS risk, and this information has already been used to identify candidate biomarkers of MS risk, and may prove useful in assessing drug response.[9]

Do the MS110 indicate therapeutic options?

Proof of principal that the list of genes will be useful for finding new drugs, is that two of the risk genes are targets for existing drugs. IL2R, or CD25, is the target for the monoclonal antibody Daclizumab.[10] Natalizumab is a monoclonal antibody to α4-integrin of VLA-4, the CD49d antigen of leukocytes, blocking interaction with its ligand VCAM1, another of the MS risk genes.[11] There was also a potential explanation for some therapies working in rheumatoid arthritis but not MS: the genetic variants of CD40[12] and TNFRSF1A[13] have different associations in the two diseases.

The MS110 include many cytokines, their receptors, and other cell surface proteins for which pharma already have libraries of potential ligands. The risk gene products function like levers, the allele state altering the way the lever is pulled, and biological studies have followed to identify how these levers were increasing MS risk, and so whether ligands need to be agonists or antagonists.

There is also immediate benefit: amongst the MS110, two genes, CYP27B1 and CYP24A1 regulate vitamin D3 activation. They have no other known function. The protective variant of CYP27B1 is more highly expressed in tolerogenic dendritic cells, which produces more of the tolerising cytokine IL10 in a genotype dependent manner.[13] This is the smoking gun showing vitamin D is important in MS pathogenesis, supporting its use in reducing relapse risk,[14] and is an example of immediate benefit from finding the MS risk genes.

Are pathogens implicated in MS pathogenesis by the MS110?

If pathogens cause MS or alter its progression appropriate therapies could be employed. Genome wide analysis studies have implicated specific viruses for some autoimmune conditions. Individuals homozygous for the Crohn's disease risk allele rs601338 of FUT2, the receptor for noroviruses, are protected against norovirus infection, but are more likely to develop Crohn's and other autoimmune diseases such as type 1 diabetes and inflammatory bowel disease.[16] The Epstein Barr virus (EBV) virus has long been implicated as contributing to MS pathology.[4] Although its receptors have yet to be associated with MS risk, genetic variants of CD40 are associated with MS, and EBV uses its own analogue of human CD40 to induce infected B cells to proliferate. The genotype with higher expression of CD40 decreases MS risk.[15] Since CD40 is a costimulatory molecule, required for T cell activation, it would be expected that higher expression would increase risk of MS. A potential explanation for this paradox is that low host CD40 expression on B cells favours proliferation/survival of EBV infected B cells, using their EBV CD40. Risk genes TNFSF14 and TNFRSF6B may affect entry of herpesvirus 1; and SLAMF7 and TYK2 morbillivirus infection.[16] As CD40, TNFSF14/TNFRSF6B and SLAMF7/TYK2 also have roles affecting other aspects of the immune response, further implication of an EBV/HSV1/morbillivirus contribution to MS might follow if the MS susceptibility genotype can be shown to increase tissue damage or other infectious consequences due to these viruses.

What next for MS genetics?

Only a fraction (c.30%) of the heritability of MS has been accounted for.[3] The missing heritability could be due to risk variants of smaller effect, rare variants, and epistasis. Such vari-

ants are being sort by increasing sample numbers, and using a MS replication chip which includes all known exonic variants, including rare ones. This will also help refine the regions currently covering large blocks of linkage disequilibrium (where genetic variants are inherited as a block).

The risk factors have all been identified by comparing allele frequencies between MS and controls, so they identify susceptibility variants. Such variants must affect pathogenesis, but not necessarily progression. Since therapy choice is dependent on the likely rate of progression, with more conservative choices being favoured for benign MS, a new priority is to identify genetic factors controlling progression.

The MS risk genes identified to date provide us with a road map for dissecting out the molecular architecture of MS. So far they indicate MS is an immune cell mediated disease, support a role for vitamin D in pathogenesis and therapy, have already been used to identify candidate biomarkers, and identified new targets for investigation as therapies. This latter is particularly promising, as pharma has already built libraries of compounds to target many of the genes and pathways now known from the gene discoveries to affect MS risk. ◆

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Sir James Black Medal awarded to Professor Peter Kennedy

Professor Peter Kennedy, the Burton Chair of Neurology at the University of Glasgow, and Consultant Neurologist at the Institute of Neurological Sciences, has been awarded the prestigious Sir James Black Medal of the Royal Society of Edinburgh. This is the Senior Prize in the Life Sciences of the RSE and was awarded for his 'outstanding contribution to the field of tropical medicine though his pioneering work on human African trypanosomiasis and Neurovirology. ' He current research focuses on overcoming the toxicity of intravenous drugs used for treating CNS sleeping sickness and his laboratory has developed a novel oral form of the toxic melarsoprol. He also continues to research the cause of post-herpetic neuralgia following reactivation of Varicella-Zoster virus infection. In 2010 he was awarded the CBE for 'services to clinical science'.

WFNR Franz Gerstenbrand Award Now Open for Entries

WFNR
World Federation for NeuroRehabilitation

To support Brain Awareness Week (10–16 March 2014), the World Federation for Neurorehabilitation (WFNR) announced that the WFNR Franz Gerstenbrand Award is open for entries from clinicians, researchers and allied health professionals to recognise and reward a neurorehabilitation project that has benefited patients.

"This is the second year of our Award and we announced it during Brain Awareness Week to not only highlight our work in neurorehabilitation, but also to demonstrate our support for the global campaign to increase public awareness of the progress and benefits of brain research" said Stephanie Clarke, WFNR President.

Named after Professor Franz Gerstenbrand, in recognition of his continuous contributions to neurorehabilitation, the Award is worth £3000 and open to WFNR members and non-members worldwide. Entries can come from any aspect of neurorehabilitation and examples include a patient or clinic management initiative, research project, best practice development or the use of a new technological development.

The annual, single prize will be awarded as either a travel bursary to a clinical conference, professional development course or research project.

For further details and details on how to apply for the Award visit www.wfnr.co.uk

Introduction to the ACNR Stroke Series

In the next instalment of our ACNR stroke series, we tackle the question of how to manage extracranial and intracranial arterial stenosis, an increasingly common challenge within and outside the stroke field. Many trials have emerged in recent years, requiring clinicians to make sense of a large amount of complex data. A key question is when should revascularisation be used in preference to modern medical prevention. In this excellent article, Fiona Kennedy and colleagues present a clear and concise summary of the evidence needed to make clinical decisions, and also outline areas of uncertainty requiring further research.

David Werring,
Reader in Clinical Neurology,
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What to do about Extracranial and Intracranial Stenosis

Summary

- Medical therapy for stroke prevention has improved in the last 20 years, including widespread use of statins
- Optimised medical management should be implemented in all patients with extracranial or intracranial stenosis
- Patients with stenosis should be evaluated on an individual basis in order to decide on the best management
- Up to date clinical trials are required to determine the efficacy of modern medical therapy for the treatment of atherosclerotic stenosis compared with revascularisation

Dr Fiona Kennedy
MB Bch BAO MRCP(UK) works as a Clinical Research Associate with the Stroke Research Group at the Institute of Neurology, UCL. Her research focuses on carotid artery disease, especially carotid plaque composition and optimal treatment for patients with stenosis. Fiona is involved in running and recruiting to ECST-2.

Dr Marc Randall
is a Consultant Neurologist and Stroke Physician from Sheffield Teaching Hospitals with research interests that include Young Stroke, Cryptogenic Stroke, and Carotid Intervention. As a member of the Sheffield Vascular Intervention team he has published on outcomes from Stenting as an alternative carotid intervention technique.

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Conflict of interest statement:
The authors declare that there are no financial or other conflicts of interest.

Provenance and peer review:
Commissioned and externally reviewed.

To cite:
Kennedy F, Randall M, Brown M, ACNR 2014;V14(2):14-16

Introduction

Stroke is a major cause of morbidity and mortality in the UK with around 11,000 strokes occurring in England every year.[1] An important cause of stroke is atherosclerosis of the extracranial and intracranial arteries supplying the brain. Atherosclerosis is commonly found at sites of arterial branching, with the major sites of relevance to stroke being the origins of the internal carotid and vertebral arteries. Atherosclerotic stenosis can also be asymptomatic and patients may be identified during investigations for contralateral ischaemia, cardiac surgery and peripheral vascular disease. Challenges arise when faced with the decisions of how to treat patients with symptomatic and asymptomatic stenosis, whether extracranial or intracranial. Controversy exists regarding whether medical treatment is superior to recanalisation, and certainly physicians and surgeons may have different views. In this review we aim to summarise the existing evidence for the treatment of intracranial and extracranial stenosis providing arguments for and against different strategies.

Extracranial carotid artery disease

Approximately 20% of ischaemic strokes can be attributed to atherosclerosis at the carotid bifurcations, causing ipsilateral carotid artery territory ischaemia. The management of carotid stenosis focuses on revascularisation and optimising medical treatment.

Carotid endarterectomy (CEA), which was first performed in the 1950s, can reduce the risk of recurrent stroke. The European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) both showed a benefit in reducing the overall risk of stroke in patients with recently symptomatic carotid artery stenosis greater than 70%.[2,3] As a consequence of these reports CEA is

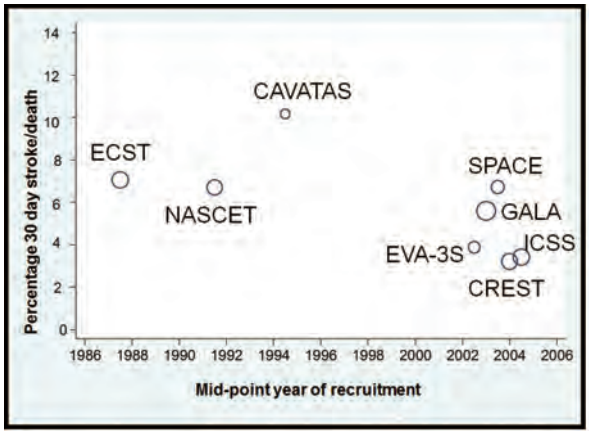

Figure 1: The percentage of patients with stroke or death within 30 days of CEA in symptomatic carotid stenosis trials by mid-point year of recruitment.

recommended to all patients with similar characteristics to the trial patients. In 2004 Rothwell et al developed a risk model using ECST data that predicted the future risk of stroke in patients managed with medical treatment only.[4] This model was validated in the NASCET dataset and showed that only patients with a high-predicted five-year risk of stroke (>20%) were likely to benefit from endarterectomy. Rothwell showed that surgery was not beneficial, and may even be harmful, in certain patients with a lower risk of recurrent stroke. Surgery itself is not without risk. The 30-day risk of stroke and death following endarterectomy was 7% in ECST but has improved in the last 30 years with a reported perioperative rate of stroke and death of 3.4% in the surgical arm of the International Carotid Stenting Study (ICSS) (see Figure 1).[5]

Treating asymptomatic carotid stenosis is more contentious. The risk of stroke in asymptomatic or remotely symptomatic patients is significantly lower than that seen in recently symptomatic patients.[6] The annual ipsilateral risk of stroke in patients with asymptomatic carotid artery stenosis may be as low as 2%.[7] The Asymptomatic Carotid Surgery Trial (ACST) randomised asymptomatic patients found to have 60-99% carotid artery stenosis, between CEA and medical therapy.[8] Over 10 years follow-up, the risk of stroke or perioperative death was reduced in those allocated CEA compared to those allocated deferral of any carotid procedure, but the absolute risks were low (13.4% vs. 17.9%) with a net gain over 10 years of only 4.6% (95% CI 1.2 to 7.9).

