ISSN 1473-9348 VOLUME 13 ISSUE 1 MARCH/APRIL 2013

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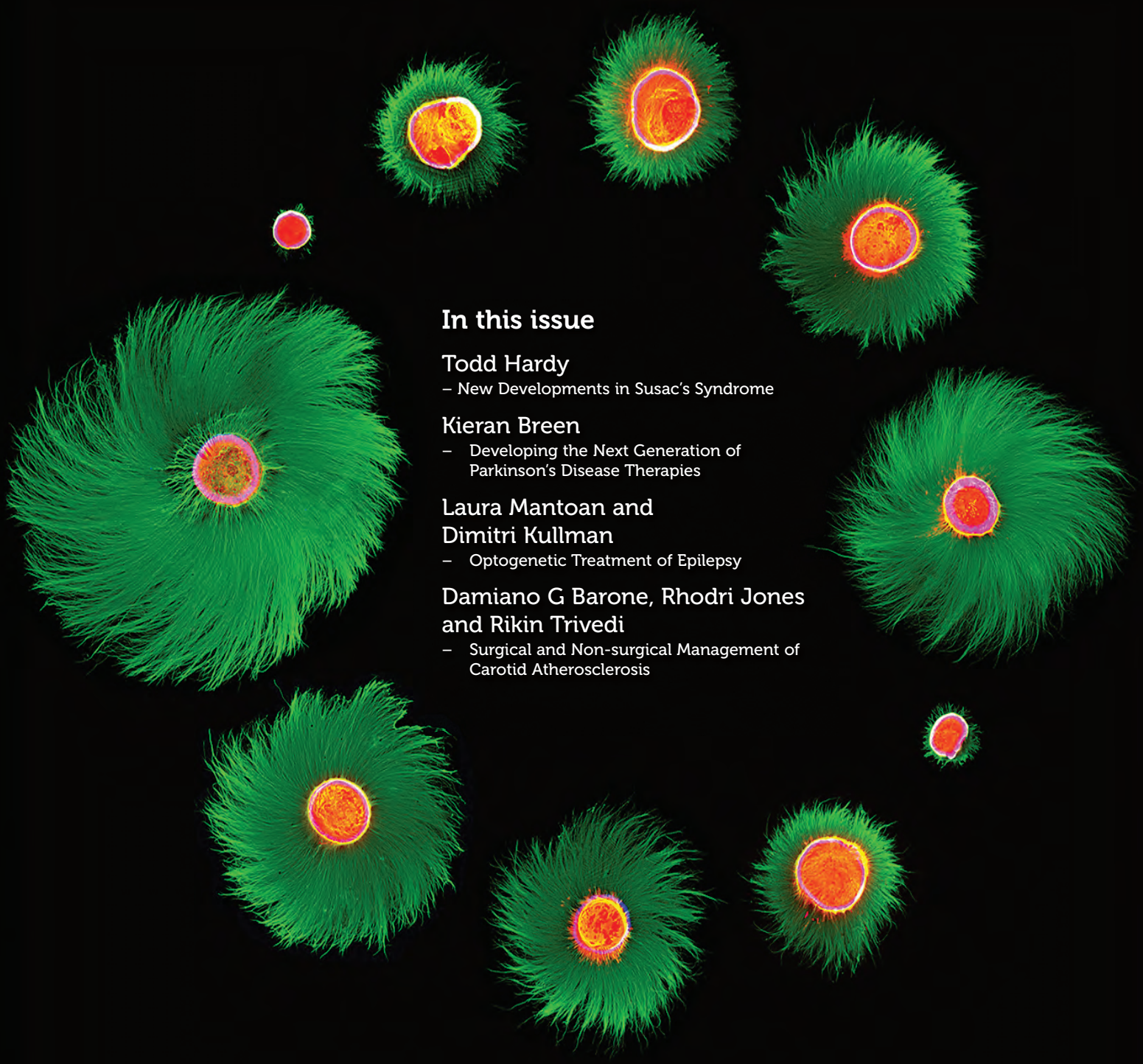

In this issue

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Alan Emery's achievements receive further recognition

Emeritus Professor Alan Emery - an Honorary Fellow of Green Templeton College - has received the Muscular Dystrophy Campaign's (MDC) Lifetime Achievement Award 2012 for his contributions to scientific and clinical work in muscular dystrophy.

He was the first to describe a form of dystrophy now referred to as Emery-Dreifuss muscular dystrophy, and the defective protein Emerin which causes the disease is named after him. You can read Professor Emery's ACNR article on the subject at http://www.acnr.co.uk/pdfs/volume5issue2/v5i2legends.pdf

Professor Emery has also been awarded an Excellence in Education Award from the American Society of Human Genetics.

"Prof. Emery has been one of the most prodigious authors of important genetics texts in the world," said ASHG Executive Vice President Joann Boughman. "One of his textbooks has been republished in 12 editions translated into seven languages. For many in the field of human genetics, he is simply known as 'the expert'.

The ASHG award recognises an individual for contributions of exceptional quality and great importance to human genetics internationally.

Appointment of the first Rowling Fellow

The Anne Rowling Clinic in Edinburgh has announced the appointment of Dr Rickie Patani of Cambridge University as the first Rowling Fellow. Dr Patani is a post-doctoral Clinical Research Associate at Cambridge University and Specialist Registrar in Neurology at the National Hospital for Neurology and Neurosurgery, Queen Square. His research focuses on motor neurone disease (MND). At present, the causes and underlying biology of this disease are poorly understood. Dr Patani is an expert in the generation of human cell-based models of MND. It is hoped that these 'disease models in a dish' will yield fundamental insights into the biology of MND, and prove to be a valuable tool in the evaluation and discovery of new targeted therapies.

The Rowling Fellow designation is reserved for outstanding collaborators outside the University of Edinburgh whose research aims align closely with the goals of the Anne Rowling Clinic.

MS Society Awards 2013

The MS Society Awards highlight the achievements of people with MS, their families and carers, and the professionals who make a difference to people living with MS. There are ten categories, recognising and rewarding the dedication and hard work of groups and individuals who do so much to improve the lives of people living with MS. This year sees the introduction of a new category for digital media, awarding innovative and creative digital media. Each year the MS Society also awards a special prize to the 'MS Inspiration of the Year'. Anyone can nominate by the closing date of 19 April 2013.

Tel. 01494 671332, E. mssocietyawards@mssociety.org.uk or see http://www.mssociety.org.uk/ms-events/2013/01/ms-society-awards-2013

New Executive Director for ABN

The Association of British Neurologists has appointed Joanne Lawrence as its new Executive Director. After graduating from Imperial College, Joanne worked in marketing and business strategy roles within Rio Tinto and Unilever before developing her own business providing B2B market research to multinational organisations. She is looking forward to building upon her corporate and voluntary experience (as school governor, sports club chairman and team leader to London 2012 Games Makers) in her role within the ABN.

We are sad in the ACNR offices that both Roger Barker and Alasdair Coles are now taking a back seat in the running of the journal, but happy that we do not have to say good-bye completely! Roger, with our publisher Rachael Hansford, delivered the first issue 12 years ago in March/April 2001, and Alasdair joined as co-editor from the second year, having contributed many neuroanatomy primers in the first. Both took ACNR forward as a journal of topical and major advances in neuroscience and clinical neurology for neurologists, which has become widely read with a readership of 5000 in the UK, and over 1200 more internationally through the website. Both have distinguished personal achievements in clinical neurology and neuroscience that will be familiar to our readers, and lead their respective research groups: Roger's in the fields of Parkinson's disease and Huntington's disease, Alasdair's in multiple sclerosis and neuroimmunology.

ACNR has grown and has been a sustained success in this time in no small part due to the talents of both Roger and Alasdair, as reflected in their own research successes. I would therefore like to thank them both personally and on behalf of all who have worked with them at the journal over the past 12 years, and am grateful that they will both continue to work with the journal. You will be pleased to read that there will be no radical changes, and as ever we are keen for our readers to be involved.

In this issue, Todd Hardy, from Sydney, writes a clear account updating us on Susac's syndrome, in particular novel imaging data, a discussion of the role of endothelial cell antibodies in the pathogenesis, and a very helpful and comprehensive guide to treatment. We welcome Todd as an associate editor of ACNR in Australia.

Director of Research and Innovation at the charity Parkinson's UK, Kieran Breen, brings us up to date in the emerging therapeutics of Parkinson's disease. Dr Breen discusses the uses of genetic studies to identify drug targets and the repurposing of existing drugs to avoid the costs and delays of novel drug development. He reminds us of the difficulties with biomarkers for clinical studies that need to be overcome.

The symptomatic treatment of epilepsy is clouded both by poor efficacy for the many and the substantial adverse effects of anti-epileptic drugs (as pointed out in a review of two new large studies by Mark Manford in the journal reviews section). Laura Mantoan and Dimitri Kullmann, from UCL and the National Hospital for Neurology and Neurosurgery, Queen Square, provide a beautiful account of the background, theory and potential uses of optogenetics in the treatment of epilepsy, including an account of their own work. The technique, which harnesses the function of light sensitive channels transfected into cortex in rat models, promises great power as a mechanism to abort seizures 'on-demand' with minimal adverse effects. This is the first article in Mark Manford's new series of advances in epilepsy, which promises to be highly informative.

In our neurosurgical article, Damiano Barone, Rhodri Jones and Rikin Trivedi, from Liverpool and Cambridge, provide a helpful dissection of all the available evidence for carotid endarterectomy versus carotid angioplasty in carotid stenosis and stroke. This is an excellent overview of this well-studied issue.

For those going to the ABN meeting in May, Edward Newman and Paul Gallagher provide a helpful introduction to the city of Glasgow, including a roundup of alternative sights to the SECC, and a hopefully helpful list of phrases to be aware of.

We have our usual book, journal and conference reviews and previews, and hope you continue to enjoy ACNR. If you have any suggestions for potential topics or authors, please let us know.

Mike Zandi, Editor.

Mike Zandi, Editor.

"... a unique opportunity to bring neuroscience to neurology and take advances in neurology out into the community of neurologists and associated specialties."

These are not my words, but were written by Roger Barker 12 years ago. They are as relevant today as when they were first written. Whilst the principles founding this publication have not changed, alas technology moves on.

I was delighted when ACNR asked me to join the team; for me ACNR has been a wonderful resource. Over the last twelve years some of the most renowned and respected in their fields have written articles on the latest thinking in neurology and the neurosciences. The newer articles provide the community with a trusted source for keeping abreast of recent advances, whilst the back catalogue is a fascinating lens into the last decade of our speciality.

With all of this great free content, accessibility is vital. If we want ACNR to be one of the go-to places for neurologists and related specialists then we need to make it easy for you to quickly find what you need. With this in mind, our new website is about to be launched. In addition to looking prettier, the site has a searchable table of contents and articles are listed under their respective categories. We would like to grow the ACNR community and provide a platform for our authors, readers and team to discuss issues raised in the journal, feedback ideas for future articles and let us know how we are doing. Rather than re-inventing the wheel we have decided to stick with those who do it best and so you can reach us on both Twitter and Facebook. Your feedback will help shape the future of ACNR and hopefully the current opinions in neurology too.

For links to both of these accounts please visit the *new* site at www.acnr.co.uk and click on the links in the top right hand corner. ◆

Stevan Wing, Web Editor.

Stevan Wing, Web Editor.

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Cover picture: Nikon Small World Competition 2012, Image of Distinction. Dr Mafia Alejandra Lopez-Verrilli Pontificia Universidad Católica de Chile, Facultad de Ciencias Biológicas, Santiago, Chile. Radial growth of sensory neurons (axons stained in green, somas in blue and actin filaments in red).

ACNR

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

New Developments in Susac's Syndrome

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is a Consultant Neurologist at Concord Hospital, Sydney, Australia. He trained in Neurology in Sydney and London and was formerly Locum Consultant Neurologist in the Department of Neuroinflammation at the National Hospital for Neurology and Neurosurgery, Queen Square. His main interests are multiple sclerosis and other neuro-inflammatory disorders. He is Australian Co-ordinator of the International Collaborative Study of Susac's syndrome.

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The diagnosis of Susac's syndrome has been facilitated greatly by appreciation of distinctive magnetic resonance imaging (MRI) findings. As a result there is now increased recognition of what was once thought to be a very rare disease. The aim of this review is to provide an update on the latest developments in Susac's syndrome and to highlight the importance of early and aggressive immunotherapy.

Clinical and epidemiologic considerations

Susac's syndrome is the triad of sensorineural deafness, branch retinal artery occlusions (BRAOs) and encephalopathy. The 'encephalopathy' refers to a range of cerebral manifestations including cognitive impairment, psychiatric disturbance, headache, seizures and focal neurologic deficits. Headache is an important but often under-appreciated symptom which frequently has a migrainous character and may precede other symptoms.[1]

The onset of Susac's syndrome is usually between 20 and 40 years but cases as young as 7 and as old as 72 years have been reported.[2] Females are affected more commonly than males in a proportion of 3:1. The syndrome is rare but the true prevalence is unknown. Because Susac's syndrome is commonly misdiagnosed as various conditions including acute disseminated encephalomyelitis, multiple sclerosis (MS), neuro-Behçet's disease, cerebral vasculitis, temporal arteritis or Cogan's syndrome[3] it may be more prevalent than originally supposed. Moreover, the full triad may take months to evolve or never evolve fully and forme frustes of the disease can frustrate diagnosis.[1]

In the majority of cases, Susac's syndrome is a monophasic self-limiting disease that remits after one or two years.[1] A polycyclic course has also been described in which patients have exacerbations of symptoms over several years. Rarer still, is the chronic continuous phase characterised by fluctuating symptoms without true periods of remission.

Recently, two clinical subtypes of Susac's syndrome have been proposed; the so-called 'encephalopathic form' with predominant encephalopathy and the 'recurrent BRAO' subset with a more prolonged and less severe phenotype.[4] The 'recurrent BRAO' group have minimal clinical or radiological evidence of cerebral involvement, but as the name suggests, develop recurrent episodes of BRAO which can continue episodically for many years without accrual of neurological deficit.[4]

Ocular manifestations

A feature of Susac's syndrome is visual field loss due to BRAOs (Figure 1). Affected patients may be asymptomatic but equally others may be too encephalopathic to notice or report difficulties with vision. If Susac's syndrome is suspected it is important to perform fluorescein angiography as BRAOs may be diagnostic. Retinal arterial wall atheromatous plaques (Gass plaques) may also be present at mid-arteriolar segments away from retinal artery bifurcations. Arteriolar wall hyperfluorescence indicates areas of active disease and may be considered supporting evidence of retinal vasculopathy.[5]

In a recent cross-sectional observational study, nine patients with Susac's syndrome with retinal involvement were assessed by optical coherence tomography and found to have a significant reduction in retinal nerve fibre layer thickness and macular volume compared to either healthy controls or patients with MS with or without a previous history of optic neuritis.[6] The reduction in thickness was present in a sectorial distribution, particularly at the macula, as might be expected with retinal microvascular damage, and different to the generalised thinning seen in MS patients.

Vestibulocochlear involvement

While hearing loss and tinnitus are common in Susac's syndrome, vestibular symptoms such as vertigo and nausea are also frequent.[7] Pure tone audiometry usually reveals bilateral sensorineural hearing loss which is asymmetric and is thought to reflect sequelae of microinfarction in the apical cochlea (Figure 2). Low-to-moderate range frequencies are preferentially affected and poor speech discrimination is common. Vestibular symptoms may be due to peripheral or central vestibular involvement.

Recently, two clinical subtypes of Susac's syndrome have been proposed

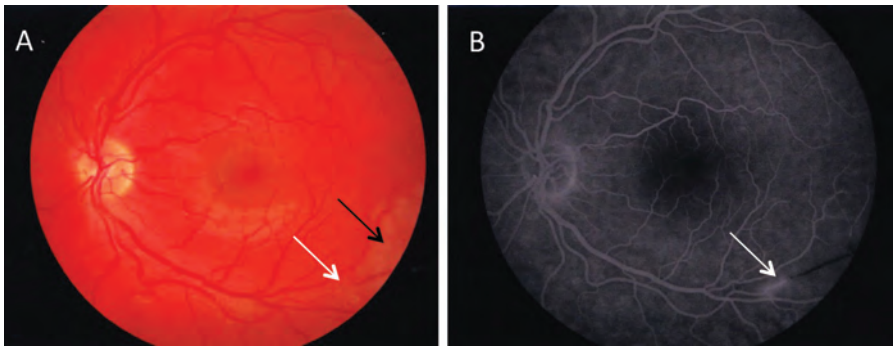

Figure 1: Fundus photograph (A) showing branch retinal artery occlusion (white arrow) with associated pale area due to focal retinal infarction (black arrow). A fluorescein angiogram (B) more clearly identifies the BRAO (white arrow). Note, peripheral BRAOs can be missed with fundoscopy underscoring the need to perform a fluorescein angiogram if Susac's syndrome is suspected.

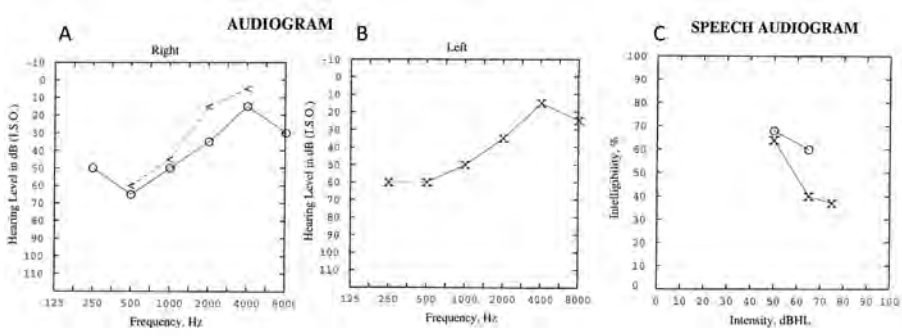

Figure 2. Pure tone audiometry assessing (A) the right ear and (B) the left ear in a patient with Susac's syndrome. There is asymmetric, bilateral low-to-mid frequency sensorineural hearing impairment. Speech discrimination in both ears (C) is also impaired.

