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Advances in Clinical Neuroscience & Rehabilitation

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When switching from another dopamine agonist follow manufacturer's guidance on discontinuation before initiating the patient on ropinirole immediate-release tablets. Only once sufficient symptomatic control is achieved can patients be switched to ropinirole prolonged-release tablets. If treatment is interrupted for one day or more, re-initiation by dose titration on ropinirole immediate-release tablets should be considered. Discontinue ropinirole gradually by reducing the daily dose over one week. *Renal or hepatic impairment:* No change needed in mild to moderate renal impairment. Not studied in severe renal or hepatic impairment – administration not recommended. *Elderly:* Clearance of ropinirole is decreased in patients over 65 years of age – titrate dose in normal manner. *Children:* Studies have not been carried out in patients under 18 years of age – do not give to children. **Contra-indications** Hypersensitivity to ropinirole or to any excipients, pregnancy, lactation and women of child-bearing potential unless using adequate contraception. **Special warnings and precautions** Caution advised in patients with severe cardiovascular disease and when co-administering with anti-hypertensive and anti-arrhythmic agents. Patients with a history or presence of major psychotic disorders should only be treated with dopamine agonists if potential benefits outweigh the risks. Pathological gambling, increased libido and hypersexuality reported in patients treated with dopamine agonists for Parkinson's disease, including ropinirole. Ropinirole has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with ropinirole. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Caution advised when taking other sedating medication or alcohol in combination with ropinirole. If sudden onset of sleep occurs in patients, consider dose reduction or drug withdrawal. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. 4 mg only – contains sunset yellow (E110) which may cause allergic reactions. **Drug interactions** Neuroleptics and other centrally active dopamine antagonists may diminish the effectiveness of ropinirole – avoid concomitant use. No dosage adjustment needed when co-administering with L-dopa or domperidone. No interaction has been seen between ropinirole and other drugs commonly used to treat Parkinson's disease but, as is common practice, care should be taken when adding a new drug to a treatment regimen. Other dopamine agonists may be used with caution. In a study with concurrent digoxin, no interaction seen which would require dosage adjustment. Metabolised by cytochrome P450 enzyme CYP1A2 therefore potential for interaction with substrates or inhibitors of this enzyme – ropinirole dose may need adjustment when these drugs are introduced or withdrawn. Increased plasma concentrations of ropinirole have been observed with high doses of oestrogens. In patients on hormone replacement therapy (HRT) ropinirole treatment may be initiated in normal manner, however, if HRT is stopped or introduced during ropinirole treatment, dosage adjustment may be required. No information on interaction with alcohol – as with other centrally active medications, caution patients against taking ropinirole with alcohol. Smoking induces CYP1A2 metabolism therefore if a patient stops or starts smoking during treatment with ropinirole, dose adjustment may be required. **Pregnancy and lactation** Do not use during pregnancy – based on results of animal studies. There have been no studies of ropinirole in human pregnancy. Do not use in nursing mothers as lactation may be inhibited. **Effects on ability to drive and use machines** Patients should be warned about the possibility of dizziness (including vertigo). Patients being treated with ropinirole and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved. **Adverse reactions** *Psychiatric disorders; common:* confusion, hallucinations, *uncommon:* psychotic reactions including delusion, paranoia, delirium. Patients treated with dopamine agonists for treatment of Parkinson's disease, including ropinirole, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation. *Nervous System Disorders; very common:* somnolence, dyskinesia, syncope *common:* dizziness (including vertigo), *uncommon:* extreme somnolence, sudden onset of sleep. *Vascular disorders; common/uncommon:* hypotension, postural hypotension. *Gastrointestinal disorders; very common:* nausea, *common:* abdominal pain, vomiting, dyspepsia, constipation. *General disorders and administrative site conditions; common:* peripheral oedema. *Hepatobiliary disorders;* very rare: hepatic enzymes increased. **Overdosage** Symptoms of overdose likely to be related to dopaminergic activity. **Legal category** POM. **Marketing Authorisation Holder** SmithKline Beecham plc t/a GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex UB11 1BT. **Further information is available from:** Customer Contact Centre, GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex UB11 1BT; Freephone 0800 221 441. **Prescribing information last revised:** May 2008. **REQUIP®** is a trademark of the GlaxoSmithKline group of companies.

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References:
1. Tompson D *et al.* Clinical Therapeutics 2007 Dec; 29(12): 2654-66.
2. Pahwa R *et al.* Neurology 2007; 68: 1108-15.

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September/October 2008

Additional web content **www.acnr.co.uk**
Cognitive Findings In Central Sleep Apnoea Syndrome
AJ Larner and EJ Ghadiali

Our first article is written by John Duncan, in which he discusses the role of MRI in epilepsy, not only in terms of identifying abnormalities, but in how it can be used to determine the success and consequences of surgery for this condition. In this richly illustrated article we benefit from an account from an authoritative author who has made a significant contribution in this area of clinical science.

In our second review article Mark Fish and Gareth Llewellyn summarise the current classification, pathogenesis, presentation, and treatment of Guillain-Barré syndrome. This relatively common, acute neurological problem has become more complex of late with the recognition that subtypes of it exist which are often associated with different anti ganglioside antibodies. This wonderfully succinct account helps clarify this and is a very useful summary of this condition.

At 8.52 am on the 8th October 2005 Arsalan Ahmad was doing a ward round on the Medical ITU in Islamabad when an earthquake struck killing 75,000 people. In the sobering account that follows he takes us through the process of trying to rehabilitate victims of the disaster using a more or less non existent system without any of the specialists many of us take for granted. Nevertheless, despite these problems the team took shape and helped in a way unimaginable before the natural disaster.

In our neurophysiology series David Allen and Ramamurthy Arunachalam treat us to a discussion on the investigation of patients with problems of muscle fibre excitability. In particular, they discuss how neurophysiology can help in the differential diagnoses of patients where this may be the case with a particular emphasis on critical illness myopathy – a condition which can often be hard to diagnose in the weak patient on ITU.

I have always assumed that infection in the context of stroke results from the physical disability that the stroke induces in the patient. Whilst this is true, Chris Price in his Controversies in Neurology article also introduces us to the concept that the stroke itself affects the immune system by suppressing it and by so doing increases the vulnerability to infections. Whether this is truly the case remains unproven but is an area eloquently covered in this article.

In a Medtronic sponsored article, Erlick Pereira, Dipankar Nandi and Tipu Aziz discuss the use of deep brain stimulation (DBS) in the treatment of a range of disorders that now extends to include psychiatric conditions (e.g. OCD) as well as pain syndromes. The evidence base for using DBS in these conditions is considered, as is the safety and cost-effectiveness for this therapy. In our other sponsored article in this issue of ACNR, Jane Bradshaw and Anita Rose discuss the important interplay between the affective and cognitive aspects of MS as well as fatigue. They emphasise the need to consider these aspects of disease in all cases of MS and that their optimal management may involve non-pharmacological measures as much as drug treatments.

As always we have our usual reviews, including a wonderfully comprehensive summary of the recent International Movement Disorder meeting in Chicago by Tom Foltynie.

So we hope you continue to enjoy the magazine and will let us know if there are other topics or areas you would like us to cover.

Roger Barker, Co-Editor,
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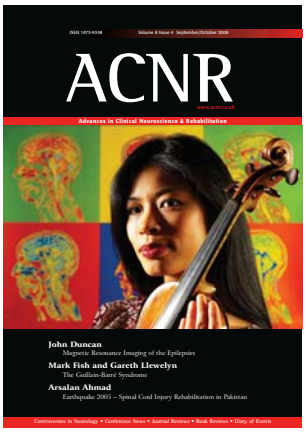

Cover Picture shows violinist Vanessa Mae, who recently featured in the BBC One Science series, "The Making of Me". Picture courtesy of the BBC.

Magnetic Resonance Imaging of the Epilepsies

John Duncan is a Consultant Neurologist at the National Hospital for Neurology and Neurosurgery, and the National Society for Epilepsy where he is Medical Director. He is Professor of Neurology at the Institute of Neurology UCL. Current research interests include structural and functional MRI, and the medical and surgical treatment of epilepsy.

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Much progress has been made over the last decade in the structural and functional imaging of the brain in epilepsy. The correlation of structure with function is essential in the understanding of the epilepsies and epileptic seizures, which may have a structural basis.

The superiority of magnetic resonance imaging (MRI) over X-ray computed tomography (CT) scanning in terms of sensitivity and specificity for identifying the cause of epilepsy in both adults and children is firmly established. The most common abnormalities identified are hippocampal sclerosis (HS), malformations of cortical development (MCD), vascular malformations, tumours, and acquired cortical damage. X-ray CT, however, may be preferred to MRI if a patient is disturbed or acutely unwell, as the patient is more accessible during the procedure. An X-ray CT scan is also valuable for the investigation of possible acute intracranial haematomas and skull fractures, and if there is a contra-indication to MRI such as a cardiac pacemaker or cochlear implants. CT is also useful as a supplement to MRI for clarification of possible intracranial calcification that is not shown easily by MRI.

Rapid advances are being made in MRI techniques so that patients who were previously regarded as being 'MRI negative' may have relevant abnormalities, which can be identified with contemporary optimal imaging.

MRI epilepsy protocol

In the non-acute situation an MRI scan should include T2-weighted, proton density and fluid attenuated inversion recovery (FLAIR) sequences to cover the whole brain in at least two orthogonal planes, with the minimum slice thickness possible. There should also be a T1-weighted volume acquisition with a partition size of 1.5mm or less, to allow reformatting in any orientation and three-dimensional reconstruction of the data set. The FLAIR sequence produces images in which parenchymal lesions have high signal and CSF gives low signal (Figure 1). This may help in the differential diagnosis of areas of high signal on T2-weighted images and increase the conspicuity of lesions. In the first two years of life, incomplete myelination results in poor grey-white matter contrast, making identification of cortical abnormalities difficult, and in these cases MRI may need to be repeated after 1-2 years.

The best practice is to obtain MRI in all patients with epilepsy, with the exception of those with a definite diagnosis of idiopathic generalised epilepsy or benign rolandic epilepsy of childhood with centrotemporal spikes, who go into early remission. MRI is particularly indicated in patients with one or more of the following:

- Onset of partial seizures, at any age
- Onset of generalised or unclassified seizures in the first year of life, or in adulthood
- Evidence of a fixed deficit on neurological or neuropsychological examination
- Difficulty obtaining seizure control with first-line antiepileptic drugs (AEDs)
- Loss of seizure control, or a change in the pattern of seizures.

In situations in which access to MRI is limited, essential indications for MRI are:

- Patients with partial or secondarily generalised seizures, and apparently generalised seizures, that are not controlled with AEDs
- Patients who develop progressive neurological or neuropsychological deficits.

A recent survey in the UK shows that optimal practice is not applied universally, and the quality of MRI scans obtained in community hospitals was significantly less than those obtained at an epilepsy centre.[1]

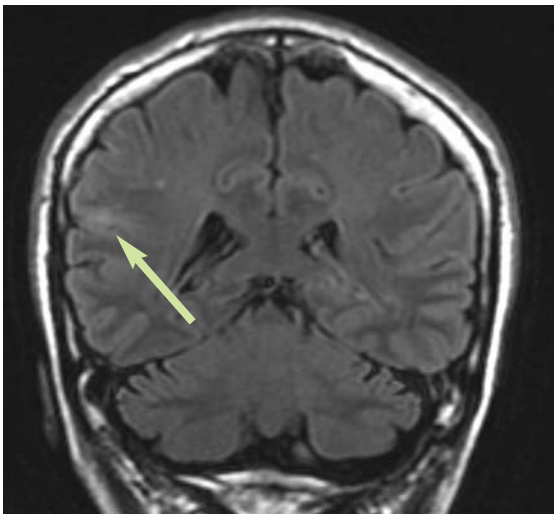

Figure 1: Coronal FLAIR sequence showing focal cortical dysplasia in right lateral inferior frontal gyrus, previous MRI had been unremarkable.

Presurgical candidates

Patients who are being considered for surgical treatment merit the most sophisticated MR imaging that is available and may also benefit from functional imaging with positron emission tomography (PET) and single photon emission computed tomography (SPECT). Identification of a structural lesion, however, does not always indicate the site of seizure origin. Clinical, EEG and other data all need to be considered.

A typical presurgical MRI protocol would be:

- Volume acquisition T1-weighted data set that is acquired in an oblique coronal orientation, orthogonal to the long axis of the hippocampi, and covers the whole brain in 0.9mm partitions. This sequence produces approximately cubic voxels, allowing for reformatting in any orientation, subsequent measurement of hippocampal morphology and volumes, and for three-dimensional reconstruction and surface rendering of the brain;
- Oblique coronal spin-echo sequence, with proton density (TE = 30), heavily T2-weighted (TE = 90 or 120) and FLAIR acquisitions that are orientated perpendicular to the long axis of the hippocampus, to demonstrate any increase in T2-weighted signal intensity.

Structural cerebral abnormalities underlying epilepsy identified with MRI

Hippocampal sclerosis

Hippocampal sclerosis (HS) is the single most common pathology underlying refractory partial seizure disorders, and is amenable to surgical treatment. The hippocampus is best visualised orthogonal to its long axis. This plane is parallel to the anterior border of the brainstem.

The MRI features of HS are hippocampal atrophy, best demonstrated with coronal T1-weighted images, and increased signal intensity within the hippocampus on T2-weighted images, decreased T1-weighted signal intensity and disruption of the internal structure of the hippocampus. Atrophy of temporal lobe white matter and cortex,

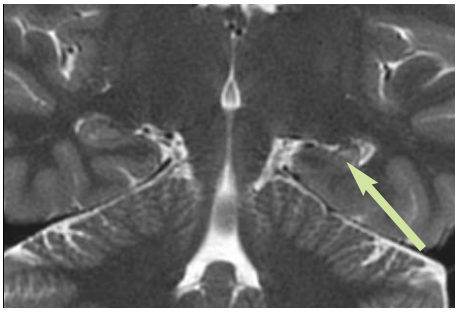

Figure 2: Coronal PROPELLER sequence showing left hippocampal sclerosis with atrophy and increased T2-signal.

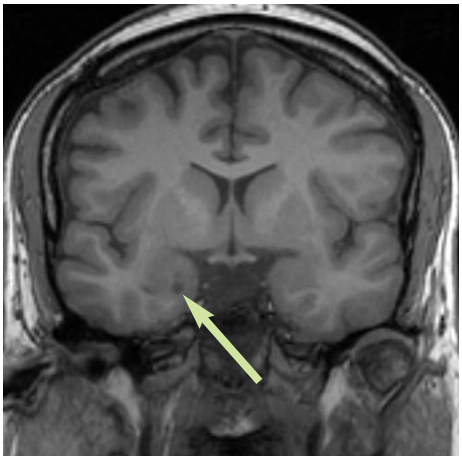

Figure 3: Coronal T1-weighted scan showing dysembryoplastic neuroepithelial tumour in right parahippocampal gyrus.

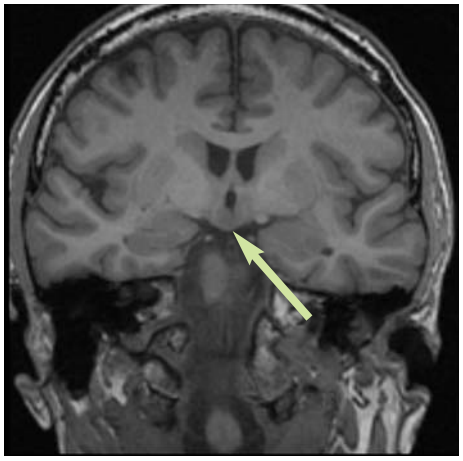

Figure 4: Coronal T1-weighted scan showing hypothalamic hamartoma.

dilatation of the temporal horn and a blurring of the grey-white matter margin in the temporal neocortex variably accompany HS. New sequences such as PROPELLER are showing the subregions of the hippocampus with increased definition.[2] (Figure 2)

Assessment of hippocampal atrophy can be improved by measuring hippocampal volumes. In clinical practice, hippocampal asymmetry of 20% or more is reliably visually apparent to skilled neuroimaging specialists, but lesser degrees of asymmetry require quantification. The T2-weighted signal intensity may be quantified by measurement of hippocampal T2 relaxation time (HT2) and this is a useful identifier of hippocampal pathology. Hippocampal T2 mapping has been shown to be robust at 3T as well as 1.5T.[3]

HS may be of varying severity along the length of the hippocampus and this may be identified by measurement of hippocampal cross-sectional area and T2.

Hippocampal volume corrected for intracranial volume and HT2 are useful for identifying any contralateral hippocampal abnormality which is very important when surgical resection of one hippocampus is being considered, as abnormality of the contralateral hippocampus indicates a risk of serious memory impairment.

Malformations of cortical development

Malformations of cortical development (MCD) are increasingly being recognised in patients with seizure disorders. The range of MCD identified with MRI include schizencephaly, agyria, diffuse and focal macrogyria, focal polymicrogyria, minor gyral abnormalities, subependymal grey matter heterotopias, bilateral subcortical laminar heterotopia, tuberous sclerosis, focal cortical dysplasia and dysembryoplastic neuroepithelial tumours (DNTs). Dysembryoplastic neuro-epithelial tumours are benign developmental tumours and commonly underlie refractory partial seizures. The features are of a focal, circumscribed cortical mass that may indent the overlying skull and also extend subcortically, with low signal intensity on T1-weighted images, high signal on T2-weighted images that is similar to CSF, and slightly higher signal intensity in the lesion than CSF on proton density images (Figure 3).

Hypothalamic hamartomas, sometimes associated with gelastic epilepsy, precocious puberty and cognitive impairment, are clearly demonstrable using MRI (Figure 4). More subtle abnormalities such as focal nodular heterotopia and band heterotopia may only be apparent if optimal MRI techniques are used.

Focal cortical dysplasia may result in refractory partial seizures, is surgically treatable and may be more easily identified on a FLAIR sequence (Figure 1)[4] and also by reconstructing the imaging dataset in curvilinear planes and by quantitative assessment of signal and texture.

Cavernomas

Cerebral cavernomas commonly underlie epilepsy and are circumscribed and have the characteristic appearance of a range of blood products. The central part contains areas of high signal on T1- and T2-weighted images, reflecting oxidised haemoglobin, with darker areas on T1-weighted images due to deoxyhaemoglobin. The ring of surrounding haemosiderin appears dark on a T2-weighted image. There may be calcification, which usually appears dark on T1- and T2-weighted images. There is no evidence of arteriovenous shunting.

Granulomas

Worldwide, the commonest causes of refractory focal epilepsy are cysticercosis and tuberculomas. These lesions have characteristic appearances on MRI that evolve with time and which, unless calcified, may resolve and be regarded as 'disappearing lesions'.

Post-acquisition processing of MRI

Voxel-based morphometry is a research tool that is suited to comparing groups of patients and controls, but is relatively insensitive at thresholds that do not give false positive results in individual patients.[5,6] VBM of T1–weighted datasets may be combined with T2-maps, and abnormalities largely coincide.[7]

Curvilinear reconstructions may increase the visibility of subtle neocortical lesions. Three-dimensional reconstruction of the neocortex may assist visualisation of abnormalities and surgical planning.

Longitudinal studies of the effect of epilepsy on the brain

Voxel and anatomically-based methods may be applied in longitudinal studies to identify subtle changes in the brain and to determine the effects of epilepsy. The majority of previous cross-sectional studies have inferred that more severe hippocampal damage is associated with a longer duration of epilepsy and a greater number of seizures. Two studies suggested atrophy of the hippocampus occurring over three years of active epilepsy in patients attending epilepsy clinics.[8,9]

A community-based study has shown that those with a history of a prior neurological insult had smaller neocortical volumes and an accelerated rate of brain atrophy, and that in patients with newly diagnosed epilepsy without a history of prior insult the rate of atrophy was no different from age-matched controls. Patients with chronic epilepsy, however, were more likely to have had significant loss of neocortical, hippocampal or cerebellar volume over 3.5 years. 54% of those with chronic epilepsy, 39% of those with newly diagnosed seizures and 24% of controls had areas of brain volume loss,[10] implying that secondary brain damage might occur in the context of chronic epilepsy.

Recent developments in MRI acquisition

Diffusion tensor imaging (DTI) reveals lesions found with conventional MRI and also abnormalities that are not visualised on routine sequences. Other new MRI sequences include magnetisation transfer ratio imaging, double inversion recovery imaging and fast FLAIR T2-mapping. The yield of these sequences, analysed with voxel-based methods, however, is limited, and there are issues of balancing sensitivity and specificity.[6]

Improved gradient performance is improving speed and spatial resolution. Phased array surface coils improve signal-to-noise ratio in superficial cortex and hippocampal regions and this may lead to improved spatial resolution, but have the limitation of restricted anatomical coverage. Imaging at high field strengths may also improve spatial resolution. 3T MRI scanners are now become increasingly regarded as standard clinical instruments.

Tractography

The visualisation of cerebral white matter tracks is a derivation of diffusion tensor imag-

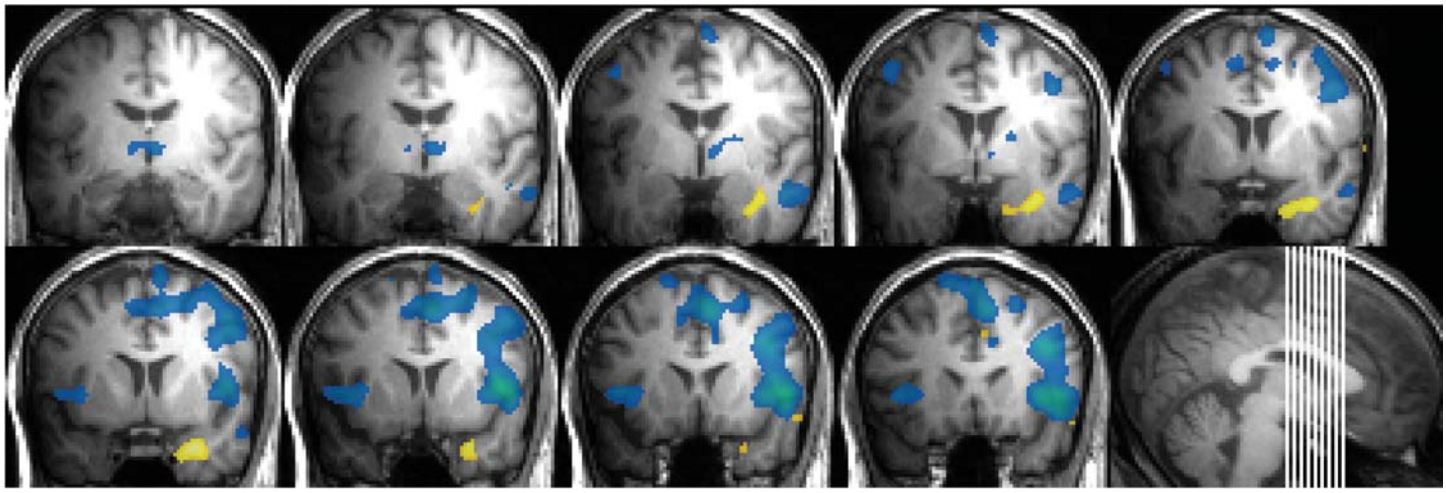

Figure 5: Coronal T1 MRI with fMRI activation associated with interictal epileptic discharges (yellow) and with language (verbal fluency) (blue).

Integrated structural and functional MRI can reveal the structural abnormalities underlying epilepsy and the relation of these to eloquent areas of the brain and areas involved in generating epileptic activity

ing. A variety of software packages is available, each with its own particular features, and the field is rapidly evolving. It needs to be appreciated that current in vivo tractography has a spatial resolution that is limited by voxel sizes of approximately 2mm,[3] and so the images do not indicate the white matter tracks per se, but the movement of water related to these tracks.[11]

Tracking from areas of functional activation gives an indication of the white matter connectivity of those functionally eloquent areas. This has been used to demonstrate the connectivity of Broca's area, the side-to side asymmetry in healthy controls, and the relative augmentation of connections on the right side in those with left TLE.[12]

Of immediate clinical relevance is the ability to visualise the optic radiation, as compromise of this during anterior temporal lobe resection (ATLR) may result in a visual field defect that can prevent driving.[13,14] This information can now be acquired pre-operatively and can inform the discussion with the patient regarding the risk of resection causing a visual field defect, and may lead to a modification of surgical technique.

Functional MRI

Ictal and inter-ictal epileptiform activity

Focal increases in cerebral blood delivery have been identified in patients with frequent interictal epileptic discharges (IED). Continuous recording of EEG and functional MRI (fMRI) is possible, with methods to remove the artifact on the EEG trace caused by the fMRI acquisition and the movement caused by the heart beat. Clinically, these methods will aid EEG interpretation and understanding of the pathophysiological basis of epileptic activity. Their application, utility and limitations in defining the irritative zone of the cortex (that generates IED) and its relationship with the epileptogenic zone (that gives rise to seizures) in patients in whom surgical treatment is undergoing evaluation. At present it is evident that the area generating IED may be at some distance from the area that generates seizures.[15]

Distinctive patterns of increased and deceased BOLD signal changes have been described in association with generalised spike-wave discharges, that reflect changes in perfusion.[16] In contrast, temporal lobe IED are associated with an increase in BOLD signal in the ipsilateral hippocampus and decreased BOLD signal in the precuneus (Figure 5).

EEG source localisation shows some concordance with areas of spike-related activations found with EEG-fMRI. Some BOLD activations are not matched by focal EEG changes. The implication is that the latter are the result of propagation of epileptic activity.[17]

BOLD changes may occur prior to the detection of IED on scalp EEG, implying that the pathological process precedes the appearance of scalp spikes by several seconds.[18]

Localisation and lateralisation of cognitive function

An important role for fMRI in patients with epilepsy is to delineate areas of brain that are responsible for specific functions, such as the primary sensory and motor cortex, and to identify their anatomical relation to areas of planned resection. In patients with cerebral lesions, the localisation of cognitive activation may differ from the pattern in normal subjects.

Lateralisation of language function may also be accomplished using fMRI[19] (Figure 5). There was a strong correlation between language lateralisation measured with the carotid amytal test, and using fMRI with a semantic decision task and other fMRI language studies have generally concurred with carotid amytal testing. The high proportion (33%) of left-TLE patients showing bilateral or right hemispheric language-related lateralisation with fMRI implied plasticity of language representation in patients with intractable TLE.[20]

fMRI results do not always accord with carotid amytal data and a combination of language tasks may be more reliable than a single task. Artefacts and technical difficulties may adversely affect both methods and false lateralisations may occur. Further, identification of the areas of brain involved in language is not the same as determining if someone can speak when half of the brain is anaesthetised.

As well as predicting the lateralisation of language function, fMRI may localise cerebral areas involved in language. For example, in a recent fMRI study of healthy right-handed subjects, tasks of reading comprehension activated the superior temporal gyri, and verbal fluency and verb generation tasks activated the left inferior and middle frontal gyri and left insula.[21]

In the future, these data may assist in planning surgical resections in the language-dominant hemisphere. There are, however, important caveats. Absence of activation on one language task does not guarantee that that part of the brain is inert. Conversely, an area that is activated may have only a peripheral and non-essential role in verbal communication.

Decline of language and memory function following anterior temporal lobe resection, particularly of verbal memory after left-sided anterior temporal lobe resection, is a major concern. The ability to localise eloquent cerebral regions and map neural networks involved in memory may lead to a more targeted / individualised surgical approach and may be able to predict post-operative memory decline.[22]

Early evidence is that memory fMRI may be a better predictor of material specific memory changes after anterior temporal lobe resection than baseline neuropsychological assessment or structural MRI.[23,24]

Functional MRI studies have also provided evidence for functional dissociation of verbal and visual memory encoding of prefrontal cor-

tices and mesial temporal lobe structures. and activation may be less on the side of the focus.

It is likely that, in the next 2-3 years, language and memory fMRI will become standard techniques in the consideration of the surgical treatment of epilepsy, and will assist in the optimal management of individual patients.

Acknowledgements

I am grateful to the Wellcome Trust, Medical Research Council, Action Medical Research, European Union, The National Society for Epilepsy and The UCL/UCLH Comprehensive Biomedical Research Centre for support.