Carotid artery stenting (CAS) may be an alternative to endarterectomy (Figures 2 and 3). Trials comparing CEA and CAS in symptomatic patients have been published. The largest of these trials, the International Carotid Stenting Study (ICSS) included 1713 patients. The 30-day per protocol analysis showed a higher risk of stroke, death or procedural myocardial infarction in the stenting group compared with the CEA group (relative risk 1.83, 95% CI 1.21, 2.77, p=0.003)[9] but the long-term results did not show any difference in disabling or fatal stroke between both revascularisation techniques over a median of four years follow up. A recent analysis looking at modified Rankin score in both groups of patients also did not show any significant difference. EVA-3S, which also compared stenting and endarterectomy, was prematurely stopped due to safety concerns.[10] The 30-day incidence of any stroke or death was 3.9% after endarterectomy and 9.6% after stenting (relative risk 2.5. 95% CI 1.2-5.1, p=0.01). Similar to ICSS, SPACE and CREST did not report a significant difference between both treatment groups in relation to their end-points.[11,12]

Medical therapy for the secondary prevention of stroke has improved dramatically since the initial carotid trials. During ECST and NASCET statins for lowering cholesterol were not widely available. It was not until the mid-

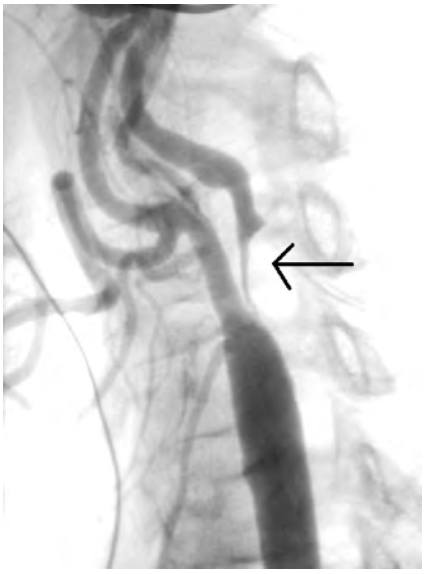

Figure 2: Severe internal carotid artery stenosis (arrow) shown on conventional angiogram.

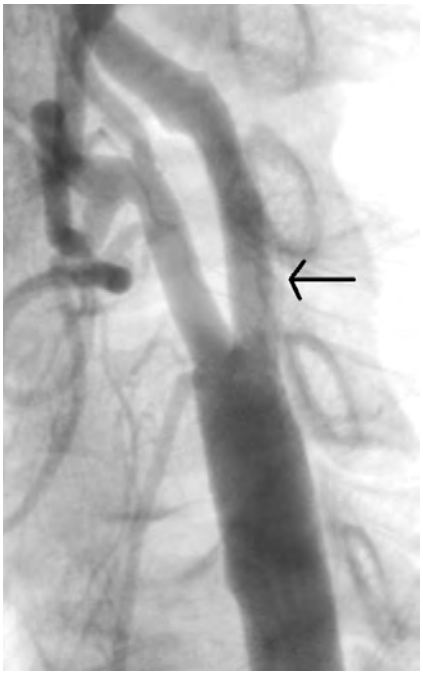

Figure 3: Carotid wall stent inserted into internal carotid artery and angiogram shows recanalisation of the vessel.

late 1990s that statins were used to lower cholesterol and were shown to reduce the risk of myocardial infarction. Only 17% of patients in ACST were taking statins.[5] Even in the more recent trials like CREST and ICSS, only approximately ¾ of patients were taking statins for secondary prevention. Observational studies have shown that patients who take statins have a 30-50% risk reduction in recurrent stroke rate.[13,14,15] Combined with improvements in the management of blood pressure and newer anti-platelet agents, the validity of the older trials might be questioned. New trials investigating the effect of modern medical therapy on patients with carotid stenosis are ongoing. The Second European Carotid Surgery Trial (ECST-2) is currently randomising patients with asymptomatic or symptomatic carotid stenosis who have a low to intermediate risk of stroke[16] between modern optimal medical therapy (OMT) alone and immediate revascularisation plus OMT. OMT includes targets for blood pressure and cholesterol and modifying lifestyle factors like smoking.

Vertebral artery stenosis

There is currently little evidence to guide the management of symptomatic vertebral stenosis and what is available is based on small case-series or single case-reports. Medical treatment for posterior circulation stroke and transient ischaemic attacks has been the standard treatment but evidence is emerging to support the use of revascularisation. The risk of recurrent events on medical treatment alone has been reported as high as 30%. Endarterectomy can be performed for extracranial vertebral artery stenosis but this is technically difficult and many complications are recognised.[17] Endovascular treatment with percutaneous transluminal angioplasty and stenting may be a safe and effective treatment for vertebral artery stenosis but data on long-term outcomes and procedural risks is required and may be available from the Vertebral artery Ischaemia Trial (VIST) (www.vist.sgul.ac.uk) and Vertebral Artery Stenting Trial (VAST).[18,19] Until then patients should be randomised into trials and not treated with stenting outside a clinical trial setting.

The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) included recruitment of patients with vertebral disease, however only eight patients (two randomised to angioplasty and two randomised to stenting) with symptomatic vertebral stenosis were randomised in this trial. None of these patients had a recurrent posterior circulation event during follow-up. However, it is very difficult to draw any conclusions, as the numbers were so small.[20]

Intracranial large artery stenosis

Intracranial artery stenosis causes approximately 8-10% of strokes[21,22] and is more common in the Asian and Afro-Caribbean populations. Patients with severe intracranial stenosis (70-99%) are at high risk of recurrent events, therefore it is important to define treatment strategies to prevent these events. Historically these patients have been treated medically but the high recurrent stroke rate on medical therapy has led to an interest in revascularisation. Revascularisation has been proven successful in certain patients with extracranial disease, therefore studies and trials have been designed to test the safety and efficacy of angioplasty and stenting in the patient population with atherosclerotic intracranial disease. However the long-term effect of such treatments have not been well established.

A meta-analysis of 31 suitable intracranial stenting studies by Groshel et al concluded that intracranial angioplasty and stenting is feasible and has a high initial success rate however highlighted the associated procedural risks and high restenosis rates.[23] However, this analysis pre-dated SAMMPRIS and there was limited randomised data comparing stenting to medical therapy. Most of the evidence-based medicine in this area comes from small registries that conclude stenting is feasible and can be safely performed.

The Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) trial is the first RCT in patients with atherosclerotic intracranial stenosis. SAMMPRIS compared revascularisation using the Wingspan stent with aggressive medical management. SAMMPRIS was stopped after enrolling only 451 patients because there was a high-observed risk of stroke and death in the stenting group.[24] In January 2014 the final results from SAMMPRIS were published in The Lancet. Patients were followed up for a median of 32.4 months and results supported the use of aggressive medical management in high-risk patients with atherosclerotic intracranial stenosis over percutaneous transluminal angioplasty and stenting (PTAS) with the Wingspan system.[25]

SAMMPRIS and several published studies have suggested that medical therapy for high-risk patients with intracranial stenosis is superior to stenting. Other studies however, have reported lower perioperative risks associated with angioplasty and stenting. The contradiction that exists in terms of success rates and adverse events may reflect differences in the perioperative management of patients and also the risk associated with individual patients. Tight risk factor control, especially blood pressure, can help reduce the risk associated with revascularisation procedures in any arterial territory.

Different revascularisation techniques have been used in these trials and studies including different types of stents. The stents that are used in these situations are often not specifically designed for the intracranial circulation and are modifications of cardiac stents. Patient risk profiles also differ amongst studies. In order to eliminate these biases further studies are needed to investigate which stents should be used, optimised risk factor management and patient selection for the procedures.

Conclusion

Understanding the risks and benefits of different treatments in specific patient groups with atherosclerotic stenosis is the key to making the correct decisions. More evidence is required from randomised trials, especially more detailed assessment of risk factors and the composition of the atherosclerotic plaque. Medical treatment for the prevention of stroke has evolved over the last 20-30 years and in some cases requires re-evaluating the results from older trials. In intracranial stenosis there is very little evidence to help physicians make an informed decision but with ongoing trials we can hope that more answers are on their way. Patients should be evaluated on an individual basis and the correct treatment decided. In intracranial and vertebral disease the focus has shifted towards revascularisation whereas in extra cranial carotid disease optimised medical management may be the way forward for patients at lower risk of recurrent stroke. It is important to develop a way of risk-scoring individuals, which can help identify those at high risk who may require a more aggressive approach.

Aggressive medical management should be implemented in all patients where it is safe to do so, including BP control and lipid lowering therapy, good diabetic management and cessation of hazardous lifestyle habits, most importantly smoking. This type of medical management will not only reduce the risk of stroke associated with the stenosis but also the perioperative risk of stroke and death that is too often quoted for revascularisation procedures. ◆

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Fatigue after Acquired Brain Injury: a model to guide clinical management

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Conflict of interest statement:
The authors have no conflict of interest to declare.
The research was supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care East of England at Cambridgeshire and Peterborough NHS Foundation Trust. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Provenance and peer review:
Commissioned and internally reviewed.

To cite:
Malley D, Wheatcroft J, Gracey F, ACNR 2014;V14(2);17-19

Summary

- Fatigue experienced following ABI is multifactorial and difficult to measure
- Fatigue impacts on rehabilitation, levels of social participation and quality of life
- There is a growing evidence base around fatigue, but this remains limited regarding management
- This clinical model may support development of a shared understanding, guide intervention and reduce vulnerability to fatigue for individuals
- More research into both the subjective (experienced, reported) and objective (physiological and neuropsychological) aspects of fatigue, and their interplay, is required

Fatigue is one of the most commonly reported, distressing and persistent of symptoms after acquired brain injury (ABI), including traumatic head injury and stroke, with an estimated incidence of more than 60% across the range of injury severity.[1,2] Injury severity is not necessarily a predictive factor in severity of fatigue experienced, with fatigue reported after mild and very severe ABI.[3] Persistent fatigue is associated with lower rates of return to work[4] and higher mortality post-stroke.[5] Despite this, evidence for management remains inadequate[6] and clinically people report feeling unprepared for this consequence of their brain injury.

Defining and therefore operationalising fatigue is challenging as there are many confounding factors associated with it. It is now widely accepted as a multidimensional, biopsychosocial construct, authors describing both primary and secondary, or physiological (central and peripheral) fatigue and psychological fatigue impacting resultant behaviour, felt experience and its presentation within societal and cultural contexts.[2] Central fatigue is considered to result from impairment to structures within the central nervous system and is characterised by depletion of hormones and neurotransmitters. Peripheral fatigue is considered as a diminished ability to contract muscles, involving the peripheral motor and sensory systems.[2,7] Brain structures and networks thought to be involved include the hypothalamic-pituitary axis, ascending reticular activating system, frontal cortex and basal ganglia. For example, neural circuits involved in the regulation of attention and executive function may contribute to development of tiredness and aversion to effort leading to fatigue,[8] whilst other authors[9] note involvement of the ventro-medial prefrontal cortex following penetrating traumatic brain injury.

Confounding factors contributing towards fatigue following brain injury incorporate pathophysiological, physical, mood and cognitive elements, including slowed speed of processing and difficulty sustaining attention,[10] executive dysfunction,[11] reward and effort perception,[9] anxiety and depression,[12,13] sleep disturbance[12] and pain.[14,15] Clinically these interacting elements may be considered as 'vulnerability factors' for fatigue as they are common consequences of an acquired brain injury and so addressing these factors may lead to a reduction in fatigue experienced

and enhance levels of social participation.

Many people experience fatigue as a consequence of participating in everyday activities. Pathological fatigue, which may indicate need for clinical intervention, does not necessarily dissipate with rest and is of greater intensity and duration compared to 'normal fatigue' experienced following exertion, with a corresponding impact on ability to undertake functional activities. People experiencing pathological fatigue following ABI frequently refer to their brain as "shutting off", with an intolerance to sensory stimuli and struggle to think and communicate effectively. 'Mental' fatigue (as opposed to peripheral fatigue) is frequently described as unpleasant and people perceive a lack of control over it with a negative impact on their level of self-efficacy.[16] Cantor and colleagues[6] suggests a 'coping hypothesis' with fatigue experienced considered a response to reduced cognitive functioning and tasks requiring more effort. They consider fatigue after brain injury as an "umbrella term" describing "different symptom clusters with potentially heterogeneous aetiologies and consequences" [6] [p. 880]. Patients report that fatigue significantly impacts upon their ability to participate in rehabilitation and daily living activities and influences their mood, relationships and quality of life. Eilertsen, Ormstad and Kirkevold[17] identified the need for acknowledgement of this distressing symptom from others as a key factor influencing coping as it presented as a 'hidden dysfunction' which could be misinterpreted by others.