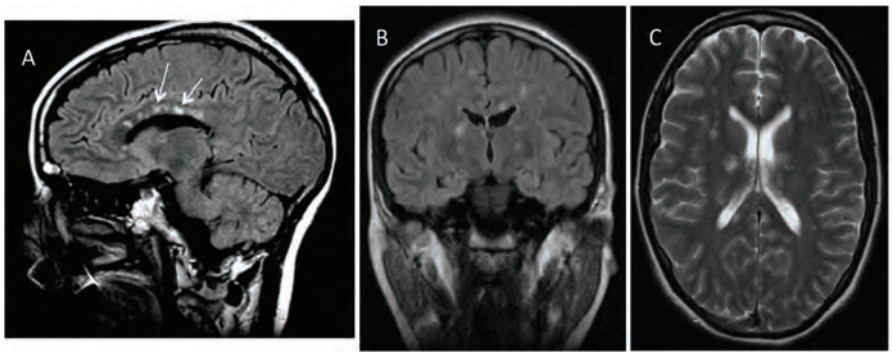

Figure 3. MRI brain of a patient with Susac's syndrome. (A) Sagittal fluid attenuated inversion recovery (FLAIR) sequence showing corpus callosal 'snowball' lesions (arrows) whose central location in the callosum makes them pathognomonic of Susac's syndrome. (B) Coronal FLAIR and (C) Axial T2 sequences showing focal, punctate microinfarcts in the subcortical white matter and callosum. Figure 3A has been reproduced with permission from Elsevier.[9]

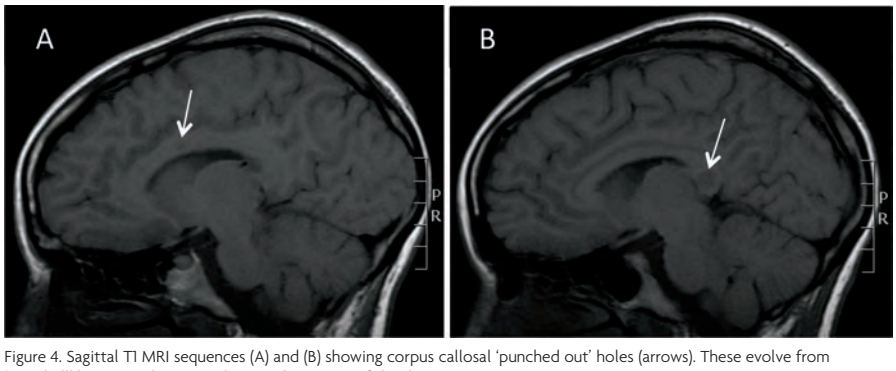

Figure 4. Sagittal T1 MRI sequences (A) and (B) showing corpus callosal 'punched out' holes (arrows). These evolve from 'snowball' lesions and so occur later in the course of the disease.

Pregnancy

Several authors have noted an association between Susac's syndrome and pregnancy.[8-11] Among eight female patients, most with a new diagnosis of Susac's syndrome, three developed new BRAOs during pregnancy and three patients experienced a relapse in the postpartum period.[8] While this may be due to chance, other autoimmune conditions such as rheumatoid arthritis and thyroid disease may flare in the perinatal period. It is conceivable, therefore, that fluctuations in circulating hormones may be relevant to the underlying mechanism of the disease, perhaps by inducing a hypercoaguable state, and may also be relevant to the overall female preponderance.

Radiological findings

Susac's syndrome is associated with pathognomonic MRI lesions in the central fibres of the corpus callosum referred to as 'snowball' lesions[12] (Figure 3). Central callosal 'icicle' and 'spoke' lesions in contact with the roof of the callosum and a characteristic 'string of pearls' appearance of microinfarcts in the internal capsule have also been recognised.[4] All of these lesions are best seen on sagittal fluid attenuated inversion recovery (FLAIR) and/or T2 MRI sequences and are often visible on diffusion weighted imaging. Later, as callosal lesions become chronic they assume the appearance of 'punched out' holes best seen on T1 sequences (Figure 4). In addition to these findings, punctate subcortical and infratentorial lesions are usually present and these may coalesce (Figure 3). The commonest areas affected are the periventricular regions, centrum semiovale, cerebellum, brainstem and middle cerebellar peduncles. Deep gray matter may be involved. Gray and white matter lesions often enhance (70%) with leptomeningeal enhancement less common[4,12].

Many patients with Susac's syndrome are more disabled than their limited lesion load on imaging would indicate. Newer studies using diffusion tensor imaging (DTI) have demonstrated evidence of widespread axonal damage not visible on conventional MRI which may account for this mismatch[13]. In particular, microstructural degeneration in the genu of the corpus callosum on DTI appears to be characteristic of Susac's syndrome. Studies with 7 Tesla MRI have shown that white matter lesions in Susac's syndrome rarely exhibit a hypointense rim and are less often located in a perivascular location making them morphologically distinct in this regard from the lesions of MS.[14]

Immunopathogenesis

It is now widely held that Susac's syndrome occurs as a result of an endotheliopathy of small vessels due to underlying autoimmune dysfunction. Brain biopsy specimens in patients with Susac's syndrome show areas of microinfarction due to thickening of arteriolar media and loss of capillary networks. While

frank vasculitis is not observed, sparse perivascular lymphocytic infiltrates are often described.[3]

Immunofluorescence studies have identified anti-endothelial cell antibodies (AECAs) in patients with Susac's syndrome.[2,15] Serum from eleven patients with Susac's syndrome (among whom six of the patients had the full triad) was assessed by indirect immunofluorescence using generic cutaneous microvascular cells. Nine patients were positive for AECAs and eight patients had a characteristic 50-kDa protein detected by western blot that was not present in comparator samples from patients with other autoimmune diseases.

It is not yet clear if AECAs have a pathogenic role in Susac's syndrome or are merely an epiphenomenon. AECAs are not specific to Susac's syndrome but have been identified in other autoimmune diseases including scleroderma, systemic lupus erythematosis and Behcet's disease.[2] In support of an antibody-mediated aetiology for Susac's syndrome, more than 50% of capillaries in brain biopsy specimens stain strongly for the complement protein C4d2.

Immunotherapy

Susac's syndrome is sufficiently rare that randomised controlled therapeutic trials have not been possible and treatment is based on the results of physician experience supported by individual reports and case series. There is broad agreement that treatment with high dose corticosteroids should be first line therapy. What is less certain is what other agents should be used in conjunction. Immunomodulatory agents most commonly used include intravenous immunoglobulin (IVIg), plasma exchange, azathioprine, mycophenolate mofetil (MMF), methotrexate, cyclosporin A and cyclophosphamide. Ideally, an agent, or combination of agents, which can improve disability due to acute lesions but is also able to exert a sustained disease modifying effect is desirable.

At present, the choice of a particular drug regimen depends on the clinical picture. There is increasing recognition that early, aggressive treatment of the 'encephalopathic form' of Susac's syndrome is necessary. Initial treatment with intravenous corticosteroids is recommended followed by slowly tapering oral corticosteroids and addition of a steroid sparing agent such as MMF. Both IVIg and cyclophosphamide are also suggested on a monthly basis for at least six months.[4,5] Maintenance immunomodulatory treatment may be necessary for at least two years from remission[11].

For patients in the 'recurrent BRAO' group, less aggressive therapy may be warranted as the clinical sequelae are usually less significant.[4] In this group, treatment is the same as in the 'encephalopathic form' except that oral corticosteroid taper is more rapid and that cyclophosphamide can be withheld in favour of monthly IVIg alone for six months. Patients with a first ever episode of BRAO should probably be treated aggressively from the outset as their disease subtype remains undeclared and the potential neurological sequelae of a relapse may be devastating meaning that the potential benefits arguably outweigh the risks of immunomodulatory therapy.

For patients that deteriorate, continue to relapse, or are intolerant of this regimen then treatment with monoclonal antibodies has been attempted with some success. It may be that these agents will become the preferred therapeutic option as an adjunct to corticosteroids for early aggressive treatment of Susac's syndrome as further data emerge. Specifically, there is growing experience with the anti CD20 monoclonal antibody, Rituximab in Susac's syndrome.[4,5,10] The tumour necrosis factor (TNF) inhibitor, Infliximab may also be beneficial.[9] Both of these agents have efficacy in juvenile dermatomyositis, a condition believed to share a similar immunopathogenesis to Susac's syndrome.[5,15]

Treatment of hearing loss and tinnitus

Intratympanic injection of dexamethasone in the acute phase of hearing loss and tinnitus may provide transient benefit and may help justify more aggressive immunotherapy on the grounds of potential for reversibility. In those patients with profound sensorineural hearing loss consideration of cochlear implants is warranted[7].

Treatment of ocular manifestations

The aim of treatment of visual deficits is prevention of further damage with immunotherapy as, once established, retinal infarcts are permanent. Hyperbaric oxygen may improve acute onset visual symptoms in Susac's syndrome[16]. Neovascularisation resulting from retinal ischaemia has been treated with laser photocoagulation with some success[8].

Prognosis

Prognosis is to some extent determined by whether patients have an 'encephalopathic form' of Susac's syndrome or a clinical picture more in keeping with a 'recurrent BRAO' subtype (see Clinical and Epidemiologic Considerations and Immunotherapy). Prior to the recognition of the need for aggressive treatment of the encephalopathic form of Susac's syndrome, approximately 50% of patients suffered ongoing cognitive impairment.[1] However, if treated early, many patients with Susac's syndrome are now able to make an excellent recovery despite significant encephalopathy at presentation.

Conclusion

Susac's syndrome is a rare but likely underdiagnosed condition. Recent research developments have led to improved diagnosis and growing insights into its underlying immunopathogenesis. Treatment with early aggressive immunotherapy is warranted in many cases and a role for monoclonal antibody therapy is emerging as an adjunct to more traditional immunosuppression. ◆

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Developing the Next Generation of Parkinson's Disease Therapies

Dr Kieran Breen,
is Director of Research and Innovation at Parkinson's UK - a post that he has held for over seven years. His primary role is to develop and strengthen the charity's research capacity by the development and implementation of the charity's cure-focused research strategy. He has an academic background with a PhD in neuroscience and has over 60 peer reviewed publications.

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Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder associated primarily with the death of the dopaminergic neurones in the substantia nigra. All of the treatments currently available for the treatment of PD address the primary motor symptoms. In addition, the management of non-motor symptoms requires a multi-drug therapeutic approach. However, none of the therapies currently available influence the progression of the condition and some can have significant deleterious side effects.

In the longer term, strategies need to be developed that will actually target the disease itself rather than the symptoms – agents that will slow down or halt the progression of the neurodegenerative process or even the development of a pre-symptomatic preventative strategy. If disease-modifying treatment is provided at a sufficiently early stage prior to the onset of the primary motor symptoms, this could essentially be considered as being a cure.

This review will outline some of the potential strategies that may target the neurodegenerative process and target the disease rather than the symptom.

Genetic studies to identify drug targets

If clinically effective disease modifying strategies are to be developed, a detailed understanding of the cellular and molecular basis of the neurodegenerative process is required.

Genome-wide association studies (GWAS), in addition to the identification of specific family cohorts, have allowed us to identify genes that are associated with PD.[1] This has led to the identification of a number of potential drug targets. Due to its potential as a genetic risk factor for the development of PD (1-3% of sporadic cases), the LRRK2 gene has been studied extensively.[2] While the exact protein function remains unknown, it is likely to be a serine/threonine kinase and may play a role in neurite outgrowth, protein translation and vesicular storage and mobilisation. The majority of LRRK2 mutations are associated with an increased kinase activity. Therefore, enzyme inhibitors may provide a potential therapeutic target.[2] Studies of other genes associated with inherited forms of PD suggest that mitochondrial dysfunction and abnormal protein processing are also associated with PD.[3] A greater understanding of the roles of the biochemical pathways associated with PD-associated gene mutations will help in the identification of targets that will form the basis of the next generation of disease-modifying therapeutic agents.

Alpha synuclein (α-Syn) is the primary component of Lewy bodies which are the pathological hallmarks of the disease. Additionally, the gene has been identified in GWAS studies as being associated with inherited forms of PD.[1] The protein is present in Lewy bodies as an insoluble misfolded form of the protein and this is probably due to a dysregulation of the lysosomal and proteosomal protein processing pathways within the cell. There is an increasing body of evidence to suggest that the misfolded form of α-Syn, which is the basis of Lewy body pathology, can then spread between cells from affected to unaffected regions of the brain. Post mortem studies of foetal tissue grafted into the brain of a PD patient identified Lewy body-like lesions in the transplanted tissue although, due to the age of the tissue in the graft, this is unlikely to have occurred spontaneously.[4] Furthermore, a single intracerebral inoculation of misfolded α-Syn into the brains of animal models has been reported to induce neurodegeneration. This is accelerated in transgenic mice over-expressing α-Syn.

Collectively, these findings support the hypothesis that α-Syn can exist as a prion-like protein that can adopt a self-propagating conformation that contributes towards the neurodegenerative process.[5] This is likely to play an important role in the development of PD and agents that could prevent protein misfolding, aggregation or transmission may form the basis of future neuroprotective therapies.[6]

Another therapeutic target that may be influenced by PD-associated gene mutations is the mammalian target of rapamycin (mTOR). This protein serine/threonine kinase plays a role in cellular differentiation, development, regeneration and repair.[7] The blockade of mTOR activity in cell culture models during oxidative stress can lead to dopaminergic neuronal cell death as a result of autophagy activation. It also plays a role in many aspects of homeostasis that are critical for cellular health. Recent studies have also reported that rapamycin can rescue cellular mitochondrial dysfunction associated with certain PD genes.[8] However, mTOR activation as a therapeutic target may require a fine level of modulation because other studies suggest that inactivation of mTOR and an increase in autophagy may actually preserve dopaminergic neurons in PD, possibly through an α-Syn associated pathway.

The repurposing of existing drugs to treat PD

The development of new drugs is a lengthy and costly process, so there has been an increasing interest in the repurposing of existing drugs.[9] These agents are already in use in humans so could go straight into phase II trials to assess their clinical

effectiveness and particularly their potential to modify the rate of disease progression.

One class of drugs that has gained considerable interest for the treatment of PD is the GLP-1 antagonist class which is used to treat diabetes. Indeed, based on epidemiological studies, patients with diabetes mellitus have been reported to have a 36% increased risk of developing PD.[10] Initial studies in animal models have suggested that one of these drugs, exenatide, may have neuroprotective properties.[11] Furthermore, the thiazolidinedione class of anti-diabetic drugs have been reported to have a neuroprotective effect in PD and it has been proposed that this is achieved at least in part through anti-inflammatory and anti-oxidant activities. However, the thiazolidinediones have been reported to demonstrate the adverse cardiovascular effects in a small number of subjects.

Calcium channel blockers have been proposed as a suitable class of drugs due to their potential neuroprotective properties. Based on studies on the tolerability of the drug for people with PD,[12] a phase II study of isradipine is currently underway. Other drugs that may be suitable for repurposing based on preclinical studies include statins[13], iron chelating agents[14] and cannabinoids.[15]

Animal models

In order to rigorously assess the potential effectiveness of new drugs to influence the progression of PD, reliable animal models that mimic the key components of the condition such as cell death and the development of PD pathology are essential. While the current gold standard models are based on the degeneration of dopaminergic neurons following the administration of the toxins MPTP or 6-OHDA, these toxins act acutely with the rapid and irreversible death of dopaminergic neurons at the site of toxin injection. They are useful for assessing symptomatic drugs but have limited use in screening neuro-restorative therapies. Even when administered slowly and at low doses, they neither replicate the pathology nor the changes in other neurotransmitter systems that are observed in the latter stages of the disease.

The next generation of models that can be used to assess disease-modifying therapies are therefore being developed based on an understanding of the genetics of the condition in addition to the environmental factors that have been associated with the onset of PD such as pesticides.[16] While none of these models recapitulate exactly all of the behavioural and pathological changes that are characteristic of PD, when combined they may provide us with a useful library with which to assess potential new therapeutic compounds which could influence the development and progression of the disease.[17] An illustration of the complexity of disease modelling is the role of LRRK2 mutations in the generation of animal models. Transgenic mice constitutively expressing an LRRK2 mutation do not show any specific degeneration of dopaminergic neurons, although there is an impairment of dopamine release with parallel behavioural problems. However, transient expression of a mutant form of the gene using specific viral vectors induces degeneration of dopaminergic neurons. Furthermore, neuronal degeneration has been observed in C. elegans and Drosophila which constitutively express the mutant gene.[2] The reason for this remains obscure although the role of gene dosage and duration of expression may play a key role.

While initial clinical studies on the glial-derived neurotrophic factor (GDNF) in humans demonstrated clinical efficacy, there was a lack of neuroprotective effect against the toxicity of human wild-type α-Syn in an animal model of PD.[18] Again, this highlights the potential differences between animal models and the clinical setting and the importance of using a number of animal model systems in the early stages of drug screening.

Ultimately, the use of animal models to screen prospective drug compounds should be fit for purpose and recapitulate the events that occur in humans corresponding to the time at which the drugs are prescribed in the clinic.[19]

Biomarkers and clinical trials

If drugs that act to influence the course of PD progression are to be effective, a reliable and early diagnosis is required, ideally in the pre-motor stage of the disease. A number of early symptoms have been identified including the loss of olfaction, REM sleep behavioural disorder and constipation. However, the development of a specific and sensitive blood biomarker is the ultimate goal if the rate of disease progression is to be monitored accurately.[20]

Most importantly, if potential disease modifying agents are to be confirmed as being clinically effective, the drug trial should be designed appropriately. This includes specific patient inclusion and exclusion criteria and it is important that negative trial results should not be associated with bad clinical trial design. Furthermore, care must be taken to assess appropriate outcome measures. Not all clinical rating scales represent a meaningful change for the trial participants.

