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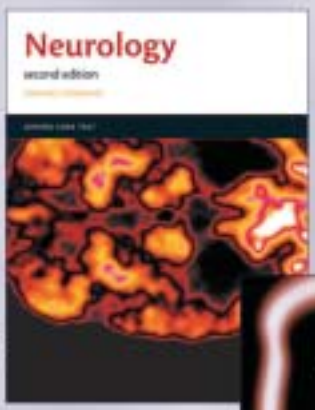

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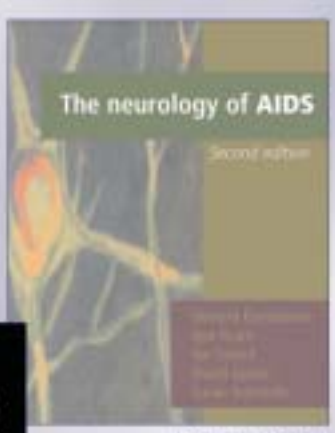

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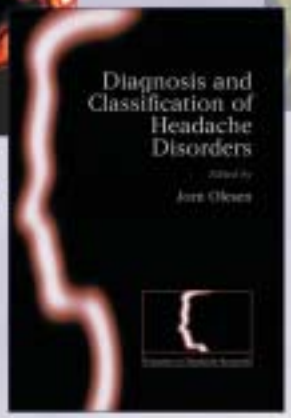

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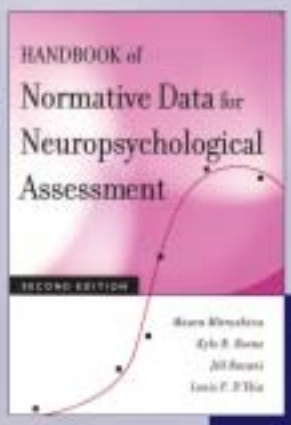

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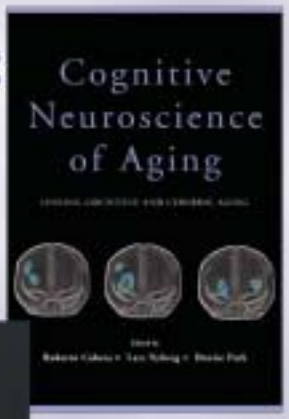

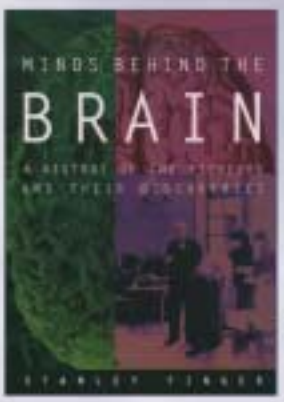

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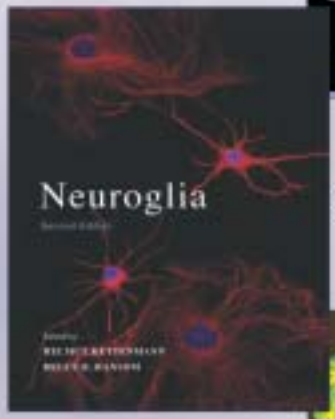

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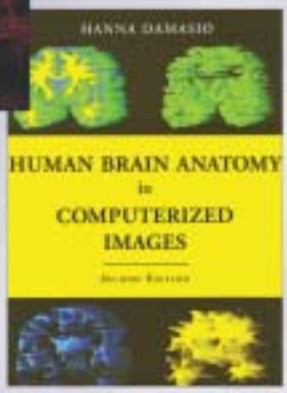

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Contents

January/February 2005

8 Review Article
Functional Symptoms in Neurology: Diagnosis and Management
Jon Stone, Alan Carson and Michael Sharpe

12 Review Article
Congenital Myasthenic Syndromes
David Beeson

16 Special Feature
NICE Guidelines for Epilepsy Management
Mark Manford

17 Neuropathology Article
Primary Brain Tumours
Daniel du Plessis

22 Rehabilitation Article
Visual Stress in Neurological Disease
Arnold Wilkins

24 Events

27 Conference News
International Symposium on PD and Restless Legs Syndrome; ECTRIMS; Vas-Cog Society News; Sino-British Joint Conference on Neurology

33 Drugs in Neurology
Pregabalin – a New Treatment for Partial Epilepsy and Neuropathic Pain
John Paul Leach

35 History of Neurology & Neuroscience
The Neurology of 'Alice'
Andrew Larner

38 Management Topic
The Management of Degenerative Lumbar Spine Disease
Nick Haden, Peter Whitfield and Anne Moore

40 Reviews

45 Books

46 News

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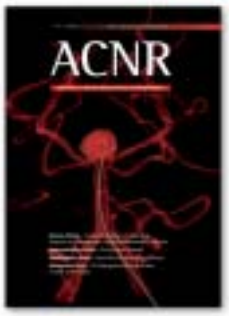

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This is the final issue of the fourth year of ACNR, and comes at a time that the website is attracting over 3000 visitors a month – a great tribute to Rachael Hansford, the force behind the logistical organisation of the journal and developer of the website. The site is home to our case reports and the latest, a case of tuberculous spinal arachnoiditis, is now available for you to download.

The two review articles in this issue come from Oxford and Edinburgh with David Beeson concentrating on congenital myasthenic syndromes and Michael Sharpe on "functional" disorders. The congenital myasthenic syndromes (CMS) are rare, and although many of us will not see such cases, are of great scientific value in revealing how the neuromuscular junction is organised and maintained. We are therefore fortunate to have David Beeson, who has made such a significant contribution to this field, lay out the various types of CMS and their basis ranging from abnormalities in the acetylcholine receptor and channel to mutations in proteins such as rapsyn and ColQ. This account encapsulates all that ACNR hopes to achieve through linking neurology to neurobiology.

Michael Sharpe and colleagues in their article take on the thorny issue of functional symptoms in neurology – an all too common scenario for those practising general neurology. Typically such patients are thought not to have a real neurological problems by neurologists and not to have a real psychiatric disorder by Psychiatrists – and so they are left floundering with little hope of receiving help. In this beautifully written review, Sharpe and colleagues tackle our prejudices head on with a series of helpful comments and strategies which will help convert a nihilistic approach to such patients into a more constructive one.

The neurosurgery series moves south to target the lumbar spine. Degenerative disease of the lumbar spine is common and often requires no major interventions, a point clearly made by Haden et al in their article. The authors take us through the anatomy, pathology and clinical presentations of lumbar spine disease before discussing how best to manage such patients. In particular they highlight that surgical treatment is rarely needed and that when it is indicated, relatively simple procedures may be as successful as more complex operations.

The neuropathology series in this issue, by Dr Daniel du Plessis, tackles brain tumours and lays out our current understanding of their histological classification and genetic basis. This review clearly describes the different imaging, clinical and neuropathological characteristics of brain tumours and complements well an earlier article by Jeremy Rees on their treatment (see volume 2, issue 2, available at www.acnr.co.uk). The article is lavishly illustrated and appears at a time when "brain-cancer stem cells" (Singh SK et al. Nature 2004;432:396-401) are beginning to be found which, in turn, may lead to further refinements in classification and therapy.

The rehabilitation article tackles the interesting topic of visual stress in neurological disease. Professor Arnold Wilkins, who has pioneered this concept, presents a thought provoking account which highlights the basic tenets of the theory and how this translates into effective therapies. In particular he discusses the use of coloured filters for glasses for disorders such as dyslexia and migraine.

Andrew Larner in our historical series takes us through the "looking glass" into the neurological world of Alice. In this fascinating account Andrew discusses a range of disorders which link incidents and characters in the two fictional works about Alice with the neurological problems of Dodgson and his acquaintances. This article is a real treat.

Mr and Mrs Burn provide our conference reports with Aileen reporting from Vienna on the ECTRIMS and RIMS meetings whilst poor old David only gets to go to Beijing to attend the Joint Sino-British conference on neurology. Both reports serve as very useful updates on several different neurological fields, including the various effects of different immunomodulatory drugs in MS. We also have the second in our "Drugs in Neurology" series with John Paul Leach from Glasgow discussing pregabalin – a new drug for epilepsy and neuropathic pain.

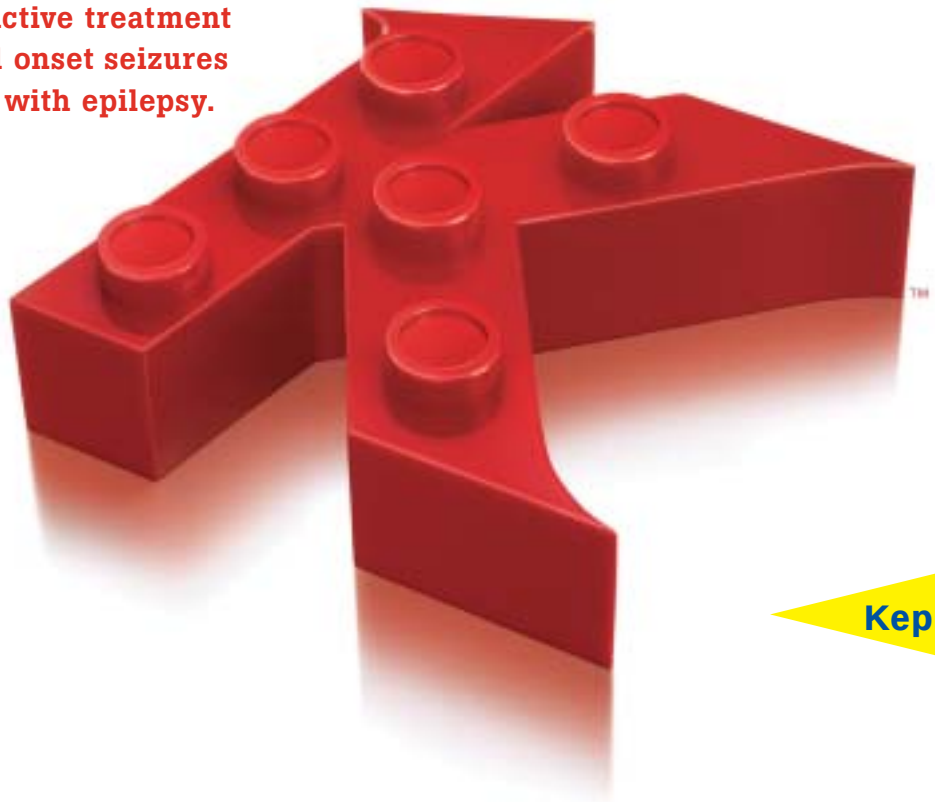
We also have an overview of the NICE guidelines on epilepsy from Mark Manford and our usual book and journal reviews.

So that's about it for another year. Thanks for all your support and feedback (see our "Letter to the Editor," an author's response to one of our earlier reviews), and do keep letting us know what you think and would like to see in ACNR – this includes any suggestions for relevant case reports, organised by Alastair Wilkins (E-Mail: aw255@cam.ac.uk).

We look forward to our fifth year!

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

For adjunctive treatment of partial onset seizures in adults with epilepsy.



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References:
1. Krakow K, Walker M, Otoul C, Sander JWAS. Long-term continuation of Levetiracetam in patients with refractory epilepsy. *Neurology.* 2001; 56: 1772-1774. **2.** Patsalos PN. Pharmacokinetic profile of Levetiracetam: toward ideal characteristics. *Pharmacol Ther.* 2000; 85: 77-85. **3.** French J, Edrich P, Cramer JA. A systematic review of the safety profile of levetiracetam: a new antiepileptic drug. *Epilepsy Res.* 2001; 47: 77-90.

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Functional Symptoms in Neurology: Diagnosis and Management

Around one third of all new neurology outpatients report symptoms such as dizziness, weakness, tingling and blackouts that have little or no disease to explain them.[1,2] This fact is often startling to medical students who imagine neurology is all lesion localisation, but is usually greeted with heavy hearted recognition by anyone who has been in the speciality for a while. In this article we try to offer some guidance on how patients with these symptoms can be diagnosed and effectively managed in the short space of time available for a typical neurological consultation. We will focus on the management of patients with the more severe symptoms of functional paralysis and non-epileptic attacks. This approach can however be modified for those with different or less severe symptoms.

What should we call these symptoms?

There is a baffling array of terms, to list a few: 'non-organic', 'psychogenic', 'hysterical', 'somatisation', 'conversion disorder' and (the title we were given for this review) 'unexplained neurological symptoms'. We prefer the old term 'functional' symptoms because: (a) it doesn't offend the patient by implying their symptoms are 'all in the mind'[3]; (b) it sidesteps unhelpful and illogical dualistic debates about whether symptoms are in the mind or the brain; (c) functional imaging studies are beginning to discover the neural correlates for some symptoms;[4] (d) neurologists can diagnose them reliably and on positive criteria; and (e) it provides a useful explanation to the patient for why things have gone wrong ('Your nervous system is not damaged but it is not functioning properly') and what might be done to improve them ('These are the things that you can do to help your nervous system function again') in a way that gently opens the door to psychological treatments and potential drug treatments. But more of that later….

Patients with functional symptoms – why bother?

For a neurological readership, this is a question that unfortunately still needs to be addressed. Functional symptoms receive scant attention from authors of textbooks or in training. Despite making up such a large proportion of the workload, many neurologists consider these patients to be merely an irritation and 'not proper neurology'. The following concerns about these patients often arise to defend this point of view:

1. **Are they making it all up?** – Distinguishing malingering (where symptoms are under voluntary control) from hysteria (where they are not) is extremely difficult since both diagnoses rely on inconsistency. The only reliable way of telling the two apart is to obtain a confession or uncover an example of gross inconsistency between the consultation room and other situations (for example a wheelchair bound patient who is filmed playing tennis). In favour of the idea that most patients are not making their symptoms up are long term follow up studies that find most patients remain symptomatic and disabled in the long term,[5-7] the similarities in the way patients describe their complaints and the keenness of most patients to pursue investigations. There is no doubt that some patients who simulate symptoms do find their way in to NHS neurology clinics, although many more of these will be seen in medico-legal assessments. However, we take the approach that (a) outside medical legal practice it is our job simply to help the patient and not to detect those malingering for financial gain and (b) simulating symptoms solely in order to obtain medical care (factitious disorder) is itself a sign of a significant problem. Finally if a patient is apparently exaggerating their symptoms it is worth asking yourself whether they might be doing this to try to convince you, as a sceptical doctor, that there is something wrong.

2. **Are they really treatable?** Studies of neurological symptoms have lagged behind other functional symptoms but there is systematic review level evidence for the effectiveness of cognitive behavioural therapy[8] (similar to treatment given by neurologists in the 19th century and then called 'rational persuasion') and antidepressant drugs[9] ('nerve tonics') in the treatment of a wide range of other functional somatic symptoms such as fatigue, fibromyalgia and irritable bowel syndrome. For chronic fatigue systematic reviews indicate that the number of patients that need to be treated with CBT to achieve a good physical outcome is only two. Of course many patients don't get better but that's no different to most other conditions we manage as neurologists.

3. **Perhaps many will develop a disease cause for their symptom?** Neurologists generally don't worry about this too much; but psychiatrists do, largely because of an influential paper by Slater[10] published in 1965.

Table 1: Key points when taking a history from someone with functional symptoms
(in a suggested order)

1. List the symptoms	*Start by writing a list of all current symptoms. Say that you'll come back to them individually later. Ask everyone about fatigue, pain, sleep and concentration. Avoid descriptions of past events at this stage*
2. Onset and time course	*If vague, use a 'graph' of symptoms over time. If sudden, look carefully for somatic symptoms of panic especially derealisation / depersonalisation*
3. Previous functional symptoms	*For example: Irritable bowel syndrome, chronic fatigue, early hysterectomy in women, testicular complaints in men. Try to corroborate with medical notes.*
4. What do they think is wrong with them?	*What have they been worrying about? Anything specific like MS? What have other doctors said? What does the patient think will help?*
5. Asking about depression and anxiety	*Leave until the end of the history. Instead of 'Are you depressed or anxious?' try 'Do your symptoms get you down?' or 'Do you worry about your symptoms?'*

Jon Stone is an SpR in Neurology in Edinburgh. He has spent the last five years engaged in research on functional symptoms in neurology, particularly the symptom of weakness.

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Slater was wrong, and the misdiagnosis rate at follow up for patients with functional neurological symptoms in modern case series is consistently under 10% and usually around 5%.[5-7] This is the same rate as for other neurological and psychiatric conditions such as MS and schizophrenia. When neurologists do get it wrong, gait and movement disorders and patients with a psychiatric history (probably because this biased the diagnosis) figure disproportionately.

4. **Aren't they just the worried well? Surely patients with 'real' disease are much more deserving?** This traditional attitude leads to irritable doctors and angry patients. Disease is just one of many causes of symptoms and illness. Normal physiology, psychology and the society we live in all play their part. We know that patients with functional symptoms are just as disabled and even more distressed than their diseased counterparts.[11] There is a personal choice to make here about your role as a doctor; are you interested in helping all patients with symptoms, or only those whose symptoms are accompanied by disease?

Assessing the patient with functional symptoms

Table 1 outlines an approach to history taking in the patient with functional symptoms. We find that starting with an exhaustive list of the patient's physical symptoms ('draining the symptoms dry') gets the consultation off to a good start and can actually save time later on. Eliciting the patient's fears and beliefs about their symptoms and their previous experience of doctors can be helpful in helping you to individualise the explanation you give them for their illness. Depression and anxiety are best asked about at the end of the history framing the question around the physical symptoms (e.g. 'has this weakness got you down?' rather than 'do you feel depressed?') to avoid the patient assuming that you are jumping to unwanted (psychological) conclusions. Whilst all of this information is helpful in planning management, it does not really assist greatly in making the neurological diagnosis. For that we are particularly reliant on the physical examination (Table 2), partly to make sure there are no definite signs of organic disease but largely to look for positive physical signs that the symptom is functional.

The most useful physical sign in the detection of functional paralysis is Hoover's sign (Figure 1). It is simple to learn and use - but be careful in patients who might have neglect. Bedside tests for sensory symptoms are unreliable and isolated sensory symptoms are hard to distinguish with certainty from demyelination and other central causes. Checklists for diagnosing non-epileptic attacks are notoriously unreliable but the features listed in Table 1 are a starting point. Video EEG is the gold standard investigation (although even this can miss frontal and other seizures with a deep source). Psychogenic movement disorders are increasingly recognised but are particularly difficult to diagnose.[12] Intravenous sedation or hypnosis demonstrating reversibility over a significant length of time may be particularly useful both diagnostically and for treatment if handled sensitively. Further useful information on diagnosis of these and other symptoms is available elsewhere.[12-17]

Managing the patient with functional symptoms

A good assessment is the basis for effective treatment. We try wherever possible to show the patient how we are making the diagnosis. This may include a demonstration of Hoover's sign or perhaps a videotape of an examination under sedation. Patients appreciate this as they can 'smell' a doctor who appears to be keeping things from them.

Table 2: Physical Signs and investigations of functional neurological symptoms

Helpful signs	Unhelpful signs
Weakness and Sensory disturbance[13;17] *Hoover's sign (Figure 1)** *The monoplegic 'dragging' gait*	***General*** *'La belle indifference'** *Looking depressed*
Non-epileptic attacks[14] *Eyes shut during attack** *Resistance to eye opening** *Prolonged attack (>2 minutes)** *'Reactivity' during unconsciousness** *Post-ictal crying** *Videotelemetry*	***Weakness and Sensory Disturbance*** *Collapsing weakness* *Midline splitting** *Split vibration across the forehead**
Movement disorders[12] *Entrainment of tremor**	***Non-Epileptic attacks*** *Tongue biting** *Incontinence** *Pelvic thrusting** *Injuries**
Visual Symptoms[15] *Tubular field defect* *Spiralling visual fields*	***Movement Disorders*** *Worsening with anxiety*

Further explanation can be found in the references given. *some evidence from controlled studies

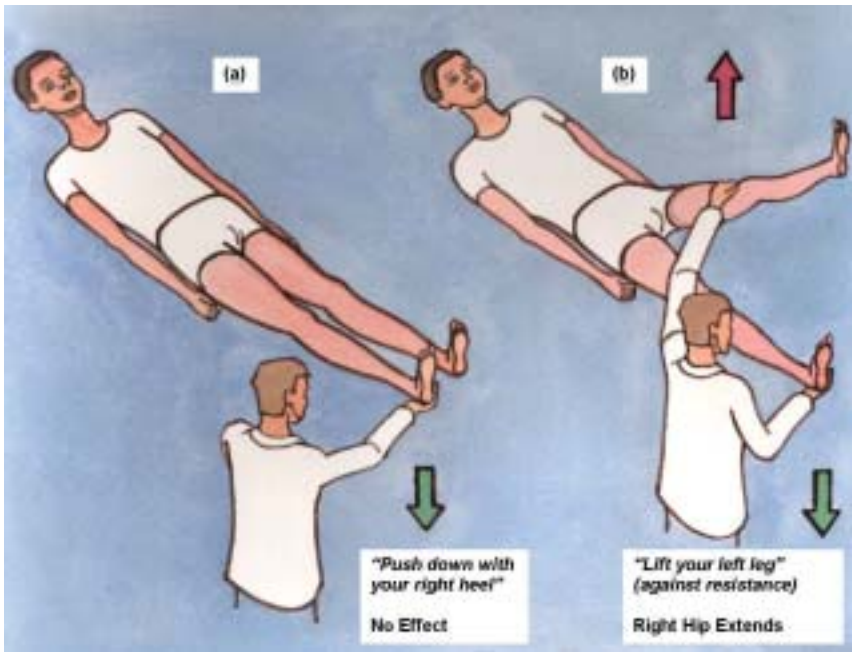


Figure 1: Hoover's sign - (a) Hip extension is weak when tested directly (b) Hip extension is normal when the patient is asked to flex the opposite hip against resistance. (reproduced by permission of BMJ group[13])

There is a misconception that all the patient wants at this stage is reassurance that they don't have disease. Of course patients benefit from being told that they do not have epilepsy or MS but usually what they want more is to be told what they do have.

Table 3 gives an indication of the kind of explanations that help in our experience. Using the phrases 'functional paralysis' or 'non-epileptic attacks' rather than 'psychogenic' makes the diagnosis more acceptable to the patient and makes it easy to give the patient a copy of their clinic letter and a leaflet about their symptoms (Figure 2). This is all part of persuading the patient that (a) you believe them; (b) they have something recognisable and

Table 3: The elements of a constructive explanation of functional neurological symptoms

Element	Example
1. Indicate you believe the patient	*"I do not think you are making up or imagining your symptoms"*
2. Explain what they don't have	*"You do not have MS, epilepsy etc"*
3. Explain what they do have	*"You have 'functional weakness' – this is a common problem. Your nervous system is not damaged but it is not working properly. That is why you cannot move your arm"*
4. Emphasise that it is common	*'I see lots of patients with similar symptoms'*
5. Emphasise reversibility	*'Because there is no damage you have the potential to get better'*
6. Emphasise that self-help is a key part of getting better	*'I know you didn't bring this on but there are things you can do to help it get better'*
7. Metaphors may be useful	*'The hardware is alright but there's a software problem'; 'Its like a car / piano that's out of tune'; 'Its like a short circuit of the nervous system' (non-epileptic attacks)*
8. Introducing the role of depression/anxiety	*'If you have been feeling low/worried that will tend to make the symptoms even worse'*
9. Use written information	*Send the patient their clinic letter. Give them a leaflet*
10. Suggesting antidepressants	*'We find that 'so-called' antidepressants often help these symptoms, even in patients who are not feeling depressed by 'altering nervous system function.'*
11. Making the psychiatric referral	*'I don't think you're mad but Dr X has a lot of experience and interest in helping people to manage and overcome their symptoms'*

potentially reversible and (c) that they can help themselves to get better. For some patients this may be all that is required.

More advanced treatment involves some form of rehabilitation. This may mean referral to an experienced physiotherapist, a liaison psychiatrist, specialist rehabilitation service or perhaps in the future a nurse practitioner with specific expertise in a cognitive behavioural approach to somatic complaints. In some patients there is a role for treatment with antidepressants. However, public belief about these agents is such that very careful explanation may be required, for example: 'These are drugs that have widespread effects on the nervous system and are helpful even in people who are not depressed'. For some patients there may be also a role for more unusual treatments such as hypnosis[18] or examination under sedation.[19]

Conclusion

Patients with functional symptoms make up a large proportion of an average neurologist's workload. These patients are, on the criteria of distress, disability and persistence of symptoms, as deserving as patients with pathologically defined disease. If you are prepared to accept the reality of their symptoms and to use a less overtly 'psychological' approach than has traditionally been advocated you may find that they can be much more rewarding to treat than you thought.