There are numerous self-report fatigue scales available, though few valid and reliable measures have been developed for people with ABI. Such scales include the Barrow Neurological Institute Fatigue Scale[18] for acute stages post-injury, the Mental Fatigue Scale[19] which has been developed for the ABI population, the Neurological Fatigue Index – Stroke[20] which has been developed for Stroke. As a consequence, many clinicians and researchers make use of scales initially developed for other diagnostic groups, such as the modified Fatigue Impact Scale[21] and the Fatigue Severity Scale.[22] Additionally subscales of more generic ABI symptom questionnaires may indicate presence of clinically significant fatigue such as the Rasch-analysed EBIQ subscale[23] or the Profile of Mood States.[24]

Scales available may address different aspects of fatigue (e.g. intensity, severity, characteristics and impact on activities of daily living) over different timeframes. Therefore from a clinical rehabilitation perspective, measures are selected based upon the clinical question to be addressed or the domain which is expected to be changed as a result of intervention. In our experience, when people begin to feel less fatigued, they naturally attempt to engage in more activity and so their overall level of fatigue may not reduce significantly, as measured on a fatigue scale. However, it is possible to capture changes in their felt experience, such as a reduction in level of worry about their fatigue, an increase in their sense of control or self efficacy, an increase in their perceived quality of life or an increase in their awareness and understanding of fatigue. This change can be captured through using a recognised scale of these constructs or for example using an individualised likert scale before and after intervention.

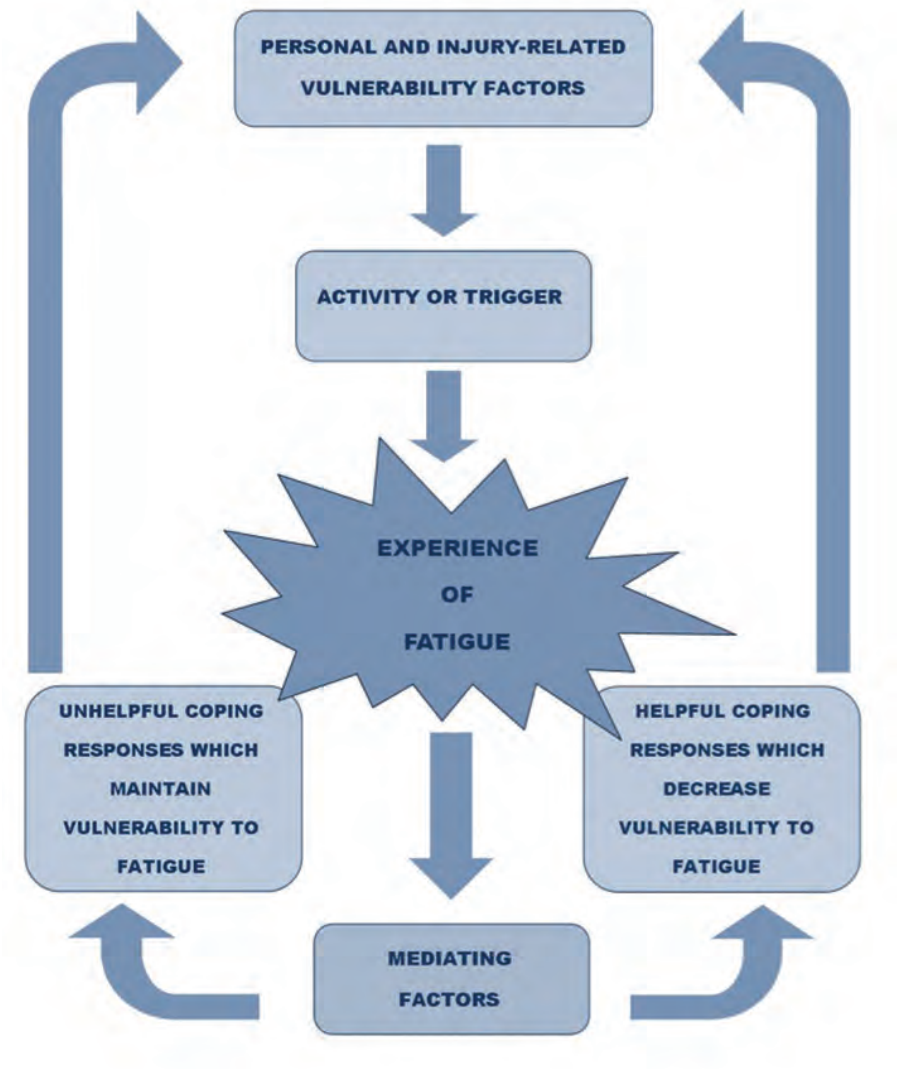

Figure 1: Clinical model for understanding responses to fatigue following acquired brain injury.

In terms of clinical management, given that fatigue is considered a multidimensional construct, attention should be paid to the variety of factors which may contribute to both performance fatigability (objective signs) and perception of fatigue (subjective symptoms). This involves identifying and addressing both personal and injury-related factors (primary causes and secondary consequences) that make an individual vulnerable to fatigue following ABI. Awareness of indicators of fatigue for that individual, mediating factors affecting behaviour (e.g. what they know about management, what they are doing and context) and potential triggers need to be considered in order to understand how an individual may respond to fatigue and support them to develop more helpful coping strategies. Fatigue management aims to increase a person's ability to participate in their desired activities more effectively, improve their quality of life and improve their sense of control over their fatigue.

There is an acknowledged discrepancy between objective signs (performance fatigability) and subjective experience (perception) of fatigue in the literature, which has led to a proposal for a unified taxonomy to guide assessment and intervention.[25] Several models of fatigue have been proposed in the literature. However, to date, none of these have been found to be clinically useful for understanding fatigue following acquired brain injury, to capture all aspects of this challenging construct and an individual's potential responses to it. The following model has therefore been developed by our clinical team, inspired by the fatigue model proposed for multiple sclerosis [cited in 26], current evidence and clinical experience, and it has been found useful when working with people with fatigue following ABI.

The clinical model proposed provides guidance on domains of functioning to assess and support fatigue management. A review of personal factors, including coping styles and

co-morbid illness, is recommended, with evaluation of injury-related vulnerability factors that could be contributing to fatigue based on pathology and assessment of associated physical, cognitive and psychological factors. This may indicate medical referral if physiological or psychiatric conditions are suspected which require further assessment and intervention e.g. endocrine dysfunction.

In terms of identifying triggers for fatigue, it is recommended to support the individual, and/or their significant other, to keep a 'fatigue diary' by monitoring changes in levels of fatigue before and after engagement in certain activities. By operationalising changes in energy levels, this could potentially enable assignment of 'points' to different activities to support pacing, identifying those activities or situations which 'drain' the resources and those which may 'recharge the body/mind' to support participation throughout the day. Use of analogies in fatigue management, such as recharging a phone battery, can be helpful. One important aspect of clinical intervention for people with ABI is to notice signs and symptoms of fatigue before they perceive their brain as 'shutting down' or fully 'draining their battery'. Self-monitoring of fatigue levels can be challenging following ABI secondary to dysexecutive syndrome, or as a consequence of reduced interoception. Identifying personal signs and symptoms of fatigue, through discussion, observation and asking others for signs of fatigue they notice will enable creation of a personalised 'fatigue scale' to indicate signs and symptoms of fatigue at an early enough stage to take action.

Neuropsychological formulation and multidisciplinary assessment can then support identification of current coping responses (helpful and unhelpful) and mediating factors influencing choice of coping, which may include knowledge and awareness of fatigue and management strategies, the context, beliefs and preferred coping styles. Unhelpful coping responses may include a 'boom and bust' approach, avoidance of activity and overuse of stimulants such as coffee or energy drinks. Education about fatigue has been demonstrated as an effective intervention via group[27,28] and/or individual intervention for people with Stroke and ABI. Mindfulness-Based Stress Reduction has also been demonstrated as effective when delivered as an eight week group programme.[29] Sinclair and colleagues[30] have identified short wave (blue) light therapy as a potentially useful intervention. Cognitive and environmental strategies and mood management all contribute towards reducing effort involved in completing activities and associated errors, which may then contribute towards reducing rumination and self criticism. Adequate hydration, nutrition and physical exercise, implementing good sleep hygiene and having an understanding of preferences and challenges in sensory processing will also aid fatigue management depending on vulnerability factors identified. Use of behavioural experiments to test out the impact of coping strategies and beliefs about the self has been useful in fatigue management intervention within our neuropsychological rehabilitation setting. It is recommended to identify helpful coping responses to both reduce effort involved and to re-energise oneself, both 'in the moment' and 'in anticipation' of certain triggers when planning to support an individual to pace themselves. Through creation of a personalised fatigue formulation and management plan, based on the proposed clinical model, a shared understanding and validation of the fatigue experience can be facilitated.

Assessment and management of fatigue remains complex and challenging for both clinicians and researchers. A clinically useful model to aid a shared understanding and response to fatigue and thereby reduce an individual's vulnerability to fatigue is proposed. This model, developed by the clinical team at the Oliver Zangwill Centre for Neuropsychological Rehabilitation (www.ozc.nhs.uk), seems to provide a helpful tool to support management advice and is based upon current evidence available. Further research is required to operationalise and validate fatigue assessment tools and to identify specific interventions that may reduce an individual's vulnerability to fatigue following ABI. Given the multiple factors and interventions that may be involved, a specialist neurological multidisciplinary rehabilitation team are likely best placed to support people with fatigue following ABI. ◆

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Louisa May Alcott and Headache

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Statement of conflict of interest:
The author has indicated that there are no financial or other conflicts of interest.

Provenance and peer review:
Submitted and internally reviewed

To cite:
Larner A, ACNR 2014;V14(2):20

Introduction

The American author Louisa May Alcott (1832-1888) is mostly remembered for her novel, *Little Women, or Meg, Jo, Beth and Amy* (1868), although she was a prolific author with many other works to her name. Such was the popularity of this one book, detailing the exploits of the March sisters (loosely based on the author's own siblings), that a sequel quickly emerged, *Little Women, or Meg, Jo, Beth and Amy, Part Second* (1869; this book is sometimes published under the title of *Good Wives*, presumably to distinguish it from the original *Little Women*). The March family, and in particular Jo March (based on Alcott herself), also form the axis around which revolve the characters in two later books, *Little Men: Life at Plumfield with Jo's boys* (1871) and *Jo's boys, and how they turned out* (1886).

To the neurological eye, the trilogy (or tetralogy, depending on how you count *Part Second*) permits an analysis of headache disorders seen in one family over a period of about 20 years (all subsequent page references are to the Library of America edition[1]). A brief account of the headaches in *Little Women* (1868) has previously been offered,[2] although some errors in reporting the sisters' ages were made: at the outset Meg is 16, Jo 15, Beth 13, and Amy, the youngest, is probably 12 (10,155).

The Little Women

Meg, aged 16, attends a party, following which she was "glad when it was all over, and she was quiet in her bed, where she could think and wonder and fume till her head ached" (98). At a subsequent party, the girls' neighbour, Laurie, warns Meg of the possibility of "a splitting headache tomorrow" if she drinks too much champagne (106). Many years later, Meg's daughter, Daisy, has headache when her paramour is about to depart to Europe (884).

At age 15, Jo gets "raging headaches by reading too long" (121) when her usual daily routine of looking after a trying elderly relative, Aunt March, comes to an end and the "experiment" of not working is tried. Aged 19, she undertakes "to be as lively and amiable as an … aching head … would allow" when preparing for visits to the house from Amy's superior friends (276). An entrée into literary society subjects Jo to philosophical discussions, "and the only thing 'evolved from her inner consciousness', was a bad headache after it was all over" (374); at this time she may be 20 or 21 (since Beth is between the ages of 18 (341) and 19 (397)).

At the age of around 25, Jo, meeting her suitor, Mr Bhaer, reports herself "so tired" when she "discovered that … her head ached". Five years later, aged 30, she is now married ("Mrs Bhaer"), has two children, and helps with the teaching and care of the pupils at Plumfield, bequeathed to her by Aunt March. One pupil, Nan, a girl of perhaps 10, reports "Didn't my sage tea make Mother Bhaer's headache go away?" (712). (Sage Tea or infusion of Sage, Salvia officinalis, has been claimed to relieve nervous headache. Sage was officially listed in the United States Pharmacopoeia from 1840 to 1900.)

