ACNR

www.acnr.co.uk

In this issue

Gavin Giovannoni
– Primary Progressive Multiple Sclerosis

Janet C Rucker
– Neuro-Ophthalmology – Disorders of Supranuclear Eye Movements

Richard AA Kanaan
– Clinical Dilemmas in Neuropsychiatry – Functional or Feigned: a neurological dilemma

NEWS REVIEW > CONFERENCE REPORTS > BOOK REVIEWS > JOURNAL REVIEWS > EVENTS DIARY

Now with NICE approval[1]

An MS treatment that's oral

Prior IFN treatment
Failed response to full and adequate course

+

Relapse
Unchanged or increased rate, or ongoing severe relapses

▶

Prescribe Gilenya
Once daily oral MS therapy

NOVARTIS

Abbreviated Prescribing Information: GILENYA® (fingolimod)
Important note: Before prescribing, consult Summary of Product Characteristics (SmPC). **Presentation:** Hard capsule containing 0.5 mg fingolimod (as hydrochloride). **Indications:** Gilenya is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups:
- Patients with high disease activity despite treatment with a beta-interferon. These patients may be defined as: those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gadolinium-enhancing lesion. A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.
- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.
Dosage: Adults: Treatment should be initiated and supervised by a physician experienced in multiple sclerosis. One 0.5 mg capsule to be taken orally once daily. Patients can switch directly from beta-interferon or glatiramer acetate to Gilenya provided there are no signs of relevant treatment-related abnormalities, e.g. neutropenia. Use with caution in patients aged 65 years and over. No dose adjustments required in patients with mild to severe renal impairment or mild to moderate hepatic impairment. Exercise caution in patients with mild to moderate hepatic impairment. Do not use in patients with severe hepatic impairment (Child-Pugh class C). Use with caution in patients with diabetes mellitus due to an increased risk of macular oedema. **Contraindications:** Known immunodeficiency syndrome, patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies), severe active infections, active chronic infections (hepatitis, tuberculosis), known active malignancies, except for patients with cutaneous basal cell carcinoma, severe liver impairment (Child-Pugh class C), hypersensitivity to the active substance or to any of the excipients. **Warnings/**

Precautions: *Bradyarrhythmia:* Initiation of treatment results in a transient decrease in heart rate (HR), which may be associated with atrioventricular block. Patients should have an ECG pre-dose, 6 hours post dose and observed for 6 hours with hourly HR and BP. Continuous ECG monitoring is recommended for 6 hours. In the event of bradyarrhythmia-related symptoms, initiate appropriate clinical management and monitor overnight. Also monitor overnight if at 6 hrs: HR <45 bpm, new onset 2nd degree heart block or higher, QTc >500 msec, or 3rd degree heart block at any time. If HR is lowest at 6 hrs monitor for >2 hrs until HR increases. The same precautions apply if Gilenya is discontinued for more than 2 weeks. Do not use Gilenya in patients with Mobitz type II or higher AV block, sick-sinus syndrome, sino-atrial block, symptomatic bradycardia, recurrent syncope, QTc >450 msec significant cardiovascular disease, or severe sleep apnoea unless in consultation with a cardiologist and monitored overnight. Gilenya should not be given to patients taking beta blockers, HR lowering calcium channel blockers or other HR lowering substances (e.g. digoxin, diltiazem, ivabradine) unless in consultation with a cardiologist. *Infections:* Reduction of the lymphocyte count to 20-30% of baseline values occurs with Gilenya. Perform a complete blood count (CBC) at baseline and periodically during treatment, and in case of signs of infection, stop Gilenya until recovery if absolute lymphocyte count <0.2x10⁹/L is confirmed. Consider VZV vaccination of patients without a history of chickenpox or VZV antibody negative patients prior to commencing Gilenya. Gilenya may increase the risk of infections. Employ effective diagnostic and therapeutic strategies in patients with symptoms of infection while on Gilenya and for 2 months after discontinuation. *Macular oedema:* Macular oedema with or without visual symptoms has been reported in patients taking Gilenya. Perform an ophthalmological evaluation 3-4 months after Gilenya initiation. Evaluate the fundus, including the macula in patients reporting visual disturbances. Perform ophthalmological evaluation prior to initiating therapy and periodically thereafter in patients with diabetes mellitus or a history of uveitis. Discontinue Gilenya if a patient develops macular oedema. *Liver function:* Do not use Gilenya in patients with severe pre-existing hepatic injury (Child-Pugh class C). Delay Gilenya initiation in patients with active viral hepatitis until resolution. Recent transaminase and bilirubin levels should be available before initiation of Gilenya. Monitor liver transaminases at months 1, 3, 6, 9 and 12 and periodically thereafter. Institute more frequent monitoring if transaminases rise above 5 times the ULN, including serum bilirubin and alkaline phosphatase (ALP) measurement. Stop Gilenya treatment with repeated confirmation

www.gilenya.co.uk

GILENYA™
(fingolimod) 0.5mg

Have you ever thought of the immunopathology of different forms of multiple sclerosis (MS) being similar to that seen in the different forms of leprosy? Gavin Giovannoni in his stimulating article on primary progressive MS gives reasons as to why this may be the case, as he discusses the evidence for regarding this form of MS as a unique form of the condition.

The use of phenol to treat spasticity is not straightforward and Moheb Gaid lays out in great clarity how this agent can be used to target different nerves and muscle groups in patients with lower limb spasticity. He describes not only how best to effect the nerve block, but why one might consider doing it in the first place.

The diagnosis of epilepsy in adults can be very tricky and often relies on a good history and especially a witnessed account. In children it is no easier as Tekki Rao discusses in his article in our series on Paediatric Neurology. In his article he lays down the ground work by which a diagnosis can be made whilst also highlighting all the mimics of epilepsy that can easily be misdiagnosed.

The prognosis in patients with high grade gliomas (HGG) remains poor at only 12-18 months. Stephen Price and colleagues in their article for the Neurosurgery series discuss the latest thinking in these tumours and how we are beginning to better stratify gliomas using molecular markers which can then be used as prognostic indicators. In addition they discuss new ways by which to better delineate tumour margins and treat these malignant tumours.

Richard Kanaan really challenges us with the case he presents in the latest in the series on Clinical Dilemmas in Neuropsychiatry. The question that the case throws up is whether the patient is feigning their condition, and if so how can we prove it, what does it matter and finally what does that mean therapeutically. A must read!

The neural control of supranuclear eye movements is complex and trying to explain the range of pathways involved is a daunting prospect. However Janet Rucker shows us how to do this with a superbly clear account on this topic, with excellent illustrations and descriptions, that is hugely informative at so many different levels.

We have a bumper group of conference reports in this issue of ACNR, which contain much useful up-to-date information on a whole variety of neurological conditions.

Finally, we have a series of demands from UKABIF on what a life with brain injury should involve in terms of proper care and management, as well as our usual array of other reviews and news items.

So we hope you enjoy this new issue of the ACNR. ◆

Roger Barker, Co-Editor.

Roger Barker, Co-Editor,
Email. Rachael@acnr.co.uk

About The Brain Prize

The Brain Prize was established in 2010, and it was awarded for the first time in 2011 to György Buzsáki, Támas Freund and Péter Somogyi. This year's winners are Christine Petit and Karen Steel.

The object of the Foundation is to boost interest in brain research and its results, to stimulate and reward outstanding brain research and to stimulate Danish research through an expanded interplay with other European brain research, and thus to improve the scientific basis for progress in the prevention, diagnostics and treatment of diseases and disorders of the brain and nervous system.

The term 'brain research' is to be understood as research into any aspect of the normal nervous system and into any pathological conditions of the nervous system. It is thus a broad field of research ranging from basic molecular research, cell biology research and physiological research to clinical research into the diseases and disorders of the brain and nervous system, including prevention, identification of disease aetiology and pathogenesis, and improvement of diagnostics and treatment.

The € 1 million Brain Prize is awarded every year. It is a personal prize that can be awarded to one or more outstanding researchers individually or to a group of researchers who have distinguished themselves by making an outstanding contribution to European brain research and who are likely to be active in research for at least a further decade.

The Brain Prize may be distributed among researchers in the same area or different areas of the broad field of research. The Brain Prize is awarded to European researchers, scientists who have conducted research in Europe or scientists who have close research affiliations with research conducted in Europe.

Anyone can nominate candidates for The Brain Prize except members of the Board and administration, members of the Selection Committee.

Recipients of the Brain Prize are under an obligation to contribute to the advancement and internationalisation of Danish brain research through interaction with Danish researchers and research environments, e.g. in the form of lectures, master classes, seminars, summer schools or researcher exchange programmes, or in some other way agreed upon with the Foundation.

**For further information –
www.thebrainprize.org**

Grete Lundbeck European Brain Research Foundation **Call for Nominations for**

THE BRAIN PRIZE

THE PRIZE OF € 1 MILLION WILL BE AWARDED IN COPENHAGEN IN MAY 2013
Nominations by 15 September 2012

Nominations will be reviewed by the Selection Committee:

YVES AGID, FRANCE, **HUDA AKIL,** USA, **COLIN BLAKEMORE,** UNITED KINGDOM, CHAIRMAN

FRED. H. GAGE, USA, **TOMAS HÖKFELT,** SWEDEN, VICE-CHAIRMAN, **FLORIAN HOLSBOER,** GERMANY

RANGA R. KRISHNAN, SINGAPORE, **JES OLESEN,** DENMARK

FOR THE NOMINATION FORM AND DETAILS OF NOMINATION PROCEDURE PLEASE VISIT: **WWW.THEBRAINPRIZE.ORG**

Prize Winners 2012 Christine Petit, the Institut Pasteur and Collège de France, Paris, France and Karen Steel, the Wellcome Trust Sanger Institute, Cambridge, UK

GRETE LUNDBECK
EUROPEAN
BRAIN RESEARCH
FOUNDATION

THE
BRAIN
PRIZE

The Brain Prize recognizes and rewards outstanding contributions to European neuroscience, from basic to clinical

CONTENTS

JULY/AUGUST 2012

New Web Content

Editorial board and contributors

ENCALS Young Investigator Award

Dr Martin Turner receives his award from panel chair Professor Ammar Al-Chalabi

The ENCALS Young Investigator Award was presented to Dr Martin Turner from Oxford University for work over several years developing a theme of loss of cortical inhibitory (interneuronal) influence in ALS pathogenesis, using PET, TMS and advanced MRI. Dr Turner gave a short presentation 'Faulty brakes: is there a fundamental loss of inhibition in ALS?'.

The European Network for the Cure of ALS inaugurated the prestigious Young Investigator Award in 2011. The prestigious Young Investigator Award is given to the delegate who, in the opinion of the panel, has generated research that is most outstanding or innovative. Criteria include any or all of novelty, challenge to existing ideas about ALS, results with patient benefit, and impact on the understanding of ALS.

The annual meeting was held in Dublin this year (May 25th-27th), hosted by Professor Orla Hardiman.

For more information see: www.ENCALS.eu

Professor John Aggleton elected Fellow of Royal Society for memory research

Breakthroughs on the physical structure of memory has won a Cardiff academic one of the highest honours in world science. Professor John Aggleton has been elected a Fellow for his neuroscientific work which has widely expanded understanding of how memory is stored in the brain.

Cardiff University's School of Psychology now has two Fellows of the Society, the oldest scientific community in continuous existence.

Professor Aggleton joined the School in 1994. When he started his research, ideas about how day-to-day events are remembered were heavily focussed on one part of the brain called the hippocampus. Professor Aggleton's highly influential research has revealed the roles of other brain structures to create a far more comprehensive picture of how different types of memory are formed and recalled.

He said: "The point of the research is to understand what happens when memory breaks down. I've shown that we can't tackle these questions just by looking at the hippocampus. There is a long way to go, but we must look at the complex interplay between structures if we are to understand problems like amnesia."

Professor Aggleton is now working on exactly how the structures he has indentified, in the diencephalon and medial temporal lobe, work together to ensure memory function.

For more information contact: RouseS@cardiff.ac.uk

Primary Progressive Multiple Sclerosis

**Gavin Giovannoni,
MMBCh, PhD**

Queen Mary University of London,
Blizard Institute, Neuroscience and
Trauma Centre, Barts and The
London School of Medicine and
Dentistry

Correspondence to:
Blizard Institute,
4 Newark Street,
London, E1 2AT, UK.
Tel: +44 (0)20 7377 7000,
Email: g.giovannoni@qmul.ac.uk

Abbreviations
CNS – central nervous system
CSF – cerebrospinal fluid
DMT – disease-modifying therapy
GA – glatiramer acetate
IFNb – interferon beta
MS – multiple sclerosis
MSer* – someone with MS
MSers* – a group of people with MS
RR – relapsing remitting
SP – secondary progressive
PP – primary progressive

What term do you use to refer to someone with MS?

MSer (noun) – someone with MS, *MSers* (plural) – group of people with MS.

To the best of my knowledge the term MSer was first used on the social network site shift.ms (www.shift.ms), for young people with MS. A subsequent survey conducted on our multiple sclerosis research blog (www.ms-res.org) amongst people with MS revealed that MSer is the preferred term that people with MS would like to be referred to when addressed either as individuals (MSer) or as a collective group (MSers). MSer was preferred to the terms MS'er, which is the abbreviation for MS sufferer, patient, client or person with MS.

Introduction

MS is the commonest non-traumatic disabling disease to affect young adults in the UK. Although current dogma states that it is an organ-specific autoimmune disease of the central nervous system the antigenic targets of the autoimmune attack have yet to be identified. Despite the cause of MS remaining undefined there is an increasing understanding of the causal pathways that underlie the disease. MS is considered by most to be a complex disease due to an interaction between genetic and environmental factors.[1]

Clinical course

The clinical phenotype of MS is heterogeneous and determines the clinical classification of the disease.[2] Approximately 85% of MSers in the UK present with attack onset disease that follows a relapsing-remitting (RRMS) course that in the pre-DMT era became secondary progressive (SPMS) in the majority of MSers (65-80%).[3] Whether this latter figure remains as high as this in the post-DMT era is unknown at present; it is unclear whether or not DMTs delay or in some cases prevent the onset of the secondary progressive phase of MS. A minority of patients (15%) have a progressive course from outset and are referred to as having primary progressive MS (PPMS).[5] The average age of onset of relapsing MS is between 28 and 31 years of age with a median time to the onset of SPMS of approximately 10 years. Interestingly the average age of onset of PPMS coincides with the age of onset of the secondary progressive phase of ~38-40 years of age. Importantly, the clinical courses of MS in the SP and PP phases are indistinguishable.[5] When followed longitudinally anything from 5-25% of PPMSers go on to have superimposed relapses and are referred to as having progressive-relapsing MS (PRMS).[2] Often MSers presenting with a PPMS-type course are found on detailed enquiry to have had a prior sentinel event compatible with a demyelinating attack; this typically occurs decades before the onset of disease progression. These MSers have been referred to in the past as having transitional MS,[6] however, the current Lublin and Reingold classification categorises these MSers as having SPMS.[2] Why bother with a detailed clinical classification? It turns out that relapses, and the presence of gadolinium(Gd)-enhancing lesions on MRI, predict a therapeutic
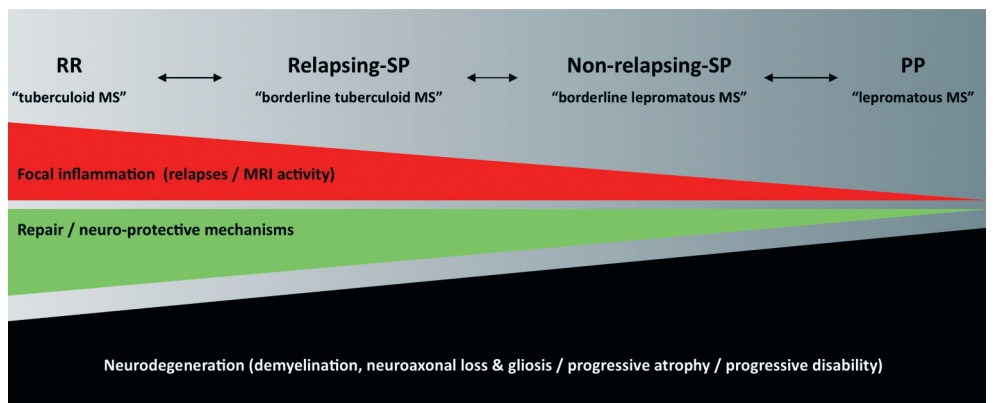
Figure 1: Although MS is a clinically heterogeneous disease it can be viewed as an inflammatory neurodegenerative disease with the clinical spectrum or phenotype determined by the presence or absence of focal inflammation, similar to that which occurs in infectious diseases, e.g. leprosy. The underlying neurodegenerative component of the disease may or may not be ongoing but it is modified by superimposed focal inflammatory events. The focal inflammation may be an appropriate host response directed at an unidentified aetiological agent or an inappropriate autoimmune response. These focal inflammatory events are responsible for clinical attacks and MRI disease activity. Although damaging in itself, the focal inflammation provides the biological substrate in the form of trophic and growth factors which promote repair and clinical recovery. Inhibiting the focal inflammatory events, e.g. with generalised immunosuppression, would reduce the relapse rate and MRI activity and remove the important trophic and growth factor support provided by the inflammatory infiltrates, but it may not affect the underlying primary neurodegenerative processes. This strategy would simply convert relapsing remitting disease into non-relapsing progressive disease (Adapted from [14]).

