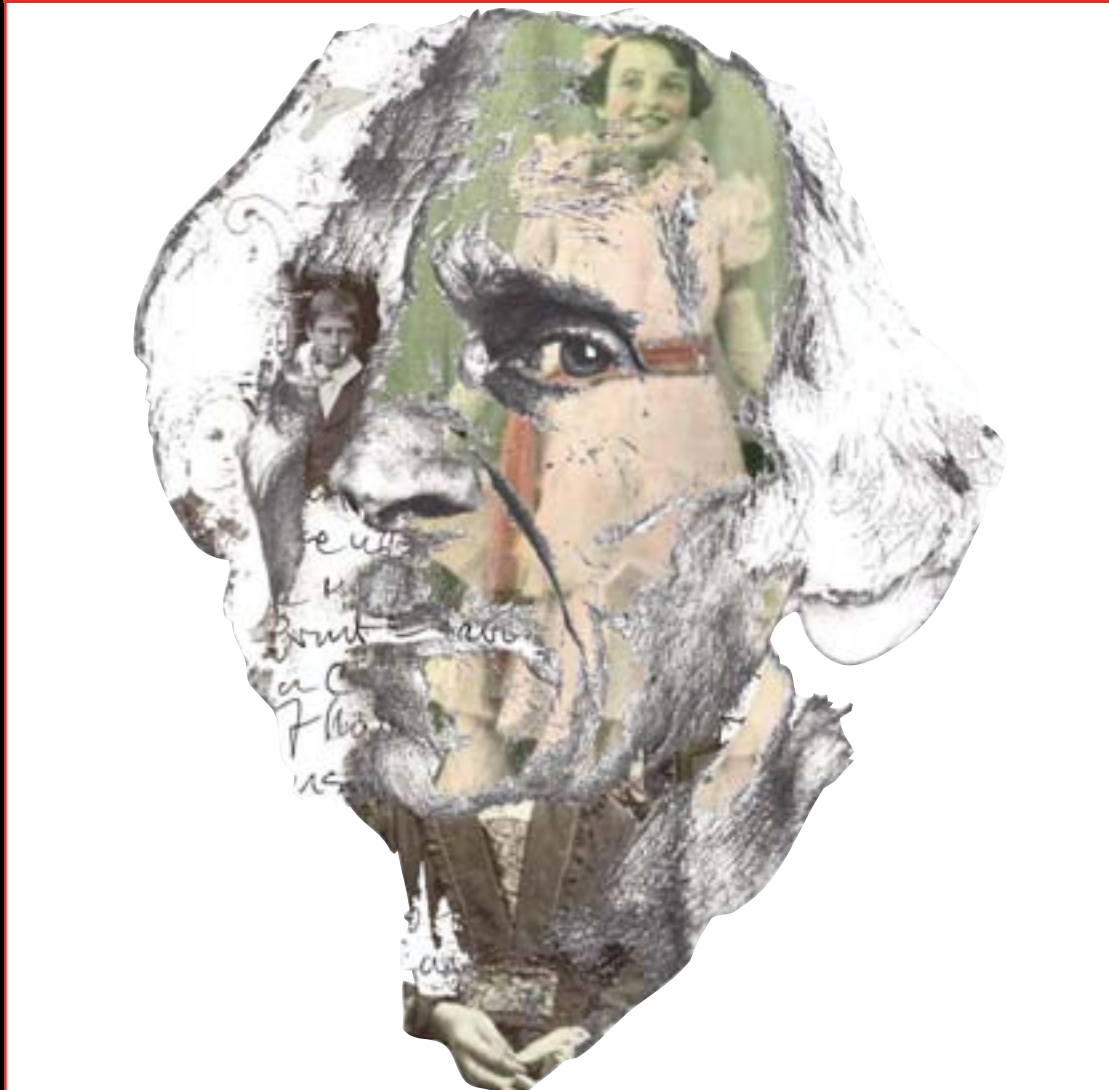


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Advances in Clinical Neuroscience & Rehabilitation



Paul Reading

The Neurological Sleep Clinic – Part 2 – Insomnia and parasomnias

Declan Chard and David Miller

Magnetic Resonance Imaging in Multiple Sclerosis – A Brief Review

Reuben Johnson and Hilary Madder

Prevention and Treatment of Vasospasm following Subarachnoid Haemorrhage

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ERRATUM: The book review of "Understanding Neurology - A Problem Oriented Approach" by John Greene and Ian Bone published in ACNR 2008;8(1):51 was by John Bowen, not by Andrew Larnar. Apologies to the authors of both the book and the reviewer for this error.

Over the last 10-15 years it has become increasingly clear that the problem with MS is more than just one of areas of inflammation, demyelination and then repair. The early loss of axons coupled to the widespread pathology consequent on early inflammation has challenged those working in the field as to how best to treat this condition and then how best to measure any effect from such therapies. Declan Chard and David Miller, in their beautifully succinct article, discuss the power of MRI in this process, both in terms of what it has been able to show and what it may be used for in the future. This article highlights how technical developments for research can translate into more mainstream clinical practice.



Our other major review article is the second in his series on the Neurological Sleep Clinic by Paul Reading and tackles the insomnias and parasomnias. He discusses, again from a personal perspective, the therapeutic options and useful discriminators in distinguishing the causes of these types of sleep disorder.

There are some articles which we publish that cause me to stop and think about greater questions than just treatments in patients with neurological problems. One such article by Joanna Collicut does just this, as it engages with the ethical challenges posed by acquired brain injury. Whilst we have discussed the problems in patients in a vegetative state in other issues of *ACNR*, this article takes the debate to a wider remit. It is a fascinating read about some of the current dilemmas and problems that face medical practitioners dealing with such patients and I strongly urge you to read this article given its thought provoking content.

This article in our Neuropathology series by Tibor Hortobagyi and Safa Al-Sarraj, discusses the best ways to stain for axonal injury and how this can be used to ascertain the cause of that pathology. In particular, APP immunohistochemistry seems an especially sensitive tool for detecting damaged axons and its use is becoming more mainstream and, with this, its utility in establishing the cause of diffuse axonal injury.

One of the major problems in those surviving their initial subarachnoid haemorrhage is subsequent vasospasm that occurs in most cases and which has a significant effect on outcome. In their article in the Neurosurgery series Rueben Johnson and Hilary Madder discuss the optimal management of this aspect of subarachnoid haemorrhage and the challenges that such management presents.

In our series from India, Uday Muthane describes the causes of the different types of movement disorders seen in this part of the world. He also discusses the challenges of managing such cases, in terms of the availability of diagnostic tests and therapeutic options and the problem that the vast majority of individuals have no means of paying for such treatments.

Andrew Larner, after four excellent articles on headache, takes us into the world of cognition and literature. As usual this is a highly entertaining account with plenty to reflect on.

Nick Kane, in his contribution to the Neurophysiology series, edited by Andrew Michell, discusses the role of evoked potentials and other neurophysiological tests in the evaluation of

comatose patient and their utility as tools for prognosis. He concludes that they are probably underused, as are all neurophysiological tests, probably underused in the ITU setting with patients who have prolonged coma states. The ease with which such neurophysiological tests could be used does make them attractive tools of assessment with the caveat that it requires experience and expertise to interpret them accurately.

In our ENS supplement, Steven Laureys and colleagues gives us another article on the challenge in accurately assessing patients with prolonged abnormalities in consciousness and awareness. The critical importance of diagnosing the vegetative state over a minimally conscious state or locked in syndrome cannot be over emphasised and in their review Laureys et al demonstrate how this field has progressed using functional imaging and neurophysiology.

Also don't forget our case reports which this month features a fascinating case of a spontaneous anterior intracranial artery dissection by Gina Kennedy and colleagues, along with a new case of CNS vasculitis from Nick Gutowski et al. We also have our usual series of reviews, including a wonderful update on Muscular Dystrophies by Rajith de Silva in the conference report section which also features a picture of our very own Dr Alasdair Coles. So I hope you continue to enjoy *ACNR* and do let us know how we can do things better.

Roger Barker, Co-Editor,
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UWE Artist illuminates Alzheimer's Disease from Scientific and Artistic Perspectives

The front cover artwork is one of a series created by Jan Martin for a project for Alzheimer's week in October 2007. Jan was one of a group of artists from the University of the West of England (UWE) working alongside a team from Bristol University, and BRACE (Bristol Research into Alzheimers and Care for the Elderly), to explore and illuminate Alzheimer's disease from scientific and artistic perspectives. The project culminated in the 'Remember Me' exhibition at Bristol's Create Centre.

Jan's artwork aims to capture the poignancy of the individual story, while exploring the common experience of memory. Using the emotional charge which memory carries, she tries to encourage empathy with an individual subject by evoking a sense of common human experience. Sculpting the face from elements of a person's life helps to illuminate their history and create a feeling of empathy, both on an individual and human level.

Jan welcomes private portrait commissions and illustration briefs around this theme.

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Cover picture shows artwork created by Jan Martin as described above.



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1,000 mg daily did not affect the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel). Levetiracetam 2,000 mg daily did not affect the pharmacokinetics of digoxin and warfarin and prothrombin times were not modified. **Pregnancy and lactation:** Should not be used during pregnancy unless clearly necessary. Breast-feeding not recommended. **Driving, etc:** Caution recommended when performing skilled tasks, e.g. driving vehicles or operating machinery. **Adverse Effects:** Incidence of undesirable effects considered to be at least possibly related in controlled clinical studies: **Very common** (≥10%): asthenia/fatigue, somnolence. **Common** (between 1%–10%): GI disturbances, anorexia, weight increase, accidental injury, headache, dizziness, hyperkinesia, tremor, ataxia, convulsion, amnesia, balance disorder, disturbances in attention, memory impairment, emotional lability/mood swings, hostility, depression, insomnia, nervousness/irritability, agitation, personality disorders, thinking abnormal, vertigo, rash, eczema, pruritus, diplopia, vision blurred, myalgia, infection, nasopharyngitis, cough increased, thrombocytopenia. Consult SPC in relation to other side effects. **Pharmaceutical Precautions:** *Tablets:* None. *Oral solution:* Store in original container. After first opening use within 2 months. *Infusion:* Use immediately after dilution. **Legal Category:** POM. **Marketing Authorisation Numbers:** 250 mg x 60 tabs: EU/1/00/146/004. 500 mg x 60 tabs: EU/1/00/146/010. 750 mg x 60 tabs: EU/1/00/146/017. 1,000 mg x 60 tabs: EU/1/00/146/024. *Solution x 300 ml:* EU/1/146/027. *Infusion (500 mg/5 ml) x 10 vials:* EU/1/00/146/030. **NHS Cost:** 250 mg x 60 tabs: £29.70. 500 mg x 60 tabs: £52.30. 750 mg x 60 tabs: £89.10. 1,000 mg x 60 tabs: £101.10. *Solution x 300 ml:* £71.00. *Infusion (500 mg/5ml) x 10 vials:* £135.00. **Name and Address of PL Holder:** UCB S.A., Allée de la Recherche 60, B-1070 Bruxelles, Belgium. **Further information is available from:** UCB Pharma Ltd., 208 Bath Road, Slough, Berkshire, SL1 3WE. Tel: 01753 534655. Fax: 01753 536632. Email: medicalinformationuk@ucb-group.com **Date of Revision:** October 2007
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The Neurological Sleep Clinic – Part 2

Insomnia and parasomnias

Virtually everyone has experienced short-term insomnia from time to time, usually in the context of some stressor or the anticipation of an exciting event. However, chronic insomnia is also very common, affecting up to 10% of the population. It is rather blandly defined as the perception of inadequate or insufficient sleep for a period of three weeks or more, with most insomniacs having a history that dates back for many years. Most commonly, the problem is one of both sleep onset and subsequent sleep maintenance although some have only one or other of these elements. In typical chronic or so-called ‘psycho-physiological insomnia’, a trigger or adverse life event can usually be identified at the start of symptoms. Subsequent insomnia and concerns over poor sleep seem to fuel further symptoms although it is usually presumed there is also some ill defined constitutional predisposition or central ‘wiring problem’ combined with varying degrees of maladaptive habits developed by the sufferer. Examples of the latter include frequent checking of the clock through the night or using the bedroom for activities other than sleep. Although psychological or even psychiatric factors are clearly important in most forms of insomnia, additional elements of more interest to neurologists are often relevant as will be discussed.

Parasomnias, literally ‘events during sleep’, can almost be considered normal in children. However, abnormal behaviours arising from sleep, invariably with reduced awareness, are not uncommon in adults, usually in those with a childhood background of sleep-walking. It can be important to diagnose these sleep-related phenomena confidently from history alone, especially since tests are rarely helpful. A mis-diagnosis of nocturnal epilepsy is not rare and can lead to unnecessary treatment and restrictions.

Insomnia

At best, the majority of UK sleep centres deal with insomniacs poorly. At worst, they refuse even to see them. This is mostly because the best recognised treatment for primary insomnia, certainly that occurring at sleep onset, is cognitive behaviour therapy for which it is extremely difficult to find interested practitioners with expertise, at least in the NHS. However, not infrequently, secondary causes of insomnia can be recognised and successfully treated with relative ease. An algorithm is shown in Figure 1.

If symptoms are not volunteered, RLS can be missed as a relatively common and treatable trigger for sleep onset insomnia or, indeed, poor sleep maintenance. Associated periodic limb movements during sleep may also be worth treating even if the diagnosis is not expected from a bed partner’s history and movements are subsequently picked up with overnight recording. In addition, it can be appropriate to address pain or discomfort arising from musculoskeletal disorders including fibromyalgia and other general medical conditions such as reflux oesophagitis which can act as a significant ‘hypnotoxin’.

Another category of sleep disorder that merits addressing as an explanation for some forms of insomnia is delayed sleep phase syndrome (DSPS), especially in young populations. In this under-recognised phenomenon, a subject’s internal ‘clock’ appears to run a few hours behind the average, making it difficult to settle before 2am and very difficult to wake up before, say, 10am. This latter feature is very unusual in simple chronic insomnia. The genetics of DSPS are an active area of research and many such subjects may have specific polymorphisms or mutations of genes

intimately involved in central clock mechanisms.

Some authorities are enthusiastic about the use of diaries or wrist actigraphy in the assessment of insomnia. Although the former may give valuable insight into an individual’s habits, some of which may be maladaptive, the latter is only rarely helpful in documenting the severity of insomnia. Since it is only a surrogate measure of actual sleep, if a subject remains completely still although awake, misleading information may be obtained.

A number of neurological conditions, both common and rare, may have insomnia as a prominent disabling symptom, assuming it is picked up from the history. Somnolent parkinsonian patients frequently have fragmented overnight sleep with early wakening as key elements of their disturbed sleep-wake cycle. This presumably directly reflects brainstem pathology although drugs and mood disorder may be additional factors. The ultimate rare neurodegenerative cause of insomnia, namely fatal familial insomnia, probably reflects the result or relatively specific thalamic dysfunction caused by prion protein accumulation.

Several rare autoimmune or paraneoplastic syndromes such as limbic encephalitis may also produce severe insomnia with or without hallucinatory intrusions as part of the clinical spectrum. Indeed, a good sleep history is often a useful diagnostic marker in such conditions.

Parasomnias

Parasomnias are usually classified according to the sleep stage from which they arise and are broadly divided into REM and non-REM types. The latter are extremely common in children and form a spectrum of night terrors, confusional arousals and actual sleepwalking. Events occur when a subject arouses abnormally and incompletely from deep non-REM sleep usually within 90 minutes of sleep onset. It is not uncommon for such phenomena to persist into adulthood in which case their nature may change. Complex behaviours such as cooking or even driving are well described and violent parasomnias are increasingly seen in medico-legal contexts. If parasomnias start to occur in adults with a distant childhood history of



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Figure 1: Algorithm for assessing subjects with insomnia.
RLS – restless legs syndrome;
OSA – obstructive sleep apnoea

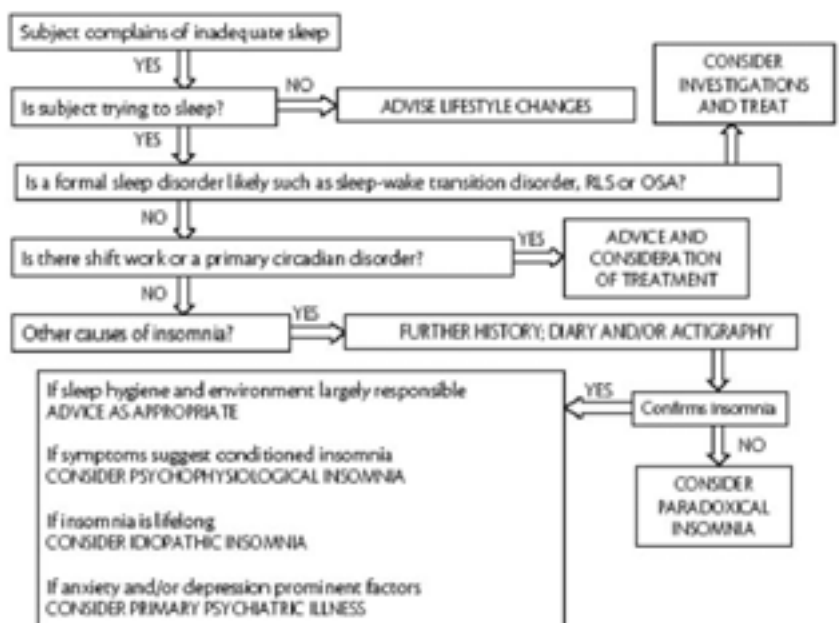


Table 1: A summary of some key differences between non-rapid eye movement (non-REM) parasomnias and nocturnal epilepsy.

	Non-rapid eye movement sleep arousal disorder	Nocturnal (bilateral lobe) epilepsy
Age at onset	Early childhood	Adolescence or later
Positive family history	30–50%	<4%
Number per month	1–3	Usually > 10
Number per night	1	Usually several
Semiology	Complex and non-stereotyped	Stereotyped
Duration	Minutes	Seconds
Timing	First third of night	Random
Sleep stage	Non-rapid eye movement stage II or IV	Most often stage II
Local EEG	High amplitude delta activity	Epileptic activity rarely seen
Triggers	Commonly identified	Rare
Natural history	Spontaneous remission	Persistent

similar phenomena, it is always worth considering whether another sleep disorder such as sleep apnoea is present and acting as a trigger, potentially fuelling partial arousals from deep sleep. It is fairly common for parasomnias to be confused with nocturnal epilepsy although a good history usually suffices for a confident diagnosis. Some key pointers for distinguishing the two entities are given in Table 1.

Occasionally, there is considerable doubt as to the nature of abnormal nocturnal behaviours and investigations may be considered. Unfortunately, it is relatively rare to capture non-REM parasomnias with overnight monitoring and recording between events is generally normal or non-specific. Providing a patient with video equipment for home monitoring may be cost effective.

In a neurological setting, violent parasom-

nias arising from sleep in the context of REM sleep behaviour disorder are not uncommon. Most subjects are elderly males, often with a parkinsonian syndrome already present or in sub-clinical evolution. Injuries, especially to bed partners, may be significant and more than justify long term treatment. The diagnosis is usually clear from history alone. Typically the subject lashes out in deep sleep with brief upper limb movements and vocalisations. The eyes are usually closed and complex behaviours including mobilisation are rare. Dream recall is the norm and subjects usually describe defensive manoeuvres as an explanation for the violent behaviour. Since REM sleep occurs at intervals through the night, events may also recur with a particularly high incidence at around 4am. If overnight polysomnography is performed, the loss of the normal muscle atonia

seen in REM sleep is diagnostic and is present even in the absence of frank movements. Long term treatment with clonazepam is usually successful with melatonin gaining a reputation as a useful second line agent.

Conclusion

In summary, as one commentator famously noted: "sleep is by the brain and for the brain". Although many fundamental questions about sleep remain unanswered, it is crucial for normal brain function and, indeed, mental health. With a broad knowledge of what can go wrong with sleep, both in normal subjects and those with neurological problems, a confident diagnosis to explain sleep-related symptoms can usually be made without recourse to sophisticated tests. Investigations and, more importantly, their proper interpretation, have an important role, however, and it is strongly hoped that neurologists will have an increasing profile in sleep medicine, a discipline that deserves and needs their attention.

Key references for further reading

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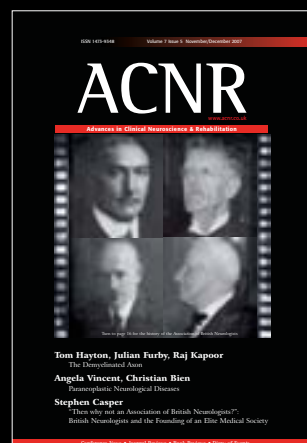
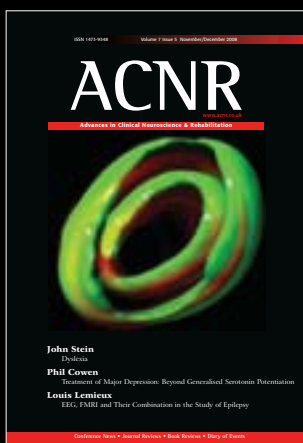
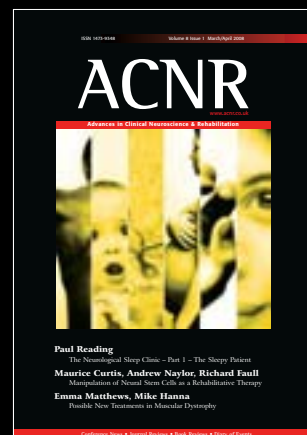
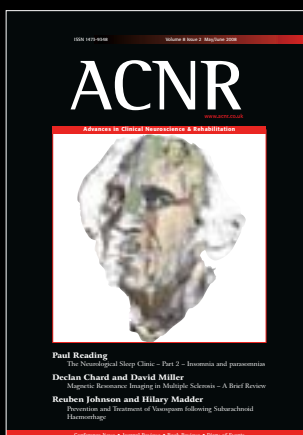
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Magnetic Resonance Imaging in Multiple Sclerosis – A Brief Review

MS pathology

Our concept of pathology in multiple sclerosis (MS) has recently evolved from one of relatively focal white matter (WM) inflammatory demyelination, to one of a more global process affecting the whole central nervous system (CNS), both WM and grey matter (GM), with spatially variable inflammation, demyelination and remyelination, glial proliferation, and neurodegeneration.^{1,2,3} It has also become clear that focal WM lesions explain only a fraction of the disability accrued by patients; changes in regions not overtly abnormal on conventional magnetic resonance imaging (MRI) scans contribute at least as much to clinical outcomes.⁴ Indeed, it is thought that widespread neurodegeneration, which seems to be only partly related to focal WM inflammation, is a key factor determining long term clinical outcomes in MS.