Finally, it is vital to be able to distinguish between true disease modification and a symptomatic effect of the therapy. A long-lasting placebo effect can be common in PD and most treatments that have been shown to exhibit potential disease modifying properties are also likely to exhibit pro-dopaminergic symptomatic effects. This underlines the fact that an objective and reproducible biomarker is ultimately required to assess the disease state and whether this is being modified by the therapy.

This is an exciting time for the development of the next generation of PD drugs which will target the disease rather than the symptoms. However, we must ensure that all of the studies are carried out using the most appropriate models and effective clinical outcome parameters. It is only then that we can say that we are really moving closer towards our ultimate goal – a cure for PD. ◆

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Targeting Rehabilitation Medicine

Dr Fayez Morcos, Consultant in Rehabilitation Medicine, The Pennine Acute Hospitals NHS Trust.

Dr Fayez Morcos (pictured right) is a Consultant in Neurological Rehabilitation at The Floyd Unit, The Pennine Acute Hospitals NHS Trust. Spasticity management is one of Dr Morcos' main clinical interests. He regularly treats patients with focal spasticity using botulinum toxin injections. Dr Morcos has excellent experience in localising muscles that need to be injected with a great deal of accuracy, especially using ultrasound guidance. He provides training and mentors for methods of accurate localisation of different muscles of the body.

The use of ultrasound needle guidance to accurately target injections is now widely-established for regional anaesthesia and analgesia, thanks to recent advances in the resolution and ease of use of hand-carried ultrasound instruments such as the SonoSite Edge® system. As these instruments become ever more accessible and familiar in the healthcare setting, clinicians are finding an increasing number of novel applications for ultrasound, both as a diagnostic tool and to aid in the treatment of patients. Rehabilitation medicine is one area which has seen growing interest in the use of ultrasound over the last few years, particularly for the treatment of spasticity, applying the needle guidance techniques developed for anaesthesia to alleviate symptoms and improve outcomes for patients with neurological injuries.

The march of progress

The use of botulinum toxin to relieve spasticity is nothing new, but the accuracy with which injections can be delivered has been vastly improved by the introduction of ultrasound needle guidance. Previously, clinicians would have to rely on palpation techniques, electromyography or nerve stimulation to try and identify the correct location for injection of the toxin; palpation and electromyography methods are highly inaccurate and do not account for anatomical variations between individuals, while nerve stimulation methods can be both uncomfortable for patients and time consuming to perform. In contrast, ultrasound is highly accurate – allowing you to visualise the position of the needle tip relative to the muscle and surrounding structures in real time – rapid, and less invasive, leading to more accurate injections and a far better, more comfortable patient experience.

Despite these obvious advantages, ultrasound has only really become viable for needle guidance applications since the advent of robust, portable and easy-to-operate ultrasound instruments. Launched in 1999, the SonoSite 180 was the first hand-carried, battery-operated ultrasound system that was designed for use outside of the radiology department, giving clinicians access to this powerful technique without the need for specialist sonography training or arduous patient transfers. This ease of use, combined with the affordability of modern hand-carried systems, led to the rapid and widespread adoption of ultrasound needle guidance by anaesthetists as a practical alternative to nerve stimulator techniques. Since this time, point-of-care ultrasound systems have become commonplace in virtually every hospital in Britain, with an ever increasing number of clinical specialties using multifunctional instruments for a diverse array of applications.

The rehabilitation revolution

The needle guidance techniques developed by anaesthetists are directly applicable to neurological rehabilitation therapies, allowing localised, accurate injection of botulinum toxin. Unlike nerve stimulator or anatomical methods, ultrasound needle guidance ensures accurate needle placement regardless of patient physiology. This greatly improves the success rate of procedures, and probably also the desired clinical effects in terms of both the degree and duration of relief offered to patients. It also provides access to deep muscle groups, such as the iliopsoas muscles, which are not possible to be injected without imaging. Ultrasound guided injections allow visualisation of these muscles, measuring the depth and avoidance of neighbouring delicate structures and vessels during the injection.

As well as improving the comfort of patients both during and after treatment, ultrasound is a useful tool to help patients to understand what their treatment involves, and what the likely outcome might be. Explanations illustrated by ultrasound images of the target area can help the patient to feel more involved in the decision-making process, giving them a more thorough understanding of the aim of the procedure, whether that is to improve motor function or simply to make them more comfortable.

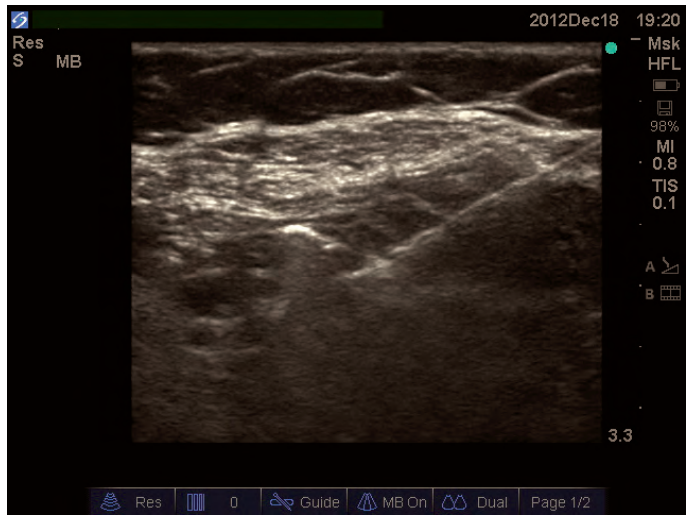
Beyond botulinum

The improved accuracy achieved by ultrasound needle guidance also offers the potential for new treatment strategies, such as the use of nerve blocks as an alternative to botulinum toxin. Highly localised injection of long-acting neurotoxins, such as phenol derivatives, could provide an alternative to direct injection of the muscle to treat spasticity. This technique provides effective relief for the patient, but the high toxicity of these agents demands even greater accuracy of needle placement, making ultrasound guidance essential.

In addition to guiding injections, ultrasound can be used as a diagnostic aid, offering better insight into the morphology and extent of damage within spastic muscles. For example, recent observations have shown that the degree of muscle contracture can be estimated from the degree of fibrous tissue within the muscle. This fibrous growth is more echogenic than normal, healthy muscle tissue, and so can easily be identified by ultrasound.

A sound future

The advent of robust, portable and easy-to-operate ultrasound instruments has been a significant breakthrough throughout the healthcare sector, allowing faster, better targeted treatment of patients than ever before. The intuitive design and clinically-focused features of multi-functional point-of-care instruments – such as SonoSite's Advanced Needle Visualisation – have helped to expand the role of ultrasound in rehabilitation medicine, leading to more accurate and effective treatment of a wide range of neurological injuries. The accuracy offered by ultrasound guided techniques is vital to the continued development of rehabilitation therapies and, by moving this technology from the radiology department to the bedside, the clinic or even the patient's own home, we are better able to provide the right care at the right time.



Ultrasound guided botulinum toxin injection to right biceps muscle

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Optogenetic Treatment of Epilepsy

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Pharmacoresistant epilepsy is common, and surgery to remove the epileptogenic zone is only indicated for a minority of patients referred for consideration of such treatment. Although some progress has been achieved with gene therapy in experimental models of epilepsy, this is usually considered irreversible, in that the excitability of neurons or their synaptic properties are permanently altered. Here we discuss an alternative experimental approach that potentially offers the ability to suppress seizures 'on demand', while leaving neuronal and synaptic functions intact the rest of the time. It relies on the ability to inhibit neurons by activating light-sensitive prokaryotic membrane proteins that act as ion channels and transporters. Substantial practical and regulatory obstacles will need to be overcome before optogenetics can be brought to the clinic. Nevertheless, it offers the prospect of temporal, regional and cellular specificity, which cannot be achieved by other treatments.

Introduction

Epilepsy affects over 50 million people worldwide, of whom only 60-70% are seizure free on medication.[1] Patients who have failed to respond to adequate doses of two first-line drugs have a less than 20% expectation of achieving seizure freedom with the addition of a new antiepileptic drug.[2] Pharmacoresistance is common and resective surgery is only appropriate when the epileptogenic zone does not involve eloquent cortex.[3] Because seizures are intermittent, developing a method for rapid and reversible suppression of activity in a restricted area of neocortex would be an important advance, but progress in local manipulation of brain excitability has been slow, and is mainly focused on electrical brain stimulation,[4] focal brain cooling[5] or targeted drug delivery.[6]

A potentially powerful alternative way to suppress seizure activity 'on demand' is to photoactivate prokaryotic light-sensitive ion channels and transporters known as opsins, expressed in neurons.[7,8] Opsins are a family of photosensory receptors found in all animal kingdoms, where they subserve a wide diversity of functions: from phototaxis in algae to eyesight in vertebrates. 'Optogenetics' is a novel technology that relies on optical control of opsins targeted to living cell membranes by gene transfer. This technique has revolutionised large areas of neuroscience in recent years, allowing specific and minimally invasive control of neuronal function that cannot be achieved with electrophysiology alone. Optogenetics has been used to manipulate the firing of specific classes of neurons *in vitro*[9,10] and in intact brain tissue *in vivo*, in vertebrate[11-13] and invertebrate[14] models. Some recent applications have focused on opsins as potential therapeutic tools.[13,15,16] Building upon these recent technological advances, we and other groups have investigated the therapeutic potential of optogenetic tools to inhibit epileptic activity *in vitro* and *in vivo*.

Opsins and optogenetic tools

Opsins are a family of proteins that combine with the vitamin-A derived chromophore retinal (or retinaldehyde). Many photosensory receptors, such as our own visual pigments, are opsins. They deliver the information carried by light to organisms by absorbing single photons, and are the molecular basis for a variety of light-sensing systems from phototaxis in flagellates to eyesight in animals. They were first successfully harnessed as a tool to control neuronal firing by G Miesenboeck's team at Yale.[17] Since then, several other groups have contributed to methodological developments and applications of this technology. Among the most prominent are those of K Deisseroth at Stanford University, G Nagel at the Max Planck Institute for Biophysics, and E Boyden at MIT.[10] In a remarkable series of experiments over only a few years they developed optogenetic tools with the necessary temporal resolution to manipulate the firing of neurons with millisecond precision.[18,19]

The first opsins to be widely adopted as optogenetic actuators in neuroscience were Channelrhodopsin-2 (ChR2) and Halorhodopsin (NpHR). Channelrhodopsin-2 is a light-switched cation-selective ion channel found in the green flagellate alga Chlamydomonas reinhardtii.[20] The absorption spectrum of ChR2 has its maximum at ~460nm. When activated by blue light, ChR2 allows positive charge into the cell, depolarising the cell membrane and functioning as an important mediator of light control of phototaxis and the photophobic response in Chlamydomonas. ChR2 was chosen to attempt genetically targeted photostimulation with fine temporal resolution because of the efficacy and speed of its natural light-transduction mechanisms. A versatile gene delivery tool is lentivirus, derived from HIV, engineered to drive ChR2 expression with an appropriate promoter, and with the yellow fluorescent protein (YFP) gene fused to the C-terminus of ChR2 to visualise the expressed protein. Lentiviruses and adeno-associated viruses (AAVs) have been successfully used to target ChR2 to mammalian neurons. Expression of ChR2 was stable over weeks and safe, as it did not alter the electrical properties or survival of neurons.[10] Furthermore, ChR2 could drive neuronal depolarisation without the addition of external cofactors, as the retinal present in the mammalian brain was shown to be sufficient to constitute a functional rhodopsin.[10,22] Illumination with blue light induced rapid, large

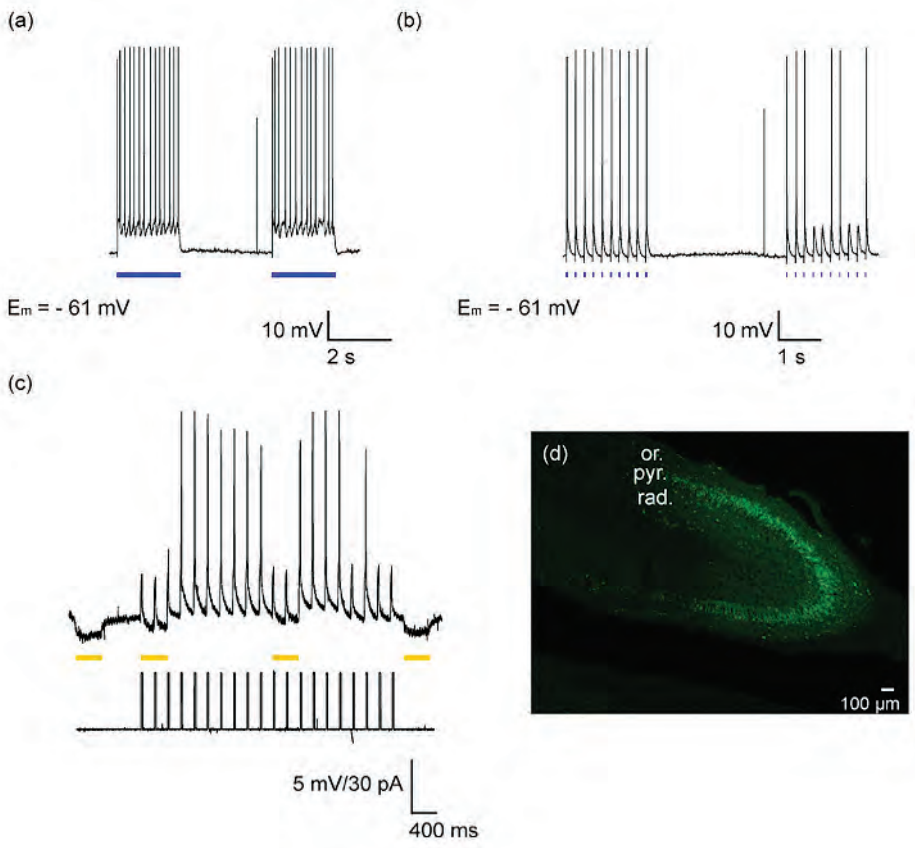

Figure 1: Optogenetic experiments in vitro: Co-expression of ChR2 and NpHR allows bi-directional modulation of neuronal firing. Animals were injected with AAV-eNPAC, an adeno-associated virus carrying both ChR2 and NpHR fused with a GFP reporter gene to visualise cells expressing the opsins. (a) Sample trace of a current-clamped CA3 pyramidal neuron expressing AAV-eNPAC, showing depolarisation and action potentials elicited with 2 s pulses of 473nm laser light (irradiance 5mW/mm^2). (b) 5ms laser pulses (left part of trace) reliably drove neuronal firing, and even 1ms pulses (right part of trace) elicited action potentials, albeit less reliably. (c) A hippocampal CA1 pyramidal neuron expressing AAV5-eNPAC was stimulated with a 593nm laser (13mW at 10x objective). Yellow light (400 ms pulse duration) hyperpolarised the membrane by approximately 2.5 mV (top trace), and inhibited action potentials elicited by brief current injections via the recording pipette (30pA, 20ms pulses - bottom trace). (d) Fluorescence micrograph showing the extent of expression in hippocampus injected with 1 µl AAV-eNPAC. Slices were counterstained with anti-GFP antibodies and AF 488 secondaries to amplify the GFP signal. Stratum radiatum (rad.), pyramidale (pyr.) and oriens (or).

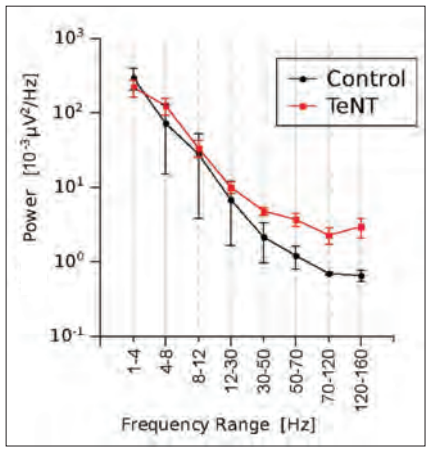

Figure 2: The tetanus toxin model of focal epilepsy. Power values at different EEG frequency bands for control animals (n=5) and tetanus toxin (TeNT) injected animals (n=6) recorded on day 7-10 post injection (mean ± SEM): delta (0-4Hz), theta (4-8Hz), alpha (8-12Hz), beta (12-30Hz), low gamma (30-50Hz), high gamma (50-70Hz), high frequency activity (HFA) › 70Hz (displayed in two bands of HFA 70-120Hz and HFA 120-170Hz). The graph shows an increase in the HFA › 70Hz in TeNT injected animals.

amplitude depolarising currents, which rapidly deactivated after the light was switched off. We have confirmed that action potentials can be reliably elicited in hippocampal neurons recorded in acute brain slices from injected rats (Figure 1a). Pulsed optical activation of ChR2 was also able to elicit precise, repeatable spike trains in a single neuron (Figure 1b), and to drive sustained naturalistic trains of spikes in a physiologically relevant spike range (5-30Hz). Finally, ChR2 has also been shown to drive subthreshold depolarisations and to control excitatory and inhibitory synaptic transmission.[10]

A complementary high-speed hyperpolarising Cl–pump was discovered in the archaeon Natronomonas pharaonis (NpHR).[9] NpHR has an excitation maximum in the yellow /green light spectrum near 580nm. In voltage-clamp experiments, illumination of NpHR-expressing cells with yellow light induced outward currents. We have confirmed that NpHR-mediated hyperpolarisation can abolish firing induced by depolarising current pulses (Figure 1c). Furthermore, as the absorption maxima of the two opsins are far apart, co-expression of NpHR and ChR2 in the same neurons can be combined to achieve bidirectional, independently addressable modulation of membrane potential by light of different wavelengths (Figure 1a-d).