We hear of no further headaches in the subsequent 10 years of Jo's life, despite her pupils being involved in various vicissitudes, including shipwreck and imprisonment, although some of her pupils are occasionally afflicted: George Cole ("Stuffy": 788, 1000, ascribed to overeating); Nat (888, "took his head in both hands as if it ached"); and Dan (1048, allegedly being read to too fast).

Beth, aged 13, has headaches which force her to lie on the sofa and cuddle her cats (42). Later she develops headaches at the onset of a febrile illness, which she self-diagnoses as scarlet fever based on her reading of her mother's book, and from which she nearly dies (186,187).

Amy, the youngest of the March sisters, seems unaffected by headache throughout the saga.

Louisa May Alcott

Alcott herself certainly suffered from headaches (subsequent references are from Harriet Reisen's biography of Alcott,[3] unless otherwise stated), for example in 1843, after harvesting at her father's ill-fated utopian farm, Fruitlands (79). During her work as a nurse (entirely without training) in a Washington DC hospital during the American Civil War in 1863, she suffered a febrile illness with headache, forcing her to return home.[4]

Problems with headache were particularly notable in the early months of 1867 when, according to her journal, Alcott "Did nothing all month but sit in a dark room and ache. Head and eyes full of neuralgia." (205). She frequently used opiates to treat these headaches (210,223,242,250). In 1869 she complained that headaches kept her from working as she once could "fourteen hours a day" (221), and also suffered from headaches and other symptoms (rheumatism, laryngitis) when writing later in that year (223). Whether the headaches were part of, or entirely separate from, a multisystem disorder characterised by later diagnosticians as lupus[5] is not entirely clear, but certainly in 1869 they occurred with other symptoms possibly indicative of a multisystem disease (223).

Conclusion

Louisa May Alcott may be included in the cadre of nineteenth century female novelists who wrote of and suffered from headaches, such as Charlotte Brontë,[6] Elizabeth Gaskell,[7,8] and (probably) Jane Austen.[9,10] ◆

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The Netter Collection of Medical Illustrations: Nervous System, Volume 7

Netter's has always set the Rolls-Royce standard in understanding of clinical anatomy and pathophysiology of disease process, particularly of nervous system. The new edition of the Netter collections of medical illustrations (2nd Edition Volume 7) is subdivided into Part 1 for 'Brain' and Part 2 for 'Spine'. Coming from the stable of the leading medical publisher, Elsevier, it is edited by H. Royden Jones, Ted burns, Michael Aminoff and Scott Pomeroy – eminent names in the world of Neurology. Together, they have enhanced the original work of Dr Netter.

Over two volumes, the book covers the entirety of the nervous system. It is very well written with excellent use of short concise text, beautiful illustrations and good use of correlation with the various imaging techniques. It provides the reader with a systematic approach to evaluate any particular central nervous system disorder. It fits in very nicely with 'system based' approach, now widely used in the medical schools throughout the world. It will be particularly useful for medical students in developing a systematic approach to complex clinical problems. However, it should be equally useful for the Neurology trainee or to a practicing neurologist (or any other clinician wishing to 'brush up' on a specific point). Its style is sufficiently clear, without assuming prior knowledge, that it should also be accessible to allied health professionals.

The book is well referenced and, for the eager learners, it also provides an exhaustive list of additional reading.

For the radiologist in me, it would have been slightly better if there were more medical illustrations correlated with the MRI images.

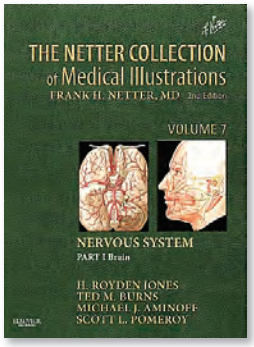
Part I on Brain contains 14 sections. Over 368 pages, it gives you a systematic approach in learning about various brain disorders. It starts with the basics of embryology, dealing with normal and abnormal development, pivotal in understanding various brain disorders. It systematically takes you through the cerebral cortex and neurocognitive disorders. The third section, on epilepsy covers Neurobiology to Semiology and touches upon the treatment. In sections 4, 5 and 6, it covers psychiatric disorders, deals with complex anatomy and pathways of hypothalamus, sleep and consciousness. I found section 7 and 8 on movement disorders, cerebellum and ataxias particularly well done.

Sections on stoke and multiple sclerosis are exhaustive. They cover pathophysiology to the recent advances in diagnosis and treatment. Sections on infections and neuro oncology are relatively short yet deliver good understanding as so the headache and cerebral trauma sections.

Part II deals with the spinal cord and peripheral motor and sensory systems. It is subdivided into 12 sections. Over 290 pages and with the use of sharp, concise text, illustrations and correlation with up to date imaging techniques, including spinal cord and cranial and peripheral nerve disorders. In the last 3 sections, it deals with the motor neuron, neuromuscular junction and muscle, and their respective ailments.

Netter has always been in a difficult position of being a benchmark against which all other books are compared. Many good books are available in the same niche, among which, 'Clinical Neuroanatomy' by Richard Snell stands out.

Currently available for £64.99 for each volume. It is well worth a read. If you want to drive a Rolls-Royce, I am afraid you have to pay for it!



Authors: H Royden Jones, Ted Burns, Michael J Aminoff, Scott Pomeroy
ISBN: 978-1416063865
Published by: Elsevier, 2013
Price: £64.99

Reviewed by:
Dr Manesh Bhojak, Consultant Neuroradiologist, Liverpool.

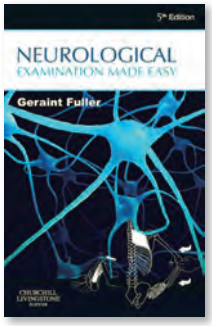
Neurological Examination Made Easy

The new fifth edition of this book is an improvement of this 'staple' pocket book, which covers the neurological examination in enough detail for the neurologist in bud. It is a well written, comprehensive and succinct guide to the clinical skills required by a junior doctor involved in the day-to-day care of patients suffering from neurological conditions.

The book is divided into a number of short chapters, which make for quick and easy referencing. The chapters are laid out in a logical way with specific emphasis on the main points. The techniques required for clinical examination are located at the start of each chapter and these are then followed by logical steps in the interpretation of abnormal findings, as well as common aetiologies. This is ideal for medical students and junior doctors; inevitably, Neurology speciality trainees will find some of these sections a bit too basic. Speciality trainees will need to supplement this book with one of the classics, such as John Patten's "Neurological Differential Diagnosis" or Paul W Brazis's "Localization in Clinical Neurology".

The flow charts are an excellent addition to the chapters as they permit prompt reference by the struggling junior doctor in the interpretation of particular neurological signs. I found the flow charts on nystagmus and gait interpretation particularly helpful, as they provide a structured and logical approach to these conceptually difficult subjects. The colour scheme of the fifth edition is a significant improvement on its predecessor; it is much easier to read, and gentler on the eyes. The final chapters on passing professional clinical examinations are especially good, drawing parallels with the everyday thought processes of Neurology specialists in 'the field'.

"Neurological examination made easy" is aimed at providing medical students and junior doctors with a solid foundation upon which to develop this important accomplishment. It is a book which any aspiring neurologist should read at least once, early on in their careers, and would very much be in my shortlist of pocket books to take around on the wards.



Author: Geraint Fuller
ISBN: 978-0702051777
Published by: Churchill Livingstone, 2013
Price: £24.99

Reviewed by:
Michael Bonello, Specialist Trainee in Neurology, Walton Centre NHS Foundation Trust, Liverpool

Neuronal hyperexcitability contributes to cell pathology?

Reviewer: Dr Sian Alexander, Academic Clinical Fellow (Neurology), Addenbrooke's Hospital, Cambridge, UK.

The causal relationship between neuronal dysfunction, including disorders of membrane excitability and synaptic transmission, and neurodegeneration is poorly understood. However, research in this area offers an important opportunity to identify targets for intervention early in disease that can prevent or delay neurodegeneration.

In this paper, Wainger and colleagues demonstrate neuronal hyperexcitability in Amyotrophic Lateral Sclerosis (ALS) patient-derived neurons, and seek to show the significance of this finding for cell survival. In cells from ALS patients with mutations in superoxide dismutase 1 (SOD1), C9orf72 or Fused in sarcoma (FUS), the authors used inducible pluripotent stem cell (IPSC) technology to generate motor neurons in vitro. They compared the excitability of these neurons (action potential firing, sodium and delayed rectifier potassium currents) using a combination of standard patch-clamp electrophysiology, for resolution of single-cell properties, and multi-electrode arrays, in which a net of 64 electrodes samples population excitability. Disease mutation-bearing cells were more excitable and generated more action potentials than control cells, attributable to reduced delayed rectifier potassium conductances. Cells treated with a Kv7 activator (causing hyperpolarisation), potentially have improved survival, consistent with the authors' hypothesis that hyperexcitability contributes to cell death. Unfortunately, the data relating hyperexcitability to cell death are not convincing due to the effect of a significant outlier in a single differentiation.

There are several IPSC quality control measures to appreciate in this paper. Two of note are the use of genetically identical (isogenic) cell lines aside from the identified mutation, and the study of several cell differentiations. Both of these measures are time and labour-consuming, but contribute significantly to the experiment's robustness. It would also be interesting to know whether the hyperexcitability phenotype was restricted to motor neurons or seen more widely in, for example, cortically-differentiated cells, given the apparent neuron specificity clinically.

Relating individual cell excitability to longer-term sequelae, including cell death, remains a difficult question and is the least convincing part of data presented here. Using new automated time-lapse microscopy, Tsvetkov et al demonstrated that risk of cell death is predicted by individual cell differences in clearance of mutant huntingtin (found in Huntingdon's disease). A similar technology for the study of excitability and cell fate is an exciting, if futuristic, prospect that could deliver some much-needed answers to this difficult question.

Tsvetkov AS et al, 2013. Nat Chem Biol. 9:586-92.

Wainger BJ, Kiskinis E, Mellin C et al. Intrinsic Membrane Hyperexcitability of Amyotrophic Lateral Sclerosis Patient-Derived Motor Neurons. Cell Rep. 2014. doi: 10.1016/j.celrep.2014.03.019. [Epub ahead of print].

Coming off the baseline

Reviewer: Dr Lloyd Bradley, Consultant in Rehabilitation Medicine St Richard's Hospital, Chichester, UK.

When teaching students or junior doctors about rehabilitation, one of the most important concepts I try to get across is that of a "baseline". The processes and outcomes of rehabilitation for an individual are guided by goals and these goals are specific to that individual. With the occasional exception, most people's goals will be toward the pattern that their life adopted pre-injury or illness. For this reason, an understanding and appreciation of that pattern is important. A place in Arsenal's midfield may be an unrealistic (and unachievable) aim for someone that struggled to get up two flights of stairs pre-admission.

Accumulating data suggests that recovery from a traumatic brain injury may be at least as dependent on pre-injury factors as on patterns of neuronal rewiring or synaptic change. The complex and individual nature of recovery and outcome, as well as the numerous symptom-defined complaints that accompany acquired brain injury mean that a "good" outcome is difficult to define. This means that researchers tend to either adopt the most reductionist of approaches (the Glasgow Outcome Scale) or qualitative descriptions that are challenging to understand and apply in a real world setting.

In order to get around this issue, the authors of this paper have constructed their own patient-reported questionnaire with 50 yes/no items to assess quality of life and disability. These questions were given to a well-defined group who had been inpatients on an intensive care unit following a severe traumatic brain injury over a four year period. The SF-36 and Glasgow Outcome Scale were also used for the study group. Unfortunately there are no controls, but because the study was performed in Sweden, there are population-wide databases available on pre-morbid sick leave and employment status. The authors looked at how levels of employment or sick leave prior to the injury influenced outcomes. After multivariate analysis, being unemployed or on sick leave for over 12 months pre-injury were associated with a significantly worse outcome on quality of life and participation measures, but not physical or psychological functioning. Of course, it is perfectly possible that the same factors that may "cause" unemployment or sick leave are likely to be persistent after a brain injury, but the important point is that overall outcome is predicted by factors above and beyond neural repair and change post-injury. In planning, delivering and evaluating rehabilitation interventions, it is appropriate, therefore, to unpick the baseline and judge outcomes relative to this rather than an absolute measure. It would also be interesting to explore whether recovery and change from other acute neurological presentations (a relapse of multiple sclerosis, stroke or acute Guillain-Barré) bears any relationship to pre-morbid factors in this way.