Conventional magnetic resonance imaging

Conventional structural MRI is readily able to detect focal WM lesions, but is not so good for spotting GM lesions or diffuse changes. WM lesions may be seen on both T2 (as hyper-intensities) and T1 (as hypo-intensities) weighted images, with more lesions usually seen on the T2-weighted scans. This mismatch between lesion visibility on T2 and T1 weighted images is thought to reflect differences in pathological specificity; persistent lesion hypo-intensity on T1 images seems to correlate with axonal loss, while T2 hyper-intensity is pathologically non-specific.⁵

The differentiation of acute inflammatory from non-inflammatory lesions is aided by contrast-enhancing MRI scans with gadolinium chelates; these agents non-specifically mark regions where the blood brain barrier is compromised through a variety of processes, including inflammation.⁶ Iron based contrast agents have the potential to illuminate different aspects of inflammatory activity in the CNS: ultra-small particles of iron oxide given

intravenously are taken up by phagocytic monocytes and macrophages, tagging them even after they have entered the CNS;⁷ and antibody-conjugated micro particles of iron oxide can target specific CNS molecules, with a recently developed vascular cell adhesion molecule marker hinting at the potential value of such labels in MS.⁸ However, use of MR contrast media is not without potential risk; nephrogenic systemic fibrosis has been described in people who have received gadolinium based contrast agents, and this has led to a re-evaluation of its use, particularly in people with pre-existing renal impairment.⁹

Quantitative magnetic resonance imaging

MRI is moving from a paradigm of photography to one of cartography, requiring ever more technically demanding acquisition and processing protocols that, at present, limit the use of many quantitative MRI measures to research projects rather than routine practice; perhaps those nearest to application in the clinic are measures of brain atrophy. Brain atrophy is thought to reflect neuronal and axonal loss, and as such has been of particular research interest recently. Measurement of brain atrophy relies on high quality structural images, with sufficient contrast to reasonably define tissues. Broadly, methods can be divided into registration or segmentation-based measures, although most combine elements of both. Registration-driven approaches seek to determine how much a region defined on one scan has to be stretched or crushed to fit an equivalent region on another scan; when applied to serially acquired MRI data, differences between scans approximate the degree of atrophy; when applied to single scans registered to a reference image, estimates of relative volume differences, i.e. normalisation factors, are obtained. Segmentation-powered techniques seek to deliver absolute measures of tissue volumes, but results are often presented as ratios to concurrently determined

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Table 1: Main currently available MRI techniques and their routine clinical applications in MS

MRI modality	Main pathological substrate and localisation of abnormalities in MS	Clinical Application
T1 and T2 weighted structural imaging	Visualises mostly white matter lesions. Not pathologically specific, but T1 hypo-intensity appears correlate better than T2 hyper-intensity with axonal damage.	Core element of the current McDonald MS diagnostic criteria, and monitoring disease course.
Gadolinium chelates contrast imaging	Localised non-vascular enhancement represents disruption of the blood brain barrier; in MS this is associated with active inflammation, mostly seen in white matter lesions.	Core element of the McDonald MS diagnostic criteria, and monitoring disease course.
Volumetric imaging	Brain and cord atrophy represents a combination of cellular atrophy and loss, and appears to mirror irreversible neuronal loss. Atrophy has been observed in both grey and white matter.	Not routinely used.
Diffusion tensor imaging	Assesses tissue, in particular tract, integrity; it is usually abnormal in white matter lesions, but may also be subtly abnormal in normal appearing tissues.	Not routinely used in MS, but increasingly used to determine the age of vascular lesions.
Magnetisation transfer imaging	Assesses tissue myelination; it is usually abnormal in white matter lesions, but may also be subtly abnormal in normal appearing tissues.	Not routinely used.
Spectroscopy	Provides relatively cell specific measures of neuronal damage (as represented by concentrations of N-acetyl-aspartate) and glial activation or proliferation (as represented by concentrations of myo-inositol). Reductions in N-acetyl-aspartate concentrations have been detected in grey and white matter, and lesions; increases in myo-inositol have been seen in normal appearing and lesional white matter.	Not routinely used.

Table 2: McDonald criteria (2005) for establishing a diagnosis of MS.

<i>Relapse onset MS, after a single clinical event and with initial signs of one focal abnormality in the CNS, so requiring further evidence of both dissemination in space and time.</i>	
Dissemination in space	Dissemination in time
<p><i>If unmatched CSF oligoclonal bands are not detected, or have not been tested for, at least three out of the following:</i></p> <ul style="list-style-type: none"> • One or more gadolinium enhancing lesions in the brain or spinal cord; • If no gadolinium enhancing lesions are seen, then nine or more brain and/or spinal cord lesions visible on T2-weighted scans; • One or more infratentorial or spinal cord lesions; • One or more juxtacortical lesions; • Three or more periventricular lesions; <p>Or</p> <ul style="list-style-type: none"> • Objective clinical evidence consistent with at least one further focal CNS lesion. <p><i>If unmatched CSF oligoclonal bands are detected:</i></p> <ul style="list-style-type: none"> • Two or more MRI visible lesions consistent with the diagnosis. <p>Or</p> <ul style="list-style-type: none"> • Objective clinical evidence consistent with at least one further focal CNS lesion. 	<p><i>Any of the following on MRI:</i></p> <ul style="list-style-type: none"> • Compared with a reference T2-weighted scan undertaken at least 30 days after the onset of the index clinical episode, any new lesions seen on any subsequent T2-weighted scans; • Three or more months after the initial clinical event, any gadolinium enhancing lesion observed in any CNS region to which the original symptoms and signs cannot be attributed; <p>Or</p> <ul style="list-style-type: none"> • A further clinical event, lasting at least 24 hours, consistent with the diagnosis.
<i>Primary progressive MS, after at least one year of clinical disease progression as determined retrospectively or prospectively.</i>	
<p><i>Two of the following:</i></p> <ul style="list-style-type: none"> • If visual evoked potentials are normal, or have not been tested, nine or more brain lesions visible on T2-weighted images; • If visual evoked potentials are abnormal and consistent with demyelination, four or more brain lesions visible on T2-weighted images; • Two or more focal spinal cord lesions visible on T2-weighted images; • Unmatched oligoclonal bands detected in the CSF. 	
<i>The criteria assume that no viable alternative explanation for a person's symptoms and signs has been found after appropriate investigation.</i>	

intracranial volumes; this adjustment yields measures which are naturally less variable between people, and which are less susceptible to scanner calibration drift, which can be a problem with serial MRI studies. GM specific measures may be of added value in MS, offering better surrogate markers of disease progression compared with WM or whole brain parameters.¹⁰ In clinical trials of potential neuroprotective agents, the inclusion of MRI brain atrophy measures may reduce both the number of participants and the follow-up period required to show a significant treatment effect, when compared with studies relying purely on clinical outcome measures.¹¹

As presently acquired, conventional structural MRI is designed to maximise spatial clarity but not to serve as an objective quantifiable measure of a tissue's intrinsic characteristics; however a suite of newer MRI techniques are able to provide such information. Magnetisation transfer (MT) imaging offers insight into myelination,¹² estimating the proportion of membrane associated macromolecular protons (not readily seen with conventional MRI) in a region; abnormalities in MT have been detected in both lesional and non-lesional tissues in MS, and such measures have been recommended for use in studies of treatments aimed at promoting remyelination.¹³ Diffusion tensor imaging yields a measure of tissue integrity, with changes again seen in both MS lesional and non-lesional tissues,¹⁴ and has demonstrated potential in the assessment of MS associated WM tract damage.¹⁵ Proton spectroscopy allows the estimation of brain chemical concentrations: N-acetylaspartate, which is found almost exclusively in neurons and their axonal projections in the adult brain, offers a measure of neuronal

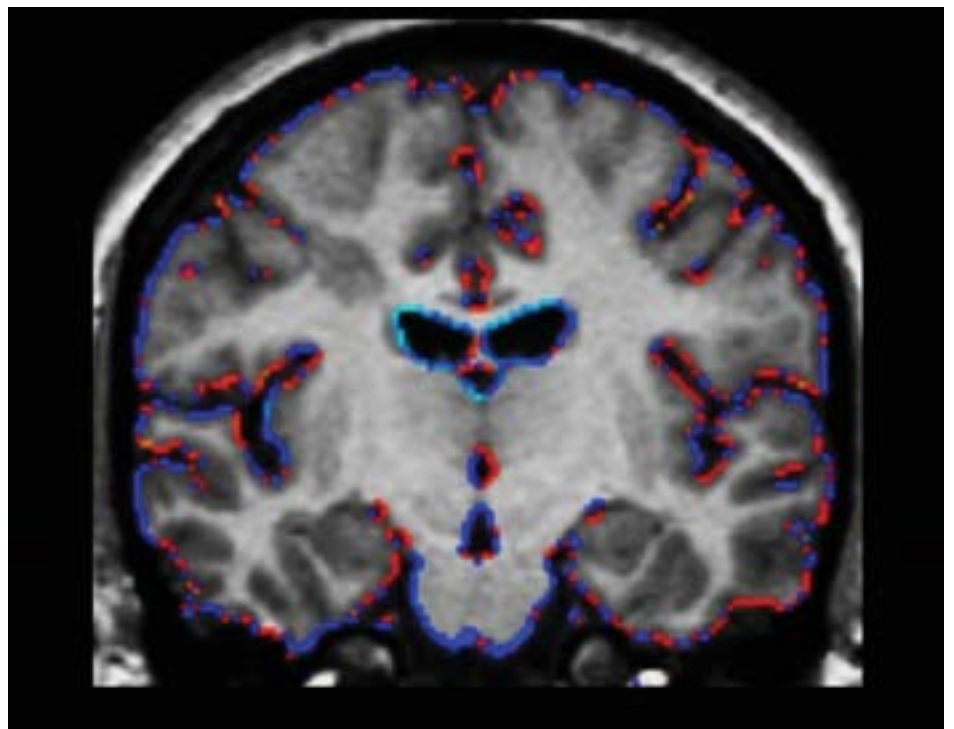


Figure 1: Brain volume loss in MS demonstrated using the 'Structural Image Evaluation, using Normalisation, of Atrophy' technique applied to two MRI scans acquired one year apart. A coronal brain slice is presented, rendered with a colour overlay, where blue indicates volume loss and red indicates gain. For further details see Anderson et al.¹⁰ Image courtesy of Valerie Anderson.

health and density, and has been found to be reduced early in the clinical course of MS, in WM and GM; myo-inositol, which is preferentially concentrated in glia, has been found to be elevated in lesions and normal-appearing WM, suggesting glial activation and or proliferation.¹⁶ Using MRI, it is also possible to quantitatively measure T1 and T2 relax-

ation times, and tissue perfusion, although these measures have been less extensively employed in MS, compared with those mentioned previously.

The functional impact of MS is also being addressed with MRI, beyond that of simply associating measures of tissue damage with clinical outcomes; recent functional MRI studies

suggest that cortical plasticity may attenuate the effects of focal damage in MS, and promote recovery beyond that achievable through localised innate tissue repair mechanisms alone (for example ¹⁷).

McDonald diagnostic criteria and other clinical applications

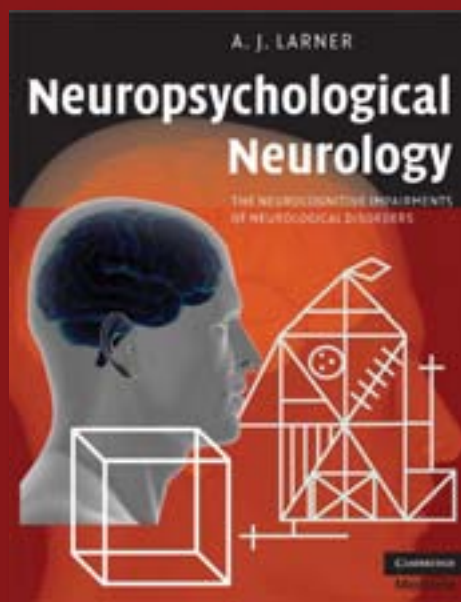
Technical limitations and the complex data processing required to derive quantitative MR measures have meant that routine clinical application of MRI has focused mainly on identifying lesions to support the diagnosis of MS, and excluding or confirming alternative diagnoses. MRI on its own cannot be used to establish a diagnosis of MS, but can provide key evidence for evolving multifocal pathology. The latest diagnostic guidelines in MS, the revised McDonald criteria,¹⁸ allow the diagnosis of MS after a single clinical event, where there are sufficient MRI visible brain and cord lesions, and lesion accrual is demonstrated on scanning undertaken after the index clinical event. A very recent study suggests that in people who have had no episodes suggestive of CNS demyelination, the incidental detection on MRI of MS-like lesions is associated with a relatively high risk of a person having a clinical event consistent with MS within five years.¹⁹ However, while lesions do appear to predict onset of MS, they are not so good at predicting subsequent disability, even in the longer term, i.e. they mark the process better than its effects.²⁰ While MRI has established itself in a diagnostic role in MS, it is only just beginning to find a clear place in treatment decisions; lesion activity measures form part of the National Institute for Clinical Excellence (2007) recommended criteria for the prescription of natalizumab in rapidly evolving severe relapsing-remitting MS.

Where next?

MRI has already made invaluable contributions to our understanding of MS. In the short term, it remains for quantitative MRI measures to realise their potential in clinical practice: such measures may help make the diagnostic criteria even more sensitive and specific; may yield more reliable prognostic indicators; and provide timely and effective surrogates of pathological progression, in a way that can usefully inform treatment decisions, preferably before such progression becomes clinically manifest. In the long term, it may be possible to deliver truly cell and process-specific information from MRI, and integrate such measures with immunological and genetic data to better characterise the disease's genesis and evolution. From this it is to be hoped that we can develop a range of more effective disease specific treatments, optimise their use on a person-by-person basis, and observe their effectiveness dynamically with a view to eliminating, or at least markedly curtailing, the clinically apparent effects of MS.

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The Ethical Challenge Posed by Acquired Brain Injury

Perhaps our first thoughts on seeing the phrases 'acquired brain injury' and 'ethical challenge' in close proximity to each other, are the extremely difficult and controversial decisions about the end of life for people who are deemed to be in a persistent vegetative state (PVS). These centre on questions of sentience; the nature and value of human life; human dignity and quality of life; the inferred wishes of the affected person pre-injury; the interests of their loved ones; and the interests of society at large.

But PVS is an extreme case, and what is less widely recognised is the significant and compelling challenge posed by the more common kind of severe brain injury that spares the patient's sentience, but may devastate her ability to move, feel, think, remember, communicate, and make meaningful relationships. The situations faced by these people, their families, and those who care for them are replete with moral overtones which make themselves felt as ethical dilemmas. These are complex problem situations that involve tension and paradox, where all potential solutions appear to be unfavourable, where potential solutions conflict, and where it is difficult to act.¹ It is thus not surprising that they evoke strong feelings and conflict both within and between the individual stakeholders.

The treatment and rehabilitation of people with acquired brain injury is a potent and distinctive source of ethical dilemmas because it involves profound novelty, great complexity, only partial information, and a coming together of several different value systems and assumptive worlds.^{2,3} While some of the ethical issues that arise in the context of acquired brain injury also arise in the context of other disabling neurological conditions, such as spinal cord injury, multiple sclerosis, or the dementias, there is a unique combination of factors that applies to acquired brain injury. These factors have specific psychosocial consequences, and raise specific ethical issues:

- The onset of the condition is sudden in previously healthy individuals
- Physical, cognitive, emotional, behavioural control systems and their capacity for seamless functional interaction are all potentially compromised
- Because of this complexity an unusually large range of professionals may be involved
- The outcome is uncertain and improvements may continue for many years
- A relatively young population is affected
- Life expectancy is often normal

The particular combination of sudden and dramatic cognitive and physical losses, primary emotional processing difficulties, change of appearance, and the psychological reaction of the affected person and others result in a deconstruction of 'personality'⁴ and profoundly changed sense of personal identity.⁵ I have argued that the central task facing the patient, family, and clinicians is therefore establishing a new sense of identity continuous with, but not stuck in, the past, while managing the medical complications, pain, and emotional distress



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that arise during the process.⁶ The basic activities and attitudes required are:

- Sensitivity to and respect for the affected person's physical and psychological boundaries
- Taking seriously issues related to their personal appearance
- Treating their impairments
- Optimising their agency and liberty
- Training in meaningful activities
- Supporting them in the resumption of valued roles and relationships
- Helping them to integrate the experience into a meaningful personal narrative
- Managing any associated physical and psychological conditions

The crunch comes in optimising liberty and agency. There is little doubt that brain injury robs individuals of agency through its direct effects, and of liberty through the actions of others who admit them to hospitals or care homes, terminate their employment, and so on. There seems little doubt that some sort of reinstatement of agency and liberty should be the aim of good patient-centred practice. But here the ethical dilemmas start to emerge: whose agency and liberty are we talking about?

Is it the pre-injury person – now idealised and set in stone in family photos, videos, or advance directives? Is it the profoundly changed person of the present? Is it some, again idealised, aspirational person-in-becoming – the person who has achieved all his rehabilitation goals? And is it worth tolerating a degree of restriction in agency and liberty now for the later and greater good of increased agency and liberty in the future? And what if optimising the agency and liberty of the patient has detrimental effects on other aspects of his wellbeing or on the agency and liberty of others (other people competing for limited health and social care resources, family and friends, clinicians and other professional carers, the general public)?

My recent book⁷ includes a series of case studies which include the following main issues:

- Mental/cognitive capacity and the issue of 'acquired imprudence' associated with executive impairment – the right to make 'bad' decisions
- The naturalness and danger of paternalism when dealing with people who are learning to walk, talk, be continent, behave in a socially appropriate manner

- The limits of 'duty of care'. Is the fact that there are many people who do not have identified acquired brain injury at liberty in the community who are a risk to themselves and others because of poor social, emotional, and behavioural control relevant, or not?
- The role of carers in advancing the agendas of very physically dependent people where these agendas are not congruent with their own value system. Should carers ever act exclusively as 'objects' under the direction of the affected person?
- Unpredictability of treatment gains and very large inter-individual variation makes fair allocation of resources particularly challenging. For instance individualised treatment programmes have a tenuous link to evidence bases, which are limited, and often consist of large group studies of homogenous treatment programmes
- The special needs of children – including protection and appropriate autonomy
- Interdisciplinary conflict due to diverging professional and personal values – moral and epistemological
- Psychological versus physical risk – is physical safety to be pursued at all costs, including personal despair?

Ethical dilemmas relating to these issues are by their nature rarely resolvable to the satisfaction of all those involved. Nevertheless, a systematic approach that makes the issues explicit and gives them due consideration is a highly desirable component of clinical practice in this area. The psychological impact of engaging with these issues, especially if the process has involved significant conflict, should also be recognised and managed for patient, family, and clinical staff. Good decisions and the management of the process of ethical decision making and action is likely to be helpfully informed by individuals with expertise in the areas of moral philosophy and psychology, philosophy of mind, religion and spirituality, and law. All these may add enlightening perspectives (but not answers!) and contribute to the development of wisdom in clinical services and teams.

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Information about adverse event reporting can be found at www.yellowcard.gov.uk and adverse events should also be reported to UCB Pharma Ltd.



References: 1: Watts RL et al. *Neurology* 2007; 68: 272-6. 2: Neupro Summary of Product Characteristics. 3: Giladi N et al. Poster presented at EFNS 2006.

Date of literature preparation: February 2008.

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Evoked Potentials and the Prognosis of Comatose Patients Receiving Intensive Care

Whilst death is relatively easily identified, its prediction on an individual patient basis during the course of critical illness is more complex. In a hospital setting, anticipating death allows the carers to advise the patient and their loved ones of the prognosis, to withdraw futile, burdensome treatment and to implement end of life care pathways. In comatose patients clinical observation forms the basis of prognostic predictions but is prone to error; for example the widely used Glasgow Coma Scale (GCS), really a clinical measure of consciousness, can be unduly pessimistic.¹ A systematic review of 1,914 comatose survivors of cardiac arrest found five clinical signs which strongly predict death or poor neurological outcome: absent corneal reflexes, absent pupillary response, absent withdrawal response to pain, no motor response at 24 hours, and no motor response at 72 hours, but none which strongly predicted a good neurological outcome.² The prediction of good outcomes is perhaps equally important, particularly in identifying those survivors of coma who will require intensive neurorehabilitation. Over the last 25 years there have been many attempts to improve prognostication by adding electrophysiological and biochemical measures of functional integrity and neuronal damage, respectively. Is it time then to introduce such measures into routine clinical practice?

Electrophysiological assessment of the central nervous system initially concentrated on the electroencephalogram and short latency evoked responses, in particular the somatosensory evoked potential (SSEP), whilst latterly investigators have evaluated long latency event related potentials (ERPs), such as the P300 and mismatch negativity (MMN).³ The assumption is that their detection reflects functional integrity of cerebral neuronal pathways, which are not accessible to the brainstem-focussed clinical examination, and may therefore provide early indications of the potential for neurological recovery and cognition (see reference 4 for a review). In contrast to the GCS, they are not measures of consciousness per se and it is important to emphasise that they provide complementary information to clinical observations. It has recently been elegantly demonstrated by imaging studies, in this and other journals, that there are 'islands' of preserved cerebral function in patients who are unresponsive.⁵ Electrophysiological probing of these islands may indicate higher levels of information processing which underpin awareness and responsiveness if not consciousness itself, although of course information processing alone is not consciousness as such. What then is the evidence for the clinical application of evoked and event-related potentials?

We have the benefit of a number of systematic reviews of the significance of bilateral absence of SSEPs in both traumatic and non-traumatic coma 24 hours after onset.^{6,7,8} It appears that the bilateral absence of short latency cortical potentials is very nearly 100% specific for prediction of a poor outcome (defined as death or persistent vegetative state)⁶ after hypoxic ischaemic and intracranial haemorrhagic insults, but is slightly less predictive after traumatic brain injury (TBI), particularly in children.⁷ Indeed after TBI as many as 12 patients out of 777 had favourable outcomes (good or moderate disability) despite bilaterally absent SSEPs.⁸ This observation has been detailed in a number of case reports of patients making good recovery after both anoxia and TBI, where barbiturate coma or raised intracranial pressure may have contributed to the loss of cortical responses.^{9,10} Clearly this gives cause for concern,

especially when poor prognoses tend to become self fulfilling, and demonstrates a need for the judicious use and timing of evoked potential recordings. However, this is true for clinical observations alone and it seems that the predictive value of SSEPs is superior to clinical tests,¹¹ and can be predictive of a poor outcome even when brainstem function is preserved after anoxia.¹² Indeed the American Academy of Neurology has endorsed the use of SSEPs (with a level B rating) in a decision algorithm for prognostication of comatose survivors after successful cardiopulmonary resuscitation.¹³ Perhaps of greater consequence than medication effects, which can potentially be reversed, is that a multicentre trial revealed that there was only moderate interobserver agreement on the interpretation of evoked potentials.¹⁴ Furthermore, although the absence of short latency responses is a poor prognostic feature, their presence does not guarantee the return of consciousness or survival, and we must look to other electrophysiological probes.¹⁵

Long latency event related potentials (ERPs) have been the subject of several reviews,^{16,17} and the findings of one meta-analysis are now known.¹⁸ This analysis pooled data from 10 studies of patients in coma and other low responsive states (GCS <12) of various aetiologies in order to estimate the predictive power (odds ratio, OR, and its confidence limits, CI) of several ERPs measures (see Table).¹⁸ Since the greater the value of the OR (or more precisely the lower limit of its CI) indicates that presence of the ERP component is a significant predictor of awakening, the P300 would seem to be the test of choice. Indeed P300 was the original ERP component reported in four patients who recovered from traumatic coma,¹⁹ which was subsequently confirmed in a large cohort.²⁰ However, MMN is an automatic process in both sleep and wakefulness whilst P300, in the awake state at least, is modulated by arousal and attention, which clearly can be neither controlled nor assessed in an unresponsive patient. It was largely this potential confounding factor that encouraged investigators to assess the automatic pre-attentive MMN auditory novelty detection mechanism, and which may account for its apparent greater specificity (91% versus 77% for P300).¹⁸ The presence of MMN has been shown to be predictive of awakening from both acute traumatic and non traumatic coma,^{3,21,22} and the vegetative state.²³ Unfortunately its presence has also been seen to falsely predict a favourable outcome (in 16 out of 460 patients).¹⁸ As with short latency responses we are uncertain of the interaction of MMN with sedating agents, and indeed it has been shown to be attenuated by deep sedation with propofol.²⁴ Its absence is uninformative of prognosis.