Expression of microbial light-sensitive proteins has since been used to interrogate specific classes of neural cells, from cultured neurons to intact brain tissue *in vivo*.[13,23] Targeting specific neuronal subpopulations has been achieved using cell-type specific promoters in viral vectors and in transgenic animals[24] or cre-lox systems,[25] or by combinations of these technologies.[26,27] To allow optical stimulation *in vivo*, an integrated fibre-optic and optogenetic technology has been developed, and many laboratories now implant custom-made optical cannulae into brain areas following virus injection, or in transgenic mice, to target regions and circuits of interest.[28]

Applying optogenetics to epilepsy

An optimal therapeutic strategy for epilepsy would be minimally invasive, targeted to the epileptogenic zone, and only suppress neuronal activity when needed. The versatility and the electrophysiological characteristics of ChR2 and NpHR make optogenetic tools potent candidates to control neuronal firing in models of epilepsy and to provide insights into the pathophysiology of epileptic network organisation and synchronisation.

The first proof of concept that activation of NpHR could inhibit epileptiform activity came from M Kokaia's group in Sweden, who used an *in vitro* model of pharmacoresistant epilepsy generated by electrical stimulation-induced burst firing in organotypic hippocampal cultures. They transduced principal neurons using a lentivirus carrying NpHR under the calcium calmodulin-binding kinase IIa (Camk2a) promoter. When NpHR was photoactivated with yellow light, neurons were hyperpolarised, preventing the generation of burst firing.[15]

We have recently asked whether such a strategy could be extended to suppress seizures in an established neocortical epileptic focus *in vivo*.[29] Our long-term aim was to test the feasibility of a new approach to treatment for human focal neocortical epilepsy, and to provide the backbone for the development of other optogenetic neuromodulation therapies.

We used the tetanus toxin rat model of refractory focal neocortical epilepsy: toxin injected stereotactically to motor cortex of rodent brain is followed within a few days by spontaneous bursts of high-frequency EEG activity in the motor cortex, near the site of tetanus toxin injection, lasting over five weeks. We collaborated with K Hashemi (Brandeis University) who developed a wireless implantable EEG transmitter able to send a continuous EEG signal for several weeks.[30] EEG spectral analysis revealed a large increase in high-frequency (>70Hz) power (Figure 2). Spontaneous seizures in this model are resistant to systemically delivered drugs, and are characterised by contralateral clonic movements, bilateral facial twitching, behavioural arrest, and head nodding.[29,31] However, motor manifestations occurred at a frequency lower than the EEG bursts. In many respects the motor cortex tetanus toxin model resembles epilepsia partialis continua. We found that epileptogenesis was accompanied by persistent increases in the intrinsic excitability of layer five pyramidal neurons.[29]

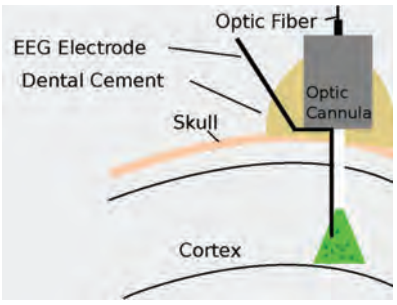

Figure 3 above: The optogenetic setup. Schematic of the implanted headstage for simultaneous EEG recording and optical stimulation.

Figure 4 below: Optogenetic suppression of neuronal excitability reduces high frequency activity in focal neocortical epilepsy. (a) Mean EEG power in the 120-160Hz band before, during and after laser stimulation in animals injected with tetanus toxin (TT) and NpHR lentivirus (n=6), showing a significant decrease. (b) Baseline HFA EEG power was lower in animals injected with NpHR lentivirus alone, and unaffected by laser illumination (green: mean ± SEM). (c) Laser illumination had no effect on HFA EEG power in control animals injected with TT together with either GFP-expressing control virus or fluorescent beads. (d) Representative EEG traces before, during and after 561 nm laser illumination, showing a decrease in HFA. Reproduced from ref. 29.

In one group of experimental animals, we co-injected tetanus toxin together with 500 – 1,250nL high-titre lentivirus carrying NpHR under the Camk2a promoter to drive expression in excitatory neurons. Control animals were injected either with NpHR virus alone or with tetanus toxin together with a virus expressing only green fluorescent protein (GFP). An optical fibre was implanted above the injection site, as well as an electrode connected to the subcutaneous transmitter (Figure 3).

We examined the effect of NpHR activation for a block of 1,000 seconds of intermittent 561nm laser light delivered via an optical fibre (20 s duration, 40 s duty cycle), and compared the EEG to a baseline 1,000 s period, and a subsequent 1,000 s after stopping the illumination. In order to quantify effects on the EEG we used several measures. Consistent results were obtained whether the data were analysed by measuring high frequency power (Figure 4), or by measuring the EEG coastline (effectively how much ink would be used to draw the EEG for a given duration), or by counting the rate of automatically detected epileptiform events (Figure 5). In all cases NpHR photoactivation decreased the electrographic signature of seizures. We observed no behavioural side effects, and subsequent histological analysis confirmed that the fluorescent reporter was mainly expressed in principal cortical neurons with no evidence of abnormal cytoplasmic accumulations. No effect on the EEG was observed by laser illumination in animals injected either with the NpHR lentivirus alone or in animals injected with tetanus toxin without NpHR. These controls imply that the effect of photoactivation of NpHR was relatively selective for the abnormal high frequency activity seen in the focal epilepsy model.

Although our results provide the first evidence that focal neocortical seizures can be suppressed with optogenetics, it remains to be seen whether this effect can be harnessed to achieve a long-lasting decrease in seizure frequency or severity. Moreover, because we used a mild form of epilepsy with relatively with relatively few over motor seizures, we do not know whether generalisation of ictal activity can be prevented.

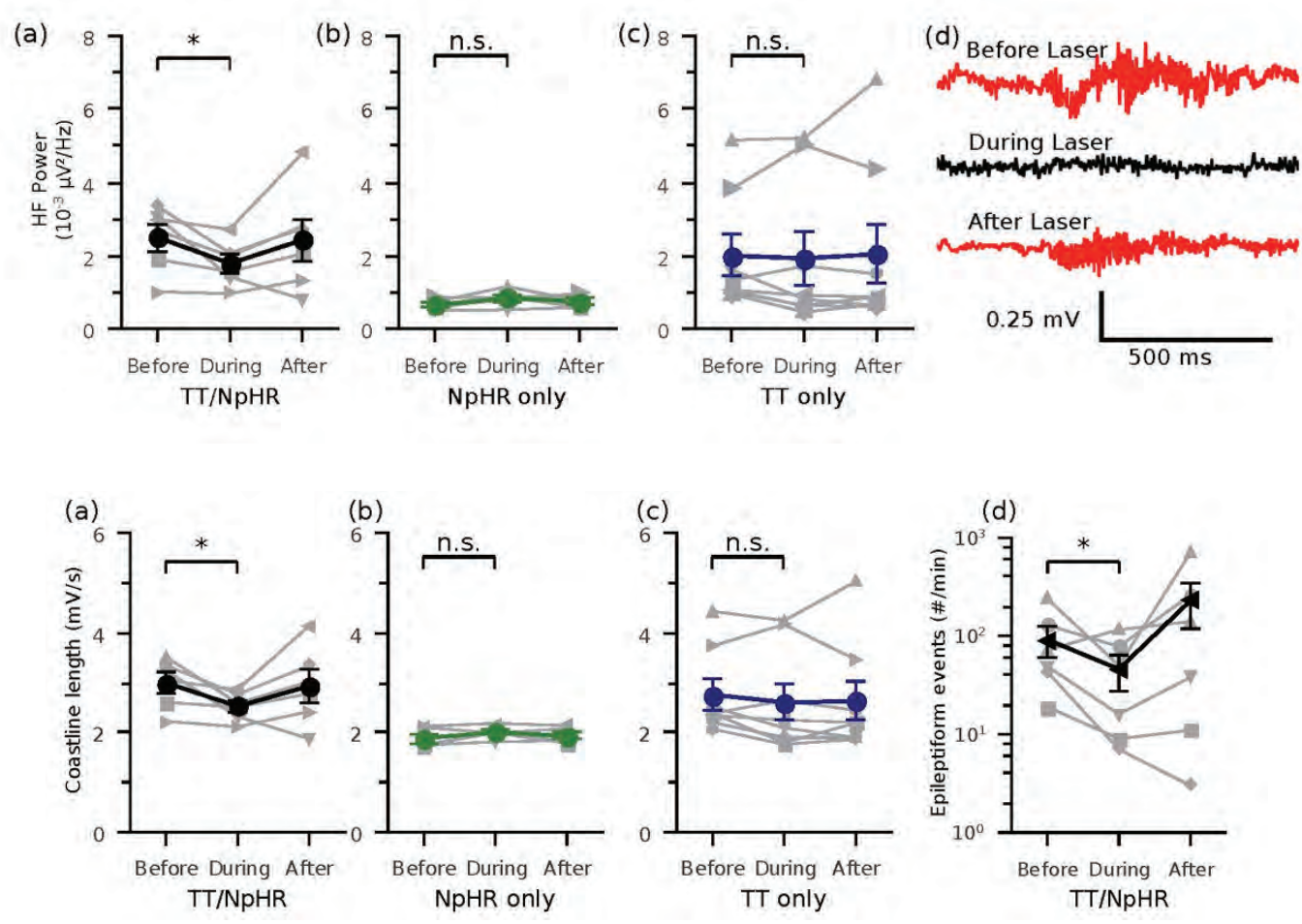

Figure 5: Antiepileptic effect of NpHR assessed by coastline analysis and automated event detection. (a) Mean EEG coastline (sum of the absolute difference in voltage between consecutive sample points) length was significantly reduced by laser illumination in animals injected with TT/NpHR (symbols as in Fig. 4). (b) Baseline coastline was lower in animals injected with NpHR lentivirus alone, and unaffected by illumination. (c) EEG coastline length was unaffected by laser illumination in animals injected with TT together with GFP lentivirus or fluorescent beads. (d) Automated event classification used to detect bursts of high-frequency activity revealed a significant decrease upon laser illumination. Reproduced from ref. 29.

Towards a closed-loop optogenetic therapy for epilepsy

Ultimately, to take full advantage of optogenetics, the photoactivation could be triggered by the onset of a seizure, or even by an EEG signature of an impending seizure. In our study we were unable to ask if 'on demand' seizure suppression could be achieved: the electrographic events were relatively brief, so that by the time they are detected by the automated algorithm it is too late to ask if laser activation could shorten them.

Two other groups have, however, very recently reported the development of a closed-loop system consisting of on-line detection of ictal activity coupled to lasers optically coupled to the animal. In one of these studies, from the Stanford group of J Huguenard,[32] the investigators used a rat cortical stroke model that is followed by the delayed development of thalamocortical seizures resembling absence epilepsy.[33] Photoactivating NpHR, expressed in thalamocortical neurons using AAV, terminated seizures and the associated behavioural arrest. The EEG signal used to trigger the laser was akin to the coastline measure that we have used, although easier to distinguish from background because of the large amplitude of the spike-wave complexes.

I Soltesz's group at University of California Irvine, on the other hand, used a mouse model of temporal lobe epilepsy induced by unilateral intrahippocampal kainic acid injection, which is followed by the development of bilateral seizure foci. They also showed that temporal lobe seizures can be shortened either by NpHR-mediated inhibition of excitatory neurons or by activation of ChR2 in parvalbumin-positive inhibitory neurons in the hippocampus.[34] In this case, the investigators exploited cre lox technology to restrict expression to one cell type or another. Interestingly, optogenetic manipulations either to the ipsilateral or to the contralateral hippocampus was successful, even when the EEG was recorded from the opposite hemisphere. This implies that the 'mirror focus' can be targeted with an anti-ictal effect at least in this rodent model.

Optogenetic inhibition as a future epilepsy treatment

We have demonstrated rapid and reversible suppression of epileptic EEG activity upon photoactivation of NpHR in a model of focal neocortical epilepsy.[29] Other *in vivo* studies show that optogenetic treatment approaches for epilepsy are feasible in models of either thalamocortical[32] or temporal lobe[34] epilepsy. An optogenetic approach offers the prospect of aborting seizures without disrupting interictal brain function. However, when considering optogenetics as a therapeutic tool for human epilepsy, several challenges will need to be addressed. First, the safety of viral vectors needs to be established. Random insertion of lentiviral sequences into the genome in principle has the potential for mutagenesis and oncogenesis. Second, the level of transgene expression in targeted neurons can vary extensively. Third, because the opsins are non-mammalian membrane proteins they are potentially immunogenic, although there is no evidence so far that long-term expression of opsins causes an immune response,[35] possibly because neurons reside in an immunologically privileged environment. Fourth, the timing and duration of illumination would need to be optimised and coupled to reliable seizure detection algorithms developed and validated in human epilepsy. Fifth, the spatial extent of viral transduction would need to be tailored to the individual, and as yet there is little agreement as to the size of the zone that generates seizures in human focal epilepsy. Finally, the hardware necessary to deliver light to the transduced area presents a substantial engineering challenge. Hitherto most of the work *in vivo* has used fibre-optic coupled lasers, but light-emitting diodes are showing promise, because of their size and energy efficiency. None of these challenges is insurmountable, and so we foresee the development of implantable devices analogous to automatic defibrillators that generate light pulses upon the automated electrographic detection of a seizure. This could lead to a radically new treatment alternative for a common and frequently devastating human disease. ◆

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Surgical and Non-surgical Management of Carotid Atherosclerosis

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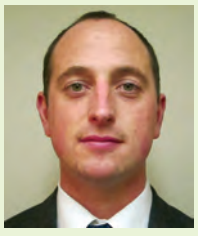

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Epidemiology and natural history of stroke

Stroke is a significant cause of mortality and morbidity with the worldwide incidence of new strokes being approximately 16 million per year, resulting in approximately 5.7 million deaths.[1] Within the UK it is the third largest cause of death, accounting for 11% of all deaths in England, and is the single largest cause of disability in England.[2] This equates to stroke consuming approximately 5% of the total NHS costs, with treatment of, and productivity loss arising from stroke totalling societal costs of £8.9 billion per year.[3] It is well documented that ischaemic etiology is the cause of 90% of strokes, and of these carotid atherosclerosis is responsible for approximately 15%.[4] Indeed, carotid atherosclerosis has been found to result in an increased risk of short term stroke reoccurrence and an increase in long term morbidity.[5]

Medical therapy

Secondary prevention is the rationale of treating carotid atherosclerosis. Firstly the medical treatment concentrates on modifying the risk factors associated with ischaemic stroke and thromboembolic disease, such as hypertension, diabetes mellitus, heavy alcohol consumption, smoking and hypercholesterolaemia.[6-9] In addition several randomised controlled trials have shown reduction in the risk of stroke in patients on platelet anti-aggregate therapy (i.e. aspirin, dipyridamole, clopidogrel or ticlodipine), which has become the mainstay of the medical treatment of carotid atherosclerosis.[10] There are no data demonstrating the superiority of combined agents (i.e. aspirin + clopidogrel).

Surgical therapy

Since C Miller Fisher described the relationship between carotid artery disease and stroke in 1951,[11] the use of carotid endarterectomy has increased exponentially. Many good quality randomised trials have been conducted on the topic, offering clinicians the opportunity to make evidence based clinical decisions.

Management in Symptomatic patients

In the 1990s two large-scale randomised clinical trials were conducted, in order to establish whether the surgical treatment was superior to the best medical treatment in symptomatic carotid stenosis. One of them was carried out in North America (NASCET) and the other one in Europe (ECST). Both trials demonstrated the efficacy of carotid endarterectomy over best medical treatment in selected patients with TIA or non-disabling stroke, within the previous six months.

The North American Symptomatic Carotid Endarterectomy Trial (NASCET)[12] was reported in 1991. The patients included were younger than 80 years old, had symptoms within four months of enrolment into the trial and had carotid stenosis diagnosed with catheter angiography. All patients (659) received best medical treatment (high dose aspirin and risk factors modification), and those randomised to surgical treatment (328) also had carotid endarterectomy. The trial was stopped earlier than planned after an interim analysis clearly showed a significant benefit of surgical treatment for high-grade stenosis (70 to 99%) over medical treatment, with an absolute risk reduction of 17% (±3.5%) and 12.7% when the complication rate was also considered.

The European Carotid Surgery trial (ESCT),[13] was reported in 1998 and reported similar results to the NASCET trial with an absolute risk reduction of 11.6%.

The main controversy of the above-cited trials is the way the two groups measured the degree of stenosis: NASCET – diameter at greatest narrowing/diameter beyond the carotid bulb; ECST – diameter at greatest narrowing/estimated probable original diameter. These differences create obvious problems in comparing the results from the two studies.

Management in Asymptomatic patients

The role of carotid endarterectomy in asymptomatic carotid stenosis is more contentious than that of symptomatic stenosis. This is because the natural history of asymptomatic stenosis is more varied. Asymptomatic stenosis is often found as an incident finding. The risk of having a stroke from asymptomatic carotid stenosis is dependent on the severity of stenosis and the rates are;[14]

Degree of stenosis	<50%	50-80%	>80%
Annual risk stroke	<1%	0.8-2.4%	1-5%

There have been several randomised clinical trials comparing best medical treatment with CEA. The Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Veterans Affairs Cooperative Study (VACS) compared outcomes of management with CEA and aspirin with only aspirin.

The later trial[15] involved only male patients with 50% stenosis or greater on angiography and showed that the incidence of ipsilateral neurological events in the four years of follow up was 8.0% in the CEA group compared with 20.6% in the medical group. The incidence of ipsilateral stroke was 4.7% in the CEA group compared with 9.4% in the medical group. However, taking into

account the perioperative risk of death of 1.9%, the difference in death or stroke outcomes between the two groups was not statistically significant. Most of the mortality was due to coronary atherosclerosis.