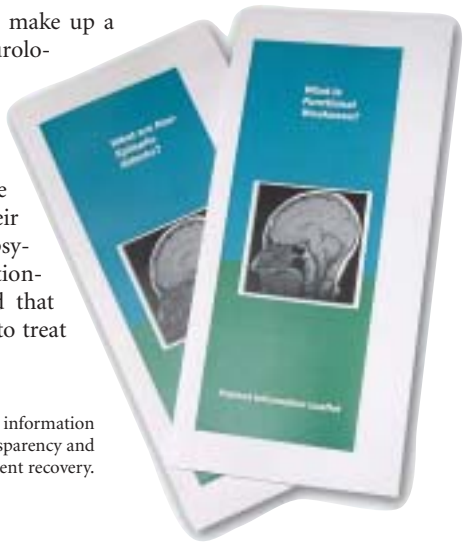


Figure 2: Written information helps transparency and patient recovery.

References

1. Carson AJ, Ringbauer B, Stone J, McKenzie L, Warlow C, Sharpe M. *Do medically unexplained symptoms matter? A prospective cohort study of 300 new referrals to neurology outpatient clinics.* J Neurol Neurosurg Psychiatry 2000;68:207-10.
2. Nimnuan C, Hotopf M, Wessely S. *Medically unexplained symptoms: an epidemiological study in seven specialities.* J Psychosom Res 2001;51:361-7.
3. Stone J, Wojcik W, Durrance D, Carson A, Lewis S, MacKenzie L et al. *What should we say to patients with symptoms unexplained by disease? The "number needed to offend".* BMJ 2002;325:1449-50.
4. Vuilleumier P, Chicherio C, Assal F, Schwartz S, Skusman D, Landis T. *Functional neuroanatomical correlates of hysterical sensorimotor loss.* Brain 2001;124:1077-90.
5. Carson AJ, Best S, Postma K, Stone J, Warlow C, Sharpe M. *The outcome of neurology outpatients with medically unexplained symptoms: a prospective cohort study.* J.Neurol.Neurosurg.Psychiatry 2003;74:897-900.
6. Stone J, Sharpe M, Rothwell PM, Warlow CP. *The 12 year prognosis of unilateral functional weakness and sensory disturbance.* J Neurol Neurosurg Psychiatry 2003;74:591-6.
7. Crimlisk HL, Bhatia K, Cope H, David A, Marsden CD, Ron MA. *Slater revisited: 6 year follow up study of patients with medically unexplained motor symptoms.* BMJ 1998;316:582-6.
8. Kroenke K, Swindle R. *Cognitive-behavioral therapy for somatization and symptom syndromes: a critical review of controlled clinical trials.* Psychother Psychosom 2000;69:205-15.
9. O'Malley PG, Jackson JL, Santoro J, Tomkins G, Balden E, Kroenke K. *Antidepressant therapy for unexplained symptoms and symptom syndromes.* J Fam Pract 1999;48:980-90.
10. Slater ET. *Diagnosis of 'hysteria'.* BMJ 1965;i:1395-9.
11. Carson AJ, Ringbauer B, MacKenzie L, Warlow C, Sharpe M. *Neurological disease, emotional disorder and disability: they are related. A study of 300 consecutive new referrals to a neurology outpatient department.* J Neurol Neurosurg Psychiatry 2000;68:202-6.
12. Gálvez-Jiménez N, Lang AE. *Psychogenic movement disorders.* In Watts RL, Koller WC, eds. Movement disorders: neurologic principles and practice, pp 715-32. New York: McGraw-Hill, 1997.
13. Stone J, Zeman A, Sharpe M. *Functional weakness and sensory disturbance.* J Neurol Neurosurg Psychiatry 2002;73:241-5.
14. Reuber M, Elger CE. *Psychogenic nonepileptic seizures: a review and update.* Epilepsy and Behaviour 2003;4:205-16.
15. Beatty S. *Non-organic visual loss.* Postgrad.Med.J. 1999;75:201-7.
16. Furman JM,.Jacob RG. *Psychiatric dizziness.* Neurology 1997;48:1161-6.
17. Lempert T, Brandt T, Dieterich M, Huppert D. *How to identify psychogenic disorders of stance and gait. A video study in 37 patients.* J Neurol 1991;238:140-6.
18. Moene FC, Spinhoven P, Hoogduin CA, Van Dyck R. *A randomized controlled clinical trial of a hypnosis-based treatment for patients with conversion disorder, motor type.* Int J Clin Exp Hypn 2003;51:29-50.
19. White A, Corbin DO, Coope B. *The use of thiopentone in the treatment of non-organic locomotor disorders.* J Psychosom Res 1988;32:249-53.

Congenital Myasthenic Syndromes

The congenital myasthenic syndromes (CMS) are a heterogeneous group of inherited disorders affecting neuromuscular transmission. The syndromes show characteristic 'myasthenic' fatigable muscle weakness that varies in severity. The superficial phenotypes of the various CMS are often similar but electrophysiological, cytochemical and morphological studies have helped delineate those associated with postsynaptic, synaptic or presynaptic functions (reviewed[1,2]). Moreover, careful clinical examination may often provide clear pointers both to identify the clinical syndrome and to the particular gene involved. A definite genetic diagnosis is important not only for genetic counselling but also because the various gene mutations can give rise to syndromes that have very different underlying molecular mechanisms requiring different treatments.

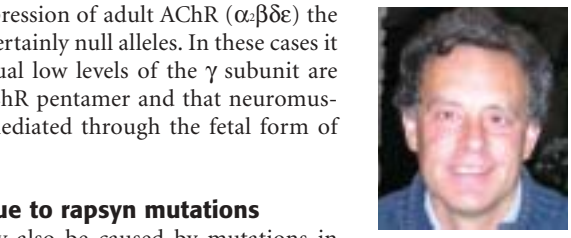
To date, the majority of CMS have abnormalities in postsynaptic function at the neuromuscular junction. Underlying mutations have been located within the genes that encode the muscle acetylcholine receptor (AChR) and the AChR-clustering protein, rapsyn (Figures 1 and 2).

AChR deficiency due to ε-subunit mutations

AChR deficiency is a recessive disorder with age of onset in infancy but is generally non-progressive. As its name suggests, the syndrome is characterised by reduced numbers of AChR in the postsynaptic membrane. Although mutations causing AChR deficiency occur rarely in other AChR subunits, the overwhelming majority are in AChR ε-subunit gene, and at least 80 different mutations have now been identified. Patients may have a homozygous mutation or be compound heterozygotes for different defective ε-subunit alleles. The mutations are located along the length of the gene and the only clear example of a founder effect is seen in the ethnic gypsy population of south east Europe where the single nucleotide deletion ε1267delG is frequently found.[3] Although some of the ε-subunit mutations may result in low level expression of adult AChR ($\alpha_2\beta\delta\varepsilon$) the majority are almost certainly null alleles. In these cases it is thought that residual low levels of the γ subunit are recruited into the AChR pentamer and that neuromuscular transmission mediated through the fetal form of the AChR ($\alpha_2\beta\gamma\delta$).

AChR deficiency due to rapsyn mutations

AChR deficiency may also be caused by mutations in rapsyn. Rapsyn is a 43 kDa protein involved in the development and maintenance of the neuromuscular junction and, in particular, plays a primary role in clustering the AChR at the tops of the postsynaptic junctional folds (Figure 2).[4] By contrast with the AChR ε-subunit mutations where most kinships have 'private' mutations, the missense mutation rapsyn-N88K has been found either homozygous or as a compound heterozygote in all rapsyn deficiency patients (except those with rapsyn gene promoter mutations). The common occurrence of N88K mutations facilitates rapid genetic screening. Although both AChR ε-subunit and rapsyn mutations can result in loss of AChR at the endplate with similar histopathological and electrophysiological properties, clues as to which gene harbours the mutations can be gleaned from analysis of the clinical features and disease history. In particular, patients with rapsyn mutations frequently show mild joint contractures at birth and are prone to severe sudden apnoeic attacks during infancy and early childhood usually associated with upper respiratory tract infections. Between these episodic attacks myasthenic symptoms are usually mild. By contrast, patients with ε-subunit mutations show profound ophthalmoplegia, do not, in general, show a fluctuating disease course or have joint contractures at birth.[5] Some patients with rapsyn mutations do not present with symptoms in childhood but rather present in adolescence or adulthood.[6] This 'late-onset' phenotype may be easily be mistaken for seronegative immune-mediated myasthenia gravis.



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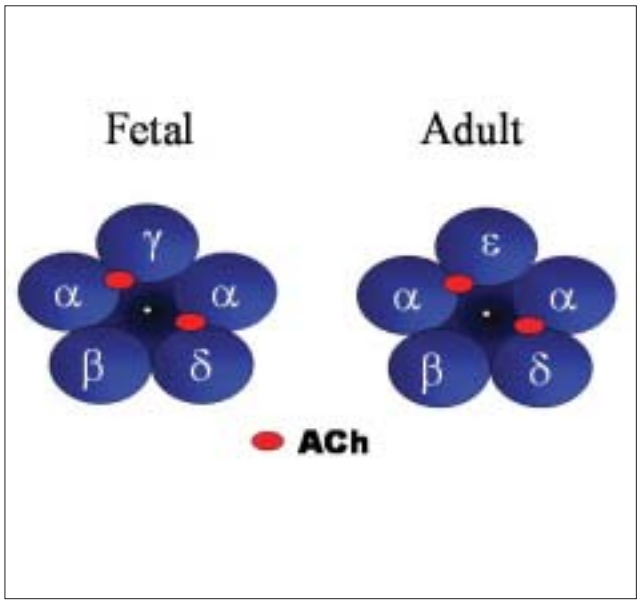

Figure 1: Representation of the AChR as viewed from the synaptic cleft. Each AChR molecule has a molecular mass of around 250,000 kDa, and is made up of five subunits arranged pseudosymmetrically around a central ion pore. In mammalian muscle there are two types of AChR, a fetal form consisting of $\alpha_2\beta\gamma\delta$ and an adult form, $\alpha_2\beta\varepsilon\delta$, in which the ε subunit replaces the γ. In normal synaptic transmission the binding of two ACh molecules to a site at the αδ and αγ/αε interface results in a brief opening of the channel pore.

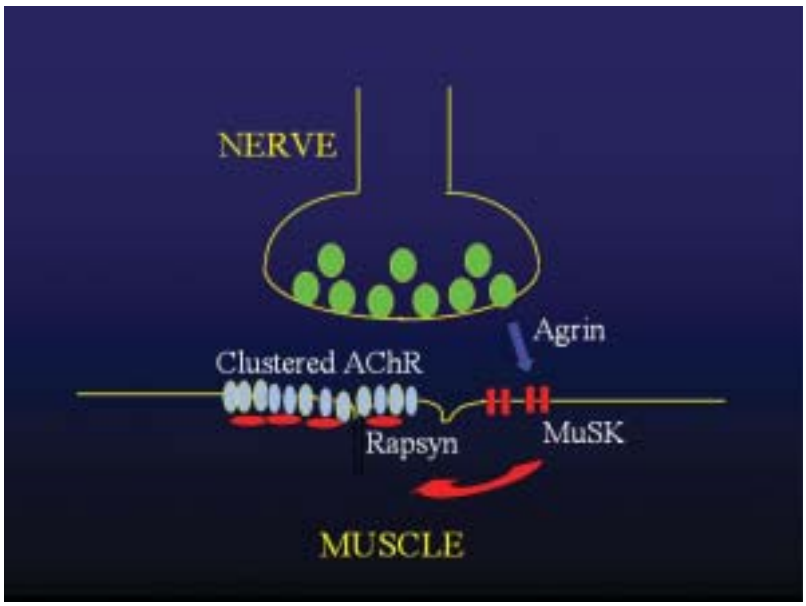

Figure 2: AChR are highly concentrated (~10,000 μM^2) on the crests of the postsynaptic folds at the neuromuscular junction. The pathway that results in the localisation of the AChR involves the release of agrin from the nerve terminal, its interaction with muscle specific tyrosine kinase (MuSK), phosphorylation of rapsyn which then clusters and anchors the AChR to the cytoskeleton. Mutations of rapsyn underlie many cases of AChR deficiency syndrome.

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Slow channel and fast channel syndromes

In these syndromes kinetic abnormalities of AChR ion channel function rather than AChR number are the primary underlying cause of disease. The fast channel syndrome (autosomal recessive) has a similar phenotype to AChR deficiency, but is rarer. The slow channel syndrome (autosomal dominant) may present in childhood, adolescence or adult life and is progressive. In the fast channel syndrome the combination of a null allele, such as εS143L, with the mutation εP121L unmasks the phenotypic effects of this mutation that are not seen in the heterozygous state. εP121L causes AChR activations to be fewer and shorter than normal and thus overall AChR containing the εP121L mutation have a reduced response to ACh.[7] Mutations with similar kinetic effects to εP121L are also found in AChR α and δ subunits.

The slow channel syndrome was first described by Engel and colleagues in 1982.[8] Electrophysiological recordings showed an extended decay phase of the miniature endplate potentials suggesting that prolonged ion channel opening might cause the disorder. In addition, it was noted in ultrastructural studies that there was damage to the muscle at the synaptic sites suggesting that this might be an excitotoxic disorder caused by "calcium overload" in the endplate region. To date, at least 15 different mutations underlying the slow channel syndrome have been identified. The mutations occur in all four subunits that make up adult AChR, and each is a point mutation leading to a single amino acid change. In vitro expression studies demonstrate that each of the mutations prolongs ion channel activations and thus is responsible for the pathogenic gain of function for the AChR. The mutations may be located in different functional domains within the subunits and detailed electrophysiological analysis has defined varying molecular mechanisms through which the channel activations are prolonged. In brief, mutations which are located in the M2 transmembrane domain region, which, as previously mentioned, is thought to line the channel pore, act predominantly by slowing channel closure, and thus result in long individual channel openings. The primary effect of some mutations in the extracellular domain (i.e. αG153S) is to increase the affinity of AChR for ACh. In this case, rather than long individual openings, the AChR oscillates between the open and closed states during the extended period of ACh occupancy before it finally dissociates and the channel remains shut.

Mutations in other proteins at the neuromuscular junction

In addition to mutations in the AChR subunit genes, mutation in other molecules at the neuromuscular junction could also be responsible for some CMS. Mutations in the gene encoding ColQ, the collagen-like tail that attaches the asymmetric form of acetylcholinesterase to the basal lamina at the neuromuscular junction, have been identified[9,10] and underlie endplate acetylcholinesterase deficiency syndrome (autosomal recessive). Loss of acetylcholinesterase from the synaptic cleft increases the time that ACh is available to bind to the AChR with physiological consequences similar to the slow channel syndrome. Mutations in choline acetyltransferase (ChAT) affect the release of ACh from the presynaptic nerve terminal, and give rise to a CMS-with episodic apnoea, in which the sudden apnoeic attacks are similar to those seen in patients with rapsyn mutations.[11] Finally, a CMS associated with mutations in the voltage gated sodium channels (SCN4A) located in the depths of the postsynaptic folds has been reported.[12]

Treatment strategies

An understanding of the molecular mechanisms that underlie disease allows a rational approach to therapy. Thus patients with AChR deficiency syndrome, the fast channel syndromes, rapsyn and ChAT mutations respond well to anticholinesterase treatments which prolong the lifetime of ACh within the synaptic cleft. Similarly, 3,4-diaminopyridine, which increases quantal release of ACh and consequently the effective concentration of ACh within the synaptic cleft, has been found to be particularly effective for patients with fast channel syndrome. Conversely, compounds which block the AChR when in the open state, are potentially therapeutic for patients with slow channel syndrome, and indeed, quinidine sulphate, a long-lived AChR channel blocker, has been found to be beneficial. At present no effective treatment is available for patients with acetylcholinesterase deficiency.

Summary

The diversity of mutations and clinical phenotypes of inherited disorders at the neuromuscular junction is providing novel insights into the detail of ion channel function and the pathogenic consequences of dysfunction. Their study provides a model for the investigation of ligand-gated ion channel dysfunction in the CNS.

References

1. Engel AG, Ohno K, Sine SM. *Sleuthing molecular targets for neurological disease at the neuromuscular junction.* Nat Rev Neurosci 2003;4:339-352.
2. Beeson, D. and Newsom-Davis, J. *Mutations affecting muscle nicotinic acetylcholine receptors and their role in congenital myasthenic syndromes.* In Channelopathies, eds F. Lehmann-Horn and K. Jurkat-Rott. Elsevier Science B V. 2000;pp85-114.
3. Abicht A, Stucka R, Karcagi V, et al. *A common mutation (epsilon 1267delG) in congenital myasthenic patients of gypsy origin.* Neurology 1999;53:1564-1569.
4. Sanes J, LichtmanJ. *Induction, assembly, maturation and maintenance of a postsynaptic apparatus.* Nat Neurosci Rev 2001;2:791-803.
5. Burke G, Cossins J, Maxwell S, Robbs S, Nicolle M, Vincent A, Newsom-Davis J, Palace J, Beeson D. *Distinct phenotypes of congenital acetylcholine receptor deficiency.* Neuromuscul. Disord. 2004;14:356-364.
6. Burke G, Cossins J, Maxwell S, Owens G, Vincent A, Robb S, Nicolle M, Hilton-Jones D, Newsom-Davis J, Palace J, Beeson D. *Rapsyn mutations in hereditary myasthenia: distinct early- and late- onset phenotypes.* Neurology 2003; 61:826-828.
7. Ohno K, Wang H-L, Milone M, Bren N, Brengman J, Nakano S, Quiram P, Pruitt J, Sine S and Engel AG. *Congenital myasthenic syndrome caused by decreased agonist binding affinity due to a mutation in the acetylcholine receptor ε subunit.* Neuron 1996;17:157-170.
8. Engel AG, Lambert H, Mulder DM, Torres CF, Sahashi K, Bertorini TE, Whitaker JN. *A newly recognised congenital myasthenic syndrome attributed to a prolonged open time of the acetylcholine-induced ion channel.* Ann. Neurol.1982; 553-569.
9. Donger C, Krejci E, Serradell AP, Eymard B, Bon S, Nicole S, Chateau D, Gary F, Fardeau M, Massoulie J, Guicheney P. *Mutation in the human acetylcholinesterase-associated collagen gene, ColQ, is responsible for congenital myasthenic syndrome with end-plate acetylcholine esterase deficiency (type 1c).* Am J Hum Genet 1998;63:967-975.
10. Ohno K, Brengman J, Tsujino A, Engel AG. *Human endplate acetycholinesterase deficiency caused by mutations in the collagen-like tail subunit (ColQ) of the asymmetric enzyme.* Proc Natl Acad Sci USA 1998;95:9654-9659.
11. Ohno K, Tsujino A, Brengman J, Harper M., Bajzer Z, Udd B, Beyring R., Robb S, Kirkham F, Engel AG. *Choline acetyltransferase Mutations cause myasthenic syndrome associated with episodic apnea in Humans.* Proc Natl Acad Sci USA. 2001;98:2017-2022.
12. Tsujino A, Maertens C, Ohno K, Shen X-M, Fukuda T, Harper M, Cannon S, Engel AG. *Myasthenic syndrome caused by mutation of the SCN4A sodium channel.* Proc. Natl. Acad. Sci. USA. 2003;100:7377-7382.

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Mirapexin 0.088mg, Mirapexin 0.18mg and Mirapexin 0.7mg tablets containing 0.125mg, 0.25mg and 1mg respectively of pramipexole salt (dihydrochloride monohydrate). **Indications:** The treatment of the signs and symptoms of idiopathic Parkinson's disease, alone (without levodopa) or in combination with levodopa. **Dosage and Administration:** Adults and Elderly Patients: Administration: Give tablets orally with water in equally divided doses three times per day. Initial treatment: 3 x 0.088mg base (3 x 0.125mg salt) per day for first 5 days. Then 3 x 0.18mg base (3 x 0.25mg salt) per day for 5-7 days, and then 3 x 0.35mg base (3 x 0.5mg salt) per day for 5-7 days. Increase the daily dose by 0.54mg base (0.75mg salt) at weekly intervals to a maximum dose of 3.3mg base per day (4.5mg salt per day). If necessary, increases of administration can be made at doses higher than 0.09mg base per day (0.125mg salt per day). Maintenance treatment should be in the range of 0.264mg base (0.375mg salt) up to a maximum of 3.3mg base (4.5mg salt) per day, adjust dose based on clinical response and tolerability, reduce doses used in titration and maintenance phases if necessary. Treatment discontinuation: Abrupt discontinuation of dopaminergic therapy can lead to the development of neuroleptic malignant syndrome. Reduce dose by 0.54mg base (0.75mg salt) per day, to 0.54mg base per day (0.75mg salt per day). Thereafter reduce dose by 0.264mg base (0.37mg salt) per day. Renal impairment: See SPC for revised dosage schedules. Hepatic impairment: Dose adjustment in hepatic failure is probably not necessary. **Children:** Not recommended. **Contra-indications:** Hypersensitivity to pramipexole or any other component of the product. **Warnings and Precautions:** Reduce dose in renal impairment, inform patients that hallucinations (mostly visual) can occur. Somnolence and, uncommonly, sudden sleep onset have been reported, patients who have experienced these must refrain from driving or operating machines. A reduction of dosage or termination of therapy may be considered. If dyskinesias occur in combination with levodopa during initial titration of pramipexole in advanced Parkinson's disease, the dose of levodopa should be reduced. Patients with psychotic disorders should only be treated with dopamine agonists if the potential benefits outweighs the risks. Ophthalmologic monitoring is recommended. If regular eye tests or if vision abnormalities occur. In cases of severe cardiovascular disease, care should be taken. It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of postural hypotension associated with dopaminergic therapy. **Drug Interactions:** There is no pharmacokinetic interaction with selegiline and levodopa. Inhibitors of the cationic secretory transport system of the renal tubules such as cimetidine and amantadine may interact with pramipexole resulting in reduced clearance of either or both drugs. Consider reducing pramipexole dose when these drugs are taken concomitantly. The dosage of diuretics should be reduced, and other Parkinsonian medication kept constant, while increasing the dosage of pramipexole. Caution with other sedating medication or alcohol due to possible additive effects. Coadministration of antipsychotic drugs with pramipexole should be avoided. **Pregnancy and Lactation:** Effects in pramipexole in human pregnancy or lactation have not been studied. Pramipexole should not be used in pregnancy unless the benefit outweighs the potential risk to the foetus. Pramipexole should not be used during breastfeeding. **Undesirable Effects:** Nausea, constipation, somnolence, insomnia, hallucinations, dizziness, dyskinesia and peripheral oedema occurred more often than with placebo. Most frequent adverse reactions in combination with levodopa were dyskinesias. Constipation, nausea and dyskinesia tended to disappear with continued therapy. Hypotension may occur at the beginning of treatment in some patients, especially if Mirapexin is titrated too fast. Vertigoes has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes. **Overdose:** There is no clinical experience with massive overdosage. Expected adverse events include nausea, vomiting, hyperkinesia, hallucinations, agitation and hypotension. General symptomatic supportive measures may be required, along with gastric lavage, intravenous fluids and electrocardiogram monitoring. **Basic NHS Cost:** 0.088mg x 30 £10.00, 0.18mg x 30 £20.20, 0.18mg x 100 £66.67, 0.7mg x 30 £66.67, 0.7mg x 100 £212.24. **Legal Category:** POM. **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, D-55216 Ingelheim am Rhein, Germany. **Marketing Authorisation Number:** Mirapexin 0.088mg x 30 tablets EU/1/97/061/001, Mirapexin 0.18mg x 30 tablets EU/1/97/061/002, Mirapexin 0.35mg x 100 tablets EU/1/97/061/004, Mirapexin 0.7mg x 30 tablets EU/1/97/061/005 Mirapexin 0.7mg x 100 tablets EU/1/97/061/006. Further information is available from: Boehringer Ingelheim Ltd., Ellesfield Avenue, Bracknell, Berkshire RG12 8YS. **Date of preparation:** September 2004.

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NICE Guidelines for Epilepsy Management

www.nice.org.uk/CG020adultsquickrefguide

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I welcome any guidelines that raise the profile of epilepsy and encourage improvements in care. The aims should be aspirational – there is no point writing a document that aims to perpetuate an unsatisfactory status quo. Will clinicians and managers be able to get together to implement these guidelines, especially given that in all probability there will be no resources to accompany the recommendations? Each year my children write a Christmas list and burn it in the fireplace in the hope that the ashes will magically reconstitute into the requested goodies on a return journey down the chimney on the night of December 24th. The question is: as the festive season approaches, should I go and talk to my manager or should I reach for the matches, guidelines in hand?