In conclusion, there is evidence that both evoked and event related potentials could help refine clinical predictions of outcome from coma. It is fair to say that evoked potential recordings are reliable predictors of poor outcome and are inexpensive, non-invasive tests that can be safely recorded at the patient's bedside. The neurophysiologist



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Table of Odds Ratio with Confidence Intervals (CI) for prediction of survival by various Event Related Potential (ERP) components from pooled data.

ERP component	Odds Ratio (OR)	95% CI	Patient Number
N100	2.85	1.91-4.27	548
MMN	6.53	3.55-12.01	470
P300	8.79	4.88-15.83	313

needs experience to be aware of certain caveats in their clinical application, and in spite of being widely available throughout the UK are probably under-utilised. My own telephone survey of 20 Clinical Neurophysiology departments across England and Wales revealed that all but one regularly record EEGs in Intensive Care Units, but only five ever record evoked potentials, with just

two recording them on a fairly frequent basis. Although in their infancy event-related potentials have shown some promise in heralding awakening and favourable neurological prognoses, and can therefore complement evoked potentials. ERPs are more complex in both their recording technique and interpretation, and will require further evaluation before clinical utility

can be achieved. The inherent false positive rates may of course limit the use of electrophysiological predictors of outcome in coma, which is generally a self-limiting condition.

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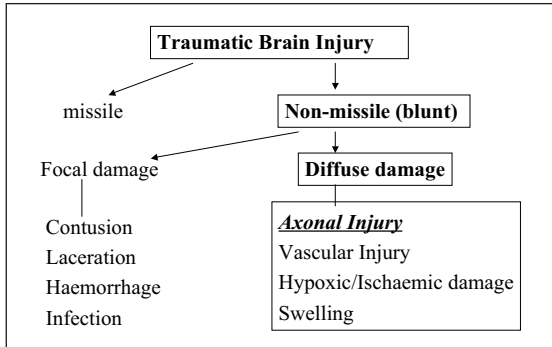


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The Significance of Diffuse Axonal Injury: how to diagnose it and what does it tell us?

Traumatic brain injury (TBI) is a leading cause of death and disability worldwide. TBI can be classified as missile and non-missile. The latter can further be subdivided as focal and diffuse damage, which often overlaps (Table 1).¹

Table 1: Classification of Traumatic Brain Injury.



Focal damage includes contusions, which are usually superficial bruises of the brain, affecting the cortex and in more severe cases also the underlying white matter. Contusions often have a triangular shape, with a wide base on the surface of the crest of a gyrus as opposed to ischaemic damage, which tends to be more severe and at the depths of the sulci. They are classified as i) indirect ('contre-coup'), frequently seen in the anterior and inferior surfaces of the frontal and temporal lobes, and ii) direct ('coup') contusions seen at the site of severe impact on the surface of any region of the brain. Lacerations occur when the damage is severe enough to cause tearing of the leptomeninges. Bleeding is common after TBI. Intracranial haemorrhage may develop over a period of time, which may extend into the subarachnoid space causing subarachnoid haemorrhage (SAH); other causes of SAH include skull fracture with tearing and/or dissection of arteries such as the vertebral arteries. Extradural haematoma (EDH) is usually associated with skull fracture and torn meningeal arteries, whereas subdural haematoma (SDH) results from the tearing of the bridging veins in particular those related to the superior sagittal sinus. Focal infection is frequently a complication of skull fracture and contamination with bacteria.

Diffuse damage includes diffuse axonal injury (DAI)(see below), diffuse vascular injury and diffuse hypoxia/ischaemia. Diffuse vascular injury results from shear stress and traction of parenchymal blood vessels resulting in petechial haemorrhages. Diffuse hypoxic-ischaemic damage sometimes accompanies TBI, especially in patients with raised intracranial pressure (over 30 mmHg) and severe long-lasting hypotension.

Classification of axonal injury

Axonal injury is frequently a consequence of traumatic brain injury which may cause other focal damage in the brain like contusions, lacerations or haemorrhage. Depending on the severity of trauma, the axonal injury can be focal, multi-focal or diffuse. In focal and multi-focal axonal injury the damaged axons are seen in one or few locations in the supratentorial parts of the brain, mainly in the corpus callosum and internal capsule, but not in the infratentorial brain regions. Diffuse axonal injury (DAI) is usually associated with rapid angular (rotational) acceleration and deceleration of the brain.

The damaged axons are more widespread and seen in several parts of the brain, including those in the supratentorial and infratentorial brain regions, such as the cerebellum and pons. DAI should be considered as a serious and significant head injury. However, it is graded according to the severity of pathology, clinical presentation and likelihood of survival (Table 2).²

Table 2: Grading of Diffuse Axonal Injury (according to Adams et al.)²

	Diffuse Axonal Injury	Haemorrhage in corpus callosum	Lesions in dorsolateral rostral brainstem
Grade 1	Present	Absent	Absent
Grade 2	Present	Present	Absent
Grade 3	Present	Present	Present

The identification of diffuse damage to the axons in the brain should follow a detailed histological examination of many parts of the brain which are more susceptible to axonal injury. These include the frontal parasagittal white matter, parietal lobe (including deep white matter), anterior corpus callosum, posterior corpus callosum, basal ganglia (to include the internal capsule), cerebellum (to include middle cerebellar peduncle) and pons (to include dorsolateral rostral brainstem).^{3,4}

Axonal injury can be caused by immediate (primary) axotomy which occurs at the time of injury or delayed (secondary) axotomy which evolves over a few minutes or hours after impact. In the majority of cases of head injury, secondary axotomy is the major mechanism.⁵ The focal damage to the axonal cytoskeleton is followed by formation of axonal swellings and varicosities proximal to the site of injury. These swellings contain accumulated material which cannot be transported due to disruption of axoplasmic flow.⁶ Therefore, the axonal swelling usually occurs some time after head trauma and indicates some period of survival.

Detection of axonal injury

Several histological methods can detect damaged axons with variable degrees of sensitivity and depend on minimum survival time of patients after head trauma (Table 3). The most widely used and most reliable method is amyloid precursor protein (APP) immunohistochemistry.⁷ APP (Table 4) is a membrane glycoprotein which is

Table 3: Methods and their time dependency to detect axonal injury

Silver	15-18h
H&E	24h
Immunohistochemistry: GFAP	5d <
CD68	36-48h
Neurofilament	60 min
Chromogranin A	
Cathepsin D	
SNAP-25	
APP	< 35 min



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Table 3: Methods and their time dependency for detection of axonal injury (AI) in paraffin embedded human brain tissue. (Silver: silver impregnation technique; H&E: Haematoxylin and eosin stains; The other methods listed are immunohistochemical. GFAP: Glial Fibrillary Acidic Protein; SNAP-25: Synaptic Protein-25; APP: Amyloid Precursor Protein).

Table 4: The role and significance of Amyloid Precursor Protein (APP).

Amyloid precursor protein (APP)
<ul style="list-style-type: none"> • ubiquitous membrane glycoprotein coded on chromosome 21 • alternate splicing and proteolytic processing - > 3 major subtypes
<i>Physiological/pathological significance:</i> <ul style="list-style-type: none"> • cell-adhesion • ?neuroprotective (via secreted N-terminal fragments) • amyloidogenic proteolytic pathways ▶ β-Amyloid plaque • fast anterograde axoplasmic transport ▶ synaptic function ▶ accumulation proximal to AI • APP is a sensitive marker of AI of any cause • non-specific for traumatic aetiology of AI
<i>In axonal injury:</i> <ul style="list-style-type: none"> • size and staining pattern correlates with survival time • helpful but not sufficient for exact timing of injury

produced in cell bodies and neurones. Its major physiological role is in cell adhesion, neuroprotection and synaptic function. This is the same protein which is implicated in β-amyloid plaque formation in Alzheimer's disease following an abnormal proteolytic cleavage by an enzyme called gamma secretase. To this end, head injury is a known environmental risk factor for Alzheimer's disease, in particular in subjects carrying the apolipoprotein E (APOE) ε 4 allele as an additional genetic risk factor.⁸

In normal circumstances, APP travels from the neurone to the peripheral axons via fast transport mechanism which cannot be detected by immunohistochemistry. This transport is an ATP-dependent process, and the speed is influenced by axonal diameter and age of the individual. If there is axonal disruption for any reason, including trauma, the APP can accumulate at the site of injury and can be demonstrated by immunohistochemistry. It is important that very small amounts of protein are detected in these cases, so antigen retrieval techniques (e.g. microwaving), careful optimisation of the immunohistochemical method and selection of the antibody are crucial. When such issues are addressed, APP immunohistochemistry can be detected within one hour survival period, and in some cases following 35 minutes survival period.⁹ With an optimised method, including microwave and citrate pre-treatment of histological sections, APP immunohistochemistry can detect axonal injury with post TBI survival times of less than 60 minutes and a minimum of 35 minutes.⁹

The APP intensity increases with time up to 24 hours. After that, the staining may become more granular, slightly pale after a few days and disappears after one month or less.

It has been demonstrated that wide sampling and APP immunohistochemistry can determine the cause of axonal injury in most cases.¹⁰

Differential diagnosis

It is important to emphasise that axonal injury can not only be caused by trauma but by different mechanisms such as ischaemia, hypoglycaemia, inflammation, haemorrhage, drugs, alcohol and even ageing.¹¹ Therefore, APP immunohistochemistry should be considered to be a sensitive, but not specific, marker of axonal injury. The distinction between traumatic and other causes of axonal injury can be difficult and, in many cases, only a probability can be established. The most frequent problem is to distinguish hypoxic-ischaemic damage to the axons from that caused by trauma. This is made more complicated by virtue that ischaemia and hypoxia are frequent occurrences and sometimes considered an integral part of head injury. Many cases of head injury are associated with subdural or extradural haematoma which can cause brain shifting and herniation and subsequent axonal injury due to vascular damage.

In traumatic head injury, the APP immunohistochemistry usually reveals well-defined fusiform swellings of different sizes, beaded and thickened filaments and globules which, in some places, are seen along white matter tracts (such as those seen in the internal capsule and corpus callosum) with no granular background (Figure 2). In cases of hypoxia and ischaemia or other vascular damage, the APP immunohistochemistry is usually associated with heavy deposition in ill-defined areas, and sometimes a geographical pattern (following the areas of ischaemia) with a heavy granular background.¹² (Figure 3).

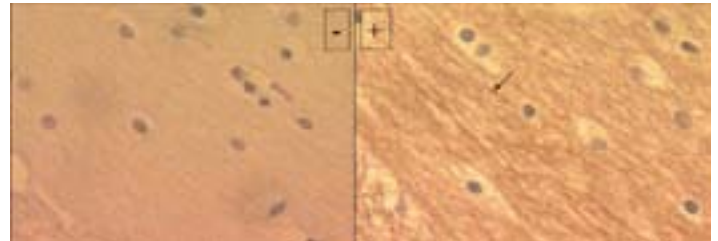


Figure 1: Immunohistochemical detection of APP without (left) and with (right) antigen retrieval. The accumulation of APP proximal to the site of axonal injury is visualised only after application of antigen retrieval techniques.

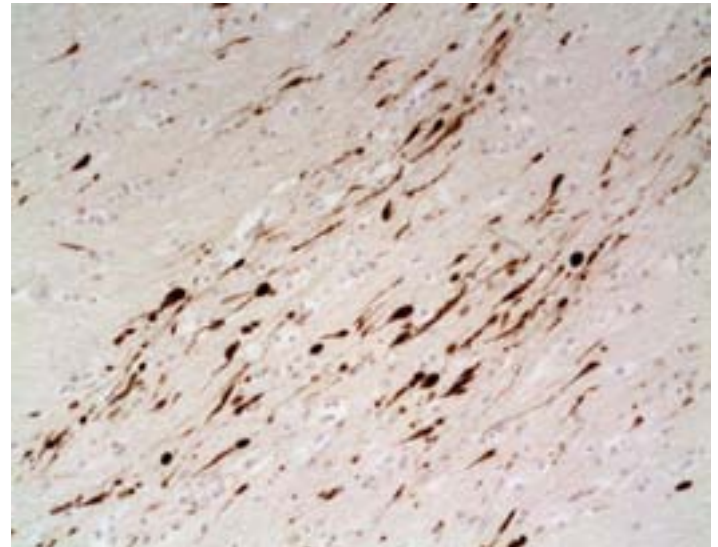


Figure 2: APP immunohistochemistry in a case of severe brain trauma. Note the strong labelling of damaged axons on a clear background with fusiform swellings, thickened filaments and globules.



Figure 3: APP immunohistochemistry in a case of acute cerebral ischaemia. There is a heavy granular staining revealing an ill-defined, geographical pattern on a 'dirty' background.

The 'shaken baby syndrome'

One of the rare causes of head injury in children is non-accidental injury (shaken baby syndrome or shaken-impact baby syndrome). The brain usually shows no evidence of contusions or lacerations but swelling and oedema associated with ischaemic damage. Therefore, the damaged axons in these cases are more frequently seen in a pattern consistent with ischaemic damage than traumatic damage.^{13,14} There are two possible explanations for the mechanism of brain swelling and hypoxia in shaken baby syndrome.¹⁵ The first is an alteration in the blood brain barrier leading to oedema and increased intracranial pressure followed by ischaemia. However, recently it has been proposed that focal damage to

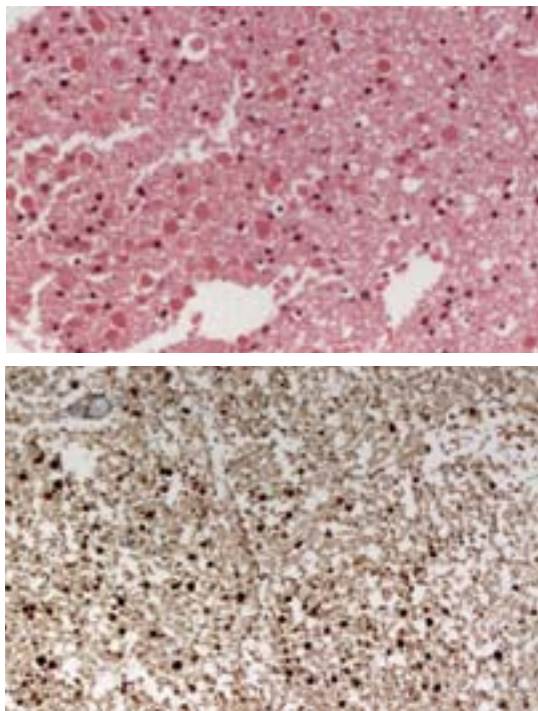


Figure 4: Histological appearances at the level of an injured cranio-cervical junction in a case of paediatric non-accidental injury ('Shaken Baby Syndrome').
a) (top image) Haematoxylin & Eosin stain reveals the dilated axons as pink globules.
b) (bottom image) Immunohistochemistry highlights the dilated axons, rich in accumulated APP.

the medulla may cause cardio-respiratory arrest and ischaemia; the axonal damage can be demonstrated in a proportion of victims by APP immunohistochemistry (Figures 4a & b).

Conclusions

Diffuse axonal injury is a significant traumatic brain injury which involves widespread damage to axons in supra- and infratentorial parts of the brain and is graded 1-3, according to the severity of pathology and the likelihood of survival. It should be differentiated from focal or multi-focal axonal injury. APP immunohistochemistry is the most sensitive tool to detect damaged axons. However, it is not specific as it could occur in any other condition which causes damage to the axons, such as ischaemia. APP immunohistochemistry can detect axonal injury within one hour and as early as 35 minutes after trauma, which has medico-legal implications.

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'Neurological literature': Cognitive Disorders

Cognitive disorders may not perhaps lend themselves well to literary description, in the way that, for example, headache disorders, as almost purely subjective states, do. Nonetheless, some attempts have been made, examples of which are reviewed here.

Amnesia

Amnesia is, of course, a staple of Hollywood hokum (see Box: film buffs will surely be able to recall more examples); it is perhaps as popular a theme as the maverick cop or the wrongly accused. Loss of personal identity is a frequent aspect of these formulaic screen episodes of amnesia, and recovery an inevitable part of the filmic denouement, both features suggestive of psychogenic amnesia or fugue. In connection with loss of personal identity, boys of a certain vintage will recall that this is the fate which befell the quintessential toy doll action hero Action Man, sadly without recovery.

Amnesia as a feature of Alzheimer's disease has also attracted screen portrayals: Mia Farrow in *Forget Me Never* (1999), Julie Christie in *Away From Her* (2006), and perhaps most famously Judi Dench in *Iris* (2001), based on John Bayley's memoir of his wife Iris Murdoch's illness, the linguistic consequences of which have also been chronicled, more objectively, through analysis of novels written at three stages of the author's career.¹

Memory problems are also the defining characteristic of Mr Forgetful, number 14 in the Mister Men series of children's books by Roger Hargreaves: entrusted with a message, Mr Forgetful forgets it, in as much as he is only able to pass on a garbled version, only to recall the correct message later, suggesting his problem is one of retrieval rather than encoding and storage. In *Harry Potter and the Chamber of Secrets*, Gilderoy Lockhart, Hogwarts' Defence Against the Dark Arts teacher, threatens Harry and Ron with a 'Memory Charm' after admitting he was not in fact the perpetrator of the heroic deeds described in his books, but he is 'impaled upon his own sword', according to Dumbledore, when the charm backfires on the threshold of the Chamber of Secrets.²

An 'amnesia drug' given as a 'shot' is available at the Supreme Headquarters of the Alien Defence Organisation (SHADO) in the 1970s Gerry and Sylvia Anderson serial *UFO*, to be administered to individuals who unwittingly come into contact with aliens or SHADO. In the US TV serial *Monk*, about the detective Adrian Monk who has obsessive-compulsive disorder,



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the protagonist develops memory problems and goes missing after a head injury (season four: *Mr Monk Bumps His Head*). The police surmise amnesia (= loss of identity), but Monk's psychiatrist Dr Kroger states that what they suggest is very rare and thinks some kind of dissociative state more likely. Although Monk is apparently unaware of his identity, nonetheless his obsessive-compulsive traits persist, which allows him to solve a murder despite not knowing that he is a detective.

Other authors have been fascinated by memory, for example Jane Austen in *Mansfield Park*.^{3,4} As pointed out by Papanicolaou in his textbook on amnesia,⁵ the villagers of Macondo in *One Hundred Years of Solitude* by Gabriel Garcia Marquez suffer loss of memory for object names following an 'insomnia plague', in response to which they paste labels to objects bearing their names and functions.⁶ Poor sleep quality is of course not an uncommon accompaniment, and of probable aetiological significance, in memory clinic attenders complaining of poor memory, although in the case of Marquez the trope is probably symbolic rather than naturalistic.⁷

Aphasia

Wings by Arthur Kopit,⁸ initially conceived as a radio-play and later adapted for the stage, portrays a woman with post-stroke aphasia. Kopit was prompted to examine this issue when his father suffered a stroke, although the author describes the piece as 'speculation informed by fact' (xv) and not a case study. The central character, Emily Stilson, is in her 70s when she suffers a stroke. She has what appears to be a fluent aphasia with paraphasias and neologisms, which the author describes, evidently advisedly from the material contained in his introduction, as jargon (42). We hear her words from both her own and her medical auditors point of view, indicating the lack of self-monitoring of

verbal output. These phenomena are the result of a 'left cerebral infarction' (66), although interestingly the patient is left handed (57) which may complicate any simple interpretation. Mrs Stilson also seems to have an 'out of body experience' near the end of the play (74).

Kopit's work is also mentioned in the context of a (non-fictional) case of global aphasia characterised by recurrent utterances, sometimes also known as verbal stereotypies, stereotyped aphasia, or monophasia.⁹ This of course differs from the total anarthria of the locked-in syndrome reported from the inside, as it were, by Bauby.¹⁰

Apraxia

David Perkin identified a possible case of 'dressing apraxia' in Arnold Bennett's novel *Clayhanger* (1910) in the character of Darius Clayhanger, a portrait perhaps based on the illness of the author's father, Enoch Bennett. Perkin suggests a pathological diagnosis of Pick's disease confined to the parietal lobes in Bennett père, based on analogy with a case described by Lhermitte.¹¹ Certainly a corticobasal degeneration syndrome with the neuropathological substrate of tau-positive Pick body Pick's disease has been described on occasion.¹² However, the symptom of dressing apraxia is now regarded as a disorder of visuoperceptual function rather than an apraxia per se.

Difficulty dressing is one feature manifested by a character in the short story *No One's Guilty* by the Argentinian author Julio Cortázar (1914-1984), which has been interpreted as an example of ideomotor apraxia. Other symptoms mentioned may be thought representative of alien hand, dystonia, myoclonus and postural instability, which together have been suggested to constitute the gestalt of corticobasal degeneration.¹³

Agnosia

Previous articles in ACNR have alluded to possible cases of agnosia, specifically visual object agnosia in Anton Chekhov's short story *The Kiss* (1887),⁴ and prosopagnosia afflicting Lewis Carroll's Humpty Dumpty in *Through the Looking-Glass and What Alice Found There* (1872).¹⁴

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Some films featuring characters with amnesia/memory loss

Shattered (1991). Tom Berenger: car crash, coma, memory erased, unfaithful wife, torrid affair, etc, etc

The Long Kiss Goodnight (1996). Amnesiac suburban housewife Samantha, aka Charly (Geena Davis), was a ruthless assassin: "Like Charly's alter ego .. you may have trouble remembering what happened once its all over" (Time Out).

Jackie Chan's Who Am I? (1998). Any more explanation required??

Memento (2000). Shelby (Guy Pearce) suffers from a kind of memory loss whereby he remembers life before the murder of his wife but is unable since then to recall anything for more than a few minutes.

Santa Who? (2000). Santa (Leslie Nielsen) suffers amnesia after crashing his sleigh into the car of a Scrooge-like TV reporter.