The ACAS[16] involved male and female patients with a mean age of 67 and carotid artery stenosis of 60% or greater. From their results, they estimated the five-year risk of ipsilateral stroke, perioperative stroke or death was 5.1% following CEA compared with 11.0% following medical management. This equated to an average 53% lower five-year risk of ipsilateral stroke in the surgical arm versus the medical arm. This average was quantified into a 66% reduced risk for men and a 16% reduced risk for women. There was no statistical benefit seen when the five-year risk of major strokes and mortality were analysed.

The Asymptomatic Carotid Surgery Trial (ACST)[17] involved randomising male and female patients with 70% or greater stenosis on duplex USS into surgical and best medical treatment arms. The five-year stroke risk of surgery versus medical management was 6.4% versus 11.8% (P<0.0001) respectively, with mortality and disabling stroke rates being 3.5% versus 6.1% for both sexes. A caveat to these findings was that there was no statistical benefit for patients aged 75 or over. Ten-year follow-up of this trial[18] echoed the original findings of reduced stroke rates for those whom had CEA. At ten years the reported stroke risk in the CEA arm was 13.4% compared with 17.9% in the medical arm.

Carotid Endarterectomy versus Carotid Angioplasty

Since the early 1990's endovascular management of carotid stenosis has become an important alternative to CEA and, despite an early trial producing data to the contrary, there are now several randomised controlled trials that support its use. As such, the National Institute of Clinical Excellence supports its use for both symptomatic and asymptomatic patients (www.nice.org.uk). The initial concerns of carotid angioplasty and stenting (CAS) were of the immediate risk of thromboembolic risks, and the long-term risk of re-stenosis. An initial study[19] into carotid angioplasty involved only 23 patients with severe carotid stenosis of 70% or greater. The ten patients who were randomised into the CEA arm had no complications. Unfortunately, five out of seven of the carotid angioplasty patients had strokes (P=0.0034), three of which had disability at 30 days. The trial was stopped at 17 patients.

CAVITAS[20] was published in 2001 and randomised 504 patients in a multicentre trial; 251 had endovascular treatment (26% stenting, 74% angioplasty) and 253 had CEA. The major outcomes at 30 days (disabling stroke or death) were not statistically different. However, relatively minor morbidity such as transient cranial neuropathy, was higher in the CEA arm (8.7% compared with 0% p<0.0001). This study also found that at one-year follow-up the CAS group had a much higher rate of severe ipsilateral carotid artery stenosis (70-99%) compared with CEA, 14% vs 4% respectively. Despite this finding, at three years, there was no substantial difference in the rate of ipsilateral stroke between the groups (adjusted hazard ratio=1.04, (95% CI 0.63-1.70, p<0.9). The higher rate of stenosis but non-significantly increased risk of ipsilateral stroke has been echoed in long-term follow-up of patients involved in the original study.[21]

Following this trial, the SAPPHIRE group carried out a RCT hypothesising that carotid stenting with the use of an emboli protection device was not inferior to CEA.[22] They enrolled 334 high-risk patients with either symptomatic stenosis with 50% or greater occlusion, and asymptomatic patients with 80% or greater occlusion. They found that the 30-day MI, stroke rate or mortality rate with CEA and CAS were 9.8% and 4.8% (P=0.9) respectively. At one year they showed morbidity and mortality rates in the CEA and CAS groups of 20.1% and 12.2% respectively. It was concluded that carotid stenting with emboli-protection device was not inferior to CEA. Four year follow up showed that there was no statistical difference in long-term outcomes.[23] The subsequent SPACE trial investigated inferiority of CAS versus CEA in non-high risk patients with symptomatic carotid artery stenosis with 70% or greater occlusion.[24] They showed that the 30 day risk of ipsilateral stroke or mortality were equivalent between treatment modalities (6.3% CEA vs 6.8% CAS). However, statistical analysis showed the study to be underpowered due to its small size so the hypothesis could not be accepted nor refuted. Despite this, it was reported that the CAS group had a higher risk of severe carotid stenosis at two years (10.7 % vs 4.6%, P=0.0009).[25]

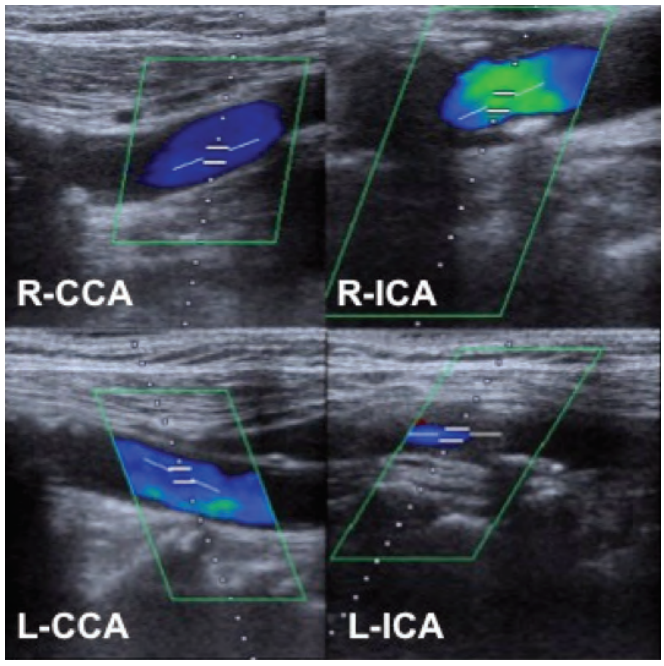

Figure 1 – Doppler Ultrasound: Left Internal Carotid artery stenosis (greater than 70% - NASCET criteria).

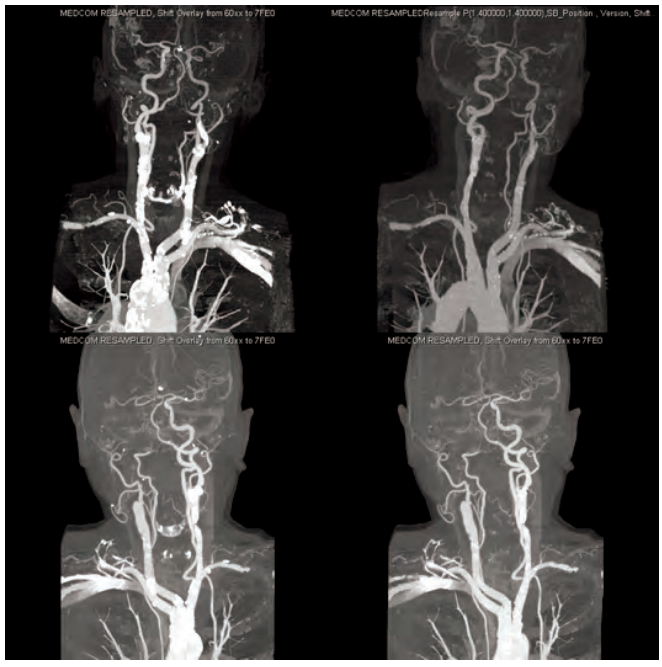

Figure 2 – CT ANGIO 3D reconstruction: Evolution of Right Internal Carotid Artery Stenosis.

Contrary to the previous trials, the EVA – 3S multicentre RCT showed a higher risk of stroke or mortality at 30 days and at six months following CAS compared with CEA.[26] They randomised patients with symptomatic stenosis of 60% or more. Their findings showed a risk of any stroke or mortality at 30 days to be 3.9% and 9.6% in the CEA and CAS groups respectively, and 6.1% and 11.7% at six months. The relatively low rate of complications in the CEA arm and high complication rate in the CAS arm were thought to be due to the fact that in the CAS arm no embolic protection was used and the physicians were relatively inexperienced compared with the surgeons carrying out the CEAs. Consistent with other trials, cranial nerve injury was more common after CEA than CAS.

The Carotid Revascularisation Endarterectomy versus Stenting Trial (CREST) was published in 2010 and has provided more robust data.[27] This multicentre RCT recruited 2502 patients with a mean follow-up of 2.5 years. It involved symptomatic patients with carotid stenosis of 50% or greater on angiography and asymptomatic patients with stenosis of 60%

or greater on angiography (or higher percentage of occlusion if other imaging modalities were used). The primary endpoint was the occurrence of any stroke, MI, or death during the peri-procedural period, or ipsilateral stroke in the following four-year follow-up period. The trial reported that there was no significant difference in primary endpoint with either CAS or CEA (7.2% vs. 6.8%; HR=1.11;95 CI, 0.81-1.51;P=0.51). Despite no difference in primary endpoints, there were significant differences in the type of complications seen. CEA had a higher risk of MI in the perioperative period (2.3% vs. 1.1%, P=0.032), whilst the risk of stroke was greater in the CAS patients (4.1% vs. 2.3%, P=0.012). There were no differences in outcomes of asymptomatic patients and symptomatic patients, nor was there a sex bias. The results did suggest that outcomes were improved by CAS for patients less than 70 years and improved by CEA for patients older than 70 years. Once again, there were fewer cranial nerve palsies with CAS than with CEA (0.3% vs. 4.7%).

The early trials show that CEA is superior to CAS with regards to peri-procedural risk of stroke and mortality, but may have increased risk of MI. This is confirmed by many metanalyses including the most recent.[28] However, with careful patient selection and continued improvements in the endovascular arena, the inferiority of CAS may change. We await further trial data from the International Carotid Stenting Study, SPACE 2 and ACST-2 trials. The interim data of the former seems to show that CEA is associated with reduced risk of peri-procedural stroke, MI and death but increased risk of cranial nerve damage, however completion of the study is necessary for the final statistical comparisons.[29]

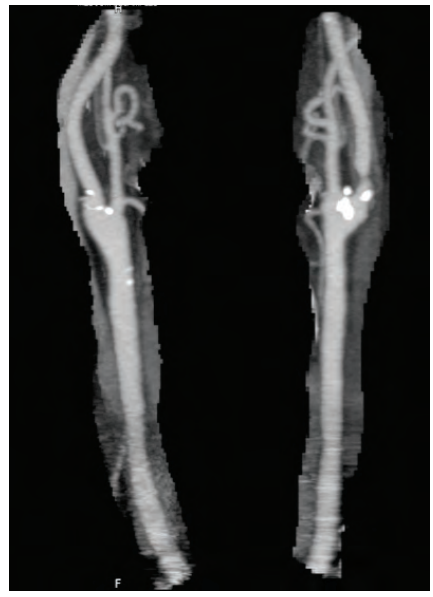

Figure 3 - CT ANGIO 3D reconstruction: Left Internal Carotid Artery stenosis.

Conclusion

In the UK, the National Institute for Health and Clinical Excellence (NICE clinical guideline 68 – Stroke 13 - 2008) divides the symptomatic population (stable neurological symptoms from acute non-disabling stroke or TIA) in two subgroups: carotid stenosis of 50–99% (NASCET criteria), or 70–99% (ECST criteria); carotid stenosis of less than 50% (NASCET criteria), or less than 70% (ECST criteria). The first group, according to NICE, should be assessed and referred for carotid endarterectomy within one week of onset of stroke or TIA symptoms, undergo surgery within a maximum of two weeks of onset of stroke or TIA symptoms and receive best medical treatment. The second group, with less severe stenosis should not undergo surgery, but only receive best medical treatment.

In the asymptomatic group the above mentioned trials show that in patients who are less than 75 years old with a carotid artery stenosis exceeding 60%, the long-term outcome is better with CEA and medical management than with medical management alone, provided the patient has a low surgical risk. A recent trial looking into CEA versus carotid angioplasty and stenting [30] in both symptomatic and asymptomatic patients showed no significant difference in the occurrence of total numbers of stroke, MI or death in four-year follow-up. This was broken down into reduced numbers of stroke following CEA, but reduced incidence of MI following endovascular intervention. This may therefore be the avenue for the asymptomatic high-risk patient in the future. Two further trials are ongoing investigating CEA vs endovascular treatment in asymptomatic patients. ◆

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25. Eckstein HH, et al. *Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial.* Lancet Neurol, 2008;7(10):893-902.
26. Andziak P. [Commentary to the articles: SPACE Collaborative Group. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. Lancet 2006;368:1239-47. Mas JL, Chatellier G, Beyssen B, et al. EVA-3S Investigators. *Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis.* N Engl J Med. 2006;355:1660-71]. Kardiol Pol, 2006;64(12):1458-60; discussion 1460-1.
27. Mantese VA, et al. *The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST): stenting versus carotid endarterectomy for carotid disease.* Stroke, 2010;41(10 Suppl):S31-4.
28. Liu ZJ, et al. *Updated systematic review and meta-analysis of randomized clinical trials comparing carotid artery stenting and carotid endarterectomy in the treatment of carotid stenosis.* Ann Vasc Surg, 2012;26(4):576-90.
29. Ederle J, et al. *Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial.* Lancet, 2010;375(9719):985-97.
30. Brott TG, et al. *Stenting versus endarterectomy for treatment of carotid-artery stenosis.* N Engl J Med, 2010;363(1):11-23.

An Insider's Guide to Glasgow: ABN Annual Meeting, 21st-24th May

Edward Newman

is a SCREDS Clinical Lecturer in Neurology at University of Glasgow. He has a clinical and research interest in movement disorders. He is also actively involved in medical education. He is currently the deputy ABNT Treasurer.

Paul Gallagher

is an ST4 Neurology Registrar at the Institute of Neurological Sciences in Glasgow. After completing his undergraduate and Foundation years in Glasgow, he subsequently trained in New Zealand and Newcastle (UK), before returning to his hometown in 2011. He hopes to pursue his interest in Epilepsy in the future.

Correspondence to:
Email: edward.newman@nhs.net

The ABN annual meeting will be held in Glasgow in May. It has been 10 years since the last Glasgow ABN and we thought you might appreciate a few tips to help get the most out of your brief visit.

A wee bit of background

Glasgow has always adapted to the times, changing from a hugely important trading port to a powerhouse of the industrial revolution. More recently Glasgow's economy has shifted from manufacturing, most famously in its shipyards, to a more service-based economy. These days Glasgow is renowned for its culture, student life, football, and architecture, notably its red and blonde sandstone tenements. Glasgow is also busy preparing to host the Commonwealth Games in 2014.

Glasgow has provided more than its fair share of innovation within science and economics. Founded in 1451, the University of Glasgow is proud of such alumni as Joseph Black, Lord Kelvin, James Watt and Adam Smith. Landmarks within medicine such as the first surgical procedure performed under sterile conditions (Joseph Lister, 1865), the pioneering of diagnostic ultrasound (Ian Donald, 1958), and the development of a clinical score for assessing coma (Graeme Teasdale and Bryan Jennett, 1974), all took place within Glasgow.

The neurological hub for the West of Scotland lies within the Institute of Neurological Sciences (INS), at the Southern General Hospital. This regional unit provides neurological care to 2.2 million Scots and boasts 48 consultants across neurology, neurosurgery, neurophysiology and neuroradiology. In addition to being a productive clinical unit Glasgow is currently the lead centre for the following studies: Parkinson's Repository of Networked Datasets (PRoBaND), Pilot Investigation of Stem Cells in Stroke (PISCES) and International Guillain-Barre Outcome Study (IGOS).

Getting about

The ABN will be held at the Scottish Exhibition and Conference Centre (SECC) and this is easily accessible from all transport hubs. It is 15-20 minutes by taxi from Glasgow Airport and 10 minutes by taxi from the city centre. The SECC has its own train station and relevant timetables can be found at www.scotrail.co.uk. Glasgow boasts a subway system that was built in 1896, but this remains a slightly limited way of navigating the city. Subway and bus timetables can be found at www.spt.co.uk and www.firstgroup.com/ukbus/glasgow/

What to see

It is definitely worth exploring the city's West end, located 1.5 miles from the SECC. At the centre of this area is the University of Glasgow and you will find a mix of stylish independent shops, parks, and excellent bars, cafes and restaurants. At the meeting local neurologists will gladly make recommendations and point you in the right direction.

A hop on/hop off open-top bus tour of Glasgow is an excellent way to see the city and can be organised through www.citysightseeingglasgow.co.uk

Cloisters, Glasgow University ©Imaginative Lens Photography
http://www.imaginativelensphotography.com

Glasgow has some great museums. One recent and exciting addition is the Riverside Museum, designed by multi-award winning Zaha Hadid. This is only half a mile walk from the SECC and also looks out on to the Clyde. It houses an impressive transport and maritime collection and has the Glenlee, a 19th Century tall ship, moored outside. The ABN Gala dinner will be held within the Kelvingrove Art Gallery and Museum. This arresting building houses a particularly diverse collection of natural history and art pieces, and includes Dali's Christ of Saint John of the Cross.

The Hunterian Museum, housed within Glasgow University's main building, is Scotland's oldest public museum and has scientific and cultural exhibits including 'Whistler's Mother' and much Charles Rennie Mackintosh design. Away from the West End, the Gallery of Modern Art exhibits sculpture and installations in an impressive neoclassical edifice in the city centre. The Burrell Collection in the Southside of Glasgow has extensive Egyptian, medieval and Roman displays.

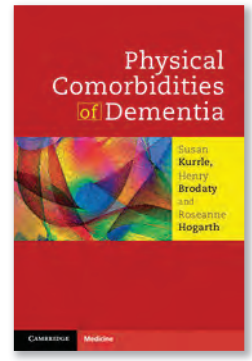
Glasgow vernacular

Glaswegians speak fast and, like much of the UK, have a unique accent and patois. For those of you wishing to converse with the natives here are a selection of words and phrases that may be unfamiliar:

'Wheesht' – be quiet
'Gaun yersel' –well done, I approve of your actions
'Eejit' – idiot
'Motor' – car
'Ginger' – soft drink
'Greeting' – crying
'Glaikit' – vague, detached (adjective frequently employed by witnesses of absence seizures)
'Jaky' – dishevelled person (cf. 'Shaky Jaky' refers to such an individual in midst of alcohol withdrawal symptoms)

Themes of this year's ABN include headache, functional movement disorders and the potential role of stem cell therapies in neurological disease. The preliminary programme looks varied and stimulating and we look forward to seeing you there. ◆

Physical Comorbidities of Dementia



Editors: Kurrle S, Brodaty H, Hogarth R
Published by: Cambridge University Press, 2012
Price: £27.99
ISBN: 9781107648265

Reviewed by: AJ Larner, Cognitive Function Clinic, WCNN, Liverpool, UK.