References

1. Von Oertzen J, Urbach H, Jungbluth S, Kurthen M, Reuber M, Fernandez G, Elger CE. *Standard magnetic resonance imaging is inadequate for patients with refractory focal epilepsy.* J Neurol Neurosurg Psychiatry 2002;73(6):643-7.
2. Eriksson SH, Thom M, Bartlett PA, Symms MR, McEvoy AW, Sisodiya SM, Duncan, JS. *PROPELLER MRI visualizes detailed pathology of hippocampal sclerosis.* Epilepsia 2008;49(1):33-9.
3. Bartlett PA, Symms MR, Free SL, Duncan JS. *T2 relaxometry of the hippocampus at 3T.* AJNR Am J Neuroradiol 2007;28(6):1095-8.
4. Focke NK, Symms MR, Burdett JL, Duncan JS. *Voxel-based analysis of whole brain FLAIR at 3T detects focal cortical dysplasia.* Epilepsia 2008;49(5):786-93.
5. Colliot O, Bernasconi N, Khalili N, Antel SB, Naessens V, Bernasconi A. *Individual voxel-based analysis of gray matter in focal cortical dysplasia.* Neuroimage 1-1-2006;29(1):162-71.
6. Salmenpera TM, Symms MR, Rugg-Gunn FJ, Boulby PA, Free SL, Barker GJ, Yousry TA, Duncan, JS. *Evaluation of quantitative magnetic resonance imaging contrasts in MRI-negative refractory focal epilepsy.* Epilepsia 2007;48(2):229-37.
7. Pell GS, Briellmann RS, Pardoe H, Abbott DF, Jackson GD. *Composite voxel-based analysis of volume and T2 relaxometry in temporal lobe epilepsy.* Neuroimage 1-2-2008;39(3):1151-61.
8. Briellmann RS, Berkovic SF, Syngeniotis A, King MA, Jackson GD. *Seizure-associated hippocampal volume loss: a longitudinal magnetic resonance study of temporal lobe epilepsy.* Ann Neurol 2002;51(5):641-4.
9. Fuerst D, Shah J, Shah A, Watson C. *Hippocampal sclerosis is a progressive disorder: a longitudinal volumetric MRI study.* Ann Neurol 2003;53(3):413-6.
10. Liu RS, Lemieux L, Bell GS, Hammers A, Sisodiya SM, Bartlett,PA, Shorvon SD, Sander JW, Duncan JS. *Progressive neocortical damage in epilepsy.* Ann Neurol 2003;53(3):312-24.
11. Yogarajah M, Duncan JS. *Diffusion-based magnetic resonance imaging and tractography in epilepsy.* Epilepsia 2008;49(2):189-200.
12. Powell HW, Parker GJ, Alexander DC, Symms MR, Boulby PA, Wheeler-Kingshott CA, Barker GJ, Koepp MJ, Duncan, JS. *Abnormalities of language networks in temporal lobe epilepsy.* Neuroimage 15-5-2007;36(1):209-21.
13. Powell HW, Parker GJ, Alexander DC, Symms MR, Boulby PA, Wheeler-Kingshott CA, Barker GJ, Koepp MJ, Duncan JS. *MR tractography predicts visual field defects following temporal lobe resection.* Neurology 23-8-2005;65(4):596-9.
14. Nilsson D, Starck G, Ljungberg M, Ribbelin S, Jonsson L, Malmgren K, Rydenhag B. *Intersubject variability in the anterior extent of the optic radiation assessed by tractography.* Epilepsy Res 2007;77(1):11-6.
15. Laufs H, Duncan, JS. *Electroencephalography/functional MRI in human epilepsy: what it currently can and cannot do.* Curr Opin Neurol 2007;20(4):417-23.
16. Hamandi K, Laufs H, Noth U, Carmichael DW, Duncan JS, Lemieux L. *BOLD and perfusion changes during epileptic generalised spike wave activity.* Neuroimage 15-1-2008;39(2):608-18.
17. Grova C, Daunizeau J, Kobayashi E, Bagshaw AP, Lina JM, Dubeau F, Gotman J. *Concordance between distributed EEG source localization and simultaneous EEG-fMRI studies of epileptic spikes.* Neuroimage 15-1-2008;39(2):755-74.
18. Hawco CS, Bagshaw AP, Lu Y, Dubeau F, Gotman, J. *BOLD changes occur prior to epileptic spikes seen on scalp EEG.* Neuroimage 1-5-2007;35(4):1450-8.
19. Gaillard WD, Balsamo L, Xu B, Grandin CB, Braniecki SH, Papero PH, Weinstein S, Conry J, Pearl PL, Sachs B, Sato S, Jabbari B, Vezina LG, Frattali C, Theodore WH. *Language dominance in partial epilepsy patients identified with an fMRI reading task.* Neurology 23-7-2002;59(2):256-65.
20. Adcock JE, Wise RG, Oxbury JM, Oxbury SM, Matthews PM. *Quantitative fMRI assessment of the differences in lateralization of language-related brain activation in patients with temporal lobe epilepsy.* Neuroimage 2003;18(2):423-38.
21. Powell HW, Parker GJ, Alexander DC, Symms MR, Boulby PA, Wheeler-Kingshott CA, Barker GJ, Noppeney U, Koepp MJ, Duncan JS. *Hemispheric asymmetries in language-related pathways: a combined functional MRI and tractography study.* Neuroimage 1-8-2006;32(1):388-99.
22. Richardson MP, Strange BA, Duncan JS, Dolan RJ. *Memory fMRI in left hippocampal sclerosis: optimizing the approach to predicting postsurgical memory.* Neurology 14-3-2006;66(5):699-705.
23. Powell HW, Richardson MP, Symms MR, Boulby PA, Thompson PJ, Duncan JS, Koepp MJ. Reorganization of verbal and nonverbal memory in temporal lobe epilepsy due to unilateral hippocampal sclerosis. Epilepsia 2007;48(8):1512-25.
24. Powell HW, Richardson MP, Symms MR, Boulby PA, Thompson PJ, Duncan JS, Koepp MJ. *Preoperative fMRI predicts memory decline following anterior temporal lobe resection.* J Neurol Neurosurg Psychiatry 2008;79(6):686-93.

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The Guillain-Barré Syndrome

A subacute onset of areflexic paralysis with recovery accompanied by acellular cerebrospinal fluid with an elevated protein was described in two soldiers in 1916 by the French neurologists Georges Guillain, Jean-Alexandre Barré, and Andre Strohl. The eponym Guillain-Barré Syndrome (GBS) covers a spectrum of presentations and pathologies.

Classification (see Figure 1)

Classification is according to clinical features; time course, predominance of sensory or motor involvement, and involvement of cranial nerves.[1] Nerve conduction usually distinguishes between demyelination and primary axonal degeneration, but the timing of nerve conduction studies is important - indices may be normal in the very early stages and when the illness is very advanced the nerves may be unexcitable. By definition the onset phase (the time from first to worst symptoms) in GBS is less than four weeks. Classification of variants based upon antibody profile rather than clinical features and neurophysiology has been proposed.[2]

Epidemiology

Worldwide, the incidence of GBS is 0.6-4.0 per 100,000. Men are 1.5 times more likely to be affected. In the West, incidence increases with age, but in China the incidence of all forms across age groups is more uniform. Acute motor axonal neuropathy (AMAN) is the commonest form in China and shows a marked seasonal variation and paediatric predominance;[3] elsewhere, cases are mostly sporadic but clusters and epidemics do occur, often in association with outbreaks of bacterial enteritis. Rabies vaccination (which contains brain material) is followed by GBS in about one in a thousand cases. There may be a very small increase (one per million over background) in risk of GBS after influenza vaccination. A small proportion of patients report symptom recurrence after routine immunisation but relapse is rare.[4] Evidence of preceding Campylobacter jejuni infection is found in about 25% of GBS cases. Cytomegalovirus and Epstein–Barr virus occur in about 10% of cases.[5]

Pathogenesis[1]

Antibodies generated by the immune response to infection and directed against neural epitopes (the molecular mimicry hypothesis) may be the basis of axonal GBS and Miller-Fisher Syndrome (MFS). Strains of C jejuni which trigger GBS are more likely to possess lipo-oligosaccharide epitopes similar to gangliosides GM1, GD1a or

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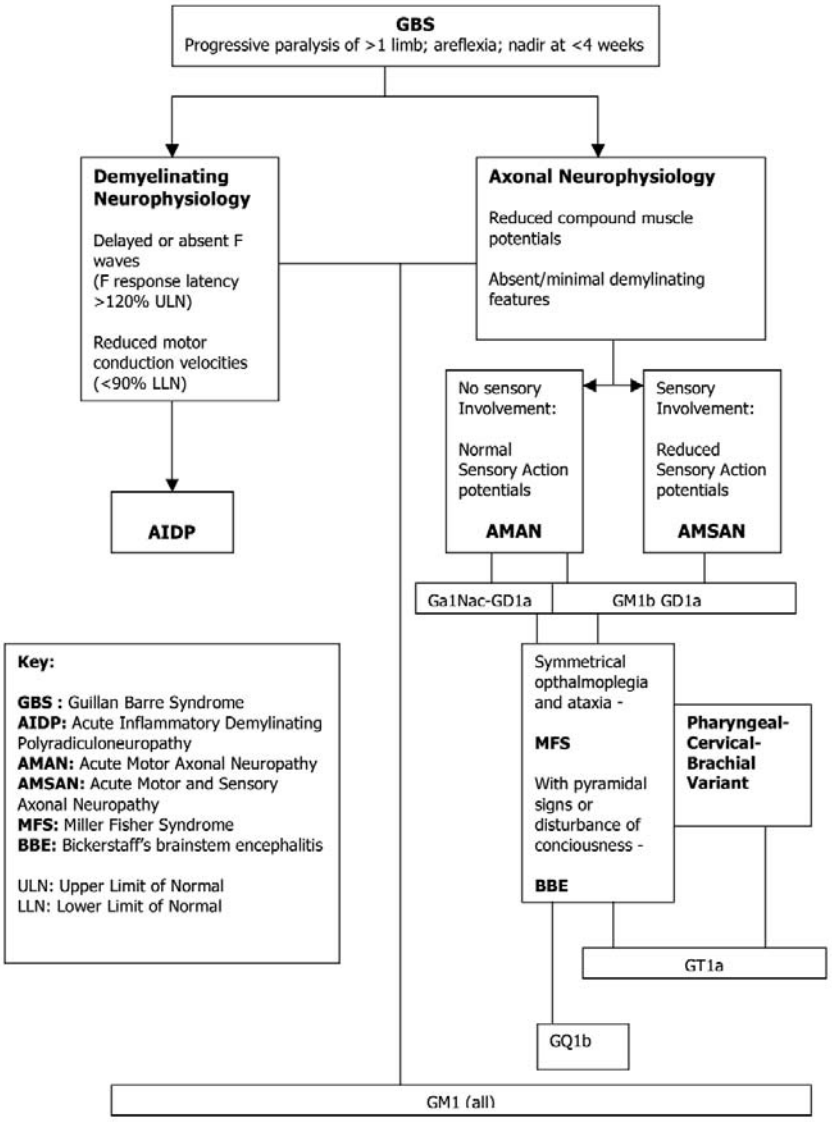

Figure 1: Clinical and neurophysiological classification of GBS and variants showing antibody associations.

Figure 2: Differential diagnosis of GBS

Syndrome	*Aetiology*	*Suggestive Features*
Brainstem	*Stroke* *Encephalitis*	*Cranial nerve Involvement* *Encephalopathy* *Upper motor neurone signs*
Myelopathy	*Acute compressive lesion* *Myelitis*	*No signs or symptoms above neck* *Sensory (and motor) level* *Sphincter involvement* *Localising symptoms and signs* *Inflammatory CSF*
Anterior Horn	*Poliovirus* *Other enteroviruses*	*Endemic area. Typically in children. Acute febrile illness. Meningism. Asymmetric paresis* *Absence of sensory involvement*
Peripheral Neuropathy	*Diphtheria* *Lyme disease* *Porphyria* *Vasculitis* *Lymphoma* *Paraneoplastic* *HIV sero-conversion* *Toxic*	*Palatal palsy, bulbar dysfunction. Cellular CSF. Raised CSF protein* *Exposure, headache, arthralgia, erythema migrans rash, facial weakness* *Abdominal pain, psychiatric illness. Lymphocytic CSF* *Systemic disease, rash, painful. No systemic markers if vasculitis is confined to peripheral nerves* *Systemic disease. Rash. Elevated ESR. Lymphocytic CSF* *large fibre involvement* *A form of GBS. Recent exposure. Mild lymphocytic pleocytosis. Probably under-diagnosed* *Sub-acute axonopathy. Exposure (could be iatrogenic / occupational / environmental / intentional)*
Neuromuscular junction	*Myasthenia* *Botulism*	*Absence of sensory symptoms or signs* *Bowel symptoms, dysphagia, autonomic features, mydriasis, pure motor*
Muscle	*Inflammatory myopathy* *Hypokalaemic periodic paralyses*	*Reflexes may be preserved. Very elevated CK* *Episodic. Inherited (AD). May wake with weakness. Cranial nerves typically spared*

GQ1b. These antigens seem to induce neuropathy-causing ganglioside antibodies in animal models. The titre of anti-GQ1b correlates with disease severity in MFS, and GQ1b ganglioside is concentrated in nerves supplying extra-ocular muscles.

The pathophysiology of the more common acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is less well understood. T cells appear to play an important part in inducing macrophage attack against Schwann cells or myelin. The correlation between neurophysiology and clinical and immunological markers is only approximate.

Presenting features and diagnosis

Although GBS is generally considered a straight-forward diagnosis by neurologists, multiple physician assessments prior to correct diagnosis are common.[6] Patients may have been screened and signs matured by the time they reach neurological evaluation. In a casualty case series, less than 50% of patients had weakness as their main complaint, with a minority presenting with the 'typical' symptoms of weakness and numbness. One fifth presented initially with only sensory complaints.[6]

Whilst most patients presenting with an acute flaccid paralysis will have GBS, the differential is wide. GBS is a clincal diagnosis, and in practice, investigations are employed to exclude alternative possibilities. (See Figure 2)

Management

i) Supportive[7] (see Figure 3)

There are no studies specifically addressing thromboprophylaxis in GBS, however this is an important aspect of supportive care.

Dysautonomia - which includes paralytic ileus and bronchial dysfunction as well as instability of pulse and blood pressure - occurs in 20% of patients with GBS. Wide blood pressure swings may augur severe bradycardia, which can precede asystole. These complications occur mostly in severely affected patients with generalised weakness and respiratory failure.

Neuromuscular respiratory insufficiency ensues in 17-30% of patients with GBS. Accumulating secretions secondary to bulbar and bronchial mucosal dysfunction may further compromise gas-exchange. Rapid progression and pattern of involvement signal risk of respiratory compromise,[8] (see Figure 4).

Pain occurs in 90% of patients with GBS and at least six types of pain have been identified[9] (see Figure 3). Commonly, sensory symptoms exceed the signs. Neurogenic pain may arise from the loss of inhibition of the substantia gelatinosa by larger myelinated fibres and from small unmyelinated C fibres. Radicular pain and meningeal irritation may be secondary to inflammation of spinal nerve roots. Weakness of paraspinal muscles may result in mechanical back pain. Rate related cardiac ischaemic pain and discomfort from constipation and urinary

Figure 3: Important aspects of supportive management in GBS

Thromboprophylaxis	*Dysautonomia*	*Neuromuscular respiratory and bulbar compromise*	*Pain*	*Early rehabilitation*
• *Low molecular weight heparin* • *Compression stockings*	*2-4 hourly monitoring of:* • *Blood pressure* • *Pulse* *(increase frequency depending upon severity and rate of progression. Cardiac monitor if non-ambulant.)* • *Daily urine output*	• *Vital capacity – 12 hourly* • *Respiratory rate – 2-4 hourly* *(increase frequency if deteriorating or evidence of respiratory distress (see Figure 4))* • *Daily assessment of facial strength and swallow* • *Daily assessment of limb and neck strength*	*Identify type of pain(s)* • *Consider: Dysesthetic, radicular, meningitic, myalgic, arthralgic, visceral* • *Choose simple analgesic or anti-neuropathic agent as appropriate.*	• *Mobilisation* • *Prevent formation of contractures – splints* • *Bed sore prevention* • *Nutrition*

Figure 4: Predictors of mechanical ventilation and warning signs of respiratory failure in GBS

Risk factors for mechanical ventilation	*Warning signs of impending respiratory failure*
• *Rapid progression*	• *Tachypnoea*
• *Weak cough*	• *Tachycardia*
• *Bifacial weakness*	• *Sweating*
• *Inability to stand*	• *Use of accessory muscles*
• *Inability to lift elbow off bed*	• *Asynchronous movements of chest and abdomen*
• *Inability to lift head off bed*	• *Rapidly declining vital capacity or vital capacity <50% of baseline or vital capacity approaching 15ml/Kg*
• *Chest radiograph abnormalities*	
• *Elevated liver enzymes*	
• *Vital Capacity <20ml/Kg*	

retention could be mis-interpreted as radicular pains. Both carbamazepine and gabapentin are effective in reducing pain scores and requirement for opioid analgesia in GBS patients. Gabapentin seems to have a quicker onset and be most effective.[10] Amitriptyline is also frequently used.

ii) Immunotherapy

When given to non-ambulant patients within four weeks of presentation, intra-venous immunoglobulin (IVIg) and plasma exchange (PE) have a similar efficacy both in terms of disability measured one month after treatment and long term outcome.[11] IVIg is usually used (0.4g/Kg body weight /day for five days) because of convenience despite the theoretical risk of transmission of virus or prion. IVIg may work by multiple mechanisms, including blocking Fc receptors, provision of anti-ideotypic antibodies, interference with complement activation and T-cell regulation.

Monoclonal antibodies show promise as future treatments. Eculizimab disrupts the complement cascade, protecting terminal motor nerves from anti-GQ1b antibody induced injury.[12]

Rehabilitation and outcome

Death or severe residual disability occurs in up to 17% of patients, and lesser degrees of disability and fatigue are common in the remainder; 35 to 45% report persisting adverse changes in their employment, domestic function and leisure activities.[13] Outlook is poorer in the elderly, in those with previous diarrhoea, rapid onset, severe deficit at nadir, initial axonal involvement, unexcitable motor nerves, and C jejuni or CMV infection.[5] One Chinese study with a large population of children showed no difference in recovery time between AMAN and AIDP, with a median time to regain the ability to walk with assistance being one month.[3]

Although 40% of patients require inpatient rehabilitation, there is a paucity of systematic research of rehabilitation strategies in GBS. Medium term complications to be aware of in the rehabilitation setting include decubitus ulcers, peripheral nerve compression, hypercalcaemia, and disturbed central respiratory drive secondary to persistent ventilatory compromise.[14] Decreased range of movement in joints may be caused by contractures, muscle injury, pain, thrombosis, fractures and heterotopic ossification (of which elevated alkaline phosphatase is a useful indicator).[15] Patients should be advised that over-exercise may lead to paradoxical weakening.

Future directions

The clinical phenotype of GBS is likely to be due not only to the immunogenic components of the infecting organism, but also the host immune response and distribution of epitopes. Examination of the immune response in GBS variants will allow the development of more targeted therapies such as complement inhibition, anti-cytokine therapy and specific antibody adsorption.[1]

References

1. Hughes RA, Cornblath DR. *Guillain-Barré syndrome.* Lancet 2005;366(9497):1653-66.
2. Odaka M, Yuki N, Hirata K. *Anti-GQ1b IgG antibody syndrome: clinical and immunological range.* J Neurol Neurosurg Psychiatry 2001;70(1):50-5.
3. Ho TW, Li CY, Cornblath DR, Gao CY, Asbury AK, Griffin JW, et al. *Patterns of recovery in the Guillain-Barré syndromes.* Neurology 1997;48(3):695-700.
4. Pritchard J, Mukherjee R, Hughes RA. *Risk of relapse of Guillain-Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy following immunisation.* J Neurol Neurosurg Psychiatry 2002;73(3):348-9.
5. Hadden RD, Karch H, Hartung HP, Zielasek J, Weissbrich B, Schubert J, et al. *Preceding infections, immune factors, and outcome in Guillain-Barré syndrome.* Neurology 2001;56(6):758-65.
6. McGillicuddy DC, Walker O, Shapiro NI, Edlow JA. *Guillain-Barré syndrome in the emergency department.* Ann Emerg Med 2006;47(4):390-3.
7. Hughes RA, Wijdicks EF, Benson E, Cornblath DR, Hahn AF, Meythaler JM, et al. *Supportive care for patients with Guillain-Barré syndrome.* Arch Neurol 2005;62(8):1194-8.
8. Lawn ND, Fletcher DD, Henderson RD, Wolter TD, Wijdicks EF. *Anticipating mechanical ventilation in Guillain-Barré syndrome.* Arch Neurol 2001;58(6):893-8.
9. Pentland B, Donald SM. *Pain in the Guillain-Barré syndrome: a clinical review.* Pain 1994;59(2):159-64.
10. Pandey CK, Raza M, Tripathi M, Navkar DV, Kumar A, Singh UK. *The comparative evaluation of gabapentin and carbamazepine for pain management in Guillain-Barré syndrome patients in the intensive care unit.* Anesth Analg 2005;101(1):220-5.
11. Hughes RA, Swan AV, Raphael JC, Annane D, van Koningsveld R, van Doorn PA. *Immunotherapy for Guillain-Barré syndrome: a systematic review.* Brain 2007;130(Pt 9):2245-57.
12. Halstead SK, Zitman FM, Humphreys PD, Greenshields K, Verschuuren JJ, Jacobs BC, et al. *Eculizumab prevents anti-ganglioside antibody-mediated neuropathy in a murine model.* Brain 2008;131(Pt 5):1197-208.
13. Bernsen RA, de Jager AE, Schmitz PI, van der Meche FG. *Long-term impact on work and private life after Guillain-Barré syndrome.* J Neurol Sci 2002;201(1-2):13-17.
14. Meythaler JM. *Rehabilitation of Guillain-Barré syndrome.* Arch Phys Med Rehabil 1997;78(8):872-9.
15. Zeilig G, Weingarden HP, Levy R, Peer I, Ohry A, Blumen N. *Heterotopic ossification in Guillain-Barré syndrome: incidence and effects on functional outcome with long-term follow-up.* Arch Phys Med Rehabil 2006;87(1):92-5.

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Selection and Recruitment 2008

Following the debacle of medical recruitment in 2007, we followed the plans for 2008 carefully. Thankfully, selection was carried out in house, and the neurology community had rather more say in the proceedings, to some good effect. A large number of good candidates were interviewed (~85), and approximately 40 of them selected for appointment, either starting in August 2008, or for deferred entry.

Figure 1
Single nationalised interview
Advantages:
1. Time and cost efficient (interviewers and interviewees)
2. Removes forced choices, i.e. with multiple interviews
3. Identical interview conditions

Disadvantages
1. Single opportunity to perform well
2. Only one recruitment round per year
3. Unknown format for most
4. Less local involvement

What was different?

While in the past all recruitment was performed at a local level, there are increasing moves to centralise and streamline this process, using national application forms, selection centres, and standardised interview procedures. There are obvious advantages and disadvantages in national recruitment (which was the choice of the then lead dean for Neurology, Prof William Burr), summarised in Figure 1. A standardised, OSCE-style format was used, encompassing clinical, research /teaching and ethics/governance stations. Performance was scored, and appointments were made using a matching algorithm based upon the candidates' choice of location (up to 4). Because of the new format this year, and in response to concerns from several trainees, we conducted a piece of research looking at satisfaction with the process. A short questionnaire was sent by email to all candidates who were interviewed. Responses were returned by 41 individuals.

• 13 got the job they wanted • 19 were unsuccessful • 10 had not completed research • 27 were in the process of completing a research degree • 4 had completed a research degree • Candidates were more likely to be satisfied with the process if they were then offered a post (p=0.004).

What did trainees think?

Application form

In general, trainees were positive about the application form, indicating that they felt it enabled them to express themselves well.

Clinical stations

These were felt to be a good concept, and appropriate for inclusion in the interview process, but the way in which questions were asked was unpopular. There were concerns that the validity of an 'exam approach' was untested, that the questions asked were unnecessarily indirect, and that the marking scheme was overly rigid.

Personal Achievements

There was a strong feeling that the interview structure inhibited personal expression, and that previous achievements were not given due credit.

Communication

Candidates felt that they were not properly informed regarding the shortlisting, interview, and appointment process, particularly relevant as deadlines were changed to meet with deanery capacity. Almost all respondents wanted more information about the training programmes being offered (in summary form or including job descriptions for each post) prior to making choices.

Local vs. national selection

Although national selection was supported by some, there was a clear call from the majority for a return to local selection procedures.

Organisation

There were lots of positive comments regarding the organisation of the day, commenting on the friendliness of the atmosphere, and comparing positively with experiences in 2007.

What we're doing about it

There were clear problems, but none of these are insurmountable. There is a clear call for local selection, not only from trainees, but also from consultants, although a final decision about next year's process is yet to be taken. Whatever form next year's interviews take, we hope the organisers will take note of these results. We support the notion that previous achievements should be given due credit (either through more points for the CV, or a CV-based interview station). In addition, we believe that improving communication with candidates is vital to the success of any process. We are using the information we've gathered to inform further discussions with the Lead Dean for Neurology and the SAC, with a view to improving the experience next year.

Biba Stanton ABN Trainees Committee secretary, Royal Free Hampstead NHS Trust.
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Cognition, Depression and Fatigue in Multiple Sclerosis

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Multiple sclerosis (MS) is the most frequent central nervous system (CNS) disease of early and mid adulthood, 20-40 years of age,[1] affecting approximately 85,000 people in the UK.[2]

The various neurological symptoms associated with MS result from the neurological damage that occurs throughout the CNS, brain and spinal cord.[3] MS is a heterogeneous disease, with substantial variability in the clinical course and symptoms among individual suffers.[4]

Often overlooked are the multiple neuropsychological symptoms associated with MS, including cognitive dysfunction, fatigue and depression. Neuropsychological disorders are prevalent in MS, however, the effect of these symptoms has been underestimated and neglected in the past.[5] It is, however, now recognised that these symptoms are linked to considerable disability and impairment of daily living. Depression and fatigue, for example, have been shown to be significant and independent predictors of quality of life (QoL).[6] Early identification and management of cognitive dysfunction, fatigue and depression may have a significant impact on patients' work and social relationships, and overall QoL.

Impact of neuropsychological symptoms

Cognitive impairment

Cognitive impairment occurs in between 45% and 65% of MS sufferers[7] and can present in patients at any time during their disease process from diagnosis. The severity of cognitive dysfunction can vary from mild to severe and the most frequently affected cognitive domains are memory, attention, information processing, and executive function.[3,8] Cognitive impairment has a tremendous impact on patients' lives over the long-term, mainly due to the impaired information processing, lack of attention/ability to concentrate, and decline in recent memory.[9] It can also lead to significant restrictions in the intellectual abilities of patients.[10] Furthermore, cognitive impairment may affect driving performance.[11]

Cognitive impairment may manifest early in the disease course prior to physical disability, and although it worsens with disease progression it is neither predictable nor linear. It has been estimated, however, that following a new diagnosis of MS, the prevalence of moderate and severe cognitive dysfunction doubles every four years.[12]

Several screening tests are available for diagnosing and assessing cognition and include a core battery of neuropsychological tests e.g. attention/concentration, memory executive functions etc. Cognitive testing in patients with MS, however, is expensive and complex, and is complicated by the lack of standardised testing.[5]

Fatigue

Fatigue is extremely common in MS and is experienced by 78%-91% of patients.[13-15] Furthermore, the majority of patients with MS (up to 69%) consider fatigue to be one of the most debilitating aspects of the disease.[13-15] Fatigue is a multi-dimensional symptom and is characterised by an overwhelming sense of tiredness, a feeling of complete exhaustion, or a total lack of physical or mental energy, and is often the first noticeable sign that patients with MS experience.[14,16] Fatigue in MS is very different from that experienced by healthy individuals as it has a tremendous affect on physical and cognitive functioning, and is known to be exacerbated by heat.[13,17] Fatigue can be so severe as to affect work and social relations and daily mental and physical activities,[18] and is a major reason cited for unemployment among patients with MS.[19] Fatigue, however, is a subjective symptom that varies from patient to patient. Consequently, it can be difficult to measure. Although assessment tools such as the Fatigue Impact Scale (FIS), the Fatigue Severity Scale (FSS), and the Expanded Disability Status Scale (EDSS) are available for use, in clinical practice they tend to be subjective, self reported questionnaires rather than objective measures of fatigue.[20]

Depression

Major depression is common in MS, with a lifetime prevalence of up to 50%.[21] The annual prevalence of major depression is much higher in patients with MS aged between 18-45 years old (25%)[22] than the general population (6%).[23] Depression is usually diagnosed early in the course of the disease and is associated with increased suicide rates (1.95% to 18.5%).[21,24] The presence of depression can reduce adherence to treatment and seriously affect patient self care.[10] The high incidence of depression and the increased risk of suicide in depressed patients with MS make it very important to actively identify and treat depression. There are several questionnaire based assessments tools available that identify depression, including the Hamilton Rating Scale for Depression (HRSD).[6] A diagnosis of major depression must include being sad, depressed mood, and/or loss of interest and pleasure in usual activities.[25]

Causes of neuropsychological symptoms

Cognition, fatigue and depression all present as a direct result of the CNS damage that occurs in MS. Structural changes in the brain are responsible for cognitive decline. Cognitive impairment has been shown to be linked to white matter disease within the cerebral hemispheres of MS sufferers. The deficits in cognitive functioning have been shown to correlate with brain lesions[26] and atrophy, using magnetic resonance imaging (MRI).[27] The extent of cognitive decline is dependant on lesion location and size, particularly in the frontal lobes.[28]

Although the aetiology of depression in MS remains unclear, it too is linked directly to brain lesions and atrophy. Furthermore, it appears to be associated with lesions in specific areas of the brain, in particular the left anterior temporal/parietal regions.[25] MRI has also shown that there is a correlation between global brain volume loss and the incidence of depression.[29] Psychosocial factors such as illness, intrusiveness and the burden of the disease also have an impact on depression in chronic disease such as MS.

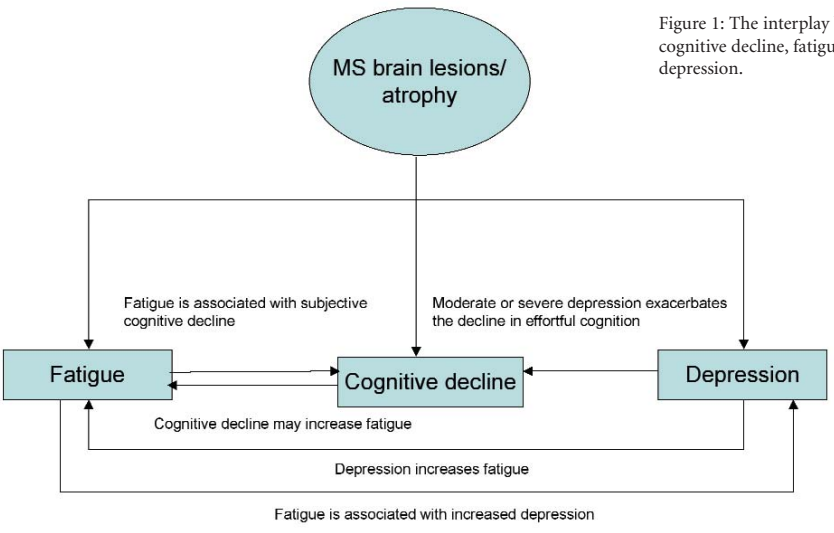

Figure 1: The interplay between cognitive decline, fatigue and depression.

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The underlying pathogenesis of fatigue in MS is the least well understood of the neuropsychological symptoms. Fatigue may be caused by the disease process (primary fatigue) or by other problems such as insomnia, infections, or psychological reasons i.e. coping with the disease (secondary fatigue).[20] There is some evidence from neuroimaging that suggests that fatigue is associated with brain atrophy[30] and diffuse axon damage in some patients.[31]

Complex interrelation between neuropsychological symptoms

There is a complex interplay between cognitive impairment, fatigue and depression in patients with MS (Figure 1). It is recognised that healthy people with depression are susceptible to cognitive deficits.[25] Despite this and rather curiously, most early studies showed no correlation between depression and cognitive decline in MS.[25] These early studies, however, focussed on the effect of depression on cognitive performance.[25] More recent studies seem to offer an explanation for these early findings.[32-34] These recent studies suggest that in MS, cognitive performance may be unaffected and that effortful aspects of cognition, rather than automatic information processing, are influenced by moderate or severe depression. Consequently, areas of cognition that require attention such as tests of information processing, working memory and executive functioning are affected by depression, while performance often remains normal.[25] This is supported by Diamond et al who have shown that slower information processing correlates with higher levels of depressed mood.[35] A significant degree of depression, however, must be present before there is any effect on cognition.[36]

There is also evidence showing that depression has an effect on fatigue in MS. One study has demonstrated a significant correlation between fatigue and mood level, and suggests that mental rather than physical fatigue is affected by the presence of depression.[37] Furthermore, treating depression seems to have a positive effect on subjective measures of fatigue.[38]

The link between fatigue and cognitive decline is less clear; however, there is likely to be an interaction between the two symptoms.[5] There is a strong association between self reported fatigue and a decline in subjective, but not objective, measures of cognition.[39] Indeed, many patients report that their cognitive performance is reduced by fatigue.[40] One recent study, however, has shown a correlation between fatigue and slower information processing using an objective measure of cognition, the California Verbal Learning Test (CVLT).[35] It is also possible that cognitive impairment may increase fatigue.[5]

Managing neurophyschological symptoms

Clearly cognition, depression and fatigue have a tremendous impact on patients' QoL and everyday living. It is important, therefore, to detect and treat each of these conditions early in MS. Treating depression and fatigue is imperative not only because they are both common in MS and have a huge affect on the lives of suffers, but also because treatment of these symptoms is likely to have a positive impact on cognitive function. The interplay between these neuropsychological symptoms requires a multi-modal approach to treatment. Careful monitoring and individualisation of pharmacological and non-pharmacological interventions is necessary in order to manage the neuropsychological symptoms of MS.