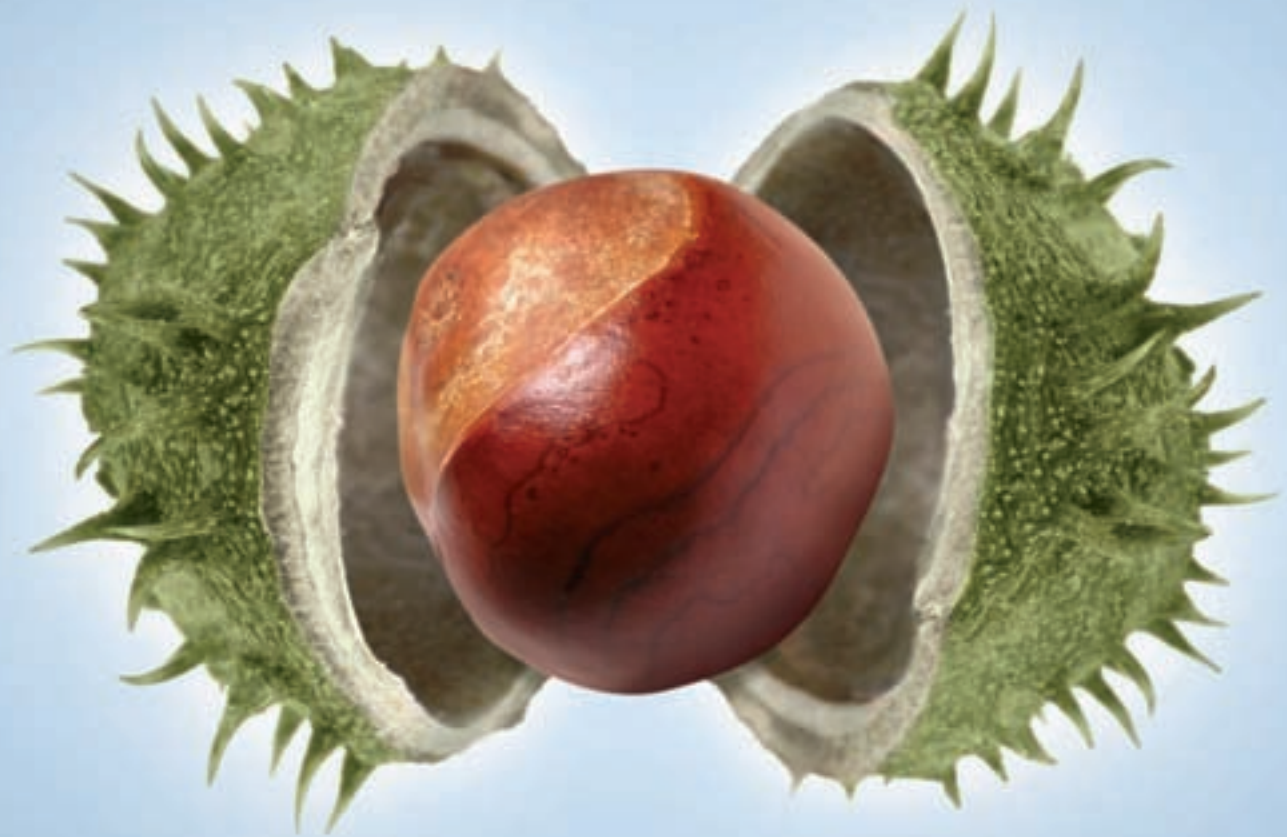
The Bourne Identity (2002). Amnesiac (Matt Damon) was deadly CIA assassin, now the target of his former employers; memory still troubled in **The Bourne Supremacy** (2004).

Blind Horizon (2003). Amnesiac (Val Kilmer) believes US president in peril.

Gothika (2003). Psychiatrist (Halle Berry) develops amnesia after a car crash, then is incarcerated in her own hospital accused of murdering her husband. An every day tale of psychiatry practice?

50 First Dates (2004). Amnesiac Lucy (Drew Barrymore) must be wooed afresh each day by would-be Don Juan (Adam Sandler).

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Date of revision of text: January 2008. Xeomin® is a registered trademark of Merz Pharmaceuticals GmbH. **References:** 1. Benecke R *et al.* Neurology 2005; 64: 1949-1951. 2. Roggenkämper P *et al.* J Neural Transm 2006; 113: 303-312. 3. XEOMIN® protein load. Data on File, Merz Pharma UK Ltd. 4. Jost WH *et al.* Drugs 2007; 67(5): 669-683. 5. XEOMIN® Summary of Product Characteristics. ¹Allergan Botulinum neurotoxin type A. **Date of preparation of item:** January 2008. 1012e/XEO/NOV/2007/BB

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Movement Disorders in India

The ancient texts of the Indian system of medicine 'Ayurveda', describes Parkinsonism and tremors as early as 5000-3000 BC.¹

Parkinsonism

The Ayurvedic physician, Charaka, was possibly the first to describe Parkinson's disease (PD) in his treatise "Charaka Samhitha" where he called it 'Kampavata', literally meaning 'tremors of neurological origin'. Interestingly, the treatment recommended in Ayurveda for PD is the seeds of *Mucuna Pruriens* whose extract contains levodopa. All this was known much before James Parkinson described this disease in modern times.

The prevalence of PD in Indians is lower than people of European origin. Parsis who immigrated to India centuries ago from Persia have a much higher prevalence of PD than the Indians.² A recent epidemiological study from Kolkata showed a low prevalence (Crude Prevalence: 45.8 and Age Adjusted Prevalence: 71.6 per 100,000) of Parkinsonism.³ On the contrary, the prevalence of PD in Anglo-Indians, a mixed race from marriage between a European man and an Indian woman is about 40% lower than the prevalence in the Caucasian population.⁴

Normal Indians have 40% fewer melanised nigral neurons than British Caucasians and these neurons are not lost with increasing age.⁵ The number of melanised nigral neurons between the British and Nigerians did not differ significantly suggesting that factors other than neuronal numbers contribute to differential susceptibility to PD between non-white and white races.⁶

Genetic studies in familial PD have shown that alpha-synuclein,⁷ Parkin,⁸⁻¹¹ LRRK2,¹⁰ PINK and DJ-1 mutations occur in a small number of Indian patients. SCA2 commonly causes ataxia in the Indians but Ragothaman et al have described a family with homozygous SCA2 mutation, who presented as levodopa responsive parkinsonism. However, unlike the ataxic phenotype that have slow saccades, they had normal eye movements. These patients develop motor fluctuations and dyskinesia, hence early in the illness they can be mistaken as PD. Furthermore these SCA2 patients with parkinsonism develop slow saccades, psychosis and dementia about six years after disease onset.¹²

Manganese-induced Parkinsonism is common in the manganese mine workers in India. These patients typically walk on their toes and fall frequently as they have severely impaired postural reflexes. They typically have a pathological laughter and deep pigmentation of gums, palate and uvula, and their parkinsonism does not improve with levodopa.^{13,14} Bhatt et al reported parkinsonism on exposure to household pesticides.¹⁵ In Japanese encephalitis-endemic regions, parkinsonism occurs in ~80% of patients during the acute illness but a long-term follow up showed that it persists in only a few adults, whilst in children they develop dystonia. JE antibodies and antigen were absent in the CSF of patients who developed these movement disorders, showing that the virus

does not remain in the nervous system. These patients do not improve with levodopa.¹⁶

Surgery was the treatment of choice for PD before levodopa was introduced. In 1963, Prof Varma attempted to lesion the ventrolateral thalamic nucleus by injecting alcohol via needle inserted through the foramen ovale to control tremors.^{17,19} Using this outpatient procedure he stopped advancing the needle when the tremors stopped, thinking he had reached the planned target, the VL thalamic nucleus. However, when these lesions were mapped using the Schaltenbrand atlas, they were located in the subthalamic nucleus. This anatomical localisation was confirmed at autopsy, using a stereotaxic atlas and, recently, using MRI.¹⁸

In the modern era, surgical treatment for advanced PD has resurfaced as a treatment and Doshi and Bhatt reported depression following deep brain stimulation of the subthalamic nucleus possibly due to spread of the stimulation to the limbic region of this structure. Kishore et al have also observed motor improvement following stereotactic lesions to treat levodopa-induced dyskinesia but this is dependent on the volume of lesions in the ventral globus pallidus and suggested different anatomical substrates might be involved in controlling 'off signs' and dyskinesia.

Behari et al evaluated the quality of life (QoL) in PD patients and observed that female gender, depression, reduced independence, higher levodopa dose (>400 mg/day) and UPDRS scores were associated with worse QoL.¹⁹

Medicines and surgical interventions have improved the quality of life of PD patients but are still expensive and unaffordable to many living in developing countries. Managing PD in Indians where only 3% have health insurance is a challenge. Indian patients spend nearly 40% of their average gross income to buy medicines and despite the costs of treating PD in India being lower than in developed nations, optimal treatment is still out of reach for many Indian patients.²⁰

Chorea

Rheumatic fever is still common in India and chorea still occurs frequently. The prevalence of Huntington's disease (HD) in Indians is not known, it occurs in 1.75 per 100,000 population of Indians living in the United Kingdom.²¹ Salem et al, found that the distribution of alleles (D2642 and D4S127) in Indian HD patients are similar to West European populations and suggest that this admixture possibly occurred when British troops were located in South India during various wars.²²

Wali et al reported a large South Indian family with autosomal dominant paroxysmal kinesogenic choreathetosis (PKC) and onset in early childhood. Choreathetosis was precipitated by activities such as hyperventilation (46%), swimming (23%), exposure to cold (30.8%) and prolonged exercise (23%). This family has a second PKC mutation localised to the long-arm of chromosome 16q13-q22.1.²³



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Patients in India present with a wide variety of movement disorders and these pose challenges, especially in terms of treatment, given the therapeutic limitations due to a near total lack of health insurance

Dystonia

Naiya et al evaluated DYT1 mutations in patients with primary dystonia from eastern India and found three reported and two novel mutations suggesting these mutations rarely cause dystonia in Indians.²⁴ Behari et al identified chewing betel nut with tobacco increased the risk of developing Meige syndrome.²⁵ Ragothaman et al reported task specific dystonia while playing the Indian percussion instruments 'tabla' and wind instrument 'Nadaswaram'.²⁶ Dystonia due to Niemann-Pick type C, GM1 gangliosidosis and Hallervorden Spatz have been reported.²⁷⁻³⁰ GM1 gangliosidosis patients have generalised dystonia with prominent facial dystonia, severe dysarthria and normal eye movements, with Gaucher-like foam cells in the marrow and their MRI shows typical symmetrical putamen lesions. The diagnosis is confirmed by deficiency of beta-galactosidase. Dystonia following Japanese encephalitis occurs in children, and typically develops one to three weeks after the acute illness. Some patients relapse after a partial recovery suggesting a biphasic illness pattern. During the second phase, patients develop behavioural changes, dystonia, peri-oral dyskinesia and drooling.³¹

Tremors

Infantile tremors syndrome has been described in Indian infants from poor, malnourished families. Tremors are generalised and are prominently seen in distal extremities, appearing suddenly after a brief febrile illness lasting for six weeks. Frontal lobe biopsy showed features of encephalitis and meningoencephalitis but CSF examination is normal and negative for common viruses.

Wilson's Disease

Wadia and Dastur reported that 30% of Wilson's disease cases in India

present with osteomalacia.^{32,33} Wilson's disease is though a common cause of dystonia and other movement disorders in Indians. Patients present with neurological deficits (69%) in the first or second decade of life and ~15% have hepatic dysfunction.³⁴ Autopsy shows caudate atrophy (100%) or central pontine myelinolysis (83%)³⁵ and treatment with D-Penicillamine can initially worsen the neurological deficits in ~50% of patients.

Myoclonus

Subacute Sclerosing Encephalitis (SSE) still unfortunately occurs and is a common cause of myoclonus as measles vaccination is still not mandatory and is often unaffordable. It can occur in children and adults. Adult SSE occurs at a mean age of 20.9 years with the patients presenting with generalised myoclonus, behavioural changes, seizures, cognitive decline, visual impairment and extrapyramidal features like parkinsonism and dystonia. SSE still poses diagnostic challenges for clinicians in India.³⁶ Neuronal ceroid lipofuscinosis is another cause of myoclonus (83.8%) in children and is associated with regression of milestones (83.3%), chorea (50%), visual impairment (42%), ataxia (33.3%) and abnormal behaviour (17%). Eye examination shows optic atrophy (50%), macular degeneration (33.3%) and retinitis pigmentosa (8.3%). Skin biopsy shows characteristic PAS and Luxol Fast Blue (LFB) positive, autofluorescent intracellular ceroid material in neurons and astrocytes.³⁷

Conclusion

Patients in India present with a wide variety of movement disorders and these pose challenges, especially in terms of treatment, given the therapeutic limitations due to a near total lack of health insurance.

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ABNT - Message from the Chair

The ABN Spring Meeting was held jointly this year with the British Society of Clinical Neurophysiologists, at Croke Park Stadium in Dublin, and featured a programme that is increasingly geared towards education, and the needs of trainees. Further details of this meeting will be reported separately in ACNR, but I'd like to draw your attention to the ABNT forum that was held at the close of the meeting.

In the past this has been poorly attended, due partly to an unappealing 7.30am slot! Attendance this year was much better, attracting between 30 and 40 trainees, and a number of related issues were discussed.

European Working Time Directive (EWTD)

The UK will move to a 48-hour working week in August 2009, potentially causing huge problems for the NHS. In neurology, some centres have already moved to a partial shift system, where others are trying to maintain an on-call system: to be compliant with EWTD, most on-call rotas need between 10 and 12 middle graders, with obvious funding implications. Although the Tooke Report implied that EWTD may be enforced with variable efficiency in the future, it is European law at present, and UK employment legislation theoretically has to comply. An employee opt out is a theoretical possibility, and alternative plans exist (such as the Barbados Plan, devised by Remedy UK); both leave trainees wide open to harassment and undue pressure from managers, and have significant logistical difficulties. From hospitals where trainees already have to work night shifts (either neurology only, or hospital at night), with compensatory time off day duties, there are already concerns that training is suffering. Although training is meant to be competency based, this is still blue-printed onto the reasonable amount of time that an individual can be expected to take to acquire that competency, i.e. is still time based in reality.

Post-CCT Fellowships

Context

Last year, the MMC Programme Board invited bids from all specialties for funded post-CCT fellowships, lasting one year. Their stated purpose was to provide extra training not covered in standard curriculum, but additionally they could help with the 'bulge' in trainee numbers, allowing trainees to vacate their numbers early, granting a salary for a year, and assisting in number recycling. Approximately 100 positions have been awarded to the applying specialties – the bulk of these are in the surgical specialties, but O&G, anaesthetics and psychiatry have also been reasonably successful, and JRCPTB has been awarded a few for the medical specialties. Some of the applications are a bit opaque – the skills they are meant to develop are not clearly super-specialist in some cases, and consultant jobs for these highly specialised trainees are still lacking!

Completely independently, the ABN Training and Education Committee have opened discussions with several of the major neurological charities to develop sub-

specialty fellowships in neurology. Although these are in the very early stages of development, and their future prospects are by no means clear, they are probably going to be shorter (around six months), and are designed to provide sub-specialty training in centres of excellence. There is scope to develop them further, including more widespread implementation, but funding arrangements are the obvious limiting factor. The background to, and pros and cons of post-CCT fellowships are summarised in Figure 1.

A potential solution

Opinion was canvassed from trainees with regard to the above issues, and discussion ranged around possible solutions. In general, it was felt that widespread implementation of Post-CCT fellowships in neurology was not in the best interest of patients or training, but that a more limited introduction would be of definite benefit to individual trainees. There was significant support from trainees for a lengthening of training to maintain CCT quality in the face of reduced experience due to EWTD, with a recognition that neurology should continue to be a consultant-led service, and that there was not a place for an extra grade between StR and Consultant. In this context, could subspecialty training could be incorporated as part of extra training instead of as a 'bolt-on' module?

The ABNT urgently needs to know more about your opinions on this – we will be discussing our concerns further with TEC and the Neurology SAC, and it's important that we represent you properly during this process. Please get in touch with your views via the ABN Offices (see contact details).

Next Meeting

The next ABNT meeting will be on Wednesday 10th September in Aviemore.

Andrew Kelso is Chair of the ABNT. He is an SpR in Neurology in Edinburgh, with a special interest in epilepsy. He is also a member of the BMA Junior Doctors Conference Agenda Committee, Junior Doctors Committee and Scottish Junior Doctors Committee.

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Figure 1
Post-CCT fellowships
The need

Shorter training
Perhaps no research experience?
Increasingly competitive job market
Recognition that neurology increasingly sub-specialised
Potential shortage of consultant jobs
PMETB imposed restrictions on dual accreditation with neurophysiology

Pros

Extra training
Benefits of national expertise
Improve CV

Cons

Non-standard jobs – national terms and conditions of service may not apply
No clearly defined training outcome
"Yellow box" (sub-consultant grade)
threat Loss of 6 month period of grace



Additional web content www.acnr.co.uk

See the website for an additional Case Report:

A Case of Isolated Central Nervous System Vasculitis

by Kalra S, Harries S, Gutowski NJ

MOVING YOUR PATIENTS

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(natalizumab)

* There have been no head to head prospective studies to compare TYSABRI and other MS therapies

** Patients with ≥ 2 relapses in previous year and ≥ 1 Gd+ lesion at baseline

References:

1. Galeffi SL, et al. *Arch Intern Med* 2002; 162: 2161–2169.
2. Polman CH, et al. *NEJM* 2006; 354(9): 899–910.
3. TYSABRI SmPC, Biogen Idec Ltd.
4. TY00-032, Data on file. Biogen Idec Ltd.

Date of preparation:
January 2008
TY00-PAN-22968

Prescribing information: TYSABRI® (natalizumab)

Presentations: 300 mg concentrate for solution for infusion. Colourless, clear to slightly opalescent solution. Each ml of concentrate contains 20 mg of natalizumab. When diluted, the solution for infusion contains approximately 2.6 mg/ml of natalizumab.

Indications: Single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following patient groups: patients with rapidly evolving severe relapsing remitting multiple sclerosis or patients with high disease activity despite treatment with a beta-interferon. **Dosage and Administration:** The recommended dosage is 300 mg administered by intravenous infusion once every 4 weeks. The diluted solution is to be infused intravenously over 1 hour at a rate of approximately 2 ml/minute and patients are to be observed during infusion and for 1 hour after the completion of the infusion for signs and symptoms of hypersensitivity reactions. TYSABRI® therapy is to be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions, in centres with resources for management of hypersensitivity reactions and timely access to MRI. Continued therapy must be carefully reconsidered in patients who show no evidence of therapeutic benefit beyond 6 months.

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Contraindications: Hypersensitivity to natalizumab or to any of the excipients, progressive multifocal leukoencephalopathy (PML); patients with increased risk of opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies, e.g. mitoxantrone or cyclophosphamide); combination with beta-interferons or glatiramer acetate; known active malignancies; children and adolescents. TYSABRI® is not recommended for use in patients aged over 65 years.

Special Warnings and Precautions; CNS: Use of TYSABRI® has been associated with increased risk of progressive multifocal leukoencephalopathy (PML). Before initiation of treatment with TYSABRI®, an MRI image of the patients should be available 3 months within starting treatment. Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs suggestive of PML. If new neurological symptoms occur, further dosing should be suspended until PML has been excluded. If the symptoms are suggestive of PML, or if any doubt exists, further evaluation, including MRI scan (compared with pre-treatment MRI) and repeat neurological

assessments should be considered. Once PML has been excluded, dosing of TYSABRI® may resume. If patients develop PML, the dosing of TYSABRI® must be permanently discontinued.

Other Opportunistic Infections: Other opportunistic infections have been reported with use of TYSABRI®. If an opportunistic infection is suspected, dosing with TYSABRI® is to be suspended until such infection can be excluded through further evaluation. **Hypersensitivity:** Hypersensitivity reactions have been associated with TYSABRI®, including serious systemic reactions. These reactions usually occur during the infusion or up to 1 hour after completion of infusion. If a hypersensitivity reaction occurs TYSABRI® must be permanently discontinued. **Immunogenicity:** In the case of disease exacerbations or infusion related events the presence of antibodies should be evaluated. Treatment should be discontinued if persistent antibodies develop. **Stopping Therapy:** If therapy is discontinued be aware that TYSABRI® has pharmacodynamic effects for up to 12 weeks. **Pregnancy and lactation;** if patients become pregnant while taking TYSABRI®, discontinuation of TYSABRI® should be considered. Patients receiving TYSABRI® should not breastfeed their infant. **General:** Physicians must discuss the benefits and risks of TYSABRI® therapy with the patient and provide them with a Patient Alert Card. Patients should be instructed that if they develop any infection they should inform their physician that they are being treated with TYSABRI®. **Drug interaction:** Combination with beta-interferons or glatiramer acetate is contraindicated. The safety and efficacy of TYSABRI® in combination with other immunosuppressive and antineoplastic therapies have not been fully established. Concurrent use of these agents with TYSABRI® may increase the risk of infections including opportunistic infections. No formal interaction studies have been conducted with TYSABRI® in humans. **Undesirable Effects:** The most commonly reported symptoms are: **Infections and infestations:** Urinary tract infection, nasopharyngitis. **Immune system disorders;** urticaria. **Nervous system disorders;** headache, dizziness. **Gastrointestinal disorders;** vomiting, nausea. **Musculoskeletal and connective tissue disorder;** arthralgia. **General disorders and administration site conditions;** rigors, pyrexia, fatigue. Other less common events include: hypersensitivity reactions, infusion reactions, PML, other opportunistic infections, immunogenicity. For further information regarding adverse events please refer to the Summary of Product Characteristics. **Legal Classification:** POM. **Pack size:** 1 vial/pack. **NHS Price:** UK; £1130/vial, Ireland; €1636.85/vial. **Package Quantities:** 300 mg/15 mL. **Product Licence Number:** EU/1/06/346/001. **Product Licence Holder:** Elan Pharma International Ltd., Monkstown, Athlone, County Westmeath, Ireland. **Date of last revision of Prescribing Information:** August 2006. Please refer to the Summary of Product Characteristics for further information.

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Prevention and Treatment of Vasospasm Following Subarachnoid Haemorrhage

Delayed ischaemic neurological deficit (DIND) is a major cause of morbidity and mortality following aneurysmal subarachnoid haemorrhage (SAH). This condition is potentially preventable and treatable. The pathogenesis of the condition is unclear although vasospasm is of paramount importance. The diagnosis of DIND secondary to vasospasm remains contentious and is reliant upon clinical status and cerebral imaging techniques. Therapeutic interventions require high dependency care and are not always effective. In this article the historical recognition of cerebral vasospasm is described, the broad pathophysiological mechanisms that may be involved are outlined and the management options are reviewed.

Introduction

In 1949, the Australian neurologist Edward Graeme Robertson hypothesised that arterial spasm may be responsible for post-subarachnoid haemorrhage (SAH) cerebral infarction.¹ In 1951, Denny-Brown attributed post-SAH deterioration to cerebral vasospasm.² The same year two Americans, Ecker and Riemenschneider, demonstrated angiographic spasm in six patients with aneurysmal SAH.³ In the mid 1960s Stornelli and French reported that angiographic vasospasm indicated a poor prognosis.⁴ Allcock and Drake conducted a thorough angiographic examination of 83 patients before and after treatment of their intracranial aneurysms and found evidence of vasospasm in over 40% of patients.⁵ They reported that patients with vasospasm were more likely to have a poor outcome and concluded that arterial spasm was the main cause of morbidity and mortality in patients with ruptured intracranial aneurysms. The time course of vasospasm was shown by Fischer, who reported that neurological deterioration occurred in one third of SAH patients, and was maximal between days 2 and 4 following the bleed.⁶

In 1970 the normal sizes of the carotid artery and the major cerebral branches were reported enabling objective assessments of vasospasm.⁷ Weir et al. reported that the ratio of intracranial to extracranial vessel diameter was reduced in some subarachnoid patients.⁸ They also demonstrated that this vasospasm was maximal between days 4 to 8 following the initial bleed and had resolved by day 12. In the International Cooperative Study, Kassell et al. showed that the clinical and radiological features of vasospasm were discordant. Delayed ischaemic neurological deficits (DINDs) occurred in 30% of patients whereas angiographic vasospasm was observed in up to 70% of cases.⁹ In addition DINDs were also noted to occur in the absence of angiographic vasospasm in some cases.