This document covers a broad remit of issues for epilepsy patients from diagnosis to long-term care. Perhaps the most interesting thing in the abridged NICE guidelines for epilepsy management is that only four recommendations are said to be supported by grade A evidence (randomised controlled trials): 1) treatment is generally recommended after a second seizure; 2) the value of rectal diazepam in status epilepticus; 3) unspecified psychological interventions for epilepsy and 4) the value of vagal nerve stimulation. All other recommendations rely on a poorer evidence base. This clearly says something about the science upon which we practice and the scientific rigour underpinning the guidelines.

They recommend that all patients with a suspected seizure should be seen within 2 weeks by a specialist and that EEG and neuroimaging should be undertaken within a further 4 weeks. MRI is clearly the recommended imaging modality. Whether this is truly necessary in all cases is in my view debatable, and in some cases speed of imaging may be a more important issue. For example in elderly patients the role of imaging may just be to rule out an obvious tumour. The guidelines helpfully provide reasons for not requesting an EEG as well as for requesting one, for example in patients with a clinical diagnosis of syncope where there may be false positive results. Where investigations remain uncertain, video-EEG-telemetry or ambulatory monitoring should be undertaken. These crucial resources are scarce in some areas and hopefully the guidelines will be a boost to them. Neuropsychology is recommended if there is a lesion in areas involved in cognitive function (virtually all imaging-positive patients) as well as those with symptomatic cognitive problems. Clearly this represents a massive increase in demand.

Treatment should generally be started after a second seizure, although may be considered after a first seizure in patients at high risk of further seizures (e.g. with tumours) or those where seizures may carry a particularly high risk, for example for a patient taking warfarin. Monotherapy is recommended where possible and proprietary preparations rather than generics are also supported. A full blood count, renal function, liver function, vitamin D and other tests of bone metabolism are recommended every 2-5 years for patients taking enzyme-inducing drugs. Whilst I can understand anticipating osteoporosis, I am not sure how helpful these other tests will be. The issue of new drugs has been dealt with in a previous set of NICE guidelines, which gave clinicians a fairly free rein. Essentially carbamazepine and valproate are recommended first line unless the clinician feels differently, for example avoiding valproate in women of child-bearing age. There is no restriction on using newer AEDs if initial treatment fails but the importance of withdrawing unsuccessful treatment is pointed out, in order to prevent unnecessary polypharmacy.

There is a large section, 4 pages of the 18 page summary, devoted to a syndrome by syndrome analysis of drug efficacy which clinicians will find useful and a list of major adverse effects of each drug. If treatment works well then the patient should be reviewed annually either in the hospital or in general practice. If the patient's epilepsy proves refractory for 2 years, a tertiary referral is recommended and the patient should then be seen within 4 weeks. Whilst desirable that all patients are seen quickly, it does not make much sense to emphasise a 4 week limit for a patient whose problem has been going on for 2 years.

In the treatment of status epilepticus, the guidelines support the use of buccal midazolam as an alternative to rectal diazepam, although this use is currently unlicensed.

There is an appropriate emphasis on information for patients to cover every aspect of life and work and the role of the specialist nurse is stressed. Sudden unexplained death is highlighted and the view of NICE is that all adult patients should be informed and any preventive measure can be taken. The NICE guidelines emphasise current best practice for women of child-bearing age with epilepsy. They highlight the difficulties in diagnosis and management in patients with learning disability but do not give specific recommendations.

There is little to argue with in these guidelines. If they are enacted, our patients will receive a much better service from us. The key is implementation if they are not to go down in history as yet another puff of chimney smoke.

For information on the NICE guideline for the Management of Multiple Sclerosis in Primary & Secondary Care, see www.acnr.co.uk/pdfs/volume3issue6/v3i6specMSguide.pdf (ACNR volume 3, issue 6, Jan/Feb 2004).

Letter to the Editor

Dear Editor,

This letter is in response to your review of our paper on the efficacy of vagal nerve stimulation therapy (VNST) in adults with medically refractory generalised epilepsy syndromes[1] ('Epilepsy: A shocking pain in the neck' *ACNR volume 4, issue 5*). The reviewer contends that the results are 'modest'. In fact, 7/16 patients had at least a 50% reduction in seizures, a clinical improvement that most logically can be attributed only to VNST, since antiepileptic drug (AED) regimens were held constant during the study period. This response is comparable to that observed in new AED trials. Moreover, although it is true that VNS will rarely result in seizure-freedom in patients where medications have failed, several of our patients did have a dramatic, meaningful reduction in debilitating tonic or atonic seizures, as the reviewer himself points out.

One should recall that all the subjects in this series had severe epilepsy for years, and most for decades, and had failed multiple drug trials. The epilepsy syndrome and seizure type for every patient was carefully established on the basis of the history, clinical findings, EEG-video monitoring, and neuroimaging. None were candidates for epilepsy surgery. There was little else to offer in terms of treatment. The reviewer expressed a desire for 'useful selection criteria'. We respond that VNST may be a reasonable therapeutic option in patients with medically intractable epilepsy who are not good candidates for surgical therapy.

The clinical experience with VNST approaches nearly a decade, with over 30,000 patients worldwide having been treated with the device. Nearly all investigators report similar response rates to VNST, and note that the beneficial effects are maintained over time. While one may debate the precise role of VNST in epilepsy management, we doubt that it is likely to be simply a 'passing fad'.

1. Holmes M, Silbergeld D, Drouhard D, Wilensky A, Ojemann L. *Effect of vagal nerve stimulation on adults with pharmacoresistant generalized epilepsy syndromes.* Seizure 2004;13:340-345.

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Primary Brain Tumours

Introduction

Primary CNS neoplasms represent 2% of all cancers and are the sixth most common group of tumours in adults and the second most common form of cancer in children, accounting for 20% of cancers in children under the age of 15 years. Although the incidence of tumours metastatic to the central nervous system outnumbers the combined incidence of tumours arising in the brain, spinal cord and meninges, primary tumours of the CNS present an enormous burden for the individual, their families and the health care system. Despite advances in the diagnosis and management of primary brain tumours and the availability of successful therapies for some tumours, brain tumours remain the leading cause of cancer mortality in children and only about 50% of patients with a CNS neoplasm are alive one year after diagnosis.[1-4] The objective of this short review is to present a brief overview of the diagnosis of primary brain tumour from a neuropathologist's standpoint, and to discuss the role of pathology and genetics in guiding management and treatment of this group of tumours.

Classification

The histopathological diagnosis of primary brain tumours is most commonly based on the World Health Organisation (WHO) classification system, which assigns tumours to histological subtypes according to cytological and histological similarity of tumour cells to cells in the adult or developing nervous system (Table 1). The WHO system also incorporates a grading system as an estimate of malignancy (grades I-IV). Grading may be automatic according to subtype or different grades of malignancy may be recognised within a subtype.[5] Different subtypes of similar grade, however, do not necessarily share a similar prognosis or response to therapy.

The neuroepithelial group of tumours account for approximately 60% of all primary brain tumours. The majority of these are astrocytic tumours, often referred to loosely as "gliomas". 75% of astrocytic tumours are diffusely infiltrative tumours. These tumours show a propensity for progression to higher grade lesions, providing for a spectrum of increasing histological malignancy (anaplasia) from low grade diffuse astrocytoma (grade II) to high grade tumours such as anaplastic astrocytoma (grade III) and at the worst end of the spectrum, glioblastoma multiforme (grade IV) (Fig 1e-h). The latter is the most common primary brain tumour in adults, representing 50% of gliomas and with a median survival of less than 1 year. More circumscribed astrocytomas such as pilocytic astrocytoma (Fig 1c,d) and pleomorphic xanthoastrocytoma, generally have a far more favourable prognosis due to a limited ability for invasive spread and a lower potential for anaplastic progression.[5-7]

The presence of an oligodendroglial phenotype, pure as in oligodendrogliomas and mixed as in oligoastrocytomas, has long been known to confer a more favourable prognosis compared with pure astrocytomas of similar grade (63% 5 yr survival for all oligodendrogliomas versus 49% for diffuse astrocytomas). Diagnostic distinction between an oligodendroglial and astrocytic phenotype may be difficult in the absence of one of its diagnostic hallmarks, the "perinuclear halo", an inconstant artefact of delayed fixation (Fig 2a-c). The recent recognition that anaplastic oligodendroglial tumours may be very sensitive to chemotherapy has increased pressure on neuropathologists to recognise an oligodendroglial component. The reported incidence of oligodendroglial tumours has since risen from 4% to as high as 33%, mainly due to the diagnosis of morphologically ambiguous tumours as oligoastrocytomas.[5,8,9]

There are three other major types of tumour that present particular challenges to clinicians and pathologists. Medulloblastomas are malignant, invasive embryonal tumours of the cerebellum with an inherent tendency to metastasise via CSF pathways. This is the most common childhood brain tumour, usually occurring within the first decade of life.[4,5] Meningiomas have a very varied spectrum of histological appearance, are more common in women and in adults and account for 13-28% of primary tumours.[1,5,6] Primary CNS lymphomas (4% of primary tumours) arise in the CNS in the absence of lymphoma outside the nervous system at the time of diagnosis. Steroids provide a high (40%), but transient therapeutic response rate and should preferably be avoided before biopsy as histological interpretation can become impossible due to the disappearance of tumour cells. Subtyping according to criteria used for nodal lymphomas remains problematic and appears to be of little practical importance at this stage.[1,5,6]

Diagnosis

The definitive diagnosis of brain tumours (subtyping and grading according to WHO recommendations) relies on the morphological assessment of stained tissue sections. This approach often allows for a confident diagnosis, but the process should nevertheless be an informed one, requiring correlation with clinical and imaging features.[1,2] It is envisaged that future tumour classification schemes will formally incorporate clinical, imaging and molecular

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Table 1: Abridged WHO Classification of Tumours of the Central Nervous System (2000)

TUMOURS OF NEUROEPITHELIAL TISSUE

Astrocytic tumours
Diffuse astrocytoma (variants)
Anaplastic astrocytoma
Glioblastoma
Pilocytic astrocytoma
Pleomorphic xanthoastrocytoma

Oligodendroglial tumours
Oligodendroglioma
Anaplastic oligodendroglioma

Mixed gliomas
Oligoastrocytoma
Anaplastic oligoastrocytoma

Ependymal tumours
Ependymoma
Anaplastic ependymoma
Myxopapillary ependymoma
Subependymoma

Choroid plexus tumours
Choroid plexus papilloma, carcinoma

Glial tumours of uncertain origin
(e.g. chordoid glioma of the 3rd ventricle)

Neuronal and mixed neuronal-glial tumours
(e.g. dysembryoplastic neuroepithelial tumour; ganglioglioma; central neurocytoma)

Neuroblastic tumours
Pineal parenchymal tumours
(e.g. pineocytoma; pineoblastoma)

Embryonal tumours
(e.g. medulloblastoma; atypical teratoid/rhabdoid tumour)

TUMOURS OF THE MENINGES

Tumours of meningothelial cells
Meningioma variants
Atypical meningioma
Anaplastic meningioma

Primary melanocytic lesions
(e.g. melanocytosis, malignant melanoma)

Tumours of uncertain histogenesis
Haemangioblastoma

LYMPHOMAS AND HAEMOPOIETIC NEOPLASMS

GERM CELL TUMOURS
(e.g. germinoma)

TUMOURS OF THE SELLAR REGION
(e.g. craniopharyngioma)

METASTATIC TUMOURS

UNCLASSIFIED TUMOURS

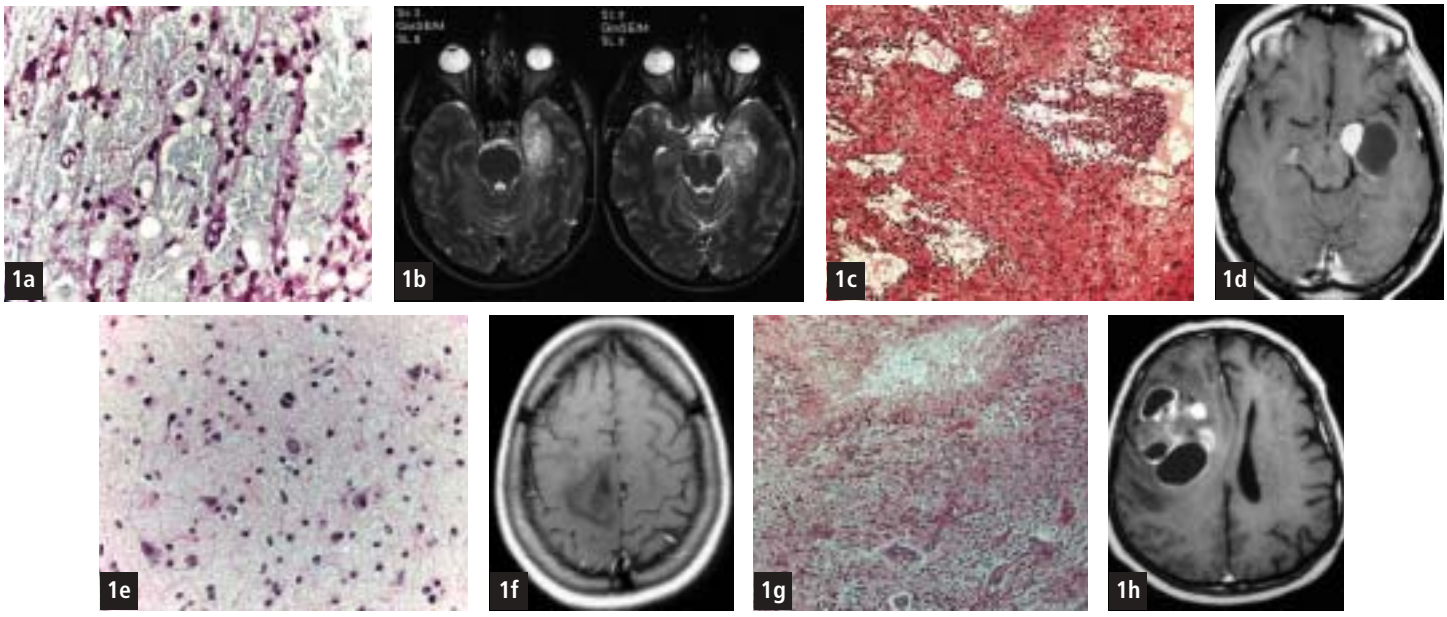

Figure 1
a,b – Dysembryoplastic neuroepithelial tumour (DNT) may show histological overlap with a variety of other neuroepithelial tumours, but the diagnosis is aided by the recognition of (a) specific glioneuronal elements containing "floating neurons" (H&E stained section) and (b) imaging characteristics, i.e. a predominantly cortical lesion without mass effect (MRI T2-weighted image).
c,d – Pilocytic astrocytoma showing diagnostically helpful (c) "biphasic" architecture of alternating compact and microcystic regions (H&E) and (d) imaging features of a cystic, homogenously enhancing tumour (T1-weighted MRI with gadolinium).
e,f – Diffuse astrocytoma (Grade II WHO). (e) Cortical infiltration by scattered mildly atypical astrocytic cells (H&E). (f) T1-weighted MRI with gadolinium reveals a hypointense, non-enhancing lesion.
g,h – Glioblastoma multiforme (Grade IV WHO). (g) Highly cellular astrocytic tumour showing necrosis (top) and florid microvascular proliferation (bottom) (H&E). (h) T1-weighted MRI with gadolinium reveals an inhomogeneous, ring-enhancing lesion.

genetic criteria.[8,10] This combined approach has already greatly benefited research and shows much promise for enhanced diagnosis, prognostication and determining which tumours will respond to treatment.

Clinical features

Patient age may be relevant to the diagnosis.[1,2] Most childhood tumours (70-80%) arise infratentorially (astrocytomas, ependymomas and medulloblastomas) or in the midline (germ cell tumours or craniopharyngiomas). Pilocytic astrocytomas and ependymomas occur mainly in the posterior fossa in children whereas cerebral diffuse astrocytomas and anaplastic astrocytomas are more common in adults. Glioblastomas are more frequently seen in the cerebral hemispheres of older adults and are rare in the spinal cord. A superficially situated cerebral pleomorphic astrocytic tumour in a child or young adult is far more likely to be a pleomorphic xanthoastrocytoma (WHO Grade II) and should not be confused with a glioblastoma. The diagnosis of dysembryoplastic neuroepithelial tumour (DNT) (Fig 1a,b), an indolent tumour with an excellent prognosis, may also be subject to certain clinical criteria such as no associated progressive neurological deficit and the presence of partial seizures usually beginning before the age of 20.[5]

Imaging

Neuro-imaging provides two additional pieces of information essential for diagnosis, namely tumour site and enhancement characteristics.[1-3,5] Knowledge about the exact tumour site allows for the consideration of more appropriate differential diagnoses, e.g. tumours with an oligodendroglial appearance with a ventricular/paraventricular situation require the exclusion of an ependymoma or central neurocytoma, both of which may share cytological characteristics with the former. Diffuse astrocytomas and well differentiated oligodendrogliomas are usually non-enhancing whereas their more anaplastic counterparts commonly show inhomogeneous enhancement or enhance in a ring-like pattern (Fig 1f,h).[5] Enhancement in either a diffuse astrocytoma or well differentiated oligodendroglioma (both with a low-grade histology) should therefore raise some concern about the true biological potential of the lesion and the representative nature of the biopsy. Contrast enhancement may correlate with microvascular proliferation, a histological feature mandating subtyping as an anaplastic oligodendroglioma or glioblastoma. Evidence is accumulating that tumours considered to be anaplastic oligodendrogliomas/oligoastrocytomas, but showing ring enhancement may rather represent small cell glioblastomas with a much poorer prognosis and response to therapy.[11] Not all enhancing gliomas are, however, associated with biological aggressiveness. Pilocytic astrocytomas are almost invariably homogeneously enhancing (Fig 1d) and the histological diagnosis of pilocytic astrocytoma should be questioned in tumours showing no enhancement. Imaging characteristics may also aid the diagnosis of DNTs. DNTs should show a predominantly cortical topography, no mass effect except if related to a cyst and no peritumoural oedema.[5] (Fig 1b).

Pathology

CSF specimens, cyst aspirates, biopsies and resection specimens may all aid the diagnosis of brain tumours. Targeted image guided biopsies, especially serial stereotactic biopsies, allow the sampling of various regions of interest such as areas of enhancement. This helps to overcome the limitations of small sample size often encountered in neuropathological practice, which is compounded by intratumoral heterogeneity and overlapping morphologies common to the group of neuroepithelial tumours. Frozen section or smear preparations provide a rapid, intra-operative diagnosis and are usually used to assess the representative quality of the biopsy (Fig 2a,b). A rapid diagnosis may also aid the intra-operative management of tumours by allowing the assessment of excision margins and influencing the choice of brachytherapy (placing of intra-tumoral radioactive seeds) during a stereotactic procedure.[1-3] Routine histology assessment is only obtained after a delay of 1-2 days given the requirements of tissue fixation, processing and routine staining. Immunocytochemistry identifying specific proteins within tumour cells has become an essential technique for the diagnosis of brain tumours as with tumours elsewhere in the body.

Genetics

Genes so far implicated in the more common types of brain tumours are not specific, but the combination and accumulation of genetic changes are often characteristic. This has permitted the distinction of genetic subtypes in tumours of similar morphological appearance and has elucidated pathways of tumour progression. Some of these genetic alterations have also helped resolve certain histogenetic controversies and shown diagnostic potential.[12] The identification of genetic markers predictive of prognosis and response to therapy has so far best being realised in the case of oligodendroglial neoplasms. Losses on the short arm of chromosome 1 (1p loss) correlate strikingly with chemosensitivity in anaplastic oligoden-

drogliomas. Molecular genotyping allows for the identification of subgroups of anaplastic oligodendroglioma showing correlation with patient age, tumour location, neuro-imaging characteristics, frequency and duration of response to chemotherapy and survival time after diagnosis (Fig 3).[8,13] Tumours with 1p loss have been shown to have a response rate as high as 100%, but combined 1p/19q loss without other genetic changes appears to confer a significantly longer duration of response compared with those without 19q loss or with other changes. 1p and 19q losses are seen in 80-90% of oligodendrogliomas and in 50-80% of anaplastic tumours.[5,8] Fluorescent in situ hybridisation (FISH) (Figure 2d) and quantitative PCR have the potential to demonstrate these changes in a routine diagnostic setting.[2,8,10] Genetic alterations in mixed tumours (oligoastrocytomas) either resemble those associated with "pure" oligodendroglioma (1p/19q loss) or those associated with diffuse astrocytomas (17p losses and TP53 mutation). These genotypes are mutually exclusive and are respectively seen in about half and a third of cases.[5,8] Diffuse astrocytomas have also demonstrated genotypic correlations with phenotypic variation, tumour progression and behaviour. Distinctive genetic pathways have been demonstrated in primary and secondary glioblastomas (Fig 4) and a variety of genetic alterations in astrocytic tumours have been correlated with an adverse prognosis.[5,6,7,10] Markers of potential prognostic benefit have also been identified in medulloblastomas, ependymomas, meningiomas and CNS lymphomas.[5,10]

Future developments

There are already many indicators of the future developments in the study of primary brain tumours most especially in the correlation between their clinical behaviour, imaging characteristics, histopathology and genetics in the search for the most appropriate therapies for this group of devastating tumours.

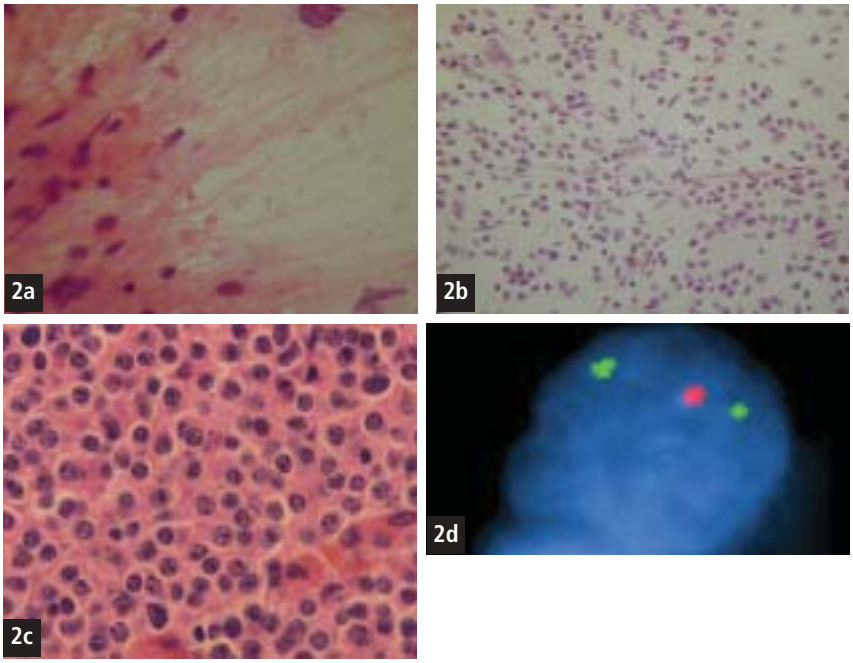

Figure 2
a,b - Intra-operative smear preparations (H&E stained) showing (a) an astrocytic phenotype with elongated dark nuclei and prominent fibrillary cell processes; and (b) an oligodendroglial phenotype with rounded, regular nuclei, prominent capillarity and absence of process formation.
c,d – Oligodendroglioma. (c) classical histology showing diagnostically helpful perinuclear clearing (halos) and round regular nuclei (H&E). (d) – Fluorescent in situ hybridisation (FISH) demonstrating 1p36 loss on one of the arms of chromosome 1 (control green signals locates to 1q25 loci, orange-red signal corresponds to the 1p36 locus, one of which is lost).