Cognitive decline

There are currently no approved medications for treating cognitive decline in MS; however, treatment of underlying disease with disease-modifying drugs has been shown in the case of one drug to slow the progression of cognitive decline.[41] Four disease-modifying agents are currently available for the treatment of relapsing MS, interferon beta-la intramuscular (IFNβ-1a-IM), interferon beta-lb (IFNβ-1b), glatiramer acetate, and interferon beta-1a subcutaneous (IFNβ-1a-SC). IFNβ-1a-IM is the first disease-modifying medication to demonstrate significant benefits on several measures of cognition in a large, controlled clinical trial. In a Phase III study, 166 patients with MS received IFNβ-1a-IM 30 μg or placebo for two years.[41] Patients received a comprehensive and a brief neuropsychological battery. Patients treated with IFNβ-1a-IM performed significantly better than those receiving placebo on tests of information processing and learning/memory (P=0.011), with a positive trend in visuospatial abilities and problem solving. Patients in the IFNβ-1a-IM treatment group also showed a significant delay in sustained deterioration in the Paced Auditory Serial Addition Test (PASAT) processing rate, compared to placebo (P=0.023). Overall, a 47% reduction in the risk of cognitive deterioration was observed with IFNβ-1a-IM. In the same study, IFNβ-1a-IM reduced the rate of brain atrophy by 55% during the second year of treatment. Both glatiramer and IFNβ-1b have failed to show such benefits in the most susceptible areas of cognition in well controlled trials[42,43] and there are no reports of the effects of IFNβ-1a-SC on cognitive impairment.[42]

Cognitive dysfunction should also be managed with non-pharmacological interventions such as cognitive rehabilitation, counselling, education and lifestyle changes. Cognitive rehabilitation includes skills retraining and compensatory approaches, which allow patients to manage memory and recall better. Specific attention-training and neuropsychological counselling for example can improve cognitive performance.[5] Education will allow patients to better understand their condition and recognise the neuropsychological symptoms if and when they occur. A large-scale randomised controlled trial in older adults with cognitive impairment has shown that cognitive training delays cognitive and functional decline over a five-year follow-up.[44] This provides support that cognitive training is a potentially effective method of delaying cognitive decline in people with cognitive impairment, including in MS.

Interestingly, exercise may have a positive effect on cognition. One study in healthy older women showed that long-term regular physical activity, including walking, is associated with significantly better cognitive function and less cognitive decline. In another study in patients with dementia, regular physical activity was shown to be a potent protective factor against cognitive decline.[45] Although this has not been assessed in patients with MS, exercise may help improve or stop the progress of cognitive impairment.

Depression

Moderate and severe depression has a negative effect on cognitive function so its treatment should improve cognitive impairment. With the depression treated and cognition improved, patients should then be able to take on board strategies for dealing with cognitive impairment such as memory loss, which would then help improve general well-being and QoL.

Depression contributes significantly to fatigue in MS, and it has been shown that treating depression reduces fatigue.[46] In a study of patients with relapsing MS and moderate to severe depression, after 16-week of treatment for depression (individual cognitive behavioural therapy, group psychotherapy, or sertraline), scores on the total fatigue assessment instrument and the global fatigue severity subscale were significantly reduced over the course of treatment ($p<0.02$). These findings suggest that treating depression is associated with reductions in the severity of fatigue, and that this relationship is due primarily to treatment related changes in mood.

Interestingly, the treatment of depression (cognitive behavioural therapy, group psychotherapy and anti-depressant therapy) has been shown to decrease the production of the pro-inflammatory cytokine IFN-γ in patients with relapsing-remitting MS.[46] This finding highlights the need for more research into the potential disease modifying properties associated with the treatment of depression in MS.

Fatigue

Owing to the complex aetiology of fatigue a multidisciplinary approach to treatment is required that includes a range of pharmacological and non-pharmacological interventions. Drug treatments include amantadine, modafinil and 4-aminipyridine.[10] Amantadine is the treatment of first choice in most patients.[10] Non-pharmacological interventions include regular exercise programmes, energy conservation strategies, and hyperthermia

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avoidance. Once fatigue has been addressed it may be possible to obtain a baseline for cognitive function that will enable certain strategies to be applied in order to manage any cognition decline.

Treating fatigue has been shown to improve depression and cognition. In a study investigating the effects of the wake promoting drug modafinil in other wise healthy patients with depression, significant improvements in fatigue (VASF, FSI) were observed.[48] This corresponded with significant improvements in depression (HDRS, BDI, CGIS), as well as to significant gains in cognition using the Stroop Interference Test. These effects in healthy depressed patients are also likely to be observed in depressed patients with MS.

The effect of fatigue management and energy conservation has also been evaluated.[49] In one study, patients with MS were assessed immediately after attending a fatigue management course and then seven to nine months later. The total score on the Modified Fatigue Impact Scale (MFIS) showed significant improvements at both time points. Interestingly, the cognitive subscores of the MFIS were also significantly improved. Furthermore, the depression score decreased significantly to a normal level at the end of training, and at the seven to nine month follow-up. This research demonstrates that fatigue management not only has a positive effect on fatigue in MS, but also on cognition and depression.

Conclusions

Neuropsychological symptoms in MS include cognitive impairment, depression and fatigue. These symptoms, experienced very frequently by MS suffers, result directly from the brain lesions and atrophy that are characteristic of the underlying disease pathophysiology. Furthermore, there is a complex interplay between cognition, depression and fatigue; with each symptom impacting negatively on the others. These neuropsychological symptoms impinge tremendously on the social and working lives of MS suffers. Consequently, it is imperative to identify and treat these symptoms early in the course of MS. Treating one symptom can also result in significant improvements in the others. For example, effectively treating fatigue also has a positive effect on depression and cognition. Adopting a multi-modal approach to treating these neuropsychological symptoms that incorporates both pharmacological and non-pharmacological interventions, will have a significant impact on patients' well being and QoL.

References

1. Julian LJ, Mohr DC. *Cognitive predictors of response to treatment for depression in multiple sclerosis.* J Neuropsychiatry Clin Neurosci 2006;18:356-63.
2. Graham J. *What is MS?* Multiple Sclerosis Society, UK 2002:3.
3. Crayton HJ, Rossman HS. *Managing the symptoms of multiple sclerosis: a multimodal approach.* Clin Thera 2006;28:445-60.
4. Galetta SL, Markowitz C, Lee AG. *Immunomodulatory agents for the treatment of relapsing multiple sclerosis: a systematic review.* Arch Intern Med 2002;162:2161-9.
5. Winkelmann A, Engel C, Apel A, Zettl UK. *Cognitive impairment in multiple sclerosis.* J Neurol 2007;254(Suppl 2):II/35-42.
6. Amato MP, Ponziani G, Rossi et al. *Quality of life in multiple sclerosis: the impact of depression, fatigue and disability.* Multi Scler 2001;7:340-4.
7. Rao SM. Leo GJ, Bernardin L et al. *Cognitive dysfunction in multiple sclerosis. Frequency patterns and predictions.* Neurology 1991;41:685-91.
8. Bagert B, Camplair P, Bourdette D. *Cognitive dysfunction in multiple sclerosis: natural history, pathophysiology and management.* CNS Drugs 2002;16:445-55.
9. Rao SM, Leo GL, Ellington L, Nauertz T, Bernardin L, Unverzagt F. *Cognitive dysfunction in multiple sclerosis, II: impact on employment and social functioning.* Neurology 1991;41:692-6.
10. Henze T. *What is new in symptom management?* Int MS J 2007;14:22-7.
11. Lincoln NB, Radford KA. *Cognitive abilities as predictors of safety to drive in people with multiple sclerosis.* Multiple Sclerosis 2008;14:123-8.
12. Amato MP, Ponziani G, Pracucci G et al. *Cognitive impairment in early-onset multiple sclerosis.* Arch Neurol 1995;52:168-72.
13. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. *The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus.* Arch Neurol 1989;46:1121-3.
14. Fisk JD, Pontefract A, Ritvo PG, Archibald CJ, Murray TJ. *The impact of fatigue on patients with multiple sclerosis.* Can J Neurol Sci 1994;21:9-14.
15. Freal JE, Kraft GH, Coryell JK. *Symptomatic fatigue in multiple sclerosis.* Arch Phys Med Rehabil 1984;65:135-84.
16. Bergamaschi 1997, Romani A, Versino M, Poli R, Cosi V. *Clinical aspects of fatigue in multiple sclerosis.* Funct Neurol 1997;12:247-51.
17. Bakshi R. *Fatigue associated with multiple sclerosis: diagnosis,impact, and management.* Mult Scler 2003;9:219-27.
18. Hubsky EP, Sears JH. *Fatigue in multiple sclerosis: guidelines for nursing care.* Rehabil Nurs 1992;17:176-80.
19. Edgley K, Sullivan M, Dehoux E. *A survey of multiple sclerosis: II. Determinants of employment status.* Can J Rehabil 1991;4:127-32.
20. Johnson SL. *The concept of fatigue in multiple sclerosis.* J Neurosci Nurs 2008;40:72-7.
21. Feinstein A. *An examination of suicidal intent in patients with multiple sclerosis.* Neurology 2002;59:674-8.
22. Patten SB, Beck CA, Williams JVA et al. *Major depression in multiple sclerosis: a population-based perspective.* Neurology 2003;61:1524-7.
23. Andrews G, Henderson S, Hall W. *Prevalence, comorbidity, disability and service utilisation: an overview of the Australian national Mental Health Survey.* Br J Psychiatry 2001;178:145-53.
24. Stenager EN, Stenager E, Koch-Henriksen N et al. *Suicide and multiple sclerosis: an epidemiological investigation.* J Neurol Neurosurg Psychiatry 1992;55:542-5.
25. Siegert RJ, Abernethy DA. *Depression in multiple sclerosis.* J Neurol Neurosurg Psychiatry 2005;76:469-75.
26. Rao SM, Leo GL, Haughton VM et al. *Correlation of magnetic resonance imaging with neuropsychological testing in multiple sclerosis.* Neurology 1989;39:161-6.
27. Zivadinov R, Specic J, Nasuelli D et al. *A longitudinal study of brain atrophy and cognitive disturbances in the early phase of relapsing-remitting multiple sclerosis.* J Neurol Neurosurg Psychiatry 2001;70:773-80.
28. Rovaris M, Filippi M. *MRI correlates of cognitive dysfunction in multiple sclerosis.* J Neurovirol 2000; 9(Suppl 2):S172-5.
29. Benedict RH, Carone DA, Bakshi R. *Correlating brain atrophy with cognitive dysfunction, mood disturbances, and personality disorder in multiple sclerosis.* J Neuroimaging 2004;14 (Suppl 3):36S-45S.
30. Mikol D. *Management of fatigue, cognitive dysfunction, and mood disorders.* International Journal of MS care 2006, February Supplement.
31. Tartaglia MC, Narayanan S, Francis SJ et al. *The relationship between diffuse axonal damage and fatigue in multiple sclerosis.* Arch Neurol 2004;61:201-7.
32. Arnett PA, Higginson CI, Voss WD, et al. *Depressed mood in multiple sclerosis: relationship to capacity-demanding memory and attentional functioning.* Neuropsychology 1999;13:247-446.
33. Arnett PA, Higginson CI, Voss WD, et al. *Depression mood in multiple sclerosis: relationship to working memory capacity.* Neuropsychology 1999;13:546-56.
34. Arnett PA, Higginson CI, Voss WD, et al. *Depression mood in multiple sclerosis: relationship to planning ability.* J Int Neuropsychol Soc 2001;7:665-74.
35. Diamond BJ, Johnston SK, Kaufman M, Graves L. *Relationships between information processing, depression, fatigue and cognition in multiple sclerosis.* Arch Clin Neuropsychol 2008;23:189-99.
36. Pierson S, Griffith Nathan. *Treatment of cognitive impairment in multiple sclerosis.* Behav Neurol 2006;17:53-67.
37. Ford H, Trigwell P, Johnson M. *The nature of fatigue in multiple sclerosis.* J Psychosom Res 1998;45:33-8.
38. Schreurs KMG, de Ridder DTD, Bensing JM. *Fatigue in multiple sclerosis: reciprocal relationships and physical disabilities and depression.* J Psychosom Res 2002;53:775-81.
39. Fraser C, Stark S. *Cognitive symptoms and correlations of physical disability in individuals with multiple sclerosis.* J Neurosci Nurs 2003;35:313-20.
40. Parmenter BA, Denney DR, Lynch SG. *The cognitive performance of patients with multiple sclerosis during periods of high and low fatigue.* Mult Scler 2003;9:111-18.
41. Fischer JS, Priore RL, Jacobs LD. *Neuropsychological Effects of Interferon b-1a in Relapsing Multiple Sclerosis.* Annals Neurol 2000;48:886-92.
42. Halper J, Kennedy P, Murphy Miller C. *Rethinking cognitive function in multiple sclerosis: a nursing perspective.* J Neurosci Nursing 2003;35:70-81.
43. Weinstein A, Schwid SIL, Schiffer RB. *Neuropsychologic state in multiple sclerosis after treatment with glatiramer.* Arch Neurol 1999; 56:319-24.
44. Belleville S. *Cognitive training for persons with mild cognitive impairment.* International Psychogeriatrics 2008;20:57-66.
45. Laurin D, Verreault R, Lindsay J et al. *Physical activity and risk of cognitive impairment and dementia in elderly persons.* Arch Neuro. 2001;58:498-504.
46. Mohr DC, Hart SL, Goldberg A. *Effects of treatment for depression on fatigue in multiple sclerosis.* Psychosom Med 2003;65:542–7.
47. Mohr DC, Goodkin DE, Islar J et al. *Treatment of depression is associated with suppression of nonspecific and antigen-specific TH1 responses in multiple sclerosis.* Arch Neurol 2001;58:1081-6.
48. DeBattista C, Lembke A, Solvason H et al. *A prospective trial of modafinil as an adjunctive treatment of major depression.* J Clin Psychopharmacol 2004;24:87-90.
49. Sauter C, Zebenholzer K, Zeitlhofer J, Vass K, Hisakawa J. *A longitudinal study on effects of a six−week course for energy conservation for multiple sclerosis patients.* Mult Scler 2008;21:1352−4585.

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Earthquake 2005 – Spinal Cord Injury Rehabilitation in Pakistan

At 8:52am on October 8, 2005, I was doing my morning rounds in the medical intensive care unit (ICU) on the second floor of our 550 bed private teaching hospital in the capital city of Islamabad, when the floor shook, I commented 'What was that'? Before I could get a reply the building began to shake violently. I can never forget the one minute or so it took me to run out of the five storey building. It felt as if the building would collapse on me. As we returned inside after 15 minutes, we were greeted by another series of jolts. Within the next 30 minutes we heard that the most luxurious apartment complex in the city had collapsed to the ground.

The casualties on the Pakistan side were 73,338 dead, while on the Indian side there were 1,360 dead. It affected a population of 3.5 million, destroyed 60% of the health facilities in the region and affected an area of 30,000 square kilometers.[1] There were 667 patients with spinal cord injury (SCI).[2] The majority were relocated to Islamabad and Rawalpindi. Women comprised 57.2%[3] to 74%,[4] although this figure included a large number of patients from a women only facility. Most of them had thoracolumbar injuries.[4] 46% were complete spinal cord injuries.[5]

A total of 685 patients arrived at our emergency room, of whom 294 were admitted and the rest were discharged after minor treatment. Eighteen patients had head injury and 44 had spinal injury – 39 thoracolumbar and 5 cervical.[6] There were 19 patients with unstable thoracolumbar injuries (Figure 1) with a female: male ratio of 8.5:1, who were managed with spinal surgery and stabilisation[7] and aggressive spinal rehabilitation (Figure 2).

Day one to thirty

All major health facilities in the earthquake zone and the twin cities of Rawalpindi and Islamabad were flooded with disaster patients. A cinema hall in Islamabad was converted into a make-shift facility for women. Volunteer medical teams from other cities set up relief camps and field hospitals in the smaller towns. Some casualties were airlifted to military facilities by helicopters and international search and rescue teams; others used private transport or were brought in by community relief workers.[3,8] Orthopaedic surgeons, neurosurgeons, trauma surgeons, cardiothoracic surgeons and anaesthetists worked round the clock for 72 hours. In the first month alone, more than 1700 doctors from 23 countries came to the affected areas, either as self motivated individuals or as part of an organised relief mission.[9]

Location Map

The major issues during the initial two weeks were provision of medications, wound care, prevention of bed sores and shelter for the relatives. Luckily donations poured in, and we were able to provide appropriate antibiotics, analgesics, wound dressings, air-mattresses and shelter for the families. We also purchased tilt tables to be delivered from the UK by air.

Dearth of training institutions

Rehabilitation of the disabled has been a neglected specialty in Pakistan.[10] Very few good centres exist at present and most of them are in Karachi and Lahore with one in Rawalpindi. There are only three major schools of physiotherapy in Pakistan: the Jinnah Postgraduate Medical Center (JPMC) and Liaquat National Postgraduate Medical Center in Karachi, and the King Edward Medical University in Lahore. The only occupational therapy school in Pakistan is in JPMC Karachi, and it is unable to take more than one batch of 25-30 female students every two years because of a dearth of teaching faculty. There is only one school of orthotic/prosthetic engineering, which is in Peshawar: this was set up by the Germans in the eighties for victims of the Afghan war (POIPOS). It produces 10-12 graduates per

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Figure 1: Radiological imaging of our paraplegic patient 'S'. Left to right: (a) Pre-op X-ray showing a displaced fracture of L3 vertebra (b) Coronal MRI and (c) post-op X-ray.

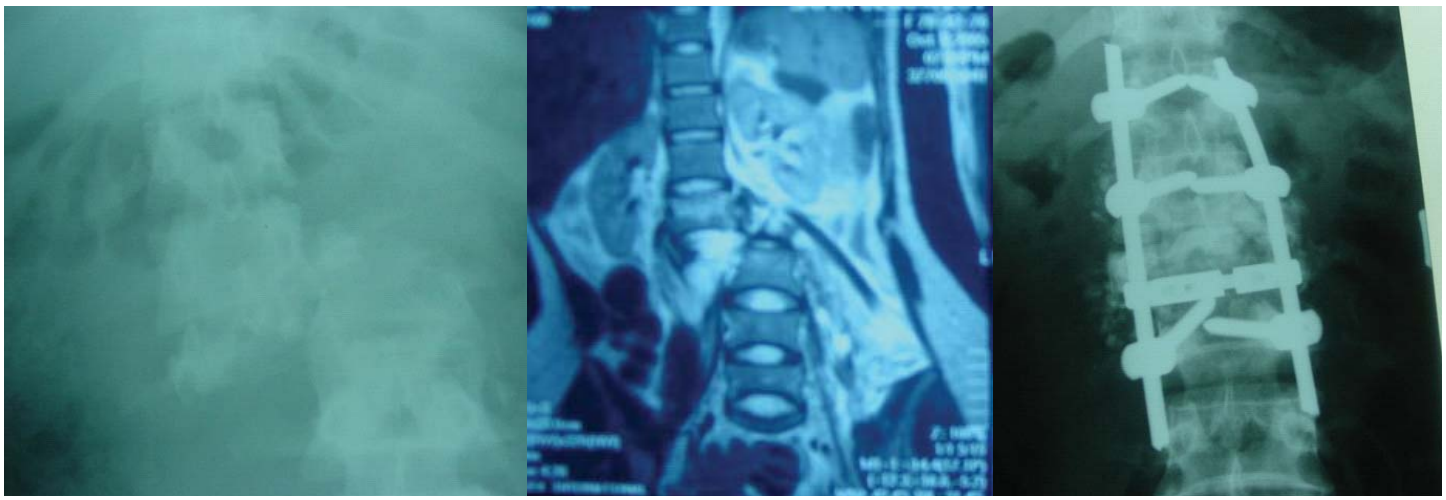

Figure 2: Left to right: (a) Our first patient to walk December 14, 2005 (b) Patients in our Rehabilitation Centre.

year. There is a dearth of neurologists and psychiatrists in the country, and there exist very few facilities or trained professionals in neurorehabilitation and spinal rehabilitation in the country.

One to three months

The non-governmental organisations (NGOs) got together under one roof, held weekly meetings, identified needs and issues as well as pooled resources for collective benefits, and supplemented deficiencies in the public sector. Volunteers from the Paraplegia Foundation in Lahore were a great motivating force for the paraplegic patients. Physiotherapists, occupational therapists and orthotists, mostly sponsored by local and international NGOs, came from other cities and the rest of the world and conducted short workshops for the locals to fill the knowledge gap. We organised one such workshop on December 13-14, 2005, and our first patient walked with a walking frame the same day.

One of the major hurdles was, and remains, the difficult mountainous terrain and the harsh winters. On returning home, patients had to be carried on mules for long distances to reach the nearest primary heath care facilities, thus forcing many of them to return to government heath facilities.

Three to six months and beyond

Ideally a centre dedicated to providing for the complete rehabilitation needs of such victims should be located near the affected areas, for ease of access. However, a major constraint was a serious dearth of expertise in this field of medicine. Professionals were not willing to relocate. Difficult terrain was hampering return of SCI patients. Most institutions and professionals were based in major cities like Karachi, Lahore and Islamabad. Hence, moving away from a major city was not feasible. With most victims relocated to Islamabad, several major centers in this city with outreach facilities for community based rehabilitation (CBR) were desperately needed. Four inpatient spinal rehabilitation centres were established in the public sector and one in the private sector in Islamabad. One spinal rehabilitation facility was upgraded in Peshawar. Two rehabilitation centres were established in the earthquake affected areas. The government announced hundreds of jobs for physical therapists, occupational therapists and clinical psychologists and gave them salaries equal to medical officers, thus encouraging them to relocate to the northern areas. Several international relief organisations are still working in the affected areas. In 2007, a group of neurologists, psychiatrists, international relief organisations and philanthropists in USA and Pakistan launched the Spinal Cord Injury Project for Pakistan Earthquake Rehabilitation (SCIPPER) with an aim to provide long-term rehabilitation for these patients. Our facility, together with two other centers - the Paraplegia Centre in Peshawar and the Armed Forces Institute of Rehabilitation Medicine in Rawalpindi have been designated as centres of excellence, with plans to set up tele-rehabilitation facilities in the near future.

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One of the major hurdles was, and remains, the difficult mountainous terrain and the harsh winters

References

1. BBC News: http://news.bbc.co.uk. Published 2006/10/4/ 11:13:57.
2. WHO South Asia Earthquake Health Situation Report # 31, 15-21 January 2006
3. Rathore MF, Rashid P, Butt AW, Malik AA, Gill ZA, Haig AJ. *Epidemiology of spinal cord injuries in the 2005 Pakistan earthquake.* Spinal cord. 2007;45(10):658-63. Epub 2007 Jan 16.
4. Tauqir SF, Mirza S, Gul S, Ghaffar H, Zafar A. *Complications in patients with spinal cord injuries sustained in an earthquake in Northern Pakistan.* J Spinal Cord Med 2007;30(4):373-7.
5. Mirza S, Tauqir SF, Gul S, Ghaffar H, Malik AZ. *Evaluation of levels and patterns of spinal cord injuries in the Earthquake victims.* J Surg Pakistan 2006;11(4):172-4.
6. Nadeem M, Khan I. *Paraplegics can walk.* (Abstract). Pak. J. Neurological. Sci. 2006;Vol.1(1):59.
7. Khan I, Nadeem M, Rabbani ZH. *Thoracolumbar junction injuries after earthquake and their management with pedicle screws.* Submitted to J. Ayub. Med Coll.
8. Brennan RJ, Waldman RJ. *The South Asian Earthquake Six Months Later-An Ongoing Crisis.* N Engl J Med 354;17.
9. Wasay M, Shafqat S. *Preparing for the next natural disaster-need for a WHO coordinating centre.* Bulletin of the World Health Organization. October 2006;84(10).
10. Rathore FA, Farooq F, Muzammil S, New PW, Ahmad N, Haig AJ. *Spinal Cord Injury Management and Rehabilitation: Highlights and shortcomings from the 2005 Earthquake in Pakistan.* Arch Phys Med Rehabil. 2008;89:579-85.

Deep Brain Stimulation: an underused panacea?

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Summary

Deep brain stimulation (DBS) enables structures in the brain to be stimulated electrically by an implanted pacemaker after a minimally invasive neurosurgical procedure and has become the treatment of choice for Parkinson's disease refractory to or complicated by drug therapy. Many clinical indications for DBS now exist including dystonia and tremor in movement disorders; depression, obsessive-compulsive disorder and Tourette's syndrome in psychiatry; epilepsy, cluster headache and chronic pain. DBS is a standard and widely accepted treatment for Parkinson's disease after two decades of experience, but for most other clinical indications it remains restricted to a handful of experienced, specialist centres. Current challenges highlighted include consideration of referral for DBS by clinicians and the securing of funding for its use from National Health Service healthcare providers.

Deep brain stimulation (DBS) is neurosurgery that enables brain structures to be stimulated electrically by a pacemaker implanted under the skin. In the 1980s, over a decade after its first use in pain,[1] implantable DBS of the thalamus was performed to suppress tremor in Parkinson's Disease (PD) refractory to drug treatments.[2] Primate-based research soon afterwards identified the subthalamic nucleus, a basal ganglia structure, as a putative brain target for both ablation and DBS.[3,4] Alongside the resurgence of thalamic DBS and basal ganglia lesional surgery[5,6] and improvments in neurostimulator technology, scientific discoveries from primate research cultivated a renaissance in neurosurgery for PD in the 1990s resulting in increasing use of DBS over the last decade. Its efficacy in PD has been demonstrated robustly by clinical trials with multiple novel brain targets having been discovered recently. Several other indications for DBS now exist such as tremor and dystonia in movement disorders; psychiatric disorders like obsessive-compulsive disorder (OCD), depression and Tourette's syndrome; cluster headache, epilepsy and chronic pain.[7]

Devices

At present, only one commercial manufacturer (Medtronic Inc, Minneapolis, MN, USA) produces deep brain electrodes widely used for DBS. Two models are currently available - the 3387 and the 3389. Both are quadripolar electrodes, having four electrical contacts with the brain.

Several stimulation parameters can be altered in DBS, in particular voltage, frequency and pulse width. Stimulation can be monopolar or bipolar over any combination of the four contacts of each electrode and multiple contacts can be specified as anodes or cathodes. The DBS electrode is secured to the skull and connected to a lead tunneled to the chest or abdomen where a pulse generator (pacemaker) is implanted under the skin. Recent developments include commercially available transcutaneously rechargeable pulse generators, which will be included in a new DBS platform being introduced by Medtronic, and the potential entry of other device manufacturers from related fields like spinal cord stimulation. Detailed device issues are described elsewhere.[8,9]

Efficacy

As several decades of clinical experience with established drug treatments have accrued so patient subgroups refractory to medical therapies have been identified, not just in PD, chronic pain and epilepsy, but also in other movement disorders including dystonias, tremor, Tourette's syndrome, psychiatric disorders of depression and obsessive-compulsive disorder (OCD) and cluster headache. These disorders have all been successfully treated by DBS after failed drug treatment (Table 1).[7] Each is summarised below.

Parkinson's disease

PD is a slowly progressive, neurodegenerative disease characterised by tremor, rigidity, bradykinesia and postural instability. It is common in middle or late life with prevalence rising to 1% in people over 60

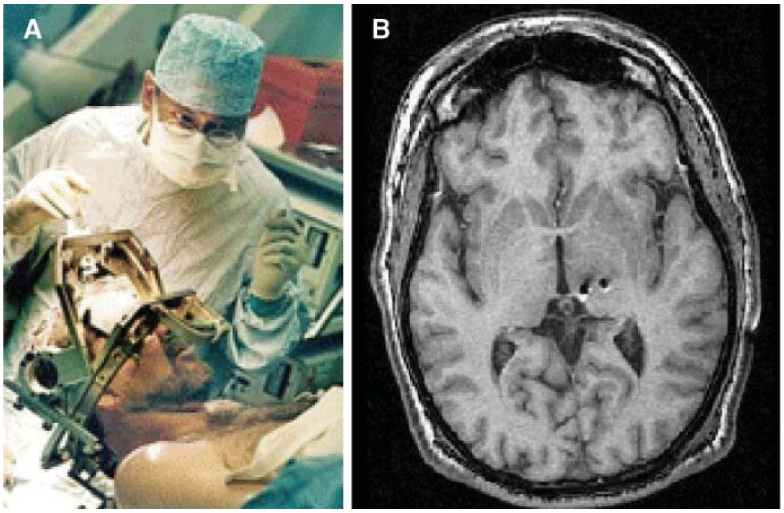

Figure 1: (A) Intra-operative awake deep brain stimulation; (B) axial MRI of deep brain stimulators for pain in situ.

Table 1. Clinical indications for deep brain stimulation, approximate numbers of patients treated worldwide and common brain structures targeted.