Epidemiology

In the UK aneurysmal subarachnoid haemorrhage has an incidence of approximately 8-10 per 100,000 per year, although population-based studies suggest that the incidence may be higher.¹⁰ DINDs are a major cause of morbidity and mortality following subarachnoid haemorrhage.^{11,12} National Audit Data on 2420 SAH patients found no statistically significant difference in the incidence of DINDs between coiled and clipped patients.¹² Even though The International Subarachnoid Aneurysmal Trial (ISAT) provided Grade 1 evidence for improved one year outcome for coiling over clipping of small anterior circulation aneurysms, a recent meta-

analysis found that there was no difference in the incidence of DINDs between coiling and clipping.^{13,14}

Pathophysiology

DINDs may be due to focal or global ischaemia and do not necessarily occur in arterial territories directly related to the site of the aneurysmal rupture. Whether the ischaemia is due to spasm of the large arteries, microvascular insufficiency or some other unelucidated mechanism is uncertain. Most pharmacological research has focused on the role of vasospasm in causing DINDs. It appears that the initial trigger for vasospastic ischaemic deficits is leakage of blood into the subarachnoid space. Fisher et al. noted that vasospasm appears to be associated with the blood load in the subarachnoid space.¹⁵ Oxyhaemoglobin and platelets have been implicated as molecular agents that must be present in the subarachnoid space in order for vasospasm to occur.^{16,17} Various molecular mechanisms have been implicated in the development of DIND downstream of this 'blood-trigger'. These include reduced endothelial synthesis of the vasodilator nitric oxide (NO); reduced vasodilatory action of nitric oxide; and increased release of the vasoconstrictor endothelin-1 (ET-1). The possible imbalance of NO and ET-1 in mediating the protein kinase C dependent contractile system in vessel walls has provided potential new therapeutic strategies by means of NO activators/donors and ET-1 antagonists. In addition free radical generation may be a contributing factor to the pathogenesis of DINDs (Figure 1).¹⁸⁻²⁰

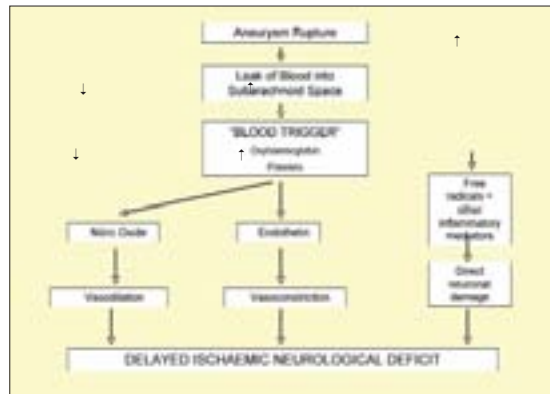


Figure 1. Pathophysiology of vasospasm.

Assessment of a patient with a DIND

Clinical assessment, transcranial Doppler ultrasonography (TCDs), cerebral perfusion imaging and digital subtraction angiography (DSA) are all used in the clinical arena to assess cerebral blood flow parameters in patients with a DIND.

Clinical assessment

Clinical assessment is a robust method of assessing the functional integrity of cerebral tissue and is carried out by careful close monitoring of neurological status. A diagnosis of DIND is made when other possible causes of neurological deterioration such as rebleeding, hydrocephalus, seizures and electrolyte abnormalities have been excluded. Neurological deterioration may include focal deficits such as unilateral limb weakness or dysphasia, or global impairment such as confusion or



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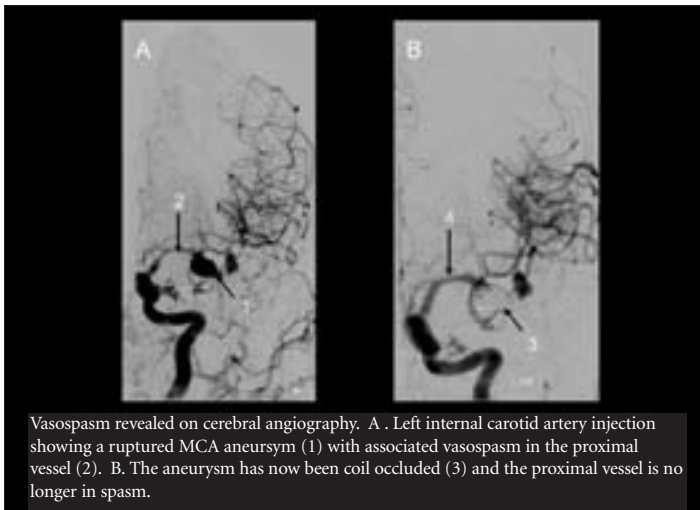


Figure 2. Vasospasm revealed on cerebral angiography.

DIAGNOSIS & MANAGEMENT OF PATIENTS WITH VASOSPASM WITH A SECURED RUPTURED ANEURYSM	
Diagnosis	
1) Clinical evidence of vasospasm	
<ul style="list-style-type: none"> • Focal neurological deficit in the absence of another underlying cause • CT head to exclude rebleed prior to treatment • Exclude electrolyte abnormalities 	
2) Angiographic evidence of vasospasm at the time of coiling procedure or diagnostic angiography	
3) Patients at risk of vasospasm	
<ul style="list-style-type: none"> • High Fisher grade 3 on CT • EEG change/epilepsy fit • Central cell swelling 	
4) CT perfusion, TCDs, consider cerebral angiography if interventional treatment proposed	
Management	
1) HDU monitoring: arterial line, CVP, 4 hourly ABC, twice-daily US&Mg, daily urine Na ⁺ /hemat, daily TCDs	
2) HHH Therapy	
Hypertension	• BP parameters set according to neurological improvement, may need inotropic support
Hypervolaemia	• CVP 8-10 cmH ₂ O in spontaneously ventilating patients
	• Background crystalloids 120ml/hr • Fluid bolus as required
	• May need to consider hypertonic saline
Haemodilution	• Aim for haematocrit 30-35%
3) Continue prophylactic measures with nimodipine	

Figure 3. Diagnosis and management of patients with vasospasm with a secured ruptured aneurysm.

increased drowsiness. Several risk factors have been identified which independently predict symptomatic vasospasm. These include blood load in the basal cisterns, a Glasgow Coma Scale score of less than 14 at presentation and rupture of anterior cerebral (ACA) or internal carotid (ICA) aneurysms.²¹ Raised troponin levels and the presence of cerebral salt wasting syndrome may also be risk factors for the development of vasospasm.^{22,23}

Transcranial Doppler (TCD) ultrasonography

Blood flow velocity through the cerebral arteries is inversely proportional to arterial diameter. TCD is used to measure flow velocity and thereby indirectly assess the severity of vasospasm.²⁴ However, one of the main conceptual difficulties with TCDs is that flow velocity may be raised due to increased flow (hyperaemia) or arterial narrowing (vasospasm). To help distinguish vasospasm from hyperaemia the Lindegaard ratio of middle cerebral flow velocity to extracranial carotid flow velocity is used. A Lindegaard ratio > 6 represents severe vasospasm.²⁵ Lindegaard et al. also showed that MCA flow velocity > 200 cms⁻¹ was predictive of a 3-fold constriction in the diameter of the artery.²⁵

One of the criticisms of TCDs has been that they do not correlate with cerebral blood flow or perfusion as measured by modalities such as Xenon CT or PET scanning.²⁶ Despite the conceptual limitations of TCDs, there is good evidence to support their clinical application. Vora et al. compared MCA velocities with angiographic studies in 101 patients retrospectively and 44 patients prospectively and found that TCDs had positive predictive values of 87% for velocities >200 cms⁻¹

and negative predictive values of 94% for velocities <120 cms⁻¹.²⁷ One of the interesting findings of Vora et al's study was that the Lindegaard ratio did not alter the predictive value of TCDs. Fontanella et al. undertook a prospective study of 786 patients with anterior circulation aneurysmal SAH where any patient with a MCA velocity of > 120 cms⁻¹ underwent cerebral angiography. They reported that TCDs had a 97% predictive value in middle cerebral artery spasm.²⁸ TCD's have a distinct advantage over angiography in that they are less expensive, non-invasive and can be used at the bedside to monitor response to treatment. Certainly TCD's are user dependent and provide more reliable data if serial measurements are recorded in individual patients.²⁹ TCDs should be viewed as a useful adjunct in the management of DIND patients when used appropriately.

Cerebral perfusion imaging

The numerous modalities available include positron emission tomography (PET), xenon-enhanced computed tomography (Xe-CT), single-photon emission computed tomography, and CT-perfusion techniques. CT-perfusion is less time-consuming and more readily available and therefore appears set to become a widespread tool in the detection of early vasospasm.³⁰ Xe-CT scanning protocols are well described and can provide evidence of cerebrovascular reactivity if used in conjunction with CO₂ provocation testing. PET is not widely available but does help determine not only the cerebral blood flow in a DIND patient but also the oxygen uptake (oxygen extraction fraction) and cerebral metabolic rate (CMRO₂). Such studies assess the degree of coupling between CBF and brain metabolism and may provide an insight into the reasons for the discordance between the prevalence of angiographic vasospasm and DIND. Functional MR imaging is hampered to some extent by the restless nature of many of the patients with DINDs.

Digital Subtraction Angiography (DSA)

The evolution of non-invasive techniques to assess cerebral perfusion has reduced the utilisation of DSA to those cases where an endovascular therapeutic option is being pursued (Figure 2).

Management

Cerebral vasospasm results in altered autoregulation of cerebral blood flow and ultimately reduced cerebral perfusion resulting in ischaemic damage to the brain. Due to the delayed onset of vasospasm, prophylactic strategies may be effective. Therapeutic modalities have evolved that aim to reverse vasospasm and protect potentially ischaemic cerebral tissue (Figure 3).

Hypertensive, Hypervolaemic and Haemodilution (HHH-therapy)

Kosnik and Hunt were the first to report the effects of raising arterial pressure in cerebral vasospasm in 1974.³¹ They reported a series of seven patients in whom the neurological deficit was reversed promptly by the elevation of systemic blood pressure and found that infarction was prevented in some of these patients. Kassell et al. carried out a larger study in 1982 in which hypertensive therapy and intravascular volume expansion in a series of 58 patients permanently reversed neurological deficits in 47 patients and transiently reversed deficits in four patients.³² Since these early studies, HHH-therapy evolved with the inclusion of haemodilution to augment rheological properties of blood flow. Although HHH-therapy has not been examined with a randomised controlled trial, it has become the mainstay of medical therapy for the treatment of vasospasm and more recent investigations using cerebral monitoring support its continued use.³³ There is a lack of consensus as to how HHH-therapy should be achieved although monitoring of clinical condition, CVP measurement, arterial BP measurement and serial TCD measurements in a high-dependency setting are commonly employed. HHH-therapy is associated with significant complications including pulmonary oedema, myocardial ischaemia and electrolyte abnormalities including dilutional hyponatraemia.³⁴ Raab et al. have found that in poor grade subarachnoid patients the use of moderate hypertension, normovolaemia, and haemodilution may improve cerebral oxygenation but with less complications than aggressive hypertensive therapy.³³ The prophylactic use of HHH-therapy has not

been widely supported and preliminary trials have not shown any benefits.^{35,36} Hypotension and hypovolaemia should be avoided in all patients at risk of DIND. In future years functional imaging modalities and invasive cerebral tissue monitoring may lead to refinements in the optimisation of cerebral perfusion augmentation therapy.

Calcium antagonists

Allen et al. reported the first randomised, double-blind, placebo-controlled trial (RCT) of nimodipine.³⁷ They looked at prophylactic use of nimodipine for 21 days following aneurysmal SAH in 125 patients of good grade and found that nimodipine was effective in reducing neurological deficits. Pickard et al. reported the largest RCT in 1989 which included 554 SAH patients.³⁸ Follow-up at 3 months showed that 21 days of nimodipine treatment was effective in reducing the incidence of cerebral infarction by one-third (22% with nimodipine compared to 33% with placebo) and also improved overall clinical outcome. At least five other RCTs of prophylactic nimodipine have been carried out. A meta-analysis concluded that the effectiveness of nimodipine had been well demonstrated and supported routine prophylactic nimodipine administration.³⁹ Although other calcium antagonists such as nicardipine have been investigated a systematic review of 27 RCTs concluded that there was only evidence to support the prophylactic use of nimodipine.^{40,41}

Magnesium sulphate

Magnesium is a cerebral vasodilator and may also have neuroprotective effects by preventing influx of calcium into injured neurons via excitatory amino acid receptor blockade. The preliminary results of the IMASH trial showed that a 14 day infusion of magnesium sulphate may reduce the incidence of symptomatic vasospasm and justifies the continuation of the study to try and establish a clinically useful prophylactic treatment.^{42,43}

Statins

Statins are known to increase the eNOS activity and theoretically, therefore, may reduce vasospasm. Two small randomised studies have demonstrated a reduced incidence of vasospasm in patients treated with simvastatin or pravastatin.^{44,45} In the pravastatin study the incidence of TCD detected vasospasm was reduced by 32% with a reduced incidence of DIND and mortality. At six months beneficial effects on physical and psychological aspects of functioning were reported.⁴⁶ A multicentre randomised controlled trial looking at the potential benefit of simvastatin (40mg for 21 days) in aneurysmal SAH (STASH) is underway.⁴⁷

Erythropoietin

Erythropoietin (EPO) has been found to have neuroprotective effects in the central nervous system.⁴⁸ It is unclear how this effect is exerted although there is evidence to suggest activation of endothelial nitric oxide synthase

(eNOS) occurs.⁴⁹ However, a double-blind randomised trial of EPO versus placebo in 73 patients failed to show any beneficial effect in cerebral vasospasm.⁵⁰

Endothelin-receptor antagonists

There has been much interest in agents which will redress the putative imbalance in the control of PKC-dependent contractile mechanisms in vasospasm. These include NO donors and ET-1 antagonists. The preliminary results of a randomised clinical series treated with the ET-1 antagonist clazosentan appears to show improvements in CBF in patients with established vasospasm.⁵¹ Further work is required in this area.

Pharmacological implants

Aneurysm surgery provides an opportunity to investigate the effects of local pharmacological treatments as prophylaxis against vasospasm. No beneficial effects were reported in the only randomised controlled trial published using a thrombolytic agent.^{52,53} Kasuya et al. reported the effect of placing prolonged-release nicardipine implants in the basal cisterns after aneurysm clipping. Although initial results are promising for the proximal vessels, the effect is less on the more distal cerebral circulation and requires further investigation.^{54,55}

and colforsin daropate carries the theoretical benefit of delivering a high dose of vasodilator directly to the resistance vessels, clinical studies have shown vasodilatation to be transient and without sustained benefit.^{61,62} In addition vasodilatation may cause an elevation of intracranial pressure.⁶³ Such strategies remain experimental.

Conclusion

DINDs following subarachnoid haemorrhage are devastating and are associated with a high morbidity and mortality rate. The delayed-onset of this disorder which appears to be associated with vasospasm and impaired cerebral perfusion continues to stimulate clinicians and neuroscientists to find preventative and therapeutic treatment strategies. There is no consensus regarding the underlying pathology or the optimal methods to diagnose and treat DINDs. Effective management is demanding on resources and involves input from neurosurgical, neuroradiological and neurocritical care specialties. A 'same-hymn-sheet' approach may be required within individual centres in order to establish consistency of investigation and treatment so that new therapeutic modalities can be accurately assessed. Cerebral vasospasm remains a challenge for all clinicians interested in reducing the adverse outcomes associated with subarachnoid haemorrhage.

Clinical vasospasm is a diagnosis of exclusion

Endovascular therapies

Endovascular techniques employed in the therapy of vasospasm include mechanical dilatation of major cerebral arteries using transluminal balloon angioplasty (TBA) and local injection of vasodilator agents. TBA was first reported in 1984 in a series of 33 SAH cases.⁵⁶ Since that time defined criteria to determine the applicability of endovascular techniques have been described.⁵⁷ These include the absence of an established infarct on CT scanning, the persistence of neurological deficits despite medical management (HHH-therapy) and angiographic evidence of vasospasm in a distribution consistent with the neurological deficit.

Two large studies support a role for TBA in the management of vasospasm.^{58,59} In both of these TBA improved angiographic spasm in over 90% of cases and improved clinical status in 30-40% of patients. However the complications of TBA include vessel rupture which has been reported at a rate of 4%.⁶⁰ Since many radiologists consider any beneficial effects of TBA to be short-lived the technique has not been universally adopted. A peer reviewed publication of the Balloon Prophylaxis of Aneurysmal Vasospasm Study is awaited.

Although the intra-arterial injection of vasodilators such as papaverine, nimodipine, nicardipine, verapamil, milrinone, fasudil,

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Spontaneous Anterior Intracranial Artery Dissection: An Important Cause of Stroke in Young People

Intracranial artery dissection (IAD) is rarely reported and possibly underdiagnosed. We present a case of spontaneous right middle cerebral artery dissection causing repeated small ischaemic lesions in the right hemisphere, presenting with frequent, mild intermittent left-sided neurological symptoms and right-sided headache in a 28-year-old female. The presentation was subtle and diagnosis unusual, highlighting the importance of considering dissection as a cause of neurological deficits with associated headache in young people. Contrast-enhanced magnetic resonance angiography (CE-MRA) is fast and effective and is the recommended imaging modality for detecting vascular pathology.

Introduction

IAD causing ischaemic stroke or subarachnoid haemorrhage is rare but possibly under-reported, with only 10-20 documented cases to date.¹⁻³ The mean reported age of IAD is 25 years,⁴ however IAD has also been reported in children.^{5,6} Predisposing risk factors include; preceding trauma and collagen disorders such as fibromuscular dysplasia, cystic medial necrosis,⁷ Moya Moya disease, Marfan's syndrome and Ehlers-Danlos syndrome type IV. Common vascular risk factors (hypertension, smoking, diabetes mellitus, hyperlipidaemia and oral contraceptives) have also been implicated in the pathogenesis of arterial dissection. There are individual case reports of intracranial dissection in the context of orgasmic headache,⁸ post-coitus⁹ and post partum,¹⁰ but in the majority of cases no cause is found.

Anterior intracranial dissections typically present with ipsilateral headache and a contralateral neurological deficit with altered consciousness. Presentation with subarachnoid bleeding secondary to intracranial dissection is more common in the posterior circulation. Pseudoaneurysm formation is another complication resulting from blood tracking through the media to the subdural layer and causing dilatation of the outer wall of the vessel, which tends to occur more commonly in the posterior circulation but has also been known to occur in the anterior circulation.¹¹ Previously, those reported in the literature have usually presented with significant morbidity and the diagnosis in some has only been realised at post-mortem. Those presenting with mild transient ischaemic attacks are vanishingly rare, or perhaps go undiagnosed.

The diagnostic imaging modalities for intracranial artery dissection include formal catheter digital subtraction angiographic techniques (DSA). Less invasive techniques include conventional MRA revealing a 'rat's tail' or 'string sign' or T1-weighted axial MRI revealing a double lumen or intramural thrombus.¹² Contrast-enhanced MRA can be performed efficiently in a single breath hold and is comparable to DSA in providing diagnostic information of body arteries¹³ and provides more extensive and accurate information than conventional MRA. Computerised tomography angiogram (CTA) can also be an adequate fast screening modality for cerebral artery pathology, especially with modern 3-D digital subtraction techniques.

We present a case of spontaneous right middle cerebral artery dissection, which resulted in repeated small cerebral ischaemic insults in a young female. This presented

with relatively subtle symptoms and signs, which could have been easily missed if not considered in the differential diagnosis. See Table 1 for summary characteristics of intracranial dissections.

Table 1: Key points in intracranial artery dissection.

1. An important cause of TIA/stroke in young people (mean age 25 years old).
2. Pain (unilateral headache) is a predominant presenting symptom.
3. Intracranial artery dissection is less common than extracranial artery dissection.
4. Posterior circulation (vertebrobasilar artery) dissection is more common and more likely to be associated with subarachnoid bleeding than anterior circulation dissection.
5. Risk factors for cerebral artery dissection include trauma, collagen disorders (fibromuscular dysplasia, cystic medial necrosis, Marfan's syndrome, Ehlers-Danlos syndrome type IV), and common vascular risk factors (hypertension, smoking, diabetes mellitus, hyperlipidaemia and oral contraceptives).
6. Contrast-enhanced MRA is the most efficient imaging modality of choice with comparable diagnostic yield to formal angiography.
7. Treatment options include surgery, stenting, anticoagulation and antiplatelets, although evidence for favouring one option over another is not yet available.

Case report

A 28-year-old female presented with a one month history of progressive left sided sensory symptoms. This started with intermittent numbness in her left hand, involving the thumb and first two fingers, followed by left facial numbness and then left leg numbness. These sensory symptoms would last a few minutes at a time over a period of several weeks. At the time of initial consultation, she had mild weakness of her left leg and face. The patient also described a continuous right frontal throbbing headache. There was no previous history of headache but her mother was known to suffer migraines. Her only medication was the oral combined contraceptive pill. Blood pressure was 135/90 with no other vascular risk factors.

An initial MRI brain revealed some high signal abnormalities, with one predominant lesion in the right corona radiata suggestive of inflammation or ischaemia (Figure 1a). A lumbar puncture was acellular with a normal protein level and an absence of intrathecal oligoclonal band synthesis. An interval brain scan three months later showed similar findings with the addition of a further new lesion in the right peritrigonal area. Unusual radiological features on the second scan included restriction of the lesions to the territory of the right middle cerebral artery and a cavitating appearance of some of the lesions which was more in keeping with ischaemia than inflammation (Figure 1(a) and 1(b)).

To investigate further, a contrast-enhanced MRA (CE-MRA) was performed. This provided views from the aortic arch to the circle of Willis and other intracranial vessels, not routinely included on the normal field of view when assessing the neck vessels in patients with ischaemic



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Dr Shelley Renowden, BSc, MRCP, FRCR, is a consultant neuroradiologist based at Frenchay Hospital, Bristol and has been in post since January 1996, having trained previously at the Radcliffe Infirmary, Oxford. Her main interest is neurointervention and neurovascular disease. She currently works in a tertiary referral centre for complex neurovascular disorders and one of her main objectives, with her clinical colleagues, is to enhance and expand stroke services/treatment in North Bristol.



David Cottrell, MBChB, BSc, MRCP, PhD, was appointed as a consultant neurologist and senior clinical lecturer at Frenchay Hospital, Bristol in 2005. He specialises in multiple sclerosis and in particular primary progressive multiple sclerosis.

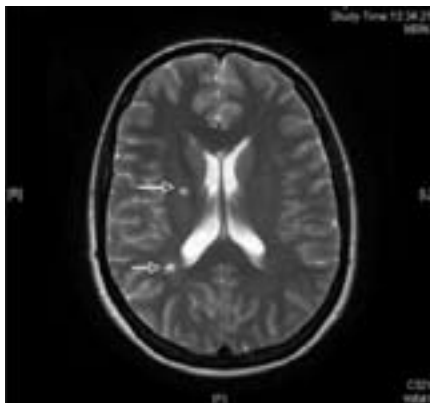


Figure 1(a): T2-weighted axial MRI brain showing high signal lesions in the right hemisphere (white arrows).