Table 1: Concordance rates for disease course within sibships (adapted from[11])

Disease course	Frequency	Dichotomised disease course	Frequency
RR vs. RR	84		
RR vs. RRSP	68.3		
RR vs. PP	33.7	RR* vs. RR*	191.7
RRSP vs. RRSP	39.3	RR* vs. PP	60.7
RRSP vs PP	27	PP vs. PP	9.7
PP vs. PP	9.7		
RR = relapsing remitting, RRSP = secondary progressive, PP = primary progressive			

Table 2. PPMS may be diagnosed in subjects with (adapted from [29]):

1. One year of disease progression (retrospectively or prospectively determined)
2. Plus 2 of the 3 following criteria[a]:
    A. Evidence for dissemination in space in the brain based on ≥1 T2[b] lesions in at least one area characteristic for MS (periventricular, juxtacortical, or infratentorial)
    B. Evidence for dissemination in space in the spinal cord based on ≥2 T2[b] lesions in the cord
    C. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

[a]If a subject has a brainstem or spinal cord syndrome, all symptomatic lesions are excluded from the Criteria.
[b]Gadolinium enhancement of lesions is not required.

response to currently licensed disease-modifying therapies, or more broadly anti-inflammatory drugs. MSers with relapses and/or focal Gd-enhancing MRI activity indicative of focal inflammation respond to DMTs and this probably applies to PPMSers. [7]

Differential diagnosis

The majority of PPMSers present with a progressive spastic paraparesis. However, several other well-defined primary progressive phenotypes have been described including a progressive cerebellar syndrome, progressive optic atrophy and progressive hemispheric or subcortical pseudotumoral presentation. Important conditions that can mimic PPMS that need to be considered in the differential diagnosis are neurosarcoidosis, HTLV1-associated myelopathy, adrenomyeloneuropathy and Sjögren's myelopathy. Sjögren's myelopathy is not a well-defined clinicopathological entity and may simply represent an association between Sjögren's syndrome and PPMS.[9]

Pathogenesis

Is PPMS a different disease to relapse onset disease? This is unlikely for several reasons. Firstly, PPMSers are as likely to be positive for major at risk HLA-DRB1*15.01 as MSers with relapse-onset disease.[10] Secondly, in sibling pairs concordant for MS only 50% are concordant for clinical course (see Table 1).[11] If RR and PPMS were different diseases you would expect the disease course to be concordant between siblings. Finally, pathological studies have not been able to differentiate relapse-onset from a primary progressive MS.[12,13] Although there are a smattering of publications suggesting quantitative immunological differences between PPMS and relapse-onset MS; however, none of the findings are robust enough to make definitive claims. I therefore believe that PPMS and relapse-onset disease are part of the same spectrum and what determines whether or not someone has relapses depends on qualitative differences in the type of inflammatory response that occurs within the central nervous system in response to whatever is causing or triggering the disease. I have previously proposed that the MS spectrum is not dissimilar to what is seen with regard to the clinical course or phenotype in leprosy[14]; with relapsing MS, characterised by well circumscribed areas of focal inflammation, being referred to as tuberculoid MS and PPMS, with more low grade chronic inflammation, being referred to as lepromatous MS and a spectrum between them (Figure 1). To test this hypothesis the inciting antigens, be they autoimmune or not, need to be defined.

Epidemiology of PPMS

The epidemiology of PPMS is not dissimilar to that of relapse-onset disease with the exception that PPMS is very rare in children, occurs more frequently in males and its incidence seems to be relatively static. The female to male ratio is generally 1:1 with regard to PPMS and 2 or even 3:1 for relapse onset disease. The increasing female preponderance of MS, as seen by changes in the sex ratio, seems to be driven by relapse-onset disease, with the incidence of PPMS remaining relatively constant.[15]

Diagnostic criteria

PPMS is diagnosed using the same principles as relapse-onset disease; you have to demonstrate dissemination in time and space and exclude other potential causes.[16] The original McDonald diagnostic criteria required an abnormal or positive CSF examination, as an absolute requirement, to make a diagnosis of PPMS[17]; a positive CSF was defined as intrathecal oligoclonal IgG bands and/or a raised IgG index. These criteria were subsequently changed so that a diagnosis of PPMS could be made with a normal CSF examination (Table 2). These changes were prompted by finding that 189/938 (20%) subjects in the glatiramer acetate in PPMS study (PROMiSe study) had a normal CSF study.[18] The PROMiSe Study was subsequently terminated early due to a lack of efficacy; interestingly in this study the CSF negative group had a more benign course that the CSF positive cohort (Jerry Wolinsky, personal communication). This would imply that CSF negative PPMS is not the same disease as CSF positive PPMS and is a strong argument for reinstating the original McDonald criteria for PPMS. In fact, two contemporary clinical trials in PPMS require an abnormal CSF as an inclusion criteria,[19,20] which is a vote of no confidence for the current criteria.

Treatment

Unfortunately, no clinical trials of licensed MS DMTs have shown an impact on the course of PPMS; both interferon beta[21,22] and glatiramer acetate[23] trials have been negative. Recently, however, during the five-year period without treatment after termination of the two-year clinical trial of interferon beta-1b for the treatment of PPMS,[22] the interferon beta-1b group had better 9-hole-peg-test, word list generation test scores and magnetisation transfer ratios in the normal-appearing white matter than subjects treated with placebo.[24] The placebo group also showed a greater decrease in brain volume over the seven years of observation than the actively treated subjects.[24] These observations led the investigators to suggest that immunomodulation should not be abandoned as a possible treatment for PPMS and augurs well for two large phase 3 studies of fingolimod[19] and ocrelizumab (anti-CD20)[20] in PPMS. Fingolimod is an oral, small molecule, sphingosine phosphate-1 (SP1) receptor modulator that traps lymphocytes in lymph nodes and may have direct neuroprotective effects with the CNS. Fingolimod has recently been licensed for the treatment of RRMS[25]. Rituximab is a chimeric monoclonal antibody and ocrelizumab a humanised monoclonal antibody, that both deplete B-cells by targeting CD20 on the surface of B cells. The ocrelizumab (anti-CD20) PPMS study[20] is a follow-on of the phase 2 rituximab in PPMS study[26]; this was a 96 week study that randomised 439 PPMSers, in a 2:1 ratio, to receive either two 1,000 mg intravenous doses of rituximab or placebo infusions every 24 weeks. Although there were no differences in time to confirmed disability progression on the EDSS between rituximab and placebo, a subgroup analysis showed that the time to confirmed disability progression was delayed in rituximab-treated PPMSers less than 51 years of age, in those with Gd-enhancing lesions on MRI and in those aged less than 51 years with

Gd-enhancing lesions compared with placebo.

PPMSers are subject to a similar array of symptoms that relapse-onset MSers suffer from. However, PPMSers are particularly prone to spinal cord disease, typically progressive spastic paraparesis with increasing walking difficulties due to weakness and spasticity, sphincter involvement and myelopathic pain. There are recent developments regarding symptomatic treatments you should be aware of including the licensing of an oromucosal mouth spray containing a fixed ratio of the cannabinoids, tetrahydrocannabinol and cannabidiol, for treating MS-related spasticity[27] and fampridine, a slow-release formulation of 4-aminopyridine, to improve walking speed in MSers.[28] Both these drugs have yet to be reviewed by NICE, therefore their availability for PPMSers under the NHS is limited at present.

Conclusion

Although PPMS is relatively uncommon it remains a significant clinical problem both diagnostically and therapeutically. PPMS is almost certainly part of the MS spectrum and there is no clinicopathological evidence to support PPMS as being a separate disease. Unfortunately, there are no licensed DMTs that have been shown to modify the course of PPMS. Despite this there is some emerging evidence that PPMS may respond to immunomodulatory therapies. Two large phase 3 trials are currently underway to test this hypothesis. ◆

References

1. Ramagopalan SV, Dobson R, Meier UC, Giovannoni G. *Multiple sclerosis: risk factors, prodromes, and potential causal pathways.* The Lancet Neurology [Internet] 2010;9(7):727–39. Available from: http://dx.doi.org/10.1016/S1474-4422(10)70094-6

2. Lublin FD, Reingold SC. *Defining the clinical course of multiple sclerosis: results of an international survey.* National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Neurology [Internet] 1996;46(4):907–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8780061

3. Weinshenker BG, Bass B, Rice GP, et al. *The Natural History of Multiple Sclerosis: a Geographically Based Study.* Brain [Internet] 1989;112(1):133–46. Available from: http://brain.oxfordjournals.org/cgi/doi/10.1093/brain/112.1.133

4. Scalfari A, Neuhaus A, Degenhardt A, et al. *A geographically based study 10: relapses and long-term disability.* 2010;1914–29.

5. Cottrell D, Kremenchutzky M, Rice GP, et al. *The natural history of multiple sclerosis: a geographically based study. 5. The clinical features and natural history of primary progressive multiple sclerosis.* Brain : a journal of neurology [Internet] 1999;122 (Pt 4:625–39. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10219776

6. Stevenson VL, Miller DH, Rovaris M, et al. *Primary and transitional progressive MS: a clinical and MRI cross-sectional study.* Neurology [Internet] 1999 [cited 2012 Jun 5];52(4):839–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10078736

7. Hawker K, O'Connor P, Freedman MS, et al. *Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial.* Annals of neurology [Internet] 2009 [cited 2012 Mar 13];66(4):460–71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19847908

8. Seze JD, Devos D, Castelnovo G, Labauge P, Dubucquoi S. *The prevalence of Sjögren syndrome in patients with primary progressive.* 2001;1359–63.

9. Giovannoni G, Thorpe J. *Is it multiple sclerosis or not?* Neurology [Internet] 2001;57(8):1357–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11673570

10. Martinelli-Boneschi F, Esposito F, Brambilla P, et al. *A genome-wide association study in progressive multiple sclerosis.* Multiple sclerosis (Houndmills, Basingstoke, England) [Internet] 2012 [cited 2012 Mar 30];Available from: http://www.ncbi.nlm.nih.gov/pubmed/22457343

11. Chataway J. *Multiple sclerosis in sibling pairs: an analysis of 250 families.* Journal of Neurology, Neurosurgery & Psychiatry [Internet] 2001 [cited 2012 May 2];71(6):757–61. Available from: http://jnnp.bmj.com/cgi/doi/10.1136/jnnp.71.6.757

12. Lucchinetti C, Brück W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H. *Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination.* Annals of neurology [Internet] 2000;47(6):707–17. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10852536

13. Revesz T, Kidd D, Thompson a J, Barnard RO, McDonald WI. *A comparison of the pathology of primary and secondary progressive multiple sclerosis.* Brain: a journal of neurology [Internet] 1994;117 Pt 4:759–65. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7922463

14. Giovannoni G. *The Yin and Yang of Inflammation in Multiple Sclerosis.* In: Hommes OR, editor. Early Indicators Early Treatments Neuroprotection in Multiple Sclerosis. Milan: Springer Milan; 2004. p. 181–9.

15. Koch-Henriksen N, Sorensen PS. *Why does the north-south gradient of incidence of multiple sclerosis seem to have disappeared on the northern hemisphere?* Journal of the neurological sciences [Internet] 2011 [cited 2012 Jun 5];311(1-2):58–63. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21982346

16. Gafson A, Giovannoni G, Hawkes CH. *The diagnostic criteria for multiple sclerosis: From Charcot to McDonald.* Multiple Sclerosis and Related Disorders [Internet] 2012 [cited 2012 May 2];1(1):9–14. Available from: http://linkinghub.elsevier.com/retrieve/pii/S2211034811000058

17. McDonald WI, Compston a, Edan G, et al. *Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis.* Annals of neurology [Internet] 2001;50(1):121–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11456302

18. Wolinsky JS. *The diagnosis of primary progressive multiple sclerosis.* Journal of the neurological sciences [Internet] 2003;206(2):145–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18431323

19. Novartis. *FTY720 in Patients With Primary Progressive Multiple Sclerosis* - Full Text View - ClinicalTrials [Internet]. 2008;:NCT00731692. Available from: http://clinicaltrials.gov/ct2/show/NCT00731692?term=NCT00731692&rank=1

20. Roche H-L. *A Study of Ocrelizumab in Patients With Primary Progressive Multiple Sclerosis* - Full Text View - ClinicalTrials [Internet]. 2010; Available from: http://clinicaltrials.gov/ct2/show/NCT01194570?term=NCT01194570&rank=1

21. Leary SM, Miller DH, Stevenson VL, Brex P a, Chard DT, Thompson a J. *Interferon beta-1a in primary progressive MS: an exploratory, randomized, controlled trial.* Neurology [Internet] 2003;60(1):44–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12525716

22. Montalban X, Sastre-Garriga J, Tintoré M, et al. *A single-center, randomized, double-blind, placebo-controlled study of interferon beta-1b on primary progressive and transitional multiple sclerosis.* Multiple sclerosis (Houndmills, Basingstoke, England) [Internet] 2009 [cited 2012 Jun 5];15(10):1195–205. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19797261

23. Wolinsky JS, Narayana P a, O'Connor P, et al. *Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial.* Annals of neurology [Internet] 2007 [cited 2012 Apr 1];61(1):14–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17262850

24. Tur C, Montalban X, Tintoré M, et al. *Interferon β-1b for the treatment of primary progressive multiple sclerosis: five-year clinical trial follow-up.* Archives of neurology [Internet] 2011 [cited 2012 Jun 5];68(11):1421–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22084124

25. Kappos L, Antel J, Comi G, et al. *Oral fingolimod (FTY720) for relapsing multiple sclerosis.* The New England journal of medicine [Internet] 2006;355(11):1124–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21727148

26. Hawker K, Connor PO, Freedman MS, et al. *Rituximab in Patients with Primary Progressive Multiple Sclerosis.* Results of a Randomized Double-Blind Placebo-Controlled. 2009;460–71.

27. Lakhan SE, Rowland M. *Whole plant cannabis extracts in the treatment of spasticity in multiple sclerosis: a systematic review.* BMC neurology [Internet] 2009 [cited 2012 Mar 23];9:59. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2793241&tool=pmcentrez&rendertype=abstract

28. Goodman AD, Brown TR, Krupp LB, et al. *Sustained-release oral fampridine in multiple sclerosis : a randomised , double-blind , controlled trial.* The Lancet [Internet] 2009;373(9665):732–8. Available from: http://dx.doi.org/10.1016/S0140-6736(09)60442-6

29. Polman CH, Reingold SC, Banwell B, et al. *Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria.* Annals of neurology [Internet] 2011 [cited 2012 Feb 29];69(2):292–302. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3084507&tool=pmcentrez&rendertype=abstract

Neural Control and Clinical Disorders of Supranuclear Eye Movements

Janet C Rucker MD

is an Associate Professor in the Departments of Neurology and Ophthalmology at the Mount Sinai School of Medicine in New York. Dr Rucker's area of clinical practice, research, and academic teaching is Neuro-Ophthalmology. Dr Rucker's primary research interest is utilisation of eye movements for the advancement of the understanding of brain neural connections and facilitation of clinical diagnosis.

Correspondence to:
Associate Professor,
Departments of Neurology and
Ophthalmology,
The Mount Sinai Medical Center,
One Gustave L Levy Place Box
1052, New York,
New York 10128, USA.
Email: janet.rucker@mssm.edu
Tel: +1 (646) 537-9217.

Extensive knowledge exists about anatomic and pathophysiologic mechanisms governing eye movements.[1] The shared goal of all eye movements is stable, clear vision via placement of an object of visual interest on the fovea, the retinal region with the best visual acuity. Several types of eye movements exist to achieve this shared goal, including smooth pursuit, vergence, vestibulo-ocular reflexes, optokinetic nystagmus, and saccades. Separate anatomic supranuclear neural networks exist for each eye movement type and converge upon a 'final common pathway' that includes the motoneuron originating in cranial nerve nuclei, the neuromuscular junction, and the extraocular muscle. Systematic exam of each type of eye movement, including range and dynamic aspects of motion, is essential for accurate localisation of supranuclear eye movement abnormalities.

Eye movement types and brainstem anatomy

Smooth pursuit maintains the image of a small, slowly moving target on the fovea. Vergence is a disconjugate eye movement by which a single foveal image is maintained with gaze shifts from near to far (divergence) or from far to near (convergence). Vestibulo-ocular reflexes generate compensatory eye movements during brief head movements that are essential for seeing clearly while walking or when the head is in motion. Optokinetic responses (OKN) are reflexive and generated by movement of a large visual scene and during sustained head rotation. OKN consists of slow eye movements in the direction of a moving stimulus, followed by quick movements to reset the eyes in the opposite direction.

Saccades are conjugate, extremely rapid eye movements with which we shift gaze and explore the visual world. Several factors, including sufficient force to overcome the elastic inertia of the extraocular orbital tissues, high saccadic velocity, and the need for a high degree of accuracy to place the small fovea on target, make saccades a demanding task for the brain.[2] These demands result in the requirement of a high-frequency neural discharge from brainstem excitatory burst neurons (EBN) to stimulate the motoneuron to generate a saccade of a specific size and in a specific direction.