Indication	Patients treated	Deep brain targets
Parkinson's disease	40,000	Globus pallidus internus, subthalamic nucleus
Chronic pain	2,000	Ventral posterior medial and lateral thalamic nuclei, Periventricular and periaqueductal grey matter
Tremor (not including Parkinson's disease)	1,000	Ventralis intermedius thalamic nucleus, Zona incerta
Dystonia	500	Globus pallidus internus
Cluster headache	100	Posterior hypothalamus
Epilepsy	50	Anterior thalamic nucleus
Tourette's syndrome	100	Ventromedial thalamic nuclei, Anterior limb of internal capsule, Globus pallidus internus
Obsessive-compulsive disorder	100	Anterior limb of internal capsule
Depression	50	Subgenual cingulate cortex, Anterior limb of internal capsule

years of age. Established basal ganglia brain structures currently targeted for PD DBS include the globus pallidus interna (GPi), Ventralis intermedius nucleus of the thalamus (ViM), and subthalamic nucleus (STN), over 30,000 patients having been implanted to date.[10]

GPi has traditionally been targeted mainly for dyskinesia symptoms, STN for levodopa refractory patients and ViM for tremor. Despite its smaller size, the STN recently gained dominance over GPi as the surgical target of choice for PD due to reports of favourable motor outcomes.[11] A 156 patient randomised, controlled, multi-centre trial of STN DBS versus medical treatment alone showed a 25% benefit in motor function and 22% improvement in quality of life outcomes at six months after.[12] Sustained benefit with STN DBS has also been described after five years of follow-up.[13,14] GPi and STN have been compared at four year follow-up,[15] however long-term, back to back, randomised, blinded, controlled trials of the two surgical targets are yet to be completed.[16]

The pedunculopontine nucleus (PPN) has been discovered in the last decade as a deep brain target, stimulation of which reduces gait abnormalities and postural instability.[17] Like the STN, its clinical utility has been realised by non-human primate research.[18,19] Initial results favour its use in PD patients blighted most by postural instability, in PD-plus syndromes of multiple system atrophy and progressive supranuclear palsy and in those with symptoms not ameliorated by STN stimulation alone.[20]

Tremor

Tremor is the involuntary, rhythmic oscillation of a body part. Essential tremor prevalence varies greatly throughout the world and can be up to 2%. DBS can alleviate contralateral limb tremor in essential tremor, Holmes' tremor, cerebellar tremor, tremulous multiple sclerosis and tremor after head injury.[21] For trunk, head and voice tremors, bilateral DBS is considered.[22] Brain targets considered in patients refractory to medication are the ViM and the zona incerta (ZI).

Sustained and consistent motor improvements with ViM DBS have been shown six years after surgery in 19 patients with essential tremor.[23] Quality of life improvements have also been demonstrated in 40 patients one year after surgery.[24] In multiple sclerosis, patient selection is paramount.[25] Distal limb tremor responds best to ViM DBS and proximal limb tremor to ZI DBS.[26] Post-operative benefits in motor function for 88% of patients and in daily functioning for 76% have been shown in a systematic review of 75 multiple sclerosis.[27] Brain targets in DBS for head injury depend upon the prevailing movement disorder with excellent results described in the small numbers of cases reported.[28]

Dystonia

Dystonias are disorders of involuntary sustained muscle contractions that can affect certain body regions or be generalised. They may begin in childhood or young adulthood, often progressing from focal limb involvement to a severe generalised form, or manifest in later adulthood when they are usually focal or segmental and frequently craniocervical (spasmodic torticollis). Prevalence of early onset dystonias is up to 50 per million with a greater, up to 0.01%, prevalence of the late onset type. DBS is considered for children refractory to medical therapy, usually by anticholinergic, dopaminergic or benzodiazepine treatments, and adults refractory to botulinum toxin injections.

Stimulation of the posteroventral GPi is performed for primary dystonias.[29] GPi DBS is particularly effective in childhood dystonias,[30] and in those patients carrying a mutation in the DYT1 gene.[31] Secondary dystonias are less responsive.[32] Moderate benefits have also been observed with ViM but not STN DBS.[33] Motor improvements are often not fully realised until weeks to months later.[34] Sustained motor and quality of life improvements without cognitive impairment have been shown three months after surgery in a prospective, multi-centre trial of 40 patients,[35] and three years after surgery in 58% of patients in a trial of 22 patients.[36]

Depression

Depression is extremely common. Lifetime prevalence for major depressive disorder has been estimated at 16%, half of all patients having reduced function and role impairment. Patients with major depressive disorder are twice as likely to die as those who are not depressed. One trial of DBS in drug refractory depression targeted the subgenual cingulate cortex bilaterally, four out of six patients showing improvement.[37] Another targeted the anterior limb of the internal capsule as for OCD in five patients,[38] three patients showing a greater than 50% symptom improvement. Both studies were uncontrolled and had less than one year of follow-up. While DBS for severe depression appears promising, further studies are required to confirm efficacious targets and successful outcomes.

Obsessive compulsive disorder

OCD can manifest at any age, but first onset is usually in a person's third decade. Prevalence is 0.8% in adults and lower in children. About 10% of patients are refractory to pharmacotherapy and frequently become housebound. The anatomical target for DBS derives from the success of the lesional procedure of anterior capsulotomy that improves symptoms in approximately half of patients treated.[39] Long-term outcomes for bilateral DBS of the anterior limb of the internal capsule and adjacent ventral striatum have been reported by two groups. In one study, blinded assessment of four patients followed up for at least 21 months after surgery revealed significant improvements in three patients.[40] In another study, of ten patients evaluated three years after surgery, seven showed a one third or greater percentage reduction in symptoms and six had an improvement in activities of daily living.[41]

Tourette's syndrome

Tourette's syndrome has 0.1-1% prevalence, usually affecting children and adolescents. It is more common in people with autistic spectrum disorders and is characterised by motor and vocal tics. Simple tics typically involve one muscle group and complex tics may mimic a purposeful movement such as an obscene gesture. Simple vocal tics are sounds or noises like grunting and complex vocalisations include echolalia and coprolalia, the latter affecting 10% of patients. For most sufferers, symptoms decline in adulthood, but DBS may be considered for those with debilitating tics refractory to drugs such as neuroleptics and anti-convulsants.

Brain regions targeted for DBS have included the medial intralaminar thalamic (centromedian and parafascicular) nuclei (three patients)[42] and case reports of stimulation of the anterior limb of the internal capsule,[43] and GPi.[44-46] With this initial experience and experience of ablative surgery for Tourette's syndrome,[47] criteria for DBS suitability have been proposed.[48]

Epilepsy

Epilepsy is a debilitating neurological condition affecting 50 per 100,000 people with higher prevalence in children and the elderly. Symptomatic

epilepsy is estimated to reduce life expectancy by up to two decades. Sudden death in medically refractory epilepsy is 0.5% and highest in young adults. Neurosurgical treatment is considered after poor seizure control despite trial of at least three antiepileptic medications.

DBS of the anterior thalamic nuclei has been undertaken by several groups. In one study, five of six patients had improvements in their seizures over an average follow-up period of five years.[49] In another study, four of five patients showed significant reductions in frequency and severity of seizures after 6-36 months without adverse complications.[50] A third study showed significantly reduced seizures in all four patients over an average 44 month follow-up period.[51] Putative targets of stimulation may depend upon seizure localisation and also include the STN, caudate, hippocampus, cerebellum, hypothalamus and medial intralaminar thalamic nuclei.[52]

Cluster Headache

Cluster headache is characterised by severe unilateral periorbital pain with concomitant autonomic sequelae of vasodilatation and periorbital oedema. Prevalence is less than 1% with men more commonly affected. DBS can be performed for cluster headache refractory to medical treatments, targeting the ipsilateral posterior hypothalamus. After mean follow-up of almost two years, 13 out of 16 patients were reported symptom free or almost headache free in the largest study to date.[53] Another group has reported three of six patients considerably improved.[54] Initial reports appear extremely successful.[55]

Chronic pain

Chronic pain presents a considerable burden to society, occurring in cancer, stroke, trauma and failed surgery. It may affect as many as one in five people. DBS has been undertaken for almost four decades. Targets have included the internal capsule and medial intralaminar thalamic nuclei, but most current treatments target the ventral posterolateral and ventral posteromedial thalamic nuclei (VPL/VPM) and periaqueductal and periventricular grey matter (PAG/PVG). 1300 recipients of DBS for pain have been reported.[56,57] Chronic pain aetiologies with good outcomes in contemporary series are stroke,[58] amputation,[59] anaesthesia dolorosa,[60,61] and plexopathies with success also seen in multiple sclerosis[62] and malignancy.[63]

Safety

As an intracranial neurosurgical procedure, DBS has small but significant risks. Aside from multidisciplinary assessment to determine suitability for the procedure, the patient must be refractory to medical treatment and able to give informed consent (where appropriate) to risks of stroke (1-3%), seizures (<1%), death (0.1%), skin erosion, lead breakage and the need for implantable pulse generator (IPG) revision surgery every one to ten years depending upon indication, and infection (3%) - a small proportion of cases requiring complete removal of the DBS system.[56,64-66] Patients should also be counselled for the possibility that they may derive no benefit from DBS or not tolerate it well, again necessitating its removal. Likelihood of this varies from indication to indication, but it should be emphasised when treating less established indications.

Indication and target specific complications can arise, for example dysarthria with bilateral ViM DBS,[67] altered libido with medial thalamic stimulation,[42] and anxiety with PAG/PVG DBS.[57] A full list of such specific complications is beyond the scope of this review and is discussed elsewhere.[9,68] However, their incidence with DBS is usually smaller than for the same target if lesioned, and furthermore DBS confers adjustability and reversibility.

The limited lifespan of IPGs is accentuated by disorders requiring large voltages or pulse widths and high frequencies of stimulation. For OCD and depression 5 to 10 volts is required requiring IPG changes almost yearly, and for dystonia large pulse widths are often used requiring IPG replacements approximately every 3 years. Stimulation failure due to IPG charge loss is an emergency in dystonia as relapse with respiratory compromise can be sudden and require intensive care.[69] New rechargeable IPGs coming to market are still likely to need replacement every nine years.

Cost-effectiveness

DBS is clearly a specialised treatment. In the British National Health Service, national tariffs for procedures are set and in 2007 pre-operative assessment was priced at over £1,000, surgery at approximately £21,000, replacement IPGs at over £8,000 and clinic follow-up visits at £800. Considering equipment alone, a stereotactic frame costs £80,000 and a computer planning station £65,000, their estimated lifespans being three years. A single electrode lead, extension, IPG and patient DBS controller cost around £12,000. To put the figures in context, Britain prices a cardiac pacemaker implantation at around £3,000 and a spinal discectomy similarly.[70]

Despite, or perhaps because of, its expense few studies have been published regarding the cost-effectiveness of DBS. A North American analysis of PD made several assumptions to suggest that DBS for PD may be effective with quality of life improvements of at least 18% over medical treatment alone.[71] For STN DBS in PD, a German study of 46 patients attributed 32% increased healthcare costs for the first post-operative year due to surgical and equipment expense, but 54% cost reductions for the second post-operative year concomitant with significantly improved motor outcome measures and reduced medications. The results suggest that the procedure is highly cost-effective after the first year and overall,[72] findings supported by other studies.[73,74] Two British studies have been conducted in dystonia and multiple sclerosis tremor. For dystonia, quality of life measures of 26 patients were used to demonstrate a quality adjusted life year (QALY) improvement of almost one year with DBS at a cost of £34,000 per QALY.[65] In contrast, one small study for multiple sclerosis suggested that benefits in 15 patients did not justify the high costs of DBS.[75]

One North American study sampled hospitals in the year 2000 when 88% of PD surgery performed was DBS and in 1996 when no DBS was performed.[76] Intriguingly, younger age, Caucasian ethnicity, private insurance, higher socioeconomic status, teaching hospital status and smaller annual hospital caseload all favoured DBS. Furthermore charges for DBS were 2.2 times higher than for ablative surgery, with lower charges made by higher-volume hospitals. These larger-volume hospitals also had superior short-term outcomes. Such results may reflect the early years of the treatment's diffusion from experimental status in academic settings to widespread uptake by many neurosurgical units.

Further, larger cost-benefit and cost-utility analyses with longer-term follow-up are required for each indication to verify the findings of these preliminary studies described. It is noteworthy that factors of scale could account for cardiac pacemakers being relatively inexpensive in comparison to cerebral ones. Present high costs of DBS are therefore likely to be reduced by its increasing uptake.

Discussion

Two distinct issues remain to be unequivocally determined in DBS: treatment effectiveness for indications other than PD and treatment mechanism. Discussions of mechanism vary both in emphasis from the electrophysiological to the neurochemical and by target and indication, and are presently not well understood.[77] There are also considerable practical difficulties in implementing evidence-based medicine methods when undertaking surgery for medically refractory disorders.[7]

In contemporary ablative neurosurgery there are no prospective, randomised, double-blind, placebo-controlled trials of any procedure and none is likely. Sham burr holes and lesions are considered unethical.[78] Thus, even in the era of evidence-based medicine, surgical procedures can become accepted upon little more than intuitive appeal to the 'educated eye'.[79] The uncertainty in novel indications for DBS necessitates independently reviewed and well-designed trials with heterogeneity and differences in peri-operative management controlled for where possible. Such control is admittedly difficult in patient groups who are by definition refractory to medical treatment and have frequently tried other therapies as well.

Initial claims for therapeutic success in novel indications for DBS should ideally be confirmed by blinded studies. DBS does however enable electrodes, and thus treatments, to be switched off, in principle facilitating intra-patient double-blinded trials. Such a trial was elegantly conducted in a case of OCD.[80] A similar method favoured for evaluating treatment outcomes in small groups and single cases is the N-of-1 trial. A randomised, placebo-controlled intra-patient trial is conducted whereby the patient receives paired sessions during which each intervention occurs once. Session order is randomised and effects of treatment or placebo compared between sessions. The valid-

ity of N-of-1 trials using analgesic outcome scores has been demonstrated for DBS in chronic pain.[81]

Further challenges in supra-specialist surgery with its geographically wide referral patterns are poor recruitment to trials and loss of patients to follow-up. Amid the myriad challenges, it should be emphasised that absence of 'class A' evidence from multi-centre, randomised, controlled clinical trials is not evidence of absence of efficacy. As videos taken before and after DBS for movement disorders demonstrate, some treatments have dramatic effects unlikely to reflect biases. Treatment effects can be therefore inferred from well designed case series and non-randomised cohort studies.

Particular advances in DBS will come from technological improvements. Improvements in IPG battery life and rechargeable IPG technology will reduce the frequency of further procedures in those patients presently requiring frequent IPG changes. Miniaturisation will reduce the invasiveness of the procedure and improve cosmesis. Improvements in the resolution and safety of neuroimaging may enhance targeting of deep brain structures such that targets within the target for certain symptom constellations or disorders of particular body regions could be addressed more specifically. Telemedicine may reach DBS, with remotely controlled equipment programmable during videoconferencing or over the internet avoiding patient time spent travelling to follow-up clinics. Remotely downloaded data from personal digital assistants could be used to record symptoms and assess outcomes. The field is likely to benefit from novel approaches commenced by several device manufacturers, mirroring the competitive leaps made in cardiac pacemakers four decades ago.

Amidst the exciting advances outlined above, long-term results from randomised controlled clinical trials currently underway will begin to clarify debates over which brain targets are best for which symptoms and also of timing of surgery in relation to disease progression. As more becomes known about the limitations of DBS, its current status will shift from panacea in medically refractory patients to therapeutic tool in a complex repertoire including pharmacotherapy, lesioning surgery and emerging molecular and cellular technologies. A wealth of current research into gene therapy, cellular transplantation and nanotechnology may begin to gain clinical utility, add to the gamut of functional neurosurgical treatments that might become available and clarify the therapeutic role of DBS. Such innovations show much promise, but require robust demonstration of their safety and efficacy in animal models before progression to clinical trials.[19]

Conclusion

DBS is brain surgery and is thus often regarded as a last resort treatment. However, as evidence continues to gather concomitant with mechanistic understanding, and the number of indications increases, we expect that patient, clinician and commercial interest in the technique, as assessed by treatments performed, research investment, scientific publications and market indicators, will continue to proliferate. The evidence for consideration of referral for treatment for many debilitating diseases is persuasive.

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References

1. Hosobuchi Y, Adams JE, Rutkin B. *Chronic thalamic stimulation for the control of facial anesthesia dolorosa.* Arch Neurol 1973;29(3):158-61.
2. Benabid AL, Pollak P, Louveau A, Henry S, de Rougement J. *Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease.* Appl Neurophysiol 1987;50:344-6.
3. Bergman H, Wichmann T, DeLong MR. *Reversal of experimental parkinsonism by lesions of the subthalamic nucleus.* Science 1990;249(4975):1436-8.
4. *Aziz TZ, Peggs D, Sambrook MA, Crossman AR. Lesion of the subthalamic nucleus for the alleviation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in the primate.* Mov Disord 1991;6(4):288-92.
5. Narabayashi H, Yokochi F, Nakajima Y. *Levodopa-induced dyskinesia and thalamotomy.* J Neurol Neurosurg Psychiatry 1984;47(8):831-9.
6. Laitinen LV, Bergenheim AT, Hariz MI. *Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease.* J Neurosurg 1992;76(1):53-61.
7. Pereira EA, Green AL, Nandi D, Aziz TZ. *Deep brain stimulation: indications and evidence.* Expert Rev Med Devices 2007;4(5):591-603.
8. Rezai AR, Kopell BH, Gross RE, Vitek JL, Sharan AD, Limousin P, et al. *Deep brain stimulation for Parkinson's disease: surgical issues.* Mov Disord 2006;21 Suppl 14:S197-218.
9. Bittar RG, Burn SC, Bain PG, Owen SL, Joint C, Shlugman D, et al. *Deep brain stimulation for movement disorders and pain.* J Clin Neurosci 2005;12(4):457-63.
10. Pereira EA, Aziz TZ. *Surgical insights into Parkinson's disease.* J R Soc Med 2006;99(5):238-44.
11. Kleiner-Fisman G, Herzog J, Fisman DN, Tamma F, Lyons KE, Pahwa R, et al. *Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes.* Mov Disord 2006;21 Suppl 14:S290-304.
12. Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schafer H, Botzel K, et al. *A randomized trial of deep-brain stimulation for Parkinson's disease.* N Engl J Med 2006;355(9):896-908.
13. Schupbach WM, Chastan N, Welter ML, Houeto JL, Mesnage V, Bonnet AM, et al. *Stimulation of the subthalamic nucleus in Parkinson's disease: a 5 year follow up.* J Neurol Neurosurg Psychiatry 2005;76(12):1640-4.
14. Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, et al. *Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease.* N Engl J Med 2003;349(20):1925-34.
15. Rodriguez-Oroz MC, Obeso JA, Lang AE, Houeto JL, Pollak P, Rehncrona S, et al. *Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up.* Brain 2005;128(Pt 10):2240-9.
16. Okun MS, Foote KD. *Subthalamic Nucleus vs Globus Pallidus Interna Deep Brain Stimulation, the Rematch.* Arch Neurol 2005;62(4):533-6.
17. Jenkinson N, Nandi D, Miall RC, Stein JF, Aziz TZ. *Pedunculopontine nucleus stimulation improves akinesia in a Parkinsonian monkey.* Neuroreport 2004;15(17):2621-4.
18. Nandi D, Aziz TZ, Giladi N, Winter J, Stein JF. *Reversal of akinesia in experimental parkinsonism by GABA antagonist microinjections in the pedunculopontine nucleus.* Brain 2002;125(Pt 11):2418-30.
19. Pereira EA, Aziz TZ. *Parkinson's disease and primate research: past, present, and future.* Postgrad Med J 2006;82(967):293-9.
20. Stefani A, Lozano AM, Peppe A, Stanzione P, Galati S, Tropepi D, et al. *Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease.* Brain 2007.
21. Deuschl G, Bain P. *Deep brain stimulation for tremor [correction of trauma]: patient selection and evaluation.* Mov Disord 2002;17 Suppl 3:S102-11.
22. Taha JM, Janszen MA, Favre J. *Thalamic deep brain stimulation for the treatment of head, voice, and bilateral limb tremor.* J Neurosurg 1999;91(1):68-72.
23. Sydow O, Thobois S, Alesch F, Speelman JD. *Multicentre European study of thalamic stimulation in essential tremor: a six year follow up.* J Neurol Neurosurg Psychiatry 2003;74(10):1387-91.
24. Fields JA, Troster AI, Woods SP, Higginson CI, Wilkinson SB, Lyons KE, et al. *Neuropsychological and quality of life outcomes 12 months after unilateral thalamic stimulation for essential tremor.* J Neurol Neurosurg Psychiatry 2003;74(3):305-11.
25. Alusi SH, Aziz TZ, Glickman S, Jahanshahi M, Stein JF, Bain PG. *Stereotactic lesional surgery for the treatment of tremor in multiple sclerosis: a prospective case-controlled study.* Brain 2001;124(Pt 8):1576-89.
26. Nandi D, Chir M, Liu X, Bain P, Parkin S, Joint C, et al. *Electrophysiological confirmation of the zona incerta as a target for surgical treatment of disabling involuntary arm movements in multiple sclerosis: use of local field potentials.* J Clin Neurosci 2002;9(1):64-8.
27. Wishart HA, Roberts DW, Roth RM, McDonald BC, Coffey DJ, Mamourian AC, et al. *Chronic deep brain stimulation for the treatment of tremor in multiple sclerosis: review and case reports.* J Neurol Neurosurg Psychiatry 2003;74(10):1392-7.
28. Krauss JK, Jankovic J. *Head injury and posttraumatic movement disorders.* Neurosurgery 2002;50(5):927-39; discussion 939-40.
29. Krauss JK, Yianni J, Loher TJ, Aziz TZ. *Deep brain stimulation for dystonia.* J Clin Neurophysiol 2004;21(1):18-30.
30. Parr JR, Green AL, Joint C, Andrew M, Gregory RP, Scott RB, et al. *Deep brain stimulation in childhood: An effective treatment for early onset generalised idiopathic dystonia.* Arch Dis Child 2007.

31. Coubes P, Cif L, El Fertit H, Hemm S, Vayssiere N, Serrat S, et al. *Electrical stimulation of the globus pallidus internus in patients with primary generalized dystonia: long-term results.* J Neurosurg 2004;101(2):189-94.
32. Eltahawy HA, Saint-Cyr J, Giladi N, Lang AE, Lozano AM. *Primary dystonia is more responsive than secondary dystonia to pallidal interventions: outcome after pallidotomy or pallidal deep brain stimulation.* Neurosurgery 2004;54(3):613-19; discussion 619-21.
33. Detante O, Vercueil L, Krack P, Chabardes S, Benabid AL, Pollak P. *Off-period dystonia in Parkinson's disease but not generalized dystonia is improved by high-frequency stimulation of the subthalamic nucleus.* Adv Neurol 2004;94:309-14.
34. Yianni J, Bain PG, Gregory RP, Nandi D, Joint C, Scott RB, et al. *Post-operative progress of dystonia patients following globus pallidus internus deep brain stimulation.* Eur J Neurol 2003;10(3):239-47.
35. Kupsch A, Benecke R, Muller J, Trottenberg T, Schneider GH, Poewe W, et al. *Pallidal deep-brain stimulation in primary generalized or segmental dystonia.* N Engl J Med 2006;355(19):1978-90.
36. Vidailhet M, Vercueil L, Houeto JL, Krystkowiak P, Lagrange C, Yelnik J, et al. *Bilateral, pallidal, deep-brain stimulation in primary generalised dystonia: a prospective 3 year follow-up study.* Lancet Neurol 2007;6(3):223-9.
37. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. *Deep brain stimulation for treatment-resistant depression.* Neuron 2005;45(5):651-60.
38. Greenberg BD, Friehs GM, Carpenter LL, Tyrka A, Malone D, Rezai AR, et al. *Deep Brain Stimulation: Clinical Findings in Intractable Depression and OCD.* Neuropsychopharmacology 2005;29:S32.
39. Jenike MA. *Neurosurgical treatment of obsessive-compulsive disorder.* Br J Psychiatry Suppl 1998(35):79-90.
40. Nuttin BJ, Gabriels LA, Cosyns PR, Meyerson BA, Andreewitch S, Sunaert SG, et al. *Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder.* Neurosurgery 2003;52(6):1263-72; discussion 1272-4.
41. Greenberg BD, Malone DA, Friehs GM, Rezai AR, Kubu CS, Malloy PF, et al. *Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder.* Neuropsychopharmacology 2006;31(11):2384-93.
42. Visser-Vandewalle V, Temel Y, Boon P, Vreeling F, Colle H, Hoogland G, et al. *Chronic bilateral thalamic stimulation: a new therapeutic approach in intractable Tourette syndrome. Report of three cases.* J Neurosurg 2003;99(6):1094-100.
43. Flaherty AW, Williams ZM, Amirnovin R, Kasper E, Rauch SL, Cosgrove GR, et al. *Deep brain stimulation of the anterior internal capsule for the treatment of Tourette syndrome: technical case report.* Neurosurgery 2005;57(4 Suppl):E403; discussion E403.
44. Houeto JL, Karachi C, Mallet L, Pillon B, Yelnik J, Mesnage V, et al. *Tourette's syndrome and deep brain stimulation.* J Neurol Neurosurg Psychiatry 2005;76(7):992-5.
45. Ackermans L, Temel Y, Cath D, van der Linden C, Bruggeman R, Kleijer M, et al. *Deep brain stimulation in Tourette's syndrome: two targets?* Mov Disord 2006;21(5):709-13.
46. Diederich NJ, Kalteis K, Stamenkovic M, Pieri V, Alesch F. *Efficient internal pallidal stimulation in Gilles de la Tourette syndrome: a case report.* Mov Disord 2005;20(11):1496-9.
47. Temel Y, Visser-Vandewalle V. *Surgery in Tourette syndrome.* Mov Disord 2004;19(1):3-14.
48. Mink JW, Walkup J, Frey KA, Como P, Cath D, Delong MR, et al. *Patient selection and assessment recommendations for deep brain stimulation in Tourette syndrome.* Mov Disord 2006;21(11):1831-8.
49. Andrade DM, Zumsteg D, Hamani C, Hodaie M, Sarkissian S, Lozano AM, et al. *Long-term follow-up of patients with thalamic deep brain stimulation for epilepsy.* Neurology 2006;66(10):1571-3.
50. Kerrigan JF, Litt B, Fisher RS, Cranstoun S, French JA, Blum DE, et al. *Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy.* Epilepsia 2004;45(4):346-54.
51. Lim SN, Lee ST, Tsai YT, Chen IA, Tu PH, Chen JL, et al. *Electrical stimulation of the anterior nucleus of the thalamus for intractable epilepsy: a long-term follow-up study.* Epilepsia 2007;48(2):342-7.
52. Theodore WH, Fisher RS. *Brain stimulation for epilepsy.* Lancet Neurol 2004;3(2):111-8.
53. Leone M, Franzini A, Broggi G, Bussone G. *Hypothalamic stimulation for intractable cluster headache: long-term experience.* Neurology 2006;67(1):150-2.
54. Schoenen J, Di Clemente L, Vandenheede M, Fumal A, De Pasqua V, Mouchamps M, et al. *Hypothalamic stimulation in chronic cluster headache: a pilot study of efficacy and mode of action.* Brain 2005;128(Pt 4):940-7.
55. Leone M. *Deep brain stimulation in headache.* Lancet Neurol 2006;5(10):873-7.
56. Pereira EAC, Owen SL, Green AL, Aziz TZ. *Deep brain stimulation for pain.* In: Krames E, Peckham PH, Rezai AR, editors. Textbook of Neuromodulation: Elsevier, 2007.
57. Levy RM. *Deep brain stimulation for the treatment of intractable pain.* Neurosurg Clin N Am 2003;14(3):389-99, vi.
58. Owen SL, Green AL, Stein JF, Aziz TZ. *Deep brain stimulation for the alleviation of post-stroke neuropathic pain.* Pain 2006;120(1-2):202-6.
59. Bittar RG, Otero S, Carter H, Aziz TZ. *Deep brain stimulation for phantom limb pain.* J Clin Neurosci 2005;12(4):399-404.
60. Green AL, Nandi D, Armstrong G, Carter H, Aziz T. *Post-herpetic trigeminal neuralgia treated with deep brain stimulation.* J Clin Neurosci 2003;10(4):512-4.
61. Green AL, Owen SL, Davies P, Moir L, Aziz TZ. *Deep brain stimulation for neuropathic cephalalgia.* Cephalalgia 2006;26(5):561-7.
62. Hamani C, Schwalb JM, Rezai AR, Dostrovsky JO, Davis KD, Lozano AM. *Deep brain stimulation for chronic neuropathic pain: Long-term outcome and the incidence of insertional effect.* Pain 2006.
63. Owen SLF, Green AL, Nandi D, Bittar RG, Wang S, Aziz TZ. *Deep brain stimulation for neuropathic pain.* Neuromodulation 2006;9(2):100-6.
64. Lyons KE, Wilkinson SB, Overman J, Pahwa R. *Surgical and hardware complications of subthalamic stimulation: a series of 160 procedures.* Neurology 2004;63(4):612-6.
65. Yianni J, Green AL, McIntosh E, Bittar RG, Joint C, Scott R, et al. *The costs and benefits of deep brain stimulation surgery for patients with dystonia: An initial exploration.* Neuromodulation 2005;8(3):155-61.
66. Joint C, Nandi D, Parkin S, Gregory R, Aziz T. *Hardware-related problems of deep brain stimulation.* Movement Disorders 2002;17(SUPPL. 3).
67. Limousin P, Speelman JD, Gielen F, Janssens M. *Multicentre European study of thalamic stimulation in parkinsonian and essential tremor.* J Neurol Neurosurg Psychiatry 1999;66(3):289-96.
68. Deuschl G, Herzog J, Kleiner-Fisman G, Kubu C, Lozano AM, Lyons KE, et al. *Deep brain stimulation: postoperative issues.* Mov Disord 2006;21 Suppl 14:S219-37.
69. Yianni J, Nandi D, Hyam MJ, Elliott V, Bain P, Gregory R, et al. *Failure of Chronic Pallidal Stimulation in Dystonic Is a Medical Emergency.* Neuromodulation 2004;7(1):9-12.
70. DoH U. *Payment by Results in 2007-2008*, 2007.
71. Tomaszewski KJ, Holloway RG. *Deep brain stimulation in the treatment of Parkinson's disease: a cost-effectiveness analysis.* Neurology 2001;57(4):663-71.
72. Meissner W, Schreiter D, Volkmann J, Trottenberg T, Schneider GH, Sturm V, et al. *Deep brain stimulation in late stage Parkinson's disease: a retrospective cost analysis in Germany.* J Neurol 2005;252(2):218-23.
73. Spottke EA, Volkmann J, Lorenz D, Krack P, Smala AM, Sturm V, et al. *Evaluation of healthcare utilization and health status of patients with Parkinson's disease treated with deep brain stimulation of the subthalamic nucleus.* J Neurol 2002;249(6):759-66.
74. Charles PD, Padaliya BB, Newman WJ, Gill CE, Covington CD, Fang JY, et al. *Deep brain stimulation of the subthalamic nucleus reduces antiparkinsonian medication costs.* Parkinsonism Relat Disord 2004;10(8):475-9.
75. Hooper J, Whittle IR. *Costs of thalamic deep brain stimulation for movement disorders in patients with multiple sclerosis.* Br J Neurosurg 2003;17(1):40-5.
76. Eskandar EN, Flaherty A, Cosgrove GR, Shinobu LA, Barker FG, 2nd. *Surgery for Parkinson disease in the United States, 1996 to 2000: practice patterns, short-term outcomes, and hospital charges in a nationwide sample.* J Neurosurg 2003;99(5):863-71.
77. Kringelbach ML, Jenkinson N, Owen SL, Aziz TZ. *Principles of Deep Brain Stimulation.* Nat Rev Neurosci 2007:(in press).
78. Gillett G. *Ethics of surgical innovation.* Br J Surg 2001;88(7):897-8.
79. Gillett GR. *Should we ever do sham operations?* J Clin Neurosci 2001;8(2):116-9.
80. Nuttin B, Cosyns P, Demeulemeester H, Gybels J, Meyerson B. *Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder.* Lancet 1999;354(9189):1526.
81. Green AL, Shad A, Watson R, Nandi D, Yianni J, Aziz TZ. N-of-1 *Trials for Assessing the Efficacy of Deep Brain Stimulation in Neuropathic Pain.* Neuromodulation 2004;7(2):76-81.