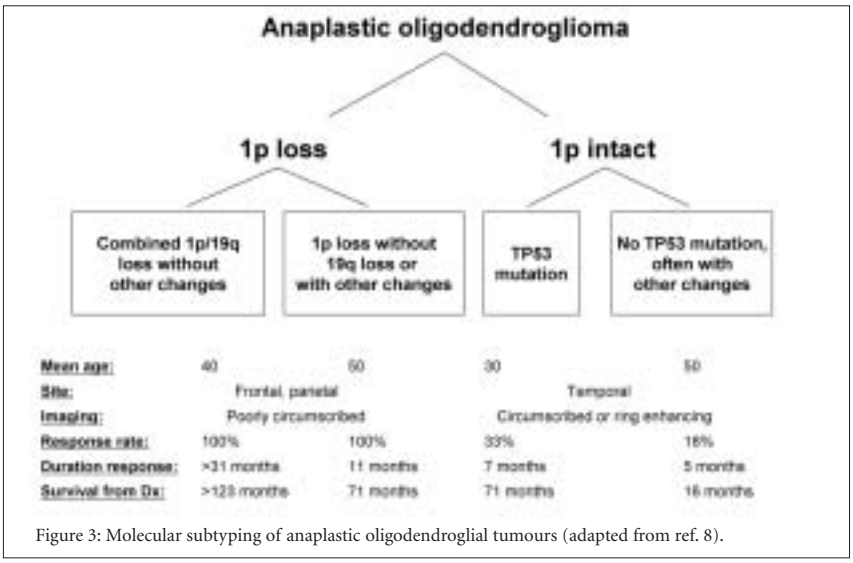

Figure 3: Molecular subtyping of anaplastic oligodendroglial tumours (adapted from ref. 8).

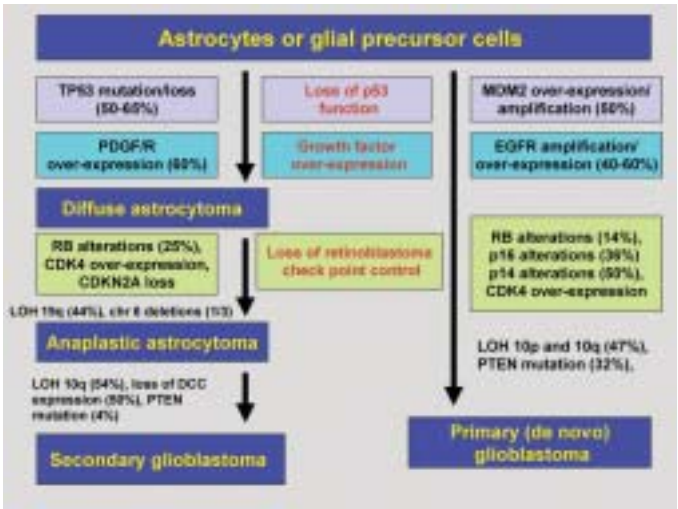

Figure 4: Molecular genetic pathways of primary and secondary glioblastoma (adapted from ref. 10).

References

1. Lantos PL, Louis DN, Rosenblum MK, Kleihues P. *Tumours of the nervous system.* In: Graham DI, Lantos PL, eds. Greenfield's Neuropathology vol II. London: Arnold 2002;767-1051.
2. Ironside JW, Moss TH, Louis DN, Lowe JS, Weller RO. *Diagnostic Pathology of Nervous System Tumours.* Edinburgh: Churchill Livingstone, 2002.
3. Ellison D, Love S, Chimeli L, Harding B, Lowe J, Roberts GW, Vintners HV. Neuropathology. London: Mosby, 2003.
4. Saran F. *Recent advances in paediatric neuro-oncology.* Current Opinion in Neurology 2002;15:671-7.
5. Kleihues P, Cavenee K, eds. *Pathology and Genetics Tumours of the Nervous System.* Lyon: IARC Press, 2000.
6. Behin A, Hoang-Xuan K, Carpentier AF, Delattre J-Y. *Primary brain tumours in adults.* Lancet 2003;361:323-31.
7. Smith JS, Jenkins RB. *Genetic alterations in adult diffuse glioma: occurrence, significance and prognostic implications.* Frontiers in Bioscience 2000;5:d213-31.
8. Reifenberger G, Louis DN. *Oligodendroglioma: Toward molecular definitions in diagnostic neuro-oncology.* J Neuropath Exp Neurol 2003;62:111-26.
9. Burger PC. *What is an oligodendroglioma?* Brain Pathology 2002;12:257-9.
10. Hilton DA, Melling C. *Genetic markers in the assessment of intrinsic brain tumours.* Current Diagnostic Pathology 2004;10:83-92.
11. Perry A, Aldape KD, George DH, Burger PC. *Small cell astrocytoma: An aggressive variant that is clinicopathologically and genetically distinct from anaplastic oligodendroglioma.* Cancer 2004, in press.
12. du Plessis DG, Rutherfoord GS, Joyce KA, Walker C. *Phenotypic and genotypic characterization of glioblastoma multiforme with epithelial differentiation and adenoid formations.* Clin Neuropathol 2004;23:141-8.
13. Walker C, du Plessis DG, Fildes D, et al. *Correlation of molecular genetics with molecular and morphological imaging in gliomas with an oligodendroglial component.* Clin Cancer Res 2004;10:7182-91.

People with Epilepsy Put at Risk by Drug Switching

Survey Highlights the Importance of Consistency of Supply

Recently Europe's largest member-led epilepsy organisation, Epilepsy Action, launched survey results revealing that last year a third of people with epilepsy were given a different version or brand of their regular anti-epileptic drug (AED).[1] Of these, nearly a quarter stated that they experienced an increase in seizures as a result.

An increase in seizures can have devastating effects for people with epilepsy. Someone who has previously had their epilepsy under control may suddenly find their driving licence revoked and their job or schooling affected. Poorly controlled epilepsy can also increase the risk of premature death.

The survey of 1,851 people demonstrates the impact that the lack of consistency of supply in AEDs can have on people's lives. Of those who had been given different AEDs, a third experienced more or different side effects. The increase in seizures and side effects is linked to switching between different manufacturers' products, being given mixed bundles of drugs, and the growing practice of importing drugs intended for other countries (parallel importing).

Twenty-four percent of people given a different version of their AED reported that they received 'mixed bundles' of AEDs at any one time, including various different versions of their medication.

Of those who received different versions of their regular AED, 23% queried the prescription with their doctor and over half spoke to their pharmacist. Of those who went to see their doctor, half were then given their usual AED compared to only 30% of people that discussed the issue with their pharmacist.

Worryingly, nearly a quarter of people reported that their GP responded in a dismissive or uninterested manner and nearly a third of pharmacists were reported to state that AED brands are all the same or that the patient had received their normal brand, just in different packaging.

The importance of consistency of supply has also been highlighted by the National Institute of Clinical Excellence (NICE), an independent organisation responsible for providing guidance on treatments and care for people using the NHS in England and Wales. The recently published NICE Guideline for the diagnosis and management of epilepsy (see overview on page 16), states that: 'Changing brand of AED is not recommended due to variances in bioavailability/difference in pharmacokinetic profiles, which leads to increased potential for reduced effect or excessive side effects'.[2]

Ellen, mother of a 10 year old boy with epilepsy, said: "This research is long overdue. My son basically 'lost' a year at school due to being in a drug-induced 'fog' as a result of constantly adjusting to different versions of Carbamazepine."

For more information contact the British Epilepsy Association,
New Anstey House, Gate Way Drive, Yeadon, Leeds LS19 7XY.
Tel: 0113 210 8800 • Fax: 0113 391 0300
Email epilepsy@epilepsy.org.uk • www.epilepsy.org.uk

References:

1. Epilepsy Action: Anti-Epileptic Medication Packaging Survey. October 2003
2. National Institute of Clinical Excellence. Epilepsy Guidelines. October 2004.

For Epilepsy Actions' Consensus Statement in response to the NICE Guideline on the Diagnosis and Management of the Epilepsies, see www.epilepsy.org.uk/action/pdf/epilepsyaction_epilepsy_consensus_statement.pdf

See page 16 for Mark Manford's overview of the guidelines.


FEMALE : 26
PRIMARY GENERALISED TONIC-CLONIC SEIZURES
MALE : 26
PRIMARY GENERALISED TONIC-CLONIC SEIZURES
Much of what makes Lamictal an appropriate choice for her...
...also makes it an appropriate choice for him
Lamictal™
lamotrigine

Visual Stress in Neurological Disease

Initial observations

Difficulty with reading (dyslexia) can sometimes be reduced by wearing coloured glasses, a claim first made by Helen Irlen in 1983.[1] Initially, the claim was dismissed as little more than a novelty effect[2] but as scientific evidence slowly accrued it became clear that coloured glasses can indeed offer an effective treatment. It is not dyslexia that the glasses treat but the visual stress[3] with which dyslexia is sometimes associated. Removal of the visual stress using coloured filters allows individuals with dyslexia to expose themselves to print for longer. In many instances this facilitates reading acquisition, but it does not necessarily remove the need for specialist teaching.

Visual stress

The symptoms of visual stress include perceptual distortions and eye-strain. The distortions may involve apparent movement of letters or words within text (the letters 'wobble', 'fly off the page'), blurring or fading of letters, changes in the apparent size and spacing of letters, patterns appearing in the dark print or the white space (sometimes described as 'worms', 'rivers' or 'waterfalls'), and colours appearing in blobs across the page or around words. The visual symptoms can be accompanied by nausea, dizziness, discomfort or even eye pain, often attributed to 'glare' from the page.[4] The symptoms are not exclusive to visual stress, but can arise from other optometric anomalies (e.g. binocular instability), so an optometric examination is necessary before the symptoms can appropriately be attributed.[5]

Coloured filters: overlays and lenses

Visual stress can often be removed using coloured filters, either coloured sheets of plastic placed upon the page (coloured overlays) or coloured ophthalmic lenses worn in spectacles. Surprisingly perhaps, there is no particular colour that is suitable because each individual benefits from their own individually selected colour.[6,7] This means that a sufficiently large number of colours must be assessed in order to find the best for an individual. The Intuitive Overlays come in a pack of 10 that can be combined two at a time to provide a pallet of 30 colours, sufficient to identify most of the individuals likely to benefit from coloured filters.[8] The overlays are useful as an inexpensive screening device, but filters worn as glasses often provide a more effective treatment: not only can they be used for tasks other than reading, but recent techniques for ophthalmic tinting mean that the appropriate colour can be selected with greater precision. The appropriate colour can sometimes improve reading speed quite dramatically, by a factor of two or three, but colours that differ from the individual optimum by as little as 6 just-noticeable-differences have little benefit.[6]

Assessment

When the overlays prove beneficial, the appropriate colour is perhaps best selected using the Intuitive Colorimeter, a device that shines coloured light onto a page of text and allows the hue and saturation (strength) of the colour to be varied independently at constant brightness.[9] The optimum colour can then be selected rapidly by successive approximation under conditions of colour adaptation. Once selected, the required colour is made up in tinted trial lenses and assessed under natural viewing conditions.[4] The lenses are designed to provide the appropriate colour under white fluorescent lighting (since this is the most ubiquitous) and to do so with as smooth a spectral transmission as possible, thus reducing the variation from one type of lighting to another. This variation is not sufficient to remove the benefit, despite the precision required.[6] Any necessary adjustments to the tint can be made by varying the combination of trial lenses, and the selected combination then forms a prescription that is sent to a manufacturing optician for making up in spectacle lenses that incorporate any refractive correction necessary.[4] The patent for this system is owned by the MRC, who awarded the licence to one manufacturing optician based in the UK.

The overlays provide a surface colour (the eyes are adapted to white light) whereas the lenses have an effect similar to that of changing the colour of the lighting, and this may be why the optimum colour of an overlay differs from that of lenses.[10]

Professor Wilkins is currently Head of the Visual Perception Unit at the University of Essex, and is co-ordinating research on the use of coloured filters of various kinds in the treatment of reading difficulties, photosensitive epilepsy and migraine. He has been responsible for several innovations, including the first demonstration that fluorescent lighting is detrimental to health. He has a wide range of research interests including the neuropsychology of vision, reading and colour, photosensitive epilepsy, migraine, typography, human memory and attention. These interests have helped him formulate the first unified theory of Visual Stress, detailed in his book with this title. His most recent book "Reading through colour" (Wiley, 2003) provides a review of the theory that underpins the use of coloured filters for reading, as well as a guide for practitioners.

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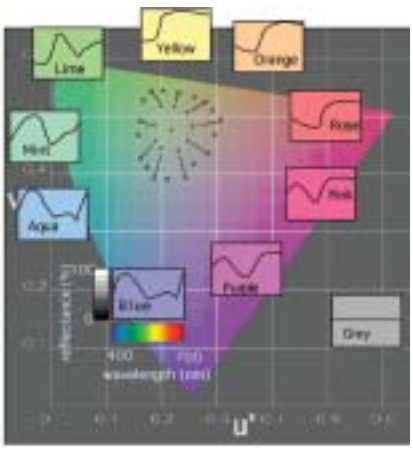
University of Essex,
Colchester, CO4 3SQ.
Email: arnold@essex.ac.uk

Intuitive Colorimeter/coloriser

Intuitive Colour Overlays

The points in the inner circle represent the colours of the overlays. The points in the outer circle represent colours provided by two overlays superimposed. The lines join those of similar colour. Panels show the spectral reflectance of the overlays.



Colorimetry procedure

1. Find best hues

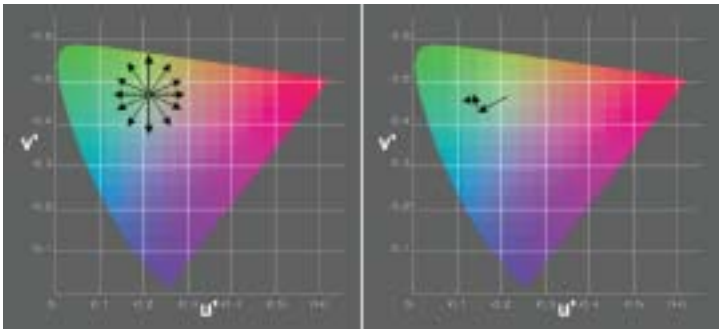
Before adaptation to colour

The saturation is increased and then decreased at each of 12 hues, evenly spaced.

2. Optimise hue/saturation

After adaptation to colour

The saturation is adjusted at the best hue and the hue adjusted at the best saturation. The process is repeated to find a stable optimum.



Headaches and perceptual distortion

Many individuals who use coloured filters have reported a reduction in headaches. Among these individuals the prevalence of a family history of migraine is twice as great as among those who do not benefit from filters.[11] Although migraineurs may be fluent readers and unaware of perceptual distortion of text, they nevertheless find bolder striped patterns aversive, particularly stripes with spatial frequencies that are epileptogenic for patients with photosensitive epilepsy.[12] This is consistent with several disparate but convergent lines of evidence that in migraine the visual cortex is hyperexcitable.[13] The fMRI blood oxygenation level dependent response to aversive patterns is abnormally large in migraineurs, particularly at epileptogenic spatial frequencies.[14] Preliminary data suggest that coloured glasses can reduce this abnormality.[15]

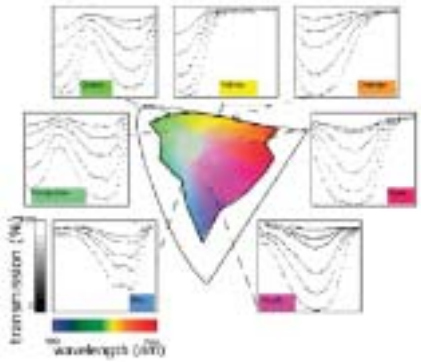
Pathophysiology of visual stress

We hypothesise that the perceptual distortions occur because a spread of excitation causes visual neurons to fire inappropriately. According to this hypothesis, the degree of susceptibility to distortions increases with, and reflects, the degree of cortical hyperexcitability. We hypothesise that the cortical hyperexcitability is non-uniform (as is manifestly the case in photosensitive epilepsy[3]), and that the tints redistribute the cortical excitation that occurs in response to a visual stimulus. The redistribution is presumed to occur because of differences in the spectral sensitivity of cortical neurons[16] and the topographic representation of colour in some cortical areas[17]. We hypothesise that comfortable colours redistribute the excitation in such a way as to reduce the excitation in hyperexcitable regions. This hypothesis explains the reduction in perceptual distortions with individually prescribed coloured filters, if these distortions are indeed due to a spread of excitation, as hypothesised above. It also explains the benefit of coloured filters in other neurological disease.

Benefit in autism, head injury and epilepsy

Coloured filters appear to be of benefit not only in dyslexia and migraine but in several other neurological disorders affecting vision. Without exception these are disorders where there is an increased risk of seizures, consistent with the hypothesis that the visual cortex is hyperexcitable. For example, (1) coloured overlays have been shown to improve reading rate in a high proportion of individuals with autistic spectrum disorders;[18] (2) the intolerance to light and sound that follows head injury is often associated with reading difficulties for which coloured lenses may offer benefit, according to preliminary observations.[19] Coloured filters have long been proposed as a possible treatment in photosensitive epilepsy, and the new techniques for ophthalmic tinting have recently been assessed in this condition.[20] Individuals with multiple sclerosis have reported benefit, but clinical trials have yet to be undertaken.

Trial Lenses



Spectral transmissions of the trial lenses (below), and the gamut (below, centre) obtainable with combinations of trial lenses from two dyes of neighbouring colour.

Where to obtain assessment

In the UK, assessment with the Intuitive Overlays is available in many schools and colleges and in many community optometric practices and hospital orthoptic departments. Assessment with the Intuitive Colorimeter is available at more than 200 optometrists and in four ophthalmology departments, and most of these are listed via a link at www.essex.ac.uk/psychology/overlays.

The response to treatment can be immediate and surprising. Some patients prefer to wear their glasses most of the time, and not only for reading; 80% of patients continue to wear their tinted glasses for more than a year,[5,11] although some discontinue use thereafter when they no longer experience symptoms.

The author would be interested to hear from any reader who wishes to conduct a clinical trial of ophthalmic tints in neurological disease.

References

1. Irlen H. *Successful treatment of learning difficulties.* in *The Annual Convention of the American Psychological Association.* 1983. Anaheim, California.
2. Winter S. *Irlen lenses: an appraisal. Australian Educational and Developmental Psychologist.* 1987;4:1-5.
3. Wilkins AJ. *Visual Stress.* 1995, Oxford: Oxford University Press.
4. Wilkins AJ. *Reading through colour.* 2003, Chichester: John Wiley and Sons.
5. Evans BJW, et al. *A review of the management of 323 consecutive patients seen in a specific learning difficulties clinic.* Ophthal Physiol Opt 1999;196:454-66.
6. Wilkins AJ, N Sihra, and A Myers. *Increasing reading fluency using colours: issues concerning reliability and specificity and their theoretical and practical implications.* Perception, 2004. in press.
7. Wilkins AJ, et al. *Double-masked placebo-controlled trial of precision spectral filters in children who use coloured overlays.* Ophthal Physiol Opt 1994;144:365-70.
8. Wilkins AJ. *Coloured overlays and their effects on reading speed: a review.* Ophthal Physiol Opt 2002:448-54.
9. Wilkins A, MI Nimmo-Smith, and J Jansons. *A colorimeter for the intuitive manipulation of hue and saturation and its application in the study of perceptual distortion.* Ophthal Physiol Opt 1992;12:381-5.
10. Lightstone A, T Lightstone, and AJ Wilkins. *Both coloured overlays and coloured lenses can improve reading fluency, but their optimal chromaticities differ.* Ophthal Physiol Opt 1999;914:279-85.
11. Maclachlan A, S Yale, and AJ Wilkins. *Open trials of precision ophthalmic tinting: 1-year follow-up of 55 patients.* Ophthal Physiol Opt 1993;13:175-8.
12. Marcus DA and MJ Soso. *Migraine and stripe-induced visual discomfort.* Achives of Neurology 1989;46(10):1129-32.
13. Welch KM. *Contemporary concepts of migraine pathogenesis.* Neurology 2003;61((Suppl 4)):S2-S8.
14. Huang J, et al. *Visual distortion provoked by a stimulus in migraine associated with hyperneuronal activity.* Headache 2003;43(6):664-71.
15. Huang J, AJ Wilkins, and Y Cao. *Mechanisms whereby precision spectral filters reduce visual stress: an fMRI study.* in *Tenth Annual Meeting of the Organisation for Human Brain Mapping.* 2004. Budapest, Hungary.
16. Zeki S. *A century of cerebral achromatopsia.* Brain 1990;113(6):1721-77.
17. Xiao Y, Y Wang, and DJ Felleman. *A spatially organized representation of colour in macaque cortical area V2.* Nature 2003;421(6922):535-9.
18. Ludlow A, A Wilkins, and P Heaton. *The effect of coloured overlays on reading ability in children with autism.* in press.
19. Jackowski MM, et al. *Photophobia in patients with traumatic brain injury: uses of light-filtering lenses to enhance contrast sensitivity and reading rate.* Neurorehabilitation 1996;6:193-201.
20. Wilkins AJ, et al. *Treatment of photosensitive epilepsy using coloured filters.* Seizure 1999;8:444-9.

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2005

January

Society of Applied Research on Memory and Cognition (SARMAC)
5-8 January, 2005; Wellington, New Zealand
www.vuw.ac.nz/psyc/sarmac/

106th Meeting of the British Neuropathological Society
12-14 January, 2005; London, UK
Tel. 020 79052135/020 278298692,
E. courses@ch.vcl.ac.uk

Phantom Limb Phenomena
15-16 January, 2005; London, UK
Tel. 020 7717 2270,
E. j.goldstein@gold.ac.uk

British Association of Stroke Physicians Annual Conference
18-19 January, 2005; Newcastle, UK
E. d.l.jones@ncl.ac.uk,
Tel. 0191 222 6779.

31st Annual Conference of the British Paediatric Neurology Association
19 - 21 January, 2005; London, UK
E. info@bpna.org.uk,
Tel. 01204 491171.

Neuropathic Pain
21 January, 2005; London, UK
Tel: 020 7290 3919.

Attention and Driving: A Cognitive Neuropsychological Approach
21-22 January, 2005;
Wurtzburg, Germany
www.neuropsychologie.de/GNPAkademie/Kurse/FB050121A.htm

3rd International Congress on the Improvement of the Quality of Life on Dementia, Epilepsy and MS
28-31 January, 2005;
Alexandria, Egypt
Fax. +30.231.023.1849,
Tel. +30.231.025.7128
E. gsamaras@forumcongress.com

February

Pain Management: The Online Series, Assessing and Treating Neuropathic Pain
1-28 February, 2005; Online
E. mark_evans@ama-assn.org

Short Courses: Neuro-Medical / Surgical Nursing
February, 2005; Cambridge, UK
E. wood@health-homerton.ac.uk

Advanced Practice in Epilepsy
February 2005, NSE, Chalfont St Peter, UK
Training department, National Society for Epilepsy,
Tel. 01494 601 371.

33rd Annual Meeting of the International Neuropsychological Society
2-5 February, 2005; St Louis, US
Tel. 001 614 263 4200,
E. ins@osu.edu

International Stroke Conference
2-4 February, 2005; New Orleans, US
E. strokeconference@heart.org

Children with Complex Epilepsy: Learning, Language and Behaviour
3 February, 2005; London, UK
Institute of Child Health,
Tel. 020 78298692.

British Neuropsychiatry Assocation Annual Meeting
9-11 February, 2004; London, UK
Gwen Cutmore,
Tel/Fax. 01621 843334,
E. gwen.cutmore@lineone.net

8th National & 2nd International Congress of Anesthesiology & Intensive Care
9-11 February, 2005; Tehran, Iran
Tel. 0098 218834989,
Fax 0098 218834989,
E. info@iranesthesia.org

Workshop on Botulinum Toxins in Neurological Practice
Date to be confirmed; Innsbruck, Austria
E. khenley@movementdisorders.org

Short Courses: Neurological Assessment for Nurses
14 February, 2005; London, UK
Tel. 020 7836 5454,
E. sue.woodward@kcl.ac.uk

Clinical Neurology and Neurophysiology
23-25 February, 2005;
Jerusalem, Israel
Tel. 97226 520574, Fax 97226 520558,
E. seminars@isas.co.il

Dementias 2005
24-25 February, 2005; London, UK
Tel. 020 7501 6743,
E. conference@markallengroup.com

1st International Congress on Immunodeficiency Disorders
28 February-2 March, 2005;
Tehran, Iran
Tel. +98 21 693 8545,
Fax. +98 21 693 8545,
E. congress@iranianpia.org

Neurological Anatomy Course
28 February, 2005; London, UK
The Royal College of Surgeons of England, Tel. 020 7869 6335.

March

Acute Medical Emergencies
2 March, 2005; London, UK
Anton Abrahams,
E. ame@confcomm.co.uk
Tel. 0207 7200 600.