EBN for horizontal saccades are located in the paramedian pontine reticular formation (PPRF) in the pons rostral to the abducens nucleus and, for vertical and torsional saccades, in the rostral interstitial medial longtitudinal fasciculus (riMLF) rostral to the oculomotor nucleus (Figure 1).[3,4] A few EBN for vertical saccades lie in the interstitial nucleus of Cajal (INC) (Figure 1). For horizontal saccades, EBN project to ipsilateral motoneurons to generate an ipsilateral saccade (for a rightward saccade, the premotor signal originates in the right PPRF EBN and projects to the right abducens nucleus).[5] For vertical saccades, single EBN project to yoked muscle pairs (for example, superior rectus and inferior oblique for upward saccades and inferior rectus and superior oblique for downward saccades).[6] Vertical EBN project to motoneurons for the elevator muscles bilaterally, but unilaterally to depressor muscles.[6,7]

Figure 1. Sagittal monkey brainstem diagram showing ocular motor-related nuclei. The shaded region in the pons represents the paramedian pontine reticular formation (PPRF), containing excitatory burst neurons (EBN) for horizontal saccades (black oval in lower PPRF). The asterisk just caudal to the CN VI rootlets represents the location of the omnipause neurons in the raphe interpositus. Abbreviations: PC = posterior commisure; riMLF = rostral interstitial medial longitudinal fasciculus; INC = interstitial nucleus of Cajal; CN III = oculomotor nerve fascicle; III = oculomotor nucleus; IV = trochlear nucleus; MLF = medial longitudinal fasciculus; VI = abducens nucleus; CN VI = abducens nerve rootlets; NRTP = nucleus reticularis tegmenti pontis. Courtesy of Jean Büttner-Ennever.
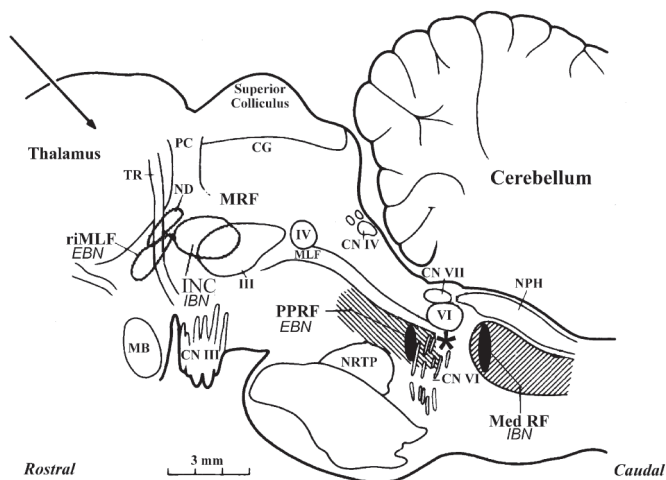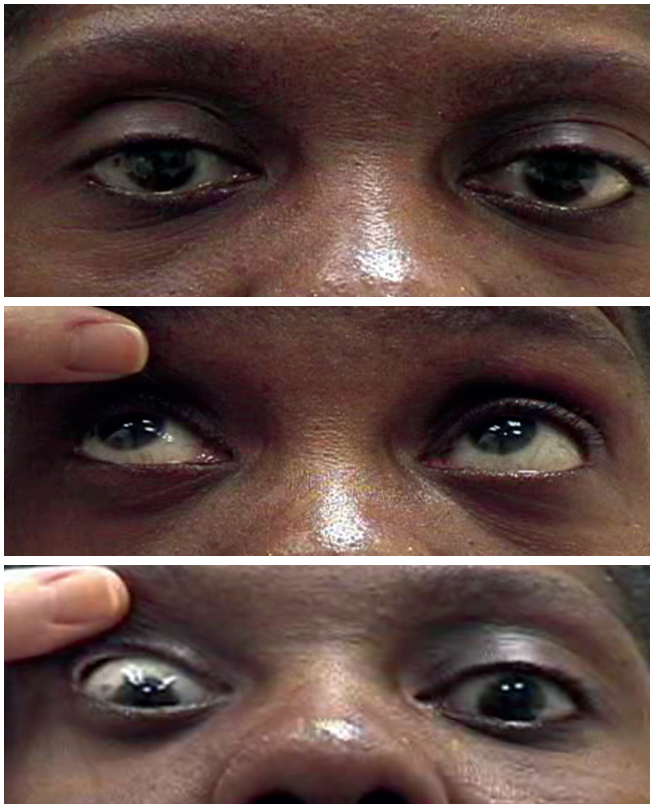
Figure 2. A downgaze supranuclear gaze palsy. A. The maximum extent of downward movement of the eyes with following of a smoothly moving target (smooth pursuit) is to the horizontal midline. B. Downward saccades are completely eliminated. This picture shows the eyes "stuck" in upgaze following an upward saccade. C. Vestibulo-ocular reflexes overcome the downgaze palsy.

Inhibition of EBN, required at all times other than during a saccade, is mediated by tonically discharging omnipause neurons (OPN) in the nucleus raphe interpositus (RIP) in the PPRF (Figure 1).[8] OPN firing ceases just before EBN firing and resumes at saccade end, however it is unclear if the OPN or the cerebellar caudal fastigial nucleus terminates the saccade.[9-11]

Clinical supranuclear and internuclear disorders

Supranuclear eye movement abnormalities may result from dysfunction of cerebral, cerebellar, and brainstem connections to the ocular motor nuclei. The focus here is on brainstem supranuclear disorders (Table). Clinical hallmarks of a brainstem supranuclear gaze palsy include disproportionate impairment in the range or velocity of saccades and impairment of OKN, with VOR retention (Figure 2). Smooth pursuit may be affected, but usually to a lesser extent than saccades. In contrast, nuclear and infranuclear (cranial nerve, neuromuscular junction, and extraocular muscle) lesions tend to affect all eye movement types equally.

Many vertical brainstem supranuclear gaze palsies affect the range of each eye movement symmetrically. As a result, visual symptoms may be minimised by the symmetry of the process. Supranuclear gaze palsies may be incidentally noted and diagnostically helpful in a visually asymptomatic patient with multifocal neurological disease. On the other hand, vague visual complaints such as visual blurring may occur, but are non-localising. Binocular diplopia will occur only when the two eyes are affected differently, causing an ocular misalignment. Diplopia may also be more common when the deficits have an acute catastrophic onset, such as with brainstem stroke.

The eye movement abnormalities discussed may be caused by any lesion affecting the structure specified. The eye movements themselves are exquisitely localising, but not indicative of underlying etiology. In the acute setting, brainstem ischaemia, hemorrhage, and demyelination are the most common causes. In the chronic setting, neurodegenerative and metabolic disease are most common. The eye movement disorders discussed may occur in isolation or in combination with other neurological findings, such as hemiparesis, ataxia, or extrapyramidal signs. When in isolation, it is possible for the lesion to be radiographically occult on MRI.

Vertical gaze palsies

Lesions of EBN in the riMLF result in slowing of vertical saccades and/or limitation in the range of vertical saccades. Vertical OKN may be absent or only slow phases generated, with no resetting fast phases. Smooth pursuit may be affected, but usually to a lesser extent than saccades. If limitation in the range of vertical eye movement is present, passive vertical VOR should overcome the limitation, as the patient fixates on a target while the examiner moves the head vertically (Figure 2). Because vertical EBN projecting to motoneurons for the elevator muscles project bilaterally and to motoneurons for depressor muscles unilaterally, unilateral riMLF lesions may preferentially impair downward saccades. Bilateral riMLF lesions may abolish all vertical saccades. Individual case reports in humans do not always match these anatomic expectations, but it is probable that the lesions extend beyond the riMLF to other structures involved in vertical eye movement control.

An acute onset vertical gaze palsy is most often due to midbrain infarction. If in isolation, the infarct is typically due to microvascular ischaemia in the territory of the thalamic-subthalamic paramedian artery, which originates from the posterior cerebral artery. Bilateral riMLF lesions may occur from a single vessel occlusion because a single thalamic-subthalamic paramedian artery, the artery of Percheron, supplies both riMLF in 20% of patients.[12] An acute onset vertical supranuclear gaze palsy in combination with other neurological symptoms such as somnolence, delirium, homonymous hemianopia, and cortical blindness may represent a 'top of the basilar' stroke with riMLF, thalamic, occipital lobe, and temporal lobe involvement. An acute onset supranuclear upgaze palsy in combination with eyelid retraction (Collier's sign), convergence-retraction nystagmus, and pupillary light-near dissociation is the dorsal midbrain syndrome (also called Parinaud's syndrome). The riMLF is not the location of the lesion, but rather the upgaze paresis is

Table. Localisation of supranuclear, nuclear, and internuclear saccadic gaze disorders.

LESION / SYNDROME	GAZE DISORDER	AETIOLOGIC EXAMPLES
riMLF* – midbrain	Supranuclear vertical gaze palsy	Acute – stroke Chronic – progressive supranuclear palsy
Dorsal midbrain syndrome	Supranuclear upgaze paresis, convergence-retraction nystagmus	Stroke, hydrocephalus, pineal pathology
PPRF**	If unilateral – ipsilateral supranuclear horizontal gaze palsy If bilateral – bilateral supranuclear horizontal gaze palsy	Acute – stroke, demyelination, Wernicke's encephalopathy Chronic – Spinocerebellar ataxia type 2
Abducens nucleus	Ipsilateral horizontal gaze palsy with saccades, pursuit, vestibulo-ocular reflexes affected	Stroke, Wernicke's encephalopathy
MLF***	Internuclear ophthalmoplegia	Demyelination, stroke
PPRF or abducens nucleus and MLF	One-and-a-half syndrome	Stroke
* riMLF – rostral interstitial medial longitudinal fasciculus ** PPRF – paramedian pontine reticular formation ***MLF - medial longitudinal fasciculus		

Figure 3. One-and-a-half-syndrome. A. The resting position of the eyes. B. Attempts to elicit rightward eye movements reveal a complete right horizontal gaze palsy from involvement of the right paramedian pontine reticular formation or abducens nucleus. C. Upon left gaze, there is impaired adduction of the right eye with intact abduction of the left eye from a right internuclear ophthalmoplegia.

due to projecting fibres from the vertical supranuclear control centres to the rostral dorsal midbrain. It is most commonly due to infarct, hydrocephalus, or pineal pathology, given the proximity of the pineal gland to the rostral dorsal midbrain. Wernicke's encephalopathy (WE), due to thiamine deficiency, consists of the classic triad of ophthalmoplegia, confusion, and ataxia. Characteristic MRI findings in acute WE are T2 hyperintensity in the periacqueductal gray and diencephalic periacqueductal regions. WE is more likely to cause prominent horizontal gaze paresis than vertical gaze paresis.

The most common chronic brainstem supranuclear vertical gaze palsy is the neurodegenerative condition progressive supranuclear palsy. The gaze palsy may be one of elevation, depression, or both. Accompanying features are parkinsonism with excessive early falls, a frontal lobe syndrome, axial rigidity, and dysphagia. A characteristic additional eye movement finding is excessive square wave jerks (small involuntary saccades that intrude upon fixation, taking the eye quickly away from centre followed after a brief interval by a small saccade that returns the eye to central fixation). Whipple's disease, due to Tropheryma whippelii infection, may cause a syndrome that mimics PSP with a vertical supranuclear gaze palsy and parkinsonism. The pathognomonic eye movement abnormality in Whipple's disease is oculomasticatory myorrhythmia (OMM), although it may not always be present. OMM consists of acquired pendular nystagmus (e.g. there are no nystagmus quick phases, only oscillating slow phases) with a convergent-divergent trajectory with accompanying rhythmic movements of masticatory structures. The metabolic disorder Niemann-Pick Type C characteristically causes vertical brainstem supranuclear gaze palsy, in addition to dystonia, dementia, seizures, ataxia, and hepatosplenomegaly.

Horizontal gaze palsies

Lesions of EBN in the PPRF result in slowing of horizontal saccades and/or limitation in the range of horizontal saccades in the direction ipsilateral to the lesion. For example, a right PPRF lesion affecting EBN will result in slowing and/or range limitation of rightward saccades. Horizontal OKN may be absent or only the slow phases generated, with no resetting fast

phases. Smooth pursuit may be affected, but usually to a lesser extent than saccades. If limitation in the range of horizontal eye movement is present, passive horizontal VOR should overcome the limitation as the patient fixates on a target while the examiner moves the head horizontally. Bilateral PPRF lesions affecting bilateral EBN will result in a complete absence of all horizontal saccades and slowing of vertical saccades.[13]

Although not supranuclear gaze disorders, a discussion of supranuclear EBN PPRF is not complete without mention of abducens nuclear lesions and internuclear ophthalmoplegia (INO). Paired abducens nuclei lie in the floor of the fourth ventricle in the dorsal pons. Each nucleus is comprised of two intermixed neuronal populations: abducens motoneurons that project to the ipsilateral lateral rectus via the abducens nerve and interneurons that decussate in the pons and project to the contralateral medial rectus oculomotor subnucleus via the medial longitudinal fasciculus (MLF) (Figure 1). An abducens nuclear lesion will result in an ipsilateral horizontal gaze palsy, however saccades, smooth pursuit, and vestibulo-ocular reflexes will all be affected with the nuclear lesion. Abducens nuclear lesions are often accompanied by ipsilateral facial weakness, since the facial nerve fascicle wraps around the abducens nucleus. A lesion of the MLF in the pons or in the midbrain will result in an INO. The lesion most often occurs in the fibres projecting to the medial rectus subnucleus after their pontine decussation. The hallmark features of INO are impaired adduction in the eye ipsilateral to the MLF lesion and abducting nystagmus in the contralateral eye. When an INO occurs in combination with a PPRF EBN or abducens nuclear lesion, the one-and-a-half syndrome results. As an example, a right PPRF EBN or abducens nuclear lesion also affecting the MLF that originated on the left and decussated already will cause a right horizontal gaze palsy (limited abduction of the right eye and adduction of the left eye) and a right INO (limited adduction of the right eye with abducting nystagmus of the left eye) (Figure 3).

An acute onset horizontal gaze palsy or one-and-a-half syndrome is most often due to pontine ischaemic or hemorrhagic stroke, although haemorrhage into a vascular lesion or demyelination may also be causes. In addition to the impairment of saccades in the ipsilateral direction, gaze may be acutely deviated contralaterally past the midline. INO is most often demyelinating, but may occur acutely due to stroke. Horizontal gaze deficits in combination with nystagmus (upbeating or gaze-evoked most often) are the hallmark eye findings of Wernicke's encephalopathy. The finding of slow horizontal saccades in chronic progressive ataxia may suggest spinocerebellar ataxia type 2. ◆

REFERENCES

1. Leigh RJ, Zee DS. *The Neurology of Eye Movements.* 4 ed. New York: Oxford University Press; 2006.
2. Horn AK, Buttner-Ennever JA, Suzuki Y, Henn V. *Histological identification of premotor neurons for horizontal saccades in monkey and man by parvalbumin immunostaining.* J Comp Neurol 1995;359:350-63.
3. Buttner-Enever JA, Buttner U, Cohen B, Baumgartner G. *Vertical glaze paralysis and the rostral interstitial nucleus of the medial longitudinal fasciculus.* Brain 1982;105:125-49.
4. Horn AK, Buttner-Enever JA. *Premotor neurons for vertical eye movements in the rostral mesencephalon of monkey and human: histologic identification by parvalbumin immunostaining.* J Comp Neurol 1998;392:413-27.
5. Strassman A, Highstein SM, McCrea RA. *Anatomy and physiology of saccadic burst neurons in the alert squirrel monkey. I. Excitatory burst neurons.* J Comp Neurol 1986;249:337-57.
6. Moschovakis AK, Scudder CA, Highstein SM. *A structural basis for Hering's law: projections to extraocular motoneurons.* Science 1990;248:1118-9.
7. Bhidayasiri R, Plant GT, Leigh RJ. *A hypothetical scheme for the brainstem control of vertical gaze.* Neurology 2000;54:1985-93.
8. Buttner-Enever JA, Cohen B, Pause M, Fries W. *Raphe nucleus of the pons containing omnipause neurons of the oculomotor system in the monkey, and its homologue in man.* J Comp Neurol 1988;267:307-21.
9. Kaneko CR. *Effect of ibotenic acid lesions of the omnipause neurons on saccadic eye movements in rhesus macaques.* J Neurophysiol 1996;75:2229-42.
10. Optican LM, Quaia C. *Distributed model of collicular and cerebellar function during saccades.* Annals of the New York Academy of Sciences 2002;956:164-77.
11. Rucker JC, Ying SH, Moore W, et al. *Do brainstem omnipause neurons terminate saccades?* Annals of the New York Academy of Sciences 2011;1233:48-57.
12. Percheron G. *The anatomy of the arterial supply of the human thalamus and its use for the interpretation of the thalamic vascular pathology.* Z Neurol 1973;205:1-13.
13. Hanson MR, Hamid MA, Tomsak RL, Chou SS, Leigh RJ. *Selective saccadic palsy caused by pontine lesions: clinical, physiological, and pathological correlations.* Ann Neurol 1986;20:209-17.

Series Editor

Alan Carson

Series editor Alan Carson is a Consultant Neuropsychiatrist and Part-time Senior Lecturer. He works between the Neurorehabiltation Units of the Astley Ainslie Hospital and the Department of Clinical Neurosciences at the Western General Hospital in Edinburgh. He has widespread interests in neuropsychiatry including brain injury, HIV and stroke. He has long-standing research and teaching collaboration with Jon Stone on functional symptoms in neurology.

Series Editor

Jon Stone

Series editor Jon Stone is a Consultant Neurologist and Honorary Senior Lecturer in the Department of Clinical Neurosciences in Edinburgh. Since 1999 he has developed a research and clinical interest in functional symptoms within neurology, especially the symptom of weakness. He writes regularly on this topic in scientific papers and for textbooks of neurology and psychiatry.

Correspondence to: Email: Jon.Stone@ed.ac.uk

W elcome to the twelfth in a series of articles in *ACNR* exploring clinical dilemmas in neuropsychiatry. In this series of articles we have asked neurologists and psychiatrists working at the interface of those two specialties to write short pieces in response to everyday case-based clinical dilemmas. We have asked the authors to use evidence but were also interested in their own personal views on topics. We would welcome feedback on these articles, particularly from readers with an alternative viewpoint.

Richard AA Kanaan

is a Consultant Psychiatrist at the Maudsley Hospital, Honorary Consultant Neuropsychiatrist at King's College Hospital and Visiting Senior Lecturer at the Institute of Psychiatry. His special interests include conversion disorder and factitious disorder.

Correspondence to:
Richard AA Kanaan,
Consultant Psychiatrist,
Dept of Psychological
Medicine,
Institute of Psychiatry,
King's College London,
P062, Weston Education
Centre,
London SE5 9RJ, UK.
Tel: +44 (0)20 7848 0158
Fax: +44 (0)20 7848 5408
Email: richard.kanaan@kcl.ac.uk

Functional or Feigned: a neurological dilemma

Case

A 23-year-old girl with a paraplegia of two years duration has been referred for a second opinion as to whether her symptoms are functional. After appropriate examination and investigation you concur that no organic explanation is possible. You find her remarkably well adjusted to her condition – indeed she tells you she hopes to represent her country in the Paralympic games. However, while she is awaiting transport you happen to notice her uncrossing and re-crossing her legs without using her hands, and become concerned that she may be feigning her symptoms. What should you do?

T he relationship between conversion disorder and feigning is not an easy one for many clinicians. Most neurologists do not see the two as entirely distinct[1] and would rather not get involved in the uncomfortable business of distinguishing them.[2] While the limited data we have suggest feigned neurological presentations are relatively rare, it may be difficult to be certain in the clinical setting, and feigning is probably under-diagnosed.[3] When faced with neurological symptoms that do not appear neuropathological in origin it is appropriate to presume these represent a conversion disorder rather than feigning, but sometimes, as in the case presented, your suspicions may be raised. This is an alarming scenario, questioning the clinician's responsibility to the patient and more widely, and threatening a serious conflict with the patient. I shall consider these challenges under three questions: How would I know if a patient with functional symptoms is feigning? What does it mean if they are? And, what should I do about it?