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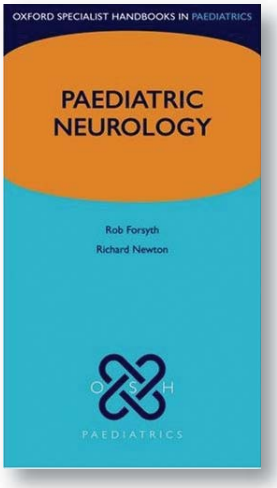
Handbook of Paediatric Neurology



Authors: Rob Forsyth, Richard Newton
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Although there is a plethora of paediatric neurology textbooks available of varying size and quality, this latest handbook, written by some of the 'great and good' of UK paediatric neurology, is a welcome addition. The book adopts a clinical approach to the subject with a couple of excellent introductory chapters on history taking, examination and neuro-diagnostic tools. Through the style of writing, which is clear and concise, the reader can appreciate the years of experience and expertise that the authors bring to the subject and although the individual chapters are brief there is a welcome emphasis on good communication with children and their carers. Interpretation of symptoms and signs and specific conditions are dealt with separately, an approach I feel is useful although it does lead to having to flick back and fore to look through the book to read about different disorders with a similar presentation. Specific conditions are listed under the usual headings e.g. CNS infection, demyelinating disorders and the discussion is presented in a mixture of prose and bullet points. I particularly enjoyed the chapter on functional illness which gives an excellent overview on dealing with this difficult problem. There is a very helpful chapter on consults with other sub-specialities, a chapter on common neurological emergencies and finally a brief pharmacopoeia.

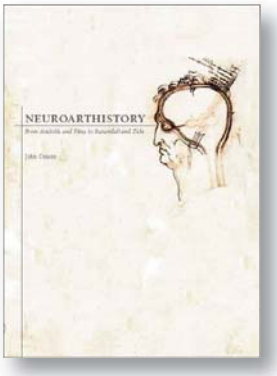
Although not specified, I think this book would be aimed at paediatric neurology trainees, general paediatric trainees rotating through a neurology unit and general paediatricians. It contains a wealth of information which is concise and well presented. It is not and does not pretend to be a comprehensive textbook of paediatric neurology but it should serve as a helpful source of basic information. To my knowledge, the only similar book available is Fenichel's 'Clinical pediatric neurology' which takes comparable symptoms and signs approach and although more detailed, Fenichel is much narrower in its approach with little discussion about history taking and examination.

Overall, this book represents an excellent starting point for trainees and consultants alike. At around thirty five pounds it represents superb value for money, paediatric neurology units would do well to keep a couple of copies for trainees to use during their attachment. A PDF version of the book would be very useful particularly for ward rounds and ward consults. I remember carrying the original Oxford handbook of medicine in the pocket of my white coat as a medical student and house officer but having dispensed with the white coat the handbook is no longer so portable. My only complaint is that this book was not available when I began my training, however I will continue to use it as I start my consultant career.

Reviewed by: Stewart Macleod, SpR paediatric neurology, Royal Liverpool Children's Hospital Alder Hey, UK.

Neuroarthistory

From Aristotle and Pliny to Baxandall and Zeki



Author: John Onians
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The 'Neurology of Art' is a subject of increasing interest, for example commanding a regular and well-attended session at the annual meeting of the European Federation of Neurological Societies (EFNS). A number of analyses of the influence of neurological disorders, such as neglect, aphasia, and dementia, on the output of creative artists, including those working in the visual arts, have been published. The neuroscientific approach to art has perhaps been most successsful in the field of aesthetics, spawning the term 'neuroaesthetics'. Hence, an attempted neural approach to art history seems not unreasonable, since cross fertilization between disciplines is often productive of new insights.

This book entails 'sketching the intellectual biographies' (xiii) of 25 individuals who have written something about the possible biological underpinnings of artistic endeavour, a heterogeneous group covering 25 centuries from Ancient Greece (Aristotle) to the late 20th century (Zeki). Most are from the European literary tradition, the only exception being the 11th century Arabic scholar al-Haytham. Some names will be familiar to most readers (e.g. Leonardo, William Hogarth, Kant, Marx, Ruskin), others were certainly unfamiliar to me, and may possibly be so to others (e.g. Vischer, Göller, Wölfflin, Riegl). Not all have necessarily written about visual art (e.g. Montesquieu); few have any specific training in the fields of medicine and/or science (Winckelmann, Freud, Zeki). The substrate of the book may thus be viewed as the 'great writings of great men' (since all are men), an approach which might be deemed 'whiggish' by medical historians. This is the first of a projected trilogy, with subsequent volumes to apply a neuroarthistorical approach to the art of Europe and then of the whole world (xiii).

Neurologists may find this a challenging but enjoyable read. There are occasional lapses ('rods, which are the colour sensors in the retina', p23; Kant's year of birth is wrongly given as 1728, rather than 1724, p79). However, there are perhaps more pressing objections concerning some of the author's assumptions. Can the bold claim, directly following Zeki, that writers on art are often neuroscientists without knowing it (13), be accepted? Or that neuroarthistory has the 'ability to reconstruct the unconscious intellectual formation of the makers, users and viewers of art' (13) such that 'the subjectivity they produce can be reconstructed hundreds or even thousands of years after the person in question has died' (15)? It is furthermore suggested that such neural formation may have helped these individuals 'to surprisingly anticipate [sic] modern science' (15). The danger of teleology (function as final cause) seems all too evident in this formulation.

Onians' neuroarthistory emerges as 'not a theory' but an 'approach. … a readiness to use neuroscientific knowledge to answer any of the questions that an art historian may wish to ask' (17). Hence this would seem to be an ever evolving endeavour as neuroscience itself develops, the validity of which may ultimately depend upon whether the human brain can ever understand itself.

Reviewed by: AJ Larner, WCNN, Liverpool, UK.

Emerging Clinical Applications of Neurophysiological Assessment of Sarcolemmal Excitability

Muscle disorders are regularly encountered by neurologists and clinical neurophysiologists. Nerve conduction studies are either normal or reveal reduced compound muscle action potential (CMAP) amplitudes. Needle electromyography (EMG) may reveal spontaneous activity (fibrillations or positive sharp waves), myopathic motor units and abnormal recruitment patterns. Structural muscle changes (variation in fibre size and a predominance of smaller fibres) contribute to the 'myopathic' EMG. Some muscle disorders however are due to muscle fibre membrane ion channel dysfunction. Increased muscle fibre membrane excitability may result in spontaneous discharges, clinically manifesting as myotonia or stiffness. Reduced excitability may cause slowing or failure of action potential propagation, which may manifest as weakness or paralysis. In a similar way to nerve excitability studies, the pathophysiological consequences of ion channel mutations on muscle membrane function can be assessed using neurophysiological techniques, complementing advancing knowledge of the genetic and molecular defects and of clinical phenotypes.

For muscle contraction to occur, conduction of action potentials along the muscle fibre membrane is dependent upon normal membrane excitability. Depolarisation is mediated by the $Na_v1.4$ Na^+ channel, product of the *SCN4A* gene. Calcium ions are subsequently released from the sarcoplasmic reticulum mediating excitation-contraction coupling. Chloride channels (encoded by *CLCN1*), which have high conductance near the resting membrane potential, stabilise it in the resting and post-excitation state.

Assessments of CMAP morphology, muscle fibre conduction velocity (MFCV) and short and long exercise tests can all be helpful in assessing membrane function. Action potential propagation velocity along the muscle fibre membrane (MFCV) can be estimated by cross-correlation of surface recorded EMG[1] or invasive methods.[2-4]

In myotonias, exercise can trigger, relieve or aggravate symptoms, so it can be used as a neurophysiological functional test, to aid diagnosis. The short exercise test, first described by Streib et al is useful in investigating myotonic disorders.[5] Repeated brief exercises are followed by rest and serial supramaximal CMAP recordings. The long exercise test, described by McManis et al is useful for the assessment of suspected periodic paralysis.[6]

To illustrate the potential utility of EMG techniques the following will describe recent work relating to the non-dystrophic myotonias and critical illness myopathy, where these investigations have been used.

Myotonias

Muscle fibre hyperexcitability is the fundamental abnormality in myotonia, resulting in spontaneous trains of action potentials, which with contraction coupling results in delayed relaxation. Myotonic discharges arise from single muscle fibres. They show rapid firing, waxing and waning of frequency and amplitude, and may be facilitated by mechanical stimuli. However, myotonic discharges are not diagnostically distinctive according to cause. In the absence of prominent clinical myotonia, electrical myotonia is observed in, amongst others, acid maltase deficiency, congenital myopathies, hypothyroidism and polymyositis. These conditions may also possess motor unit and recruitment abnormalities on EMG.

Routine assessment of myotonia relies upon needle EMG revealing myotonic discharges. Neurophysiological provocative tests including repetitive nerve stimulation,[7] short and long exercise tests, can help distinguish the main phenotypes.

Broadly divided into two groups, variants of myotonia congenita (MC) are caused by dominant or recessive mutations of the chloride channel gene (*CLCN1*). Myotonia increases after periods of rest and declines with repetition of exercise (warm up phenomenon). Mutations of the alpha subunit of the voltage gated skeletal muscle sodium channel gene (*SCN4A*) have been found to cause paramyotonia congenita (PC), where myotonia conversely is induced by exercise or cold. Clinical history and examination is frequently enough to be able to guide genetic testing, however it is sometimes unreliable or the phenotype unclear, for example, some *SCN4A* mutations produce myotonia without an increase after exercise, mimicking MC.[8]

Recent studies have addressed the utility of the short and long exercise tests in the non-dystrophic myotonias and have found them to be helpful in supporting the diagnosis and guiding genetic testing. Fournier et al studied patients with identified ion channel mutations, using a modified form of the short exercise test.[9] Instead of the originally described 10 minute rest period between tests, they used three brief exercise periods separated by only 1 minute each. In patients with myotonia congenita, Fournier, like Strieb previously, noted an initial decline in CMAP amplitude following exercise which gradually improved with further exercise, similar to the clinically recognised warm-up effect. Based on the findings they defined five electrophysiological groups, which distinguished between sodium, chloride and calcium channel mutations and also between subgroups of sodium channelopathies. The first three groups related to myotonic syndromes, which were distinguishable using repeated short exercise tests. The reported sensitivity of the repeated short exercise test was about 85%. Further work studying 54 patients with myotonia identified sodium or chloride channel mutations, describing increased sensitivity (approaching 90-100%) of the short exercise test when combined with muscle cooling.[10]

The patterns recorded correlate with the clinical symptoms. Those with PC due to the most common sodium channel mutations displayed a pattern of post exercise decreasing CMAPs, aggravated by repetition. Cold augments this decline in excitability. The common mutations impair inactivation of the channels and an increase in the sustained current, causing increased membrane excitability and myotonia or reduced excitability with paralysis,

The pathophysiological and clinical consequences of ion channel dysfunction can be assessed using neurophysiological techniques

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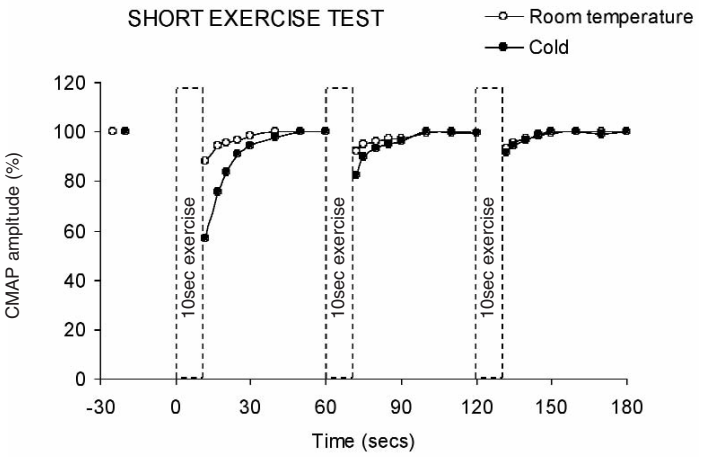

Figure 1: Example of Short exercise test result with the effect of cooling in a MC patient suggestive of a recessive Chloride channel mutation.

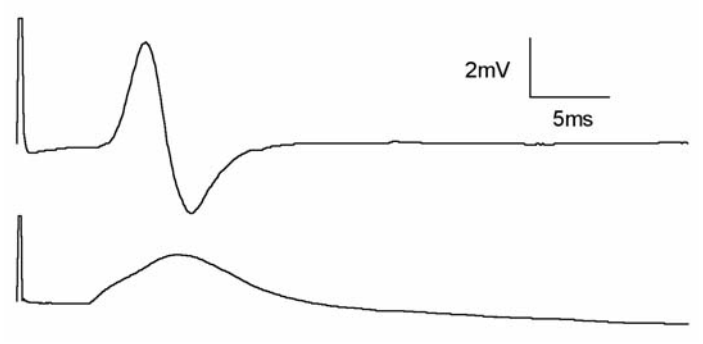

Figure 2: CMAPs recorded from a normal control (above) and from a patient with CIM demonstrating 'synchronised dispersion', which is the combined result of slowing of muscle fibre conduction velocities and widening of its range. Note the absence of the positive phase and the 'long tail'.

depending upon the degree of depolarisation.[11-13] Cooling induces membrane depolarisation by slowing ion channel kinetics; hence in PC, cold has a depolarising effect, causing myotonia and then inexcitability.[14,15] At room temperature almost all MC patients with recessive chloride channel mutations displayed a transient decrease in the CMAP when the short exercise test was performed after rest, which improves after short exercise test repetition, akin to the warm-up phenomenon. However, those with dominant mutations generally (86%) did not show this reduction following exercise under normal conditions but the majority (75%) did once there had been exposure to cold.

Fournier et al suggested that EMG can guide specific ion channel gene testing and that combining exercise tests with cold exposure improves the sensitivity. Prospective studies testing this hypothesis should be performed. Studies should also look at reproducability and at the usefulness of such testing in patients with these mutations but milder phenotypes.

Critical illness myopathy (CIM)

In contrast to hyperexcitability causing myotonia, muscle inexcitability has been demonstrated in critical illness myopathy.[16,17] Differentiating between a myopathy and neuropathy can be challenging in the intensive care unit. The differential diagnosis in ICU also includes Guillain Barré syndrome and myasthenia gravis for example. In a series of 92 patients with neuromuscular disorders acquired in the ICU, a myopathy consistent with CIM was three times as common as axonal polyneuropathy and is increasingly recognised.[18] Careful neurophysiological examination can differentiate these conditions. The ratio of the CMAPs recorded following direct muscle stimulation and motor nerve stimulation has been used to distinguish myopathy and neuropathy in ICU patients, this is however only semi-quantitative and has potential disadvantages.[17,19] Early in CIM paralysis there are fibrillation potentials and positive sharp waves on EMG. Recruitment and motor unit potentials appear myopathic. Subsequently the muscle becomes inexcitable. Myosin loss demonstrated on biopsy cannot explain muscle fibre membrane inexcitability and its loss lags behind the development of weakness.[20,21]

We recently demonstrated acquired dysfunction at the level of the muscle fibre membrane in critical illness myopathy, akin to that seen in some inherited channelopathies.[4] We found that in 90% of CIM patients, compared to controls, the CMAP duration recorded from either abductor hallucis (AH) or abductor pollicis brevis (APB) was significantly prolonged, exceeding the control mean + 2 SD in either or both the median or tibial responses. The morphology of the abnormal CMAP is also distinctive, being smoothly contoured and the positive phase is often replaced by a long negative phase (Figure 2). Other pathologies can cause CMAP duration prolongation e.g. demyelinating neuropathies; however the morphology is then typically irregularly dispersed (desynchronised) and associated with other nerve conduction abnormalities.

To further understand the underlying pathophysiology of this phenomenon we looked at MFCV, using an invasive technique. It was significantly slowed in CIM, the mean being 2.3m/s compared to 4.0m/s in controls. Some muscles and fibres were inexcitable or indirectly demonstrated muscle fibre conduction block. An inverse relationship between MFCV and CMAP duration was found, which was also proportional to the clinical severity. Hence the smooth CMAP contour probably reflects slowed and dispersed but synchronous depolarisation of muscle fibres. A paired stimulation technique was used to assess the refractory period of individual muscle fibres in vivo, which suggested a longer refractory period, CIM mean 4.7ms compared to controls mean of 2.5ms. CK is almost always normal or only mildly elevated in CIM.[4,19] In fact CK is disproportionately low for the degree of weakness, supporting the notion that weakness is due to dysfunction rather than structural change at onset. In the critically ill, the resting membrane potential may become depolarised due to generalised cellular dysfunction[22] or other factors.[23] In keeping with this hypothesis, in an animal model of CIM, inactivation of voltage dependant sodium channels has been demonstrated, which results in reduced sodium currents.[24-26]

Hypokalaemic periodic paralysis (HPP) type 2, due to SCNA4 mutations, results in sodium channel dysfunction. In HPP, MFCV is reduced interictally and further declines during attacks of paralysis.[27,28] Early on during paralytic episodes fibrillation potentials are present indicating depolarised membranes.[29] Paralysis arises following membrane depolarisation triggered sodium channel inactivation, rendering the muscle inexcitable.[8] In CIM it is presumed that a similar depolarising shift in membrane potential, due to either a generalised cellular dysfunction or the prescence of circulating factor or factors, contributes to sodium channel dysfunction and a similar dynamic pattern of electrophysiology. The neurophysiological findings in CIM and HPP share common themes. The parallels suggest a similar pathophysiology at the membrane level, although in CIM this is precipitated at least by a degree of acquired channel dysfunction. Functional polymorphisms in human cardiac muscle ion channels can mediate arrhythmia susceptibility,[30,31] and it would therefore be interesting to look for these Na+ channel polymorphisms in CIM patients. The parallels help our understanding of these conditions and might afford therapeutic possibilities.

Work on the basic pathophysiological mechanisms, has improved our understanding of critical illness myopathy and may also help its recognition, diagnosis and monitoring. In addition to fibrillations and a myopathic EMG, the synchronous dispersion of the prolonged CMAP is characteristic. Weaker patients have lower MFCV or inexcitable fibres on direct muscle stimulation and longer CMAP durations.

Conclusion

Limited studies have been performed in both CIM and in the myotonias. Further work should address reliability and reproducibility, and should investigate the interplay between genetics, neurophysiology and phenotypes. Understanding the precipitants of dysfunction also requires clarification. Our understanding and ability to accurately diagnose both common and rare muscle disorders related to sarcolemmal hyperexcitability or hypoexcitability is improving. The neurophysiological assessment can play an important role in this respect, providing accurate and timely diagnosis in the ICU and by directing genetic testing, which is more expensive and time consuming.

References

1. Arendt-Nielsen L, Mills K. *Muscle fibre conduction velocity , mean power frequency, mean EMG voltage and force during submaximal fatiguing contractions of human quadriceps.* Eur J Appl Physiol 1998;58:20-25.
2. Stålberg E, Trontelj J. *Single fibre electromyography. Studies in healthy and diseased muscle, 2nd Edn.* New York, Raven Press. 1994.
3. Troni W, Cantello R, Rainero I. *Conduction velocity along human muscle fibers in situ.* Neurology. 1983;33(11):1453-9.
4. Allen D, Arunachalam R, Mills K. *Critical illness myopathy: Further evidence from muscle-fiber excitability studies of an acquired channelopathy.* Muscle and Nerve 2008;37(1):14-22.
5. Streib E, Sun S, Yarkowski T. *Transient paresis in myotonic syndromes: a simplified electrophysiological approach.* Muscle Nerve 1982;5:719-23.
6. McManis P, Lambert E, Daube J. *The exercise test in periodic paralysis.* Muscle Nerve 1986;9:704-10.
7. Aminoff M, Layzer R, Satya-Murti S, Faden A. *The declining electrical response of muscle to repetitive nerve stimulation in myotonia.* Neurology 1977;27:812-16.
8. Lehmann-Horn F, Jurkat-Rott K. *Voltage gated ion channels and hereditary disease.* Physiol Rev 1999;79:1317-2.
9. Fournier E, Arzel M, Sternberg D, Vicart S, Laforet P, Eymard B, Willer J-C, Tabti N, Fontaine B. *Electromyography guides toward subgroups of mutations in muscle channelopathies.* Ann Neurol 2004;56:650-61.
10. Fournier E, Viala K, Gervais H, Sternberg D, Arzel-Hezode M, Laforet P, Eymard B, Tabti N, Willer J-C, Vial C, Fontaine B. *Cold extends electromyography distinction between ion channel mutations causing myotonia.* Ann Neurol 2006;60:356-65.
11. Hayward L, Brown R, Cannon S. *Inactivation defects caused by myotonia –associated mutations in the sodium channel III-IV linker.* J Gen Physiol 1996;107:559-76.
12. Lehmann-Horn F, Rudel R. *Molecular pathophysiology of voltage gated ion channels.* Rev Physiol Biochem Pharmacol 1996;128:195-268.
13. Cannon S, Brown R, Corey D. *Theoretical reconstruction of myotonia and paralysis caused by incomplete inactivation of sodium channels.* Biophys J 1993:65:270-88.
14. Ruff R. *Effects of temperature on slow and fast inactivation of rat skeletal muscle Na (+) channels.* Am J Physiol 1999;277:937-47.
15. Mohammadi B, Mitrovic N, Lehmann-Horn F et al. *Mechanisms of cold sensitivity of paramyotonia congenital mutation R1448H and overlap syndrome mutation M1360V.* J Physiol 2003;547:691-8.
16. Rich MM, Teener JW, Raps EC, Schotland DL, Bird SJ. *Muscle is electrically inexcitable in acute quadriplegic myopathy.* Neurology. 1996;46(3):731-6.
17. Rich MM, Bird SJ, Raps EC, McCluskey LF, Teener JW. *Direct muscle stimulation in acute quadriplegic myopathy.* Muscle Nerve. 1997;20(6):665-73.
18. Lacomis D, Petrella JT, Giuliani MJ. *Causes of neuromuscular weakness in the intensive care unit: a study of ninety-two patients.* Muscle Nerve. 1998;21(5):610-7.
19. Lefaucheur JP, Nordine T, Rodriguez P, Brochard L. *Origin of ICU acquired paresis determined by direct muscle stimulation.* J Neurol Neurosurg Psychiatry. 2006;77(4):500-6.
20. Showalter CJ, Engel AG. *Acute quadriplegic myopathy: analysis of myosin isoforms and evidence for calpain-mediated proteolysis.* Muscle Nerve. 1997;20(3):316-22.
21. Zifko UA, Zipko HT, Bolton CF. *Clinical and electrophysiological findings in critical illness polyneuropathy.* J Neurol Sci. 1998;159(2):186-93.
22. Cunningham JN Jr, Carter NW, Rector FC Jr, Seldin DW. *Resting transmembrane potential difference of skeletal muscle in normal subjects and severely ill patients.* J Clin Invest. 1971;50(1):49-59.
23. Friedrich O, Hund E, Weber C, Hacke W, Fink RH. *Critical illness myopathy serum fractions affect membrane excitability and intracellular calcium release in mammalian skeletal muscle.* J Neurol. 2004;251(1):53-65.
24. Rich MM, Pinter MJ, Kraner SD, Barchi RL. *Loss of electrical excitability in an animal model of acute quadriplegic myopathy.* Ann Neurol. 1998;43(2):171-9.
25. Rich MM, Pinter MJ. *Sodium channel inactivation in an animal model of acute quadriplegic myopathy.* Ann Neurol. 2001;50(1):26-33.
26. Rich MM, Pinter MJ. *Crucial role of sodium channel fast inactivation in muscle fibre inexcitability in a rat model of critical illness myopathy.* J Physiol. 2003;547(Pt2):555-66.
27. Troni W, Doriguzzi C, Mongini T. *Interictal conduction slowing in muscle fibers in hypokalaemic periodic paralysis.* Neurology. 1983;33(11):1522-5.
28. Links TP, van der Hoeven JH, Zwarts MJ. *Surface EMG and muscle fibre conduction during attacks of hypokalaemic periodic paralysis.* J Neurol Neurosurg Psychiatry. 1994;57(5):632-4.
29. Gordon AM, Green JR, Lagunoff D. *Studies on a patient with Hypokalaemic familial periodic paralysis.* Am J Med. 1970;48(2):185-95.
30. Kubota T et al. *Evidence for a single nucleotide polymorphism in the KCNQ1 potassium channel that underlies susceptibility to life threatening arrhythmias.* J Cardiovasc Electrophysiol 2001;12:1223-9.
31. Viswanathan P, Benson D, Balser J. *A common SCN5A polymorphism modulates the biophysical effects of an SCN5A mutation.* J Clin Invest 2003;111:341-6.

Stroke-Associated Infection and the Stroke-Induced Immunodepression Syndrome

Stroke remains a leading cause of death and disability in industrialised and developing countries. Whilst new therapies evolve, attention is directed towards the mechanisms that underpin deterioration and complications. The role of infection in the aetiology and later complications of stroke is increasingly recognised. This occurs within the context of complex interplay between the brain and immune systems. Considerable debate continues as to the extent to which the brain itself contributes to the systemic response, and vice versa. The array of inflammatory/anti-inflammatory mechanisms in stroke is highly regulated at the gene and posttranslational levels.[1] One component of these is the cytokine family. These molecules are pivotal to cross talk between brain and immune systems and activate autonomic and hypothalamic-pituitary-adrenal axes. In turn these give rise to catecholamine and glucocorticoid responses that modulate immune function. This articles reviews the emerging phenomenon of stroke associated infection (SAI), its mechanism and the role of antibiotic prophylaxis in stroke.

Stroke associated infection

SAI is a common complication occurring in between 21-65% of stroke patients.[2] The degree to which this occurs depends on a number of factors including stroke severity and pre-existing comorbidity. Even within specialised stroke units, SAI occurs in up to 65% of patients, where pneumonia accounts for the highest mortality.[3] The high incidence of SAI has prompted the idea of a stroke induced immunodepression syndrome (SIIS).

Infectious complications account for 20% of deaths in stroke, where pneumonia and urinary tract infection (UTI) predominate.[4] Dysphagia, in addition to reduced bulbar reflexes and drowsiness, are other factors. Despite early swallowing assessment and intervention, pneumonia remains common.[5] There also remains a complex relationship between factors such as fever (possibly central), infection per se and thrombosis. Studies that are not prospective and do not control for initial severity and a rigorous diagnosis of infection warrant critical appraisal. More recent studies have suggested that infection and stroke worsening may be independent variables.[6]

Evidence for a suppressed immune response

Animal studies

In patients, aspiration alone appears insufficient to explain the high incidence of stroke associated pneumonia. Much of the evidence in favour of an autoregulated but suppressed immune system following stroke is derived from animal studies. In support of a double hit hypothesis combining aspiration and an immunodeficiency syndrome, is one key animal study. Here, a combination of experimental stroke and inoculation was sufficient to cause severe pneumonia.[7] The role of leucocytes in the mediation of immunosuppression is also considered. Both neutrophils and monocytes invade the brain in the acute /subacute phases of ischaemic stroke, but with respect to the former it remains unclear as to whether such recruitment is pathogenic or a marker of disease.[8] During infection, monocytes remain a lead contributor to the innate response and a principal source of proinflammatory mediators. One mediator, IL-1β is thought to be critically involved in neuronal apoptosis following ischaemia. There is evidence that resident brain macrophages or microglia contribute centrally to generating IL-1β and that such cells are active in the subacute phase of clinical stroke.[9]

Other cytokines play a role here. In a number of experimental stroke models, cytokines such as TNF-α and IL-6 from a variety of sites prompt the production and release of corticotrophin releasing hormone (CRH) from the hypothalamus. CRH in turns mediates a pituitary based release of ACTH and consequent glucocorticoid release from adrenal cortex. Glucocorticoids in turn suppress, primarily at nuclear level, production of the proinflammatory cascade involving, in addition to those above, IL-11, IL-12, interferon-γ and chemokines (IL-8) whilst facilitating release of anti-inflammatory mediators such as IL-10. Hypothalamic activation additionally downgrades, via nicotinic receptors, peripheral release of proinflammatory cytokines such as TNFα from macrophages.[10] In one model, rapid and extensive apoptosis of lymphocytes is observed for up to six weeks post stroke, and such animals develop spontaneous infection after initial evidence of immunosuppression. Such effects are thought to involve the autonomic nervous system, and to an extent may be blocked by propranolol. Sympathetic nervous system activation also gives rise to an exaggerated release of noradrenalin, both from brain and adrenal glands, that in

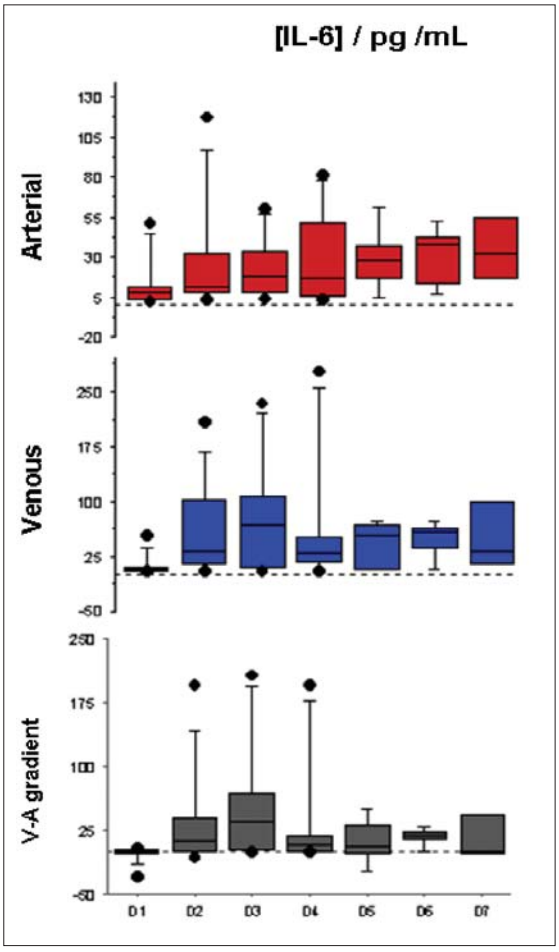

Figure 1: Box plot of arterial, venous (jugular) and arterio-jugular (V-A) gradients for IL-6 for days (D1-D7) in 12 patients with radiologically-confirmed ischaemic stroke. Significant gradients were detected on day 3 only (p= 0.02, one sample sign test), consistent with a central mechanism.