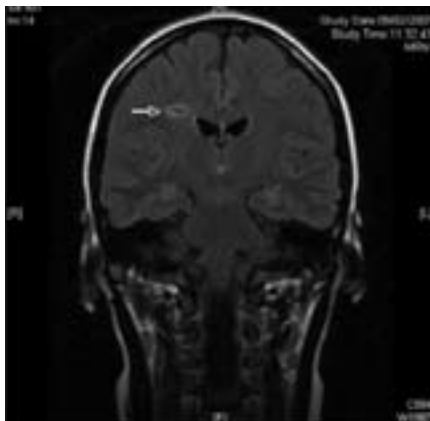


Figure 1(b): T1-weighted MRI brain coronal showing a cavitating lesion in right hemisphere (white arrow).

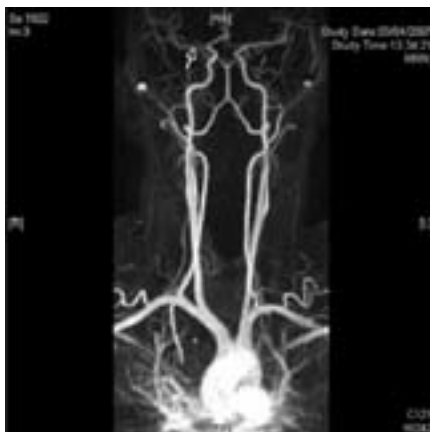


Figure 1(c): CEMRA reconstructed frontal view demonstrates normal carotid bifurcations and internal carotid arteries and a right M1 stenosis with reduced signal in the middle cerebral circulation (white arrow).

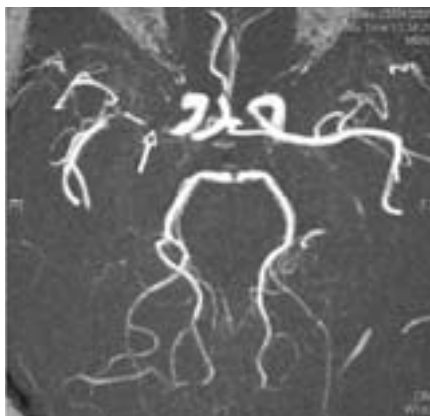


Figure 1(d): A maximum intensity submentovertical projection reconstruction 3D TOF MR angiogram centred on the Circle of Willis confirms the presence of a right M1 stenosis, likely to be the result of a dissection. (white arrow).

stroke. The CEMRA demonstrated a significant M1 stenosis with reduced signal indicating reduced flow in the more middle cerebral circulation (Figure 1c). 3D time of flight (TOF) MR angiography confirmed the M1 stenosis (a 'string sign') consistent with an arterial dissection (Figure 1d), and assumed to be responsible for repeated ischaemic insults to the right cerebral hemisphere.

Aspirin was started (75mg once a day) and the patient was advised to stop the oral combined contraceptive pill and attend regular review. At the latest review, she continued to complain of headache and residual mild left-sided sensory symptoms but the initial left facial and left leg weakness had fully recovered.

Discussion

Intracranial artery dissections can cause subarachnoid haemorrhage and ischaemic infarcts. These sequelae have often only been diagnosed at post-mortem in the past but with improved imaging techniques and awareness of this condition, intracranial artery dissection is likely to become a more familiar diagnosis. As thrombolysis is a treatment option for presumed thrombotic stroke, but not necessarily advisable with dissection, the aetiology of stroke or transient ischaemic attacks in a young person should always be carefully considered.

The mechanism of ischaemia in intracranial artery dissection is thought to be hypoperfusion due to artery occlusion rather than embolic events, which are more typical of extracranial artery dissections. The anatomy of the intracranial arterial wall differs from cervical arteries in that the media is thinner and there is no external elastic lamina. Haemorrhage as a result of dissection can occur between the arterial layers or directly across the lumen wall and as intracranial arterial walls are thinner the risk of subarachnoid bleeding is thought to be higher.⁴

Due to the rare occurrence of intracranial dissection, there is currently no evidence base to guide treatment. Options include surgery, stenting, anticoagulation and antiplatelet therapy. We favoured antiplatelet therapy over anticoagulation given the belief that there is a greater risk of intracranial bleeding. There is an obvious need for a randomised, controlled study of treatments in intracranial artery dissection.

The evidence base for treatment of extracranial dissection is larger but still inadequate.^{14,15} In order to try to answer whether we should be using antiplatelets or anticoagulation for the treatment of extracranial artery dissection, there is currently a national pilot study underway to determine whether it would be possible to perform a large-scale multi-centre, international randomised study which would aim to recruit enough patients to provide statistical power to be able to reliably compare antiplatelet with anticoagulation treatment¹⁶ (Cervical Artery Dissection in Stroke Study: CADISS - personal communication, Professor John Norris, St George's Hospital, London www.dissection.co.uk).

As imaging availability and techniques advance, contrast-enhanced MRA is seriously challenging DSA as the primary vascular imaging modality. It enables fast and reliable diagnosis of intra and extracranial artery dissection, revealing the true prevalence, course and outcome of this condition and is the recommended imaging modality of choice in suspected arterial dissection.

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If you would like to review books for ACNR, please contact Andrew Larner, Book Review Editor, c/o rachael@acnr.com

Multiple Sclerosis Care: a practical manual

Zajicek, Freeman and Porter are to be congratulated for producing a useful pocket guide to MS. Describing itself as 'a practical manual', this single volume covers a very wide range of information, from drug names and doses for neuropathic pain to a diagram of the variety of adhesion molecules at the T-cell surface.

This is not a multi-author book with three editors but a volume written by three co-authors, comprising a doctor, a therapist and a nurse. It seeks to cover the breadth of information useful for MS care. The style is consistent and very readable, without the repetition, or worse occasional contradictions or variations of emphasis, which can bedevil multi-authored books. The comprehensive content has a logical order, moving from pathology and diagnosis, to disease modifying therapies, relapses and rehabilitation. It covers symptomatic treatment, equipment and services.

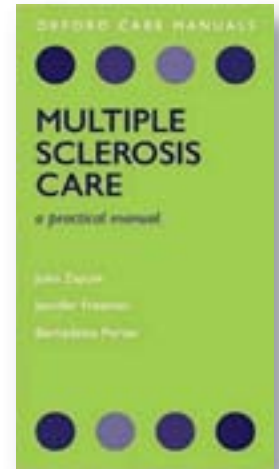
There is generally good use of supporting tables, and a number of web citations. The index is helpful but perhaps serves doctors better than other disciplines. For example, if you're aware T-cells are being researched in MS and look up T-cells under T you find nothing, but looking up immunology (ical synapse) gets you to a brief introduction to cellular immunity and self-antigens.

The authors are to be commended on some very useful sections. The description of disease modifying therapies is comprehensive, strongly evidence-based and appropriately critical. The section on scales is a nice resource for readers who need to quickly check what's in a scale, how it's administered and scored, and where they can find a reference or even download a manual. There are many sections which

would be useful for doctors who are not experienced in MS and its diagnosis and management, notably chapters on differential diagnosis, investigations, and what to say when patients ask for low dose naltrexone or advice on paying for stem cell 'treatment'. Indeed, the book would be a useful reference for many non-medically qualified readers, notably nurse specialist, therapists, and commissioners of MS services.

The authors all practise in the UK and potential buyers may wonder if there would be too much focus on British practice. Rest assured there is much here that translates to other countries. The book is strongly evidence-based; nowadays treatment trials and science are multinational. While the examples of service design happen to be British, they are described in ways which are generalisable, such as who to include in a multidisciplinary relapse clinic. The internet has made us a global village and the British and American patient organisations are web-based sources of information.

What might be improved in future editions? The diagrams and figures could be better presented. Reproducing MR scans without high production costs may be difficult but these images would be better if consistently cropped, if extraneous labelling was removed and if abnormalities were always arrowed. The illustrations for oligoclonal bands and VERs could be better. The diagram for the blood brain barrier could be clearer. The utility of the index for the non-specialist could be increased. But these are minor points. If you are looking for a single compact volume on MS care, this book would be a good choice that you could read as a refresher, or use as reference guide.



Authors/editors: John Zajicek, Jennifer Freeman, Bernadette Porter
Published by: Oxford University Press
ISBN-13: 978-0-19-856983-1
Price: £19.95

Reviewed by:
 CA Young,
 Professor of Neurology,
 WCNN, Liverpool.

Insights: Facts and Stories behind Trigeminal Neuralgia

Whether the practise of medicine is predominantly an Art or a Science provokes much heated discussion, especially amongst doctors. Those who dislike a predominantly factually based, dispassionate, 'evidence-based' method of dealing with patients have found support by recent publicity on 'narrative medicine'. Champions of this argue that doctors should spend more time listening to accounts of the patients' symptoms and how it impacts on their lives. This is meant to help to form a 'therapeutic alliance' between patient and doctor.

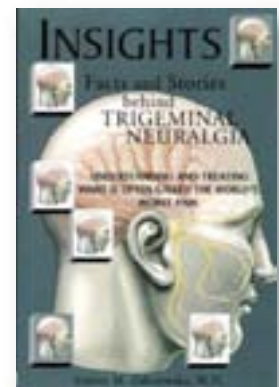
Detractors of this method of teaching and practising medicine however have argued that the pendulum has swung too far. They are worried that too much emphasis on empathy and communication skills distracts from the acquisition of core medical knowledge. These new doctors may be good at hand holding and offering their shoulders to cry on. In addition, they will need to communicate well, especially when they have to tell patients that they are ignorant of the diagnosis! It is always difficult to judge why and what the patient narrates in a consultation. Patients' methods and motives for talking about their symptoms probably vary according to which doctor they see. The late Richard Asher in his entertaining essay 'Talk, Tact and Treatment' (*Richard Asher Talking Sense. Pitman Medical. London 1972*) has analysed some of these motives.

Of course, medicine is both an art and a science and this book is an attempt to bridge this divide. The stated aim of this book is to inform patients with trigeminal neuralgia (TN) and is written by one of the undisputed experts of this condition. It is also a useful read for neurologists, neurosurgeons and maxillofacial surgeons who see these patients regularly. The book layout is patient-focused and the vignettes

contributed by patients are intermixed with the hard facts behind the science of TN. The information is well presented, starting with the basic anatomy and physiology of the trigeminal nerve. This is then followed by the presenting symptoms of TN, investigations, then medical and surgical management. One chapter is focused specifically on decision making to help patients choose the best therapy for them at a given time. In my opinion, this is the crucial chapter for both patients and doctors to read. It is notoriously difficult to compare probabilities. For example, the data on Table five on page 244 would indicate that you are more than two hundred times more likely to die from playing football than from New Variant CJD! However, I suspect that this is an oversimplification and information derived from self selecting populations tends to skew the data.

There are some minor omissions and errors. For example, it would be useful to highlight the fact that long term use of carbamazepine for TN does pose a risk of causing osteoporosis in the population most prone to this condition (post-menopausal females). A book like this takes time to produce and it is not surprising that recent studies suggesting that TN may be alleviated using triptans were not mentioned. Contrary to what is mentioned in the book, checking trigeminal reflexes is part of the neurological examination and does not need to be done by a neurophysiologist.

Overall, I found this book to be very readable and informative. It is an excellent summary of TN, and considering the price, well worth buying for trainees and established clinicians who deal with patients with facial pain. Make sure you have the facts at your finger tips; your patients will be sure to have it after they read this book.



Author: Joanna Zakrzewska
Published by: TNA Trigeminal Neuralgia Association
ISBN: 0-9672393-4-6
Price: \$27.95

Reviewed by:
 MS Chong,
 Kings College Hospital,
 London.

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References:

1. Halper J *et al.* J Neurosci Nurs 2003; 35: 70-81.
2. Rudick RA *et al.* Poster presented at ECTRIMS. October 2007; Prague.

Date of preparation: January 2008
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


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MANAGEMENT OF "COLLAPSE?CAUSE"

Tuesday 24 June 2008

In the UK, "collapse?cause" is a common term in use in emergency departments in all hospitals. An abrupt loss of postural control is often, but not always, accompanied by transient loss of consciousness (T-LOC). Often, the first-responders and subsequent clinical reviewers find no signs or symptoms, and many common tests are unhelpful. The clinical history, supplemented by an eye-witness account, is crucial, but a number of different causes of collapse and of T-LOC may look the same. This conference aims to try and steer clinicians towards a better understanding of causes and mechanisms, clarify terminology and the key points in clinical assessment and testing.

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2008

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E. i.m.huang@amc.uva.nl
T. 30-2-107-257-693, F. 30-2-107-257-532

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8-11 May, 2008; Cologne, Germany
E. info@mes-berlin.com Mrs Yvonne Beetz,
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F. 86 10 62 174 061
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E. Milda.Endziniene@endziniene@gmail.com or
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E. iaspdesk@iasp-pain.org

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F. 00 43 1 88 92 581
E. headoffice@efns.org

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Genomic Perspectives to Host Pathogen Interactions

3-6 September, 2008; Cambridge, UK
http://firstcontact.hinxton.wellcome.ac.uk

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

NEW**European Headache and Migraine Trust International Congress 2008**

4-7 September 2008, London, UK
E. enquiries@ehmtcongress2008.com
www.ehmtcongress2008.com
T. +44 (0)20 8979 8300

Understanding Neuroscience: an innovative approach for mental health practitioners

8-9 September, 2008; London, UK
E. annehaylock@markallengroup.com

BSS hosting the 19th Congress of the European Sleep Research Society

9-13 September, 2008; Glasgow
E. enquiries@sleeping.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. wtmeetings@wtconference.org.uk
http://firstcontact.hinxton.wellcome.ac.uk/

NEW**'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

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@braintretraining.co.uk
W. www.braintretraining.co.uk

Congress of Neurological Surgeons Annual Meeting

20-25 September, 2008; Orlando, USA
Congress of Neurological Surgeons
T. +847 240 2500
F. +847 240 0804
E. info@ICNS.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

NEW**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.mahealthcarevents.co.uk

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/

5th World Congress for NeuroRehabilitation

24-27 September, 2008; Rio de Janeiro, Brazil
E: traceymole@wfnr.co.uk
www.sarah.br/wfnr-rio2008

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

October**EPDA Euroyapmeet Conference**

3-5 October, 2008; Zagreb, Croatia
E. lizzie@epda.eu.com

Advanced Cognitive Rehabilitation Workshop: Attention and Information Processing

10-11 October, 2008; Ljubljana, Slovenia
E. ursacizman@ir-rs.si

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

NEW**2nd World Congress on Controversies in Neurology (CONY)**

23-26 October, 2008; Athens, Greece
www.comtecmed.com/cony
E. cony@comtecmed.com

November**International Symposium on ALS/MND**

3-5 November, 2008; Birmingham, UK
E. pam.aston@mndassociation.org

Advanced Cognitive Rehabilitation Workshop

21-22 November, 2008; London, UK
E. enquiries@braintretraining.co.uk
www.braintretraining.co.uk

NEW**Benign Paroxysmal Positional Vertigo**

22 November, 2008; Reading, UK
E: info@physiok.co.uk

2009**February****37th Annual INS Meeting**

11-14 February, 2009; Atlanta, Georgia, USA
International Neuropsychological Society
T. + (614) 263-4200
F. + (614) 263-4366
E. ins@osu.edu

April**61st Annual Meeting of the American Academy of Neurology**

25 April- 2 May, 2009; Seattle, WA, USA
www.aan.com

May**5th ISPRM World Congress**

9-13 May, 2009; Istanbul, Turkey
E: traceymole@wfnr.co.uk

October**AANEM Annual Scientific Meetings**

7-10 October, 2009; San Diego, California, USA
T. + (507) 288-0100
F. + (507) 288-1225
E. aanem@aanem.org

19th World Congress of Neurology

24-30 October, 2009; Bangkok, Thailand
www.wcn2009bangkok.com

2010**April****62nd Annual Meeting of the American Academy of Neurology**

10-17 April, 2010; Toronto, Canada
www.aan.com

September**Congress of Neurological Surgeons Annual Meeting**

16-21 September, 2010; San Francisco, USA
Congress of Neurological Surgeons
T. +847 240 2500
F. +847 240 0804
E. info@ICNS.org
www.neurosurgeon.org

October**AANEM Annual Scientific Meetings**

6-9 October, 2010; Quebec City, Quebec, Canada
T. + (507) 288-0100
F. + (507) 288-1225
E. aanem@aanem.org

2011**April****63rd Annual Meeting of the American Academy of Neurology**

9-16 April, 2010; Honolulu, HI
www.aan.com

September**AANEM Annual Scientific Meetings**

14-17 September, 2011; San Francisco, California, USA
T. + (507) 288-0100
F. + (507) 288-1225
E. aanem@aanem.org

October**Congress of Neurological Surgeons Annual Meeting**

1-6 October, 2011; Washington D C, USA.
Congress of Neurological Surgeons
T. +847 240 2500
F. +847 240 0804
E. info@ICNS.org
www.neurosurgeon.org

2012**September****Congress of Neurological Surgeons Annual Meeting**

29 September-4 October, 2012;
San Francisco, USA.
Congress of Neurological Surgeons
T. +847 240 2500, F. +847 240 0804
E. info@ICNS.org
www.neurosurgeon.org

2013**October****Congress of Neurological Surgeons Annual Meeting**

19-24 October, 2013; San Francisco, USA
Congress of Neurological Surgeons
T. +847 240 2500
F. +847 240 0804
E. info@ICNS.org
www.neurosurgeon.org

The Muscular Dystrophies

A meeting organised by the Medical Genetics Section of the Royal Society of Medicine

19 November, 2007; London, UK.



Inclement weather and London's notorious public transport system did not deter over 100 clinicians and scientists from attending this meeting. The morning sessions were chaired by Lord Walton of Detchant, an inspired choice given his personal contribution in this field, including (the audience was reminded) the first description of Duchenne muscular dystrophy (DMD) in an individual with Turner's syndrome. He excused himself from the afternoon session, as he was speaking at the House of Lords on the Human Fertilisation and Embryology Bill – a reflection of the rapid expansion of knowledge and technologies in Medical Genetics, and the consequent ethical and legal ramifications. Indeed the ethical considerations surrounding the diagnosis and management of these disorders were highlighted by Professor Alan Emery (Oxford), the organiser of the meeting who also kicked off the talks. He talked movingly of the sometimes tragic implications of establishing these diagnoses to patients and families. Professor Emery gave an overview of the explosion of knowledge there had been in the two decades since the discovery of dystrophin. Currently, there are 40 or so genes associated with the muscular dystrophies, encoding proteins many of which are now known to interlink. He pointed out that questions remained, including the explanations for phenotypic heterogeneity associated with single genes (or even single mutations) and allelic heterogeneity (where mutations in different genes result in an identical clinical phenotype). He talked also of the possible interactions of particular environmental agents (especially pathogens) with specific proteins involved in certain muscular dystrophies. He left the audience with the salutary reminder of the dangers of following dogma (for example the current view that abnormal genes equal disease) in attempting to overcome any challenge, citing the explosion of the Hindenburg in 1937 and the subsequent abandonment of airships - which up to that time had been the preferred means of transatlantic air travel.

Professor Francesco Muntoni (London) in a scintillating talk described the congenital muscular dystrophies (CMDs), which generally present before six months of age. It was interesting to note the extent of central nervous system involvement in some forms, reflecting expression of some proteins in the brain during development. He highlighted three disorders. Ullrich variant and merosin deficient CMD are associated with deficiency of two extracellular matrix proteins (collagen VI and laminin $\alpha 2$ respectively), and are phenotypically reasonably distinct. Glycosylation of alpha dystroglycan, a peripheral membrane protein, enables it to interact with extracellular matrix proteins,

and abnormal glycosylation (associated to-date with mutations in six separate genes) results in conditions such as Walker Warburg syndrome, Fukuyama muscular dystrophy and muscle eye brain disease. Whilst initially good correlation between specific gene mutations and clinical syndromes was suspected, Professor Muntoni's group has demonstrated that each of the six genes can result in a highly variable phenotype, including (confusingly) adult-onset limb-girdle muscular dystrophy (for example FKRFP).

In a commendably clinically orientated talk, Dr David Hilton-Jones (Oxford) covered Duchenne and Becker muscular dystrophies. Controversially he said that an Italian, Conte, should be credited with the first description of DMD in 1836, preceding even Meryon. This was firmly rebutted by Professor Emery at the end of Dr Hilton-Jones' talk, who maintained that the true credit should go to Meryon, as the latter's description in 1851 not only preceded Duchenne's but it included the key observations that it was maternally inherited and was primarily a disorder of muscle. DMD and Becker muscular dystrophy (BMD) are allelic disorders, and whilst 'out-of-frame' mutations resulting in truncated dystrophin cause DMD, 'in-frame' mutations cause BMD. Clinical 'gems' to take away included the observation that any boy with delayed motor, speech or general intellectual development should have his creatine kinase (CK) measured. Management with (non-invasive) ventilatory support can enable survival into the third and fourth decades. The use of drugs to manage cardiomyopathy and corticosteroids to prolong survival were mentioned. Clinical features associated with the milder BMD include exercise-induced cramp (resembling McArdle's disease) and asymmetric calf hypertrophy. It can be difficult to discriminate BMD from spinal muscular atrophy, and 10% of subjects are wheelchair-bound by 40 years. Cardiomyopathy again requires monitoring and treatment. Finally, Dr Hilton-Jones covered the specific issues of manifesting carriers (associated with non-random X inactivation), and the disorders associated with point mutations in dystrophin ranging from muscle pain and cramps without weakness to isolated cardiomyopathy and isolated 'hyperCKaemia'.

Professor Kate Bushby (Newcastle) talked on the limb-girdle muscular dystrophies (LGMD). Autosomal dominant and recessive forms exist, and whilst clinically (and genetically) heterogeneous all share a predominant pattern of proximal myopathy. It was explained that determining the exact type (if possible) was important for genetic counselling and determining prognosis, as different forms were associated with variable involvement of the cardiac and respiratory systems. The exact diagnosis could only be

achieved by the synthesis of accurate clinical data, muscle biopsy findings and selected genetic studies, and the need for close collaboration with national centres of expertise (such as Professor Bushby's) was readily apparent.

The afternoon session began with another authority in his field, Professor Padberg (Nijmegen) talking on fascioscapulohumeral muscular dystrophy (FSHD). This autosomal dominant disorder is the third most common muscular dystrophy (after myotonic dystrophy and DMD/BMD), but more than 30% of gene carriers (females more than males) may be asymptomatic. (Age of onset is older in females too.) There is often asymmetrical and frequently unrecognised facial weakness first. At clinical presentation, however, shoulder-girdle weakness is common (80%), while foot extensor (10%), pelvic-girdle (5%) and facial muscle (5%) weakness are less so. Disease progression slows in the sixth decade, but at 60 years two-thirds have foot extensor weakness, half have pelvic-girdle weakness and 20% are wheelchair dependent outdoors. Coats' disease, a retinal vasculopathy (often subclinical), can be present, and hearing loss and epilepsy have been described. Professor Padberg next considered the molecular genetic basis of FSHD. It is associated with a reduction in the number of 3.3 kb repeats (normally more than 11) in the D4Z4 locus on 4q35. Whether a transcript (DUX4) or an effect on an upstream gene (FRG1) mediates disease is a matter of debate, but epigenetic mechanisms including hypomethylation of the repeat unit seem to be implicated in the pathophysiology.