The Visual System - RSM Clinical Neurosciences Section
3 March, 2005; London, UK
Tel. 20 7290 2984/2982,
E. cns@rsm.ac.uk

Royal College of Psychiatry: Old Age Psychiatry
3-4 March, 2005; UK
www.rcpsych.ac.uk/conferences/diary/index.htm

13th Annual Conference - Association of Cognitive Analytic Therapy: Body, Brain and Beyond CAT
4-5 March, 2005, London, UK
Tel. 020 7188 0692,
E. conference@acat.me.uk

Standardised Assessment in Occupational Therapy with special emphasis on Dementia, Part 2
March, 2005; London, UK
Tel. 020 7834 3181

9th International Congress of Parkinson's Disease and Movement Disorders
5-8 March, 2005; New Orleans, US
E. congress@movementdisorders.org

GCNN 2, 2nd Global College of Neuroprotection and Neuroregeneration Annual Conference
7-10 March, 2005; Innsbruck, Austria
E. info@gcnpnr.org

The British Pain Society Annual Meeting
8-11 March, 2005; Edinburgh, UK
Tel. 020 7631 8870,
E. meetings@britishpainsociety.org

7th International Conference on Progress in Alzheimer's and Parkinson's Disease
9 - 13 March, 2005; Sorrento, Italy
Fax. 08451 275 687,
E. adpd@kenes.com

Tuberous Sclerosis Association: Professional Study Day
17 March, 2005; Birmingham, UK
Tel. 01527 871898, Fax. 01527 579452.

1st Joint International Meeting on Degos Disease
18-19 March, 2005; Berlin, Germany
E. judith@degosdisease.com

Essential Skills in Neurosurgery
22 March, 2004; London, UK
Tel. 0207 4053 474,
E. international@rcseng.ac.uk

ABN Spring Meeting
30 March - 1 April; Belfast, UK
Tel. 020 7405 4060,
E. info@theabn.org

BPS 2005 Quinquennial Conference
30 March - 2 April, 2005;
Manchester, UK
www.bps.org.uk/events/AC2005

April

18th National Meeting of the BNA
3-6 April, 2005; Brighton, UK
www.bna.org.uk

Clinical Neurophysiology BSCN Course
3-8 April, 2005; Oxford, UK
E. robin.kennett@orh.nhs.uk

International Psychogeriatric Association
5-8 April, 2005; Rotorua, New Zealand
Fax. +1 847 663 0591,
Tel. +1 847 663 0574,
E. info@ipa-online.org

27th Advanced Clinical Neurology Course
6-8 April, 2005; Edinburgh, UK
E. events@acnr.co.uk

American Academy of Neurology (AAN) Annual Meeting
9-16 April, 2005; Florida, US
http://am.aan.com/

Cognitive Neuroscience Society (CNS) Meeting
10-12 April, 2005; New York, US
E. cnsinfo@cogneurosociety.org
www.cogneurosociety.org/content/meeting

3rd World Congress Of The ISPRM
10-14 April, 2005; San Paulo, Brazil
E. ispmr2005@isprm.org

Certificate Course in Neurological Rehabilitation
11-29 April, 2005, Newcastle, UK
Tel/Fax. 0191 2195695,
E. traceymole@actionfordisability.co.uk

Neuro-Ophthalmology Clinical Course
11-15 April, 2005; Dublin, Ireland
Tel. +353 1 809 2609 or
+353 1 803 2876

Neurodegeneration - RSM Clinical Neurosciences Section
14 April, 2005; London, UK
Tel. 20 7290 2984/2982,
E. cns@rsm.ac.uk

Tuberous Sclerosis Association: Professional Study Day - the adult perspective
14 April, 2005; Birmingham, UK
E. support@tuberous-sclerosis.org
Tel. 01527 871898.

BGS Spring Meeting
14-15 April, 2005; Birmingham, UK
British Geriatric Society,
Tel. 0207 6081369

Second International Neuroacanthocytosis Symposium "Expanding the Spectrum of Choreatic Syndromes"
17-20 April, 2005; Montreal, Canada
Tel. 0207 937 2938;
E. gingerirvine@usa.net

The Management of Blackouts and Misdiagnosis of Epilepsy and Falls
19 April, 2005; London, UK
Tel. 0207 9351 174,
Fax. 0207 4875 218,
E. conferences@rcplondon.ac.uk

Otoneurologia 2005
23-24 April, 2005; Azores Portugal
otoneuro2005@mail.pt,
www.otoneuro.pt

May

Short Courses : Neuro-Medical / Surgical Nursing
May, 2005; Cambridge, UK
E. wood@health-homerton.ac.uk

6th World Congress on Brain Injury
1 - 4 May, 2005; Melbourne, Australia
E. braininjury@icms.com.au

Aspects of the Neurological Examination - RSM Clinical Neurosciences Section
Tel. 20 7290 2984/2982,
E. cns@rsm.ac.uk

Annual Meeting of the German, Austrian, Swiss section of the International League Against Epilepsy
5-7 May, 2005; Innsbruck, Austria
Tel. +43 512 5043879,
E: iris.unterberger@uibk.ac.at

4th BASP Thrombolysis Training Day
6 May, 2005; Nottingham, UK
Pamela Nicholson, sec to Professor Lees, E. pcn1w@clinmed.gla.ac.uk,
Tel. 0141 211 2176.

Neurochirurgie 2005
7-11 May, 2005; Strasbourg, France
Fax. +49 3 028 449 911,
E. nch2005@porstmann-kongresse.de

12th European Congress of Clinical Neurophysiology
9-11 May, 2005; Stockholm, Sweden
E. secretary@ec-ifcn.org
/weerd@ipe.nl

Alzheimer's Disease: Update on Research, Treatment, & Care
19-20 May, 2005; San Diego, US
E. jcollier@ucsd.edu

Annual Meeting of the German Section of the International League Against Epilepsy
20-22 May, 2005; Freiburg, Germany
www.ctw-congress.de/liga

14th European Stroke Conference
25-28 May, 2005; Bologna, Italy
E. m.g@eurostroke.org or daffertshofer@eurostroke.org

The Second Meeting of the AEP Section of Neuroimaging
26-27 May, 2005; Berlin, Germany
Tel. 01159 692 016,
Fax. 01159 692 017,
E. rp@rpa.bz

International Society of Posture and Gait Research 2005 – ISPGR XVIIth Conference
29 May -2 June, 2005;
Marseilles, France
E. assaiant@dpm.cnrs-mrs.fr or ispgr2005@atout-org.com

June

The Past, Present & Future of Neurosciences - RSM
2 June, 2005; London, UK
Tel. 20 7290 2984/2982,
E. cns@rsm.ac.uk

16th International Congress on Parkinson's Disease & Allied Disorders
5-9 June, 2005; Berlin, Germany
Tel. 0049 30 300 6690,
Fax. 0049 30 305 7391,
E. Berlin@cpo-hanser.de,
www.cpo-hanser.de

28th International Congress of Clinical Neurophysiology
5-9 June, 2005; Berlin, Germany
Fax. 001 507 288 1225,
E. aaem@aaem.net

Neurological Assessment Short Course for Nurses
6 June, 2005; London, UK
Tel. 020 7836 5454,
E. sue.woodward@kcl.ac.uk

2nd Quadrennial Meeting of the World Federation of NeuroOncology
13-16 June, 2005; Edinburgh, UK
Tel. +32 0 27 750 201,
Fax. 32 0 27 750 200,
E. eano6@fecs.be

The Royal Society *of* Medicine presents:

Common neurology, uncommon genes

Friday 11th February, 2005

Venue: The RSM, London

This meeting on Neurogenetics explores the genetic contribution to a variety of common neurological disorders. Trainees in clinical genetics and neurology are especially welcome. Topics/speakers include:

- Stroke, Professor Hugh Markus
- Multiple sclerosis, Dr Steve Sawcer
- Parkinson's disease, Dr David Nicholl
- Epilepsy, Dr Michael Johnson
- Neuropathy, Dr Mary Reilly
- Dementia, Dr Sarah Tabrizi
- Migraine and cluster headache, Professor Michel Ferrari

For further information please email:
genetics@rsm.ac.uk
Tel: +44 20 7290 2985
or browse our website at
www.rsm.ac.uk/genetics

The Royal Society of Medicine

Royal College of Physicians
Setting higher medical standards

The Management of Blackouts & Misdiagnosis of Epilepsy & Falls

Tuesday 19 April 2005

Royal College of Physicians
11 St Andrews Place, Regent's Park, London NW1

It is estimated that 20 - 30% of patients diagnosed with epilepsy in the UK are misdiagnosed (i.e. 125,000 patients in the UK) and that a third of patients with falls have syncope with retrograde amnesia. Consequently the result of a fall may be treated, not the cause. This conference aims to discuss this subject with those looking after patients with blackouts.

Topics covered: history of epilepsy and syncope, blackouts in the elderly and the young, value of cardiac tests and neurological tests, definition of terms, how to spot and treat psychogenic blackouts and a management algorithm for blackouts.

This conference would be of interest to Consultants in: A & E, Cardiology, Neurology, Neuropsychiatry and Geriatrics. Also GP's, Staff Grade Doctors and Specialist Nurses.

The programme and booking form are available on-line
http://www.rcplondon.ac.uk/calendar/2005
Or contact Conference Office, Royal College of Physicians, Tel: 020 7935 1174 Ext. 300/436/252 Fax: 020 7224 0719 Email: conferences@rcplondon.ac.uk

Neuro-ophthalmology clinical course

At the Institute of Neurosciences
Beaumont Hospital, Beaumont, Dublin 9

Monday 11th April - Friday 15th April 2005

This course covers clinical neuro-ophthalmology with emphasis on clinical demonstrations and teaching sessions. Relevant basic sciences will also be covered during the course

Course organisers:
Ms P Logan
Professor L Cassidy
Mr T Buchanan

Course Fee: €700 (euros)

Applications to:

Ms Anne Carter
Institute of Ophthalmology
UCD, 60 Eccles Street
Dublin 7
Eire
Tel: +353 1 803 2876

Ms P Logan
Neuro Ophthalmology Dept
Beaumont Hospital
Dublin 9
Eire
Tel: +353 1 809 2609 Ciara/Tina

NEUROLOGISCHE KLINIK
EPILEPSIEZENTRUM (ZEE)

International Symposium

Epileptogenesis & Therapeutic Strategies: Rational Therapy 2005

Erlangen, Germany, 23rd-25th June, 2005

Epileptologists with special expertise in basic research and clinical epileptology from 15 countries are expected to participate. Official language is English.

The first part of the symposium consists of small workshops with interactive discussion between clinical epileptologists and basic researchers concerning preconditions for the development of rational therapy.

The second part consists of open sessions - lectures (24th & 25th of June) focusing on the most important results concerning epileptogenesis, prevention, evidence based therapy, refractoriness, prediction of outcome, initial monotherapy and what next when monotherapy fails.

Finally, an overview of 60 years of epileptology will be presented.

For more information contact:
Prof. Dr. H. Stefan, University Erlangen-Nuernberg, Neurological Clinic - Epilepsy Center, Schwabachanlage 6, 91054 Erlangen / Germany. Email: hermann.stefan@neuro.imed.uni-erlangen.de
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Uses The treatment of disabling motor fluctuations (''on-off'' phenomena) in patients with Parkinson's disease which persist despite individually titrated treatment with levodopa (with a peripheral decarboxylase inhibitor) and/or other dopamine agonists.

Dosage and administration Apomorphine hydrochloride is administered subcutaneously either as an intermittent bolus injection or by continuous subcutaneous infusion. Its rapid onset (5–10 mins) and duration of action (about 1 hour) may prevent an "off" episode which is refractory to other treatments. Hospital admission under appropriate specialist supervision is necessary during patient selection and when establishing a patient's therapeutic regime. Please refer to the Summary of Product Characteristics for full details before initiating therapy. Treatment with domperidone (typical dosage 20mg three times a day) before and during apomorphine HCl therapy is essential. The optimal dosage of apomorphine HCl has to be determined on an individual patient basis; individual bolus injections should not exceed 10mg and the total daily dose should not exceed 100mg.

Contraindications Children and adolescents (up to 18 years of age). Known sensitivity to apomorphine or any other ingredients of the product. Respiratory depression, dementia, psychotic diseases or hepatic insufficiency. Intermittent apomorphine HCl treatment is not suitable for patients who have an "on"response to levodopa which is marred by severe dyskinesia or dystonia.

Pregnancy and lactation Not recommended for use in women of child-bearing potential or in nursing mothers.

Interactions Patients should be monitored for potential interactions during initial stages of apomorphine therapy. Particular caution should be given when apomorphine is used with other medications that have a narrow therapeutic window. It should be noted that there is potential for interaction with neuroleptic and antihypertensive agents.

Precautions Use with caution in patients with renal, pulmonary or cardiovascular disease, or who are prone to nausea and vomiting. Extra caution is recommended during initiation of therapy in elderly and/or debilitated patients. Since apomorphine may produce hypotension, care should be exercised in patients with cardiac disease or who are taking vasoactive drugs, particularly when pre-existing postural hypotension is present. Neuropsychiatric disturbances are common in Parkinsonian patients. APO-go should be used with special caution in these patients. Apomorphine has been associated with somnolence, and other dopamine agonists can be associated with sudden sleep onset episodes, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa when given concomitantly with apomorphine.

Side Effects Local induration and nodules (usually asymptomatic) often develop at subcutaneous site of injection leading to areas of erythema, tenderness, induration, and (rarely) ulceration. Pruritus may occur at the site of injection. Drug-induced dyskinesias during "on" periods can be severe, and in a few patients may result in cessation of therapy. Postural hypotension is seen infrequently and is usually transient. Transient sedation following each dose of apomorphine may occur at the start of therapy, but this usually resolves after a few weeks of treatment. Nausea and vomiting may occur, particularly when APO-go treatment is initiated, usually as a result of the omission of domperidone. Transient mild confusion and visual hallucinations have occurred during apomorphine therapy, and neuropsychiatric disturbances may be exacerbated by apomorphine. The use of apomorphine HCl in conjunction with levodopa treatment may cause Coombs' positive haemolytic anaemia. Eosinophilia has occurred in only a few patients during treatment with apomorphine HCl. Apomorphine is associated with somnolence. Breathing difficulties have been reported.

Presentation and Basic NHS Cost: APO-go ampoules contain apomorphine hydrochloride, 10mg/ml, as follows: 20mg in 2ml – basic NHS cost £37.96 per carton of 5 ampoules. 50mg in 5ml – basic NHS cost £73.11 per carton of 5 ampoules. APO-go pens (disposable multiple dosage injector system) contain apomorphine hydrochloride 10mg/ml, as follows: 30mg in 3ml – basic NHS cost £123.91 per carton of 5 pens. APO-go Pre-filled Syringes contain apomorphine hydrochloride, 5mg/ml, as follows: 50mg in 10ml – basic NHS cost £73.11 per carton of 5 syringes.

Marketing Authorisation Numbers:
APO-go Ampoules: 05928/0020
APO-go Pens: 05928/0021
APO-go Pre-filled Syringes: 05928/0025

Legal Category: POM.

Date of Last Review: November 2004.
Version Number: APG.API.V4

APG.AD.V4A4

Third International Scientific Symposium on Parkinson's Disease and Restless Legs Syndrome

October 14-15, 2004; Cannes, France.

Over 350 neurologists from all over the world converged on Cannes, France in October for the 3rd International Scientific Symposium on Parkinson's Disease and Restless Legs Syndrome. The two-day symposium was supported by an unrestricted educational grant from Boehringer Ingelheim and accredited by the European Federation of Neurological Societies (EFNS).

Welcoming delegates to the first day of the meeting, Oliver Rascol (Toulouse, France) pointed out that although effective treatments have deeply modified the clinical spectrum of Parkinson's Disease (PD), the presence of multiple options make it a challenge in setting a consensus and a unified strategy for the optimal management of the individual patient.

Marie Vidailhet (Paris, France) highlighted the non-motor symptoms of PD. She said that although PD is typically defined as a syndrome consisting of tremor, bradykinesia, rigidity and postural instability, the clinical spectrum was much more diverse. "Beyond these principally motor features", she said, "there is increasing recognition of non-motor problems including cognitive impairment, mood disorders and autonomic failure". And she stressed that it was these aspects of the illness rather than the motor symptoms that lead to the most profound disability, and impact on quality of life.

Anthony Schapira (London, UK) then took to the floor to discuss the dopaminergic and non-dopaminergic actions of dopamine agonists. He said that recently dopamine agonists have attracted attention as potential disease modifying agents, adding that they appear able to prevent cell death in a variety of cell culture and animal model systems. He also presented evidence showing that the D2/D3 agonist pramipexole has been shown to significantly reduce dopaminergic cell loss in the nigra of MPTP treated primates. He also presented data from the CALM-PD study that used imaging of the nigrostriatal system as a surrogate marker for disease progression in patients receiving pramipexole or levodopa. The results showed a significant reduction in the rate of loss of imaging marker over the four-year study period with pramipexole.

The focus then turned back to the non-motor symptoms of PD. Paolo Barone (Naples, Italy) said that depression was a common complication of PD with a prevalence averaging 40% in patients attending outpatient clinics. He also highlighted that the quality of life of PD patients was significantly and inversely associated with depression. Yet he stressed: "There is little evidence for the efficacy and safety of antidepressant therapies in PD". He went on to present findings from an open-label randomised study comparing the efficacy and tolerability of pramipexole versus the selective serotonin reuptake inhibitor sertraline in the treatment of depression in stable PD patients without fluctuations and under levodopa monotherapy. Pramipexole was found to have significant antidepressant effects in patients with PD. Less pramipexole patients discontinued as a result of side effects and in a secondary analysis of the intent-to-treat population, the percentage of patients recovering from depression was statistically significantly higher with pramipexole at 60.6% compared with sertraline (27.3%). Barone commented: "These findings suggest that there may be significant advantage for PD patients with depression to receive the dopamine agonist pramipexole in preference to a classic antidepressant."

Werner Poewe (Innsbruck, Austria) then reviewed disorders of sleep in PD patients. He stressed that the management of sleep disorders in PD was complex and has to target underlying mechanisms. He said that dopamine agonists might be helpful with sleep fragmentation due to nocturnal motor disability due to either restless legs syndrome or periodic limb movements in sleep.

Andrew Lees (London, UK) highlighted that a small number of PD patients develop cognitive and neuropsychiatric disturbances that may be directly related to taking increasing doses of dopaminergic drugs well in excess of those needed to control motor symptoms. He said that such patients could be identified by a demand for escalating doses of dopamine replacement therapy often against medical advice. He said that treatment involved early identification for risk and stringent enforced restriction of medication with minimisation of short duration formulations.

Ken Marek (New Haven, USA) provided an update on imaging. He said that imaging "continues to expand its role in translating clinical neuroscience into better understanding and more effective therapies for PD". One of the most exciting potential uses he spent some time elaborating on was preliminary work demonstrating that combining imaging with other potential PD screening tools may enable presymptomatic screening for PD in at risk groups.

Continuing on this theme, Christopher Goetz (Chicago, USA) highlighted the need for the development of new scales for the clinical assessment of PD. Goetz has been recruited by the MDS to organise a committee to provide a new UPDRS. The new scale retains the original structure of the UPDRS with four newly titled components: non-motor experience of daily living (part I and II), motor examination and motor complications. In addition, an official appendix recommends more in-depth assessment for several of the non-motor items including depression, cognitive deficits, insomnia and quality of life.

Concluding the first day, Warren Olanow, (New York, USA) outlined new and future therapies for the treatment of PD. These included cell based therapies; trophic factors; gene therapies and neuroprotective approaches.

The second day of the meeting was devoted to Restless Legs Syndrome (RLS). Karl Ekbom, son of Karl-Axel Ekbom who in 1945 published a doctoral thesis on restless legs, provided an introduction to the day highlighting the potential promise of dopamine agonists. Markku Partinen (Helsinki, Finland) reviewed the clinical presentation and diagnosis of RLS. He stressed that all symptoms of the RLS quartet must be present in order to make the diagnosis – an urge to move usually accompanied by unpleasant sensations in the legs; aggravation of symptoms at rest; relief of symptoms with activity and a circadian pattern with worse symptoms experienced in the evening or night.

Wayne Hening (New Brunswick, USA) then elaborated on the clinical importance of RLS. He highlighted findings from the recent REST study showing that 3% of the primary care population reported that they had RLS symptoms at least twice a week and that when the symptoms occurred they caused moderate to severe distress. Among these patients, 82% reported that they were bothered by the leg discomfort and more reported difficulties with sleep. Over half of RLS sufferers reported significant problems with functions the day after nocturnal symptoms – including fatigue and cognitive difficulties. Overall he stressed that RLS had a significant impact on quality of life, adding that treatment of RLS can both alleviate symptoms and improve quality of life.

Richard Allen (Baltimore, USA) then reviewed the pathophysiology of RLS highlighting the importance of dopamine abnormalities. He said that levodopa and all dopamine agonists provide dramatic and immediate relief of symptoms when used at doses much lower than those used for treatment of PD.

Luigi Ferini-Strambi (Milan, Italy) proposed that RLS was a poorly recognised and undertreated condition. Reviewing latest epidemiological studies he said that around one in ten of the adult population have RLS – a truly common disease; and that women were twice as often affected as men.

Turning to treatment options, Diego Garcia-Borreguero (Madrid, Spain) reviewed the efficacy and safety of dopaminergic compounds. Although he said that several ergoline-derived dopamine receptor agonists have been investigated, due to the higher incidence of side effects research is now focused on the non-ergoline derivatives including pramipexole and ropinirole. He cited studies showing that pramipexole has been shown to be more effective than placebo at a dose of 0.125 mg per day and is currently being investigated in large, double blind randomised controlled trials. He also said that pramipexole had the advantage of having therapeutic efficacy at the initial dosage. This he said meant that if confirmed by future studies pramipexole could be used not only for as a continuous treatment but also for non-daily treatment of RLS.

John Winkelman (Massachusetts, USA) reviewed the long term experience to date with dopaminergic agents. He said that dopamine agonists have replaced levodopa as first line treatment for RLS given the requirement for increased doses of levodopa due to loss of efficacy, re-emergence of symptoms in the second half of the night or worsening of symptoms during the day (augmentation). Although pergolide demonstrated persistent benefit for the majority of RLS responders when followed for 12 months, concerns regarding pleuropulmonary fibrosis and multivalvular disease have recently been raised with long term use of this dopamine agonist. Long-term experience with pramipexole was assessed in three large retrospective consecutive case studies. In two of the studies follow up information was available for a mean of 21 – 27 months of continuous pramipexole administration. Long-term efficacy was confirmed and augmentation was found in only a third of patients and was generally easily managed by earlier administration of medication.

Wolfgang Oertel (Marburg, Germany) presented new data from the European Flexible dose study of pramipexole in RLS patients. In total 37 sites in 5 European countries participated in the study, which involved nearly 350 patients. Pramipexole was significantly superior to placebo in regard to change from baseline to week 6 on the IRLS scale and CGI- Improvement after six weeks and showed an excellent tolerability profile.

The last presentation of the symposium was given by Jacques Montplasir (Montreal, Canada) widely regarded as one of the main pioneers in this field. He confirmed that dopamine agonists should be considered as the first line therapy treatment of choice for RLS. He also called for more publicity about RLS saying that well-informed patients could present themselves for treatment, and drawing an analogy with public health campaigns in relation to sleep apnoea.

Helen Reilly,
Freelance Medical Journalist, London.

European Committee for Treatment and Research in Multiple Sclerosis

October 6-9, 2004; Vienna, Austria.

Superb weather for October and a fantastic venue, Vienna, Austria, witnessed the 20th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and the 9th Annual Meeting on Rehabilitation of MS (RIMS). Delegates travelled from far afield to attend. The meeting comprised 33 lectures spread over four plenary and 12 parallel sessions and a total of 638 posters/abstracts. Fortunately, all the posters were displayed throughout the conference, allowing delegates time to view them at their leisure.

The teaching course titled "Symptom management and rehabilitation in MS" was divided into "Neurorehabilitation in MS – Applied Neuroplasticity (G. Comi, Milan) and "Symptom Management in MS (Kesselring,Valens). It illustrated that functional MRI has the potential to provide information about cortical reorganisation following MS-related tissue damage. The key target for the management of MS is the enhancement of cortical adaptive plasticity by both cognitive and physical rehabilitation. "Assessment in MS" (J. Horbart, Plymouth) demonstrated the importance of using and relying on rating scales to measure the impact of MS symptoms to evaluate the endpoints of clinical trials, with emphasis on the patient's perspective.