Ulfarsson T, Lundgren-Nilsson Á, Blomstrand C et al. A history of unemployment or sick leave influences long-term functioning and health-related quality-of-life after severe traumatic brain injury. Brain Injury. 2014;28(3):328-35.

Riboflavin and the axon

Reviewer: Dr Natalie Lakomska, Honorary Neurophysiology Registrar, The National Hospital for Neurology and Neurosurgery, Queen Square, London, UK.

The "old yellow pigment" which was first isolated from cow's milk in 1879, by an English chemist Alexander Wynter Blyth has shown to be a successful therapeutic intervention for patients for whom no disease modifying therapy had previously been available. Discovered in 1925 by a Nobel Prize winner, Professor Otto Warburg, it is now known as Riboflavin or vitamin B2, due to its ribityl side chain and Latin "flavus" for yellow. It has recently been shown to lead to symptomatic improvement when supplemented in high dosage in a childhood form of Motor Neuron Disease (MND). First described in 1894, Brown–Vialetto–Van Laere syndrome (BVVL) is a neurodegenerative disorder where children and young adults develop progressive pontobulbar palsy, sensorineural hearing loss and respiratory insufficiency. Without treatment this progressive neurodegenerative condition leads to early demise.

Riboflavin penetrates the blood-brain barrier and is taken up by the riboflavin transporter into neurons and astrocytes. The active forms flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) are cofactors for a number of redox enzymes and play key roles in the transfer of electrons in biological oxidation–reduction cycles. The exact mechanism of transport was only recently discovered (van Herwaarden et al., 2007; Yonezawa et al., 2008; Yamamoto et al. 2009).

A multicentre study based at UCL Institute of Neurology and the Institute of Child Health, also including teams in Australia, France, Lebanon and the United States, characterised patients with causative gene mutations (SLC52A2) encoding the riboflavin transporter RFVT2. RFVT2 transporter mutations were shown to lead to reduced riboflavin uptake and reduced riboflavin transporter protein expression. A core phenotype was identified (respiratory insufficiency, optic atrophy, hearing loss, sensory ataxia, upper limb and axial muscle weakness with preserved lower limb strength) in a group of 18 patients with compound

heterozygous or homozygous mutations in SLC52A2.

Biochemically high-dose riboflavin therapy (up to 50mg/kg/day in paediatric and 1500mg/day in adult patients) produced a biochemical normalisation of acylcarnitine profile and an increase in the active forms riboflavin: flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN). Clinically a reversal of continual functional decline was achieved with improvement in audiometric testing, pulmonary function tests, and visual evoked potentials. Patients in this SLC52A2-specific cohort gained improvement in hand function, walking, oral intake, were able to come off respiratory support. This is a breakthrough in finding a treatable cause for a type of motor neuron disease, lighting a candle of hope for adult MND.

Foley A, Menzes M, Pandraud A et al.
Treatable childhood neuronopathy caused by mutations in riboflavin transporter RFVT2.
Brain 2014: 137; 44-56.

Epilepsy: A family affair?

Reviewer: Dr Mark Manford, Addenbrooke's Hospital, Cambridge, UK.

There has been a wide range of studies looking into the familial risk of epilepsy over the years, and as these authors point out, they all have their methodological issues; mostly case ascertainment has been from a specialist setting. This study uses the data from Rochester Minnesota Epidemiology study, dating all the way back to 1920, is community based and also has non-affected family control data. The result is a study that must be right because it accords with my own personal clinical experience. 920 patients have been born in Minnesota and developed a seizure or more, of whom there were 660 incident probands. Of 2439 first degree relatives, 75 developed epilepsy and in 80% of these, it was before the age of 40. Similarly to previous studies and perhaps unsurprisingly, the risks to relatives were not increased if the proband had a postnatal cause of acquired focal epilepsy. For those with idiopathic generalised epilepsy, the cumulative risk to relatives before age 40 was over 7%, for those with focal epilepsy it was under 3% and intermediate for unclassifiable epilepsy. The general population risk was 1.3%. The risk for relatives of those with generalised epilepsy was greatest if the cause was prenatal or developmental. The increase in risk was greater for the same epilepsy type as the proband's syndrome; for probands with generalised epilepsy, the increase in generalised epilepsy was >8 fold, but only 2.5 fold for focal epilepsy and for relatives of probands with focal epilepsy, there was an increase of 2.6 times for focal epilepsy but no increase for generalised epilepsy. The risks for offspring of those with generalised epilepsy were not influenced by the gender of the affected parent, whereas the risk of focal epilepsy in a child was greater if the affected parent was female but not if they were male. This has been observed previously and raises an interesting and unanswered biological question. Whilst the risks are not very different from those previously described, the study allows us better to inform patients on the commonly asked question of: "Will this affect my children?"

Peljto A et al.
Familial risk of epilepsy: a population-based study. Brain 2014:137;795-805.

Hemicraniectomy in over 60's – help or hindrance?

Reviewer: Dr Gemma Cummins, Van Geest Centre for Brain Repair, Cambridge, UK.

One in twenty patients with ischaemic stroke develop the potentially catastrophic complication of "malignant oedema" which can cause death by brain compression. Decompressive craniectomy is a surgical procedure that involves removal of a large part of the skull, allowing swollen brain tissue to herniate upwards through the surgical defect rather than downwards to compress the brainstem. It has previously been shown in a pooled analysis of three RCTs restricted to patients under the age of 60, that it can reduce mortality, and has therefore been widely adopted in the management of young patients with malignant middle-cerebral-artery infarction. However, whether decompressive surgery is beneficial in older patients, has been a matter of debate amongst neurologists and neurosurgeons. Juttler et al attempted to address this issue in a trial where they randomly assigned 112 patients aged over 60 with malignant MCA syndrome to either conservative treatment in the ICU (the control group) or to hemicraniectomy.

This trial demonstrates that early decompressive hemicraniectomy doubled the rate of survival in patients over 60 at the 6 month primary end point when compared to medical management alone. Overall 6-month survival was 70% among hemicraniectomy patients, compared with 33% in those treated conservatively. Enrollment was stopped early when an interim analysis showed that the surgery was significantly improving survival. However patients that survived, in both the control and the treatment arm, were left with disability that was either moderate or severe. This is unsurprising – after all, these patients have suffered large strokes, severe enough to cause massive brain oedema. This trial does not corroborate previous claims that surgery can improve functional outcomes in this older age group. It is interesting to note, that the majority of patients in other studies examining quality of life following this type of surgery, stated that they were satisfied with the outcome post hemicraniectomy and would have consented to the procedure again, if they had to do it over. However, most patients in the control arm agreed that they did not regret the decision to opt out of surgery. As Allan Ropper comments in the accompanying editorial, "People seem content to escape with their lives".

Jüttler E, Unterberg A, Woitzik J et al.
Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke. N Engl J Med. 2014 Mar 20;370(12):1091-100.

Ropper AH. Hemicraniectomy–to halve or halve not. N Engl J Med. 2014 Mar 20;370(12):1159-60.

United Kingdom Acquired Brain Injury Forum 5th Annual Conference

Conference details: 21 November, 2013; London, UK. ***Report by:*** Louise Blakeborough, on behalf of UKABIF.

The Royal College of General Practitioners headquarters in London was host to the United Kingdom Acquired Brain Injury Forum UKABIF's 5th Annual Conference on the 21st November 2013. Professor Michael Barnes, UKABIF Chair, welcomed over 250 delegates to the prestigious venue and thanked sponsors Hunters Moor, Irwin Mitchell, Leigh Day, the Wellington Hospital, Towry and the many exhibitors for their support.

Speakers from the medical and legal world presented on topics ranging from commissioning changes, sports-related acquired brain injury (ABI) to the post-injury adjustment of mood and emotion. There were also interesting poster displays covering parenting following ABI, and the musical expression of physical and emotional pain. Delegates included rehabilitation team members, primary and secondary care doctors, case managers, personal injury lawyers, social care workers, voluntary organisations, care providers and also individuals with a brain injury and carers.

Dr David Paynton, National Clinical Lead at the RCGP Centre for Commissioning opened the conference by discussing the implications of commissioning neurorehabilitation services. In his thought-provoking presentation he reviewed the risks and opportunities for primary care, the demographic pressures and how the community teams are integrated. Clinical Commissioning Groups (CCGs) are now managing funds for hospital care, community services, prescribing costs, mental health costs and re-ablement. Accountability is now an issue because in the past the Primary Care Trust was accountable to just the Strategic Health Authority, however the CCG now has three lines of accountability - its member practices, the National Commissioning Board and the Health and Wellbeing Boards.

There are 15.4 million people in England with one or more Long-Term Conditions (LTCs). Utilisation of health services is highest amongst this group - they account for 30% of the population but 70% of NHS spending. Dr Paynton said that the new GP contract will focus on people at risk and developing care plans for them; this patient-centred approach will focus on multiple morbidities not single conditions.

Dr David Bateman, National Clinical Director for Neurological Conditions, discussed re-designing services as a cost-effective approach to tackling the future. He was the Chair of a Royal College of Physicians Working Party, which together with the Association of British Neurologists, published the report 'Local adult neurology services for the next decade'. There are approximately 660 neurologists to manage the 600,000 people newly diagnosed each year with a neurological condition. The report proposes an expansion and improvement of local services, with a shift in emphasis from scheduled to emergency care and better organised care for patients with long-term neurological conditions. This care will be managed in part through an enhanced role for specialist nurses and GPs with a special interest in neurology. This will be augmented by better local planning of services with increased clinical involvement within a commissioner/provider forum, creating a neurological network to improve clinical and financial outcomes.

Professor Michael Barnes, UKABIF Chair


Beverley Turner and James Cracknell

Alison Eddy, Partner at Irwin Mitchell, the personal injury law and rehabilitation specialists, presented the company's recently published research highlighting the fact that annually, more than 13,000 of the most seriously injured road collision victims face a rehabilitation post-code lottery which impacts on their recovery prospects. Irwin Mitchell commissioned the report 'Counting the cost of the rehabilitation postcode lottery for road crash victims' aiming to improve understanding of the current status of UK rehabilitation services, and to make recommendations about what can be done to improve access for victims. The report found there is limited access to rehabilitation – particularly the care and support following hospital discharge - and this is exacerbated by a post-code lottery. The NHS needs to make a £20 billion saving by 2015 - providing rehabilitation that meets a consistently high standard could save the NHS around £120 million. The cost of this care could be offset in as little as two years through savings from shorter hospital stays, reduced costs for support in the community and more independent living.

After lunch, conference delegates watched the revealing film 'Head Games', produced in 2012 by acclaimed director Steve James about the silent concussion crisis in American sport. This was followed by Dr Richard Hardie, Consultant Neurologist at Bristol's Frenchay Hospital who discussed concussion in sport with the highest incidence occurring in football, hockey, rugby, soccer and basketball. Every case of concussion is different but young athletes appear to have a more prolonged recovery. The acute management of concussion follows the guideline of 'when in doubt sit it out' and all symptoms need to have resolved before a 'return to play' involving a gradual step-wise increase in physical demands and sports-specific activities.

David Quinn, Consultant Neuropsychologist and founder director of Halliday-Quinn Ltd., gave a stimulating presentation on mood and emotional adjustment following ABI. Re-shaping identity post-injury is very difficult and he emphasised the importance of considering what the person was like before their injury in order to have a perspective on what they can do post-injury.

Double Olympic rowing gold medallist James Cracknell and his wife, Beverley Turner, broadcaster and journalist talked to delegates about the effects of ABI on their family. James was hit on the back of the head over three years ago by the wing mirror of a petrol tanker whilst cycling in Arizona which caused severe frontal lobe damage and doctors were unsure if he would recover. The impact on their relationship and family resulted in Beverley and James writing the book 'Touching distance' to document their experiences. ◆

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PREVIEW Rehabilitation in MS Conference

Conference details: 6-7 June 2014; Brighton, UK.