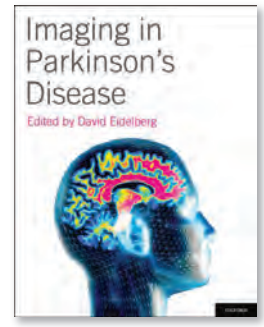
Canonical definitions of dementia, like that enshrined in the *Diagnostic and statistical manual of mental disorders* (DSM-IV-TR, 2000), acknowledge that the dementia syndrome may be associated *inter alia* with such features as functional decline, falls, sleep disturbance, and epileptic seizures, as well as the cognitive decline. These physical comorbidities of dementia have perhaps attracted less research attention than the cognitive aspects, because they are not *sine qua non* in diagnosis. However, they are of disproportionate practical significance since they, rather than cognitive decline *per se*, may determine the need for nursing home placement and, for both patients are carers, may constitute the most distressing aspects of living with dementia.

The book takes the form of a systematic literature review of selected physical comorbidities of dementia, covering the period 1990-2011 and retrieving over 2500 references. The authors summarise their findings in chapters devoted to falls, delirium, epilepsy, weight loss and nutritional disorders, incontinence, sleep disturbance, visual dysfunction, oral disease, and frailty. Each chapter describes, where known, epidemiology, aetiology, assessment and management, and culminates in recommendations, two brief case studies, and key points.

Although much of the material may be familiar to clinicians who see patients with dementia, the review is welcome, and there is always something new to learn (I was entirely ignorant of the links between oral disease and dementia).The use of the generic descriptor 'dementia' rather than specific dementia subtypes probably reflects the historic (and current) lack of sophistication of studies in the literature. Where differences are known (e.g. sleep disorders in DLB, continence issues in FTD) these are covered. The recommendations in each chapter make this a practical resource for patient management, rather than simply an arid literature review, although in some spheres (e.g. epilepsy) the evidence base for intervention is limited or non-existent. It may be hoped that some of the areas of uncertainty will be addressed by the time of the next edition. ◆

> *Although much of the material may be familiar to clinicians who see patients with dementia, the review is welcome, and there is always something new to learn*

Imaging in Parkinson's Disease



Editor: David Eidelberg
Published by: Oxford University Press
Price: £70.00
ISBN: 978 0 19 53948 4

Reviewed by:
Sundus Alusi, Consultant Neurologist, Liverpool, UK.

This book is a comprehensive and balanced review of the advanced imaging techniques in Parkinson's disease. It addresses important aspects in this field, including the science behind the imaging tools, their potential usefulness for diagnosis as well as advantages and shortcomings of emerging imaging techniques in everyday clinical practice.

The book is intended for neurologists in the field of movement disorders, neuro-radiologists and basic neuroscience researches. It is clear, and takes the reader step-by-step.

The first couple of chapters address the role of dopaminergic imaging, PET and SPECT, in clarifying the pathophysiology of Parkinson's disease, particularly presynaptic nigrostriatal dysfunction. The third chapter, however, looks at the study of glucose metabolism and brain blood flow in the improving our understanding of the neuronal circuitry of Parkinson's Disease pathophysiology. The fourth chapter explores the imaging of structural abnormalities, whilst the fifth outlines the limitations of transcranial sonography in Parkinsonian disorders.

Imaging to investigate specific problems in Parkinson's disease is covered in a series of dedicated chapters: tremor, motor deficits, cognitive dysfunction are studied in Chapters 7,8, 9 and 10.

In terms of more fundamental neuroscience, theories of aetiology receive attention, in particular inflammation and activation of microglia in Chapter 11. The biomarkers of disease progression, the effects of treatment, medical and surgical, and complications of therapy are elegantly described in chapters 12, 13, 15 and 14 respectively. Last but not least, potential applications in research and clinical trials, are discussed in the final chapters.

The book as a whole or its component parts, depending on the reader's interest, may be recommended for general reading. It contains invaluable citation lists and high quality illustrations, to make it a good source of reference. Its description of numerous hypotheses may well stimulate, or inspire, the research readership. Its price, £70, is as handsome as its illustrations. ◆

If you would like to review books for ACNR, please contact Rhys Davies on rhys.davies@thewaltoncentre.nhs.uk or call the Publisher, Rachael Hansford on 01747 860168.

Clinical Pocket Reference **Neurosciences**

Authors: Juliet Bostwick and Deborah Slade, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford.
ISBN: 978 0 9543065 7 1

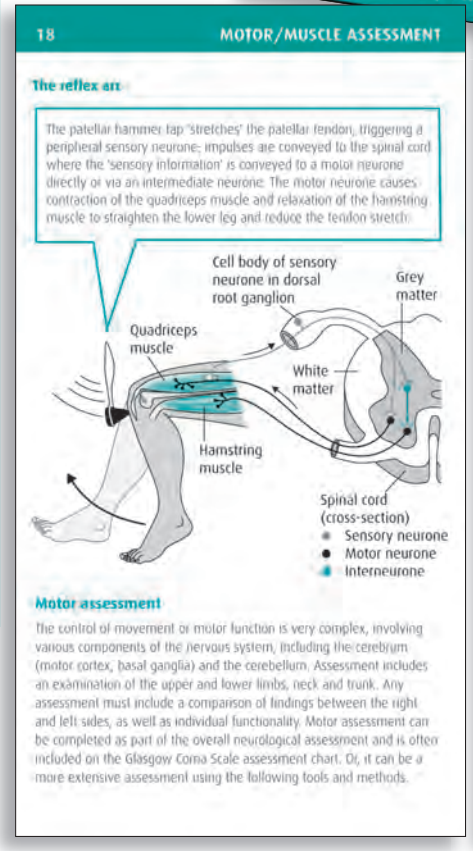
Selected pages from Clinical Pocket Reference Neurosciences - *third instalment*.

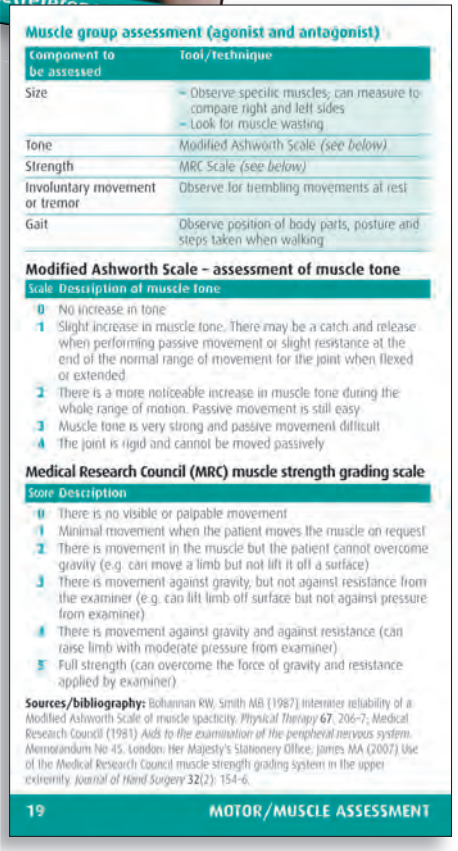
Reviewer's comments:

From a nurse's perspective, I recommend this booklet as a handy reference guide to neurological aspects of nursing care.... The format is clear, logical and easy to read.

...It will be most useful as a reference for general nurses and nurses new to Neuroscience. However, the referencing and bibliographies mean that it would also be a useful acquisition for more experienced nurses and other practitioners.
ACNR

This book will be an invaluable resource for nurses and allied healthcare professionals of all backgrounds and levels of experience...
It is clear and concise, pitched at the right level, with good use of images.
British Association of Neuroscience Nurses





ACNR are publishing selected content from **Clinical Pocket Reference: Neurosciences** over current issues... neuroscience nurses will find this a useful aide memoire. Ideal for keeping on the ward or in the pocket as a teaching and reference tool.

Beware old friends

When I started in epilepsy, two eminent epileptologists held a debate, in which one argued that all patients should be give valproate from the outset and see what happens, as it is a broad spectrum drug effective against a range of epilepsies and only change to something else if necessary. Whilst he was adopting a position for the purposes of debate, it is a salutary lesson that this drug is rapidly becoming the spaghetti bolognaighs of the AED world and that this is happening forty years after the launch of the drug. Whilst data collection is better than it was, I am also reminded of the fall from grace of vigabatrin, several years after marketing as a result of visual disturbances that were really very common. This highlights an issue that very long term use of new drugs requires a different mindset from that which we use for many drugs. Absence of proof of long term effects is not proof of their absence and vigilance is required for many years. Two more nails in the coffin of valproate, at least for women of childbearing age, have been hammered into place recently. Bromley et al show that neurodevelopmental disorders including autism and ADHD are up to ten times commoner in children born to women taking the drug than to those taking carbamazepine, lamotrigine or controls. Valproate is still one of the most profitable AED, but that is largely through its role in psychiatry. Do psychiatrists know about these problems? Meador et al provided data at six years of age for children born to women taking AED. They found that children born to mothers taking valproate had lower scores across a range of function, including verbal, non verbal, and executive function than compared to those on lamotrigine, carbamazepine or phenytoin, with some subtle variations. There was a clear difference between women above the median dose of 1000mg and those below and preconception folate improved function in all groups. So, for my patients for whom nothing apart from valproate works, and they are not such a tiny number, is it better to give low dose valproate and something else or high dose valproate on its own? I veer to the former, in that there seems to be something in the mechanism of valproate that is not shared by other drugs, which predisposes to this problem, but I should be interested to hear if others disagree. **– *MM***

Bromley RL, Mawer GE, Briggs M, et al. On Behalf of the Liverpool and Manchester Neurodevelopment Group. The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs. J NEUROL NEUROSURG PSYCHIATRY. 2013 Jan 31. doi:10.1136/jnnp-2012-304270. [Epub ahead of print]

Meador KJ, Baker GA, Browning N, et al. NEAD Study Group. Fetal antiepileptic drug exposure and cognitive outcome at age 6 years (NEAD study): a prospective observational study. LANCET NEUROL 2013 Mar;12(3):244-52. doi: 10.1016/S1474-4422(12)70323-X. [Epub ahead of print]

Warts on the brain

I am never quite sure whether honest ignorance or disingenuous reassurance works better for patients. Overall, my ignorance being so all-encompassing, I find it easier to share it than to try and make something up. I have colleagues however, who never let a patient out of the clinic without a diagnostic label. Of course you could call it idiopathic, which as my Professor of Medicine, Oliver Wrong at UCH, sadly deceased last year, taught me means 'the idiots do not know the pathology'. Over the years, however, I have learned to be very suspicious of claims of: "don't worry it's only a virus". Of course, finding out that something may be due to a virus, particularly one for which we have a vaccine is very exciting. So it was with great interest that I learned that all of 50 specimens of Taylor type focal cortical dysplasia with balloon cells, otherwise known as FCDIIB, "robustly" expressed human papilloma virus HPV16 DNA. The DNA was not present in control areas from the same brains or from control brains. HPV16 is the virus associated with cervical cancer and some forms of oropharyngeal cancer. The virus induces a protein called HPV16 oncoprotein, which activates signalling of mammalian target of rapamycin complex (mTORC1). This is already recognised to be a player in animal studies of epilepsy and in association with tuberose sclerosis where its activity is increased. An inhibitor, everolimus, has already been used in the treatment of malignantly transformed TS lesions. Will the next generation of children born to girls immunised against HPV16 suffer with less FCDIIB? **– *MM***

Chen J, Tsai V, Parker WE et al. Detection of human papillomavirus in human focal cortical dysplasia type IIB. ANNALS OF NEUROLOGY. 2012 Dec;72(6):881-92. doi: 10.1002/ana.23795.

Leukotriene receptor agonists for brain repair?

The interaction between neuroinflammation and neurodegeneration, or their co-existence, generally is considered to be a bad thing. Zebrafish seem to possess the innate ability to regenerate neurons in response to injury, and Kyritsis et al. from Michael Brand's group in Dresden, take advantage of this property and demonstrate a mechanism that links inflammation and repair. Kyritsis et al. first inject the fungal derivative zymosan A into zebrafish telencephalons and demonstrate a similar upregulation of macrophages and leukocytes, subsequent upregulation of radial glial cells and neurogenesis (measured by bromodeoxyuridine labelling), as seen with traumatic brain lesioning. They show that dexamethasone suppresses neurogenesis in the lesioned but not control fish. Through analysis of a transcriptome comparison, they show that cysteinyl leukotriene receptor 1 (cysltr1) is upregulated after injury (locally and in the ventricular zone), and blocking its signalling with Pranlukast inhibits neurogenesis. Use of a leukotriene agonist of the cystltr1 enhances neurogenesis. A further round of experiments with gata3 signalling supports the conclusion that this injury evoked repair is injury-specific. Reconciling this with the prevailing view that inflammation, through promotion of glial scarring and other effects, is deleterious to repair in mammals, is difficult but probably valid, and the work does reveal a potential target for clinical trials. **– *MZ***

Kyritsis N, Kizil C, Zocher S et al. Acute Inflammation Initiates the Regenerative Response in the Adult Zebrafish Brain. SCIENCE 2012 Dec 7;338(6112):1353-6. doi: 10.1126/science.1228773.

Neuro-cortico-myelitis optica?

Saji and colleagues from Niigata, Japan combine a neuropsychometric study with a smaller and more intriguing neuropathological one, declaring prevalent cognitive impairment in neuromyelitis optica, but also widespread cortical inflammation in the absence of demyelination. In the first study, Rao's Brief Repeatable Battery of Neuropsychological Tests, which includes the PASAT test and others of attention, verbal and visual memory and language, was applied to 5 patients with NMO (all AQ4 antibody positive) and 9 with limited NMO (cord or optic nerve, but all had AQ4 antibodies). Patients with NMO were compared to unspecified healthy controls and the degree of matching and subsequent analysis is hard to interpret, suffice to say that a large proportion of NMO patients and 17 MS patients were defined as cognitively impaired (57% and 47% respectively), of which a large part may just reflect disease activity and medications. The authors then examined 6 NMO brains in comparison with control brains, and demonstrate increased meningeal inflammation, with no evidence of B-cell follicle-like structures, and cortical neuronal loss with microglial activation without cortical demyelination or lymphocytic infiltration. Whether there is primary or secondary cortical involvement, the results are interesting and need replication. This is clearly a controversial area, with other authors, for example Calabrese et al. using neuroimaging, claiming no cortical involvement in NMO. **– *MZ***

– Saji E, Arakawa M, Yanagawa K, et al. Cognitive impairment and cortical degeneration in neuromyelitis optica. ANNALS NEUROLOGY. 2013 Jan;73(1):65-76. doi: 10.1002/ana.23721. Calabrese M, Oh MS, Favaretto A et al. No MRI evidence of cortical lesions in neuromyelitis optica. Neurology. 2012 Oct 16;79(16):1671-6.

To list your event in this diary, email brief details to Rachael Hansford at Rachael@acnr.co.uk by 6th April, 2013

2013

March

Glia and Neurons: a symbiotic partnership
20-22 March, 2013; Cambridge, UK
T. 01223 331160, E. skt37@cam.ac.uk

April

Festival of Neuroscience 2013
7-10 April, 2013, London, UK
T. 0208 166 8713, E. office@bna.org.uk

6th Meeting of the UK PD Non-Motor Group
Hosted in Partnership with Europar and the NIHR London (South) Comprehensive Local Research Network
11 April, 2013; London, UK
E. chaudhuriray@hotmail.com, www.pdnmg.com

6th European Workshop on Cannabinoid Research
18-20 April, 2013, Dublin, Ireland
www.bps.ac.uk/meetings/137a2bf33cd,
E. becky.hughes@bps.ac.uk, or T. 0207 239 0176.