How would I know if a patient with functional symptoms is feigning?

The detection of feigned or induced illness is rarely easy. In general medicine, most cases are detected because the methods they have used to feign or induce their illness leave an evidence trail (the culturing of faecal bacteria from a wound that will not heal,), or their methods are observed (putting their thermometer in their cup of tea).[4] Unfortunately, there are few such exogenous tools needed to feign most neurological illness – all the patient needs is a flair for the theatrical – and consequently the means of its detection is limited, typically to confession or the exposure of some other aspect of their deception, such as a false identity.[3] Of course, a patient who feigns weakness is unlikely to convince most neurologists that they have any serious organic pathology for very long – the history and examination alone will probably show a pattern inconsistent with known disease. But this very same inconsistency is characteristic of conversion disorder. How could you possibly tell *those* two apart?

The short answer is you probably can't – at least not without the sort of help you are unlikely to get in the clinic. The difference between a conversion disorder and feigning lies primarily in the conscious awareness or intentionality with which the symptoms are produced by the patient. So, to tell them apart would require finding out what the patient thinks, when they are presumably (if feigning) determined to hide it: whether, if you like, they are lying when they say they can't move their leg. And that kind of detection has proven beyond all tested professions, whether military, judicial or clinical.[5] Of course, there can be many clues that someone is lying, and sometimes their behaviour can be taken as proof of what they know. In the medico-legal setting, for example, it is common for private detectives to be hired when a feigned disability is suspected, hoping to catch the patient in an act of exertion incompatible with their avowed limitations.

But caution must be exercised in conversion disorder, since a degree of inconsistency is, again, char-

acteristic, a key diagnostic feature[1,6] and quite uninformative about intentionality: the patient who stands unaided having previously shown zero power at hip extension is very likely to be surprised if you point out the incompatibility, but most unlikely to collapse and admit they were feigning. To be confident it is feigned, an inconsistency would have to be so obvious that the patient really couldn't have it without knowing it, such as playing football while claiming paraparesis. Similarly, other clues to a feigned illness – an obvious benefit or gain to their being ill, a *belle indifference* to their symptoms, a resistance to investigation, a history that is vague – have also been claimed to a degree for conversion disorder.

So, unless you follow the patient home, recognise them from their previous malingering or elicit a confession, you are unlikely to be certain; but you may well, as in this case, have grounds for suspicion: she does seem unconcerned, she is obviously benefitting, and it would be hard not to realise you're voluntarily moving your legs when you claim they are paralysed. But is even a strong suspicion enough? We shall return to the question of the standard of proof when we consider what to do about it.

What does it mean if they are feigning?
There are several forms that medical deception can take. The most familiar is malingering – feigning for disability benefits or litigation, to evade conscription or prison. Others feign illness for what are thought to be pathological reasons, however – to get the sympathy and care of the sick role – in what is called factitious disorder (of which Munchausen's Syndrome may be considered a chronic subtype). The difference between the two lies only in whether the motives for the deception are 'internal' (such as sympathy) or 'external' (such as money) but, importantly, factitious disorder is considered a psychiatric condition whereas malingering is not considered a medical condition at all, merely criminal behaviour. This makes the distinction of vital, legal importance – which may seem unfair, given the vague nature of the distinction.[7] Consider our case: does being a paralympian represent an external benefit (fame and success) or an internal one (sympathy and admiration)?[8]

Deception may mean neither of these things however. It is important to remember that everyone lies at some time or another, and patients are no exception.[9] The medical encounter is enormously important for most patients, and they are likely to be strongly motivated to present their case in the most convincing way possible, even if that requires exaggerating or lying to a clinician whom they feel does not take them sufficiently seriously.[10] A single act of deception does not mean the whole performance is a sham. Equally, many clinicians have wondered whether the conscious/subconscious boundary for conversion disorder is entirely fixed: whether a patient with a subconscious paralysis may not gain conscious control yet stick with the presentation as it has proven useful or face-saving; or a

patient with a feigned paralysis come to believe in it and its maintenance then become automatic. Again, a single moment of conscious awareness does not necessarily mean it was always so. For these reasons, among others, the distinction is thought by some to matter less clinically than it undeniably does legally or to the patient or their family.[7]

But are they, if considered feigning, even your patient any longer? If a malingerer does not have an illness, are they even a patient, or just someone pretending to be a patient?[11] There are at least two issues here: there is the fraud that may have been practised on you, and the question of their medical care. With regards to the fraud, you may well feel very aggrieved; with regards to their medical care, you may well feel it is no longer your responsibility.[1] In either case you are likely to wish to be rid of the patient, and to warn others off; but caution is needed here, more than anywhere.

What should I do if they are feigning?
There are real dangers in the management of medical deception. The patient has tried to trick you, and your desired response may be to punish them and save the world from them. But it is not a fair fight. You, unlike the patient, have a duty of care; you, unlike the patient, can't break confidentiality.

If the patient has behaved so badly you cannot contemplate treating them further, you may wish to have nothing further to do with them. But your responsibilities as a doctor do not end simply because the patient is not honouring their side of the medical contract. They remain a patient of yours as long as they are under your care – even if (as for many other patients) it turns out there is nothing wrong with them. You may discharge them if you feel your relationship has been irretrievably damaged, of course, but to whom, and how?

With a malingerer it may not seem necessary for anyone to take over their care, and to discharge back to the GP; for a factitious disorder it may be appropriate for a psychiatrist to be involved. But any letter you write will come up against the barrier of confidentiality: you cannot tell anyone anything the patient does not want you to say without their consent (unless there is the risk of serious harm to someone else, or they lack capacity to consent). With other health professionals, such as their GP, there is an implied consent for disclosure, yet in such a situation, where you think it likely the patient will not want something disclosed, the onus would be on you to tell the patient what you are planning to write – at which point it is likely they will withdraw their consent. The contents of the letter will have to be negotiated and agreed with the patient, painful as that may be. Equally, with agencies such as the benefits agency (or the Paralympics Committee): you are obliged to tell the truth if asked, but you cannot make spontaneous disclosure and cannot disclose anything to which the patient does not consent.

There is no such restriction on your medical notes – indeed it is paramount that you keep a

full and contemporaneous record, as the chance that this will be drawn upon is considerable. A second opinion is a very good idea, for the same reason: there is strength in numbers if your opinion is ever challenged. For the risks you face in reaching such a view are, in addition to a very uncomfortable patient encounter, being sued by the patient, and being referred to your medical licensing authority. Here, at least, there is some comfort, for the diagnostic standards to which your behaviour will be held in court are (in the UK at least) those of a responsible body of medical opinion; for the licensing authority (in the UK at least) they are likely to be lower still. If your suspicions are those you think a responsible body of fellow neurologists share with equal strength, then the law is likely to find in your favour should your care be legally challenged; but that may be scant comfort for the other challenges you will have faced along the way.

So, finally, what would I do in this case? Given the risks, doing the right thing will take courage, but here, alas, it's not even clear what the right thing to do is.[2] Though I have given only a bare clinical outline, this accurately reflects the conditions of uncertainty under which we are likely to operate. Simply put, I don't know if this lady is feigning but I think it's a strong possibility; moreover, other than by what may emerge from a discussion of this with her, I see no clear path to deciding it one way or the other. So on balance, if I were feeling sufficiently brave that morning, I would have the discussion. I would tell the patient what I'd seen, and what it could mean. I would tell them that my differential diagnosis included both conversion disorder and feigning, and would wait – with bated breath – for her response… ◆

REFERENCES

1. Kanaan RA, Armstrong D, Wessely SC. *Neurologists' understanding and management of conversion disorder.* Journal of neurology, neurosurgery, and psychiatry. 2011.

2. Kanaan R, Armstrong D, Wessely S. *Limits to truth-telling: neurologists' communication in conversion disorder.* Patient Educ Couns. 2009;77(2):296-301.

3. Kanaan RA, Wessely SC. *Factitious disorders in neurology: an analysis of reported cases.* Psychosomatics. 2010;51(1):47-54.

4. Krahn LE, Li H, O'Connor MK. *Patients who strive to be ill: factitious disorder with physical symptoms.* The American journal of psychiatry. 2003;160(6):1163-8.

5. Aamodt MG, Custer H. *Who can best catch a liar? A meta-analysis of individual differences in detecting deception.* Forensic Examiner. 2006;15(1):6-11.

6. Kanaan R, Armstrong D, Barnes P, Wessely S. *In the psychiatrist's chair: how neurologists understand conversion disorder.* Brain. 2009;132(Pt 10):2889-96.

7. Kanaan RA, Wessely SC. *The origins of factitious disorder.* History of the Human Sciences. 2010;23(2):68-85.

8. Turner MA. *Factitious disorders: reformulating the DSM-IV criteria.* Psychosomatics. 2006;47(1):23-32.

9. Burgoon M, Callister M, Hunsaker FG. *Patients Who Deceive: An Empirical Investigation of Patient-Physician Communication.* Journal of Language and Social Psychology. 1994;13(4):443-68.

10. Kanaan RA. *Hysteria and the Varieties of Deception.* American Journal of Bioethics - Neuroscience. 2010;1(1):55-64.

11. Ford CV, Abernethy V. *Factitious illness: a multidisciplinary consideration of ethical issues.* Gen Hosp Psychiatry. 1981;3(4):329-36.

Paroxysmal non-epileptic seizures in children:
recognition and approach to diagnosis

Dr Tekki S Rao
DCH, DNB(paeds),
MRCPCH

is a Consultant in Paediatrics at Luton and Dunstable University Hospitals. He graduated from Kurnool Medical College, India and was trained further in paediatrics acquiring additional qualifications, DCH from AP University of Health Sciences and DNB (Paediatrics) from National Board of Examinations, New Delhi. He passed MRCPCH in 2002 and obtained specialist training in Paediatrics from Leicester University Hospitals. He has a special interest in Paediatric Epilepsy and Paediatric Neurology. He has honorary attachment with the Paediatric Neurology Department, Addenbrookes Hospital, Cambridge, UK.

Correspondence to:
Department of Paediatrics
Luton and Dunstable University
Hospitals Foundation NHS Trust
Luton, Bedfordshire,
LU4 0DZ, UK.
Email: sreeni.tekki-rao@ldh.nhs.uk
Tel: +44 (0)1582 497203.

Non-epileptic seizures (NES) constitute an important differential diagnosis for epileptic seizures in all age groups. NES should be carefully considered and should be ruled out before making a diagnosis of epilepsy. Confident diagnosis of NES in children is often more challenging than making a positive diagnosis of epilepsy. A significant proportion of children suspected of epilepsy or even those who have been labelled with a definite diagnosis of epilepsy or even refractory epilepsy, have never had an epileptic seizure.[1]

Epidemiology
The prevalence of epilepsy is estimated to be 4-5/1000 children in the European and North American population. Up to 30% of these individuals may have a misdiagnosis. The rate of misdiagnosis in epilepsy in adults is estimated to be 25% in one study.[2] There is no data to provide an estimate of rates of misdiagnosis in children but at an enquiry of a tertiary paediatric neurology service in the UK, the misdiagnosis rate was found to be 32%. A significant proportion of misdiagnoses comprise NES which are mislabelled as epileptic seizures. Syncope is more prevalent than either epilepsy or psychogenic seizures and is common across all age groups. Prevalence of dissociative (psychogenic) seizures in adults is estimated to be between 2 and 33 per 100,000 population.[11] Psychogenic seizures are more prevalent in females (75%) and typically begin in late teens. Common causes of misdiagnosis are; poor history taking, diversity of presentation of epileptic events, no sensitive or specific diagnostic tests available for epilepsy and many imitators that are confused with the diagnosis of epilepsy.

How important is it to get it right?
The cost of misdiagnosing NES as epilepsy falls mainly on the National Health Service in the UK, but also on education, social care and wider society. Beyond economic factors one should also be aware of potentially irreparable damage caused as a result of making the wrong diagnosis. This diagnosis makes an immeasurable negative impact on the psychological wellbeing of the child and family, loss of school days, loss of parent's working days, impact of drugs on an individual's cognition and the long-term impact on career, driving and lifestyle etc.[2] In addition to this, there is a risk of missing another serious diagnosis such as Long QT syndrome (Figure 1) that leads to death from ventricular tachyarrhythmias (torsades de pointes).[3] Therefore, it is the responsibility of the physician to identify and separate NES from true epilepsy right at the beginning. Hence, the National Institute for Health and Clinical Excellence (NICE) recommends that all children and young adults who have been suspected of epilepsy should be seen by an expert in epilepsy.[4]

Diversity of non-epileptic events
There are a wide number of conditions which can mimic epilepsy and these have been extensively described in text books and review articles.[1,5,6,7] These conditions can be grouped by the system that is probably involved (Table 1) and by symptom of presentation (Table 2).
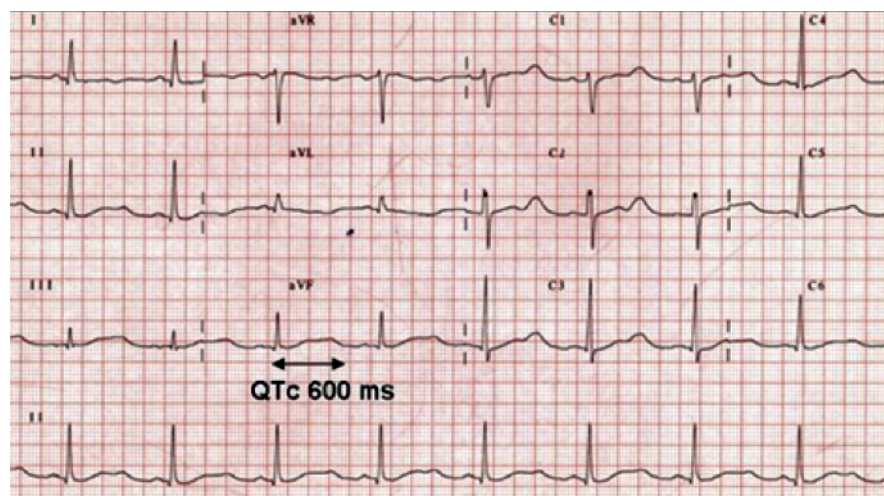

Figure 1: ECG in patient with corrected prolonged QT interval. QTc of more than 0.44sec is significant.

Table 1: Classification of NES based on system

System	Condition
Cardiac	Long QT syndrome Postural Orthostatic Tachycardia Syndrome (POTS) Brugada syndrome Ventricular tachy arrhythmias Heart blocks Congenital heart disease with paroxysmal pulmonary hypertension Reflex anoxic seizures
Vascular	Orthostatic syncope Vaso-vagal syncope
Respiratory	Breath holding attacks Prolonged expiratory apnoeas
Neurological	Tics Hyperekplexia Episodic ataxias Paroxysmal dyskinesias Alternating hemiplegia of children Cataplexy Chiari type 1 malformation Raised intracranial pressure Tetany Encephalitis/Encephalopathies
Psychological	Day dreams Gratification Stereotypies Out of body experience Panic/anxiety Conversion disorder / Psychogenic pseudo seizures (NEAD)
Gastrointestinal	Gastro-oesophageal reflux Sandifer syndrome Vaso-vagal syncope Familial rectal pain syndrome
Sleep related	Arousal disorders Night terrors Nightmares Sleep-wake transition disorders Benign neonatal sleep myoclonus Sleep starts Restless leg syndrome Narcolepsy
Channelopathies	Benign paroxysmal torticollis in infancy (BPTI) Episodic ataxia (EA) types 1 and 2 Familial hemiplegic migraine Benign paroxysmal vertigo of childhood (BPVC) Cyclical vomiting Benign paroxysmal tonic up gaze of childhood Hyper/hypokalemic periodic paralysis Paroxysmal dyskinesia
Unclassifiable or involving more than one system	Vaso-vagal syncope Hyperventilation syncope Benign myoclonus of early infancy (BMEI) Benign infantile spasms Fabricated illness Non-epileptic head drops Functional blinking Jitteriness Shudder Tetany

Challenges in differentiating NES from epilepsies

Every condition in the NES group mimics an epileptic condition. There is no single symptom which is generally linked to the central nervous system that can confidently be excluded as epileptic. Even certain symptoms which are only distantly related to the CNS (isolated vomiting, hiccups, sweating, facial flushing and a feeling of unfamiliarity) could also be manifestations of epilepsy. Particular challenges include;

- Symptoms are often of very short duration and difficult to capture on a video.
- The first account witnesses, who are often very frightened parents, may give a poor description of the event. It is quite challenging even for professionals trained in epilepsy to give a clear description of a paroxysmal event.
- Infants and children younger than four or five years are usually unable to provide a useful subjective description of their own symptoms.

- There is no reliable diagnostic test to differentiate NES from epilepsies. The EEG is a very poorly sensitive and specific test in diagnosing or ruling out epilepsy.
- Paediatricians are often pressurised by carers, school teachers, paramedics and other allied professionals who observe and report seizures.

Syncopes are the most common non-epileptic disorders misdiagnosed as epilepsy.[2] Conversion disorder was seen in children over five years of age, becoming the most common type of paroxysmal non-epileptic event among adolescents.[7] Common conditions that paediatricians encounter regularly in their clinical practice that pose diagnostic challenge are shown in Table 3.

Clues to the diagnosis

Table 4 outlines the key features of more common NES conditions. Features such as incontinence, tongue biting and external injury do not help in distinguishing psychogenic seizures from epilepsy. Seizure duration of more than two minutes, closed eyes, thrashing, pelvic thrust, opisthotonus, fluctuating course and recall for a period of unresponsiveness suggest psychogenic seizures although may also occur with less frequency in epilepsy. Ictal observation gives useful clues to the diagnosis (Table 5).