Dr Christopher Price is currently completing his clinical neurology training as an SpR at the Royal Devon & Exeter Hospital. He has an established interest in cerebrovascular disease, in particular neuroinflammatory aspects of ischaemic stroke and neuroprotection.

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turn has a net inhibitory effect on proinflammatory T helper type 1 lymphocyte activity whilst the Th2 response remains essentially unaffected.[11]

Finally, evidence is now emerging for a possible genetic component to SIIS. A number of polymorphisms relate to inflammatory processes linked to subtypes of stroke, whilst some evidence exists to suggest that the type of stroke is dictated by the host immune response.[12]

Clinical studies

In stroke patients, a variety of systemic effects are reported within the aftermath of stroke. These include high or low levels of ACTH that have been reported in conjunction with poor outcome, larger volume infarcts, reduced peripheral lymphocyte counts and impaired natural and T cell activity.[13] Longitudinal data from acute stroke patients would suggest that the anti-inflammatory cytokine IL-10 and monocyte count were the two best immune based predictors of infection.[14] Within this cohort of patients, rapid rises in proinflammatory plasma cytokines such as TNF-α precede infection, as do increases in peripheral white blood cell counts and a high levels of catecholamines. Limited data from our own laboratory would suggest no clear brain derived cytokine gradients, although IL-6 may form a peak at three days post stroke (Figure 1, personal communication). In other forms of acute brain injury, e.g. trauma, higher levels of IL-10 levels are associated with greater levels of infection, perhaps by switching off circulating monocytes. Overall the extent to which the brain influences such processes remains largely unknown.

Interventional studies

In experimental models of stroke, antibiotics not only prevent pneumonia but also reduce mortality and improve outcome.[15] Based upon such data, clinical trials have sought to evaluate the effectiveness of prophylactic antibacterial therapy. The Early Systemic Prophylaxis of Infection After Stroke (ESPIAS) trial included 136 patients using levofloxacin 500mg daily for three days within 24 hours of non-septic stroke. The ESPIAS trial was stopped short as the drug did not prevent post stroke infection or improve outcome. Indeed a non-significant trend towards higher mortality was observed.[2] Many explanations have been put forward for this. They include choice of antibiotic, particularly with respect to the spectrum of levofloxacin against anaerobes, that the drug was given too early to prevent later complications, and that the study population comprised a highly heterogenous group including haemorrhagic strokes. To an extent, such factors are addressed in a small study, the Preventative Antibacterial Therapy in Acute Stroke (PANTHERIS) trial (PLoS ONE. 2008; 3(5): e2158. Published online 2008 May 14. doi: .1371/journal.pone.0002158). This trial used moxifloxacin (thought to have a broader antibiotic profile) for longer periods with predefined protocols if pneumonia occurred subsequently. Despite lowered rates of pneumonia, this trial was insufficiently powered to detect improvements in survival and outcome.

Conclusion

Post stroke infection is common. Active debate centres upon the contribution of neuroendocrine responses versus that of neurological worsening per se. Evidence is now emerging that mechanical factors alone are perhaps insufficient to account for the high rates of post stroke infection. SIIS may account for this where a series of interrelated events involve leucocytes, cytokines and the sympathetic nervous system occur. Only to a very limited degree has such data been taken forward in the form of a clinical trial. A number of methodological issues remain outstanding. To some extent these are being addressed in the design of future, larger scale clinical trials.

Acknowledgments

The author wishes to acknowledge the support of the Medical Research Council, the Raymond & Beverley Sackler Fellowship, Dr Elizabeth Warburton, Mrs Diana Day and Dr Rainer Doffinger (Addenbrookes NHS Trust) and Professors David Menon and Jean-Claude Baron (University of Cambridge).

References

1. Samson Y, Lapergue B, Hosseini H. *Inflammation and ischaemic stroke: current status and future perspectives.* Rev Neurol (Paris) 2005;161(12 Pt 1):1177-82.
2. Chamorro A, Horcajada JP, Obach V, Vargas M, Revilla M, Torres F, Cervera A, Planas AM, Mensa J. *The Early Systemic Prophylaxis of Infection After Stroke study: a randomized clinical trial.* Stroke 2005;36(7):1495-500.
3. Katzan IL, Cebul RD, Husak SH, Dawson NV, Baker DW. *The effect of pneumonia on mortality among patients hospitalized for acute stroke.* Neurology 2003;60(4):620-5.
4. Meisel C, Schwab JM, Prass K, Meisel A, Dirnagl U. *Central nervous system injury-induced immune deficiency syndrome.* Nat Rev Neurosci 2005;6(10)775-86.
5. Dennis MS, Lewis SC, Warlow C. *Effect of timing and method of enteral tube feeding for dysphagic stroke patients (FOOD): a multicentre randomised controlled trial.* Lancet 2005;365(9461)764-72.
6. Vargas M, Horcajada JP, Obach V, Revilla M, Cervera A, Torres F, Planas AM, Mensa J, Chamorro A. *Clinical consequences of infection in patients with acute stroke: is it prime time for further antibiotic trials?* Stroke 2006;37(2):461-5.
7. Prass K, Braun JS, Dirnagl U, Meisel C, Meisel A. *Stroke propagates bacterial aspiration to pneumonia in a model of cerebral ischemia.* Stroke 2006;37(10):2607-12.
8. Price CJ, Warburton EA, Menon DK. *Human cellular inflammation in the pathology of acute cerebral ischaemia.* J Neurol Neurosurg Psychiatry 2003;74(11):1476-84.
9. Price CJ, Wang D, Menon DK, Guadagno JV, Cleij M, Fryer T, Aigbirhio F, Baron JC, Warburton EA. *Intrinsic activated microglia map to the peri-infarct zone in the subacute phase of ischemic stroke.* Stroke 2006;37(7):1749-53.
10. Pavlov VA, Wang H, Czura CJ, Friedman SG, Tracey KJ. *The cholinergic anti-inflammatory pathway: a missing link in neuroimmunomodulation.* Mol Med 2003;9(5-8):125-34.
11. Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. *The sympathetic nerve--an integrative interface between two supersystems: the brain and the immune system.* Pharmacol Rev 2000;52(4):595-638.
12. Revilla M, Obach V, Cervera A, Davalos A, Castillo J, Chamorro A. *A -174G/C polymorphism of the interleukin-6 gene in patients with lacunar infarction.* Neurosci Lett 2002;324(1):29-32.
13. Schwarz S, Schwab S, Klinga K, Maser-Gluth C, Bettendorf M. *Neuroendocrine changes in patients with acute space occupying ischaemic stroke.* J Neurol Neurosurg Psychiatry 2003;74(6):725-7.
14. Chamorro A, Amaro S, Vargas M, Obach V, Cervera A, Torres F, Planas AM. *Interleukin 10, monocytes and increased risk of early infection in ischaemic stroke.* J Neurol Neurosurg Psychiatry 2006; 77(11):1279-81.
15. Meisel, C, Prass K, Braun J, Victorov I, Wolf T, Megow D, Halle E, Volk HD, Dirnagl U, Meisel A. *Preventive antibacterial treatment improves the general medical and neurological outcome in a mouse model of stroke.* Stroke 2004;35(1):2-6.

To list your event in this diary, email brief details to Rachael Hansford at rachael@acnr.co.uk by 7 October, 2008

2008

September

Genetics of Epilepsy
September, 2008; ILAE–VIREPA
distance learning course
E. office@epilepsy-academy.org,
www.epilepsy–academy.org

EEG in the diagnosis and management of epilepsy
September, 2008; ILAE–VIREPA
distance learning course
E. office@epilepsy-academy.org,
www.epilepsy–academy.org

Neuroimaging
September, 2008; ILAE–VIREPA
distance learning course
E. office@epilepsy-academy.org,
www.epilepsy–academy.org

Clinical Pharmacology and Pharmacotherapy
September, 2008; ILAE–VIREPA
distance learning course
E. office@epilepsy-academy.org,
www.epilepsy–academy.org

Federation of the European Societies of Neuropsychology
2-5 September, 2008; Edinburgh, UK
T. 01332 254679,
www.ncore.org.uk

Genomic Perspectives to Host Pathogen Interactions
3-6 September, 2008; Cambridge, UK
http://firstcontact.hinxton.wellcome.ac.uk

6th International Conference on Frontotemporal Dementia
3-5 September, 2008; Rotterdam,
The Netherlands
E. office@FTD2008.org,
www.ftd2008.org/site/

Making the Evidence Work for your Patients and their Families
4-5 September, 2008; Southampton, UK
T. +44 (023) 8079 8669
F. +44 (023) 8079 4340
E. neurorehab2008@soton.ac.uk,
www.neurorehab2008.soton.ac.uk

European Headache and Migraine Trust International Congress 2008
4-7 September 2008, London, UK
E. enquiries@ehmticongress2008.com,
www.ehmticongress2008.com
T. +44 (0) 20 8979 8300

Festschrift for Professor David Milner "The Neuropsychology of Perception and Action"
6 September, 2008; Durham, UK
E. l.h.de-wit@durham.ac.uk

Understanding Neuroscience: an innovative approach for mental health practitioners
8-9 September, 2008; London, UK
E. annehaylock@markallengroup.com

Brain and Behaviour: exploring how neuroscience can support clinical treatment in child and adolescent mental health
8-9 September, 2008; London, UK
E. annehaylock@markallengroup.com

BISWG South Wales Regional Meeting
9 September, 2008; Cardiff, UK
E. kate.coles@hughjames.com,
www.biswg.co.uk

BSS hosting the 19th Congress of the European Sleep Research Society
9-13 September, 2008; Glasgow
E. enquiries@sleeping.org.uk

11th Annual Advanced Rehabilitation Event
10, 11 & 12 Sept, 2008; Derby, UK
NCORE
T. 01332 254679 or
www.ncore.org.uk

ABN Autumn Scientific Meeting
10-12 September, 2008; Aviemore, UK
E. Karen.reeves@theabn.org

Genome Informatics
10-14 September, 2008; Cambridge, UK
http://firstcontact.hinxton.wellcome.ac.uk

VIIIth Congress of the EANO
12-14 September, 2008; Barcelona, Spain
T. +43 1 4051383 0,
F. +43 1 4078274,
E. eano2008@medacad.org

Evolution of Brain, Behaviour & Intelligence
12-14 September, 2007; Hinxton, UK
T. 01223 495000, E. wtmeet-ings@wtconference.org.uk,
http://firstcontact.hinxton.wellcome.ac.uk/

Enabling People with Long-Term Conditions: How Telecare, Electronic and Computer-based Technologies can help
16 September, 2008; London, UK
F. 020 7760 7193,
T. 020 7921 0002,
www.innervate.co.uk

Epilepsy in Later Life: Guiding Good Practice
17 September, 2008; Edinburgh, UK
E. enquiries@epilepsyscotland.org.uk
T. 0141 427 4911.

"Mind in the Brain" (a Festschrift in honour of Professor Chris Frith, FRS)
17-18 September, 2008; London, UK
E. Rosalyn Lawrence
rosalyn.lawrence@ucl.ac.uk

AANEM Annual Scientific Meeting
17-20 September, 2008; Providence, Rhode Island, USA
T. + (507) 288 0100,
F. + (507) 288-1225,
E. aanem@aanem.org

ECTRIMS/LACTRIMS/RIMS
17-20 September, 2008; Montreal, Canada
T. 001 212 476 0469,
F. 001 212 476 0485,
E. msmontreal@nmss.org,
www.nationalMSsociety.org

2nd International Symposium On Pheochromocytoma
17-21 September, 2008; Cambridge, UK
E. isp2008@hamptonmedical.com

Chronic Fatigue Syndrome
18 September, 2008; Bristol, UK
E. joyce.achampong@rsm.ac.uk,
T. 020 7290 2980

7th Mediterranean Congress of Physical Medicine & Rehabilitation Medicine
18-21 September, 2008; Potorose, Slovenia
E. marincek.crt@mail.ir-rs.si

Understanding and Dealing with Behaviour Problems
19-20 September, 2008; London, UK
E. enquiries@braintreetraining.co.uk,
www.braintreetraining.co.uk

Congress of Neurological Surgeons Annual Meeting
20-25 September, 2008; Orlando, USA.
Congress of Neurological Surgeons
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F. +847 240 0804,
E. info@1CNS.org,
www.neurosurgeon.org

10th International Symposium On Thrombolysis And Acute Stroke Therapy
21-23 September, 2008; Budapest, Hungary
E. tast2008@kenes.com,
www.kenes.com/tast2008

8th European Congress on Epilepsy
21-25 September, 2008; Berlin, Germany
E. berlin@epilepsycongress.org,
www.epilepsyberlin2008.org

10th National Conference - Parkinson's Disease: responding to mental health issues in Parkinson's
23 September, 2008; Birmingham, UK
MA Healthcare Ltd
T. 01722 716007
F. 0207 733 8174
www.mahealthcareevents.co.uk,
E. annehaylock@markallengroup.com

18th Ion Channel Meeting
23-26 September, 2007; Presqu ile de Giens, France
E. arnaud.monteil@igf.cnrs.fr,
http://congres.igh.cnrs.fr/canaux-ioniques/

Exploring Gait as it Relates to Posture & Balance for qualified staff
24 September, 2008; Derby, UK
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T. 01332 254679 or
www.ncore.org.uk

New Venue
5th World Congress for NeuroRehabilitation Brasilia, Brazil
24-27 September, 2008;
www.wcnr-brasilia2008.com

6th World Stroke Congress
24-27 September, 2008; Vienna, Austria
E: stroke2008@kenes.com,
www.kenes.com/stroke2008

International E-coli Alliance
24-28 September, 2008; Cambridge, UK
http://firstcontact.hinxton.wellcome.ac.uk

2nd Seminar on Clinical Neurology
27-28 September, 2008; Rhodes, Greece
Mrs. Ifigenia Tambaki,
T. 302 310 253 465 7,
E. info@airmarit-erasmus.gr

Understanding the pelvis and its function in the neurological patient (Bobath trainer)
29, 30 September & 1 October, 2008; Derby, UK
NCORE
T. 01332 254679 or
www.ncore.org.uk

Anxiety and Depression: diagnosis and management, A National Conference on Child and Adolescent Mental Health
29-30 September, 2008; London, UK
E. annehaylock@markallengroup.com

Drug Information Association (DIA) Innovation Forum
29-30 September; London, UK
E. Joe.Krasowski@diahome.org

October

Integrative Approaches to Brain Complexity
1-5 October, 2008; Hinxton, UK
E. meetings@cshl.edu

BISWG 8th Annual Brain Injury Legal Seminar
2 October, 2008; London, UK
E. lbellgard.rhn.org.uk,
www.biswg.co.uk

The story of polymyositis, Dr Russell Lane
2 October, 2008; Royal Society of Medicine, London, UK
E. cns@rsm.ac.uk
www.rsm.ac.uk/cns

North America Brain Injury Society's 6th Annual Conference on Brain Injury
2-4 October, 2008. New Orleans, USA
E. conference@nabis.org
www.nabis.org

EPDA Euroyapmeet Conference
3–5 October, 2008; Zagreb, Croatia
E. lizzie@epda.eu.com

The Seventh North American Conference on Shaken Baby Syndrome (Abusive Head Trauma)
5-8 October, 2008; Vancouver, Canada
E. mail@dontshake.org
T. 801-627-3399 / 888-273-0071

PD Nurses Association 9th Annual Conference
6-7 October, 2008; Warwick, UK
www.pdnsa.net

Recent Advances in Brain Injury Rehabilitation
8 October, 2008; London, UK
E. nicholas.hall@homerton.nhs.uk

Advanced Cognitive Rehabilitation Workshop: Attention and Information Processing
10-11 October, 2008; Ljubljana, Slovenia
E. ursa.cizman@ir-rs.si

A New Era for Stroke Patients
14 October 2008; London, UK
Royal College of Physicians,
T. 020 7935 1174 ext 436/252/300,
F. 020 7224 0719,
E. conferences@rcplondon.ac.uk
www.rcplondon.ac.uk/conferences

MipTec – Drug Discovery Event
14 -16 October, 2008; Basel, Switzerland
E. friederike.gutmann@akm.ch

Neuroscience – The Plastic Brain: Memory in Health and Disease
14-17 October, 2008; Arachon, France
E. neuroscience@conferences.aquitaine.fr

Practical Cognition Course
16-17 October, 2008; Newcastle, UK
E. umbereen.rafiq@newcastle.ac.uk

Mental Dysfunctions in Parkinson's Disease
16-19 October, 2008; Dresden, Germany
T. +41 22 908 0488,
F. +41 22 732 2850,
E. pdment2008@kenes.com
www.kenes.com/pdment2008

International Symposium on Rare Diseases. Inherited Neuromuscular Diseases: Translation from Pathomechanisms to Therapies
16-18 November, 2008; Valencia, Spain
T. 0034 96 197 46 70

Dystonia Europe 2008
17-19 October, 2008; Hamburg, Germany
www.dystonia-europe-2008.org

Headway Conference and Exhibition
20 October, 2008; Stratford upon Avon, UK
Rachel Broughton,
eventsandconferences@headway.org.uk
T. 0115 924 0800.

2nd World Congress on Controversies in Neurology (CONy)
23-26 October, 2008; Athens, Greece
www.comtecmed.com/cony
E. cony@comtecmed.com

9th International Congress of Neuroimmunology
26-30 October, 2008; Texas, USA
T. 0039 06 5193499,
F. 0039 06 5194009,
E. m.martinez@isniweb.org

3rd UK Dementia Congress
28-30 October, 2008; Bournemouth, UK
T. 020 7498 3023,
E. shital@hawkerpublications.com

November

MS Trust Annual Conference
2-4 November, 2008; Leeds, UK
T. 01462 476700,
E. Info@mstrust.org.uk

Progress: Advancing Parkinson's Research - Parkinson's Disease Society
3-4 November, 2008; York, UK
E. conference@parkinsons.org.uk

International Symposium on ALS/MND
3-5 November, 2008; Birmingham, UK
E. pam.aston@mndassociation.org

P-CNS meeting
6 November, 2008; Cardiff, UK
www.p-cns.org.uk

One headache after another
6 November, 2008; Royal Society of Medicine, London, UK
E. cns@rsm.ac.uk
www.rsm.ac.uk/cns

Clinical Conundrums in Epilepsy, Epilepsy Syndrome Series meeting
7 November, 2008; RCP London, UK
E. olga.howard@ucb-group.com
T. 07979 532104

European Charcot Foundation University Classes in Multiple Sclerosis V
12 November, 2008; Taormina (Sicily) Italy
www.charcot-ms.eu

Epilepsy and Co-morbidities Conference,
14 November, 2008; London, UK
E. jacob.k.burd@pfizer.com
T. 07968 439 662

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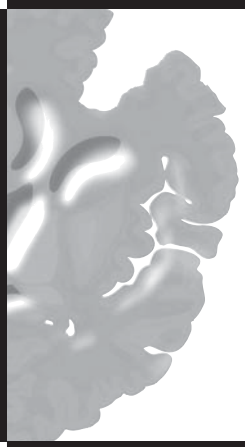

Sessions on:
- Acute Stroke
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email: seminars@isas.co.il

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epilepsy action

Epilepsy Action Research Grants Programme 2008-2009

In 2008 -2009 Epilepsy Action Research Grants Programme will offer funding worth more than £250,000. It will include large and small research grants, PhD studentships, postgraduate bursaries and travel bursaries. Researchers and students working within the British Isles, including Eire, will be eligible to apply for funding.

Epilepsy Action is the largest member-led epilepsy organisation in Britain. It acts as the voice for the UK's estimated 456,000 people with epilepsy, as well as their friends, families, carers, health professionals and the many other people on whose lives the condition has an impact.

Closing date for applications is 10 October 2008

Further information can be found on Epilepsy Action's website http://www.epilepsy.org.uk/research/awards.html or by contacting Margaret Rawnsley on 0113 210 8800, email reseach@epilepsy.org.uk

epilepsy action
New Anstey House, Gate Way Drive, Yeadon, Leeds LS19 7XY
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Call for proposals

Epilepsy Research UK invites applications for grants to support basic and clinical scientific research in the UK into the causes, treatment and prevention of epilepsy. We encourage applications on all aspects of epilepsy including basic and social science, clinical management and holistic management of patients.

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Deadline for receipt of completed applications: Friday 17 October 2008. More information and an application form are available from www.epilepsyresearch.org.uk, or:

Delphine van der Pauw
Research and Information Executive
Epilepsy Research UK, PO Box 3004
London W4 4XT Tel: 020 8995 4781
email: delphine@eruk.org.uk

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- Medical problems and solutions whilst on the KD
- When the Diet should be offered
- Matthew's Friends – Being part of the team
- Supporting the Professional as well as the Parent
- PM Workshop Session – The role of the Epilepsy Nurse
- PM Workshop Session - MCT & Classical diets inc fine-tuning

SPEAKERS INCLUDE:
Dr. Sunny Philip, Gwyneth Magrath & Bernie Concannon – BCH
Dr. Elizabeth Neal – Institute of Child Health & Great Ormond Street
Hannah Chaffe – GOSH, Emma Williams – Matthew's Friends

This is a 'free of charge' day, including lunch & refreshments, however places are limited and must be reserved before the event.
A 2nd day for parents/carers/schools/respite will be held Sat 18th Oct.

E: julie@matthewsfriends.org, T: 07748800438
www.matthewsfriends.org

PARKINSON'S DISEASE NON-MOTOR GROUP

4th Meeting of the UK Parkinson's Disease Non-Motor Group

Saturday 21st March 2009,
Royal Society of Medicine, London

Dear Colleague,
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- Plenary lectures on key non motor problems in PD
- Symposia on key topical issues such as therapy in advanced disease, psychiatric issues and dopamine agonists, and co- morbidities and QoL in PD.

This will be a whole day meeting and there is a nominal charge of **£75** for the day and lunch, coffee and refreshments are provided.

Speakers include: A Schapira, P Barone, F Stocchi, P Jenner, C Trenkwalder, I Arnulf, N Giladi, H Reichmann, C Fowler, DJ Brooks, E Wolters, DJ Burn, D MacMahon, G Macphee, N Quinn.

For registration please contact Ms Yogini Naidu at yogi-ni.naidu@uhl.nhs.uk or by visiting www.pdnmg.com
The meeting will be accredited with 6 CPD points

The PDNMG is a non profit academic organisation and acknowledges educational grants and funding from Boehringer Ingelheim, Britannia Pharmaceuticals, Solvay Pharmaceuticals and Lundbeck Limited and Teva Pharmaceuticals Ltd. PDNMG is chaired by Professor K Ray Chaudhuri and he acknowledges sponsorship from the Parkinson's Disease Society of the UK and the Movement Disorders Society.

Parkinson's Disease Society
The *Movement* Disorder Society

Date of preparation:
August 2008

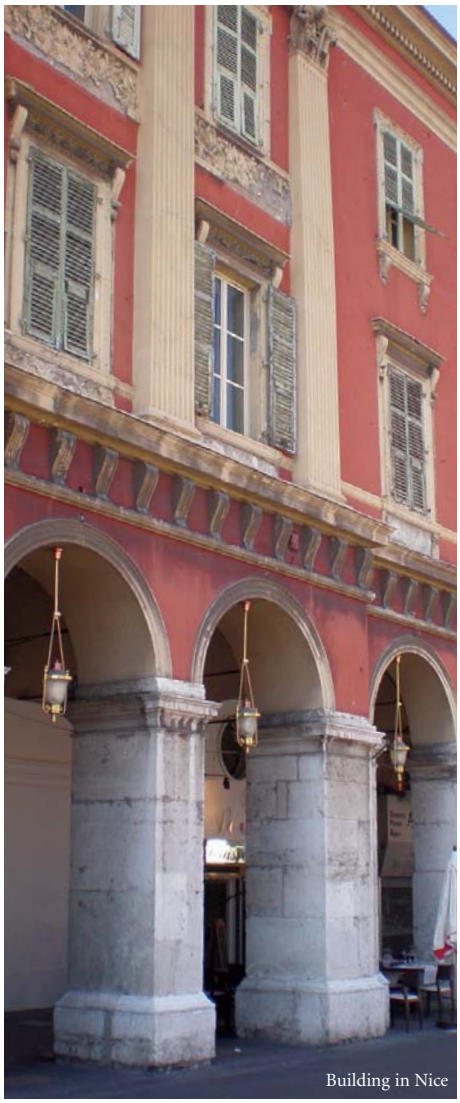
European Neurological Society Meeting

7-11 June, 2008; Nice, France.

This year the scientific programme of the European Neurological Society meeting, which was held in Nice (France) on June 7-11, included six symposia devoted to important topics. The Presidential symposium covered disorders of consciousness, with talks by prominent researchers, including Gustave Moonen (Liege, Be) on differentiation of vegetative state from minimally conscious state and the classical locked in syndrome in which pain and emotional perceptions are preserved. In this symposium, Brain-computer interfaces in the locked-in syndrome, Doctor A Kubler, exposed the remarkable work on voluntary regulation of neuro-electrical activity or brain activity as a response to sensory stimulation which is used to control cursor movements or switches on a computer. Such technology is aimed at restoring communication in the locked-in syndrome. The second symposium focused on Behavioural disorders and dementia, which represent an increasing health problem worldwide. Dr Cappa reported on behavioural changes in synucleinopathies. Such manifestations include executive dysfunction, which reflect the pathological involvement of fronto-subcortical mechanisms rather than the specific mechanism of disease. Depression or agitation may be due to environmental interactions, or represent side effects of symptomatic pharmacological treatments. Some features of cognitive and behavioural dysfunction may be relatively specific for the synucleinopathies. In the case of Parkinson's disease (PD), depression is an important clinical issue, which may be more frequent in this disorder than in other neurodegenerative disorders, reflecting the complex combination of neurotransmitter abnormalities, involving dopamine, serotonin and norepinephrine. Another clinically important aspect in the management of PD is impulse control disorders, such as pathological gambling and hypersexuality, and which appear to be related to dopaminergic medication. It has been proposed that a form of parasomnia (REM sleep behaviour disorder) may be a relatively specific behavioural marker of the synucleinopathies.

E Scarpini and D Galimberti reported on mutations in the progranulin gene associated with highly variable clinical phenotypes, including progressive supranuclear palsy and corticobasal degeneration syndrome. They suggested that unidentified environmental and genetic factors produce considerable phenotypic variability in patients carrying the same mutations.

In the symposium on autoimmune disorders of the nervous system, Professor Angela Vincent discussed myasthenia gravis (MG), in which thymoma occurs in up to 10% of patients, mostly presenting between the ages of 30 and 60 years. Ocular MG occurs in about 20% of patients, and only 50% of these have acetylcholine receptor (AChR) antibodies. About 10% to 15% of all patients with MG and generalised symptoms do not have anti-AChR antibodies detectable by radioimmunoprecipitation test. A proportion of patients without AChR antibodies have antibodies to MuSK which is a receptor tyrosine kinase restricted to the neuromuscular junction in mature muscle. Interestingly, the prevalence of MuSK antibodies among patients without AChR antibodies is highly variable between different centres around the world, suggesting a possible environmental interaction. MuSK antibodies are mainly IgG4 class, and are almost never found in patients with AChR antibodies or with thymoma. The distinctive features of MuSK-MG comprise marked ocular, bulbar, neck or respiratory symptoms and, in contrast to AChR-MG, the patients may have normal electrophysiology in limb muscles with evidence of neuromuscular defects in facial muscles. They respond to immunosuppression with prednisolone and azathioprine but alternative immunosuppressive treatments are often required. Two other autoimmune diseases of the neuromuscular junction, the Lambert Eaton myasthenic syndrome (LEMS) and acquired neuromyotonia, are associated with antibodies to voltage-gated calcium and potassium channels, respectively. In LEMS the antibodies are found equally in cases with or without small cell lung cancer (or rarely other tumours) but those with cancer may also develop cerebellar ataxia. The peripheral symptoms tend to improve with treatment whereas the central symptoms rarely show a good response. About 20% of cases of acquired neuromyotonia are associated with thymoma and/or myasthenia. Most patients may be managed with anti-epileptic drugs and do not need immunosuppression.