Professor Glen Morris (Oswestry) next talked about Emery-Dreifuss muscular dystrophy (EDMD), which is caused by mutations affecting the genes encoding emerin (X-linked), lamin A/C, or the nesprins. Crucially, all three proteins are co-located in the nuclear membrane. Clinically EDMD is characterised by early contractures (Achilles tendons, elbows and neck), muscle wasting and weakness initially in proximal upper limbs and distal lower limbs, and cardiac conduction defects. The importance of the insertion of cardiac pacemakers and defibrillators in management was stressed. Lamin A/C mutations (associated with dominant EDMD) can cause dilated cardiomyopathy necessitating cardiac transplantation, and provides a further example of phenotypic heterogeneity - being associated with a form of CMD and one type of LGMD, both complicated by cardiac disorders too.

Professor Bjarne Udd (Tampere) covered the confusing area of the distal muscular dystrophies. Once again, rapid growth in knowledge has taken place and more than 16 genetically distinct types are now recognised. About half cause distal disease exclusively, whilst the other

half can be associated with scapuloperoneal, proximal or generalised phenotypes. Most of these genes appear to encode sarcomeric proteins, as do the recently identified genes associated with distal arthrogryposis (which is probably a manifestation of congenital distal myopathy). The highly selective nature of muscle involvement is striking, and is even better appreciated by magnetic resonance studies.

Finally, in this section, Dr Gurman Pall (Glasgow) spoke on myotonic dystrophy (DM1). He explained that the triplet-repeat expansion characteristic of the disease produced mRNA containing expanded CUG repeats which are 'toxic' to cells. Dr Pall and colleagues have identified short (CUG)_n-RNA fragments in cells expressing mRNA containing expansions characteristic of DM1, which may represent an intermediate degradation product of the 'toxic' repeat-containing transcripts. Characterisation of this potential decay pathway may obviously yield opportunities for ther-

apeutic interventions in DM1.

In the last part of the meeting, Professor Kay Davies (Oxford) and Dr Jennifer Morgan (London) tackled the treatment of DMD, addressing gene and stem cell therapies respectively. There seem to be numerous (some very ingenious) interventions capable of correcting or ameliorating the absence of dystrophin, and it may be that a combination of approaches will need to be utilised eventually. It was heartening to note the phase I/II trials in planning or progress, and Professor Davies' view that there was "great promise...(for the successful treatment of DMD)...in the next decade".

All in all, this was an outstanding meeting, bringing together a faculty of true opinion leaders in their respective specialities. For workers in the field there were unrivalled opportunities for networking and sharing recent knowledge behind the scenes, and in this regard it resembled an international symposium. I found it of enormous educational value, and felt that

the field (with only a few exceptions, such as oculopharyngeal muscular dystrophy) had been comprehensively covered. Neurologists in training, especially those with an interest in the genetic aspects of disease are encouraged to join the Medical Genetics Section of the RSM, which is one of its youngest Sections and, on the evidence of this meeting, also one of its most dynamic.

I am grateful to Professor Emery for reviewing the manuscript.

*Rajith de Silva, Department of Neurology,
Queen's Hospital, Romford, Essex, UK.*

References

1. Barnes PRJ & Hilton-Jones (eds.). (2003) *Myopathies in clinical practice*. London & New York: Martin Dunitz.
2. Emery AEH & Muntoni F. (2003) *Duchenne muscular dystrophy*. 3rd ed. Oxford: Oxford University Press.
3. Winder SJ (ed.) (2006) *Molecular mechanisms of muscular dystrophies*. Georgetown, TX: Landes Bioscience.

Society for Research and Rehabilitation Winter Meeting 2008

15 January, 2008; Oxford, UK.

The SRR Winter conference was held on the 15th January 2008 at Oxford Brookes University, hosted by Dr Helen Dawes. Despite only being a one day conference there was a wide range of material presented: free research papers, poster presentations, work in process posters and three symposia. The day's proceedings were started by Professor Paul Matthews' interesting symposium on the utility of different brain imaging techniques to explore the relationship between brain plasticity and rehabilitation.

After a quick coffee and the first chance to view the posters, Professor Cath Sackley gave the first of her presentations on a cluster randomised controlled trial of physiotherapy and occupational therapy intervention to enhance mobility and activity in care home residents. The first session also included a qualitative paper examining experiences of an Exercise Referral Scheme from the perspective of people with chronic stroke presented by Helen Sharma, a randomised single blind trial of the use of multi-sensory stimulation to improve functional performance in older people with dementia, by Dr Lesley Collier, and a survey of the circumstances surrounding falls among people with Parkinson's disease by Professor Ann Ashburn.

Following lunch, Professor Derick Wade gave a thought-provoking symposium exploring how, paradoxically, rehabilitation may prolong disability and illness behaviours, which generated an interesting discussion. This was followed by an interesting and entertaining symposium by Dr Tom Manly on how investigating variability within impairment measures can be utilised in rehabilitation for examining attention and executive function.



During the coffee break delegates had their final chance to view both the posters presentations and the work in progress posters: Poster presentations included: lower limb muscle weakness in Huntington's disease by Dr Monica Busse; walking and wheelchair navigation in stroke patients with left sided visual neglect by Mrs Kelly O'Leary; the 'Dark Art' of physiotherapy: experiences of people with cerebellar ataxia by Elizabeth Cassidy; modulating performance on wheelchair navigation in patients with unilateral neglect following stroke by Dr David Punt; self-optimisation of walking speed following stroke by Dr Johnny Collett; modeling recovery after stroke, Ms Shweta Malhotra; can botulinum toxin, administered in the early stages following a stroke help the recovery of arm function; estimating effect size from a phase II pilot study by Ms Elizabeth Cousins. Work in progress posters included: examining outcome measures of inpatient care in profound brain injury; economic analysis of return to work after traumatic brain injury; reintegration outcomes following spinal cord injury; and the feasibility of NIRS in detecting neural activation in the DLP cortex

during cognitive tasks.

The day concluded with final free research presentations. Dr John Saxton presented his work on the physiological responses to treadmill walking with Nordic poles in patients with intermittent claudication, Mr Atzori his study of concurrent validity of the IDEEA activity monitor to quantify mobility related activities among people with stroke in free-living conditions, Dr Eimear Smith on examination of the prevalence of low bone mineral density in patients at a national rehabilitation centre and we finished where we started with Dr Cath Sackley talking about a phase II randomised controlled trial of bilateral limb movement exercise in chronic hemiparetic stroke patients.

Many thanks to all the presenters and delegates for an interesting, informative and thought-provoking day. The Summer Meeting will be held in Preston, hosted by Professor Caroline Watkins of the University of Central Lancashire.

*Dr Helen Dawes,
Oxford Brookes University, Oxford UK.*

The Parkinson's Disease Non-Motor Group 3rd Annual Meeting

8 March, 2008; London, UK.

The Parkinson's Disease Non-Motor Group (PDNMG) 3rd annual meeting was held at the Royal Society of Medicine, London, on 8th March 2008 and was attended by 170 health care professionals. It provided an opportunity to review the past year's progress in the field of non-motor symptoms (NMS) and another informative and invaluable day of learning.

Attendees were welcomed by PDNMG Chairman, K Ray Chaudhuri, who briefly discussed the prevalence of non-motor symptoms (NMS) including dribbling saliva, constipation, depression, sleep disorders, apathy, hallucinations and dementia which complicates the lives of people with Parkinson's disease (PD). Professor E Tolosa (Barcelona) described the pre-clinical phase of PD. He examined the correlation between Braak staging with clinical manifestations, imaging of the substantia nigra, and non-motor symptoms including olfactory disturbances, depression and autonomic system disorders. Professor Tolosa suggested that NMS are not prodromal but in fact part of PD. Professor A Schapira (London) then delivered a talk on when to start treatment for PD. He discussed the 'pre-clinical' markers including depression and olfactory disturbances, the pathological clues, neuroimaging assessment of progression, and genetic linkages. He highlighted results from the DATATOP, TEMPO and QE2 studies. Professor Schapira reviewed the advantages of early monotherapy, the issue of neuroprotection and the conflicting evidence surrounding the concept. He concluded that the eventual decision to treat early must be made after a patient orientated discussion, balancing the side effects of treatment with the reported improvements in quality of life, symptom control and disease progression.

Professor D Burn (Newcastle) then examined the similarities and differences between dementia with Lewy bodies (DLB) with PD dementia (PDD), and discussed diagnostic criteria, management algorithms and drug treatments for PDD. He briefly reviewed cholinesterase inhibitors, and memantine as possible therapies, then proceeded to talk about drugs with multiple modes of action (including ladostigil and adenosine receptor antagonists). Finally, various anti-amyloid strategies for PDD, such as statins, muscarinic-M1 receptor agonists, anti-inflammatory agents and amyloid immunisation therapy were discussed.

Professor D Brooks (London) outlined the uses of FDG-PET, FP-SPECT, F-Dopa PET, Acetylcholinesterase Imaging and PET amyloid plaque imaging in PDD, DLB and Alzheimer's disease. PDD patients demonstrated decreased parieto-temporal metabolism levels, decreased mesocortical dopamine levels and globally decreased acetylcholinesterase levels. Professor Brooks talked briefly on depression and concluded that depressed PD patients were more likely to demonstrate frontal lobe hypometabolism and



limbic dopamine dysfunction.

The afternoon session began with a presentation by Professor P Barone (Milan) on the epidemiology, treatment and management of hallucinations. He highlighted the facts that atypical anti-psychotics were recommended, long term treatment is the rule, patients with concomitant dementia with visual hallucinations should probably start a cholinesterase inhibitor, and that testing cognitive function is an essential part of the clinical examination.

Professor C Clarke (Birmingham) offered an appraisal of drug therapy for motor and non-motor symptoms. He summarised the shortfalls of previous trials in symptomatic early PD treatment and then introduced the ongoing PDMED trial, which looks at both the patient-related quality of life and health economics. He then discussed the surgical options for PD including bilateral subthalamic stimulation. Finally, he discussed the future of drug therapy in PD, including prolonged release ropinirole, safinamide, and antidyskinesia agents such as istradefylline, an adenosine A2a receptor antagonist.

Professor F Stocchi (Rome) discussed the management of respiratory dysfunction and sleep problems in PD. He reported the early results of his own study in 30 patients (all non-smokers) with respiratory dysfunction and PD. Assessments of maximal inspiratory pressure, pulmonary function tests and dyspnoea perception in patients in 'on' and 'off' phases showed that 90% of patients had difficulties when 'off' compared to 78% when 'on'. He postulated that the results can be explained by bradykinesia of the diaphragm and intercostal muscles, and postural problems. He then went on to review sleep problems which are highly prevalent in PD, and their effect on quality of life. He suggested treatments for nocturnal akinesia, rigidity and dystonia (prolonged release levodopa and COMT-I), sleep initiation problems (benzodiazepines) and sleep maintenance problems (amitriptyline, clonazepam and clozapine).

Professor R Brown (London) emphasised the importance of screening and detection of symptoms such as depression which are frequently stigmatised, and mentioned the various assessment tools for measuring these symptoms. For mild depression, he recommended anti-depressants and general measures such as anxiety man-

agement and exercise. For more severe depression, he suggested SSRIs, but called for more research into PD and depression since there is currently no established treatment algorithm. Ongoing trials suggest the use of combined serotonin-noradrenaline therapies such as venlafaxine and D2/D3 agonists such as pramipexole, for patients with treatment resistant depression with PD. However all have limited evidence of safety and tolerability, and cognitive behavioural therapy may therefore also have an important role.

Mrs J Johnson (London), a clinical specialist speech and language therapist in progressive neurological disorders, outlined the main motor features of dysarthria. She reviewed the drug treatments, therapeutic devices and the management programmes (including the Lee Silverman Voice Treatment) available to patients. Mrs Johnson concluded by calling attention to the paucity of drug trials that use speech assessment as end points.

Professor P Odin (Bremerhaven) discussed sexual dysfunction and highlighted previous studies which showed that 68.5% of patients with PD suffered from such problems, compared to 33% in a healthy group of the same mean age. While a combination of autonomic dysfunction and psychological anxiety was blamed for hyposexuality, Professor Odin recommended the involvement of gynaecological and urological teams, psychosocial counselling, anti-anxiety medication, the use of sildenafil and related agents, and a reduction in PD medication (if possible).

Dr G MacPhee (Glasgow) discussed gambling, impulsive and compulsive behaviour, outlining the progression from 'recreational', 'problem' and 'pathological' gambling (PG), drawing parallels with obsessive compulsive disorder. Dr MacPhee ended with a review of management. Whilst the evidence base remains poor, an individualised approach utilising neuroleptics, mood stabilisers and psychological counselling, including CBT and Gambler's Anonymous, was advised.

Dr M Visser (Netherlands) discussed quality of life determinants in PD. Sexual, urinary, gastrointestinal and thermoregulatory problems appear to be most predictive of low Health Related Quality of Life scores. Dr Visser suggested that future treatment should target improvement in activities of daily living, psychosocial problems such as depression, and the autonomic nervous system.

The valuable questions which followed many of the presentations made a significant contribution to the proceedings and ensured that lively discussion continued in-between sessions. A fourth meeting is already at an advanced stage of planning.

*Kartik Logishetty, Sharon Muzerengi
and K Ray Chaudhuri,
King's College Hospital,
Denmark Hill, London, UK.*

The MS Society Convention for People with MS – MS Life 2008

29-30 March, 2008; Manchester, UK.

MS Life 2008 was held in Manchester and was Europe's biggest ever event for the MS community. The convention was a massive achievement, attended by more than 3,500 people touched by multiple sclerosis, including over 350 wheelchair users and 450 visitors with mobility aids.

Every part of the UK was represented and there were many European and international visitors who were drawn to the event by the research presentations, workshops and over 80 exhibition stands aimed at offering information on improvements in quality of life for people affected by MS. Highlights of the weekend also included live cookery demonstrations, Kinky Myelinky – the exclusively inclusive club night and the My Style fashion show featuring models from the MS community in front of a sell out crowd of 400.

In response to delegate feedback from previous years the research sections of the convention were expanded and improved. The Meet the Scientist zone, where delegates could link up with research scientists to gain an insight into basic laboratory projects in the field of MS, was developed to become the Meet the Expert zone. As well as scientists, there was representation from many parts of the multi-disciplinary team involved in the care of a person with MS, including MS nurses, clinicians and clinical psychologists. The zone also boasted information stands focusing on magnetic resonance imaging (MRI) and the UK MS Tissue bank.

In parallel with around 30 workshops on varied topics including social care, living with primary progressive MS, managing fatigue, care services and starting a family, seven international research speakers gave talks on a diverse range of topical subject areas in the field of MS throughout the two day conference. Dr Alasdair Coles, an academic neurologist in Cambridge working on experimental therapies for MS, began the sessions with a discussion of risks, placebos and myth busting. He presented some of the trends and conclusions which can be drawn from looking at longitudinal data from people with MS and discussed the balance which needs to be achieved between potential benefits and risks associated with treatment of a long term condition such as MS. He also reviewed data on the effectiveness of current therapies for MS and discussed the need for open and candid information to be provided on the benefits of these treatments.

Prof David Miller, Head of the Department of Neuroinflammation at the Institute of Neurology followed this with an update on research using MRI methods to improve diagnosis, identify prognostic markers, understand disease mechanisms and monitor new treatments in MS. He showed how a new and more powerful generation of MRI scanners is now being manufactured which are able to detect the damage to nerve fibres that causes disability as well as the repair of myelin that enables



recovery to take place.

Dr Brenda Banwell, Director of the Paediatric Multiple Sclerosis Clinic in Toronto, Canada, discussed why MS is increasingly being recognised in children and showed why the diagnosis of MS in a child or teen may be complicated and delayed. Dr Banwell's talk highlighted the fact that research into the causes of MS may be particularly important in the youngest people diagnosed with the condition because environmental triggers may be more readily detected in people closer to the onset of the condition. Dr Banwell also focused on the impact of MS on the lives and activities of children and teens.

Saturday closed with an open debate chaired by broadcaster Nicholas Owen which explored the issue of patient choice. A panel comprising MS Society Chief Executive, Simon Gillespie, people with MS, a representative of MS Therapy Centres and a neurologist hosted a lively discussion on many topics including new MS treatments and how best to balance the benefits against harmful side effects.

Prof George Ebers, a clinician at the Wellcome Trust Centre for Human Genetics, opened the research presentations on Sunday with a talk on genetics in MS and the inheritance of MS susceptibility. He summarised his work investigating the genetic epidemiology of MS as well as his primary interest in studying gene environment interactions in MS.

The audience then heard from Prof Charles ffrench-Constant, whose session described how

two MS Society funded centres, The Cambridge Centre for Myelin Repair and the Edinburgh Translational Research Centre, would address the issues of prevention of nerve fibre loss, which causes chronic progressive disease and the promotion of myelin repair using new technologies such as stem or precursor cell reactivation or transplantation in the search for new therapies for MS.

Prof David Bates, a clinical neurologist at the University of Newcastle upon Tyne followed with a discussion on the future of disease modifying therapy. He focused on potential therapies which are currently in phase III trials, assessing their effectiveness in treating MS. He also touched on key contemporary issues, questioning how to treat those for whom traditional MS therapies are not effective and future possibilities for treating MS progression.

The research talks, one of the most popular elements of the MS Life weekend, ended with a fascinating presentation from Prof Carolyn Young, who heads a Neurological Rehabilitation Unit at the Walton Centre in Liverpool. Prof Young's talk, entitled 'If I had MS...', covered topics such as exercise, diet, medication, stress and rehabilitation for people with MS. She gave expert advice on the best way to make the most of clinical consultations and MS teams as well as information on how trials are run and her views on the benefits of participation in research.

The conference was an excellent opportunity for people affected by MS to hear about the latest advances in research and provided the opportunity for people from every area of the MS community to share experiences and their ideas about the many aspects of living with MS. Interviews with the scientists and a full conference breakdown are available on the MS Society website.

*Dr Laura Bell,
Research Communications Officer,
Multiple Sclerosis Society.*

PREVIEW: British Neuro-Oncology Society (BNOS) Annual Conference 2008

25-27 June, 2008; Lancashire, UK

The University of Central Lancashire together with the Lancashire NHS Trust Royal Preston Hospital are hosting this year's BNOS conference from June 25th to the 27th. BNOS is the modern development of the British Neuro Oncology Group, formed in 1980, and includes UK leaders in basic science research together with a clinical membership drawn from consultant neuropathologists, neurosurgeons, oncologists, nurses and other health professionals who all have a common interest in malignant CNS tumours in both adults and children.

The conference venue will be in the Darwin and Foster buildings at the centre of the University campus a few hundred yards from Preston city centre. Accommodation will be at the nearby Holiday Inn and Travel Lodge. Preston is well served for transport routes and there is a direct rail link with Manchester International Airport.

This year it is estimated that the conference will attract approximately 280 delegates, and as well as the scientific sessions, will also include an extensive trade exhibition, 'education afternoon' and postgraduate forum. Consistent with the Society's original aims of promoting a dialogue on the management and biology of primary malignant brain tumours between basic scientists and clinicians, the meetings are kept as informal as possible.

Scientific sessions will be inter-disciplinary

and consist of short presentations and posters in addition to key note addresses. This year the conference is pleased to include talks from Professors Vescovi (Milan, Italy) and Lamzus (Hamburg, Germany) upon the involvement of stem cells in brain tumour and Professors Burnet (Cambridge) and Stummer (Dusseldorf, Germany) on novel advances in radiotherapy and neurosurgery. BNOS actively collaborates with the UK brain tumour charities and with the IBTA (International Brain Tumour Alliance) who have generously given their financial support towards hosting these eminent speakers.

Peer reviewed abstracts, including extended short papers from the main speakers, will be published in the British Journal of Neurosurgery. Copies of the edition, which will have a particular emphasis on brain tumour, will be available for delegates at the conference.

A full social programme is planned which includes a reception evening with the mayor of Preston in attendance at the Harris Museum, a stunning Grade I listed neo-classical building and the conference banquet at the National Football Museum, one of the UK's most original venues, with the opportunity for interactive participation and cabaret entertainment. Further details and appropriate registration and abstract submission forms may be found on the website: www.uclan.ac.uk/bnos2008



Charles Davis, Consultant Neurosurgeon, RPH, Vice-president of BNOS and Co-organiser BNOS2008.



British Neuro-Oncology Society



The Darwin Lecture Theatre. UCLan.

PREVIEW: ABN Meeting

10-12 September, 2008; Aviemore, UK

Where better to enjoy a bracing academic programme than the Scottish Highlands in the early Autumn? The conference will be held at the Hilton Coylumbridge which has ample on-site accommodation (<http://www.hilton.co.uk/coylumbridge>), and is surrounded by the beauty of the Cairngorms National Park. Why not stay on for the weekend, and bring your partner or family, to enjoy a wild adventure or two around Aviemore? You can choose from archery, gorge walking (or swimming, if you're brave), canoeing, hill walking, sled dog tours, fishing, mountain biking, pony trekking, or even golf. See <http://www.visitaviemore.com> and <http://www.rothiemurchus.net> for more details.

As well as the usual scientific presentations, case reports and the traditional CPC, there will be an educational symposium on functional problems in neurology, and a scientific symposium on multiple sclerosis sponsored by the MS Society Scotland. On the Thursday evening there will be

a highland dinner and ceilidh. The ideal way to travel if you are coming from or through London is on the sleeper to Aviemore from Euston. There are potentially 36 first class single berths, and up to 84 places in standard class double berths, which can be booked 12 weeks in advance of the date of travel. You can fly to Inverness (we will lay on coaches) from most UK airports. Deadline for abstracts will be the end of May 2008 (tbc).

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Would you like to write a short report for ACNR?

If so, please contact Rachael@acnr.co.uk or call Rachael on 01747 860168 for more information.

EDITOR'S CHOICE

COGNITION: belief and uncertainty

Is there a neurology correlate to belief? That is, is there a specific region or process that "decides" whether something is true, whether verifiable or not? And is this the same pathway that determines the belief that something is untrue, or that it is not possible to decide? Sam Harris and colleagues from the UCLA brain mapping centre set out to answer these questions by studying the functional MRI activation patterns of 14 healthy people judging written statements as "true", "false" and "undecidable". These included, amongst others, propositions about maths ("1.257 = 32608.5153"), geography ("California is larger than Rhode Island"), facts ("Eagles are common pets") and religion ("A personal God exists, just as the Bible describes"). The first finding was that subjects were much quicker to respond to say a statement was true (3.26 seconds) and slower when they thought it was false or were uncertain (3.7 seconds). The authors like to argue that the brain seems disposed to accept statements as true, with more neurological "effort" required for disbelief. We are all gullible it seems.

When comparing activation patterns of belief versus disbelief (that is the belief that something is false), a discrete region of ventromedial prefrontal cortex was found to be associated with belief. Turning the tables, the left inferior frontal gyrus, anterior insula, dorsal angular cingulate and superior parietal lobules were correlated with disbelief. Uncertainty was associated with a positive signal in the anterior angular cingulate. What to make of all of this? Well, firstly it is interesting that different types of belief (mathematical, religious) elicited a similar brain activation, and further in a region associated with linking factual knowledge to emotions. Perhaps there is a "reward" or "pleasure" in something that is true. In contrast, the anterior insula, involved in the disbelief map, is associated with perception of pain or disgust. The anterior angular cingulate, activated with uncertainty, is involved in resolving response conflict.