Visual Symptoms: Aura in migraines can be visual, sensory or motor and may suggest epilepsy. Migrainous aura and epilepsy can be distinguished when the child can describe symptoms or draw pictures of their visual aura. It is good practice in clinic to encourage children to draw what they have visualised. Visual migrainous auras are monochromatic, angulated, bright and scintillating. They start in the centre and spread to the periphery and leave scotomata. The duration of aura may last up to one hour. In contrast, focal onset seizures of occipital lobe have visual manifestations that are described as circular, amorphous, multicoloured and the duration is seconds up to a maximum of two to three minutes. They appear in the periphery of the visual field.

Investigations

Investigations should be individually tailored and carefully selected. Investigations should provide supplementary evidence to support the clinical diagnosis but are rarely diagnostic in themselves. False positive results may bias a diagnosis.

Ictal video: Video recording by parents on their mobile phone or on home video equipment assisted by community nurses or in-patient video telemetry can be an invaluable investigation in clinching the diagnosis of NES. Nowadays, most people have ready access to video technology to enable them to take a short high definition recording. In some conditions such as sleep events a longer duration of recording may be required. In our experience

Table 2: Classification according to symptom of presentation

Apnoeas Gastro-oesophageal reflux Breath holding attacks Reflex anoxic seizures Sandifer syndrome	**Staring or brief unresponsiveness** Day dreams Gratification phenomena	**Abnormal movements** Restless leg syndrome Paroxysmal dyskinesias Tics Chorea Dystonia seen as part of cerebral palsy Benign infantile spasms
Convulsive seizures Reflex anoxic seizure Syncope Long QT syndrome Heart blocks Jitteriness Hyperekplexia Gratification phenomena Sleep wake transition disorders	**Tonic spasms** Hyperekplexia Familial rectal pain syndrome Gratification phenomena Benign paroxysmal torticollis in infancy (BPTI) Raised intracranial pressure Shudders Benign paroxysmal tonic up gaze Breath holding attacks	**Myoclonic jerks** Spinal myoclonus Benign myoclonic epilepsy of infancy (BMEI) Benign neonatal sleep myoclonus Non-epileptic myoclonus Benign non-epileptic infantile spasms
Startle Hyperekplexia Sleep starts	**Psychic states** Out of body experience Schizophrenia Panic attacks	**Prolonged confusion/unresponsiveness** Encephalitis Encephalopathies Drug intoxication Basilar artery migraine
Weakness Hemiplegic migraine Periodic paralysis Alternating hemiplegia of childhood	**Sleep phenomena** Narcolepsy Nightmares Night terrors	**Sensory symptoms** Out of body experience Pseudo seizures Migraines
Prolonged unresponsive states Sleep paralysis Pseudo seizures Encephalitis/ encephalopathy Head injuries Drug intoxication		**Ataxias** Episodic ataxias Benign paroxysmal vertigo of childhood (BPVC)
Varying presentation Conversion disorder or pseudo seizures Fabricated illness Night terrors Nightmares		

Table 3: Common encounters of NES in paediatric clinical practice

NES	Imitating epileptic condition/s
Syncopes	Generalised Tonic Clonic Seizures, Focal seizures, Absences, Drop attacks, Myoclonic Epilepsies
Breath holding attacks	Tonic Spasms
Reflex anoxic seizures	Tonic, tonic clonic seizures and focal clonic seizures
Day dreams/ Childhood Preoccupation	Absence epilepsy
Apnoeas secondary to reflux disease	Infantile spasms, Tonic spasms
Sleep disorders	Frontal lobe seizures, Benign rolandic epilepsy
Benign Sleep myoclonus	Myoclonic Epilepsies, Focal Epilepsies
Migraines	Occipital lobe seizures, temporal lobe seizures
Pseudo seizures	Status epilepticus, tonic, tonic clonic seizures, absences, parietal lobe sensory seizures, Status non-convulsicus

Table 4: Pointers to some of the more common NES

Condition	Features
Day dreams or childhood preoccupation	Duration may be longer than 30 seconds in day dreams unlike absences Responding to external stimulus during staring is likely to be a day dreaming episode
Psychogenic NES	Unduly prolonged seizure with stable hemodynamics. Seizures occur in wakefulness and usually in the presence of witnesses. Consciousness is generally retained or keeps fluctuating. Convulsions are asynchronous, asymmetric, waxing and waning, accelerating or decelerating. Seizures can be interrupted. Individuals respond to suggestions. No postictal confusion. Intractable to anti-epileptic drugs.
Syncopes	There is no single differentiating feature of syncopes that distinguishes this from epilepsy but some features may help. The eyes are always open and may deviate upwards followed later by lateral eye deviation.[8] Visual hallucinations and less often auditory hallucinations are frequent in syncopes. Symptoms occur in reproducible circumstances like hot and humid weather, prolonged fast etc.

Table 5: Features of ictal observation

Feature	Psychogenic seizures	Epilepsy
Response to verbal requests	Yes	No
Rhythm and synchronic movements	No	Yes
Pupil reaction to light	Present	Absent
Eyes	Shut	Open
Attempt to open eyes when shut	Resistance	No resistance
Avoidance of danger	Yes	No
If eyes are open, mirror in front of the face	Abort seizure	Continues

admitting patients for video monitoring of paroxysmal events has been a fruitful approach.[9]

ECG: In children and young adults a 12 lead ECG should be considered in cases of diagnostic uncertainty[4] and should be undertaken in all children with suspected syncopes. More extensive cardiac investigations such as echocardiogram, prolonged ECG recording (up to seven days), cardiac memo and tilt table testing may be indicated in individual cases of NES suspected to be of cardiovascular origin.

EEG: Since the EEG is a poorly sensitive and specific investigation in the diagnosis of epilepsy, it should be used with great caution in NES. EEG should not be performed in cases of probable syncope because of the possibility of false positive results.[4] The National Institute of Clinical Excellence says that an EEG should not be used to exclude the diagnosis of epilepsy in a child, young person or adult in whom clinical presentation supports a diagnosis of non-epileptic event.[4] An approach to positive diagnosis of non-epileptic seizure should not come from ruling out epilepsy by obtaining negative EEG. Ictal EEG with simultaneous video monitoring is an extremely useful investigation in psychogenic seizures. Video telemetry, if available, is more diagnostic in psychogenic seizures. Telemetry facilities are limited in the UK and not available at all secondary and many other tertiary care paediatric neurology services. Ambulatory EEG can be useful if a paroxysmal event can be captured within the time frame.

Neuro-imaging: This is of limited help in establishing a diagnosis but could be indicated in suspected neurological conditions such as Arnold-Chiari malformation, suspected raised intracranial pressure and intracranial space occupying lesions.

Sleep studies: Sleep studies are indicated in obstructive sleep apnoea, narcolepsy and REM/non-REM sleep disorders. These could be supplemented by video recording when nocturnal epilepsies e.g. Autosomal Dominant Nocturnal Frontal Lobe Epilepsies (ADNFLE) can be identified and distinguished from NES.

Genetics: Molecular genetic tests are gaining importance in establishing diagnosis of NES especially channelopathies (Long QT syndrome, BPTI, BPVC, Episodic ataxias, Paroxysmal tonic up gaze and Hemiplegic migraine). Calcium, sodium, potassium channel genes will be supportive in strongly suspected cases.

Other investigations: Other useful investigations are pH or impedance studies in gastro-oesophageal reflux and Sandifer syndrome, blood tests such as calcium, electrolytes, magnesium and blood sugar, when indicated.

Unhelpful investigations: Serum prolactin and creatine kinase are not useful investigations in differentiating epilepsy from psychogenic seizures. NICE Guidelines do not recommend measuring prolactin in the diagnosis of epilepsy.[4]

Approach

Diagnosing NES and differentiating them from epilepsy is almost always based on clinical history. It often requires lengthy discussions and interviews of parents, patients and witnesses.[6] During the consultation it may be necessary for the physician to imitate and demonstrate physically some of the paroxysmal events to get a clearer picture of the condition. Some experienced authors promote the practice of showing video recordings of different epileptic and non-epileptic seizure examples to the parents to discover which, if any, resemble their own child's attacks – the 'that's it' phenomenon.[10]

It is a good clinical practice to encourage parents and carers to obtain video records of these episodes where possible when there is a clinical suspicion of the nature of seizures. This should remain the first line of investigation in confirming the diagnosis. Video recording can be reviewed repeatedly by the physician and a peer review and opinion from experts can be obtained if the diagnosis is still unclear.

ECG should be obtained in all convulsive seizures and in cases where cardiac cause is suspected, referral to cardiologist and cardiovascular investigations should be arranged. All other Investigations (EEG, neuro-imaging, and blood investigations) can only support or refute a clinicians' suspicion and it is advised to use these investigations very judiciously.

Wait and watch policy pays rewards in diagnosis and management of NES. Time and patience is a more valuable investment in making the diagnosis. Time spent in gathering more information from all sources (e.g. School teachers, peer students, paramedics),

obtaining video records, seeking peer review and expert opinion is rewarding and worthy. Haste in making a diagnosis should be avoided because it is often very difficult for everyone concerned to withdraw a diagnosis of epilepsy once the label is given.

Every paroxysmal condition should be analysed with suspicion. When in doubt, even a few years down the line, clinicians should have no hesitation to revisit the diagnosis and seek peer review.

Treatment will depend on the nature of the underlying condition, however recognition of NES and reassurance early in the course of presentation would facilitate more appropriate management. Most of these conditions do not require management with medicines, but some of them would require psychotherapy in particular, psychogenic seizures. Recognition and explanation of diagnosis are important components of management of these conditions.

Conclusion

There are large numbers of neurological, cardiac, psychogenic and other miscellaneous disorders that result in paroxysmal clinical events. Varied but similar presentations akin to epilepsy lead to misdiagnosis. Clinicians should be aware of differentiating features and take a thorough history. Video recording should supplement the history when the clinical picture is not clear and along with the judicious use of investigations. Nevertheless, misdiagnosis is common and may have profound psychological, physiological and socio-economic consequences to the patient, parents and economic burdens to health services. ◆

REFERENCES

1. Stephenson J, Whitehouse WP and Zuberi S. *Paroxysmal non-epileptic disorders: differential diagnosis of epilepsy.* In: Sheila J Wallace (ed.) Epilepsy in Children. 2nd Edition. Arnold, London. 2004.
2. Smith D, Defalla BA, Chadwick DW. *The misdiagnosis of epilepsy and management of refractory epilepsy in a specialist clinic.* Q J Med 1999;1:15-23.
3. Hobbs JB, Peterson DR, Moss AJ, et al. *Risk of aborted cardiac arrest or sudden cardiac death during adolescence in the long-QT syndrome.* JAMA. Sep 13 2006;296(10):1249-54.
4. *The Epilepsies. The diagnosis and management of the epilepsies in adults and children in primary and secondary care.* Clinical Guidelines, CG137. NICE guidelines for epilepsy. January 2012.
5. Rugg-gun FJ. *Non-epileptic paroxysmal neurological and cardiac events: the differential diagnosis of epilepsy.* In: Epilepsy 2009; From Bedside to Bedside; A practical guide to epilepsy. Lecture notes 12th epilepsy teaching week 18-20 September 2009. Oxford; 165-180.
6. *Differential diagnosis of paroxysmal events: epilepsy and nonepileptic seizures.* In: Panayiotopolous CP(Ed.). The Epilepsies. Seizures, syndromes and management.2nd edition. Blandon Medical Publishing. 2005;1-7.
7. Kotagal P, Costa M, Wyllie E, Wolgamuth B. *Paroxysmal nonepileptic events in children and adolescents.* Paediatrics 2002;110:E4-6.
8. Lamport T, von Brevern M. *The eye movements of syncope.* Neurology 1996;46:1086-8.
9. Rao TS, Stevens E. *In-patient video monitoring can be an invaluable diagnostic tool of epilepsy in the hands of a hospital paediatrician.* DMCN. January 2012;54:55-89.
10. Stephenson JB. *Fits and Faints.* MacKeith Press, London. 1990.
11. Benbadis SR, Allen HW. *An estimate of prevalence of psychogenic non-epileptic seizures.* Seizure 2000;9:280-1.

Cavernous Malformations of the Nervous System

Cavernous malformations (CM) are problematic for neurologists in day-to-day practice because they are common and often, but not always, harmless: their morbidity is uncomfortably similar to that of the means by which they may be treated. CM are vascular anomalies lacking shunt, major feeding artery or draining vein, their walls not possessing either smooth muscle or elastic fibres. They are known variously as cavernomas, cavernous haemangiomas and cavernous angiomas.

This book, 'Cavernous Malformations of the Nervous System' edited by Professor Daniele Rigamonti is a well researched and comprehensive text. There are 40 contributing authors from numerous international centres, providing an array of research and clinical experience. They cover current concepts in CM practice. The volume is presented very systematically in four sections with 19 chapters.

In Section 1 the authors focus on the structural pathology, epidemiology and molecular genetics of CM. They describe mutations in three genes which are linked to familial CM, inherited as autosomal dominant traits. One criticism is that these genetics subsections sometimes strayed from comprehensive to repetitive.

In Section 2, the authors detail the clinical presentations of CM and the most sensitive diagnostic imaging modalities to be used for initial assessment and for follow-up. The authors provide insights into the safety of various drugs that may be used in the presence of CM. They also give well-reasoned recommendations about activity restriction in CM. This is very practical information, potentially of great utility in advising patients with CM.

Section 3 discusses the management of CM including, both conservative and surgical, while the final section provides an update on genetic counselling in CM.

Cavernous malformations, from basic structure to diagnosis and management, are both intriguing and challenging to clinicians. With the advent of precise neuroimaging, patients asymptomatic from CM are being identified more frequently. This book attractively and effectively provides an update on current research and clinical practice as to the best approaches with both symptomatic and asymptomatic CM. It also has sufficient scientific rigour to be a reminder of how little we know of the subject. Vascular neurologists in particular will find this book very valuable. ◆
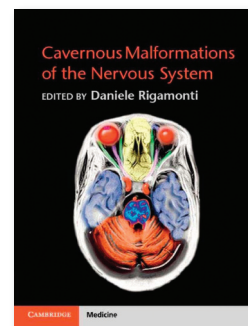
Editors: Daniele Rigamonti, Professor of Neurosurgery and Radiation Oncology at John Hopkins University Hospital, USA.
Published by: Cambridge University Press, 2011.
Price: £75.00.
ISBN: 978-0521764278.

Reviewed by: Ranjith K Menon, Clinical Fellow Vascular Neurology, Division of Adult Neurology, Sunnybrook Health Sciences Centre, University of Toronto.

The Medicalization of Cannabis
Wellcome Witnesses to Twentieth-Century Medicine. Volume 40.

Somewhere in the East of England thousands of cannabis plants are growing within a high-security secret site. Their destiny is to become a component of medical treatments for a range of conditions, and specifically for the treatment of multiple sclerosis. Medical practitioners have differing views on the likely benefits of this novel therapy: some are highly enthusiastic, whereas others remain sceptical and consider the drug to lack legitimacy in a clinical environment. Perhaps even the word "novel" is inappropriate in this setting, since cannabis has been used as a drug from the 1800s, but understanding of its potential only blossomed three decades ago when cerebral cannabinoid receptors were first identified.

Volume 40 of the "Wellcome Witnesses to Twentieth-Century Medicine" series represents a collection of transcripts of testimony provided by a diverse group of individuals – clinicians, scientists and patients – invited to contribute to a conference held in London, the topic being the medical use of cannabis over the centuries. The volume is not really a book at all, but is more of a verbatim record of what was said "on the day", with some commentary, by way of annotation. It reads like a stenographer's transcript of legal proceedings, in which the evidence in favour of and against the use of cannabis for medical purposes has been advanced and rebutted. But that is not to be critical of the style, rather the presentation tends to draw the reader in, as though they themselves were party to the debate at the time, albeit at the expense of some continuity of content.

It is clear that some of the speakers whose words are recorded in the volume are passionate advocates of the cannabinoids, whereas others express doubt. The early reluctance of "mainstream" pharmaceutical companies to embark on cannabis-related research because of the perceived stigma is stressed. Very reasonably, many contributors draw attention to the plethora of self-reports of benefit of cannabis in treating the symptoms of diverse conditions, with inevitable emphasis on MS. The exacting reader may find it disappointing that the proponents speaking strongly in favour of cannabis are not forced to scrutinise their statements with greater scientific ruthlessness, to ensure that their assertions can truly be backed up by an evidence base. The scientists whose thoughts are presented certainly make valiant efforts to maintain perspective. But overall we are still given too much anecdote, methinks, with one enthusiast noting that her experience of smoking cannabis didn't just relieve the pain and ease the spasticity imposed by her MS, but also helped her to sleep and to eat. Meanwhile another MS sufferer notes simply "Cannabis has changed my life. It really has." Quite some claims! They go largely unchallenged in the debate.

This volume will certainly be of interest to those who have coordinated research into the benefits of cannabis in neurology. However, for others, it may be rather heavy-going despite its brevity, in part because of the format. Many will find the lack of intellectual rigour in some parts disappointing. All, however, will be interested in the historical perspective offered by early sections of the book. These give insight into a potential therapeutic agent which has found favour, not just in recent years, but which in reality has a pedigree stretching back many thousands of years in the history of medical practice.

If you don't have a special interest in this area, this is one to glance at, perhaps, if it catches your eye from a top shelf in the library. ◆
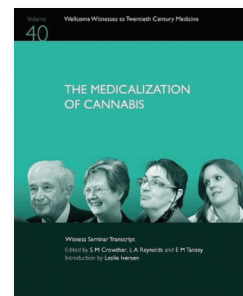
Editors: Crowther SM, Reynolds LA and Tansey EM
Published by: The Wellcome Trust Centre for the History of Medicine at UCL (2010)
Price: £6.00
ISBN: 978-0854841295

Reviewed by:
Dr Colin Mumford DM FRCP, Department of Clinical Neurosciences, Western General Hospital, Edinburgh EH4 2XU

Restless flies

Data that emanate from Genome Wide Association Studies (GWAS) are often at first difficult to construe. New findings are reported on a weekly basis, providing potential, but as yet unclear, insights into the pathogenesis of hitherto poorly understood common clinical disorders. It is worth noting here the significant advances made in areas of clinical neurology on the back of such studies. Nevertheless, identifying an association represents the very beginning of a quest to understand disease at the molecular level.