The first plenary session "New insights in primary progressive MS (PPMS)" (J.S. Wolinsky USA) illustrated that the phenotype of PPMS has an unrelenting course from the onset without discernible attacks. The PROMiSe study explored whether glatiramer acetate (GA) could slow the progression of accumulating disability in PPMS. 943 subjects were randomised to GA or placebo in a 2:1 ratio in a planned 3-year double-blind trial. The data safety monitoring committee advised early discontinuation of the study, however, because no treatment effect could be discerned on primary outcome and projected that none could be expected either. Analysis of MRI-monitored enhancement and plaque burden favoured GA treatment. The premature stopping of the study medication and the unanticipated slow progression rates complicate interpretation of this trial.

A poster by O'Rourke et al (Ireland) examined "Stopping interferon beta in Multiple Sclerosis". There are few marketing studies looking at discontinuation rates. They investigated whether the clinical disease type at treatment initiation, or the interferon formulation, influenced the rate. All patients who started IFNb between April 1996 and December 2003 were reviewed and had an annual Kurtzke EDSS measured. A total of 398 patients were started on treatment, four (1%) were non-compliant and 394 patients with a median follow up of 49 months were analysed, of whom 109 (28%) stopped IFNb. There was a significant difference between the IFNb stopping rate for relapsing-remitting MS (14%) and secondary progressive MS (23%) after three years of follow up (p=0.0003). 56 patients stopped due to side effects and 53 due to treatment failure. Patients treated initially with IFNb 1a had a higher stopping rate in the second treatment year than patients treated initially with IFNb 1b.

A review by the Therapeutics and Technology Assessement Subcommittee of the American Academy of Neurology (Goodin, 2002) concluded that the effectiveness of IFNb treatment was dependent upon dose and frequency of administration. An increase in dose to 500 mcg IFNb –1b subcutaneously every other day is being studied by the BEYOND (Betaferon Efficacy Yielding Outcomes of a New Dose, Kappos) trial to discover whether further benefits can be obtained. The first phase found that higher dose IFNb – 1b was well tolerated and a greater effect was also seen on MRI end-points. The second phase of the trial will include 2100 Relapsing-remitting MS patients with an EDSS score of 0-5.0 randomised to receive 250mcg or 500mcg interferon beta –1b or glatiramer acetate. This study will establish whether 500mcg IFNb –1b sc offers greater clinical benefit than the licensed dose, whilst maintaining safety and tolerability.

A histopathological study of spinal cord atrophy (Gilmore, UK) examined post-mortem material from 55 MS cases and 33 controls. Transverse sections were taken from five levels of the spinal cord. The total cross-sectional area of the cord and that of grey and white matter was measured. Spinal cord atrophy in MS is due to white matter, rather than grey matter, volume loss. Previous studies have demonstrated significant grey matter atrophy in the cerebral cortex and the thalamus in MS. The absence of spinal cord grey matter atrophy raises the possibility of site-specific differences in grey matter pathology in MS.

Several workers considered mitoxantrone treatment for MS. A French study examined the long-term incidence of drug–related adverse events in 802 MS patients (307 relapsing-remitting, 352 secondary progressive, 143 primary progressive). Mitoxantrone was generally well tolerated. Another study also suggested that the drug might have beneficial effects upon cognitive function in MS (Zephir, France). Recent National Institute for Clinical Excellence (NICE) guidelines for MS Management (2003) recommend that mitoxantrone is used only by an expert in the use of this drug after a full discussion and explanation of the risks to the patient. A poster (Porter, UK) described the complications encountered in the use of mitoxantrone, such as neutropenia, extravasation, infections, amenorrhoea, which were compounded by poor documentation, lack of advice on potential infertility problems and an absence of pregnancy screening. To address these issues they developed an integrated care pathway, including patient screening, informed consent, infusion protocol and long-term management monitoring.

Breaking news included the first study to demonstrate a clear association between N-acetylaspartate (NAA) levels in cerebrospinal fluid (CSF) and MRI measures of brain atrophy in MS patients. It involved 41 MS patients (21 relapsing/remitting MS, 12 secondary progressive MS and 8 primary progressive MS). Each patient underwent a lumbar puncture and an MRI-scan within one week. The CSF level of NAA correlated significantly with normalised brain volume (NBV) ($r = 0.51$ $p<0.001$) suggesting that lower CSF NAA levels might be associated with lower NBV. CSF NAA levels may therefore represent an important CSF biomarker for axonal loss (Jasperse, Amsterdam).

Disease modifying therapies for MS are moving apace and this meeting provided an ideal opportunity to catch up on the latest developments. No doubt the sands will have shifted again by the time of the next meeting in Greece.

Mrs Aileen M Burn, City Hospitals, Sunderland.

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The International Society for Vascular Behavioural and Cognitive Disorders (Vas-Cog)

The last decade has seen an increased focus on the vascular burden of the brain. In addition to vascular dementia, vascular causes have been implicated in various neurodegenerative disorders including Alzheimer's disease (AD) and in depressive illness. Current evidence suggests that stroke, hypertension, diabetes, hyperlipidemia, increased homocysteine are all risk factors for AD. The potential implications for preventing or treating vascular disease are therefore profound for the health of the ageing population. It has been increasingly apparent that a forum for discussion and education on the vascular causes of brain disorders is warranted.

To this end the International Society for Vascular Behavioural and Cognitive Disorders (Vas-Cog) was launched in 2002. It aims to bring together diverse basic science and clinical research interests to evaluate vascular factors in relation to brain injury and dysfunction leading to cognitive impairment and dementia, and to serve as an organisation for the dissemination of knowledge on current advances in cerebrovascular disease and patient advice.

Encouraged by several affiliated organisations including the World Federation of Neurology Research on Dementia Group, International Psychiatric Association, International Stroke Society, Alzheimer's Disease International and the Alzheimer's Association, Vas-Cog Society was founded by a group of some 60 international scientists with varied expertise. Vladimir Hachinski (pictured) was elected as the first chairman of the Executive Committee. Vas-Cog sees herself as the main voice to guide consensus criteria for the diagnosis of brain vascular disorders causing dementia, but its ideals include promoting worldwide representation particularly involving younger investigators, multidisciplinary and translational research, public education, and liaisons with caregivers.

The inaugural congress of Vas-Cog, hosted by Ingmar Skoog and Anders Wallin (picture), was held in Goteborg, Sweden in August 2003. This highly successful beginning was witnessed by 500 participants. The schedule featured moot but pertinent issues related to clinical diagnosis, biomarkers, neuropsychology and neuropathological substrates of vascular cognitive impairment (VCI). Interactive poster discussion sessions and lively debates on topics such as whether 'AD is a vascular disorder' were high points in the programme (J Neurolsci 226 2004). Vas-Cog congresses were preceded by a series of international meetings on 'Vascular Pathology or Factors in Alzheimer's Disease,' convened in New Jersey (1996), Newcastle upon Tyne (1999), Boston (2000) and Kyoto (2002). The proceedings of these forerunners, published largely in the Annals of the New York Academy of Sciences, have become source reference works on vascular mechanisms in dementing illness. The Second International Congress of Vas-Cog (vas-cog2005), to be chaired by Professors Leonardo Pantoni and Domenico Inzitari in Florence in June 2005, equally promises to be an exciting event with teaching sessions on VCI, plenaries on cerebral regulation, debates on treatments and oral communications on cognitive impairment after cardiac surgery among others.

For more information see www.vas-cog.org

Professor Vladimir Hachinski (left; University of Western Ontario, Canada), chair of Executive Committee of Vas-Cog, with Anders Wallin and Ingmar Skoog at Vas-Cog 2003.

Professor Raj Kalaria (University of Newcastle-Upon-Tyne, UK), chair, Scientific Committee of Vas-Cog 2005.

Sino-British Joint Conference on Neurology

November 15-17, 2004; Beijing, China.

This two day meeting was organised by the Association of British Neurologists (ABN) in conjunction with the Chinese Society of Neurology, Chinese Medical Association and Hong Kong Neurological Society. A contingent of over 60 delegates from the UK made the long journey to Beijing, although many also took the opportunity to extend their stay for sight seeing. There was some trepidation from ABN members about the effect of potential language and cultural barriers on the smooth running of the scientific programme, but these fears were soon allayed. The use of dual projection, with many UK talks pre-translated into mandarin assisted the Chinese delegates, while joint chairs for all sessions kept the meeting to time. Plenary sessions ran in the morning (beginning at 0815!), while parallel scientific sessions ran in the afternoon (finishing at 1800, for the hardy attendees). Apologies to colleagues not featured below, therefore, as it was impossible to sit in on all talks.

Professor Will (Edinburgh) gave a masterly overview of Creutzfeldt-Jakob disease, with emphasis on vCJD. This included very recent data, including description of a "preclinical" CJD case, as evidenced by PrPsc in the lymphoreticular system of a male patient dying from a ruptured aortic aneurysm who had previously received a blood transfusion from another CJD victim. Tonsillar biopsies have been positive in all 18 vCJD cases to date. Triphasic EEG complexes, not typically found in vCJD, have been recently described in the late stages of diseases in an Italian patient. One hundred cases of sporadic CJD have been reported in China since 1980, 56 of these pathologically confirmed (Lin). A single case of vCJD had worked in the UK for many years. Professor Colchester (Kent) advanced the hypothesis that BSE in the UK may have originated from Far Eastern mammal-derived imports, in association with a "spontaneous event", inducing PrPsc formation in cattle, rather than species to species transfer. Dr Murray (Edinburgh) gave a comprehensive overview of MRI in CJD. Signal changes on FLAIR sequences and diffusion-weighted imaging, in particular, may be sensitive for cortical, thalamic and basal ganglia changes in sporadic and vCJD, although the exact pathological correlate is not yet known. Intriguing preliminary data was presented (Guo, Beijing) to suggest that tetracycline may reduce protease-resistance in PrP (a feature of PrPsc), while inoculation of scrapie material treated with tetracycline into mice prolonged the incubation time for disease by several days. The authors had not, however, administered tetracycline orally to the mice prior to scrapie inoculation. Such an experiment would be of potentially greater clinical relevance.

Professor Chuanzhen (Shanghai) described a series of 226 Chinese patients with multiple sclerosis (MS) and 32 with neuromyelitis optica (NMO). The prevalence of MS in China is 5-10 per 100,000. In his series, relapsing-remitting disease comprised 30% of all MS cases, and secondary progressive disease 40%. Average age of onset for MS was 32 years. Oligoclonal bands were present in 50% of MS and 22% of NMO cases. Dr Lin (Nottingham) presented data for a modest effect of intravenous immunoglobulin upon reducing progression of brain atrophy in secondary progressive MS, particularly in the infratentorial compartment. The clinical features of 22 cases of neuro-Behcets's syndrome gathered in Wales were presented by Dr Joseph (Plymouth). 77% of the cases were parenchymal in type (brainstem, encephalitis) and 23% non-parenchymal (meningitis, raised intracranial pressure, cerebral venous thrombosis). Interestingly, one patient developed hemichorea, and another steroid-responsive parkinsonism. Ten year follow up revealed a generally favourable prognosis. Male sex, early neurological presentation, two or more relapses with neurological disease and marked CSF pleocytosis were poor prognostic factors.

In the garden of the Hidden Palace.

Professor Vincent (Oxford) gave an elegant overview of neuroimmunology, with particular reference to neuromuscular transmission defects. Myasthenia gravis (MG) is common in older people (males > females). Antibodies to the muscle specific receptor tyrosine kinase (MuSK) have been identified in a proportion of MG patients without acetylcholine receptor antibodies. MuSK Abs are mainly IgG4 class and so do not bind complement. Patients tend to have marked bulbar, neck and respiratory muscle weakness, with atrophy of facial, neck and tongue muscles. They do not respond well to conventional anti-MG treatments but plasma exchange or mycophenolate may be helpful.

Professor Turnbull (Newcastle) combined a beautifully illustrated clinical talk on mitochondrial disease with leading edge science. In particular, the possibility of pronuclear transfer, with the aim of decreasing mutant mtDNA levels in the developing blastomere was discussed, with encouraging preliminary data presented from murine studies. He estimated that there may be as many as two million people in China with mitochondrial disease. Dr Roberts (Manchester) described how mitochondrial disease may present with respiratory failure in adults, sometimes with rapid deterioration leading to death.

Dr Lane (London) is co-author of a forthcoming book on migraine. Judging by his talk on migraine auras, and how they may masquerade in the clinic as vertigo, transient amnesia and syncope, this should be a good buy for any clinician wishing to have a refreshing and helpful look at migraine in general (and I'm not on commission!).

Not unsurprisingly, given the frequency of stroke in China, there were several talks on vascular disease. Dr Lovelock (Oxford) highlighted the reasons why TIA and minor stroke should be afforded "emergency" status, not least because of the temporal risk-to-benefit dependency of carotid endarterectomy. The increased risk of delay, most marked in women, may relate to sex differences in plaque morphology (Lovett, Oxford). The frequency of different stroke types is changing in China (Wong, Taiwan), with reducing intracerebral haemorrhage (from 40% in 1970 to 20% in 2000) but increasing extracranial carotid disease (10% in 1970 to 20% in 2000). The pattern of intracranial disease is also shifting, from lacunar events to large artery lesions.

A visual highlight of the meeting came from Professor Kennard, President of the ABN (London), fresh from his Welcome Banquet and British Embassy speeches. He summarised our state of knowledge regarding the "visual brain", with reference to localising function to structure in the striate and extra-striate cortices through functional imaging and clinical lesion studies. His lecture included a video of a Gorilla walking into and out of a room while the audience concentrated on counting how many times an individual caught a ball – all but a couple of people completely missed seeing the gorilla! Professor Hughes (London) gave a measured and erudite overview of the immunology and treatment of Guillain Barre Syndrome and its variants. The GQ1b antibody is positive in 95% cases of Miller Fisher syndrome, making it possibly the most useful antibody-based test in neurology. The clinical management of epilepsy in women was comprehensively and sympathetically covered by Dr Crawford (York). Heterozygous mutations have been found in the CACNA1H gene (T-type calcium channel) in a number of patients with childhood absence epilepsy (Wu, Beijing). Alzheimer's disease (AD) and vascular dementia (VaD) are as prevalent in China as they are in Western countries, as evidenced by a methodologically rigorous multiregional study which yielded figures of 5.0% in the >65 age group (95% CI 4.5-5.5) for dementia, 3.5% (3.0-3.9%) for AD and 1.1% (0.9-1.1%) for VaD (Zhang, Beijing).

From a personal perspective, this was an all too brief glimpse of a fascinating country and culture. Our Chinese hosts were delightful and welcoming. Given the rapid economic and scientific growth in China at the present time, it is certainly a case of "watch this space" for increasingly major research outputs. The opportunity for collaboration should, perhaps, not be overlooked and future joint meetings are planned.

David J Burn, Newcastle upon Tyne.

Pregabalin – a New Treatment for Partial Epilepsy and Neuropathic Pain

In July 2004, pregabalin (Lyrica®), a new therapy was introduced to the UK with a licence covering both epilepsy (adults with partial seizures, with or without secondary generalisation), and peripheral neuropathic pain.

Unlike some other compounds used to treat these conditions, pregabalin has a well defined mode of action, binding to the alpha$_2$delta subunit of voltage-gated calcium channels to modulate calcium influx (see Figure 1). This is believed to reduce the release of excitatory neurotransmitters, thus resulting in anti-epileptic, analgesic and anxiolytic effects.[1,2,3]

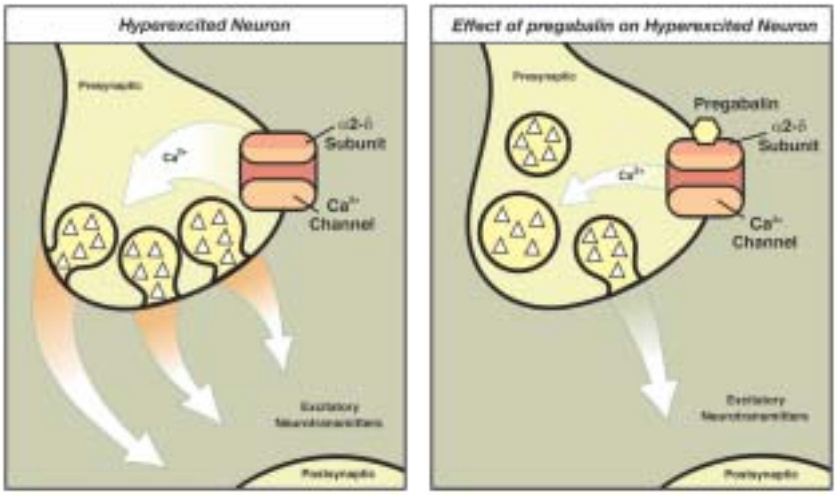

Figure 1: Pregabalin binds to the alpha$_2$delta subunit of voltage-gated calcium channels to modulate calcium influx.

Both neuropathic pain and epilepsy are notoriously complex and challenging conditions to treat. Epilepsy remains one of the major disabling neurological disorders, affecting two percent of the population.[4] In the UK, 15 anti-epileptic drugs (AEDs) are already available, yet even in the best centres, up to 30% of patients with epilepsy remain uncontrolled,[4] a figure which rises to around 50% in the community.[5]

The key question is whether pregabalin offers new possibilities and additional benefits over and above the existing therapies, and whether it can help improve the lives of patients with epilepsy. This article discusses the key clinical data for pregabalin in epilepsy and the potential place for the drug in a therapy area where therapy uptake is heavily influenced by clinicians' evolving experience.

Clinical evidence for pregabalin in epilepsy

Pregabalin's effectiveness as an adjunctive therapy has been studied in three double-blind, placebo-controlled trials of 12 weeks duration and including 1,052 highly refractory adult patients (Table 1).[6,7,8] All patients included in these trials had at least six partial seizures over the 8-week baseline period prior to the trial; and no 4-week seizure free period. In addition, patients were required to be receiving 1-3 AEDs. These cohorts comprised a highly refractory patient population, with 73% of patients on at least two AEDs at baseline and a mean baseline 28-day seizure rate of 24 (a median of 11 and a range of 1 to 436) seizures across the studies.

These studies demonstrated that the addition of pregabalin to existing treatment regimens delivered significant efficacy compared with placebo across the recommended dose range 150-600mg daily (given in either two or three divided doses) both in terms of seizure reduction (% change from baseline) and 'responder rate' (B 50% reduction in seizures). Pregabalin's onset of efficacy was seen as early as week 1.[9]

In the dose-response study by French et al,[6] both seizure frequency (pA0.0001) and responder rates (pA0.001) showed significant dose response: 150mg/day reduced seizures by 34%; 300mg/day by 44%; and 600mg/day by 54% compared with placebo at 7%. In addition, the study showed significantly more patients were responders in the 600mg group than in the placebo group (51% vs.14%).[6] These findings are consistent with those of the other two studies of similar design that evaluated similar patient populations with refractory partial seizures.[7,8] Seizure freedom (defined as the last 28 days of double-blind treatment), was achieved in up to 12% of previously refractory patients (p=0.002).[7] Pregabalin's efficacy was similar regardless of whether patients were on 1, 2 or 3 baseline AEDs[10] and both BD and TDS regimens showed similar efficacy.[8]

After training in Neurology and Clinical Neurophysiology at the Walton Centre in Liverpool, Dr John Paul Leach took up a consultant post at the Neurology Department in his home town of Glasgow. He continues his research interest into the diagnosis and treatment of epilepsy.

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Table 1: Adjunctive Placebo-Controlled Trials (n=1052)

Study	Total daily dose	Dose Regime	Titration	Double blind treatment	N (ITT)	Location
French[6] *BD dose- response study*	*50mg/day* *150mg/day* *300mg/day* *600 mg/day*	***25mg bd*** ***75mg bd*** ***150mg bd*** ***300mg bd***	*None*	*12 weeks*	*453*	*USA* *Canada*
Arroyo[7] *TDS dose- response study*	*150mg/day* *600mg/day*	***50mg tds*** ***200mg tds***	*1 week*	*12 weeks*	*287*	*Europe* *Australia* *S. Africa*
Beydoun[8] *BD/TDS Comparison*	*600mg/day* *600mg/day*	***300mg bd*** ***200mg tds***	*1 week*	*12 weeks*	*312*	*USA* *Canada*

As expected, the majority of adverse events reported on pregabalin treatment were CNS-related with somnolence and dizziness the most common.[6,7] Both were generally mild or moderate, dose-related, and somnolence was shown to be more common in patients receiving three concomitant AEDs.[6,7] Dizziness ranged from 19.2% of patients at 150mg/day up to 26.1% at 600mg/day (compared to 8.3% on placebo) and somnolence 6.1% at 150mg/day up to 29.3% at 600mg/day (7.3% on placebo).[7] When 600mg/day was initiated on day 1 without titration, as might be expected, the reported incidence of dizziness was higher (42.7% compared to 9% on placebo).[6] Between 2.3% (150 mg/d dose) and 14.1% (600 mg/d dose) of patients reported weight gain but this, and adverse events generally, resulted in few discontinuations of the treatment.[6,7] In individuals where weight gain may be a concern, physicians should be aware of this possibility so they can manage it appropriately.

Pregabalin has a predictable and linear pharmacokinetic profile, as well as a lack of pharmacokinetic drug interactions.[11] Pregabalin benefits from renal excretion, minimal hepatic metabolism (<2%) and lack of protein binding. Significantly it has no interactions with the contraceptive pill or with other AEDs.[12]

Pregabalin's recommended starting dose is 150mg/day, with efficacy demonstrated across the dose range of 150-600mg/day.[13] It is available in 25mg, 50mg, 75mg, 100mg, 150mg, 200mg and 300mg capsules (the lower doses available for patients with renal impairment who require dose reduction).[13]

The cost of treating a patient with pregabalin (bd dosing) compares favourably with other newer AEDs at about £840 per year, with a flat price structure across the dose range.[14]

Implications for clinical practice

As monotherapy fails to bring seizure freedom in a significant number of patients, polypharmacy in epilepsy is often unavoidable. A sizeable minority of patients with partial seizures will benefit from a new AED option to improve seizure control. The clinical trial results with pregabalin are promising and offer hope to refractory patients with partial seizures.

The efficacy of pregabalin in terms of responder rate (B 50% reduction in seizures) demonstrated in clinical trials compares favourably with other available AEDs[6,7,15]; future meta-analysis should help confirm this. The incidence of seizure freedom in reported studies also compares well with newer AEDs. An examination of pregabalin's list of reported adverse events shows they are similar to those seen with commonly prescribed AEDs.

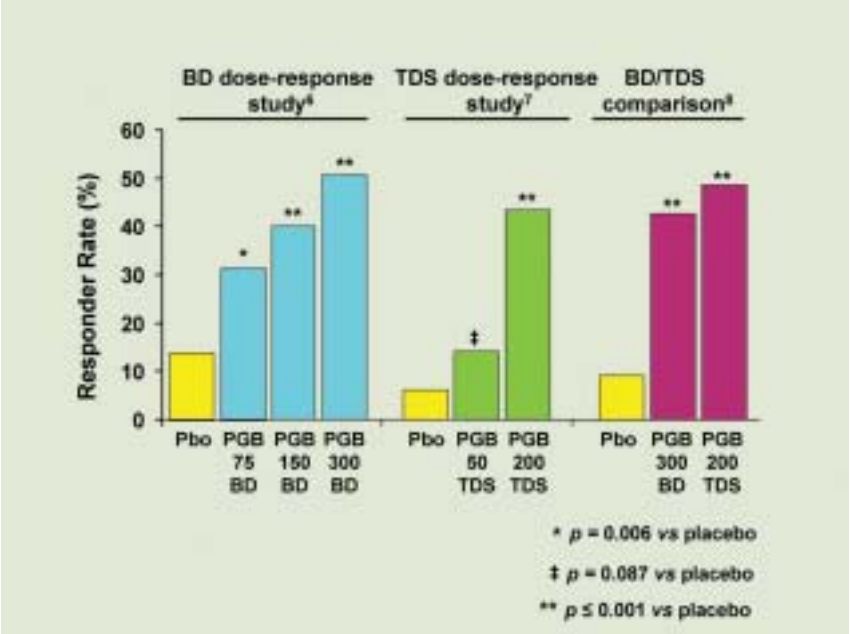

Figure 2: Responder rate: percentage of patients with B50% reduction in seizures vs. baseline.