In many ways, multiple sclerosis is an exemplar condition. There are approximately 100,000 people with a diagnosis of MS in the UK, making it the larger of the small number conditions. MS is a relatively uncommon condition with an increasingly complex range of disease modifying treatment options provided by specialist services. Yet its lifelong and largely progressive trajectory means there is equal need for much more commonly required comprehensive, locally provided services to manage symptoms and maintain participation.

In the new landscape of the NHS, this places MS in the uncomfortable position of straddling specialised and clinically commissioned services. In truth, this means two sets of cash-strapped commissioners with often irreconcilable objectives to reduce their scope of responsibility or effectively manage the tension between generalist and specialist provision. The person with MS and the people who care for and about them, care little about who holds the budget or how the money flows. What matters is the availability of responsive services, provided by people who have a proper understanding of the nature of the condition, who can offer access to the treatments they require. Not too much to ask.

The current reality is frustratingly different. Under pressure to make savings, some clinical commissioners are looking at more generic models of service provision – diluting the availability of locally based specialist practitioners, such as MS specialist nurses and allied health professionals and instead establishing posts who are 'specialist' in a number of long term neurological conditions. In effect, this means trying to provide expert sub-specialist care, balancing the demands of a mixed caseload involving conditions with very different trajectories and maintaining adequate specialist knowledge in the fast moving waters of an increasingly varied and complex choice of treatment options.

Not all MS services will or should be provided by specialists. The numbers are too small and the needs too long term to make a specialist-only model viable or appropriate. What is critical, though, is that there are enough specialists throughout the system to support non-specialist services to provide those elements of high quality care for which they are responsible. If the specialists are all located in prescribing centres, those elements of a comprehensive MS service that are more appropriately offered in the community will struggle to maintain their knowledge-base or retain timely access to the support and advice they need to manage the complex and changing needs of people with MS. Community based specialists, like MS nurses, are essential in straddling the divide between specialised and clinically commissioned services, and their future needs to be secured. They also need to be connected to the specialist centres not only for their own development but also to facilitate smooth movement for patients between the centres and locally delivered services.

Nonetheless, however services are configured and provided, people with MS will derive the greatest benefit from care provided by professionals who have the greatest level of understanding of the condition and its best management. The MS Trust has a longstanding commitment to the specialist practitioners who work with people with MS. Professional development for MS nurses and AHPs and, increasingly, neurologists and rehabilitationists, is a core activity for the MS Trust. We have a comprehensive Health Professionals programme, including training for new in post MS specialists, masterclasses, study days, the flagship conference for MS specialists and an annual educational meeting for MS specialist nurses. Through our GEMSS programme, we collect evidence on the value and impact of specialist services and we provide bursaries for all MS professionals to extend their knowledge and skills in MS care.

Rehabilitation programmes are an aspect of MS care that are vitally important and yet remain under-recognised for their role in improving function and participation. Historically, rehab services have struggled to gain the visibility or attract investment of the scale seen in, for example, the development and provision of disease modifying and symptomatic treatments. The profile of rehabilitation, growth of the evidence base and a strong set of outcome measures must remain a priority in the overall landscape of MS care. It needs to remain high on the agenda of specialised and clinical commissioners alike.

This year, the MS Trust is delighted to be part of a unique opportunity for those with an interest in MS from all the health professions to help raise the profile of rehabilitation as an essential part of MS care. In partnership with the MS team at University College Hospital London at Queen Square, we are bringing the Rehabilitation in MS (RiMS) conference to the UK for the first time. RiMS is the European network for best practice and research in MS Rehabilitation. Now in its 19th year, it represents and brings together health care professionals, researchers and patient organisations from different settings with the aim to enhance activity, participation and autonomy of people with MS by developing and advocating evidence-based rehabilitation. The long-term vision of RiMS is that all people with MS throughout Europe have access to evidence-based rehabilitation when they need it.

This year's conference is in Brighton on 6th and 7th June, with an additional half day MS Masterclass being offered at Queen Square on 5th June. There is a world class multidisciplinary programme covering clinical practice, latest research evidence, exploration of methodological issues in rehabilitation research and a pan-European perspective on service improvement. The conference is for all health professionals working in MS and those with a research interest in rehabilitation. More than 350 delegates are already registered, but a limited number of places are still available – visit www.rims2014.org to book your place. ◆

Practical Cognition Course

Conference details: 10-11 October 2013; Newcastle University, Newcastle, UK.

Report one by: Dr Thomas Miller, a Registrar based at University of Oxford.

Cognitive neurology is an often-misunderstood subspecialty of neurology, combining as it does the often-distinct areas of neurology, psychiatry and neuropsychology. Yet awareness and understanding in the cognitive disorders is improving not only within neurology but also general medicine. The Practical Cognition Course was established to try and facilitate this interest to a wide and general audience including neurologists, psychiatrists, psychologists and rehabilitation physicians. Now in its sixth year, the wide-ranging course took place on the 10-11th October 2013 at the Research Beehive at Newcastle University.

Session 1 (chaired by Professor Tim Griffiths, Newcastle University) began, as it always does, with the methods and approaches used by cognitive neurologists and neuropsychologists within the clinical setting. Dr Chris Butler (University of Oxford) began with the history taking, examination and basic investigations required for a basic cognitive assessment. Given cognition is a widely encompassing term (and includes areas such as memory, executive function, language, attention, calculation, perception and behaviour/personality) the clinician needs to be clear as to what the main problem actually is – for instance, is a dysexecutive problem responsible for the memory problem the patient's family is most concerned about? Dr Andrew Larner (Walton Centre, Liverpool) then ran through his research assessing the diagnostic utility and value of various bedside cognitive tests. Whilst historically useful in a general setting, the Mini-Mental State Examination (MMSE) has been superseded clinically by the Addenbrooke's Cognitive Examination (ACE; both the Revised and Third Edition)[1] and Montreal Cognitive Assessment (MoCA). Cognitive testing via the ACE-III is a useful method of determining those patients in whom organic pathology should be suspected and who would benefit (those in the range 73-88) from further neuropsychology assessment. Finally, Dr Tom Kelly (Newcastle General Hospital) gave an informative run-through of the common neuropsychology tests used on referred clinic patients. A word of caution was offered to the inevitability that there will be one test which will be significantly poorer than the others for any given patient – this is a normal and expected finding (after all, who can be talented at multiple sporting endeavours?) and should be taken in context of the other results.

Another over-arching theme of the Practical Cognition Course is to show how current neuroscientific research informs clinical practice, both diagnosis and treatment. To this end Session 2 (chaired by Dr Chris Butler) was a discussion of three frontal lobe disorders followed by a discussion by Dr Chris Kipps (University Hospital, Southampton) on the function and dysfunction of the frontal lobes. The relevance of this approach is borne out when one considers the ways in which frontotemporal dementia may present – orbitofrontal changes cause symptoms such as apathy, poor decision-making and emotional blunting; dorsomedial atrophy may result in patients with poor social interaction and strange behavioural patterns; and finally, dorsolateral disease can present with dysexecutive problems such as abstract thought, organisation and aspects of behavioural regulation.

Session 3 focused on functional disorders and in particular methods to distinguish between those with organic disease and the 'worried-well'. The case discussion centred on those presenting with self-reported memory problems and the common ways in which they present (i.e. alone, with a good history for how and when their memory has been a problem, anxiety and poor sleep). The second case study was an interesting case of functional memory loss and its resolution with hypotherapy. Dr Jon Stone (University of Edinburgh) then finished off the session looking at other ways in which functional disorders can present cognitively and in so doing shared his experience of the best ways to deal with such problems.

Session 4 (chaired by Prof Tim Griffiths) addressed the cognitive sequelae of closed head injuries and was led by Dr Stuart Anderson (Brighton and Sussex University Hospitals). Given the mechanisms involved with impact injuries and the relative size of the frontal lobes, it comes as no surprise that patients often present with frontal lobe dysfunction. In an echo of what Jon Stone had discussed the previous day, time was also spent discussing post-concussive syndrome (PCS). What became clear is that symptoms associated with PCS (for instance poor memory, headaches, lethargy) are actually experienced by a large proportion of the normal population and those who have suffered trauma but not a head injury. Care, therefore, is needed before diagnosing PCS.

The final session, Session 5, concluded the course and was a focus on speech disorders. Language disorders can appear overwhelming because of the multiple pathways involved in speech production from sensation to behaviour. The session was led by Dr Jason Warren (University College London Hospitals) who offered the following scheme in localising the language disorders: (i) planning (frontal-subcortical regions), (ii) content (temporo-parietal junction, medial temporal lobe, anteroinferior temporal lobe and the connections between them), (iii) grammar and structure (peri-Sylvian region) and finally (iv) motor output (inferior frontal cortex). He then gave helpful hints in distinguishing between the different forms of language disorders. For instance, progressive nonfluent aphasia presents as a slow effortful pattern of speech with a poverty of words (logopenia), some comprehension difficulties, an inability to repeat sentences and is often due to TDP-43 pathology. Semantic dementia presents with an inability to name objects (anomia), a visual agnosia and surface dyslexia (i.e. reading PINT phonologically as opposed to its usual irregular pronunciation) and is associated with ubiquitin pathology. Logopenic aphasia is a disorder of verbal working memory so presents with poor sentence repetition, word finding pauses, jargon words and pauses in spontaneous speech (with intact prosody and grammar).

With its emphasis on combining clinical neuroscience with patient videos and vignettes the Practical Cognition Course continues to provide a unique opportunity to better understand cognitive neurology and its disorders. ◆

Reference

1. Larner AL. *Addenbrooke's Cognitive Examination-Revised (ACE-R): pragmatic study of cross-sectional use for assessment of cognitive complaints of unknown etiology.* Int J Geriatr Psychiatry. 2013; 28:547-8.

With its emphasis on combining clinical neuroscience with patient videos and vignettes the Practical Cognition Course continues to provide a unique opportunity better to understand cognitive neurology and its disorders

Report two by: Dr Lloyd Bradley, Consultant in Rehabilitation Medicine, Western Sussex Hospitals NHS Foundation Trust.

Having a discussion about cognitive impairment with specialists from other backgrounds can seem like trying to conduct a conversation in two different languages. The assessment and management of these problems in clinical practice can be seen very differently depending on the perspective that one adopts. One of the strengths of this excellently run and involving course is the engagement and discussion between different professional groups around the concise and clearly delivered case studies. The different paradigms adopted by neurologists, neuropsychologists, psychiatrists, rehabilitation physicians and care of the elderly specialists in approaching challenging clinical cases was illuminating and allowed us all to see how much we could learn from one another.

Following an introductory session on assessment, delivered by Chris Butler, Andrew Larner and Tom Kelly, the course was divided into four main clinical themes (frontal lobe disorders, functional disorders, traumatic brain injury and speech disorders) delivered over two days by a variety of different speakers with varying clinical and academic interests. The use of specific case studies made the delivery of information thought provoking and involving and often stimulated occasionally heated discussion. A lecture on the pathology of frontal lobe disorders had the potential to be very dry, especially in the after lunch slot, but Chris Kipps from Southampton did an excellent job in demystifying the different functional roles of the frontal lobes in a clinically meaningful way.

Dealing with functional disorders can present very particular challenges and frustrations, but listening to Jon Stone's lucid deconstruction of how to approach these consultations was nothing short of inspiring. I'd never really thought about functional cognitive disorders in the same way as functional motor disorders before, but it is heartening that adoption of a similarly considered and robust approach can bear fruit. Jon's presentation stimulated more heated discussion which continued into the evening's dinner at the Baltic Centre.

The following morning's session, delivered by Stuart Anderson from Hurstwood Park, on traumatic brain injury continued many of the same themes, especially around the deconstruction of post-concussion syndrome and the use of effort testing. During the tea-break, we had the opportunity to "try out" a selection of neuropsychological tests. Unfortunately, my ineptitude in the Towers of Hanoi task did not go unnoticed.

The final session on speech disorders was led by Jason Warren and provided an excellent framework for the understanding of disorders of verbal communication and how to try and differentiate these in the real world.