Restless legs syndrome (RLS) is said to affect up to 10% of the population, 60% of which report a family history. Previous GWAS have identified a number of candidate genes that appear to be associated with RLS. This short list includes a SNP (Single Nucleotide Polymorphism) linked to the *BTBD9* gene that appears to account for approximately 50% of the population-attributable risk. How *BTBD9* and RLS are linked is the focus of a recently published report by Freeman et al. in the *Current Biology*.

Freeman et al. used the fruit fly, *Drosophila*, as the model organisms to investigate the function of the fly homologue of *BTBD9* (*dBTBD9*). They found that the protein product is widely expressed in *Drosophila* brains and appears to have a discrete punctate localisation within neurones. Remarkably, *Drosophila* mutants lacking *dBTBD9* displayed fragmented night-time sleep similar to human patients which could be rescued by introducing the wild-type gene. Moreover, the authors found that when the flies were enclosed in a confined space, they became hyperlocomotive, analogous to the 'restlessness' seen in RLS patients. Importantly, Freeman et al. did not observe any defect in general locomotion suggesting a motor deficit.

Patients with RLS are treated with Dopaminergic drugs, suggesting an underlying defect in dopamine signalling in patient brains. Indeed, Freeman et al. did find a 50% reduction in total dopamine in the mutant flies, and when treated with Pramipexole, the previously-seen sleep abnormalities improved to control levels. In addition, defects in iron metabolism have also been reported in RLS patients and Freeman et al. also describe data showing links between *BTBD9* and ferritin expression in cell culture.

This work therefore not only provides corroborating evidence that the GWAS findings from patients with RLS appear significant but also illustrates the potential power of ongoing genetic screening in tandem with laboratory research to understand neural function. However, many outstanding questions remain including how does *BTBD9* regulate sleep and locomotion at the molecular level and, crucially, how does the identified SNP predispose to clinical disease? The answers can only be provided by further laboratory studies.

– Rhys Roberts, Cambridge Institute for Medical Research and Addenbrooke's Hospital, Cambridge.
Freeman A, Pranski E, Miller RD, Radmard S, Bernhard D, Jinnah HA, Betarbet R Rye DB and Sanyal S. Sleep Fragmentation and Motor Restlessness in a Drosophila Model of Restless Legs Syndrome. Current Biology 2012;22:1142-8.

Pushed aside and cross-linked cleanly

Laurent Groc in Bordeaux studies the surface interactions and kinetics of the NMDA receptor and other proteins. Mikasova and others in his group show, with cell culture and animal work, nicely done single particle trafficking photographs and studies of long term potentiation (LTP), that NMDAR antibodies from the serum and cerebrospinal fluid of patients with NMDAR encephalitis rapidly disperse synaptic NR2A containing NMDA receptors on the cell surface and cross-link and internalise extra-synaptic NR2B containing receptors. Synaptic plasticity is impaired with inability to upregulate AMPA receptors via LTP. The effects are seen within minutes of application of the antibodies to hippocampal neuronal cells in culture. Activation of the Ephrin-B2 receptor in vitro and in vivo can rescue these effects, which provides a pathway that may translate to an effective adjunct therapy for patients. Christian Bien and Jan Bauer with international collaborators provide a detailed neuropathological comparative study of the old intracellular-antigen (e.g. Hu) associated encephalitides, with evidence of predominantly CD8 T-cell associated inflammation, in comparison to 'cell-surface'-encephalitides including potassium channel complex antibody associated encephalopathy and NMDAR encephalitis. 17 patients' samples are examined, 6 with post mortem analyses. Potassium channel antibody cases (including one confirmed Lgi-1 antibody case) are associated with complement deposition and less cellular infiltrate, but NMDAR encephalitis cases (albeit with a small sample of 3 cases with neocortical biopsy samples only) have barely any evidence of neuronal loss, inflammation or complement activation. This work replicates other previous studies of the neuropathology of NMDAR encephalitis, and supports the prevailing hypothesis that NMDAR antibodies are genuinely pathogenic in themselves.

– Mike Zandi, Addenbrooke's Hospital, Cambridge.
Disrupted surface cross-talk between NMDA and Ephrin-B2 receptors in anti-NMDA encephalitis. Mikasova et al. BRAIN 2012;135(5);1606–21. Immunopathology of autoantibody-associated encephalitides: clues for pathogenesis. Bien et al. BRAIN 2012;135(5):1622-38.

Lawrence and Kuypers films

Twenty films are now made freely available, for the first time, on the Brain website to accompany two classic papers of Don Lawrence and Hans Kuypers from 1968. The pair examined motor control (and recovery) after lesions to the corticospinal system (bilateral pyramidotomy), ventromedial descending brainstem pathways (posture and balance) and the lateral brainstem pathways (reach and grasp) in the Old World macaque monkey. The 16mm films were made in Cleveland between 1963 and 1966, and inspired many studies of motor plasticity.

– Mike Zandi, National Hospital for Neurology and Neurosurgery, Queen Square, London.
Lawrence and Kuypers (1968a, b) revisited: copies of the original filmed material from their classic papers in Brain. Lemon et al. BRAIN 2012;135(7):2290-5.
Lawrence DG, Kuypers HGJM. The functional organisation of the motor system in the monkey. I. The effects of bilateral pyramidal lesions. BRAIN 1968a;91:1–14.
Lawrence DG, Kuypers HGJM. The functional organisation of the motor system in the monkey. II. The effects of lesions of the descending brain-stem pathways. BRAIN 1968b;91:15–36.

Mere therapies (and mouse telemetry)

These two papers provide animal model evidence for the use of micro RNAs in the treatment of neurological disease. The first, from Nagoya, tackled Kennedy's spinal and bulbar muscular atrophy (SBMA) due to the polyglutamine expansion in the androgen receptor. MiR-196a is a micro RNA which, when given with a viral vector, silences a stabiliser of androgen receptor mRNA, CELF2 (CUGBP, Elav-like family member 2), lessening the phenotype in SBMA mice and reducing expression of the androgen receptor mRNA in fibroblasts from patients with the disease. The second paper, from Dublin, looked at the use of Mir-134, a micro RNA known to be important in the activity-regulation of dendritic spine structure and remodelling, in epilepsy. The authors demonstrate upregulation of Mir-134 in kainic acid induced status epilepticus in BL/6 mice, and found higher levels of Mir-134 in the resected temporal lobes of patients with refractory temporal lobe epilepsy compared to non-neurological controls. The authors then carried out EEG telemetry for 2 weeks on mice, comparing a group with MiR-134 silencing and those without, demonstrating marked reduction in evoked seizures in the MiR-134 silenced group. There is a case for renaming NMDAR encephalitis as NMDAR antibody associated encephalopathy.

– Mike Zandi, Addenbrooke's Hospital, Cambridge.
Viral delivery of miR-196a ameliorates the SBMA phenotype via the silencing of CELF2. Miyazaki et al. NATURE MEDICINE. Published online 3 June 2012.
Silencing microRNA-134 produces neuroprotective and prolonged seizure-suppressive effects. Jimenez-Mateos et al. NATURE MEDICINE. Published online 10 June 2012.

Phenol Nerve Block for the Management of Lower Limb Spasticity

Moheb Gaid

is a consultant in rehabilitation medicine at the Colman Centre for Specialist Rehabilitation Services in Norwich. His main interests are amputee and musculoskeletal rehabilitation, spasticity, and posture management. Moheb obtained his MRSC from the Royal College of Surgeons of England and MSc in Musculoskeletal care from the University of Warwick.

Correspondence to:
Dr Moheb Gaid,
Consultant in Rehabilitation
Medicine,
Colman Centre for Specialist
Rehabilitation Services,
Norwich NR2 2PJ, UK.
T: +44 (0)1603 255773,
F: +44 (0)1603 255750.

REFERENCES

1. Barnes M. *Medical management of spasticity in stroke.* Journal of Age and Ageing. 2001;30:13-16.

2. Ward A. *Summary of spasticity management – Treatment algorithm.* European Journal of Neurology 2002;9:48-52.

3. Garland D, Lucie R, Waters R. *Current uses of open phenol nerve block for adult acquired spasticity.* Clinical Orthopaedics. 1982;165:217-22.

4. Beard S, Hunn A, Wight J. *Treatments for spasticity and pain in multiple sclerosis: a systematic review.* Health Technology Assessment. 2003;7(40):61-4.

5. Montizan G. *IPCS Environmental Health Criteria for Phenol.* WHO Publications 1994(161).

6. Kocabas H, Salli A, Demir AH, Ozerbil OM. *Comparison of phenol and alcohol neurolysis of tibial nerve motor branches to the gastrocnemius muscle for treatment of spastic foot after stroke: a randomized controlled pilot study.* European Journal of Physical and Rehabilitation Medicine. 2010;46(1):5-10.

7. Akkaya T, Unlu E, Alptekin A, Gumus H, Umay E, Cakci A. *Neurolytic phenol blockade of the obturator nerve for severe adductor spasticity.* Acta Anesthesiology Scandinavia. 2010;54:79-85.

8. Paola M, et Al. *Precise Localization of the Motor Nerve Branches to the Hamstring Muscles: An Aid to Conduct Neurolytic Procedures.* Archive of Physical Medicine and Rehabililation. 1996;77:1157-60.

Spasticity is defined as a motor disorder with failure to inhibit velocity sensitive stretch reflexes leading to exaggerated muscle resistance. It is a cardinal feature of upper motor neuron lesions and can affect patients with congenital and acquired brain and spinal cord injuries of variable aetiologies (traumatic, vascular, neoplastic and demyelination).

The exact incidence and prevalence of spasticity is unknown. A consensus of experts in Britain believes it to be about 20% of stroke patients and 75% of patients with severe brain injury.[1] Spasticity varies in severity from muscle stiffness to severe, painful and uncontrollable muscle spasms. Spasticity can be general, involving multiple limbs and trunk muscles, regional, affecting a group of muscles in one or more limbs, or focal, affecting a single muscle.

Spasticity can affect the ability to feed and dress oneself, bladder and bowel control, hygiene and mobility. It also predisposes to complications such as pressure sore formation due to poor seating / laying posture and contracture.

General principles of spasticity management

Spasticity management is an interdisciplinary team approach that requires thorough assessment of the individual to exclude factors that would trigger spasticity, for example; infection, painful stimuli, poor posture and constipation. Formulating a management plan aims to address those factors that would contribute to and are influenced by the increased muscle tone. The medical treatment of spasticity should be tailored to the individual as part of the interdisciplinary plan of management, with clearly identified goals. The choice of treatment would depend on the set goals and on the distribution of the involved muscles.[2] It can range from the following:

- Systemic oral muscle relaxants work directly on the CNS or the skeletal muscle receptors for generalised spasticity e.g. Baclofen, Tizanidine, Dantrolene
- Intrathecal administration of muscle relaxants achieves selective spinal inhibition of the stretch reflex for lower limb spasticity. This can be administered via an electronic or pneumatic pump e.g. Baclofen, clonidine or morphine
- Blocking the acetyl-choline re-uptake at the neuromuscular junction using Botulinum toxins
- Motor outflow block using chemical neurolysis at the peripheral nerve for regional spasticity e.g. phenol

The latter is a method reserved for selected individuals with progressive or stable neurology in whom spasticity involves large muscle groups affecting the lower limbs. The use of Phenol in upper limb spasticity or as motor point block will not be discussed in this article.

Phenol Nerve Block

Mechanism of Action

Phenol (carbolic acid) in concentrations more than 3% acts as a neurolytic agent.[3] This can be used to manage spasticity by impairing the spastic muscle innervations. Phenol also has a local anaesthetic property, which explains the transient muscle relaxation within the hour following phenol block. However the desired neurolytic effect usually starts five to seven days following motor nerve block.[4]

Available preparations and recommended dosage:

Phenol in water is the recommended preparation for peri-neural block and is available in 5, 6 or 7% concentrations.[3] There are no clear studies about the recommended dose but the consensus from the literature recommends no more than 1200mg in total (e.g. 20mls of 6% concentration). The available data, from industrial toxicity with phenol show side effects if systemic absorption in adults is of 100mg/kg or more.[5]

Indications:

Phenol is reserved for regional lower limb spasticity involving large muscles for which treatment with botulinum injections will not be appropriate due to the need for high doses of botulinum.[6] The following scenarios are examples of the use of phenol nerve block.

An individual diagnosed with a chronic neurological disorder (e.g. multiple sclerosis) with bilateral adductor and or hamstring spasticity. This spasticity pattern can lead to difficulties in achieving seating posture and maintaining personal care and hygiene (e.g. perineal access for dressing and washing) Detailed assessment is important to establish that the residual muscle and joint contractures will not be significant enough to prevent seating or personal care.

In the above example phenol nerve block can be used on the obturator nerve to address hip adductor spasticity or to the sciatic nerve to address hamstring spasticity. The sciatic nerve is a mixed sensory-motor nerve and therefore it is preferable to do selective block to the hamstring branches to avoid nerve causalgia post injection.

Similarly, femoral nerve block can be used for the management of quadriceps muscle spasticity. This pattern of spasticity can be a hindrance for wheel-
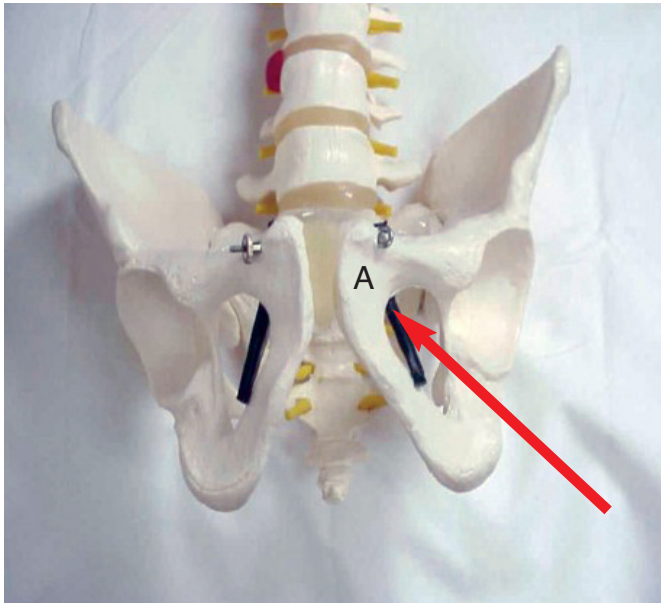
Figure 1: Obturator nerve block can be achieved 1-2cm distal and lateral to the pubic tubercle (A on image to left), or lateral to the insertion of the adductor longus muscle.

chair users as accommodating knee extension on a wheel chair increases the turning circle and impairs chair manoeuvrability.

Tibial nerve block can be used in the management of equinovarus posture due to soleus, tibialis posterior and/or tibialis anterior muscles. Diagnostic local anaesthetic block may be required to assess the effect of tibial nerve block if the individual is able to stand or step.

Technique

The most common nerve blocks done for the above-mentioned indications are the obturator nerve, hamstring branches of the sciatic nerve, femoral nerve and tibial nerve. The nerves can be located using various techniques including ultrasound scanning, X-ray, or guided electrical stimulation. The electric stimulation technique relies on a Teflon coated needle as the negative electrode with a pulsating electric current of 1-2mA at 2Hz.

Obturator nerve[7]: (Figure 1)

The obturator nerve emerges from the obturator hiatus at the obturator internus muscles at the superior medial aspect of the obturator foramen. It divides into two branches. The anterior branch supplies the adductor longus, brevis and the gracilis muscles. The posterior branch supplies the obturator externus and the adductor magnus muscles. The posterior aspect of the adductor magnus also receives innervations from the sciatic nerve.

The obturator nerve block is achieved by introducing the needle at 45° to the anterior aspect of the thigh aimed at a point 1-2cm below and lateral to the pubic tubercle. As the needle is introduced, it should hit the superior pubic ramus, the needle is then withdrawn and reintroduced at 60° to enter the obturator foramen at its superior-medial aspect. The nerve can be located using electric stimulation guidance. Patients with associated hip adduction and flexion posture usually have associated pelvic tilt and locating the obturator foramen as above may be difficult. Another method is to follow the adductor longus tendon and insert the needle lateral to its pelvic insertion under electric stimulation guidance. The nerve is then infiltrated with 200-300mg of phenol.

Hamstring branches of the sciatic nerve: (Figure 2)

Selective motor block to the hamstring branches is favourable in spasticity management to minimise the risk of nerve causalgia. The motor innervations of the hamstrings can be located at the mid-point of the line between the greater trochanter and the ischeal tuberosity. Locating the branches to the biceps femoris, semi-tendinosus and semi-membranosus muscles is feasible using electric stimulation technique by noticing the rhythmic contractions of the corresponding muscles. 300-500mg of phenol can be split between the branches according to the severity of muscle spasticity. There are reported anatomical variations, therefore
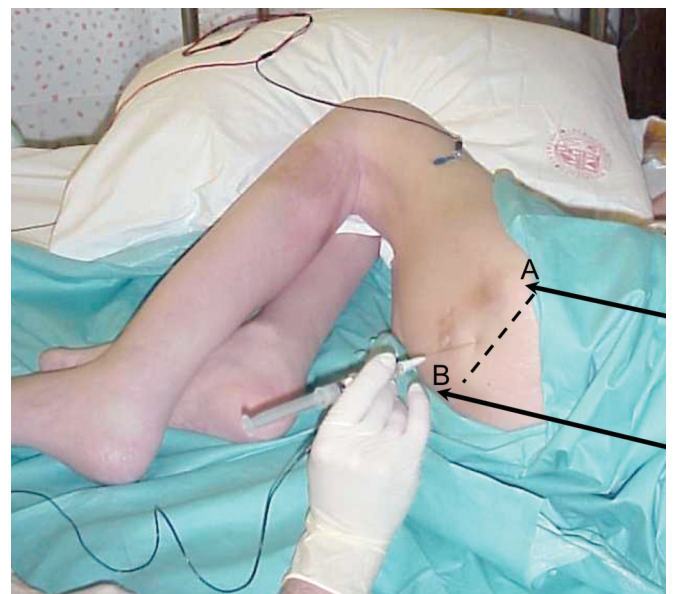

Figure 2: Nerve block to the motor branches of the sciatic nerve to the hamstrings can be achieved 1-2cm distal to the mid-point between A) the greater trochanter and B) the ischeal tuberosity
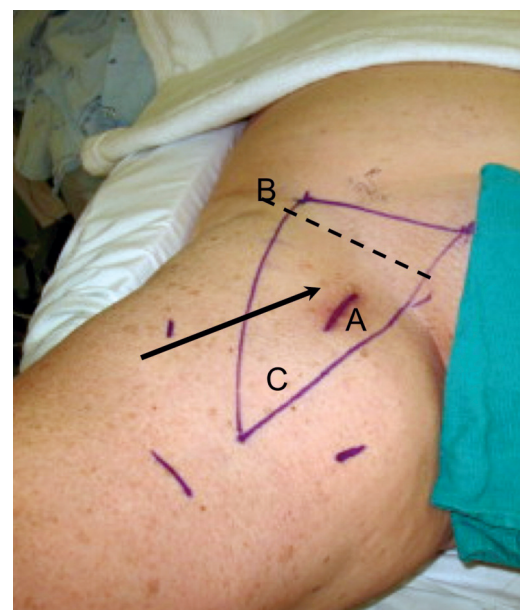

Figure 3: Femoral nerve block can be achieved in the femoral triangle (C) lateral to the pulsating femoral artery (A) and distal to the mid-point of the inguinal ligament (B)

some clinicians may use surface electrodes or USS guided techniques to localise the motor branches prior to introducing the needle.[8] Injection of phenol should be avoided if there are noticeable contractions of the foot, as this would involve the sensory component of the sciatic nerve via the tibial and common peroneal nerves.