It is easy to overinterpret such imaging studies and cleverer souls than I will have to ruminate over the experimental paradigm before we get too carried away. But, as a scientific romantic, it is hard to resist the conclusion that humans are built to love truth and hate what is false. Now, where have I heard that before? – *AJC*

Harris S, Sheth SA, Cohen MS.

Functional neuroimaging of belief, disbelief, and uncertainty.

ANNALS OF NEUROLOGY

2008 Feb;63(2):141-7.

NEUROGENESIS: Neural stem cells and behaviour

In Nature Neuroscience the group of Alvarez-Buylla et al have expanded on the observation that Sonic hedgehog is important for the proliferation and maintenance of adult neural stem cells in the subgranular zone in the hippocampus. They demonstrate that Sonic hedgehog signalling is essential for expanding the neural precursors in this region during perinatal development to establish the adult stem cell population that carries on turning over throughout life. This effect of Sonic hedgehog requires a factor known as Kif3a, which is a subunit of kinesin-II involved with microtubular proteins. The reason why this is essential for the formation of the stem cell pool is that this protein is important for the motor machinery necessary for assembling primary cilia. If they remove Kif3a, the capacity to make radial astrocytes and the production of the hippocampal precursors is lost, and thus adult neurogenesis fails in this region. Whilst they have no functional data to address what the consequences may be of not having this factor expressed in development, there is some interesting speculation in this paper about the link between certain forms of mental retardation and dysfunctional cilia.

In a related article in Nature, Zhang et al have explored more explicitly what exactly adult neurogenesis is all about in terms of what functions does it serve in the adult brain. In this paper they have used a series of ingenious strategies with various knock-out mice to investigate what drives neurogenesis. They first demonstrate that the orphan nuclear receptor TLX is a marker and necessary factor in neural precursor cell proliferation. They demonstrate this in vitro by showing that knocking out this critical receptor reduces proliferation by 80%. They then turn to a series of in vivo studies where using micro

arrays, they showed that there were significant gene differences in TLX knock out mice versus a conditional knock out model when the gene was left on. They then switched neurogenesis off in the brain using this conditional mouse model and showed there was no major changes in the morphology of the hippocampus and that neurogenesis could still be switched on to some extent by physical activities such as running. Furthermore they were able to demonstrate that whilst neurogenesis was reduced in these conditional knock out mice, there was no change in the fate of neural precursor cells in terms of how many survived and differentiated into neurons. They went on to demonstrate that there were no deficits in contextual fear learning in contrast to reports from other groups. They did however find major deficits in spatial learning using a Morris water maze test. They therefore have demonstrated that this orphan receptor is critical in the genesis of neurons in the adult hippocampus and that this neuronal population seems to be important in spatial learning. Of course those cells which do not contain this receptor and form a separate population may perform some rather different function, but as to what this is remains a mystery. – *RAB*

Han Y-G, Spassky N, Romaguera-Ros M, Garcia-Verdugo JM, Aguilar A, Schneider-Maunoury S, Alvarez-Buylla A.

Hedgehog signalling and primary cilia are required for the formation of adult neural stem cells.

NATURE NEUROSCIENCE

2008;11:277-84.

Zhang C-L, Zou Y, He W, Gage FH, Evans RM.

A role for adult TLX-positive neural stem cells in learning and behaviour.

NATURE

2008;451:1004-9.

REHABILITATION: Can you feel me touching you; can you feel you touching you?

Despite the importance of sensation for hand function, this aspect of sensorimotor control is a rather neglected area in rehabilitation. Sensory testing of patients with stroke is usually fairly cursory and is limited to determining whether a few stimuli are detected. Studies using careful testing procedures and using a number of different modalities of stimulation have found that up to 65% of stroke patients have impaired somatosensory detection. But detection alone is only part of the picture. In order to be useful, incoming sensory information must be detected, discriminated and located. A fuller understanding of impairment in sensory processing is important for developing new strategies for rehabilitation.

Some interesting findings about enhancement of somatosensory perception have recently been reported in the JNNP. Valentini et al have analysed sensory performance in a sample of 39 stroke patients. The patients were tested, blind-folded, using a Semmes-Weinstein pressure monofilament (a calibrated nylon fibre attached to the end of a hand held rod). Testing with these filaments allows the pressure to be carefully controlled but also means that the stimulus is somewhat remote from the hand it is held in. The researchers compared performance of detection, intensity rating and location when the stimuli were applied conventionally by a tester and when the filament was held in the patient's unaffected hand. In this latter condition, called 'self touch', the patient's hand was positioned and moved by the tester to reduce proprioceptive cueing. A sample of unimpaired control subjects were also tested but with a finer filament to avoid ceiling effects. These healthy volunteers were able to detect stimulations with a probability of 50-70%.

No advantage of 'self touch' was seen in the unimpaired control group. However the stroke patient group had significant and reliably improved detection, intensity estimation and location when the stimuli were delivered via the 'self touch' method. The effect was found in more than half of the patients and in both left and right hemisphere strokes. It was more frequent in patients with right hemisphere strokes, but no correlation was found between the sensory enhancement and visual hemispatial inattention.

The enhanced appreciation for touch could have been due to proprioceptive cueing, but the authors discount this. Their strategy to have the tester move the patient's limb in the self touch condition would only have partially reduced the proprioceptive information available, but if the proprioceptive element was important in enhancing performance surely the effect would have been seen in the unimpaired control group too. Instead the authors suggest that the 'self touch' enhancement is due to modulation of attention. This may explain the increased frequency in the right hemisphere patients, however further investigation will be needed to confirm any attentional mechanism. Let's hope the findings will provoke renewed attention from rehabilitation practitioners and researchers both for improving the quality of sensory assessments and for testing new ideas for therapy. – *AJC*

Valentini M, Kischka U, Halligan PW.

Residual haptic sensation following stroke using ipsilateral stimulation.

JOURNAL NEUROLOGY, NEUROSURGERY AND PSYCHIATRY

2008;79:266-70.

NEURODEGENERATION: Progranulin: a promising growth factor?

The gene, GRN, which codes for progranulin is associated with 17q-linked frontotemporal dementia FTD with ubiquitin-immunoreactive inclusions. Progranulin is a 593 amino acid glycoprotein containing 7.5 cysteine-rich tandem repeats and is the precursor of granulin proteins. Progranulin is a secreted growth factor found in many tissue types and has been found to be important in development, wound repair, inflammation and tumorigenesis and while it is highly expressed in neurons of the cerebral cortex, its function in the central nervous system is yet to be clarified. Patients with GRN mutations have variable phenotypes although usually present with frontal variant FTD (fvFTD). Le Ber et al have now carried out a detailed study examining the clinical, neuropsychological and brain perfusion characteristics of patients with progranulin mutations to illustrate the highly variable phenotypes and neuropsychological profiles associated with these mutations and provide further evidence that clinical phenotype is a poor predictor of the underlying histopathology.

The authors have examined GRN in 502 patients out of which 352 had fvFTD. They have identified 18 mutations of which 7 were novel in 24 families including 32 symptomatic mutation carriers. GRN mutations presented with a variety of phenotypes with again 63% of the carriers having fvFTD whilst the remaining 37% had a variety of clinical diagnoses including primary progressive aphasia (PPA), corticobasal degeneration (CBD), dementia with Lewy body (DLB) or Alzheimer's disease (AD). Using DNA extracted from peripheral blood from the 502 patients the authors have looked for deletions of the GRN gene which might be responsible for the partial loss of functional progranulin. After sequencing, it was observed that in patients with either fvFTD or FTD-MND no mutations were present and further analysis showed no copy number variation.

Among the various results presented in this study it is interesting to note that Parkinsonism was frequent in the patients (41%), which fits with the observation of striatal lesions in GRN mutation carriers as well as the presence of visual hallucinations (25%) and motor apraxia (25%), both of which probably have an origin in the posterior parietal cortex and supplementary motor cortex. Episodic memory disorders were frequent (89%) while results show that hypoperfusion was observed in the hippocampus, parietal lobes and posterior cingulate gyrus and frontotemporal cortices. These results associated with GRN mutations are interesting in the sense that they again show how a single "genetic" disorder can have a variety of clinical representations and pathological profiles. Thus whilst all these mutations are responsible for a progranulin haploinsufficiency, there must be other factors that interact with this to explain the variation of the clinical presentation and pathology. – **CA Le Ber I, Camuzat A, Hannequin D, Pasquier F, Guedj E, Rovelet-Lecrux A, Hahn-Barma V, van der Zee J, Clot F, Bakchine S, Puel M, Ghanim M, Lacomblez L, Mikol J, Deramecourt V, Lejeune P, de la Sayette V, Belliard S, Vercelletto M, Meyrignac C, Van Broeckhoven C, Lambert JC, Verpillat P, Campion D, Habert MO, Dubois B, Brice A; French research network on FTD/FTD-MND.**

Phenotype variability in progranulin mutation carriers: a clinical, neuropsychological, imaging and genetic study."

BRAIN

2008;131:732-46.

Journal reviewers

Heather Angus-Leppan, Royal Free & Barnet Hospitals;
Chrystalina Antoniadis, Cambridge Centre for Brain Repair;
Roger Barker, Cambridge Centre for Brain Repair;
Lloyd Bradley, Colman Centre for Specialist Neurological Rehabilitation Services in Norwich;
Alasdair Coles, Cambridge University;
Andrew Larner, Walton Centre, Liverpool;
Mark Manford, Addenbrooke's Hospital, Cambridge and Bedford Hospitals;
Wendy Phillips, Addenbrooke's Hospital, Cambridge;
Robert Redfern, Morrision Hospital, Swansea;
Ailie Turton, University of Bristol.

EPILEPSY: How long to treat epilepsy?

When do you stop AED? In adults the decision is generally made on a mixture of medical evidence and social factors; are you going to have a baby or do you drive for a living? The MRC drug withdrawal study has been the benchmark used in making decisions regarding AED withdrawal for nearly two decades. This is a smaller study but nevertheless provides up-to-date information, which has both confirmatory and new elements. As a sign of the times, the consent form was drawn up by a legal representative to include possible claims from injuries arising as a result of seizures. Patients were included after at least two years of seizure-freedom. In fact two thirds had been seizure-free more than five years and as patients were only on monotherapy, this was a cohort of patients with milder epilepsy than in the MRC study. Amongst the exclusion criteria were juvenile myoclonic epilepsy or a very active EEG in patients with idiopathic generalised epilepsy. One hundred and sixty patients were randomised to either withdrawal or no withdrawal and followed up for a median of 47 months for patients on medication and 41 months for patients off medication. Additional data were recorded, including neuropsychological assessment, EEG, quality of life assessment. Relapse rates in the first twelve months were 7% of those on medication and 15% of those withdrawing medication. At the end of the twelve month double-blind period, of the 72 seizure-free patients in the non-withdrawal group, 62 chose to taper medication. This is a surprisingly large number and meant that almost as large a cohort stopped medication at the end of a year as were randomised to initial withdrawal. Their outcome over the next year was similar. Relapse rate was greatest in the first year after withdrawal and around 80% remained seizure-free at 36 months in both groups. On an intention to treat basis this means that the two arms are comparable but I don't think it answers the question of whether staying on medication carries a lower risk of relapse than coming off it in the longer term, since from one year onwards more or less the same number in both arms were actually continuing treatment. Numerous factors did not predict seizure-freedom, including age, gender, partial or generalised epilepsy, MRI, or duration of seizure-freedom. A normal neurological examination and seizure freedom on carbamazepine were associated with a significantly lower risk of relapse on withdrawal. Since carbamazepine is generally a first-line drug, those patients on it are likely to have had the easiest to control epilepsy. The patients in this study demonstrated a small but significant improvement in a range of neuropsychological tests after drug withdrawal.

So what can one conclude from this study. Firstly, in selected patients with easy to control epilepsy, drug withdrawal carries only a 20% risk of recurrence over three years. However, we can't really say what would happen if the patients stayed on the drugs over that time as a comparator. The only thing we can say is that in the first year the withdrawal group had a relapse risk of about 15%, compared to 5% in the continuation group. Secondly, withdrawal of long term medication in this study (but not all studies) is associated with an improvement in cognitive testing which is difficult to relate to activities of daily living. But the bottom line for the patient asking if their seizures will come back is only a slightly more educated: "I don't know." – **MM**

Erikssen J, Gulbrandsen, B, Gjerstad L.

Consequences of antiepileptic drug withdrawal: A randomized, double-blind study (Akershus study).

EPILEPSIA

2008;49:455-63.

EPILEPSY: Another cause of epileptic confusion

These investigators retrospectively analysed patients in whom continuous EEG monitoring had identified thirteen critically ill patients who experienced cyclical seizures with a periodicity of 30 seconds to twenty minutes, recurring for hours. The patients ranged in age from 12 weeks to 79 years and had a wide range of causes of seizures including hypoxic ischaemic injury, posterior reversible leucoencephalopathy syndrome, Ohtahara syndrome and lead poisoning. The mean interseizure interval was 7.6 minutes and the median 6.7 minutes and cycling lasted up to 48 hours with a mean if 7.9 hours and median 3 hours. Clinical state ranged from confusion to coma. Interestingly the ictal onset was left sided in 9, diffuse in 2 and right sided in 2 patients. Clearly this pattern will only be recognised if there is continuous EEG monitoring, as in many cases it would be over, before a routine EEG could be arranged. How many patients have I unknowingly seen with this problem? – **MM**

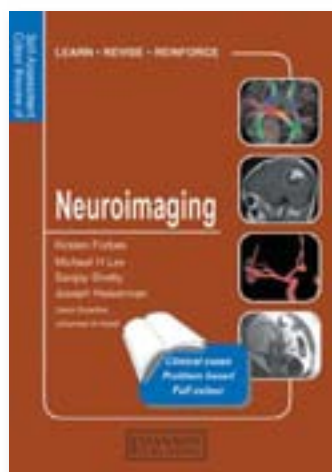
Friedman D, Schevon C, Emerson R, Hirsch L.

Cyclic electrographic seizures in critically ill patients.

EPILEPSIA

2008;49:281-7.

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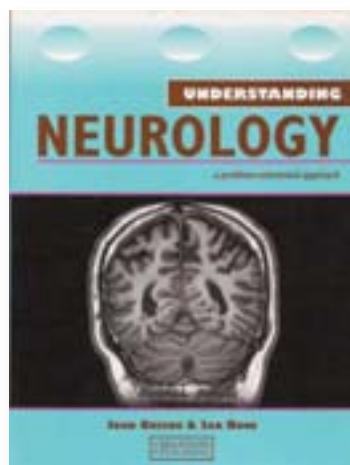
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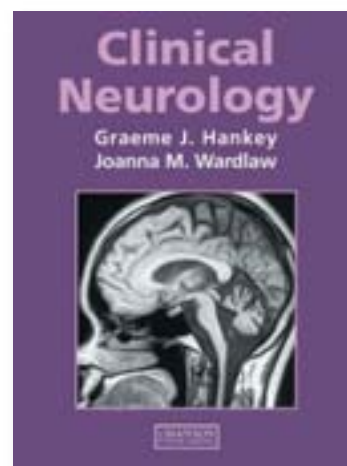
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Elekta chosen to deliver sophisticated brain mapping technology to the Nebraska Medical Center

The Nebraska Medical Center will receive its new Elekta Neuromag® MEG system in the spring / summer of 2008. With the MEG system from Elekta installed, neurosurgeons, neurologists and those in related fields will be able to non-invasively record human brain activity in real time, better and more accurately than ever before.

MEG technology is regarded as the most efficient method for tracking brain activity at millisecond resolution. Compared to EEG technology, MEG has uniquely accurate localisation capabilities. The Elekta Neuromag® 306-channel MEG sensor



array has a higher density of detectors than any other system on the market, leading to a more accurate representation of brain activity. The unique design of the sensors combined with advanced software makes it possible to gain data with unsurpassed detail, even from the deepest regions of the brain.

"The Elektra Neuromag® seems ideally suited to helping us to deal with the most difficult to treat epilepsy patients, many of whom do not respond well to medications," said Dr Sanjay Singh, Director of the Nebraska Epilepsy Centre.

For further information please contact inquiries@elekta.com

Elekta chosen to deliver advanced 3-D brain mapping technology to leading French Brain Imaging Facility



Elekta has signed a contract to deliver Elekta Neuromag®, the world-leading equipment for non-invasive registration of nerve cell activity using magnetoencephalography (MEG) technology to the new CEA facility - NeuroSpin in Saclay, France, one of the largest research sites for brain imaging in Europe.

The MEG system will be installed during spring of 2008 at the new CEA facility - called NeuroSpin - in Saclay which was recently inaugurated and is planned to soon become the largest European site for brain imaging studies. NeuroSpin will host up to 150 research scientists and engineers from CEA and INSERM with a large number of visiting groups. The core research staff of NeuroSpin has developed a long history of neuro-imaging research on method and instrumentation development (notably Position Emission Tomography (PET) and fMRI). In addition to the Elekta Neuromag MEG system, NeuroSpin will host four cutting-edge Magnetic Resonance Imaging (MRI) systems entirely dedicated to neuro-imaging research projects.

For further information please contact inquiries@elekta.com

Chelsea and Westminster opts for latest CT

Chelsea and Westminster Hospital NHS Foundation Trust has ordered the newly launched SOMATOM Definition AS and AS+ CT systems from Siemens via the NHS Supply Chain Framework.

The NHS Supply Chain infrastructure is helping to speed up the process of medical equipment procurement by opening up dialogue between suppliers and Trusts and delivering greater value for money.

The SOMATOM Definition AS and AS+ are the first CT scanners that adapt to virtually any patient and clinical need. The systems are suitable for routine diagnostic work and complex examinations including oncology, neurology and cardiology.

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fast coverage with up to 128 slices per rotation whilst maintaining delivery of crystal-clear images, free from movement artefacts and showing the finest anatomical details.

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Efficient regional anaesthesia in paediatrics

Dr Steve Roberts, orthopaedic anaesthetist at the Alder Hey Hospital in Liverpool, is using a number of SonoSite point-of-care ultrasound tools, including the SonoSite MicroMaxx® ultrasound system, to perform regional blocks on children of all ages. "The SonoSite systems are used throughout the hospital," he explained, "and have saved invaluable time, for example, in placing central lines in babies. They are especially useful for some of the children we treat with cerebral palsy for whom normal anatomical landmarks just don't apply because their limbs are quite often deformed. They may also have abnormal neurology and

sometimes don't respond to the more traditional technique of neurostimulation, so in all of these cases ultrasound makes it much easier to perform the blocks successfully."

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New titles from the Royal College of Physicians

Palliative care services: meeting the needs of patients

This Working Party report focuses on the philosophy of palliative care; the issues facing palliative care; oncological experience and its application to other diseases; mental health problems in palliative care and the organisation of palliative care and workforce provision.

The report will be relevant to all doctors and allied healthcare professionals and is essential reading for healthcare planners and commissioners of palliative care services.

Long-term neurological conditions Management at the interface between neurology, rehabilitation and palliative care

These guidelines build on the Quality Requirements in the National Service Framework for Long-term (Neurological) Conditions (LTNCs) to explore the interaction between specialist neurology, rehabilitation and palliative care services, and how they may best work together to provide long-term support for people with LTNCs and the family members who care for them. The guidelines



also provide practical advice for clinicians when caring for someone with an LTNC, as well as outlining indications for specialist referral.

For more information and to purchase copies, T. +44 (0)20 7935 1174 ext 358 or visit W. www.rcplondon.ac.uk/pubs

Spire Healthcare selects latest CT & MR imaging equipment for expansion of diagnostic services

Spire Healthcare, one of the leading independent hospital providers in the UK, has placed an order for six MRI and three CT scanners with Siemens as part of the drive to expand its range of diagnostic imaging services.

The order includes three SOMATOM Definition AS CT scanners, the first of which will be installed at Spire Norwich Hospital, a BUPA-accredited bowel cancer centre of excellence that also specialises in orthopaedic surgery. The CT scanner has a unique Adaptive Dose Shield that blocks unnecessary radiation ensuring the patient is only exposed to a clinically



relevant dose. It produces clear images whilst eliminating spiral artifacts, ensuring

high quality definition of bone and soft tissue. It can adapt to any patient or clinical need in routine diagnostic work and complex examinations in cardiology, neurology and oncology.

Six MAGNETOM Avanto 1.5T MRIs will also be delivered to Spire Healthcare sites. The systems will provide detailed image results to enable a flexible approach to examination procedures.

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Awards and Appointments

New Director of the Institute of Neurology appointed

Professor Alan Thompson has been appointed to the position of Director of the Institute of Neurology. He took up his new role on 1st April 2008, taking over from Professor Lemon who directed the Institute of Neurology for almost six years. Professor Thompson received his undergraduate and postgraduate degrees from Trinity College Dublin, and is the Garfield Weston Professor of Clinical Neurology and Neurorehabilitation at the Institute of Neurology, where he is head of the Research Department of Brain Repair and Rehabilitation. His research interests include the investiga-

tion of mechanisms that underlie disability in neurological conditions, particularly multiple sclerosis, the development of outcome measures which assess the impact of such conditions and the improvement of symptomatic management and service delivery in MS.

Ed Byrne, Dean of the Faculty of Biomedical Sciences and Head of the Medical School said, "We send our hearty congratulations to Professor Thompson and our warmest thanks to Professor Lemon for contributions past, present and future."



Doctors awarded grant from Ataxia UK

Dr Andrea Nemeth and Dr Kevin Talbot have been awarded a grant from Ataxia UK to develop high throughput genetic testing for patients with ataxia and related disorders. Each of the many forms of inherited ataxia is individually rare and, in common with other neurogenetic disorders, screening of multiple individual genes is time-consuming, laborious and expensive. Therefore, most patients do not have a formal molecular diagnosis and this also hampers research efforts and clinical trials.

This grant will allow them to utilise some of the resources which are being developed as part of the Biomedical Research Centre for translational research to develop a high throughput approach to genetic testing. The aim is to work towards providing a national service in this area.

MS Society Award Grants for project

Heidi Johansen-Berg, Margaret Esiri, Jackie Palace, Karla Miller and Steven Chance have been awarded a one-year grant for £136,000 from the MS Society. The project is entitled 'Feasibility study for MRI and neuropathological investigations of the role of anatomical connections in determining patterns of neurodegeneration in MS'. The project will

help set up collaborative post-mortem imaging and histological studies of MS and healthy human brains and will provide funds for a post-doctoral physicist, image analyst and neuroimaging/pathology researcher.



We'd love to hear your Award and Appointment news. Please send submissions to Anna Phelps
Email: anna@phelps1972.freemove.co.uk

COPAXONE® (glatiramer acetate)

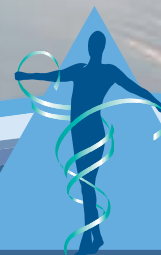
PRE-FILLED SYRINGE
PRESCRIBING INFORMATION

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 subcutaneously 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** - September 2007.

Information about adverse event reporting 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.

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COPAXONE®
(glatiramer acetate)

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Because health matters

Date of preparation: October 2007 Code: C0807/428a