Building in Nice

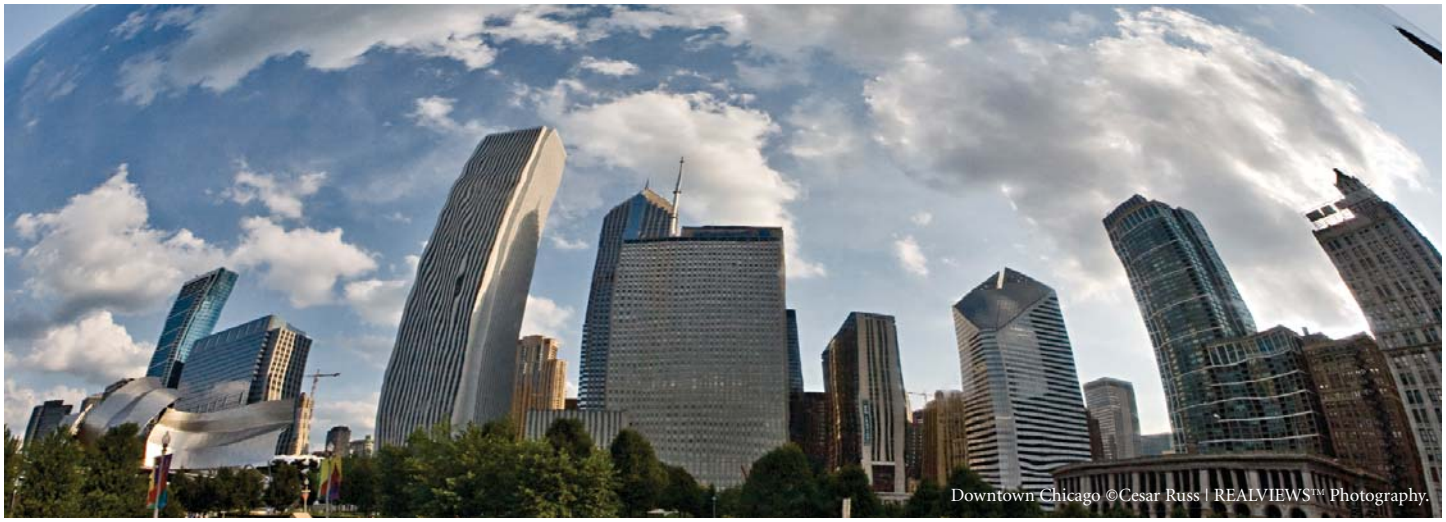
Another symposium focused on the much debated treatment of multiple sclerosis, especially when to start disease-modifying treatment and which treatment. The issues of early treatment of MS patients were summarised by Professor Compston (Cambridge, UK). The results of clinical trials support the hypothesis that inflammation is necessary for new lesion formation and leads to axon degeneration. The implication is that immunological therapies will best prevent sustained accumulation of disability and disease progression if given early in the course and before the cascade of events leading to axon degeneration is irretrievably established. This may explain the present limitations of immunotherapy in patients with secondary progressive multiple sclerosis. But it raises the dilemma of exposing individuals who may never develop disability from multiple sclerosis to the unpredictable hazards of prolonged immunosuppression.

Besides these symposia, 887 free papers were presented. The courses were enthusiastically followed by an ever-growing number of neurologists in training.

Professor Gérard Said, FRCP,
Secretary General of the ENS.

12th International Congress of Parkinson's Disease and Movement Disorders

22-26 June, 2008; Chicago, IL USA.



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The 12th MDS conference was the largest so far, with over 3500 delegates attending the Chicago Hilton. The conference remains accessible to non-movement disorder specialists, with well chosen speakers, background reviews and teaching sessions while presenting the most up to date, sometimes unpublished, findings in Parkinson's disease and other movement disorders for the specialist. The following account encompasses those aspects of the five day conference that I found the most interesting but are naturally biased by my own interests.

Parkinson's disease

Pathophysiology

More and more people seem to be knowingly saying 'calcium channels' in reference to the pathophysiology of PD. More specifically there appears to be growing interest in the calcium dependent pacemaker activity of substantia nigra pars compacta (SNc) neurons and the relevance of this activity to the vulnerability of these neurons to premature death in PD. James Surmeier spoke about SNc neurons in the mouse as pacemakers, the function of which depends on a specific calcium channel – the Cav1.3 pore. In contrast other DA neurons e.g. in the nearby ventral tegmentum, do not have this pacemaker activity. Recording from dendrites of SNc neurons show regular oscillations of the membrane potential with simultaneous fluctuations in dendritic Ca^{2+} levels. It is proposed that the dependence on calcium influx creates an ATP demand requiring oxidative phosphorylation, and thus particular vulnerability to mitochondrial stresses. This was demonstrated by showing films of the oscillatory mitochondrial fluorescence that occurs specifically in these SNc neurons. Blocking Ca^{2+} input through the Cav1.3 pore with dihydropyridine calcium antagonists leads to cells reverting to non-calcium dependant mechanisms, reduces signs of abnormal mitochondrial oscillations and reduces rotenone, 6-OH-DA, and MPTP-toxicity in animal models. In a single epidemiological study, Ca^{2+} antagonist treatment for hypertension has also been associated with lower PD risk. The hypothesis is that SNc neurons are simply vulnerable to cell loss with age and this may be accelerated by any genes and environmental factors influencing mitochondrial function and may be protected by calcium antagonists which may restore healthy pacemaker activity of these neurons. While very interesting, a great deal more evidence is required to substantiate this theory.

Of course as expected, there is also much continued interest in pharmacological methods of reducing alpha synuclein levels and interfering with its tendency to from protofibrils/oligomers; the amelioration of LRRK-2 associated toxicity through inhibitors of GTP binding and kinase activity; the susceptibility to oxidative stress of DJ-1 knockout animal models; and the accumulation of the dopaminergic toxins AIMP2 and FBP1 through loss of parkin E3 ligase activity in patients with parkin mutations and perhaps also sporadic PD.

In her tribute lecture to David Marsden, Ann Graybiel reviewed what we know about basal ganglia function, including new findings regarding the CalDAG-GEFI gene which is required for long term potentiation (LTP) induction in the striatum. Knockout mice for this gene do not exhibit features of plasticity, (seen through absence of drug induced movements) and a manuscript by Crittenden et al regarding this is in preparation. It seems that changes in CalDAG–GEF1 plasticity through this mechanism may influence the development of L-dopa induced dyskinesias (LID) in PD and this is substantiated by experiments looking at mRNA expression in the 6-OH DA mouse model.

Diagnosis and preclinical period

If patients at high risk of developing the motor features of PD can be identified, based on having a family member affected with PD, olfactory dysfunction, abnormal cardiac MIBG scintigraphy or REM sleep behaviour disorder (RBD), then earlier diagnosis, understanding of pathophysiological mechanisms and trials of potential neuroprotective treatments might all be facilitated. A longitudinal cohort of such people is being recruited in multiple centres in the USA led by Dr Matthew Stern, with a view to performing clinical trials of potentially neuroprotective agents. In line with this it seems that at least two thirds of patients with RBD will develop parkinsonism if followed up long enough, which is in keeping with the Braak stages of PD onset starting in the medulla. An inconsistency is that if patients with HY stage 1 PD are investigated RBD is rare but at stage 2, RBD is common. In a discussion regarding this presumed preclinical period, Anthony Schapira suggested that during this time, there is most likely a period of cerebral compensation through brain plasticity, perhaps by down-regulation of DA transporters, upregulation of D2 receptors, and the effects of trophic factors like GDNF and BDNF.

The utility of functional and structural imaging in multiple aspects of PD assessment was reviewed by David Brooks. Both PET and SPECT can be used to correct mistaken diagnoses of PD and allow the discrimination of drug induced parkinsonism from drug 'unmasked' PD, while glucose metabolism scans and the more widely available diffusion weighted-MRI imaging can discriminate PD from patients with established MSA, PSP or CBD. Patients with these atypical parkinsonisms all have reduced glucose metabolism in basal ganglia regions, although it is not yet confirmed whether these scans can be useful in the early phase of these diseases when it is clinically most difficult to diagnose them. Imaging has also shown that the presence of depression in PD is related to noradrenergic neuronal loss rather than serotonergic, and this has implica-

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tions for choice of anti-depressant medication type. Perhaps most interestingly, it seems that 11C-PIB PET imaging can detect differences in amyloid deposition between patients with PD +Dementia (PDD) and Dementia with Lewy Bodies (DLB) and this too may eventually have implications for treatment with e.g. γ-secretase blockers. In line with this, Glenda Halliday showed that in her post mortem series, amyloid plaques occur in both AD and DLB but not in PDD until much later.

Therapy

A press release one week prior to the conference regarding the positive results of the ADAGIO delayed start trial of Rasagiline as a possible neuroprotective treatment in early PD raised expectations of a major announcement. The drug is already licensed as symptomatic monotherapy or add on therapy at several stages of PD. However even in the pharmaceutical sponsored sessions, all discussion focussed on critique of the different types of design and analysis of trials of neuroprotective therapies. The main criticisms of the delayed start approach include the effects of differential dropout due to symptomatic effects and the differential effects that may occur depending on the absolute UPDRS scores at baseline, i.e. an interaction between symptomatic effect and severity. The message seems to be that neuroprotection is a difficult claim to prove, but despite this there is growing evidence that earlier treatment of PD may benefit patients regardless of the underlying mechanism.

Matthew Stern suggested that patients ought to be on multiple treatments even in the early stages of PD based on a recent publication suggesting a lower risk of LID among patients on L-dopa who were supplemented with slow release Ropinirole rather than having increasing doses of L-dopa. Anthony Schapira suggested that early treatment of patients with PD allows favourable plastic changes to take place and this may be the mechanism underlying the 'neuroprotective' effects seen in delayed start trials such as TEMPO and ADAGIO. To support the possible relevance of plasticity to PD, he showed experiments of an animal model of PD that used immobilisation of normal limbs to force the animals to use their parkinsonian limbs, leading to restoration of normality and upregulated VMAT2 binding on neuroimaging. In contrast, immobilisation of their affected limbs led to worse outcomes for the animals. With relevance to the subject of inter-individual variation in disease progression, the under-explored role of pharmacogenetics was discussed by Olivier Rascol in a talk on tailoring therapy to individual patients. Of proven relevance is the DRD2 polymorphism on dyskinesia risk, with other candidates including the other dopamine receptor polymorphisms DRD1-5, DAT, COMT, MAO-B, CCK, hypocretin, and APOE. However, in all likelihood multiple genes will be relevant, and he suggested that, in the future, whole genome screening of genes that influence response to treatment should be considered.

The non-motor aspects of PD were also discussed including suggestive but not unequivocal data of benefit from modafinil in management of excessive daytime sleepiness in PD, and a study in press of a 6 point improvement in Epworth scores from the use of sodium oxybate which currently is a licensed therapy for narcolepsy. While rivastigmine is licensed for the treatment of the dementia associated with PD, the maximum benefit seems to occur among patients with hallucinations, since this group appears to decline particularly quickly without treatment. Although there is an ongoing study of the use of memantine in PDD and DLB, there is insufficient evidence currently to recommend its use. (Editor's note: A small double-blind trial of memantine in PDD from the UK, presented as a poster, failed to show significant benefits, although this could simply reflect a type II error.)

Robert Gross reviewed the beneficial effects and limitations of deep brain stimulation (DBS) of the subthalamic nucleus (STN-DBS) for PD and the need to search for new targets to help the axial and dopa unresponsive symptoms. There are ongoing trials to compare further DBS of the STN and the globus pallidus pars interna (GPi) to help explore the benefits and risks of medication reduction afforded by STN DBS and the safety with respect to cognitive or behavioural side effects with GPi DBS. There are mixed expectations from the use of pedunculopontine nucleus (PPN) stimulation, which has been shown to benefit L-dopa unresponsive symptoms such as postural instability and gait freezing in centres in Bristol, Toronto and Rome. Bilateral stimulation

is probably more useful than unilateral but there is possibly a wearing off effect, and in reality there are many questions remaining that require double blind trials to answer. As with STN-DBS the benefits seem to relate to removal of pathological oscillatory activity. Stimulation of the CM/Pf nucleus of the thalamus (which has a pathway back to the striatum) can also lead to inhibition of GPi and thus increased basal ganglia output, and there is animal work and early human studies suggesting that the addition of CM/Pf stimulation to GPi stimulation improves both freezing and involuntary movements. There appears to be an intra-target difference in the mechanisms through which DBS exerts its effects, whether inhibitory, excitatory and whether axons are 'en passant' adjacent to the electrode contacts. Expansion into these new targets will likely characterise the next decade of functional neurosurgery for PD.

Cell-based and gene therapies were reviewed by Warren Olanow. He highlighted again the subgroup analysis of PD patients with UPDRS scores less than 49 at baseline who had received foetal transplants some years ago and did show significant improvements, as did the younger subgroup of patients seen in the Curt Freed trial, and he commented that future trials of transplantation are being considered for these subgroups. The off-medication dyskinesias occurring in 50% of transplanted patients which affected lower extremities and coincided with the presence of parkinsonism in other body regions, were presumably due to hot spots within the transplanted graft or perhaps were akin to biphasic dyskinesia due to suboptimal DA replacement or non-physiological replacement of dopamine. In a single patient it appears that alpha synuclein and thioflavin-staining Lewy bodies and neurites are seen within the grafted cells (which themselves are chronologically only 13 years of age) i.e. implanted cells seem to also be affected by the PD process. This observation is potentially hugely instructive in the mechanisms underlying Lewy body formation and PD pathogenesis.

Gene therapy techniques rely on appropriate choice of the therapeutic gene to be expressed, the target within the brain and the viral vector, but have been shown to have persistence of expression, safety and efficacy based on early clinical trial data. Both the AAV2 virus and one of the lentiviruses are being used, as there is good data to suggest they are not pathogenic in humans but can infect the target neurons. They are not thought to induce an inflammatory response in humans. These viruses are being used in open label trials to deliver neurturin- an analogue of GDNF into the striatum, or the GAD enzyme into the STN, or a combination of three dopamine related genes in the Prosavin trial. Initial safety studies have shown few or no adverse effects, and improvements in UPDRS off medication scores. Delivery of neurturin currently requires 4 needle tracks into the striatum and therefore will be associated with potential surgical problems. Inevitably there will be some time before theoretical concerns regarding the unregulated growth of virus, immune reactions, fears of unanticipated side effects are allayed together with uncertainty regarding how gene therapy will benefit the non-motor features of PD. In the future the 'gene de jour' (Dr J Kordower) may be DJ1, parkin or PINK1 as they all appear to be neuroprotective when over-expressed.

Restless legs syndrome

There have been genetic discoveries in restless legs syndrome (RLS) and periodic limb movements in sleep with association of several genetic SNPs in the BTBD9 gene (associated with lower iron stores) with populations with both RLS and PLMS in a dose dependent manner i.e. the more kicks per hour the stronger the association. Estimates suggest that this gene is responsible for ~50 % of cases of RLS. While this seems to be important in Europeans, with ~50% of affected individuals being homozygous for the at risk polymorphism, the finding of RLS in African populations should prompt a search for another (more likely metabolic) cause for their symptoms.

An analysis of the evidence underpinning the treatment of RLS by Claudia Trenkwalder is about to be published in *Movement Disorders*. Levodopa can be helpful for the first few hours of sleep but kick counts in the latter parts of the night become identical to placebo. Doses of 2mg Ropinirole, 0.75mg Pramipexole or 2mg Rotigotine are efficacious for a more prolonged period, however it seems that there is an optimal level of dopaminergic stimulation and too high a dose in some patients can exacerbate symptoms. There are no trials to support the use of benzodiazepines, and oral iron supplements are only of use in patients who are substantially iron deficient, whereas low grade opioids, gabapentin, some of the other anti-convulsants and clonidine have evidence to support their efficacy and are useful second line agents but may be limited by side effects.

Dystonia

The DYT-1 gene, which encodes the torsin A protein, is autosomal dominant but has a penetrance of only ~30%. Alberto Albanese reviewed studies of individuals positive for the DYT-1 gene but not manifesting dystonia, who nevertheless show subtle physical abnormalities and abnormal motor plasticity when tested in the laboratory with transcranial magnetic stimulation. Paolo Calabresi discussed the recent functional imaging evidence showing excessive activity in globus pallidus and putamen in dystonia, and microstructural changes revealed by DTI imaging. He presented the evidence from both animal models and human subjects also, showing that dystonia seems to be associated with abnormally long term potentiation/ plasticity.

Susan Bressman reviewed the range of phenotypes and endophenotypes (patients with subclinical disease features) associated with DYT1 dystonia. Although these patients usually present in the first few decades as a generalised dystonia, they can rarely present late and remain focal, particularly among Ashkenazi Jews. She also presented comparisons of non-manifesting gene carriers to healthy controls finding abnormalities on FDG PET scans, D2 receptor binding, abnormal DTI, abnormal motor sequence learning (absence of cerebellar activation and decreased prefrontal activation) and differences in neurophysiological measures of cortical inhibition. Depression can occur early and also seems to be part of the endophenotype. She presented evidence of an interaction between the DYT1 GAG deletion and another genetic polymorphism which appears to reduce torsin A expression. Seemingly, manifestation of dystonia in DYT1 carriers is only 3% in carriers of one allele compared to 35% with the other.

Aside from those few patients with Wilson's disease and dopa responsive dystonia in whom medical therapies are very beneficial, the only class A evidence of efficacy of oral treatments for dystonia is of a moderate benefit from anticholinergics. Impact of treatments on dystonia need to be measured against the impact on QOL, and the most significant improvement in QOL is from treatment with Botox for cervical dystonia in the long term. We heard that in addition to the effect of Botox on ACh release from motor synapses, among patients with focal dystonia or post stroke, injection of Botox can reduce feedback from intrafusal fibres which in turn may reduce the sensory drive to the dystonia. Benefits for cervical dystonia from the use of Botox persists for more than 10 years in 60% of patients.

A task force has been set up to review the literature and publish guidelines regarding the use of DBS for dystonia similar to the previous special issue focussing on DBS for PD – the main questions are how to optimally programme the implantable pulse generator (IPG), how to alter medication, including Botox, post operatively, how commonly are adverse effects occurring, what happens to non-dystonic extremities and when to change the IPG battery. There are published results in more than 250 patients with GPi DBS for primary generalised dystonia with improvements in motor scores between 40-91% and accompanying improvements in QOL that persist long term. Positive results have also been seen in focal, segmental, tardive and some secondary dystonias.

Ataxia

Thomas Klockgether described how histone deacetylase (HDAC) inhibitors can reduce Frataxin mRNA expression and are now being tried in phase 1 clinical trials in the treatment of Friedreich's ataxia. Other investigators have shown that mutated frataxin reduces iron-sulphur clusters which in turn decreases the activity of complexes 1-3 of the mitochondrial respiratory chain. Idabenone has a dose dependent effect on ataxia through its effects on this pathway. Treatment of the spinocerebellar ataxias is at a less advanced stage but it seems that polyglutamine repeats common to many of the SCAs lead to both a gain of a toxic protein complex and loss of a protective protein complex, and potential treatment avenues are being discovered. There may be a therapeutic benefit from either Rapamycin or perhaps even Lithium, based on animal models of SCA (Editor's note: the scientific rationale for the use of lithium in this context is not entirely clear).

Chorea

Phenocopies of Huntington's Disease are characterised by a combination of chorea, dystonia, parkinsonism, cognitive disturbance and psychiatric disturbance. Sarah Tabrizi presented cases of her favourite HD phenocopies. HDL-2 should be considered early in black South Africans with chorea, which is caused by mutated junctophilin-3 function, a calcium channel sensor and associated with ubiquitin positive inclusions at post mortem. HDL-4 due to SCA17 has similar motor impersistence of tongue protrusion and eye movements, poor saccadic initiation but more ataxia than usually seen in HD. Neuroferritinopathy has chorea at onset in 50% but normal eye movements, and cognitive dysfunction only in the late phases, in contrast to HD, serum ferritin levels are low, there is iron deposition in the basal ganglia and occasionally the eye of the tiger sign can be seen on MRI. Varying mutations in the prion protein can also cause chorea seen in vCJD and associated with psychiatric symptoms, ataxia, and myoclonus at presentation. From her series of HD phenocopies, and somewhat despairingly, it seems that if HD gene tests are negative, then 97% of patients will never receive a genetic diagnosis, and of the remaining 3%, SCA17 is the most common positive finding.

Myoclonus

The contribution of Queen Square and particularly David Marsden to our understanding of myoclonus and its origins were discussed by Jose Obeso, followed by recommendations for treatment with various anti-convulsant medications and often the need for polypharmacy. Myoclonus dystonia with epsilon sarcoglycan mutations is one of the few causes of myoclonus of subcortical origin and should be considered if neurophysiology suggests that a myoclonic disorder has a basal ganglia origin.

A highlight of the conference was the video Olympics that was hugely entertaining as the 'expert' panel were invited to comment on excellent cases of movement disorders that included – cerebrotendinous xanthomatosis, secondary hyperekplexia and cardiac pacemaker-driven abdominal myoclonus. There was a sense of pleasure in watching the panel publically struggle with these esoteric phenomena. There were over 1200 posters presented during the week in ample space at the venue, and there were the usual controversies and 'how to do it' workshops. Lifelong honorary membership to the society was awarded to Mahlon Delong and Alim Benabid for their contributions to the understanding and treatment of Movement Disorders. As the size of the MDS meeting continues to grow, the society is clearly flourishing and hopefully is on the brink of several important breakthroughs in the treatment of common movement disorders – Let's see what is announced next summer in Paris....

Tom Foltynie, Senior Lecturer & Honorary Consultant Neurologist, National Hospital for Neurology & Neurosurgery, London, UK.

Federation of the European Neurosciences Societies Forum

12-16 July, 2008; Geneva, Switzerland.

The Swiss Society for Neuroscience was honored and privileged to host the sixth Forum of the Federation of the European Neurosciences Societies (FENS) from July 12th to 16th, 2008 at the Palexpo Congress Center in Geneva. This biennial congress is the largest European event in the field of Neurosciences and attracted 5300 scientists, clinicians, and decision makers, mainly from Europe, but also from North America, Japan, and Australia. Previous FENS meetings have been held in Berlin, Brighton, Paris and Lisbon and have had a strong resonance in the respective countries. The purpose of the FENS Forum is to foster research and education in neuroscience by strengthening the links between the 33 national and supranational societies that make up the federation. At this meeting, more than 400 travel stipends were offered by FENS, IBRO, SfN and member societies.

The format of the meeting consisted of nine plenary lectures given by the world's outstanding neuroscientists, 56 symposia highlighting recent progress in all areas of neuroscience, and 3700 poster presentations, giving senior and young scientists the opportunity to present and discuss their work with their peers. In addition, ten satellite meetings took place shortly before the main congress. The FENS Forum has also become the opportunity for presenting prestigious Awards funded by private Foundations and commercial companies. These awards bring outstanding contributions of young scientists to the attention of the public and serve to promote their future career in research. Finally, a rich social program fostering interactions between participants, sponsors and officers of the FENS societies took place. One of the outstanding social events was organised by the students of the Lemanic doctoral school; they provided three evenings of entertainment for young scientists at the Lakeside of Geneva, a beautiful site that is ideally equipped for social gatherings during the summertime. For more information on these events, please visit our website (http://fens2008.neurosciences.asso.fr).

The city of Geneva has a long tradition in holding summits of prime political, economic and scientific importance and was an ideal location for a successful FENS Forum. The city offered everything needed to accommodate and entertain the 5300 participants and accompanying persons. Geneva is very attractive for its rich history, vibrant cultural scene, and prime quality of life. An additional major asset of Geneva is its central location, easy to reach from anywhere in Europe.

An international program committee, chaired by Eckart Gundelfinger, University of Magdeburg, was nominated by the FENS council to ensure a balanced representation of major research areas in basic and clinical Neuroscience, thereby maximising the impact of the Forum. The local organising committee was chaired by Ann Kato, University of Geneva, and was formed by officers of the Swiss Society for Neuroscience and pre-eminent researchers from all major Swiss universities. Everyone who participated esteemed that the Congress was a huge success. Please note in your diaries that the next FENS Forum will be held in Amsterdam from July 3rd to 7th, 2010.

Professor Ann Kato, Chairman of the Local Organising Committee (Swiss Neuroscience Society).

International Conference on Alzheimer's Disease (ICAD)

26th-31st July 2008; Chicago, USA.

Since its inception 20 years ago, when 300 delegates attended a meeting in Las Vegas, the International Conference on Alzheimer's Disease has grown dramatically, reflecting the increasing interest in this field. Over 5000 delegates attended this 11th congress, at the Lakeside Center in Chicago, adjacent to the shores of Lake Michigan, and such is demand and progress that the congress will henceforth be an annual, rather than biennial, event.

With over 2000 abstracts, clearly no summary report can do more than scratch the surface, and for this reason this article will focus exclusively on therapeutic issues. This is not to belittle in any way the developments in neuroimaging, biochemistry and genetics which featured significantly during the congress, but the ultimate aim of all these might fairly be said to be the successful treatment of AD, which still seems elusive (e.g. *Los Angeles Times, 28/07/08: F1, F4*).

The prize for the most headlines garnered in press and TV must go to the report on the use of a new drug, methylthioninium chloride (MTC), trade name Rember, presented by Claude Wischik (Aberdeen). This drug dissolves tau paired helical filaments (PHF) and prevents aggregation of tau molecules in animal models, and hence is the first specific tau aggregation inhibitor to reach clinical trials, a personal triumph for Wischik, who first characterised tau as the principal component of PHF some 20 years ago.[1] In a trial conducted in the UK and Singapore, oral MTC improved outcome (ADAS-Cog) relative to placebo over 24 weeks and stabilised disease progression over 50 weeks, suggesting a disease-modifying, rather than simply a symptomatic, effect. These promising data mandate further trials, the outcomes of which will be awaited with great anticipation by clinicians, their patients and carers.

The fact that the burden of tau pathology correlates better with clinical markers of dementia than amyloid pathology has always been a thorn in the side of the dominant, but not exclusive, hypothesis of AD aetiology, namely the amyloid hypothesis, wherein amyloid is understood to mean peptides in their soluble (Aβ) or oligomeric forms, rather than the amyloid aggregates visible as plaques in brain tissue. Experimental therapies targeting amyloid have been with us for some time, most notably the Aβ vaccine. Follow-up of a phase 1 study of the Elan AN1792 vaccine (not the ill-fated 201 study which was halted because some patients developed meningoencephalitis) found neuropathological evidence for amyloid clearance in patients coming to post-mortem, but no overall improvement in survival or time to severe dementia (Nicoll, Southampton).[2]

A problem with this active immunisation/vaccine approach is that it may take up to 6 months to develop anti-amyloid antibodies, a problem which may be circumvented by passive immunisation. Bapineuzumab, Elan-Wyeth's humanised monoclonal antibody raised against the N-terminus of Aβ, was reported to be safe in a phase 2 study. Although not powered for efficacy, the data suggested clinically favourable results in ApoE4 negative patients. A phase III trial is getting underway.

Despite the recent setbacks with other possible anti-amyloid treatments, such as tarenflurbil /Flurizan[3] and alzhemed / tramiprosate,[4] there may be other candidates to examine. Antihypertensive medications may have effects on Aβ, for example carvedilol apparently prevents oligomerisation, and valsartan lowers brain Aβ activity (Pasinetti, New York), interesting findings in view of the fact that vascular factors are risk factors for the development of AD, and treatment of these factors has been reported in some studies to prevent the development of disease. Certain NSAIDs have long been known to alter Aβ metabolism (Weggen, Dusseldorf), and even the proton pump inhibitors may reduce Aβ production (Takeda, Osaka). Development of any of these drugs as AD therapies might be quicker than is the case with novel drugs since their side effect profiles, pharmacodynamics and drug interactions are already well understood. Statins, which may affect Aβ through interactions with cholesterol, have also been examined: a placebo-controlled trial of simvastatin in AD patients (Sano, New York) proved robustly negative on all outcome parameters.

Thiazolidinediones (TZDs), PPAR-gamma agonists, may improve brain insulin sensitivity in AD (Craft, Seattle), and trials have suggested some benefit with rosiglitazone in ApoE4 negative patients.[5] Thiadiazolidinediones (TDZDs) are inhibitors of glycogen synthase kinase-3 (GSK-3), an enzyme thought to be important in tau phopshorylation and the initiation of tau pathology. TDZDs have been proposed as small molecules which might target tau, Aβ, and neurodegeneration simultaneously (Martinez, Madrid).

Dimebon has emerged as the surprise package in AD therapy in recent months: a non-selective antihistamine used in Russia for many years, a trial has now reported efficacy in the treatment of AD.[6] Evidence was presented at ICAD that dimebon does not act as a cholinesterase inhibitor (ChEI), nor is its activity likely to be mediated by NMDA receptors, but it enhances mitochondrial function in the context of cellular stress, as well as being a low potency 5HT6 receptor antagonist. Hence this drug may not be selective simply for AD, but might find a role in Parkinson's disease and disorders characterised by mitochondrial dysfunction.

Despite these many new therapeutic possibilities, the current neurotransmitter-based therapies (ChEI, memantine) are far from obsolete (Frolich, Mannheim): their modest but consistent effects may be required in established disease, including severe disease, although it is now clear from recent trials that both rivastigmine[7] and galantamine,[8] like donepezil, do not slow progression from MCI to AD.

AJ Larner, Cognitive Function Clinic, WCNN, Liverpool, UK.

References

1. Wischik CM et al. *Isolation of a fragment of tau derived from the core of the paired helical filament of Alzheimer's disease.* Proc Natl Acad Sci USA 1988;85:4506-10.
2. Holmes C et al. *Long-term effects of Abeta42 immunisation in Alzheimer's disease: follow-up of a randomised, placebo-controlled phase 1 trial.* Lancet 2008;372:216-23.
3. Wilcock GK et al. *Efficacy and safety of tarenflurbil in mild to moderate Alzheimer's disease: a randomised phase II trial.* Lancet Neurol 2008;7:483-93.
4. Aisen PS et al. *Alzhemed: a potential treatment for Alzheimer's disease.* Curr Alzheimer Res 2007;4:473-8.
5. Risner ME et al. *Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease.* Pharmacogenomics J 2006;6:246-54.
6. Doody RS et al. *Effect of dimebon on cognition, activities of daily living, behaviour, and global function in patients with mild-to-moderate Alzheimer's disease: a randomised double-blind, placebo-controlled study.* Lancet 2008;372:207-15.
7. Feldman HH et al. *Effect of rivastigmine on delay to diagnosis of Alzheimer's disease from mild cognitive impairment: the InDDEx study.* Lancet Neurol 2007;6:501-12.
8. Winblad B et al. *Safety and efficacy of galantamine in subjects with mild cognitive impairment.* Neurology 2008;70:2024-35.

Chicago skyline courtesy of Tom Foltynie.

EDITOR'S CHOICE

A new prion disease with a terrible name

Just when we were beginning to relax over variant CJD in the UK, a new prion disease has been described in the US: 'protease-sensitive prionopathy'. 11 cases (10 autopsy, 1 biopsy) were seen at the National Prion Disease Pathology Surveillance Centre. Clinically, these patients had a rather distinct phenotype: a mean age of 62 years, presenting with behavioural, cognitive and psychiatric abnormalities, then developing ataxia and parkinsonism and surviving only 20 months. 6/10 had a family history of 'dementia'. No tests proved helpful: EEG did not show periodic complexes and CSF 14-3-3 was nondiagnostic. MRI showed diffuse atrophy with no changes on diffusion weighting. Uniquely, protease-resistant PrP was not found in the neocortex; instead the abnormal prion protein found in the brain of these patients was sensitive to proteases and formed distinctive plaques in the cerebellum. All of the patients were homozygous for valine at codon 129 of the prion protein gene; this is the rarest genotype found in only 12% of healthy people, and in two forms of regular sporadic CJD (VV1 and VV2) that differ from these cases in other ways. None had a mutation in the PrP gene ORF that is characteristic of Gerstman-Straussler-Scheinker disease, although the family histories clearly suggest a genetic cause. This type of prion disease accounted for 3% of referrals to the US National Prion Disease Pathology Surveillance Centre, so it is not vanishingly rare. And it is possible that more exist, currently misdiagnosed as having Alzhemier's, fronto-temporal dementia or Lewy Body disease. But, as well as that practical point, there are some more intriguing questions. As with Gerstman-Straussler-Scheinker, we have to ask whether this new 'prion disease' is transmissible, a necessary characteristic of Pruisner's original 'prion hypothesis'. And why is this accumulate prion protein protease-sensitive? The relevant animal experiments are on-going…. – ***AJC***

Gambetti P, Dong Z, Yuan J, Xiao X, Zheng M, Alshekhlee A, Castellani R, Cohen M, Barria MA, Gonzalez-Romero D, Belay ED, Schonberger LB, Marder K, Harris C, Burke JR, Montine T, Wisniewski T, Dickson DW, Soto C, Hulette CM, Mastrianni JA, Kong Q, Zou WQ.