With any new add-on therapy, the ease of use in clinics arises from a lack of pharmacokinetic interactions, and a toxicity profile which differs from that of existing AEDs. Pregabalin's lack of pharmacokinetic drug interactions and different mode of action compared with the commonly used monotherapies (carbamazepine, valproate and lamotrigine) potentially make it a rational and sensible choice for early use as add-on therapy. As none of the other commonly used AED monotherapies possess the same mode of action, this would suggest that pregabalin may be easily added in to most treatment regimens with theoretically less risk of producing neurotoxic side effects.

Clinical practice is much more complex than that of clinical trials, so widespread use of pregabalin in the real world will be determined by the initial experiences of clinicians using it to treat their most refractory patients. The traditional pattern of use with new antiepileptic drugs involves first usage as adjunctive therapy in refractory patients. In the coming years, if pregabalin lives up to its early promise, we can expect to see an expansion in its use.

Dr Leach received an honorarium from Pfizer Ltd for writing this article. However, the views expressed are those of the author.

References

1. Fink K, Dooley DJ, Meder WP, et al. *Inhibition of neuronal Ca(2+) influx by gabapentin and pregabalin in the human neocortex.* Neuropharmacol 2002;42:229–36.
2. Dooley DJ, Donovan CM and Pugsley TA. *Stimulus-dependent modulation of [3H] norepinephrine release from rat neocortical slices by gabapentin and pregabalin.* J Pharmacol Exp Ther 2000;295:1086–93.
3. Dooley DJ, Mieske CA and Borosky SA. *Inhibition of K+ -evoked glutamate release from rat neocortical and hippocampal slices by gabapentin.* Neurosci Lett 2000;280:107–10.
4. NICE guidelines. *Epilepsy: diagnosis and management of epilepsy in children and adults - second consultation.* NICE 2004.
5. Moran NF, Poole K, Bell G et al. *Epilepsy in the United Kingdom: seizure frequency and severity, anti-epileptic drug utilisation and impact on life in 1652 people with epilepsy.* Seizure 2004;13:425–33.
6. French JA, Kugler AR, Robbins JL, et al. *Dose-response trial of pregabalin adjunctive therapy in patients with partial seizures.* Neurology 2003;60:1631–7.
7. Arroyo S, Anhut H, Kugler AR et al. *Pregabalin Add-on Treatment: A Randomized, Double-blind Placebo-controlled, Dose-Response Study in Adults with Partial Seizures.* Epilepsia 2004;45(1):20–7.
8. Beydoun AA, Uthman BM, Ramsay RE, et al. Pregabalin add-on trial: double-blind, multi centre study in patients with partial epilepsy. Epilepsia 2000; 41 (suppl 7): 253–254
9. Perruca E, Ramsay RE, Robbins JL et al. *Pregabalin demonstrates anticonvulsant activity onset by the second day.* Data presented at the 55th Annual Meeting of American Academy of Neurology, Honolulu, Hawaii, 29 Mar – 5 April 2003.
10. French JA, Lee CM, Greiner MJ, et al. *Epilepsy severity is not a determinant of pregabalin's efficacy as treatment of partial seizures.* Data presented at the 55th Annual Meeting of American Academy of Neurology, Honolulu, Hawaii, 29 Mar – 5 April, 2003.
11. Bockbrader HN, Wesche D. *Pregabalin's pharmacokinetic profile shows minimal drug-drug interations.* Data presented at 8th Congress of EFNS, Paris, France, 4-7 Sept, 2004.
12. Bockbrader HN, Posvar EL, Hunt T, et al. *Pharmacokinetics of Pregabalin and a Concomitantly Administered Oral Contraceptive Show No Drug–Drug Interaction.* Data presented at the European Congress on Epileptology, Vienna, Austria, 30 May – 3 June, 2004.
13. *Lyrica® Summary of Product Characteristics.* Pfizer Ltd.
14. *Monthly Index of Medical Specialities (MIMS).* November 2004.
15. Marson AG. *Evidence-based Medicine in Epilepsy.* The National Society for Epilepsy. September 2003.

The Neurology of 'Alice'

The Reverend Charles Lutwidge Dodgson (1832-1898) has been immortalised as Lewis Carroll, the pseudonym under which he published a number of books, amongst them the two classics *Alice's Adventures in Wonderland* (1865) and *Through the looking-glass and what Alice found there* (1872). These works have been of interest not only to children of all ages but also to neurologists since some of the phenomena they describe, or seem to describe, may be deemed suggestive of neurological conditions, a subject which has been previously discussed.[1]

"Alice in Wonderland" syndrome

The name "Alice in Wonderland" syndrome was coined by Todd in 1955 to describe the phenomena of micro- or macrosomatognosia,[2] i.e. altered perceptions of body image, which had first been described by Lippman in the context of migraine some years earlier.[3,4] It has subsequently been suggested that Dodgson's own experience of migraine, recorded in his diaries, may have given rise to his descriptions of Alice's changes in body form, so graphically illustrated in *Alice's Adventures in Wonderland* by Sir John Tenniel. These have been interpreted as somesthetic migrainous auras.[5] However, Blau has challenged this interpretation on chronological grounds, finding no evidence in Dodgson's diaries for the onset of migraine until after he had written the Alice books.[6] Moreover, migraine with somatosensory features is rare, and the diaries have no report of migraine-associated body image hallucinations.[4] Podoll & Robinson have discovered an earlier drawing by Dodgson suggesting that he did in fact suffer migraine aura symptoms before writing the Alice books,[7] but the illustration suggests a right paracentral negative scotoma rather than micro- or macrosomatognosia.

Other conditions may also give rise to the phenomena of micro- or macrosomatognosia, including epilepsy, encephalitis, cerebral mass lesions, schizophrenia, and drug intoxication.[8] It may be speculated that the latter is relevant to Alice since her experiences occur after drinking from a phial ("DRINK ME") and after eating cake ("EAT ME").

Stammering

Dodgson had a developmental stammer. Although ordained a deacon, his unwillingness to preach and to progress to holy orders has been attributed to his speech defect.[9] Carroll parodied this defect in the character of the Dodo ("Do-do-Dodgson") in *Alice's Adventures in Wonderland* (chapters 2 & 3).

Mirror phenomena

Like Leonardo da Vinci, Carroll was a noted mirror writer, penning occasional "looking glass" letters.[10,11] The poem Jabberwocky first appears (*Through the looking-glass*, chapter 1) mirror reversed, in a Looking-glass book; only by holding it up to the mirror is Alice able to read it.

Mirror writing may be associated with stammering, and is much commoner in left handers: Dodgson apparently wrote with his right hand but may have originally been left handed.[10] Gardner states that Dodgson was "handsome and asymmetric – two facts that may have contributed to his interest in mirror reflections. One shoulder was higher than the other, his smile was slightly askew, and the level of his blue eyes not quite the same."[9]

Schott notes that Carroll's mirror letters were written in varying styles, and differed from his normal script, unlike the situation with Leonardo whose two scripts were faithful mirror images,[10] and hence argues that Carroll's letters reflect not an inherent capacity but a contrivance, designed to amuse children who corresponded with him.[10,11] Hence the neural mechanisms of mirror writing, whatever they may be (hypotheses include bilateral cerebral representation of language, motor programmes or visual memory traces or engrams[10,12]), may differ between Carroll and Leonardo. The literary device of mirror letters has been used by other authors writing for children.[13]

"Mad Hatter syndrome"

The consequences of poisoning with inorganic mercury include a mild sensorimotor peripheral neuropathy, a syndrome which may resemble motor neurone disease, tremor (often circumoral), stomatitis, skin rash, and a neuropsychiatric syndrome characterised by timidity, seclusion, easy blushing, irritability, quarrelsomeness and mood lability (erethism). Hatters were liable to such problems because of the use of mercury in the felt hat industry as a stiffener of rabbit fur, leading to the expression "as mad as a hatter". Hence it might be assumed that Carroll's Mad Hatter is "mad" because of mercury exposure.[14,15] However, as Waldrom pointed out,[14] odd though his behaviour certainly is, the Mad Hatter displays none of the typical features of mercury poisoning, either at the mad tea party (*Alice's Adventures in Wonderland*, chapter 7), or during his appearance as the King's Messenger Hatta in *Through the looking-glass* (chapters 5 & 7). Tenniel's illustration of the Mad Hatter/Hatta is said to resemble one Theophilus Carter, a furniture dealer near Oxford, who was known to Dodgson, and known in the locality as the Mad Hatter because he always wore a top hat and was prone to eccentric ideas.[14,16]

Prosopagnosia

Humpty Dumpty, encountered in *Through the looking-glass* (chapter 6), is one of Carroll's most enduring characters, remembered principally for his famous definition of the meaning of a word ("just what I choose it to mean"), and his coining of the term "portmanteau word" ("two meanings packed up into one word").

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A re-reading of the encounter between Humpty Dumpty and Alice indicates two passages alluding to facial recognition: initially when Alice makes out that the egg has the face of Humpty Dumpty, and then at parting when Humpty Dumpty says he would not be able to recognise Alice if they did meet again: "Your face is the same as everybody has". On the basis of this latter passage it has been suggested that Humpty Dumpty may suffer from prosopagnosia, a rare form of visual agnosia characterised by impaired recognition of familiar faces or equivalent stimuli.[17] Sadly this hypothesis is not amenable to empirical investigation since Humpty Dumpty apparently suffered irreversible traumatic injuries in falling from a wall, thereby confounding any further assessment.

Questions for future study?

In *Alice's Adventures in Wonderland*, is the Pool of Tears (chapter 2) a consequence of pathological crying? At the mad tea party (chapter 7), does the dormouse suffer from excessive daytime somnolence, and if so is there an underlying neurological cause? Does the very ugly Duchess (chapters 6 & 9) have a dysmorphic syndrome, perhaps with behavioural features to explain her neglectful treatment of her baby?

In *Through the looking-glass*, The Red King (chapter 4) and both the White and Red Queens (chapter 9) snore whilst they are sleeping: might they have obstructive sleep apnoea-hypopnoea syndrome? Does the White Queen's statement that she "can't do subtraction under any circumstances" (chapter 9) reflect a selective acalculia?

References

1. Murray TJ. *The neurology of Alice in Wonderland.* Can J Neurol Sci 1982;9:453-457.
2. Todd J. *The syndrome of Alice in Wonderland.* Can Med Assoc J 1955;73:701-704.
3. Lippman CW. *Certain hallucinations peculiar to migraine.* J Nerv Ment Dis 1952;116:346-351.
4. Rolak LA. *Literary neurologic syndromes. Alice in Wonderland.* Arch Neurol 1991;48:649-651.
5. Kew J, Wright A, Halligan PW. *Somesthetic aura: the experience of "Alice in Wonderland".* Lancet 1998;351:1934.
6. Blau JN. *Somesthetic aura: the experience of "Alice in Wonderland".* Lancet 1998;352:582.
7. Podoll K, Robinson D. *Lewis Carroll's migraine experiences.* Lancet 1999;353:1366.
8. Takaoka K, Takata T. *"Alice in Wonderland" syndrome and lilliputian hallucinations in a patient with a substance-related disorder.* Psychopathology 1999;32:47-49.
9. Gardner M (ed.). *The annotated Alice. The definitive edition.* London: Penguin, 2001:xvi-xvii.
10. Schott GD. *Mirror writing: Allen's self observations, Lewis Carroll's "looking glass" letters, and Leonardo da Vinci's maps.* Lancet 1999;354:2158-2161.
11. McManus C. *Right hand, let hand. The origins of asymmetry in brains, bodies, atoms and cultures.* London: Phoenix, 2003:349.
12. Mathewson I. *Mirror writing ability is genetic and probably transmitted as a sex-linked dominant trait: it is hypothesised that mirror writers have bilateral language centres with a callosal interconnection.* Med Hypotheses 2004;62:733-739.
13. Ransome A. *Secret Water. Harmondsworth: Penguin,* 1972 [1939]: 175-176, 255.
14. Waldron HA. *Did the Mad Hatter have mercury poisoning?* BMJ 1983;287:1961.
15. O'Carroll RE, Masterton G, Dougall N, Ebmeier KP, Goodwin GM. *The neuropsychiatric sequelae of mercury poisoning: the Mad Hatter's disease revisited.* Br J Psychiatry 1995;167:95-98.
16. Gardner, op. cit. ref. 9:72.
17. Larner AJ. *Lewis Carroll's Humpty Dumpty: an early report of prosopagnosia?* J Neurol Neurosurg Psychiatry 2004;75:1063.

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New possibilities for partial seizure control

Lyrica® (pregabalin) Prescribing Information.
Refer to Summary of Product Characteristics (SmPC) before prescribing.
Presentation: Lyrica is supplied in hard capsules containing 25mg, 50mg, 75mg, 100mg, 150mg, 200mg or 300mg of pregabalin. **Indications:** Treatment of epilepsy, as adjunctive therapy in adults with partial seizures with or without secondary generalisation. **Dosage:** *Adults:* 150 to 600mg per day in either two or three divided doses taken orally. Treatment may be initiated at a dose of 150mg per day and, based on individual patient response and tolerability, may be increased to 300mg per day after an interval of 7 days, and to a maximum dose of 600mg per day after an additional 7-day interval. Treatment should be discontinued gradually over a minimum of one week. *Renal impairment/Haemodialysis:* dosage adjustment necessary; see SmPC. *Hepatic impairment:* No dosage adjustment required. *Elderly:* Dosage adjustment required if impaired renal function. *Children and adolescents:* Not recommended. **Contra-indications:** Hypersensitivity to active substance or excipients. **Warnings and precautions:** Patients with galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Lyrica. Some diabetic patients who gain weight may require adjustment to hypoglycaemic medication. Occurrence of dizziness and somnolence could increase accidental injury (fall) in elderly patients. Insufficient data for withdrawal of concomitant antiepileptic medication, once seizure control with adjunctive Lyrica has been reached, in order to reach monotherapy with Lyrica. May affect ability to drive or operate machinery. **Interactions:** Lyrica appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone and may potentiate the effects of ethanol and lorazepam. **Pregnancy and lactation:** Lyrica should not be used during pregnancy unless benefit outweighs risk. Effective contraception must be used in women of childbearing potential. Breast-feeding is not recommended during treatment with Lyrica. **Side effects:** Adverse reactions during clinical trials were usually mild to moderate. Most commonly (>1/10) reported side effects in placebo-controlled, double-blind studies were somnolence and dizziness. Commonly (>1/100, <1/10) reported side effects were appetite increased, euphoric mood, confusion, libido decreased, irritability, ataxia, disturbance in attention, coordination abnormal, memory impairment, tremor, dysarthria, paraesthesia, vision blurred, diplopia, vertigo, dry mouth, constipation, vomiting, flatulence, erectile dysfunction, fatigue, oedema peripheral, feeling drunk, oedema, gait abnormal and weight increased. See SmPC for less commonly reported side effects. **Legal category:** POM. **Date of revision:** July 2004. **Package quantities, marketing authorisation numbers and basic NHS price:** Lyrica 25mg, EU/1/04/279/003, 56 caps: £64.40, EU/1/04/279/004, 84 caps: £96.60; Lyrica 50mg, EU/1/04/279/009, 84 caps: £96.60; Lyrica 75mg, EU/1/04/279/012, 56 caps: £64.40, Lyrica 100mg, EU/1/04/279/015, 84 caps: £96.60; Lyrica 150mg, EU/1/04/279/018, 56 caps: £64.40; Lyrica 200mg, EU/1/04/279/021, 84 caps: £96.60; Lyrica 300mg, EU/1/04/279/024, 56 caps: £64.40. **Marketing Authorisation Holder:** Pfizer Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ, UK. Lyrica is a registered trade mark. **Further information** is available on request from: Medical Information Department, Pfizer Limited, Walton Oaks, Dorking Road, Walton-on-the-Hill, Surrey KT20 7NS.

References: 1. French JA *et al.* Neurology 2003; 60: 1631–1637. 2. Arroyo S *et al.* Epilepsia 2004; 45: 20–27. 3. Beydoun AA *et al.* Epilepsia 2000; 41(Suppl. 7): 253–254. 4. Baulac M *et al.* Poster presented at the 6th European Congress on Epileptology: Vienna, Austria; 30 May–3 June 2004. 5. LYRICA Summary of Product Characteristics.

LYR379 Sept 2004

The Management of Degenerative Lumbar Spine Disease

Definition and Anatomy

Sciatica is a misnomer freely used to describe lumbar nerve root pain, rather than specific unilateral leg pain in a radicular distribution corresponding to the sciatic nerve (L4,L5,S1,S2). It is caused by nerve root compression in the lumbar spine due to either disc prolapse, osteophytes or ligamentous hypertrophy. These can all be accentuated by spondylolisthesis.

The annual incidence of low back pain is estimated at 5%, but only 1% develops radiculopathy.[1] Lumbar disc prolapse is a disease most common between 30 and 50 years of age, with a male preponderance, as well as an association with repeated mechanical forces and smoking. It may occur at any level, but 95% occur at L4/5 or L5/S1. In the older population, with chronically degenerative discs, compression of the nerve root is more likely to be due to facet joint or ligamentum flavum hypertrophy.

Nerve roots exit the spinal canal, below the pedicle of the same numbered vertebrae, but above the disc of the next caudal disc space. Nerve root compression can occur in three locations (Figure 1a and 1b):

a. A central disc prolapse compresses the thecal sac and the roots of the cauda equina that are contained within.
b. A lateral disc prolapse or lateral recess stenosis compresses the transiting nerve root just after it has bifurcated from the dural sac. For example a lateral L4/5 disc compresses the L5 nerve root.
c. A far lateral disc prolapse compresses the nerve root that exits the foramen at the level of the involved disc. For example a far lateral L4/5 disc prolapse can compress the L4 root.

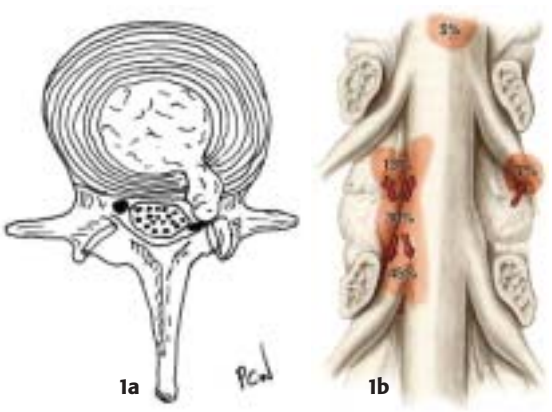

Figure 1a: Postero-lateral lumbar disc herniation causing displacement of the transiting nerve root.

Figure 1b: A coronal view to demonstrate the anatomical relationship (and relative frequencies) of lumbar disc prolapse to the exiting and transiting nerve roots. Picture courtesy of www.spine-health.com

Presentation

1) Most patients present with low back pain, often of long duration, with a more recent onset of acute pain radiating into the lower limb. Frequently the pain may be accompanied by numbness, parasthesiae or weakness. The dermatomal distribution of the pain may give an indication of the level of the pathology but frequently the pain is myotomal being described as a severe, deep sited muscular ache associated with cramps (Table 1). Awkward movements or Valsalva manœuvres often exacerbate the pain (e.g. sneezing). Sudden resolution of leg pain, accompanied by motor or sensory deficit, is more likely to represent nerve root infarction than disc resorption.
2) Neurogenic claudication (from compression on the cauda equina) is the term attached to the syndrome of usually, bilateral leg pain or ache and increasing unsteadiness or loss of balance, precipitated by a progressively decreasing amount of walking. The symptoms are relieved by rest and/ or forward flexion of the lumbar spine. It is this final relieving factor that, along with the absence of positive features or risk factors for vascular claudication, helps differentiate the two conditions. Both occur in the elderly population and without intervention are likely to be gradually progressive. On examination, limited straight-leg raising and a positive stretch test on the affected side is often the only demonstrable sign (Lasegue) of a prolapsed disc. Patients with mid- or high lumbar or far lateral disc prolapse do not generally demonstrate these signs. Patients with lumbar canal stenosis usually do not harbour abnormal neurological signs. An L5/S1 disc prolapse is frequently associated with a reduced or absent ankle jerk. In the elderly, absent ankle jerks are of low diagnostic specificity. L5 root compression frequently causes weakness of extensor hallucis longus, but occasionally profound foot drop and weak ankle eversion are evident. Significant motor deficits and abnormal sphincter function should precipitate urgent radiological investigation, as prompt surgical intervention may be indicated.

Investigation

The goal of imaging is to demonstrate or exclude correlation of clinical and radiological abnormalities amenable to treatment. Plain radiographic imaging is of limited value, although often performed as an initial investigation. Such imaging can help in the assessment of stability and diagnosis of metastatic disease.

MR imaging is currently the modality of choice (Figure 2). If no abnormality is seen at L4/5 or L5/S1 the nerve roots should be scrutinised up to the conus medullaris to exclude unexpected lesions such as an ependymoma.

Treatment

The natural history of unilateral sciatic pain is of spontaneous resolution in 80% of patients without neurological sequelae, beginning within 1 – 2 months. A trial of conservative management should be undertaken initially and investigation is not recommended within this time period.

A proportion of patients will suffer recurrent or persistent symptoms; the latter often occurring after several spontaneously resolving episodes. It is for these patients that intervention should be considered.

During the period of conservative management a short period of bed rest is only recommended where pain prevents mobilisation and should precede recommencement of low impact aerobic exercise and activity modification. Physiotherapy advice and treatment benefits a proportion of patients.[2]

The mainstays of oral analgesia are NSAIDs, with additional diazepam as an antispasmodic, as well as subsequent neuropathic modulators (gabapentin and amitriptyline) where necessary.

A proportion of patients pursue manipulative therapies successfully. However, spinal manipulation is sometimes associated with an acute exacerbation of symptoms.

Epidural injections of steroid and local anaesthetics appear to help some patients and a prospective, randomised, controlled, double-blinded study has shown the efficacy of selective nerve root blocks of patients with lumbar radiculopathy and/or stenosis.[3]

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Surgical Treatment

Less than 2% of symptomatic patients undergo operative treatment. Surgical intervention is best directed at those with unremitting nerve root symptoms.

Urgent surgical intervention is required in those with acute cauda equina compression or significant acute motor deficit (e.g. foot drop). However, urgent decompression once urinary retention and overflow incontinence has occurred seems to confer little benefit.[4]

Microdiscectomy is the gold standard operative treatment for lumbar disc prolapse. The standard approach is through a midline incision over the affected interspace with intraoperative radiographs to confirm the operative level. A fenestration of the ligamentum flavum and, if indicated minimal laminotomy exposes the thecal sac and transiting nerve root. Medial retraction of the root permits identification of the disc space and prolapse and subsequent discectomy.

Central canal, lateral recess or foraminal stenosis from facet joint or ligamentum flavum hypertrophy are surgically decompressed by removal of the offending tissue whilst maintaining stability. There are various names and terms used for the numerous surgical procedures used to achieve this goal. Whilst such nomenclature adds to the apparent mystique of lumbar decompression it can be simplified. A laminectomy (removing the spinous process and bilateral lamina) and removal of the underlying ligamentum flavum, exposes and decompresses the cauda equina in the central thecal sac. Extension of bony removal to include up to 1/3 of the medial aspect of the facet joint (thus maintaining stability) will additionally expose and decompress the transiting nerve root in the lateral recess. Performed alone and unilaterally this latter decompression is often called a medial facetectomy. Where laminectomy is to be avoided (due to the need for multiple level decompression and concern regarding post operative stability) the central canal can be decompressed more specifically where it is most compromised (usually posterior to the intervertebral disc) by removing only part of the lamina at two adjacent levels. This is termed a bilateral laminotomy or an intersegmental decompression. Foraminal stenosis requires undercutting of the offending facet joint to the lateral limit of the exit foramen. Such undercutting is preferable to facetectomy and foraminotomy in terms of post-operative spinal stability.[5]

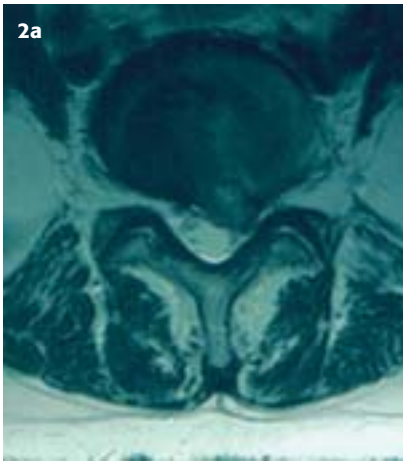
Patients with spondylolisthesis are often asymptomatic, but the resultant loss of canal and foraminal diameter can both precipitate and accentuate symptoms of compression due to the other causes. Surgical treatment is based around decompression of the affected nerve roots. However, where instability is evident on standing flexion/extension plain lateral radiographs or anticipated, fusion may be undertaken.