Femoral nerve: (Figure 3)

The nerve can be easily located lateral to the palpable pulse of the femoral artery below the inguinal ligament. A teflon coated needle is introduced at 90° with electric stimulation. The nerve can be found at 2-3cm depth with associated quadriceps contractions on stimulation. 100-300mg of phenol can be infiltrated according to the response. Aspiration before injection is an essential practice which cannot be over emphasised, in particular to avoid accidental injection into the femoral artery.

Tibial nerve: (Figure 4)

The nerve can be easily located about 0.5 to 1cm below the mid-point of the popliteal crease between the medial and lateral femoral condyles. This is to avoid including the sural nerve, which usually branches at a proximal level, and thus avoids sensory causalgia. The needle is introduced with stimulation and the nerve can be found at a depth of 2-3cm and superficial to the popliteal vessels. Calf muscle contractions and foot inversion is noticed once the nerve is stimulated. 100-200mg of phenol can be used to achieve a satisfactory block to the tibial nerve at this level. To minimise the possibility of nerve causalgia, ensure the patient reports no sensory symptoms at the time of the stimulation. If so, the nerve needs to be approached at a slightly distal level after the branching of the sural nerve.

Side effects:

Common

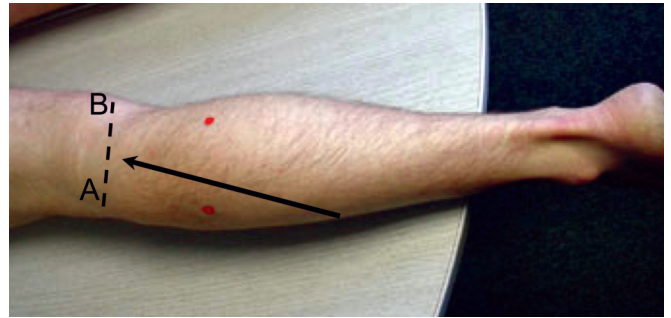– Occasional redness, discomfort or bruises at the injection site

Figure 4: Tibial nerve block can be achieved 1-2cm distal to the mid-point between A) the posterior aspect of the lateral femoral condyle and B) the posterior aspect of the medial femoral condyle.

Rare side effects

– Skin infection or abscess formation
– Haematoma
– Muscle / soft tissue fibrosis
– Nerve causalgia (in sensory-motor nerve blocks)

Very rare side effects

– Vascular injury
– Injury to pelvic organs (applicable to obturator nerve block)
– Systemic effects: arrhythmia, pulmonary fibrosis, confusion and renal impairment

Summary

Phenol nerve block is a treatment option in individuals with regional spasticity of the lower limbs. It can be used in cases with poor tolerability to systemic muscle relaxants and if large muscle groups that would exceed the safe dose of botulinum toxins. ◆

2012

July

Joint meeting of the Anatomical Society and Sociedad Anatómica Española: Motor Neurones and Diseases of Motor Neurones. e-learning: Interactive electronic teaching in anatomical sciences education
10-12 July 2012, Edinburgh, UK
E. as.meetings@ed.ac.uk,
http://www.anatsoc.org.uk/Meetings

August

10th World Congress on Sleep Apnea
27 August – 01 September, 2012; Rome, Italy
E. mario.fabiani@uniroma1.it

September

10th Meeting of the European Association of NeuroOncology
6-9 September, 2012: Marseille, France
E. eano2012@medacad.org
www.eano.eu

16th Congress of the European Federation of Neurological Societies
8-11 September, 2012; Stockholm, Sweden
T. +41 22 908 04 88
E. headoffice@efns.org
www.efns.org/efns2012

Occupational Stress
10 Sept, 2012; Derby, UK
T: 01332 254679
E: ncore@derbyhospitals.nhs.uk
www.ncore.org.uk

Exploring Gait as it relates to Posture & Balance for qualified therapists
12 Sept, 2012; Derby, UK
T: 01332 254679
E: ncore@derbyhospitals.nhs.uk

Human Brain Anatomy Course (3 day)
17-19 September, 2012; London, UK
http://www.neurocourses.com

Cognitive Behavioural Approaches to Physical Rehabilitation: Intermediate level
18 Sept, 2012; Derby, UK
T: 01332 254679
E: ncore@derbyhospitals.nhs.uk
www.ncore.org.uk

Neurological Upper Limb for Occupational Therapists
19 Sept, & 10 Oct, 2012 Derby, UK
T: 01332 254679
E: ncore@derbyhospitals.nhs.uk
www.ncore.org.uk

36th Annual Congress of the European Society of Neuroradiology
20-23 September, 2012; Edinburgh, Scotland
T. 0131 339 9235
E. esnr2012@in-conference.org.uk

Imperatives in Regional Anaesthesia: Current hot topics and future developments Workshop sessions and lectures
24th and 25th September, 2012;
The Royal College of Anaesthetists, London, UK
Anna Mawe, Event Coordinator,
Tel. 0114 2259057/36
E. anna.mawe@bbraun.com

Multiple Sclerosis: MS Trust Study Day on Postural Management
25th September 2012; Leeds U.K. (Advanced Level)
E: education@mstrust.org.uk
www.mstrust.org.uk/professionals/

Squeezing the best out of stroke care
27 September, 2012; London, UK
Conference Department
Tel: 020 3075 1436/1300/1252,
E. conferences@rcplondon.ac.uk

October

Stem Cells: Working Towards Clinical Application
3 October, 2012; London, UK
T. 07507 799380
E. enquiries@euroscicon.com
www.regonline.co.uk/discussionstem2012

3rd Annual Induced Pluripotent Stem Cells: Production and Utility in Regenerative Medicine
4th October, 2012; London, UK
T. 07507 799380
E. enquiries@euroscicon.com
www.regonline.co.uk/2012londonstemcellevent

Complex Epilepsy Conference
In collaboration with Matthew's Friends
12 October, 2012; Solihull, UK
Tel. 01342 832243 ext 296,
E. epilepsytraining@youngepilepsy.org.uk

November

3rd Parkinson's UK Research Conference
5-6 November, 2012; York, UK
T. 0808 800 0303
E. researchevents@parkinsons.org.uk

West of England Seminars in Advanced Neurology (WESAN)
22-23 November, 2012; Exeter, UK
E. cgardnerthorpe@me.com

MS Trust Specialist Health Professionals Master Class: Sexuality in MS
29th November, 2102; London
E. education@mstrust.org.uk
www.mstrust.org.uk/professionals/

December

UK Stroke Forum
4-6 December, 2012; Harrogate, UK
T. 01527 903913
E. ukstrokeforum@stroke.org.uk

2nd Annual Regulatory Cells in Autoimmunity event: Analysing and moderating function
6 December, 2012; London, UK
T. 07507 799380
E. enquiries@euroscicon.com
www.regonline.co.uk/autoimmune2012

2013

April

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

May

The 11th International Conference on Alzheimer's and Parkinson's Diseases (AD/PD™)
6-10 May, 2013; Florence, Italy
T. + 41 22 906 0488
E. reg_adpd2013@kenes.com

Neuro-ID 2012: Liverpool Neurological Infectious Diseases Course

Conference details: Thursday 17th and Friday 18th May, 2012, Liverpool, UK *Reviewed by:* Dr Sarah Logan, an infectious diseases specialist registrar at Royal Free Foundation Trust, London, UK. MA (Cantab), MBBS, MRCP, Dip HIV med.

This was the sixth year that Professor Tom Solomon and others have organised this course in Liverpool and yet again all 110 places were sold out.

The delegates were predominantly UK based though some had come from as far as Australia, Africa and Asia, many of the UK trainees were currently working overseas. There was a pretty even split between those practising in infectious diseases and those in neurology with a few paediatricians and laboratory based infection specialists as well. The experience of the delegates was very varied; some were approaching the registrar grade whilst others had been consultants for some time. This must have made pitching the talks quite a challenge. As a final year trainee, on the whole it was just about right.

The two days were divided into numerous short talks around 20 to 40 minutes in length. The approach was very practical and often involved clinical scenarios which I found very helpful. The radiology of CNS infections by Dr Kumar Das stands out as one of the most useful talks from the first day. He took us through CT and MRI changes in neurological infection in a very comprehensive and interactive way. Dr Matt Scarborough talked about bacterial meningitis, his review of the need for imaging prior to lumbar puncture and evidence for adjunctive steroids I have referred back to on several occasions since. We were also lucky enough to hear from Professor Scott Letendre from the University of San Diego, USA. He was the Chief Investigator on the CHARTER study into HIV associated neurocognitive disease and he gave a very comprehensive review of the diagnosis and management of this. The talk on encephalitis from Professor Solomon and Dr Rachel Kneen was very informative. The day was followed by an evening of socialising and dinner in a local restaurant. This was great fun and a good way to catch up with colleagues.

One of the highlights from the Friday was undoubtedly Dr Guy Thwaites talking on TB meningitis. His landmark trial in Vietnam into adjunctive dexamethasone is well known and he took us through the clinical problems with diagnostics and managing this devastating illness which we are all seeing increasingly in the UK. Dr Nick Davies also talked on Friday on peripheral nervous system infections. This was a good talk and in some respects many of us would have liked a little more on lower motor neurone infectious problems.

Preceding the course there was a day of

NeuroID 2012 delegates: From Australia to Zimbabwe

Professor Tom Solomon and Dr Benedict Michael, members of the NeuroID Course Team

NeuroID 2012 delegates enthralled by a talk on encephalitis

Brain Infections research updates. Those that attended found this a really interesting day and it incited much discussion on the days that followed. In future years this is going to be more integrated into the course.

I would definitely recommend this course to other trainees in neurology and infectious diseases. I have found myself referring back and using the principles I learnt several times over the last month. The pitch of some of the talks was perhaps not quite right for everyone but this is surely inevitable when there is such a variety of experience in the audience. With 110 delegates it was a great environment to ask questions and some of the really useful clinical tips came from these. I also enjoyed getting to know some of my neurology colleagues working in the same trust, spending two days discussing clinical problems away from the bleep has definitely enhanced our clinical interactions on our return to work! ◆

If you are interested in attending next years course it is a good idea to register early.

www.liv.ac.uk/neuroidcourse
www.facebook.com/
LiverpoolNeuroIDCourse

Many thanks to Dr Benedict Michael and the other members of the faculty for making the logistics of organising 110 people in a Grade two listed building, look incredibly easy.

Magstim Neuroscience Conference and Workshop 2012

Conference details: 12-13 May, 2012, Oxford, UK. *Reviewed by:* Dr Nick Davis. Postdoctoral Research Officer, School of Psychology, Bangor University.

The Magstim Conference and Workshop was held in the Examination Schools of Oxford University, on a sunny weekend in early summer. This is a good venue for the meeting, except for people who had been undergraduates at Oxford whose anxiety levels were rising as they stepped into the building where they sat their exams.

The meeting was sponsored by Magstim, a company that makes devices for non-invasive brain stimulation (http://www.magstim.com). However as in previous years the sponsors left the scientific organisation to an independent committee of researchers: Prof. Vince Walsh (UCL), Dr Charlotte Stagg (Oxford) and Dr Sven Bestmann (UCL). These researchers are at the forefront of the development of brain stimulation as a tool for clinical and research applications, using both of the main methods of transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS).

The constituency of the meeting is a wide array of clinical practitioners, physiologists and cognitive neuroscientists, who are positioned on a spectrum of engagement with brain stimulation from people who are developing the use of new forms of stimulation through to people who wish to use brain stimulation as a tool for aiding people with brain injuries. With such a wide field, the organisers of the meeting faced a difficult problem in providing a series of presentations that would appeal to the masses, while being detailed enough to engage the experts. As in previous years, they did so by dividing the presentations into themed sessions split across the two days of the meeting.

Day 1.

The first day opened with the usual house-keeping announcements, including the promise that the audience would be kept informed of any developments in the weekend's decisive Premiership football matches. This freed the audience to concentrate on the talks.

The first session was entitled "Cognition" and the four speakers introduced topics where brain stimulation can help in understanding the processes that underlie functions such as perceiving faces (David Pitcher, NIMH) or suppressing ongoing actions (Michal Lavidor,

Bar Ilan University; Adam Aron, UCSD). Paul Sauseng (University of Surrey) demonstrated the value of alternating current stimulation in modulating performance in a memory task.

In the second session, "Connectivity", the speakers showed the range of scales at which brain stimulation can be useful. The first speaker (Robert Chen, University of Toronto) highlighted the complex interactions that occur between excitatory and inhibitory circuits within the human motor cortex. The next presentation (Matthew Rushworth, Oxford University) widened the scale to interactions between brain areas, with the possibility that frontal brain areas may tune the activity of early visual areas to enhance detection of specific stimuli. Joseph Galea (UCL) demonstrated the effect of stimulating the cerebellum on other brain areas. The cerebellum is somewhat neglected by brain stimulation researchers due to its relative inaccessibility, however novel methods such as tDCS or patterned TMS may help to establish causal involvement of the cerebellum in functions beyond its traditional motor role. The final speaker of the session (Jenny Crinion, UCL) widened the scope of the session to the use of tDCS to restore functional networks that have been damaged by brain injury. Her research demonstrated that anodal tDCS over Broca's area can help in restoring speech in people rendered aphasic due to stroke.

Day 2.

The second day opened with the meeting's keynote lecture from Mark George, Distinguished Professor of Psychiatry, Radiology and Neurosciences at the Medical University of South Carolina. Prof. George's lecture focused on the use of daily application of TMS for treating depression. This is an area where brain stimulation has shown very promising results, with a projected figure of 12 people per day in the US showing remission from depression following TMS treatment. Prof. George used his own clinical experience to argue for more aggressive application of TMS in each patient, since higher daily doses are

associated with a higher chance of remission.

Following the keynote lecture, Charlotte Stagg (Oxford University) introduced a session on "Plasticity and Change". Yoshkazu Ugawa (Fukushima Medical University) showed how multi-pulse TMS can be used to change the excitability of the motor cortex, with the direction and extent of change depending on the temporal pattern of pulses, the experiments for which required chaining together up to eight Magstim TMS stimulators. By contrast Antonio Oliviero (SESCAM, Spain) followed this talk with a much simper idea: holding a static magnet against the head. He showed that a static magnetic field can reduce motor cortex excitability, which is true whether the North or the South pole is held against the head. Finally Gabrielle Todd (University of South Australia) suggested ways to optimise the effect of TMS in inducing plasticity, with the important message that TMS effects are highly sensitive to parameters of the stimulation, such as stimulation intensity and temporal patterning, and to the state of the brain at the time of the stimulation.

The final session of the meeting was introduced by Vince Walsh in a state of rising tension among the football fans; kick-off was due in the deciding match between Manchester United and Manchester City, with City needing the win to take the Premiership title from United. Fortunately the session on "Clinical Applications" lived up to its promise to engage the audience, with talks on the use of TMS in movement disorders (Mark Edwards, UCL) and emotional and cognitive disorders (Yuping Wang, Beijing; Ysbrand van der Werf, VU University Amsterdam). A final talk by Shirley Fecteau (Laval University) showed the potential of brain stimulation in treating addictive behaviour.

Conclusions

This was the sixth annual meeting on brain stimulation hosted by Magstim. In this time the meeting has become known for the high quality of its research presentations and for the relaxed feel of the poster sessions. Brain stimulation is a field where basic and applied research interacts fruitfully; this meeting has the feel of a place where things happen. We all left with notebooks full of new ideas. And City won with a last-minute goal. ◆

ERRATUM

In the January/February 2011 issue of ACNR in the Speciality Certificate Examination in Neurology paper it was stated that '… If you fail the exam in 2011 you are eligible for a free second attempt in 2012. However from 2012, you will need to pay the full cost of the exam again to resit.' This information was wrong as the last year for a free second attempt was 2011 and not 2012. The authors apologise for any inconvenience caused.

The 8th International Congress on Mental Dysfunction and Other Non-Motor Features in Parkinson's Disease and Related Disorders

Conference details: 3-6 May, 2012, Germany. **Reviewed by:** Dr Arshia Seddigh[1], Dr Prashanth Reddy[1], Stephanie Robinson[1], Alexandra Rizos[1]
[1]Neurology, King's College Hospital, London, UK.