A novel human disease with abnormal prion protein sensitive to protease.

ANNALS OF NEUROLOGY

2008 Jun;63(6):697-708.

EPILEPSY: injuries and Range Rovers

The Canadian Health Study identified patients with epilepsy from a door-to-door survey of 130,882 individuals over the age of 12 years, across Canada and representative of 98% of the Canadian population. 835 people with epilepsy (PWE) were found and were asked if they had suffered an injury in the last 12 months. Injuries sufficient to limit activity had occurred in 13.3% of controls and 14.9% of PWE. There was no increase fractures or sprains but a trend towards more burns and scalds (6.9% v 3.9%) in PWE. Controls were a little more likely to have injuries whilst engaged in sports, perhaps reflecting a reluctance of patients with epilepsy to undertake sport. Even though many people were sampled, the number of injuries in PWE was only 121, which means that the power of the study to identify differences between groups was limited, especially when looking at subdivisions of injuries. The study did not look at Range Rover driver behaviour. This is otherwise known as risk compensation, where those who feel at risk (Trabant drivers, who perceive themselves as vulnerable) behave in a risk averse fashion, whereas those in black Range Rovers with dark tinted windows embrace risk, as they perceive themselves as safe. It seems likely that epilepsy patients will be more risk averse than controls. Most other studies point to a slight excess risk of injury amongst patients with epilepsy and I suspect this is closer to the truth. Of course Canada is so icy in Winter that perhaps everyone is falling and breaking something so that differences are hard to detect. – ***MRAM***

Tellez-Zenteno JF, Hunter, G, Wiebe S.

Injuries in people with self-reported epilepsy: A population-based study.

EPILEPSIA

2008;49:954-61.

CHRONIC FATIGUE SYNDROME: shrinking brains

This Dutch group have previously shown that people with chronic fatigue syndrome (CFS) have reduced grey matter volume in the lateral prefrontal cortex. They now go on to ask whether this is cause or consequence of the illness. They first showed that grey matter volume was most reduced in those CFS patients with lower physical activity and slower cognition (perhaps supporting that rather annoying dictum 'if you don't use it, you lose it'). They then followed 22 women with CFS as they had 16 sessions of cognitive behavioural therapy and graded exercise programs over 6-9 months. The expected improvements in health status, physical activity and cognitive performance followed. This correlated with an increase in lateral prefrontal cortex grey matter volume, ('pain and gain'?) less marked in older patients. This increase amounted to only 12% of the difference between CFS patients and controls, raising the possibility that some of the deficit of CFS is irreversible. But much more interesting is the mechanism of the increase in grey volume….. for which the authors offer speculations only. They argue that, as neocortical neurogenesis is rare or absent from adult brains, that an increase in volume is likely to arise from increased dendritic growth or synpatogenesis.

de Lange FP, Koers A, Kalkman JS, Bleijenberg G, Hagoort P, van der Meer JW, Toni I.

Increase in prefrontal cortical volume following cognitive behavioural therapy in patients with chronic fatigue syndrome.

BRAIN

2008 Aug;131(Pt 8):2172-80.

NEURODEGENERATION: emerging new treatments

To complement the conference review by Tom Foltynie I perused the abstracts (all 1200 of them!!) of the recent Movement Disorder meeting in Chicago to find those of particular interest for restorative treatments of movement disorders. So here goes!

a) Marks et al (A96) report on the 24 month efficacy of the safety and efficacy of AAV2 virus - neurturin in 12 patients with Parkinson's disease. The result is very encouraging with 8 out of the 12 having a major response of greater than 50% in the UPDRS off score without any significant adverse effects being reported.
b) In contrast Frank et al (A568) show that there is no long term survival and efficacy of porcine striatal xenotransplants for Huntington's disease. Only 2 patients are still alive out of the original 12 and none showed any significant benefit with two patients having no surviving cells of porcine origin at post mortem.
c) Watts et al (A598) provide an update on the Spheramine trial in patients with moderately advanced Parkinson's disease. Spheramine consists of human retinal pigmentary epithelial cells, attached to a microcarrier support of matrix cells, which are capable of synthesising dopamine. Six patients receiving transplants of these cells and matrix have shown no major adverse events but there again at 60 months there have been no major improvements either.

So at the moment gene therapy with neurotrophic factor delivery is winning over novel cell therapies for neurodegenerative disorders but the full publication of these studies will ultimately help us decide on the merits or otherwise of these studies. – ***RAB***

All abstracts from MOVEMENT DISORDERS (2008) 23: Supplement 1

EPILEPSY: More than two syndromes

Some neurologists, and we all know who they are, are funny diseases doctors. They can remember all the weird and wonderful eponymous syndromes. I was never one of those and as middle age slips its tentacles ever deeper between my synapses, the chances of my ever remembering the clinical characteristics of 28 types of spinocerebellar ataxia is – well you can guess. So adult epilepsy is a great specialty for me; just two conditions to remember, focal epilepsy and generalised epilepsy. But I always knew it was too easy. It has never been realistic to think that all forms of focal epilepsy are the same, that the mechanism of the epilepsy is the same whatever the aetiology and this is one of a really small number of studies that has looked systematically at the differences. The authors studied 119 consecutive patients with refractory focal epilepsy, defined as failing two AED's. Where the cause remained cryptogenic after detailed MRI, the chances of a one year remission was 40%. Those with pathologies usually considered for surgical treatment, such as hippocampal sclerosis or dysplasia, achieved a remission of 11% and 27% of those with other forms of focal epilepsy achieved remission. Numbers were too small to analyse individual pathologies, but previously it has been demonstrated that hippocampal sclerosis carries a poor prognosis, especially if there is dual pathology. We know that dysplasia exhibits spontaneous EEG spikes and electrographically appears different from other causes and per-

haps this reflects a different mechanism and drug sensitivity. This area is crying out for some studies to try and tease out these differences, even if it means I have to remember more than two syndromes. – *MRAM*

Liimatainen S, Raitanen J, Ylinen A, Peltola M, Peltola J.
The benefit of active drug trials is dependent on aetiology in refractory epilepsy.
JOURNAL OF NEUROLOGY NEUROSURGERY PSYCHIATRY
2008;79:808-12.

MULTIPLE SCLEROSIS: CD8 cells again… and Epstein-Barr virus… again

There have been many false dawns in the search for the 'viral trigger' of multiple sclerosis. But one particular bug keeps cropping up as a risk factor in epidemiological studies of multiple sclerosis: Epstein-Barr virus infection, particularly of adolescents. And recently, the exciting discovery has been made of EBV-laden lymphoid follicles in the meninges of people with multiple sclerosis. A great deal of time and money has been spent measuring serum antibodies to EBV in this or that patient group, which is not helped by the fact that in a country like the UK, some 90% of all people will have IgG antibodies to EBV by adulthood. Far less research has been done on the cellular response to EBV in people with multiple sclerosis, probably because that is rather more difficult to do. Nonetheless, Du Pasquier's group in Lausanne have systematically studied the response of peripheral T cells in response to various EBV and CMV antigens in sub-types of multiple sclerosis (nearly 100 in total) and healthy controls. The headline result is that CD8+, but not CD4+, T cells show increased reactivity to EBV, but not CMV, in patients with clinically isolated syndromes compared to controls. But this was not seen in patients with established multiple sclerosis, of whatever type. It would be reasonable to conclude that EBV does trigger early multiple sclerosis, but does not induce relapses… Back-to-back with the Du Pasquier paper is one from Howard Weiner's lab in Boston. His group have undertaken the enormous, tedious and ultimately rewarding task of non-prejudicial screening of a vast array of surface markers on peripheral lymphocytes of people with multiple sclerosis. The bottom line is that his trawler caught one fish: people with early, but not established, multiple sclerosis have a reduced number of cells with this signature: CD4neg CD8low CD56pos. This is not a well-known cell type. But it has been proposed to be a Natural Killer Regulatory cell. Do you feel any the wiser? Well, perhaps what this means is that people with early multiple sclerosis have a reduced ability to appropriately restrain a CD8+ immune response. So, when EBV infection comes along, the immune system over-reacts and spills over, targeting anything else that looks like EBV… and certain stretches of the myelin basic protein molecule look exactly like EBV (Lang Nat Immunol. 2002 Oct;3(10):940-3)… so myelin is destroyed. Or perhaps it is the other way round: EBV infection impairs the function of the CD8low regulatory NK cells… Which somehow leads to anti-myelin T cell activity… What I think we can say is that the sharks have tasted blood and are circling… around EBV and the CD8+ T cells as important to the pathogenesis of multiple sclerosis. – *AJC*

De Jager PL, Rossin E, Pyne S, Tamayo P, Ottoboni L, Viglietta V, Weiner M, Soler D, Izmailova E, Faron-Yowe L, O'Brien C, Freeman S, Granados S, Parker A, Roubenoff R, Mesirov JP, Khoury SJ, Hafler DA, Weiner HL.
Cytometric profiling in multiple sclerosis uncovers patient population structure and a reduction of CD8low cells.
BRAIN
2008 Jul;131(Pt 7):1701-11.

Jilek S, Schluep M, Meylan P, Vingerhoets F, Guignard L, Monney A, Kleeberg J, Le Goff G, Pantaleo G, Du Pasquier RA.
Strong EBV-specific CD8+ T-cell response in patients with early multiple sclerosis.
BRAIN
2008 Jul;131(Pt 7):1712-21.

David Marsden Award 2009

The David Marsden Award was presented for the first time in 2003 by the European Dystonia Federation (EDF). Professor David Marsden (1935-1998) was one of the leading neurologists in Europe and the Federation wishes to honour the enormous part he played in developing knowledge of and interest in dystonia.

Through the generous collaboration of the Movement Disorder Society (European Section) and the European Federation of Neurological Societies, the Award will be presented during the EFNS Congress, August 2009, in Florence. The Award winner will make a presentation of his/her findings at the Basal Ganglia Club meeting during the Congress, and at the Federation's own General Assembly in September 2009 – venue to be decided. All expenses will be paid by EDF.

General Rules

- The David Marsden Award will be presented every two years.
- The Award sum is € 2,500 for papers (i.e. manuscripts for original publication – no abstracts) on aetiology, pathogenesis, diagnosis and therapies on dystonia or the psycho-social effects on people living with dystonia.
- Applicants should be under 40 years of age.
- Submitted papers may have been published within the last two years.
- Unsuccessful applicants may re-present their papers in the following year, if fundamental new scientific findings are involved.
- The applicant should be the first author.
- The research must have taken place within Europe.
- The deadline for submissions is 31st March 2009
- The Award winner will give a presentation of his/her project at the EFNS Congress and at the EDF's General Assembly in the same year.

Procedure

Papers should be submitted by email to the EDF Secretariat by the deadline of 31 March 2009, including a completed submission form (available at our website), a short Curriculum Vitae and a declaration that the paper has not been submitted for other scientific awards. Papers will be reviewed by the Federation's Medical Advisory Board.

This information and a submission form may also be obtained at www.dystonia-europe.org

Nurse receives ACE Award


Dee Elleray

Dee Elleray, a Specialist Epilepsy Nurse for Adults with Learning Difficulties, was presented with the ACE award in May 2008 for setting up an epilepsy training programme for student nurses at the University of East Anglia (UEA). This was in response to feedback from student nurses on placement who highlighted the lack of a consistent training programme for nurses, to help them understand this difficult neurological condition. Feeling that this needed to be addressed, she liaised with the University Lecturers and set up a rolling programme so that all student nurses received a three hour training session within the first six months of their training. Those specialising in learning difficulties also receive yearly training sessions in their 2nd and 3rd year.

This award is the 2nd ACE Award given to Dee. She was presented with her first ACE Award in November 2006 for setting up and developing an Epilepsy Link Nurse role across Norfolk.

For more information contact: www.esna-online.org.uk/

Fellows of the British Academy elected

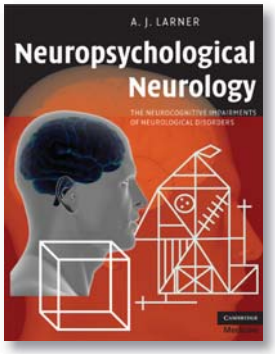

Professor Jon Driver


Professors Chris and Uta Frith

Professor Jon Driver (UCL Institute of Cognitive Neuroscience and Wellcome Trust Centre for Neuroimaging), and Professor Chris Frith (Wellcome Trust Centre for Neuroimaging) have been elected as Fellows of the British Academy. In a tribute to Professor Frith, Professor Malcolm Grant, UCL President & Provost said: "Professor Frith's election calls for special comment. He becomes one of the very few people to be elected Fellow both of the Academy and the Royal Society (Professor Sir Alan Wilson of the UCL Centre for Advanced Spatial Analysis is another). Another such is his wife, Professor Uta Frith. Hence they become the first couple ever to my knowledge to have achieved this dual distinction: an extraordinary achievement."

For more information contact: www.ion.ucl.ac.uk

ACNR Book competition



In the May/June issue of ACNR, we carried a competition for two readers to win a copy of Dr Andrew Larner's book, Neuropsychological Neurology, published by Cambridge University Press.

The lucky winners were:

Dr KPS Nair, Consultant in Neurology, Spinal Injuries and Neurorehabilitation Centre and Dr Rhys Roberts, Neurology SpR, Welwyn Garden City.

Congratulations to both of you.

ENS 2009 Fellowships Announced

The European Neurological Society has announced its 2009 fellowships. Matteo Bologna from Rome, Italy will be carrying out his project 'Synaptic tagging in human motor cortex', at the UCL Institute of Neurology London, UK, chaired by Prof J Rothwell. Vincenzo Donadio from Bologna, Italy, will carry out his project at the Institute of Neuroscience Göteborg, SE, chaired by Prof M Elamwill. His project will be, "A new methodology to study nociceptors and autonomic skin nerve fibre function: implications for pain and autonomic disorders".

Gina Necula from Brasov, Romania, will be carrying out her project "Diagnostic value of endoneurial edema, of Ig deposits and of inflammatory cells in serial sections in predicitin inflammatory neuropathy in sural nerve biopsies", at the University of Würzburg, DE. This will be chaired by Prof KV from Toyka.

The second deadline will be on 15th October 2008. Information about the application procedure can be found at www.ensinfo.org

Winner of 2008 Royal Society Rosalind Franklin Award announced


Professor Eleanor Maguire

Professor Eleanor Maguire, Wellcome Trust Senior Research Fellow in the Wellcome Trust Centre for Neuroimaging, has been awarded the presitigious Royal Society Rosalind Franklin Award.

The award is funded by the Department for Innovation, Universities and Skills (DIUS) as part of its efforts to promote women in science, engineering and technology (SET). The award is made to an individual for an outstanding contribution to any area of SET.

Professor Maguire receives the award in recognition of her scientific achievements in cognitive neuroscience, her suitability as a role model and her exciting proposals to promote women in STEM (Science, Technology, Engineering and Mathematics).

For more information contact: www.ion.ucl.ac.uk

Young Investigator Awards presented


Binith Cheeran

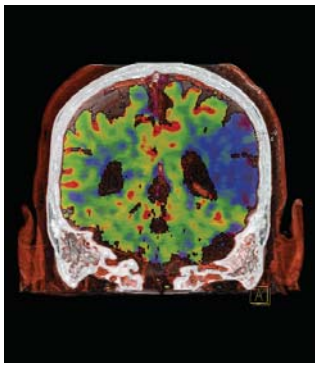

Luke Massey

Binith Cheeran and Luke Massey were presented with Young Investigator Awards at the at the 12th MDS conference held in Chicago in June. They both work as research registrars in Queen Square, London. Binith Cheeran presented his work that has used trans-cranial magnetic stimulation to evaluate the role of common polymorphisms such as BDNF on plasticity. This original work may have important impacts on the differential development of movement disorders such as dystonia and L-dopa induced dyskinesias in PD. Luke Massey showed his unique images of the STN and substantia nigra on 9.4T MRI from which he has been able to measure signal changes in PSP and PD that may have applications for future therapy and for our understanding of the cell biology of these diseases.

Emails: binith@mac.com
lmassey@ion.ucl.ac.uk

UK's first 128-slice adaptive CT scanner


Vascular study, scanned with the SOMATOM Definition AS.


Whole brain perfusion study.

BMI, The London Independent Hospital has installed the UK's first SOMATOM Definition AS+ CT scanner from Siemens. The system is one of the world's first adaptive scanners that not only provides exceptional image quality but is suited to any patient, or any clinical need. The AS+ makes complex examinations routine including scans in cardiology, neurology and oncology.

The SOMATOM Definition AS+ obtains extremely fast coverage with 128 slices per rotation. Images are free from movement artefacts and show the finest anatomical details to assist with diagnosis and treatment planning. 'Adaptive 4D Spiral' capabilities provide functional information, giving whole organ coverage in 4D for stroke or tumour perfusion. This gives clinicians the complete picture instead of preselecting a narrow section to evaluate for perfusion defects. The system minimises radiation due to a unique 'Adaptive Dose Shield' that eliminates over-radiation on either side of the scan range.

The Definition AS+ is compact in design, with a footprint of just 18m^2. Yet, its large 78cm bore, patient table capacity of up to 230kg (36 stone) and fast acquisition speed make the scanner highly useful for traditionally difficult patients such as the obese, children or those suffering from claustrophobia.

For more information contact Siemens,
T: 01276 696317.

Microscope designed for electrophysiological experiments

With the introduction of the Axio Examiner Fixed Stage Microscope, Carl Zeiss makes electrophysiological experiments easier to set-up and perform. The Axio Examiner's specially-designed sloping turret maximises the working area on the large stage and allows a working distance of more than 100 mm. The generous open space permits unimpeded access to the experimental area and a high degree of flexibility in configuring options, such as micro-manipulators, pipettes around large specimens.

The new system may be especially valuable in neuroscience research for patch clamp experiments on nerve cells, examination of brain sections, and the measurement of cellular electrical signals. Multiphoton imaging is available simply by combining the Axio Examiner fixed stage with the new Zeiss LSM 710 NLO microscope, and the new Zeiss AxioVision 4.7 software includes a special physiology module for the quantitative evaluation of many typical experimental procedures.

Freedom from mechanical and electrical interference is assured by the stable stand design and optional shielded stages. In all motorised versions, the motors are automatically deactivated after the target position has been reached and can be actively grounded.

The optical design developed for Axio Examiner also offers maximum optical quality for transmitted light techniques and for advanced fluorescence applications. With the W N-ACHROPLAN and W Plan-APOCHROMAT series, water immersion objectives specially developed to meet the requirements of neuroscience are available for visible light and infrared. Users may choose from transmitted light through to laser scanning with manual or motorised control.

For more information E. micro@zeiss.co.uk

Cutting edge MRI technology for new diagnostic centre

Lodestone Patient Care, a private diagnostic imaging group, has ordered a MAGNETOM Avanto from Siemens for its new diagnostic clinic in Brighton. The new MRI system will be used for orthopaedic, neurological and cardiac scanning.

The MAGNETOM Avanto is a premium 1.5T MRI scanner capable of providing outstanding image quality that will assist with quick and confident diagnosis of even the most complex cases. Total Imaging Matrix (TIM) technology provides seamless scans of up to 205cm without the need to reposition or change coils. It also offers exceptional magnet homogeneity for fat saturation, a large field of view (500mm) and strong gradients for high resolution and short scan times. The MAGNETOM Avanto has lightweight coils that are more comfortable for patients. A low table position also makes access easier for those with limited mobility, plus noise during scanning can be greatly reduced making lengthy procedures more tolerable. The wide bore and option of feet first examinations also eases feelings of claustrophobia for patients.

For more information contact Siemens, T: 01276 696317.

Zero-footprint ultrasound tool for musculoskeletal imaging

SonoSite, Inc. has introduced the S-MSK™ ultrasound tool, the first ultrasound system customised for use by musculoskeletal specialists – including rheumatologists, orthopaedic and osteopathic surgeons, sports physicians and physical therapists.

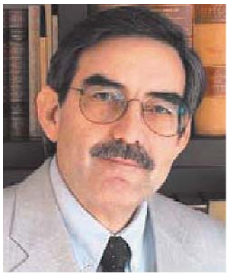
The S-MSK ultrasound tool provides exceptional imaging of superficial and deep targets for a quick assessment and guidance of interventional procedures such as injections and aspirations of the knee, shoulder, elbow and other joints in the body. The S-MSK ultrasound tool is packaged in a revolutionary design that can be carried, mounted on a pole or fixed on a wall or ceiling for zero footprint, and withstands being dropped one metre onto a hard surface.

Based on SonoSite's M-Turbo™ platform, the S-MSK ultrasound tool delivers seamless connectivity for digital image export. On-board flash memory can retain data for 20 standard examinations, and three USB slots allow direct sharing of images and video clips to a PC or Mac® computer. The S-MSK device is easy to disinfect, with a design that minimises fluid ingress to allow easy decontamination, and is backed by SonoSite's ground-breaking five-year warranty.

For more information
T. 01462 444 800,
E. europe@sonosite.com
www.sonosite.com

Concordance – a route to improved outcomes in epilepsy

A well attended session at the ILAE (UK) meeting in Dundee, 9th-11th July, dealt with the issue of 'Patient Focussed Epilepsy Care'. Prof Mike Kerr (Cardiff University) and Mel Goodwin (ESN, Northampton) discussed skills and competencies in clinical scenarios. Prof Kerr said that three big issues were adherence, treatment outcome and risk, however surveys in Australia and in Wales indicate that there is insufficient discussion with the patient in consultations regarding adherence and yet this is necessary to optimise outcome. Studies clearly indicate that patients with better compliance have less seizure and the preference is for once a day medication where possible. Mel Goodwin emphasised that the aim should be a dialogue with the patient to address specific issues and to aim for concordance rather than compliance.



Professor Hermann Stefan, Director of the Epilepsy Center, Elangen.

Prof Hermann Stefan from the Epilepsy Centre at Erlangen, Germany discussed practical aspects of epilepsy treatment. He said that to gain compliance and control then one should aim to minimise impact on the patient's lifestyle. He reported that they have an increasing proportion of elderly with epilepsy and this group present special difficulties with changed plasma protein binding and half-life as well as an increase interaction risk which is further complicated by polypharmacy related to co-morbidities. These issues along with adverse events and patient confusion can make concordance problematic with consequent effects on outcome.

Prof Stefan illustrated the improvements in outcome that can be gained by simplifying the dose regimen to a once daily dose in the evening. In a study he conducted 359 epilepsy patients were transferred from either standard sodium valproate tablets or from the Chrono version taken twice daily to a multiunit controlled release version of valproate (Episenta) that can be taken once daily. The multiunit presentation is also easier to swallow, an important factor in many patient groups. Improved compliance resulted in a drop in average seizure frequency from 2.1 to 0.5 and this medication (Episenta) was highly rated by 95% of patients.

The conclusion of the session on patient focussed epilepsy care was that improved outcomes can be obtained by working with patients and giving them an easy to take medication to enhance concordance.

For more information T. 01892 600930.

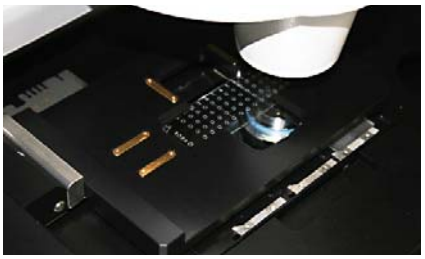
New treatment option for patients with tumours of the brain, spine and body

Elekta announced recently that Skagit Valley Hospital has purchased Elekta Axesse™. The new system is for the entire body and has features which allow clinicians to treat cancer tumours more precisely and effectively. Mount Vernon, WA-based Skagit Valley Hospital Regional Cancer Care Center has been using Elekta's pioneering technologies since 2006. The addition of Elekta Axesse means the hospital can now offer treatment to more patients for a wider range of cancer tumours.

The advanced three-dimensional (3D) imaging capabilities of Elekta Axesse facilitate rapid, precise targeting of tumours, and the highly conformal radiation delivery system effectively treats tumours throughout the body while minimising exposure to nearby healthy tissue. The system enables sub-millimeter accuracy by planning in 3D and imaging patients in 3D prior to treatment. In addition, the system's sophisticated software – including one integrated display monitor with treatment planning, electronic medical record (EMR) technology and system controls – Elekta Axesse streamlines clinicians' workflow to help cut treatment times for patients.

For further information E. Joanne.latimer@elekta.com

SlideCollector 48 simplifies and automates single cell gene expression analysis



One of the major problems inherent in the expression analysis of single cells is the large amount of sample handling involved and the subsequent risk of contamination as cells isolated and harvested using laser microdissection are manually transferred to an assay plate for expression analysis. Until now, the only way to safeguard that the genetic data collected was from cells of interest and not from surrounding tissue has been to perform numerous repeat experiments.

The answer, according to Carl Zeiss, is the new SlideCollector 48 for the PALM Microbeam and PALM CombiSystem. The SlideCollector 48 enables the seamless integration of non-contact Laser Capture Microdissection (LCM) and single-cell AmpliGrid assay technology into one continuous, automated workflow. This ensures the highest levels of sample purity for applications in immunobiology, genetics, cancer research, stem cell research and forensics. In addition, the 1 microlitre assay cells minimise reagent costs, enabling a wide variety of single cell analyses.

Single cells are cut out and isolated from the surrounding tissue or cell culture using the precise laser microdissection offered by the PALM Microbeam. The SlideCollector 48 then positions any one of the AmpliGrid's reaction sites directly above the dissected cell, which is lifted out of the specimen and into the reaction site by the PALM Microbeam's Laser Pressure Catapulting (LPC) capabilities. Because single cells can be easily harvested in this way without contaminating tissue, conventional cell pooling steps are unnecessary.

For more information E. micro@zeiss.co.uk

A better quality of life at the right price

Many wheelchairs still do not meet the needs of their users. The Genie has been designed to solve these needs and to give the user and carer a better quality of life. Good health demands that everyone should stand up regularly, thus helping to prevent bladder problems, and assisting with better circulation, digestion, bone development and pressure management.

The Genie allows the user to stand fully upright, sit, recline or even lie flat, and it can be driven around whilst in any of these positions. The Genie is crash tested, and customised to suit the user. It now has a variety of footplates, even ones which power down to the ground. The controls are versatile and can be mounted in a variety of places. Attendant or dual control, a leg raiser and its own unique head control system are also available if required. At a base price of £5,400 and most packages coming out at around £5,900 it is excellent value for money.

For more information see http://www.easycareproducts.co.uk/

COPAXONE® (glatiramer acetate)

PRE-FILLED SYRINGE PRESCRIBING INFORMATION

Presentation – Glatiramer acetate 20mg solution for injection in 1ml Pre-filled Syringe. **Indication** – Reduction of frequency of relapses in relapsing-remitting multiple sclerosis in ambulatory patients who have had at least two relapses in the preceding two years before initiation of therapy. **Dosage and administration** – 20mg of glatiramer acetate (one pre-filled syringe) administered sub-cutaneously once daily. Children (<18 years) Not recommended. Elderly No specific data. Impaired renal function No specific studies. Monitor renal function during treatment and consider possibility of deposition of immune complexes. **Contra-indications** – Known allergy to glatiramer acetate or mannitol (excipient). Pregnancy. **Special warnings and precautions** – Sub-cutaneous use only. Initiation to be supervised by neurologist or experienced physician. Supervise first self-injection and for 30 minutes after. One or more of vasodilatation, chest pain, dyspnoea, palpitations or tachycardia may occur within minutes after injection. These generally resolve spontaneously after a short time. If severe, treat symptomatically. Caution in patients with pre-existing cardiac disorders and review such patients regularly. Rarely convulsions and/or anaphylactic or allergic reactions. Rarely, hypersensitivity (bronchospasm, anaphylaxis or urticaria). If severe, treat appropriately and discontinue Copaxone. **Interactions** – No formal evaluation. Increased incidence of injection-site reactions with concurrent corticosteroids. Theoretical potential to affect distribution of protein-bound drugs, therefore concomitant use of these should be monitored. **Pregnancy and lactation** – Not to be used in pregnancy. Consider contraceptive cover. No data on excretion in human milk. **Undesirable effects** – Injection site reactions (erythema, pain, mass, pruritus, oedema, inflammation, hypersensitivity, lipoatrophy). An immediate post-injection reaction (one or more of vasodilation, chest pain, dyspnoea, palpitation, tachycardia) may occur within minutes, reported at least once by 41% of patients receiving Copaxone compared to 20% of patients receiving placebo. >1%: Nausea, anxiety, rash, sweating, chills, face oedema, syncope, vomiting, lymphadenopathy, oedema, nervousness, tremor, herpes simplex, skin benign neoplasm, eye disorder, vaginal moniliasis. Rarely: Anaphylactoid reactions, convulsions, shifts in white blood cell counts, elevated liver enzymes (with no evidence of clinical significance) and skin necrosis at injection sites. Please refer to the SPC for a full list of adverse events. **Overdose** – Monitor, treat symptomatically. **Pharmaceutical Precautions** - Store Copaxone in refrigerator (2°C to 8°C). If the pre-filled syringes cannot be stored in a refrigerator, they can be stored at room temperature (15°C to 25°C) once for up to one month. **Legal Category** – POM. **Package Quantity and Basic NHS Cost** – 28 pre-filled syringes of Copaxone: £545.59. **Product Licence Number** – 10921/0023. **Further Information** – Further medical information available on request from Teva Pharmaceuticals Limited, The Gate House, Gatehouse Way, Aylesbury, Bucks, HP19 8DB. **Date of Preparation** – May 2008.

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Teva Pharmaceuticals Ltd on telephone number: 01296 719768.

Reference: Ford C. *et al. Multiple Sclerosis* 2006; 12: 309-320.

Date of preparation: June 2008 Code: C0807/428e

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(glatiramer acetate)

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