Research for Clinicians – Integrating Research into Day to Day Practice
19 April, 2013: The Oliver Zangwill Centre, Ely, Cambridgeshire, UK
T. 01353 652173, E. Rachel.everett@ozc.nhs.uk

Providing Neurology Services in Primary Care
23 April, 2013; London, UK
E. info@p-cns.org.uk,
www.p-cns.org.uk/pcnsevents.asp

Assessment & Ideas for Treatment of the Hip and Pelvis in Adults with Neurological Damage
Trainer: Erica Malcolm
25th April, 2013; Derby, UK
E: dhft.ncore@nhs.net, www.ncore.org.uk

"Where's Your Head At?" Event for young people with acquired brain injury aged 14-19
28th April, 2013; Chessington World of Adventures Resort, Surrey, UK.
www.thechildrenstrust.org.uk/headat

May

The Children's Trust Free open day for professionals
2 May, 2013; Tadworth, Surrey
www.thechildrenstrust.org.uk/opendays

Magstim Neuroenhancement Conference & Workshop 2013
4-5 May, 2013; Oxford, UK
For more information see www.magstim.com/events-courses

Bobath Clinical Reasoning
9-10 May, 2013; Derby, UK
T. 01332 254679, E. dhft.ncore@nhs.net,
www.ncore.org.uk

Liverpool Neurological Infectious Diseases Course
9-10th May 2013; Liverpool, UK
E. nid@liverpool.ac.uk,
www.liv.ac.uk/neuroidcourse

MS Frontiers
9-10 May, 2013; London, UK
T. or call 020 8438 0941,
www.mssociety.org.uk/msfrontiers

Parkinson Advanced
13th May, 2013; Derby, UK
T. 01332 254679, E. dhft.ncore@nhs.net,
www.ncore.org.uk

Brain Injury Services Northampton Therapists Educational Day
20 May, 2013: Northampton, UK
For Psychiatrists, Psychologists, OTs, Nurses, Physios and Speech & Language Therapists.
FREE event
E. Samantha.coburn@partnershipsincare.co.uk
T. 01255 871 017

ABN Annual Meeting
21-24 May, 2013; Glasgow, UK
www.abn.org.uk, T. 020 7405 4060, E. info@theabn.org

The Clinical Science of Regenerative Neurology
Dynamic Earth, Edinburgh
30-31 May 2013
http://annerowlingclinic.com/events/clinical-science-of-regenerative-neurology

June

Myotonic Dystrophy Support Group Annual Conference
8 June, 2013; Swindon, UK
Office. 0115 9875869,
www.myotonicdystrophysupportgroup.org,
Helpline. 0115 9870080,
E. contact@myotonicdystrophysupportgroup.org

ENS 2013
8-11 June, 2013; Barcelona, Spain
E. info@ensinfo.org

Imperatives in Regional Anaesthesia: Current hot topics and future developments
13-14th June, 2013; London, UK
T. 0114 225 9057 or 0114 225 9035/36,
F. 0114 225 9119,
E. academia.bbmuk@bbraun.com
www.aesculap-academia.co.uk

17th International Congress of Parkinson's Disease and Movement Disorders
16-20 June, 2013, Sydney, Australia
T. +1 414 276 2145
E. info@movementdisorders.org,
www.movementdisorders.org

Posture & Balance as it Relates to Selective Control of the Upper Limb
Trainer: Erica Malcolm
17-18 June, 2013; Derby, UK
E: dhft.ncore@nhs.net, www.ncore.org.uk

The Advanced Balance Course
19-21 June, 2013; Southampton, UK
Fiona Barker, T. 0790 779 1619,
E. fiona.barker@windsor-ent.co.uk

Working with the systems around ABI and Stroke
21st June, 2013; The Oliver Zangwill Centre, Ely, Cambridgeshire
T. 01353 652173, E. rachel.everett@ozc.nhs.uk

A Joint Healthcare Conferences UK and PROMS 2.0 Masterclass
Masterclass: PROMs for Long Term Conditions
Wednesday 26 June 2013, London, UK
Book at www.healthcareconferencesuk.co.uk/proms-long-term-conditions-nhs-training or
E. gemma@healthcareconferencesuk.co.uk

The 4th Oxford Neurology Course
26-28 June, 2013; Oxford, UK
www.ndcn.ox.ac.uk/courses/onc,
E. events@ndcn.ox.ac.uk

Advances in the treatment of Trigeminal Neuralgia - Joint Patient / Healthcare Professional Conference with CPD accreditation
29 June 2013; London, UK
E. tna@ntlbusiness.com,
T. 07982 828 978, www.tna.org.uk

July

The Oliver Zangwill Centre Conference - Identity After Brain Injury: Survivors Stories
5 July, 2013; Newmarket, UK
T. 01353 652173, E. Rachel.everett@ntlworld.com

Managing epilepsy: improving outcomes
5 July, 2013; London, UK
www.lsbu.ac.uk/epilepsy,
E. information@epilepsysociety.org.uk

Human Brain Anatomy
15-17 July, 2013; London, UK
Book online at www.neurocourses.com

November

Parkinson Plus Study Day
13th November, 2013; Derby, UK
T. 01332 254679, E. dhft.ncore@nhs.net,
www.ncore.org.uk

Providing Community Rehabilitation – Learning from Experience

Report of the Community Therapists Network Annual Conference, 28th of November 2012

Reviewed by: Professor Pam Enderby, Birmingham, UK.

The Community Therapists Network 2012 annual conference was set up to help teams from across the UK to share different approaches of providing community rehabilitation and intermediate care. The Network had become aware of the many different models of service which have developed in the United Kingdom over the last decade. Pam Enderby reported on two projects examining the costs and outcomes of intermediate care providing information from 2003. The studies had included 32 teams, more than 300 members of staff and data from 9000 patients. The findings indicated that the different models were associated with different benefits and restrictions. Furthermore, the costs and impact on patients related to these services varied. This study emphasised the importance of a day such as this.

The Rapid Response service in Sussex was described by Lordson Simpson who underlined the importance of transdisciplinary working with a respect for cross disciplinary skills and an awareness of professional limitations. The importance of seven day week working and the challenge of this needed to be addressed. Caroline Eadson and Lynne Bakewell from Derbyshire stimulated much interest in their presentation of integrating health and social care in order to improve community rehabilitation. It had taken them time to integrate records and they pointed out the importance of needing to be flexible and to gain trust in cross boundary working in order to reduce the need for repeated assessments of the same issues by different services. It was heartening to hear how the many practical barriers had been overcome by steady and co-operative management facilitated by a common aim. Sheila Keeble and Laura Mason have also facilitated a combined health and social care approach to community intervention aiming to reduce hospital admission and facilitating early discharge in Staffordshire. They have recently been combined into one of the largest trusts in the UK and were aware of the many challenges associated with different cultures of the organisations. The case studies they presented demonstrated the real need for radical new thinking of both health and social care in order to exploit the benefits and possible savings as well as greater clarity for service users.

Exploiting opportunities by expanding the use of other public facilities such as education in the South Worcestershire College for the purposes of rehabilitation was discussed by Sally Ludlow and Alison O'Neill, both occupational therapists, who presented on the use of community education to develop and improve life skills of people with acquired brain injury. The opportunity for such patients to integrate in a non-health setting supported by the third sector had obvious benefits.

We had an award winning team present on service redesign. Cally Bennett and Sam Pessoll from the Derbyshire Community Health Care Home Support Team had won a 'Transforming Community Services Innovation Award' following the redesign and pilot which targeted local care homes. By considering equipment and training in manual handling they were able to demonstrate a 60% reduction in falls in a dementia unit. These presenters reported how encouraging and stimulating it had been to enter the competition and how motivating it had been to the team.

Reconfiguration of services was the theme addressed by most of the presenters. Anne-Marie Holliday detailed the new structure required by the intermediate care services in Leeds. The workforce had to be redesigned which required changes to roles and responsibilities with the aim of improving quality of patient care. Workforce redesign was key to their progress. This presentation was usefully followed by Lynne Peters and Sarah Ferguson who considered the very real difficulty of maintaining an effective team during times of change - communication and trust as well as leadership being key requirements.

Further change was detailed by Andrew Griffin and Nickki Adams from Bath who detailed the combining of the teams previously responsible for early stroke discharge with those providing community rehabilitation, with the aim of improving transition along the stroke care pathway. A slightly different approach had been taken by Jane Hicking and Ann Godfrey from Chesterfield. They reported developing and broadening the multidisciplinary community rehabilitation team in order to support colleagues in the acute trust to work collaboratively with them. The aim of these changes was the support and specialist care of stroke patients being discharged earlier, ensuring they received appropriate care and improved transition between hospital and home.

The day concluded with the presentation from Andrew Bateman from the Oliver Zangwill Centre in Cambridgeshire on neuropsychological aspects of rehabilitation. Andrew emphasised the importance of addressing the psychological support for patients requiring rehabilitation and the need for good record-keeping including the collection of robust outcome measures and patient reported outcomes measures in order to identify benefits or losses associated with changes to services.

In conclusion, there were several important messages coming from this day. Community rehabilitation and intermediate care across the country is still in a state of change. For these changes to result in improvements to services it is essential to have broad engagement across different agencies with an emphasis on blending services, requiring explicit and open trust between professionals. Stunningly good communication with all levels of staff and an emphasis on a shared goal facilitates engagement and energy as well as preventing inadvertent sabotage. Objective analysis allowing review of what has been gained and what has been lost can place anecdote into a context. ◆

Anyone interested in learning more about the Community Therapists Network and getting involved in the next annual conference should go to www.communitytherapy.org.uk

It was heartening to hear how the many practical barriers had been overcome by steady and co-operative management facilitated by a common aim

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- **Professor John Saxton**, University of East Anglia presenting a Pragmatic Exercise Programme
- **David Ford**, Swansea University presenting The Achievements of the MS Register in the first three years and future plans
- **Professor Charles ffrench-Constant** speaking on the work of the Edinburgh Centre for translational research.
- **Ian McDonald** memorial lecture: Professor Hans Lassman.

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Please visit our website: www.mssociety.org.uk/msfrontiers for more details or call 020 8438 0941.

The Encephalitis Society Professional Seminar 2012

Conference details: 3rd December, 2012, London, UK. ***Reviewed by:*** Sophie Miller 4th year medical student, University of Liverpool, UK.

The Encephalitis Society's Professional seminar was held in MacFarlanes LLP in London on the 3rd of December, 2012 and was to be the launch of the much anticipated diagnostic algorithm and management guidelines for encephalitis.

Nearly 50 delegates hailing from all parts of the country attended for talks from Professors, Doctors, Society members and medical students.

On arrival we were issued with name badges and a welcome pack containing the programme for the day, flyers and most helpfully our own copy of the new *Professional Guidelines for the Diagnosis and Management of Encephalitis*.

The seminar commenced with a warm welcome from Ava Easton, CEO of the Encephalitis Society.

The audience included patients and their families who are members of the Encephalitis Society and a wide variety of healthcare professionals ranging from nurses, doctors from foundation level to specialist trainees, research fellows, consultants and professors. There were also medical students from first to fifth year, neuropsychologists and art therapists, all dealing with Encephalitis in the context of their own speciality.

The range of disciplines and experiences exhibited by the delegates made the discussions totally unique since the same topic could be explored from so many points of view. It was a rare opportunity to meet with such a mix of people all of whom have the same goal: to promote education concerning Encephalitis and improve its diagnosis, treatment and management.

The first talk was a background to the National Encephalitis Guidelines by Professor Tom Solomon, Chair of the Encephalitis Society Professional Panel and Director of the Institute of Infection and Global Health. I found this presentation the most useful from a student perspective as it gave a basic introduction to Encephalitis followed by more in-depth details of the disease, and was an excellent learning opportunity for the more junior audience members like myself. Professor Solomon went through several case studies making the session interactive, entertaining and creating a warm and inviting atmosphere. The cases exhibited the many different ways in which Encephalitis can present to a health care team and how differently patients can be managed. The key message in his talk was the importance of early recognition and management of the disease in achieving better outcomes for patients.

The next talk was "The importance of a diagnostic and management algorithm – what happens when things go wrong and consequences of Encephalitis for patients and their families." Delivered jointly by Ava Easton CEO of The Encephalitis Society and Dr Benedict Michael NIHR Doctoral Research Fellow. Ava began, explaining the impact of Encephalitis on patients and their families, using case studies and emotive videos helping me to truly understand the devastation that can occur if treatment is delayed.

Dr Kneen with a copy of the new guidelines

Dr Michael then took over with "How Things Go Wrong". He talked about the research he and his colleagues had done in this area and explained that there are often delays at every stage in the management of these patients, especially when a lumbar puncture (LP) is not completed early. He emphasised the importance of early suspicion, LP, diagnosis and treatment, particularly addressing the students and junior doctors who are, or are soon to be attending to possible cases of Encephalitis.

The talk naturally prompted discussion and this was invaluable as many questions were asked and answered by experts in the field, an opportunity you rarely get to witness or participate in as a medical student.

A whistle stop tour of the new National Encephalitis Guidelines was given by Dr Michael and Dr Rachel Kneen a Paediatric Neurologist at Alder Hey Children's Hospital in Liverpool. The key messages were the clear need for improved patient care, how the guidelines will support this and an overview of the on-going research around Encephalitis.

Following an interesting discussion and a good break where refreshments were provided, we were lucky enough to hear from Professor Angela Vincent (Weatherall Institute of Molecular Medicine) who gave a talk on "Encephalitis – Chasing a moving target." This detailed the presentation of her research which had found that infection can occur with co-existing anti-bodies. Registrars, research fellows and consultants were highly engaged, absorbing information and asking questions. I learnt a great deal from this session and it prompted me to do some further reading, vastly improving my knowledge on the subject.

The next talk, in contrast to its predecessor, saw the furrowed brows in the room relax and cogs shift down a gear for a highly entertaining presentation by Professor Tom Solomon "Patient and Public Involvement: An Academic's Odyssey". He explained the value of organisations like the Encephalitis Society and of taking part in Patient and Public Involvement events. He described how he had found himself running the London Marathon as the society's very own "Mad Professor" to raise money and

Professors Solomon and Vincent taking questions

awareness for Encephalitis, raising around £20,000 and breaking a Guinness World Record as the fastest marathon runner dressed as a Doctor. He urged junior doctors and students to get involved with projects like these. The presentation was bright, funny and highly enjoyable.

Following a further short discussion, the winner of the Encephalitis Society's Student Essay Competition 2011, Sophie Binks, 5th year medical student (Brighton and Sussex University) gave a presentation of her winning entry titled "The story of a patient with childhood encephalomyelitis: the effect on the patient, family and society and the role of health care professionals". Sophie provided an overview of her essay and concentrated on the effect on the person, giving the audience insight into what happens to people on an emotional and social level rather than a physical one. She also explained the things that can improve a person's life after Encephalitis and reminded us all of the consequences of this disease.

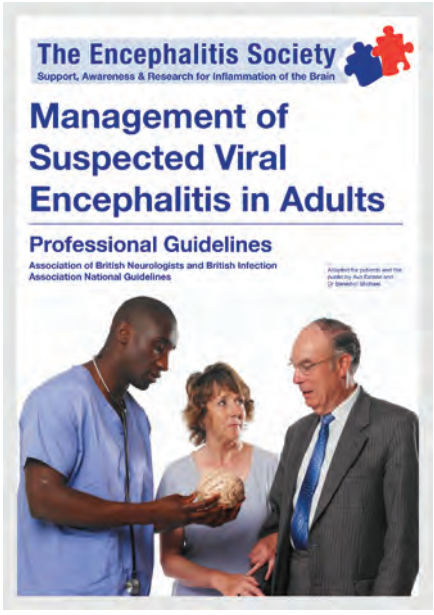
There was a final presentation of the day and the prizes were then awarded for the Encephalitis Society 2012 Student Essay Competition and Travel Bursary. The winners were:

1st Prize - Bart van Herwijnen for his essay entitled 'Bone Marrow - The future of Encephalitis Treatment'

Runner Up - Timothy Jones for his essay 'Evaluation of the Pathophysiological Mechanisms Underlying Anti-NMDA Receptor Encephalitis'

Travel Bursary – Clark Russell for his forthcoming medical elective to Vancouver.

Once the applause had ceased and pictures had been taken there was a further opportunity



for questions and Professor Solomon was on hand for answers and a final summary of the day.

The whole afternoon was followed by a lovely wine and cheese reception where we had opportunity to chat to fellow medical students and several of the doctors, and patients/family members.

Conclusions

All in all I found that the range of talks and discussions catered for everyone, whatever grade of training, discipline or interest concerning Encephalitis. The diversity of the audience could have made the pitching of the talks difficult but the speakers managed this incredibly well with a range of information and plenty of opportunity to ask questions. The juxtaposition and timing of the presentations made them easy to digest and allowed me to get the most out of the afternoon. There was an encouraging atmosphere for students and it was an excellent way to meet new people. This was a rare opportunity to hear the presentation of brand new research and talk to experts in Encephalitis. I would certainly recommend this seminar to anyone who is dealing with Encephalitis, either professionally or personally and wants a chance to expand their knowledge and have their questions answered by the leaders in this field. I feel my overall knowledge of Encephalitis as a disease and of the effect that it has on the patients and their families has been enriched.

With thanks to Macfarlanes LLP for their fabulous venue and St Andrews Healthcare for their sponsorship of the event.

Copies of the new *Guidelines for the Diagnosis and Management of Encephalitis* (both paediatric and adult version exist) can be downloaded from www.encephalitis.info Hard copies can also be obtained from The Encephalitis Society. ◆

Anyone interested in attending the 2013 seminar in December should contact The Encephalitis Society on admin@encephalitis.info

PREVIEW The 4th Oxford Neurology Course

Conference details: 26th-28th June, 2013, Oxford, UK. ***Report by:*** Ursula Schulz & Martin Turner, Nuffield Department of Clinical Neurosciences, Oxford University.

We are delighted to announce the 4th annual Oxford Neurology Course (ONC), which will run from 26th-28th June 2013 in St Anne's College, Oxford. The ONC aims to mix up-to-date clinical neurology with some of the latest neuroscience. We wish to provoke thought and discussion as well as educate consultants and trainees, and the feedback from previous years suggests this is a successful strategy.

Recognising that consultant study leave is a precious commodity, we anticipate a sizeable 15 CME credits from the Royal College of Physicians, as in previous years. We invite only expert speakers to address our delegates, and try to offer them challenging titles. We choose common clinical dilemmas, but also seek to 'myth bust'. This year we continue to pose the big questions: "Is brain scanning necessary in the diagnosis of dementia?" and "W(h)ither the Neurologist?" In addition to direct practical hints, we provide an update on the science behind some of the more complex neurological disorders, this year addressing paraneoplastic disease and the inflammatory myelopathies, as well as gaining insight into neglect and impulsivity. We also have provocative guest lectures, one covering neuroscience ethics, the other asking if genetics will solve everything.

A regular slot is "Where Neurology meets..." which considers overlap with other specialities. This year it is Dermatology. A firm favourite of previous ONCs has been the "Best Of Oxford's Grand Round": three

memorable cases hand-picked for their challenging and educational nature.

We hope that another major attraction will be the ambience. The ONC Dinner takes place in the historic dining hall of Trinity College, with pre-dinner drinks in the College Gardens. For those who want to see the many historic venues first-hand, the ONC ends with a Medical Walking Tour.

The opportunity for open and challenging discussion is central, and so we limit the number of delegates in the course to 70. We do hope that you will be able to join us. ◆

The full course programme and registration is at www.ndcn.ox.ac.uk/courses/onc (email: events@ndcn.ox.ac.uk)

PREVIEW 6th Meeting of the UK PD Non-Motor Group (PDNMG)

Conference details: 11th April, 2013; London, UK.