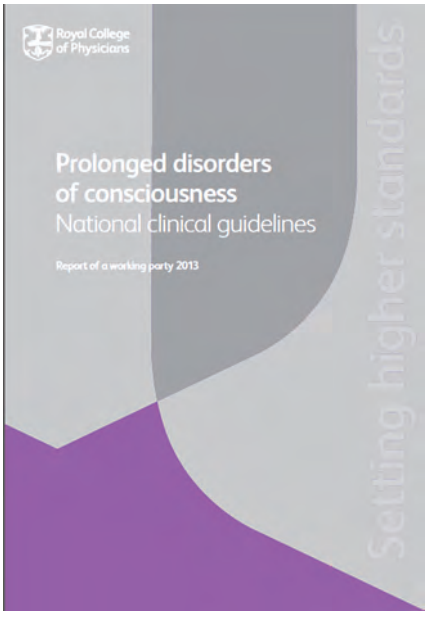
Great credit must go to Tim Griffiths and Chris Butler for putting together such a varied and engaging programme and to Anne Fitchett for her efficient organisation. I suspect that given the broad appeal and well-produced content, many of us will be returning to Newcastle again in years to come. ◆

Prolonged Disorders of Consciousness (PDoC)

Conference details: 12 December 2013. Royal College of Physicians, London, UK. ***Report by:*** Dr John Burn, Consultant Rehabilitation & Brain Injury, Poole Hospital.

It is striking that despite, in international terms, the small size of Rehabilitation Medicine in this country the UK can still occasionally punch above its weight in both service and basic science rehabilitation research. This is demonstrated by fMRI imagery studies from Cambridge in vegetative and minimally conscious states, and qualitative studies from Cardiff exploring the family experience of catastrophic brain injury in rehabilitation units and specialist nursing homes. The latter was presented in person at this meeting by Jenny Kitzinger, who documented the widespread exclusion of close relatives from treatment decisions, and lack of recognition of their personal expertise in matters relating to their family member. Professor John Pickard presented fMRI and other basic science research from Cambridge and elsewhere, with a moving tribute to Dr Martin Coleman whose contribution is emphasised in the foreword to the RCP guidelines that were the focus of this meeting.[1]

These evidence based guidelines centre on the assessment, diagnosis and management of patients with PDoC throughout their lifetime from diagnosis to death. The guidelines emphasise the application of the Mental Capacity Act (2005) to the management of these patients and careful attention to their best interests. It is easy to lose sight of this and the failings of clinicians and current legal practice were amply demonstrated by Helen Steeple's description of the medical and nursing chaos that followed her twin son's brain injury; a presentation which left no dry eye in the house. The guidelines aim to assist clinicians to manage such patients within the existing legal framework. For example it is recommended that a Best Interests Meeting is held after 4 weeks of PDoC when patients are now defined as being in a Continuing Vegetative State (VS) or Continuing Minimally Conscious State (MCS). Such a meeting would offer families the opportunity to clarify the patient's prior values and beliefs so that decisions made on the basis of their best interests can, where possible, reflect what they would have wanted if they were able to speak for themselves. A specialist service



should be involved at this point with initial transfer to a specialist rehabilitation unit and then a specialist long term nursing facility. All such patients should be in receipt of NHS Continuing Health Care and the British Society of Rehabilitation Medicine (BSRM) has produced recommendations that describe, as standards, what is required by such specialist nursing homes.[2] There should be diagnostic reassessment of such patients every 6-12 months using one or more of the following standardised assessments: The Wessex Head Injury Matrix, The Coma Recovery Scale – Revised and, when required, The Sensory Modality Assessment and Rehabilitation Technique (SMART). These will inform further Best Interest Meetings and Professor Derick Wade described, from his experience, how such delicate meetings could be approached in order to consider, amongst other issues, referral to the Court of Protection with reference to removal of clinically assisted nutrition and hydration (CANH). Previously clinicians have left it to families to raise this but it is a professional responsibility which Consultants in Rehabilitation Medicine should not avoid.

Removal of CANH should be considered for patients in a Permanent Vegetative State as they do not legally have an interest in further treatment. Legal presenters, chaired ably by Lord Justice McFarlane of the Court of Protection, confirmed that only about fifty cases have been referred to the court since 1989 but the judgement in all of them was that 'it would not be unlawful to withdraw CANH'. Management thereafter may not be straightforward and Professor Rob George recommended careful proactive palliative management to ensure that any subsequent physiological distress is controlled.

The working party also drew up useful operational parameters for emergence from MCS. It introduced the term permanent MCS for patients in whom emergence from MCS is considered highly improbable. The guidelines also describe situations in which it would be legitimate for such patients to also be referred to the Court of Protection for consideration of removal of CANH. A case has been heard but it is a contentious area without as yet legal precedent. ◆

1. Royal College of Physicians. Prolonged disorders of consciousness: National Clinical Guidelines. London: RCP/BSRM, 2013 Can be downloaded free of charge from http://www.rcplondon.ac.uk/resources/prolonged-disorders-conciousness-national-clinical-guidelines

2. British Society of Rehabilitation Medicine. Specialist nursing home care for people with complex neurological disability: guidance to best practice. London: BSRM, 2012

Definitions

Vegetative State
A state of wakefulness without awareness in which there is preserved capacity for spontaneous or stimulus-induced arousal, evidenced by sleep-wake cycles and a range of reflexive and spontaneous behaviours. It is characterised by complete absence of behavioural evidence for self- or environmental awareness.

Minimally Conscious State
A state of severely altered consciousness in which minimal, but clearly discernible, behavioural evidence of self- or environmental awareness is demonstrated. It is characterised by inconsistent but reproducible responses, above the level of spontaneous or reflexive behaviour, which indicates some interaction with their surroundings.

It is recommended that a Best Interests Meeting is held after 4 weeks of PDoC when patients are now defined as being in a Continuing Vegetative State (VS) or Continuing Minimally Conscious State (MCS). Such a meeting would offer families the opportunity to clarify the patient's prior values and beliefs so that decisions made on the basis of their best interests can, where possible, reflect what they would have wanted if they were able to speak for themselves

The Encephalitis Society Professional Seminar

Conference details: 2 December, 2013; London, UK. ***Report by:*** Sophie Miller, final year medical student, University of Liverpool (edited by Dr Ava Easton, CEO, The Encephalitis Society).

Having attended the Encephalitis Society Professional Seminar last year for the launch of the much anticipated Encephalitis Guidelines, I was delighted to return to London for this year's seminar which promised much more of last year's intellectual stimulation. This year's programme boasted a range of topics, of both local and international interest, delivered by speakers at the forefront of encephalitis research and budding neurologists alike.

The seminar was attended by a range of people, patients, doctors, nurses, family members and neuropsychologists alike. This is important and creates a great dynamic with questions asked and explored from a multitude of viewpoints. It is a rare situation to have such a multidisciplinary response and input to a subject.

After a goodie bag and a warm welcome by Ava Easton CEO of the Encephalitis Society and Professor Tom Solomon, Chair of the Encephalitis Society Professional Panel, we were shown a very moving video about encephalitis and the work of the Society. It also included a very impressive insight into the family activity weekend enabling children and families to create new friends and support networks. This is invaluable to their wellbeing and really underlined the necessity of this Society.

We were then launched into our afternoon of lectures starting with "The incidence of Encephalitis in the UK – new findings!" by Dr Julia Granerod from Public Health England. This was a striking talk and covered some of the reasons that the previously documented incidence of Encephalitis is, in fact, incomplete: that it is not reported although mandatory by law and that it is difficult to distinguish encephalitis from mimicking conditions. Julia's work involved using data from a prospective study and hospital episode statistics data in capture-recapture models to estimate the incidence for encephalitis, and established that the incidence was actually considerably higher than previously reported or estimated: 5.2 people per 100,000, but could be as high as 8.7 people per 100,000 (approximately five times higher than previously predicted). Julia suggested that although probably an underestimate, encephalitis costs the NHS £23,000,000 per year in bed costs (but could be as high as £40,000,000 if the higher incidence is used) – not including ITU stay, staffing, readmission or reduced productivity from loss of jobs. The takeaway message here was not only that encephalitis has a greater incidence than expected but in fact a higher incidence than Bacterial Meningitis and Motor Neuron Disease even though they both have a higher public and clinical profile – a stark fact when you consider that most members of the public have never heard of it and some clinicians are also in the dark about this very important condition.

Drs Benedict Michael and Sam Nightingale

Professors Barbara Wilson and Tom Solomon presenting the 2013 Encephalitis Society Medical Student Essay Prize Winner – Katarzyna Bera

Group shot of all the speakers.

Dr Parashar Ramanuj, Public Health England went on to present "Life after Encephalitis – much more than mortality and morbidity", driving home the fact that care after hospital discharge is paramount but in some cases non-existent with doctors unaware of the long term sequelae of Encephalitis. His work explored the Quality Of Life (QOL) after encephalitis, demonstrating it is greatly reduced in people after encephalitis compared to the general population. His results closely matched those found by the Encephalitis Society when exploring QOL. He urged clinicians not just to consider biological factors but to think about psycho-social problems too – suggesting not all recovery is the same and that we need to invest more in the rehabilitation of these patients.

Drs Benedict Michael and Sam Nightingale presented NeuroAccess – a collaborative project with The Encephalitis Society that aims to improve the care of patients with encephalitis and other neurological problems in sub-Saharan Africa through improving education in clinical neurology.

Benedict and Sam described how in November 2013 they undertook a pilot visit to Zambia, completing two weeks of clinical neurology teaching at the University Teaching Hospital in Lusaka. They saw that the burden of encephalitis and other neurological disease was enormous in this setting, and the greatest need for teaching is for the junior doctors in General Medicine. In the majority of cases they had not received clinical teaching from someone with a special interest in neurology. Many of these doctors found that they now had to provide the undergraduate teaching, having received inadequate teaching on this subject themselves. In all they taught over 300 students, doctors and clinical officers. The teaching was very well received. Most found the bedside teaching particularly helpful. The project is expanding during 2014 with plans to visit Malawi and Mozambique.

Dr Sarah Bate presented an absorbing lecture on "Prosopagnosia – an Encephalitis case study – research and new steps in recovery". This detailed a case report of a teenage girl who contracted HSV encephalitis in Tenerife when she was eight years old. She had experienced immediate problems with face and object recognition and lost the ability to read and write. It was very moving to hear how this impacted her life and to learn she is now only one school year behind and studying for 7 GCSEs.

Dr Sarosh Irani presented the lecture "Can we prevent cognitive impairment with early treatment of faciobrachial dystonic seizures?" covering the manifestations of a neurological autoimmune disease which he and colleagues first described in 2011. These seizures, initially observed in patients with autoimmune encephalitis and LGI1/VGKC-antibodies, are characterised by adult-onset brief (often <2 seconds), frequent (average of 50/day), dystonic ('twisting') jerks which often affect the face and arm. Patients usually have normal brain scans but may have a number of other features – auras; rising sensations in epigastrum; autonomic features; sensory changes; and they may suddenly stop talking. Patients also show some post-ictal features such as agitation. These events also precede the amnesia/confusion associated with the LGI1/VGKC-antibody encephalitis in 60-70% of patients. Importantly, treatment of the seizures with conventional antiepileptic drugs produces little benefit. By contrast, the jerks often cease after steroid therapy. In addition, the few patients treated with steroids prior to the onset of anmesia/confusion did not progress to the full-

blown encephalitis which occurred in all those not treated early with steroids. Although rare (ten patients observed in two UK neuroscience centres over two years) this is a condition worth considering due to its characteristic signs and seemingly treatable nature.

The meeting then heard presentations from the winners and runner-up of The Encephalitis Society 2012 Medical Student Essay Prizes and Travel Bursary:

- "Microbe Hunting in Vancouver: an elective in infection" by Dr Clark Russell who spent one month in an infectious diseases unit in Vancouver and one month in a medical microbiology unit with the bursary he won.
- "Bone Marrow: The future of Encephalitis?" by Bart van Herwijnen a final year medical student from Southampton. He talked us through his winning essay looking at the use of Mesenchymal Stem Cells in the treatment of autoimmune (NMDAR) encephalitis.
- "Evaluation of the Pathophysiological mechanisms underlying Anti-NMDA receptor Encephalitis" by Timothy Jones, UCL. This was an energetic approach to his science essay and even managed to get a laugh when talking about receptors!