A movement disorder seminar with a major focus on non-motor symptoms of Parkinson's disease (PD), MDPD 2012, took place in Berlin, Germany 3rd – 6th May 2012. With more than 800 participants from all over the world, attendance exceeded expectation. The opening session consisted of plenary lectures from organisers: Professors A Korczyn (cognition) and H Reichmann (pre-motor non motor features with a focus on gastrointestinal issues) along with Professor G Deuschl (President of Movement Disorders Society) and Professor E Wolters, (President of Parkinson's and related disorders section of World Federation of Neurology). Subsequent plenary lectures also included the chairmen of the scientific committees, Professor K Ray Chaudhuri and Professor B Jeon along with state of the art lectures from Professors D Brooks, D Burn, N Giladi, F Stocchi, P Jenner, D Weintraub, J Duda and P Martinez-Martin amongst others. The congress covered several industry sponsored symposiums, which covered important issues such as continuous drug delivery strategies and non motor symptoms of Parkinson's (Professors Ray Chaudhuri, Odin, van Laar and Antonini), quality of life (Professors Martinez-Martin and Ray Chaudhuri) and pain (Professors Rascol, DeFazio and Ray Chaudhuri). In particular advantages and disadvantages of therapies such as apomorphine, intra-jejunal levodopa infusion and non motor effects of deep brain stimulation (DBS) and non motor endpoints in clinical trials were discussed in detail (such as non-motor effects of rasagaline in the ADIAGO study, rotigotine on sleep in RECOVER study, pramipexole and depression, and ropinorole on sleep by Professor Stocchi). Professor Jeon argued the importance of systemic studies into musculoskeletal problems in PD to address the high frequency of postural deformities and neglected pain.

In another plenary session, novel aspects such as the need for a new Non-Motor Staging of Parkinson's was proposed by Professor Chaudhuri, who suggested a clinical translation of neuropathological findings proposed by K Jellinger. Professor Giladi reviewed the clinical features of asymptomatic mutation carriers in genetic forms of PD. Professor Burn discussed the range of visual impairments experienced by patients. Although some of these symptoms are likely to stem from "central" visual processing deficits, others may be related to lower level disturbances of visual functions.

In a subsequent plenary session, Dr V Voon from Cambridge covered the role of reward and impulsivity in Impulse Control Disorder (ICD),

showing important differences between dopamine agonist effect in terms of impulsive choice and compulsive gambling and imaging differences. Professor A Guekht from Russia spoke about the economic burden of non-motor symptoms in PD and Dr. Bergman covered the non-motor neural networks of the basal ganglia and how they respond to emotional stimuli.

In a DBS session Professors P Krack and V Kostic discussed the non motor effects of deep brain stimulation in Parkinson's and discussions were also held by Dr M Samuel and Professor W Paulus among others.

Another session covered the important sleep symptoms of REM Sleep Behaviour Disorder (RBD) in PD organised by Professors W Oertel and R Postuma. The importance and usefulness of polysomnography (PSG) in the correct diagnosis of RBD was discussed by Dr. Diederich. Minor changes of macro- and microstructure of sleep in the early stages of sleep will be more pronounced in the late stages of PD but common sleep dysfunction syndromes are not more frequent. RBD has the potential to cause serious injury as Dr. Singer mentioned and it can be the first sign of neurodegenerative disorders like synucleinopathies (>50% increased chance for PD). Due to the high risk factor of RBD leading to a neurodegenerative condition and its latency, it creates a window of opportunity for the neuroprotective agents which can be used in clinical trials. Professor Postuma explained early occurrence of dysautonomia in PD patients and its values as a predictor. The role of Diffusion Tensor Imaging (DTI) in detecting microstructural changes of brainstem, substantia nigra, and olfactory regions in idiopathic RBD based on Braak's 2003 theory of ascending degeneration was discussed. Other important symposia included one led by care of the elderly colleagues and the British Geriatric Society from the UK highlighting non motor issues in Parkinson's, presided over by Professor R Walker with lectures from Dr P Fletcher, Dr J Hindle and Dr R Genever. The session was widely attended and addressed often

neglected topics related to palliative care, cognitive issues and the role of technologies in old age Parkinson's.

A further symposium was dedicated to the role of therapies and included talks by Anne Martin (PD nurse specialist), Julia Johnson (speech and language therapist who focused on new devices to improve loudness of voice in Parkinson's). Mariella Graziano, Margarita Makoutonina and F Adib spoke on physiotherapy, the role of occupational therapy and special interst groups in Parkinson's respectively.

Several other sessions focused on the important issue of cognition, from mild cognitive impairment to dementia and scales for assessment (M Emre, I Rektorova, J Kulisevsky, R Brown, Z Pirtosek), autonomic dysfunctions (A Korczyn, E Hirsch), sleep disorders (C Trenkwalder, C Singer, A Krygowska) and olfaction (R Pfeiffer, T Hummel). Professor A Storch argued that Parkinson's is a neuropsychiatric disorder, while Professor M Emre focused on mild cognitive impairment and Professor P Barone linked non motor symptoms as a whole with cognitive problems.

There were several poster presentations with prizes for the best 5 posters as well as oral communications from D Berg, A Antonini and M Onofrj among others.

Satellite sessions covered diverse topics such as "Gilles De la Tourette (GDT) is more than tics!" which was put together by Drs Worbe, Cavana and Limousin. Anatomy and pathophysiology of Tourette syndrome (TS) was discussed based on a recent possible animal (monkey) model and the molecular basis of how abnormal movement behaviours were replicated after lesions to different parts of Globus Pallidus (GPi) and Striatum. Dr. Cavana stressed the importance of comorbid disorders, ADHD more than OCD and tics especially for treatment purposes. Only 12% of TS patients have no other recognised abnormality. New treatments for adult patients include partial dopamine agonists like aripiprazole. Dr. Limousin spoke of DBS insertion in severe cases, especially in the GPi when tics cause injury.

In another session, Professor K Bhatia, Dr S Schneider and Dr S Engelender discussed the important clinical molecular genetic aspects of neuronal brain iron accumulation syndromes.

The conference dinner was hosted at the historical "Zollpackhof" and was attended by all faculty. The planned venue for the next "niche" meeting, highlighting non motor aspects of Parkinson's, will be Seoul in South Korea in April 2013. ◆

Life After Brain Injury – UKABIF Demands Action

An acquired brain injury (ABI) is defined as a non-degenerative injury to the brain which has occurred after birth and includes traumatic brain injuries (TBIs), i.e. those caused by road traffic accidents, falls and assaults, and non-TBIs i.e. those caused by strokes and other vascular accidents, tumours and also infectious diseases. Approximately one million people live with the effects of an ABI in the United Kingdom (UK) and require specialist rehabilitation services and support both in hospital and the community.

There is very little accurate and reliable data on the provision of healthcare services for people with ABI in the UK. The National Institute for Clinical Excellence (NICE) estimates that the acute hospital care costs for TBI are £1 billion annually (this does not include all types of ABI) and Gustavsson et al (2011) stated that the overall cost of TBI in the UK (and again an underestimate for ABI) was approximately £4.1 billion.

In 2001, The Health Select Committee published their Third Report into Head Injury (Health Committee 2000-1) with a list of 28 conclusions and recommendations; most have not been acted upon. Although the National Service Framework for Long Term Neurological Conditions has been in place since 2005, very little progress has been made and rehabilitation services continue to vary hugely around the UK.

In July this year, the UK Acquired Brain Injury Forum (UKABIF) a membership organisation and charity that aims to promote better understanding of all aspects of ABI, launches a Campaign 'Life after Brain Injury? Improve Services Now' to improve rehabilitation services and support for people with ABI. UKABIF's Manifesto 'Life after Brain Injury - A Way Forward' outlines the necessity of acute and early access to rehabilitation for adults with ABI to ensure optimal recovery, focusing on the need for specialist neurorehabilitation teams to manage care pathways and the cost implications of not providing adequate rehabilitation. Published studies clearly show that by providing rehabilitation, the savings made offset the costs, even when rehabilitation is not carried out immediately after injury. Over a lifetime, optimal recovery results in significant savings to health care costs.

Acute and early access to rehabilitation services

Rehabilitation after an ABI should start acutely to prevent complications, with the patient's care pathway clearly defined, and referral to a local specialist neurorehabilitation service at the earliest opportunity; this is crucial and often overlooked. Patients who have an early referral programme in the acute stages of recovery have significantly better social integration, emotional well-being and vocational functioning (Reid-Arndt et al 2007). Turner-Stokes

UKABIF
The United Kingdom
Acquired Brain Injury Forum

**Life After Brain Injury
A Way Forward**

Manifesto for Acquired Brain Injury
July 2012
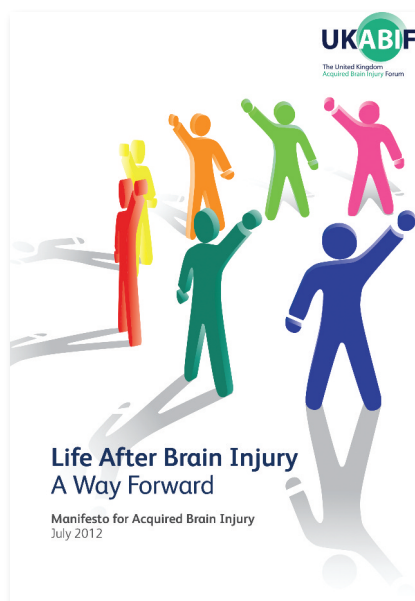
(2008) demonstrated the effectiveness of early intensive rehabilitation with specialist programmes for those with complex needs, and specialist vocational programmes for those with potential to return to work. Residential, social and behavioural rehabilitation programmes can all decrease the number of care hours needed, which also increases the brain injured person's capacity for independent social activity (Wood et al 1999). In a study up to two years post-injury, patients showed a 54% reduction in the care hours required compared to pre-admission; patients between two and five years post-injury showed a 33% reduction, and patients over five years post-injury showed a 21% reduction (Wood et al 1999).

Managing the Rehabilitation Programme

If someone has been assessed as needing rehabilitation they should be referred to a 'post-acute' rehabilitation centre. However, in many parts of the UK there is no suitable rehabilitation facility and people with brain injuries may have to go home too early or go to inappropriate places, such as nursing homes, where insufficient rehabilitation is provided. The independent sector provides much of the high quality brain injury rehabilitation available in the UK and a number of organisations offer specialist facilities and provide services to meet the needs of a range of people with ABI including the most difficult cases.

Following a specialist rehabilitation programme, ABI patients show a significant reduction in dependency at discharge, as measured by the Functional Independence Measure (Turner-Stokes et al 2006). More intensive rehabilitation is associated with rapid functional gains once the patient is able to engage (Turner-Stokes et al 2011).

A multidisciplinary team (MDT) is required with an expertise in neurorehabilitation,

comprising a core medical team and additional professionals depending on the nature of the brain injury; integrated services and an MDT rehabilitation programme promote brain recovery and enable people to recover more quickly and efficiently (Turner-Stokes et al 2011). The team should be led by Allied Health Professional specialists e.g. a physiotherapist with access to a Consultant in Neurorehabilitation over a timescale that is determined by the patients' progress and gains.

What is the Way Forward?

UKABIF is asking for the following:

- Appropriate commissioning for specialist brain injury rehabilitation should be made compulsory and each clinical commissioning group should have a named neurological lead.
- Funded National Neuro Networks should be established to ensure neurological pathways are available throughout the stages of recovery (patient journey).
- A National Audit of Rehabilitation should be carried out and the collection and reporting of accurate data on newly ABIs made compulsory by all providers along the patient journey, from Acute to Community services*
- A review is required of The Health Select Committee Report and the National Service Framework (NSF) for Long Term Neurological Conditions.

* As implemented with Stroke though Healthcare Emergency Planning and the Care Quality Commission

We need your help

To support our Campaign, please ensure that your team has a named neurological lead and if not, request one and review the information and support available for people with an ABI in your area. The full document is available to view on our website www.ukabif.org.uk. For further information on how to support this campaign, please contact:

Chloe Hayward, UKABIF, T: 0845 6080788, E: info@ukabif.org.uk www.ukabif.org.uk

References

Gustavsson A, Svensson M, Jacobi F et al. *Cost of disorders of the brain in Europe 2010.* European Neuropsychopharmacology 2011;21(10):718-79.

Health Committee Third Report Head Injury: Rehabilitation, House of Commons Session 2000-1 HC307.

National Service Framework for Long-Term Neurological Conditions. 2005. Department of Health.

Reid-Arndt S A, Schopp L, Brenneke L et al. *Evaluation of the traumatic brain injury early referral programme in Missouri.* Brain Injury 2007;21(12):1295-302.

Turner-Stokes L. *Evidence for the effectiveness of multi-disciplinary rehabilitation following acquired brain injury: A synthesis of two systematic approaches.* Journal of Rehabilitation Medicine 2008;40(9):691-701.

Turner-Stokes L, Nair A., Sedki I et al. *Multi-disciplinary rehabilitation for acquired brain injury in adults of working age (Review).* 2011. The Cochrane Library 1.

Turner-Stokes L, Paul S and Williams H. *Efficiency of specialist rehabilitation in reducing dependency and costs of continuing care for adults with complex acquired brain injuries.* Journal of Neurology, Neurosurgery & Psychiatry 2006;77:634-9.

Wood R L, McCrea J D, Wood, L M et al. *Clinical and cost effectiveness of post-acute neurobehavioural rehabilitation.* Brain Injury 1999;13(2):69-88.

Nobel Prize Winner Opens Nikon Imaging Centre at King's College London

Nikon Instruments UK opened their prestigious imaging centre at King's College London recently. Opened by Professor Roger Tsien, Nobel Prize winner, University of California, San Diego and Professor Roger Morris, Head of the School of Biomedical Sciences at King's, the Nikon Imaging Centre will allow researchers access to state-of-the-art technology all day, every day. The centre features a number of advanced imaging systems including Nikon's super resolution imaging systems N-SIM and N-STORM, spinning disk confocals, point scanning confocal and a multiphoton imaging system. Nikon's advanced imaging systems will provide a wide variety of technology to a range of disciplines, opening up access to scientific imaging for researchers. With modern science, researchers may

Professor Roger Tsien (left) and Professor Roger Morris opening the Nikon Imaging Centre at King's College London

need to undertake different imaging techniques and with limited access to the appropriate equipment, this could be a difficult task. With the Nikon Imaging Centre at King's, researchers have access to different imaging systems, providing them with the appropriate imaging technique. Having access to a centre like this will revolutionise and assist with scientific breakthroughs in cancer research, neuroscience and cardiovascular research etc. by meeting researchers' needs.

For more information see http://www.kcl.ac.uk/innovation/research/corefacilities/smallrf/nikon/index.aspx

New Q-Sense pain management tool from Medoc

The Q-Sense is a QST (Quantitative Sensory Testing) device, including advanced software package, designed for clinical use and research in the field of Pain Management.

The Q-Sense enables clinicians to perform various thermal test paradigms including the method of Limits, Levels and TSL. These test paradigms can be used for a wide range of thermal QST pain measures such as thermal pain threshold.

The unit has a simple 10-15

minute set up and installation time, an easy to use patient response unit and a simple user interface, offering maximum flexibility with minimum opportunity for user error. The test run takes just 3 steps, and there is a built in report generator.

The Q-Sense is available at £7,500.00 for a limited time only. For more information contact Brain Vision on Tel. 020 8543 0022, E. sales@brainvision.co.uk

Fujifilm recruit an additional Applications Specialist

Fujifilm is a pioneer in diagnostic imaging and information systems for healthcare, with a range of constantly evolving, clinically proven, products and technologies designed to assist medical professionals perform efficiently and effectively.

Due to the company's increasing customer base and expanding product portfolio, Fujifilm have recruited a further Applications Specialist. Laura Wilkins will provide customer support for Fujifilm's range of CR, DR and PACS systems throughout the North West and Wales.

Laura is qualified with a BSc (Hons) in Diagnostic Radiography together with a PGC in Medical Imaging. She spent her formative years working as a Radiographer for the NHS in Oldham and then Wrexham.

Commenting on her appointment as Applications Specialist, Laura said: "I enjoyed my role within the NHS especially providing regular training sessions for students. I am looking forward to providing on-site training, demonstrations and product support to our customers."

For more information contact Fujifilm on Tel. 01234 572 000.

Swisslog's Automated Guided Vehicle System chosen for the New South Glasgow Hospital

Swisslog has been awarded the contract for logistic system with 22 Automated Guided Vehicles (AGV) at the New South Glasgow Hospital. The hospital will provide the largest critical care complex in Scotland.

Swisslog worked closely with the main construction contractors, to propose a solution that fully realised the aspirations of the Greater Glasgow and Clyde NHS board to deliver a modern world-class hospitals that makes best use of the latest technological solutions. Dynamic computers simulations validated the AGV proposal and were used to identify the scope of the various equipment interfaces and human resources necessary to work alongside the robotic systems.

By moving the vast majority of goods around the hospitals by AGV provides a safer system of work and reduce the risk of moving & handling injuries. They are safe and people friendly and will allow to provide efficient and reliable deliveries to the wards and departments.

More information at www.swisslog.com or E. marjan.hulshof@swisslog.com

Hear Professor K Ray Chaudhuri discuss the EUROINF survey online

In a webinar held on Wednesday 20th June, Professor Chaudhuri (King's College Hospital, London and Clinical Director of the National Parkinson Foundation), discussed the results of the ongoing EUROINF survey. Central to this is the significant benefit of two pump based treatments - apomorphine and intrajejunal levodopa infusion. Pump based treatment may remain an option even in patients who would otherwise be unsuitable for surgical therapy.

First presented in Poster form at the 'MDS 16th International Congress of Parkinson's Disease and Movement Disorders' the 'real life' observational study is the work of EUROPAR, an academic multi-disciplinary group of movement disorders specialists, supported by EPDA and the PD Non Motor Group and is the largest cohort study so far.

Commenting on the study, Professor Chaudhuri said:

"This is the first comparative study of effects of apomorphine vs levodopa infusion which, unlike conventional studies, includes non-motor as well as motor symptoms. These include sleep, mood, fatigue and pain, which are recognised as primary determinants of quality of life in Parkinson's."

To view this webinar, visit http://microsites.streamuk.com/euroinf
For further information contact media@britannia-pharm.com

Britannia
Pharmaceuticals Limited

CANCELLED
DUE TO FLU-LIKE SYMPTOMS

Copaxone. Helping RRMS patients maintain a working life
As effective as high-dose IFN-beta at reducing relapses, with less flu-like symptoms[1,2]

COPAXONE®
(glatiramer acetate)
Standing up to
RRMS every day