Non-motor symptoms of Parkinson's disease (NMS) are the leading cause of poor quality of life for both people with Parkinson's and their caregivers. The slowness, stiffness and tremor of Parkinson's disease (PD) are well known, but non-motor symptoms afflict more Parkinson's patients. Though NMS affect every patient, they are under-recognised and under-treated. In a Parkinson's UK survey, members rated symptoms such as sleep disturbance, pain, constipation, urinary problems and dizziness as more debilitating than their motor symptoms. Hospitalisation from PD is most likely to have been caused by NMS. This loss of independent living has devastating social and economic consequences.

Despite the profound and negative effects of NMS, there is a dearth of research into causes and therapies. Treatment remains poor and quality of life progressively deteriorates. The National Institute for Health and Clinical Excellence (NICE) and Parkinson's UK have identified the recognition and treatment of NMS across all stages of PD as a key unmet need. Little research explores the cause and progression of common NMS because funders have focused their attentions elsewhere. More recently, the Movement Disorders Society has formally adopted the Parkinson's Non-Motor Group as one of their study groups.

An integrated and interactive combination of clinical and laboratory-based investigation is required that will focus on the causes and consequences of sleep disturbance, pain and autonomic dysfunction in PD. Holistic assessment is crucial rather than a piecemeal approach to NMS which tends to focus on cognitive issues alone.

This one day meeting of the Parkinson's non motor group, revitalises highly successful meetings that were held from 2006-2011 and will focus on pre-motor non motor symptoms as well as the impact of NMS during the journey of a person with Parkinson's. A multi-disciplinary faculty, including noted international opinion leaders in the field, will be speaking and the day promises to increase our understanding of the effects of PD on the brain in order to uncover the underlying causes of NMS. The meeting will also detail advances in the detection and treatment of NMS, thereby improving the quality of life of millions of people with Parkinson's, both today and in the future. ◆

6th Meeting of the UK PD Non-Motor Group

Hosted in Partnership with Europar and the NIHR London (South) Comprehensive Local Research Network
11 April 2013, 08.30am - 5.30pm
Guy's Hospital, london, UK

Event Programme (subject to change)

09.00 – 09.15 Welcome and What Has PDNMG Acheived?
K Ray Chaudhuri (UK)/P Martinez-Martin (Spain)

Session 1: Chairs: AHV Schapira and K Ray Chaudhuri

09.15 – 09.45: Non motor symptoms and genetics of Parkinson's
Schapira (UK)
09.45 – 10.15: Redefining Parkinson's? *W Poewe (Austria)*
10.15 – 10.45: Clinical trials addressing NMS in Parkinson's
P Jenner (UK)
10.45 – 11.00: Panel discussion Chairs + speakers

Session 2: **Therapies**
Chairs: K Ashkan and P Martinez-Martin

Session 3: **Pain and Fatigue**
Chairs: D Brooks, Per Odin

Session 4: **Impulse control, dysregulation and behaviour**
Chairs: G MacPhee, A Antonini , C Falup-Precurariu

Registration Fee: £50 (£20 nurses)

Information from Kami Paulson,
E. kami.paulson@gstt.nhs.uk , T. 020 7188 7604
Or register online at
www.crncc.nihr.ac.uk/about_us/ccrn/slondon/
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The Movement Disorder Society · PARKINSON'S UK · NON-MOTOR GROUP · EPDA European Parkinson's Disease Association · London (South) · NHS National Institute for Health Research

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Friday 5th July 2013
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Presented By:

Professor Barbara Wilson OBE, Professor Tamara Ownsworth
Professor Jennie Ponsford, Dr. Fergus Gracey

Conference Fees: Delegate Rate £150
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managing epilepsy: improving outcomes

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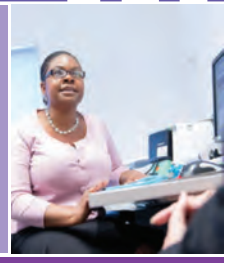
To book your place: www.lsbu.ac.uk/epilepsy
For more information: information@epilepsysociety.org.uk



This conference will:

- enhance your understanding of the commissioning landscape for epilepsy services;
- assist you to develop tools for improving epilepsy service delivery;
- discuss strategies for delivering patient-centred epilepsy care and management; and
- offer excellent opportunities for networking with other health and social care professionals within epilepsy services.

The following companies have financially supported this Epilepsy Society and London South Bank University national conference for healthcare professionals. Representatives will be present at the event.

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PREVIEW Pain Therapeutics

Conference details: 20th & 21st May 2013, Copthorne Tara Hotel, London, UK.

Examine practical issues within the industry and network with leading experts at SMi's Pain Therapeutics conference

SMi's Pain Therapeutics conference returns to London on the 20th & 21st May 2013 with a two day intensive agenda highlighting the latest developments in pain therapeutics and offering attendees a unique platform to engage with key opinion leaders and esteemed academia to learn the challenges and successes in this field.

Pain is the primary reason that patients seek medical care and the pain therapeutics industry is currently under financial strain. With this in mind, the conference will highlight improvements in R&D methods and certifying that drugs being put forward for clinical trials are given the best chance to succeed. Key factors include recent findings in areas such as: current targets for analgesic development, personalised medicine, the cannabinoid approach, imaging modalities, experimental models in early phase clinical development and improving clinical trial success rates.

Keynote Speakers

SMi are pleased to introduce Narender Gavva, Scientific Director, Amgen, who will give a presentation on greater emphasis on preclinical discovery, outlining potential false-positive hotspots and the best practices for target selection criteria.

The conference will also present a Pfizer Session on current considerations in sodium channel blockers for pain management, lead by Richard Butt, Director, Research Project Leader, Pfizer. This session will highlight discovery and preclinical development of selective sodium channel blockers as well as subtype selective sodium channel blockers.

Visit www.pain-therapeutics.co.uk for the full speaker line-up, which includes presentations from: Amgen; Eli Lilly; Convergence Pharmaceuticals; Benitec Biopharma; Nektar Therapeutics and MedImmune.

Interactive workshops

Delegates can also choose between two half day workshops, both held on 22nd May: Workshop A is on: Human Pain Models – Lost in Translation? Led by Jonathan Stewart, Consultant, Pain Medicine, Imperial NHS Trust, London, Zahid Ali, Senior Director, Pfizer and Remigiusz Lecybyl, Consultant in Chronic Pain, Lewisham Hospital.

Workshop B is on: Using phenotyping and imaging to improve early drug development and clinical trial design, led by Anthony Jones, Professor of Neuro-rheumatology, University of Manchester. ◆

Visit www.pain-therapeutics.co.uk for more information or Contact Cem Tuna on telephone +44 (0) 20 7827 6736
Email on ctuna@smi-online.co.uk

ACNR readers can claim a discount of £300 so make sure you quote ACNR when enquiring.

Alex Flynn – one man, one mission, £1 million for Parkinson's

Alex Flynn is a 41-year-old father of three boys, who has previously worked as a lawyer for numerous multinationals. However, more recently Alex has been concentrating on 10MillionMetres; a life-changing endurance project, the formation of which was encouraged as a consequence of him being diagnosed with idiopathic Parkinson's disease in 2008.

Before the end of 2014, the 10MillionMetres Challenge will take him more than 6,200 miles around the world, encompassing some of the world's more interesting and dangerous races. Alex will be running, cycling, swimming, walking or, if necessary, crawling the distance with the intent to raise more than £1Million for research into Parkinson's disease. Highlights so far include the 2010 Marathon des Sables, in 2011 traversing 1457 miles from London to Rome in 30 days – the first 10 days of which he ran the equivalent of 20 marathons, running more than 135 miles across the Bavarian Alps as well as many marathons, Ironman and Olympic Triathlons.

His last challenge was a truly epic 3256 mile traverse of the USA from Santa Monica to New York City, becoming the first to complete the crossing by riding, climbing, running and kayaking this monster of a route in 35 days while all the time fighting against the relentless progression of the disease on his own body. To date, Alex has covered 9,103,218m – 91% of the distance challenge is complete.

Alex commented "Without the input from my sponsors, in particular Britannia Pharmaceuticals, the final leg of the journey of 10MillionMetres would be nigh on impossible and I would not be able to raise as great an awareness of Parkinson's disease. For that I am truly grateful"

Britannia Pharmaceuticals are one of a number of companies sponsoring Alex to achieve his goal of raising upwards of £1million for research into Parkinson's Disease for The Cure Parkinson's Trust. His story is inspirational.

To find out more and help support the cause visit www.alexflynn.co.uk

Britannia Pharmaceuticals Ltd

New 'super nurse' project announced

A joint project to create the first ever 'national' epilepsy specialist nurse has been announced. The 'super nurse' is the brainchild of non-profit organisation Neurological Commissioning Support (NCS) – who have identified the need for a national role to support commissioning for epilepsy. The new nurse will work with NCS to provide expert advice and support to the newly established Clinical Commissioning Groups (CCGs).

Employed by Epilepsy Society and jointly funded by Epilepsy Action, the super nurse will give guidance to CCGs on how to improve epilepsy nursing services within hospitals and local neurology services. This will help them to design better services that include epilepsy specialist nurses (ESNs) and support people with epilepsy. The project will initially run for three years. During this period it is hoped that the new nurse will play a key part in the commissioning of services and advocate the importance of nurses within epilepsy services.

Epilepsy Society's chief executive Graham Faulkner said: "In today's financially challenged health service there are clear benefits to delivering a service model that can provide rapid service change and improved outcomes.

"There are around 600,000 people in the UK with epilepsy – around 70 per cent of whom could be seizure free with optimal care. We estimate that only around 50 per cent of people with epilepsy currently achieve seizure freedom. Since 2011 Epilepsy Society has been working alongside NCS undertaking audits of epilepsy services in GP practices. The audits have uncovered significant problems which could easily be improved with simple measures including the appointment of epilepsy specialist nurses. Evidence shows that the appointment of an epilepsy specialist nurse is a catalyst for service improvement, often leading to a reduction in inappropriate admissions to hospitals.

"We hope this innovative idea will influence the development of other epilepsy specialist nurse posts in the UK through mainstream funding."

UCLH hosts PET MR study day in conjunction with Siemens Healthcare

University College London Hospitals NHS Foundation Trust (UCLH), recently hosted a UK first PET MR study day in conjunction with Siemens Healthcare. A wide range of delegates attended the day course, including a number of radiologists, physicists, MR radiographers and MI radiographers. The knowledge session provided an introduction and overview of PET MR innovative technology, outlining its potential clinical and research applications.

Over twenty clinical experts from UCLH and other organisations chaired speaker sessions on topics such as quantitation in PET MR, how it will help medical research and safety and governance issues. The potential applications of PET MR were also explored, including its use in psychiatry, dementia, neurology, tumour biology, pelvic and GI cancers, lymphoma, head and neck cancers, vascular and cardiac procedures. Siemens Healthcare application and product specialists also attended to outline the key benefits of PET MR and detail features of the world's first fully integrated MR and PET scanner, the Biograph™ mMR.

The PET MR system from Siemens Healthcare is housed in the recently opened University College Hospital Macmillan Cancer Centre and is the first machine of its kind in the UK, delivering

the most accurate information from deep inside the body during a single scanning session.

"I was keen to learn more about the applications of PET MR. In a paediatric hospital MRI, with no use of ionising radiations and exquisite soft tissue anatomical definition, it is a very powerful investigative tool. Combining the functional aspects of MR and PET with the ability to significantly reduce the dose burden to the child is a very attractive proposition for paediatric imaging," states Dr Lorenzo Biassoni, Consultant Paediatric Nuclear Medicine Physician at Great Ormond Street Hospital for Children.

Siemens Healthcare hosts and supports UK study days throughout the year. For further information, please contact sarah.cowan@siemens.com.

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1. Gunthorpe M *et al. Epilepsia* 2012; 53: 412–424.

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An effective maintenance dose is expected between 600 mg/day and 1,200 mg/day. *Renal impairment:* No dose adjustment is required in patients with mild renal impairment. A 50% reduction in the initial and maintenance dose of Trobalt is recommended in patients with moderate or severe renal impairment (creatinine clearance <50 ml/min). The total daily starting dose is 150 mg, and it is recommended that during the titration period the total daily dose is increased by 50 mg every week to a maximum total dose of 600 mg/day. *Hepatic impairment:* No dose adjustment is required in patients with mild hepatic impairment. A 50% reduction in the initial and maintenance dose of Trobalt is recommended in patients with moderate or severe hepatic impairment (Child-Pugh score ≥7). The total daily starting dose is 150 mg and it is recommended that during the titration period the total daily dose is increased by 50 mg every week to a maximum total dose of 600 mg/day. *Elderly* (65 years of age and above): A reduction in the initial and maintenance dose of Trobalt is recommended in elderly patients. The total daily starting dose is 150 mg/day and during the titration period the total daily dose should be increased by a maximum of 150 mg every week according to the individual patient response and tolerability. Doses greater than 900 mg/day are not recommended. **Contra-indications** Hypersensitivity to retigabine or any of its excipients. **Special warnings and precautions** Urinary retention, dysuria and urinary hesitation were reported in controlled clinical studies with retigabine generally within the first 8 weeks of treatment. Trobalt must be used with caution in patients at risk of urinary retention and it is recommended that patients are advised about the risk of these possible effects. Caution should be taken when Trobalt is prescribed with medicinal products known to increase QT interval and in patients with known prolonged QT interval, congestive cardiac failure, ventricular hypertrophy, hypokalaemia or hypomagnesaemia and in patients initiating treatment who are 65 years of age and above. In these patients it is recommended that an electrocardiogram (ECG) is recorded before initiation of treatment with Trobalt and in those with a corrected QT interval > 440 ms at baseline, an ECG should be recorded on reaching the maintenance dose. Psychiatric disorders: Confusional state, psychotic disorders and hallucinations were reported in controlled clinical studies, it is recommended that patients are advised about the risk of these possible effects. Suicide risk: Suicidal ideation and behaviour have been reported in patients treated with anti epileptic agents in several indications. Patients (and caregivers of patients) should be advised to seek medical advice if signs of suicidal ideation or behaviour emerge. Elderly (65 years of age and above): Elderly patients may be at increased risk of central nervous system events, urinary retention and atrial fibrillation. Retigabine must be used with caution in this population with a reduced initial and maintenance dose recommended. As there is individual variation in response to all antiepileptic drug therapy, it is recommended that prescribers discuss with patients the specific issues of epilepsy and driving. **Overdose** In the event of overdose it is recommended that the patient is given appropriate supportive therapy as clinically indicated, including ECG monitoring. Further management should be as recommended by the national poisons centre, where available. **Fertility, pregnancy and lactation** Trobalt is not recommended during pregnancy and in women of childbearing age not using contraception. It is unknown whether retigabine is excreted in human breast milk. The effect of retigabine on human fertility has not been established. **Drug interactions** *In vitro* data indicated a low potential for interaction with other antiepileptic drugs. Pooled analysis from clinical studies showed no clinically significant effect of the inducers (phenytoin, carbamazepine and phenobarbital) on retigabine clearance. Steady-state data from a limited number of patients in smaller studies indicate that phenytoin and carbamazepine could reduce retigabine systemic exposure by 35% and 33% respectively. Trobalt interaction with digoxin at therapeutic doses may increase digoxin serum concentrations. Retigabine may increase the duration of some anaesthetics. Up to 750 mg/day, no clinically significant effect on pharmacokinetics (PK) of combined oral contraceptive pill (COC). Low dose COC did not significantly effect PK of retigabine. Advise patients that alcohol may lead to blurred vision. **Adverse reactions** A dose relationship seems to exist between dizziness, somnolence, confusional state, aphasia, coordination abnormal, tremor, balance disorder, memory impairment, gait disturbance, blurred vision and constipation. *Metabolism and nutrition disorders; common:* weight increase, increased appetite. *Psychiatric disorders; common:* confusional state, psychotic disorders, hallucinations, disorientation, anxiety. *Nervous system disorders; very common:* dizziness, somnolence, *common:* amnesia, aphasia, coordination abnormal, vertigo, paraesthesia, tremor, balance disorders, memory impairment, dysphasia, dysarthria, disturbance in attention, gait disturbance, myoclonus, *uncommon:* hypokinesia. *Eye disorders; common:* diplopia, blurred vision. *Gastrointestinal disorders; common:* nausea, constipation, dyspepsia, dry mouth, *uncommon:* dysphagia. *Hepatobiliary disorders; common:* increased liver function tests. *Skin and subcutaneous disorders; uncommon:* skin rash, hyperhidrosis. *Renal and urinary disorders; common:* dysuria, urinary hesitation, haematuria, chromaturia, *uncommon:* urinary retention, nephrolithiasis. *General disorders and administrative site conditions; very common:* fatigue, *common:* asthenia, malaise, peripheral oedema. **Basic NHS costs** Initiation packs of 21 x 50 mg tablets and 42 x 100 mg tablets (EU/1/11/681/013) is £24.33. Maintenance packs of 21 and 84 x 50 mg tablets are (EU1/11/681/001) £4.87 and (EU/1/11/681/002) £19.46 respectively. Maintenance packs of 21 and 84 x 100 mg tablets are (EU/1/11/681/004) £9.73 and (EU/1/11/681/005) £38.93 respectively. Maintenance packs of 84 x 200 mg tablets are (EU/1/11/681/007) £77.86. Maintenance packs of 84 x 300 mg tablets are (EU/1/11/681/009) £116.78. Maintenance packs of 84 x 400 mg tablets are (EU/1/11/681/0011) £127.68. **Legal category**: POM **Marketing authorisation holder** Glaxo Group Limited. Berkeley Avenue, Greenford, Middlesex, UB6 0NN, United Kingdom. **Further information is available from:** Customer contact centre, GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex UB11 1BT. Email: customercontactuk@gsk.com Customer Services Freephone 0800 221441. **Trobalt®** is a registered trademark of the GlaxoSmithKline group of companies. **Prescribing information last revised** November 2012
UK/RTG/0107/12

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 GlaxoSmithKline on 0800 221 441

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UK/RTG/0023/13 Date of preparation: February 2013