Lastly, we heard from Dr Roxanne Keynejad a junior doctor working in a Surrey hospital who audited the care of Encephalitis patients before the recently published adult diagnosis and management guidelines. Over a period of 7 years the care of 38 patients were successfully identified with a variety of outcomes. Dr Keynejad will present the audit at a forthcoming grand round; publicise and promote use of the Diagnostic and Management algorithm; explore options for a CSF order set which will help clinicians request all the necessary tests for patients who have suspected Encephalitis. In conclusion the audit will be repeated to assess any improvement in diagnosis and management.

This is something that will be important in other hospitals and a good starting point for any students or doctors reading this and looking for a project to do in their hospital.

The day drew to a close with announcements of the winner and runner-up of the 2013 Medical Student Essay Prize. ◆

Details of the winners and winning essays, along with the newly opened round of 2014 student prizes and travel bursaries (2014 focus is Neuropsychology students) can be found at **www.encephalitis.info/research/grants-and-awards/**

If you are interested in attending the 2014 seminar, please contact The Encephalitis Society **www.encephalitis.info mail@encephalitis.info or 01653 692583**

Our sincere thanks to MacFarlanes LLP for once again supporting this event.

To list your event in this diary, email brief details to Rachael Hansford at Rachael@acnr.co.uk by 6th June, 2014

May

4th Essential Stroke Imaging Course
10 May, 2014; Liverpool, UK
Contact Kath Tyler, T. 07799 723 925
E. essentialcourses@hotmail.com

Magstim Neuroscience Conference 2014
10-11 May, 2014; Oxford, UK
T. Angharad Lewis, 01994 240798
www.magstim.com/magstim-neuroscience-conference-2014

14th Annual Pain Therapeutics Conference
19-20 May, 2014; London, UK
See www.pain-therapeutics.co.uk or contact Fateja Begum on +44 (0)20 7827 6184, E. fbegam@smi-online.co.uk

Primary Care & Public Health 2014
21-22 May 2014; Birmingham, UK
T. 0151 709 8979, E. info@sterlingevents.co.uk

June

Parkinson's Classic Masterclass 25c
Module 1 – 3-5 June, 2014; Bristol, UK
For further information contact info@redpublish.co.uk

Practical Management of Sleep Disorders
5 June, 2014; Liverpool, UK
T. 02034795111
E. info@communitytherapy.org.uk www.communitytherapy.org.uk/events.html

Interactive Metronome Certification Basic Course (IMC)
18 June, 2014; Freeby, Leicestershire, UK
Instructor: Mary Jones OT – Sensational kids LLC and IM instructor since 2005
www.newbraintechnologies.co.uk
www.centrevents.co.uk/nbt.html

Interactive Metronome Paediatric Best Practice
19 June, 2014; Freeby, Leicestershire, UK
Instructor: Mary Jones OT – Sensational kids LLC and IM instructor since 2005
www.newbraintechnologies.co.uk
www.centrevents.co.uk/nbt.html

Neuro-fatigue: Managing fatigue in people with neurological conditions
26 June, 2014; London, UK
T. 02034795111
E. info@communitytherapy.org.uk www.communitytherapy.org.uk/events.html

Deep Brain Stimulation Masterclass Roadshows
30 June, 2014 - evening; North London
www.redpublish.co.uk/courses/other-courses
For further information contact info@redpublish.co.uk

July

ISMRM Workshop on: Functional MRI: Emerging Techniques & New Interpretations
July, 2014; Charleston, SC, USA
www.ISMRM.org, T. +1 510 841 1899

Deep Brain Stimulation Masterclass Roadshows
1 July, 2014 - 1.30 /5.30pm; South London, UK
www.redpublish.co.uk/courses/other-courses
For further information contact info@redpublish.co.uk

Introduction to a Compassionate Mind Approach with people with Acquired Brain Injury
2-3 July, 2014, Ely, UK
T. 01353 65217,
E. courses@ozc.nhs.uk
www.ozc.nhs.uk

26th Annual Meeting of the European Academy of Childhood Disability
3-5 July, 2014; Reed Messe, Vienna, Austria
Contact: Diana Lincke,
T. +49 611 97716-65
E. eacd@intercongress.de
www.eacd2014.org

Brainwaves
Bringing you the latest developments from the AAN and MDS meetings
8 July, 2014; Liverpool, UK
Please register online at: www.brainwavesmeeting.com
E. emily@brainwavesmeeting.com
T. 01932 379897

Brainwaves
Bringing you the latest developments from the AAN and MDS meetings
9 July, 2014; Sheffield, UK
Please register online at: www.brainwavesmeeting.com
E. emily@brainwavesmeeting.com
T. 01932 379897

The Historical Evolution and Future of Neurology and Psychiatry
9 July, 2014; Institute of Psychiatry, London, UK
Contact Liz Beckmann,
E. lizbeckmann@lanmarkmedical.co.uk

Brainwaves
Bringing you the latest developments from the AAN and MDS meetings
10 July, 2014; London, UK
Please register online at: www.brainwavesmeeting.com
E. emily@brainwavesmeeting.com
T. 01932 379897

Interactive Metronome Certification Basic Course (IMC)
12 July, 2014; London, UK
Instructor: Mary Jones OT – Sensational kids LLC and IM instructor since 2005,
Nina Smith – Consultant Neurological Physiotherapist – Neuromatters Ltd
www.newbraintechnologies.co.uk
www.centrevents.co.uk/nbt.html

Interactive Metronome Adult Best Practice
13 July, 2014; London, UK
Instructor: Mary Jones OT – Sensational kids LLC and IM instructor since 2005,
Nina Smith – Consultant Neurological Physiotherapist – Neuromatters Ltd
www.newbraintechnologies.co.uk
www.centrevents.co.uk/nbt.html

September

36th Edinburgh Clinical Neurology Course
15-16 September, 2014; Edinburgh, UK
www.dcn...ed.ac.uk/dcn/research/training.asp
or enquiries to Mrs Judi Clarke, E. Judi.Clarke@ed.ac.uk

Parkinson's Registrar's Masterclass 26s
17-18 September, 2014; Location TBC
www.redpublish.co.uk/courses
E. info@redpublish.co.uk

Deep Brain Stimulation Masterclass Roadshows
TBC Sept/Oct, 2014 – Evening; Newcastle, UK
www.redpublish.co.uk/courses/other-courses
For further information contact info@redpublish.co.uk

ABN Autumn Meeting
30 September-1 November, 2014; Stratford, UK
E. info@theabn.org
T. 020 7405 4060

October

Ketogenic Dietary Therapies International Symposium
7-10th October 2014: Liverpool UK
E. liverpool2014@matthewsfriends.org
www.matthewsfriends.org

Executive Function
24 October, 2014; Ely, UK
T. 01353 652173,
E.courses@ozc.nhs.uk
www.ozc.nhs.uk

November

Parkinson's Classic Masterclass 25c
Module 2-27 November, 2014; Location TBC
For further information contact info@redpublish.co.uk

Testing competency in delivering epilepsy rescue protocol medication

Buccal Midazolam is an emergency rescue medication prescribed under special license by a doctor to reduce the duration of or stop an epileptic seizure and prevent status epilepticus and the potential risks. It is administered by a trained person to the buccal mucosa (between the gums and cheek) and is receiving wide spread acceptance due to its effectiveness in stopping seizures and its social acceptability.

There are agreed guidelines on training standards for the administration for buccal midazolam produced by the JEC and the National Institute for Clinical Excellence (NICE) according to the individual agreed protocol.

Epilepsy Education and Training courses are conducted by trained experienced epilepsy nurses suitable for healthcare staff or families in line with the JEC training guidelines and current best practice.

Current training is comprehensive and exhaustive. Unfortunately different areas go about their training with different structures and packages. It is unclear if the expectations and goals of the training get fully realised for all attendees. The consequence of this could be catastrophic and devastating for the individual patient given the high risk of mortality and brain damage. There are also associated significant cost implications to the NHS.

While the risk of unconscious incompetence around Midazolam administration by individual carers cannot be eliminated, steps can be taken to help minimise this risk. A training package needs to include assessments to evidence the acquired competencies. Such an assessment needs to be standardised and adopted across a wider group with appropriate peer group approval.

A standardised 30 minute e-learning test package has been developed to enable trainers to test attendees of courses on ability to deliver consistency and gain confidence of a basic level of competency in delivering rescue protocol medication. The e-test includes graphic videos examining the candidate's ability to identify and carry out the practical procedures required in Midazolam buccal administration. These can ensure the information is retained and the trainee has gained all of the information he or she set out to during the training process.

The website has been tested for quality standards and supported as a source to improve patient safety by stakeholders including the Joint Epilepsy Council, SUDEP Action, Epilepsy Action, South West Epilepsy Nurses Group, Peninsula Academic Health Science Network and two NHS Trusts.

For more information see www.epilepsy-education.com or
E. Rohit.Shankar@cft.cornwall.nhs.uk

Nair, PP; Kalita, J, Misra, UK (2011 Jul-Sep) "Status epilepticus: why, what, and how." Journal of postgraduate medicine 57 (3): 242–52.

Hanna et al, (2002) The National Sentinel Audit of Epilepsy Related Death, The Stationary Office, London

A text from Montmartre

Figure 1: Charcot's mausoleum, Paris

A general physician friend texted this picture (figure 1) one morning. I quipped that Paris seemed a long way to go to find a neurologist. His reply? "It's Saturday".

So here was a joke between friends that points straight to the heart of the elephant in the room of UK neurology. On evenings and weekends we have acute hospitals where no consultant neurologist is available to see the patient, some in which consultant neurologists are personally assessing all acute neurology (including suspected stroke for thrombolysis), and some where the consultant neurologist is on-call one in thirty supervising a neurology registrar from home. The Future Hospitals Commission report[1] tells us that the situation needs to change. The question is whether neurology drives that change or has change imposed upon it. For those neurologists that disagree with the FHC can I respectfully ask how they might feel and react if a relative or good friend, suffering from headache, fever and confusion, was admitted to one of the UK's (neurologically) darker places?

Reference

1. http://www.rcplondon.ac.uk/sites/default/files/future-hospital-commission-report.pdf (accessed Feb 2014)

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Keywords: Emergency Medical Services
Contributorship: Written by the author. Picture taken by friend of the author.
Funding: None
Competing interests: None declared

Please refer to the Summary of Product Characteristics (SmPC) for full details of Prescribing Information. COPAXONE® (glatiramer acetate) 20 mg/ml Solution for Injection, Pre-filled Syringe Abbreviated Prescribing Information Presentation: Glatiramer acetate 20mg solution for injection in 1ml Pre-filled Syringe. **Indications:** Treatment of patients who have experienced a well-defined first clinical episode and are determined to be at high risk of developing clinically definite multiple sclerosis (MS). Reduction of frequency of relapses in relapsing-remitting MS in ambulatory patients. In clinical trials this was characterised by at least two attacks of neurological dysfunction over the preceding two-year period. **Dosage and administration:** 20mg of glatiramer acetate subcutaneously once daily. 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. *Adolescents (12 - 18 years):* No specific studies. Limited published data suggest the safety profile of 20mg administered subcutaneously once daily is similar to that seen in adults. *Children (<12 years):* Not recommended. *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. Instruct patients in self injection technique and supervise first self-injection and for 30 minutes after. 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. Rarely convulsions and/or anaphylactic or allergic reactions. 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:** Not to be used 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:** *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, rhinitis seasonal, 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: 28 pre-filled syringes of Copaxone: £513.95. **Legal category:** POM. **Marketing Authorisation Number:** 10921/0023 **Marketing Authorisation Holder:** Teva Pharmaceuticals Ltd, Ridings Point, Whistler Drive, Castleford, West Yorkshire. WF10 5HX. United Kingdom. **Date of preparation:** June 2013
Job Code: UK/MED/13/0034

Date of preparation: October 2013 **Job code:** UK/CPX/13/0008l

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