Outcome and Complications

Patients are discharged 24-48 hours post operatively and are advised to gradually return to normal activities, initially avoiding prolonged periods sitting and activities involving heavy lifting or repetitive mechanical stress. Most patients require only inpatient physiotherapy and advice, and do not need rehabilitation after discharge.

Patients are always made aware that surgery is intended to improve symptoms of leg pain, and prevent progression of symptoms of numbness and weakness. Neurological deficits may also improve. Anecdotally, discectomy rarely improves back pain, and can exacerbate it.

Nearly 80% of patients achieve relief from sciatica at 1 year.[6] However there is evidence that at 4 and 10 years after onset of symptoms there is no difference in groups treated operatively or conservatively.[7] Discectomy may therefore simply facilitate faster recovery. Lumbar decompression has been reported as equally successful in achieving significant pain relief and improvement in activities of daily living.[8]



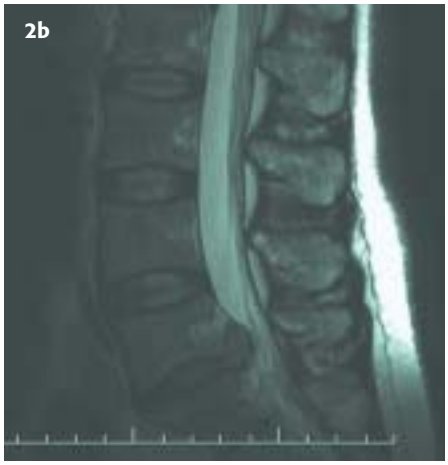


Figure 2a: Axial MRI scan showing a left sided lumbar disc prolapse with compression of the transiting nerve root.

Figure 2b: Sagittal MRI scan showing compression of the cauda equina by a large central disc prolapse.

The risk of recurrent symptoms after microdiscectomy is reported between 5 and 12%, although the risk decreases with time post surgery.[9]

Inadvertent durotomy (CSF leak) occasionally occurs but rarely causes long-term problems. It is frequently managed by a period of horizontal immobility (1-3 days) whilst the durotomy heals under reduced hydrostatic pressure. On occasion repeat surgery to achieve dural closure is necessary. The risk of neurological damage, either at the time of surgery or post operatively secondary to haematoma formation is usually quoted as less than 1%.

Destabilisation of the spine following microdiscectomy is very rare. Stability following laminectomy, facetectomy or intersegmental decompression is dependent on maintaining the integrity of the facet joints. Whilst there is some concern about the outcome after simple laminectomy there is recent evidence that it provides a good long-term outcome for 87% of patients with minimal complications.[10]

Table 1: Clinical features of nerve root syndromes associated with disc herniation

Disc	Transiting Nerve Root	Pain	Sensory	Motor	Reflex
L3/4	L4	Anterior Thigh	Anterior thigh to medial ankle	Knee extension	Patellar
L4/5	L5	Posterolateral Leg	1st web space and dorsum of foot	Dorsiflexion and Extensor hallicus longus (foot drop)	Medial hamstring
L5/1	S1	Posterior calf, plantar foot	Lateral and plantar foot	Plantar flexion and eversion	Achilles

References

1 Frymoyer JW. *Back pain and sciatica.* N Engl J Med 1988;318:291-300.

2 Frost H, Lamb S, Doll H A et al. *Randomised controlled trial of physiotherapy compared with advice for low back pain.* BMJ 2004;329:708-11.

3 Riew KD, Yin Y, Gibula L, et al. *The effect of nerve-root injections on the need for operative treatment of lumbar radicular pain. A prospective, randomized, controlled, double-blinded study.* J Bone Joint Surg Am 2000;82:1589-93.

4 Gleave JR, Macfarlane R. *Cauda equina syndrome: what is the relationship between timing of surgery and outcome?* Br J Neurosurg 2002;16(4):325-8.

5 Detweiler PW, Spetzler CB,Taylor SB, et al. *Biochemical Comparison of facet-sparing laminectomy and Christmas tree laminectomy.* J Neurosurg: Spine 2003;99:214-20.

6 Tulberg T, Isacson J, Weidenhielm L. *Does microscopic removal of lumbar disc herniation lead to better results than the standard procedure?* Results of a one-year randomized study. J Neurosurg 1993;70:869-75.

7 Weber H. Lumbar disc herniation. *A controlled prospective study with ten years of observation.* Spine 1989;14:431-7.

8 Spengler DM. *Degenerative stenosis of the lumbar spine.* J Bone Joint Surg Am 1987;69A:305-8.

9 Williams RW. *Microdiscectomy: a twelve year statistical review.* Spine 1986;11:851-2.

10 Wilby MJ, Seeley H, Laing RJ. *Laminectomy for Lumbar Canal Stenosis: Safe and Effective (abstract).* Br J Neurosurg 2004 (in press).

EDITOR'S CHOICE

Culture and developmental dyslexia

This elegant study shows that the basis of developmental dyslexia differs across cultures and, in so doing, provides insight into the neural basis of reading. The authors give a brief but fascinating description of the Chinese language. Chinese is a logographic language that differs from alphabetic languages, in which the visual, graphic forms (graphemes) map onto minimal phonological units of speech (phonemes). In Chinese, the graphic forms (characters) map onto meanings, which may then be sounded. Neither characters nor their subdivisions, however, relate consistently to phonology and the letter-sound conversion rules of alphabetical languages do not occur. As such, the left temporo-parietal dysfunction found in developmental dyslexics whose languages use alphabetic scripts, and its association with impaired grapheme-to-phoneme processing, seems an implausible model for explaining reading difficulties in Chinese children of normal general intelligence, i.e. those with developmental dyslexia.

Sixteen children attending school in Beijing were studied, aged between 10 and 12, of whom half were reading-impaired and half unimpaired. All participated in two functional MRI experiments. The first experiment consisted of a homophone judgement task: subjects decided whether or not two simultaneously-presented Chinese characters had an identical pronunciation. The control condition was to decide whether or not two characters had the same physical size. In the second experiment, the children were shown two characters, one real, one meaningless (but graphically 'legal'), and asked to decide which was which. Normal readers performed significantly better than the impaired readers at the experimental tasks but not the control task. In brief, the imaging showed weaker activation in the left middle frontal gyrus in the impaired readers. Furthermore, activation at this location correlated with task performance. The region is proposed to have a role in the integration of graphemes and semantics necessary for reading ideographic script. The paper raises the practical point that the management of developmental dyslexia should take cross-cultural factors into account. More fundamentally, it refutes the idea that neural basis for reading is universal. By contrast language, as in speech, is presumably more primitive and its neural basis less likely to vary across cultures. The authors relate their results to the recent anatomical finding that the left middle frontal gyrus is larger in Chinese-speakers than English-speakers which, in turn, suggests an influence of culture on brain development. - ***RD***

Siok WT, Perfetti CA, Jin Z, Tan LH.
Biological abnormality of impaired reading is constrained by culture.
NATURE
2004;431(7004):71-6.

HUNTINGTON'S DISEASE: real-time microscopy reveals the neuroprotective nature of inclusion bodies

★★★ RECOMMENDED

Huntington's disease (HD), a neurodegenerative disorder caused by abnormal polyglutamine expansion within the protein huntingtin (Htt), is characterised by the aggregation of Htt into intracellular deposits called inclusion bodies (IBs) and by the death of striatal and cortical neurons. The role of these inclusion bodies in the pathogenesis of HD is a hotly debated topic. Over the years, a wealth of conflicting experimental data has been generated. Inclusion bodies have been proposed as the major pathogenic species because they absorb critical cellular proteins. In contrast, they have also been hailed as protective because they sequester mutant protein. Finally to complete the debate, some believe that they are purely incidental. Arrasate et al developed an elegant real-time technique to assess factors influencing the risk of neuronal death in cell culture. They employed an established model of HD, in which striatal neurons are transiently transfected with a pathogenic fragment of mutant Htt (Htt-exon1) with polyglutamine stretches of various lengths. To visualise the deposition of Htt in the cytoplasm and nucleus of living striatal neurons, they used the construct of Htt-exon 1 fused to green fluorescent protein (GFP) and devised an automated microscopic system to track specific neurons over a period of days (at 12-24h intervals). They measured the following factors; neuronal survival, aggregation of Htt into inclusion bodies and the levels of diffuse Htt and made two conclusions. First, cells expressing the control construct (non pathogenic Htt-exon1) were at low risk of dying, whilst those expressing an expanded polyglutamine tract were at high risk of dying. Moreover, as in HD, the risk of death increased with the size of the polyglutamine tract. Second and most interestingly, it was observed that cells failing to form inclusion bodies had an increased risk of death. Furthermore, cells with equal mutant Htt-exon 1 expression had a reduced risk of dying if they formed inclusion bodies than if they exhibited diffuse Htt distribution. These findings clearly indicated that inclusion bodies were not required for polyglutamine-induced neuronal death. By improving the temporal resolution of conventional techniques, this study provides conclusive evidence that inclusion bodies are not pathogenic. In fact their formation prolonged survival and protected neurons by reducing diffuse levels of Htt. Although inclusion bodies are not pathogenic, it may be that early precursors of the inclusion body, microaggregates, may be the principal toxic species in HD. This technique could illuminate the pathogenicity of protein aggregates in other human neurodegenerative disorders, including Alzheimer's Disease. - ***LMS & SJT***

Arrasate M, Mitra S, Schweltzer ES, Segal MR, Finkbeiner S.
Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death.
NATURE
2004;431:805-10.

STROKE: Cerebral lithotripsy

In 2000, Andrei Alexandrov and colleagues from Houston published an extraordinary finding in *Stroke*: that monitoring of the effects of thrombolysis with transcranial ultrasound actually improved recanalisation rates. This spawned a great deal of experimental work on the possible mechanisms of "ultrasound-enhanced fibrinolysis". And now the same group has got into NEJM with a phase II trial, called CLOTBUST (bless stroke doctors and their acronyms!). 126 patients presenting within 3 hours of a stroke received t-PA with or without two hours of transcranial ultrasonography (using frequencies equivalent to regular diagnostic ultrasonography). Every half hour all patients had a brief diagnostic ultrasound to assess recanalisation. The one clear result is that the ultrasound group had a statistically significant improved recanalisation rate (38% versus 13%). There was a trend, which was not significant, towards an associated improvement in clinical outcome (42% versus 29% reached 0 or 1 on the Rankin scale). There were no adverse effects associated with ultrasonography, including no increased haemorrhage as earlier studies had suggested. Great stuff. Of course, more research need-

ed… and so on. The main snag is that transcranial Doppler is technically difficult and can be performed by only highly trained operators. It will be a while before hospitals have on-call transcranial clotbusters! - ***AJC***

See ACNR Volume 4 Issue 4 for the article by Dr Paul Syme, on Detection of Small Vessel Knock using Transcranial Doppler Ultrasonography. This can also be found on ACNR's web site with a video clip, see www.acnr.co.uk/controversies.htm

Alexandrov AV, Molina CA, Grotta JC, Garami Z, Ford SR, Alvarez-Sabin J, Montaner J, Saqqur M, Demchuk AM, Moye LA, Hill MD, Wojner AW; CLOTBUSTInvestigators.

Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke.

NEW ENGLAND JOURNAL OF MEDICINE

2004;351(21):2170-8.

ALZHEIMER'S DISEASE: In vitro and in vivo imaging demonstrate neurotoxicity of amyloid plaques in mouse model

★★★ RECOMMENDED

Alongside intracellular neurofibrillary tangles, extracellular ß-amyloid (Aß) plaques are the key diagnostic neuropathological hallmarks of Alzheimer's disease (AD). Their role in disease pathogenesis remains controversial. On the one hand, the "amyloid cascade hypothesis" claims that amyloid plaques are the triggering factor in AD pathogenesis and therapies aimed at reducing plaque load slow disease progression. On the other hand, it is proposed that amyloid plaques are inert tombstones of the disease process, because plaque load does not correlate with the onset or severity of symptoms. Furthermore, functional deficits and synaptic loss are often evident prior to any Aß deposition. This elegant study by Julia Tsai and colleagues at New York University aimed to investigate the effect of Aß deposition on neuronal circuitry, and hence clarify its role in AD pathogenesis. Both in vitro and in vivo imaging techniques were used to study a double transgenic mouse model of AD called PSAPP, which overexpresses mutant human amyloid precursor protein (APP) and presenilin-1 (PS1). Neuronal labelling of fixed brain slices revealed local structural abnormalities in neurites located both within and close to (< 15um) fibrillar amyloid deposits (labelled with Congo Red). The dendrites exhibited a reduction in spine density and shaft diameter and axons bore swellings that indicated major cytoskeletal disruption. Triple transgenic PSAPP mice, in which cortical pyramidal cells were fluorescently labelled, were used for in vivo transcranial 2-photon imaging to investigate the time-course of these structural neuritic changes near to amyloid plaques. This novel technique allowed specific neurites to be monitored over several weeks. It was noted that there was continuous elimination and formation (to a greater extent) of these structural abnormalities in neurites close to the amyloid plaques whilst those further away remained stable. It also became clear that such changes eventually lead to neuritic breakages. This finding suggested that amyloid plaques are more detrimental to neuronal circuitry than originally thought; not only do local axonal and dendritic abnormalities affect signal integration at the whole cell level but neurite breakage means there is a permanent, global disruption in signal integration. It is possible that secondary regenerative processes further disrupt signalling. Since up to 15% of the cortical area of AD patient brains can be made up of amyloid plaques, Tsai claims that plaques would severely disrupt connectivity and could quite conceivably contribute to disease progression and dementia. Importantly their findings also demonstrate a 'microenvironment' in the vicinity of Aß-deposits that is permissive to neuronal remodelling, highlighting the possibility of reversing plaque-induced structural abnormalities. This has important therapeutic implications: early plaque prevention or clearance is clearly an important strategy in halting disease progression. - ***LMS & SJT***

Tsai J, Gruntzendler J, Duff K, Gan W-B.

Fibrillar amyloid deposition leads to local synaptic abnormalities and breakage of neuronal branches.

NATURE NEUROSCIENCE

2004;7(11):1181-3.

PARKINSON'S DISEASE: helpful magnetism

★★★ RECOMMENDED

The components of Parkinson's disease, tremor, bradykinesia and rigidity, reflect a failure of neurophysiological mechanisms. The interference of nigriostriato-thalamic networks may have the effect of generating a deafferented motor cortex with secondary changes in pyramidal cell excitability. By readjusting motor cortex excitability, as measured by transcranial magnetic stimulation (TMS), a benefit in terms of one or more of these clinical disabilities may temporarily result. Applying trains of TMS pulses (rTMS) is known to change primary motor cortex excitability and has been demonstrated by a number of groups. The increase or decrease in excitability depends on the stimulation parameters applied (frequency and number of pulses) as well as the type of coil used and its location relative to the scalp. This research group from France used a range of 'treatments' including: high frequency, low frequency, sham rTMS (focal coil) and dopamine. They measured pre and post motor performance (gait, UPDRS, peg board and a ballistic task). Patients ('off drug'-single dose missed, n=12) with dominant bradykinesia were chosen and tremor-dominant patients were excluded.) Interestingly both high and low frequency stimulation had therapeutic effects on the contralateral arm, whilst sham stimulation had no effect. Low frequency had bilateral effects improving motor scores, bradykinesia and gait time. High frequency had similar unilateral effects but also improved ballistic scores, again unilaterally. Compared to dopamine treatment the benefit with either train of TMS was modest (28-32%). The duration of the effect was not clarified but some patients reported a benefit lasting 24 hrs. Significant changes were also seen in neurophysiological measures of cortical excitability. There were no detrimental effects. This is an exciting study with potential therapeutic implications, which need to be explored in a more heterogenous patient group to define benefit in the various subcategories of PD along with a better profile of its duration. - ***JLR***

Lefaucheur J, Drouot X,Von Raison F, Ménard-Lefaucheur,I Cesaro Pand Nguyen J.

Improvement of motor performance and modulation of cortical excitability by repetitive transcranial magnetic stimulation of the motor cortex in Parkinson's disease.

CLINICAL NEUROPHYSIOLOGY

2004;115(11):2530-41.

WRITING ACNR REVIEWS: Alcohol and the harmonious brain

Alcohol at persistently high levels of intake is neurotoxic. Damage occurs at the cortical cellular level and white matter connections are thought to be particular vulnerable, the corpus callosum can reduce in volume. It would therefore be expected that a measure of inter-cortical connectivity would show a lack of synchronicity between cortical regions in those at risk of alcohol related damage compared to controls. Surprisingly this group in the Netherlands demonstrated the reverse effect. Students were divided into heavy or light drinkers (<30 units per week, n=11 in each group) and underwent high density EEG array. Off line analysis of coherence of each EEG frequency across all electrodes was performed. In the high alcohol group there was increased synchronicity at low frequency (theta) and at a particular high frequency (gamma, thought to be involved in higher cortical processing such as memory formation), in both a passive eye closure state and also during a mental task. I don't know what this means, but the researchers suggest this is due to functional changes within neocortical hippocampal circuits. I think it is a little worrying that such changes can be detected in relatively young drinkers and clearly moderation is the way to go. I'm not put off from the odd glass and perhaps it's the associated brief periods of increased connectivity that help me put my thoughts together when writing these reviews! - ***JLR***

Bruin EA, Bijl S, Stam CJ, Böcker KB, Kenemans JL and Verbaten MN.

Abnormal EEG synchronisation in heavily drinking students.

CLINICAL NEUROPHYSIOLOGY

2004;115(9);2045-55.

REHABILITATION: Are the Americans more efficient than us?

How many of us think our rehabilitation service could be more efficient? Do we worry about the impact a reduced length of stay might have on patient outcomes? Most of us feel the pressure for change especially in this era of increasing calls for improved efficiency within a finite budget. This paper from the US looked at the change in rehabilitation outcomes over the years 1994-2001 during which there was a dramatic reduction in length of stay (LOS) in rehabilitation institutions. They used data from the large (over 1/4 million patients) national Uniform Data System for Medical Rehabilitation which uses the Functional Independence Measure as the main outcome. They sub-divided into 5 specific groups, including stroke, brain dysfunction, other neurological disorders and spinal cord injury. In summary, the end result remained unchanged despite the reduced LOS and thus there was an increased efficiency across all groups. Unexpectedly there was an increased mortality across most groups but possible confounding factors to explain this are discussed in the accompanying editorial. Above all, for me this paper highlights the dearth of extensive rehabilitation outcomes data available in most European countries. We need better routine data collection systems on which to base our decisions to change (and monitor) our rehabilitation services. Who is going to take up this responsibility? – ***JMcF***

Ottenbacher KJ, Smith PM, Illig SB, Linn RT, Ostir GV, Granger CV.

Trends in Length of Stay, Living Setting, Functional Outcome and Mortality Following Medical Rehabilitation.

JAMA

2004;292(14):1687-95.

NEOPLASIA: finding the occult tumour – my pet subject

★★★ RECOMMENDED

It is not uncommon in neurological practice to have a patient with a paraneoplastic syndrome but without an obvious tumour. In recent years the identification of increasing numbers of different antibodies associated with these syndromes has meant that the diagnosis can be made with more confidence and relies less on clinical recognition and a list of negative findings. However these patients still pose a problem as often the antibody response holds the primary tumour in check, so that it is small and hard to find with conventional investigations. A recent hope has been that whole body [18F] fluorodeoxyglucose (FDG) PET could be used to find these hidden, metabolically active, tumours. In order to try and help sort out some of these issues of sensitivity and specificity, Younes-Mhenni et al have prospectively studied 20 patients with paraneoplastic antibodies and associated syndromes but with negative conventional imaging investigations. Of these 20 patients, 18 (90%) had abnormal PET uptake and 14 of these went on to have a histological diagnosis of a tumour. Of the 18 original abnormal PET scans, two returned to normal and in the two negative PET scans one patient was found to have peritoneal carcinomatosis and in the other no tumour was seen. Thus this technique seems to be very helpful in patients with paraneoplastic syndromes with a high sensitivity although rather a low specificity. Nevertheless this paper has confirmed that when stuck with a patient with such a syndrome, especially when the antibodies are positive and conventional imaging is negative, a whole body FDG PET scan may be very helpful…although whether it ultimately makes any difference in prognosis is not clear. – ***RAB***

Younes-Mhenni S, Janier MF, Cinotti L, Antoine JC, Tronc F, Cottin V, Ternamian PJ, Trouillas P, Honnorat J.

FDG-PT improves tumour detection in patients with paraneoplastic neurological syndromes.

BRAIN

2004;127:2331-8.

STROKE: The effects of botulinum toxin treatment on arm function

Botulinum toxin is commonly used to reduce spasticity in stroke patients. Although a number of studies have reported reduced impairment, there has been little evidence of improvements in function. One reason put forward is that spasticity is not responsible for limiting function and that weakness is the only significant cause. Another is that the studies done have not had the power to detect functional gain or that inadequate measures were used. The latter reason has been addressed in an exploratory meta-analysis carried out on pooled data (n=142) from two double blind randomised controlled trials of Botulinum toxin for arm spasticity after stroke. The designs of the two studies matched sufficiently to allow pooling of the data and had the additional benefit of repeated measures post treatment to allow the temporal relationship between spasticity and function to be explored. Modified Ashworth Scale scores for the elbow, wrist and finger flexors were used to produce a composite spasticity index. Likewise a composite functional index was constructed from subjective assessments of the ability to clean the palm, cut fingernails and put an arm through a sleeve and three arm relevant items from the Barthel index. The statistical analysis demonstrated a clear relationship between changes in spasticity and changes in arm function in patients treated with Botulinum Toxin (Dysport) at 500 or 1000 units but not in those treated with placebo or 1500 units. Only a small number of patients were treated with this high dose and while spasticity was reduced it is not known whether the high dose added to the disability by over weakening injected muscles or whether their results are simply lacking in power to detect functional improvement. Many rehabilitation studies are small and meta-analysis is increasingly being recognised as the way to get answers to important questions. However the success of this method is going to depend on using common trial designs and outcome measures. In this unusual case the two studies assessed had the same first author. However in most cases in future it will be important for members of the rehabilitation research community across the world to talk to one another. - ***AJT***

Francis HP, Wade DT, Turner-Stokes L, Kingswell RS, Dott CS, Coxon EA.

Does reducing spasticity translate into functional benefit? An exploratory meta-analysis.

J NEUROL NEUROSURG PSYCHIATRY

2004;75:1547-51.

PARKINSON'S DISEASE: Another gene, PARK8!

Two independent groups have recently reported mutations in the LRRK2 gene for PARK8-inherited parkinsonism. This brings to five the number of genes to unequivocally cause the Parkinson's disease phenotype. So far, eight different mutations in the LRRK2 gene have been discovered in unrelated autosomal dominant families, some of whom had previously been linked to the PARK8 region. It is too soon to speculate on the function of LRRK2, however it is of interest that part of the gene encodes a protein kinase, especially as the recently identified PARK6 gene appears to have a similar functional domain. One of the LRRK2 mutations was identified in four Basque families and in 8% of a cohort of 137 apparently unrelated Parkinson's disease patients, some with a positive family history. A detailed phenotype characterisation of PARK8 has not yet been reported, however, between these two studies there are preliminary descriptions for approximately 50 affected individuals. Based on these, PARK8 appears similar to sporadic "idiopathic PD," with disease onset primarily in the 6th or 7th decades (range 35-78-years) and an asymmetric presentation of bradykinesia, rigidity, tremor, and levodopa responsiveness. Interestingly there is a marked variation in the pathological findings, even within individuals carrying the same disease mutation. This included some patients with Lewy-body pathology, others without (pure nigral degeneration) and one individual with tau pathology similar to progressive supranuclear palsy. It will be intriguing to know what the eventual substrates of LRRK2 will be, and in particular whether this gene phosphorylates alpha synuclein, tau protein or both. - ***DH***

Zimprich A, Biskup S, Leitner P, Lichtner P, Farrer M, Lincoln S, Kachergus J, Hulihan M, Uitti RJ, Calne DB, Stoessl AJ, Pfeiffer RF, Patenge N, Carbajal IC, Vieregge P, Asmus F, Muller-Myhsok B, Dickson DW, Meitinger T, Strom TM, Wszolek ZK, Gasser T.

Mutations in LRRK2 cause autosomal dominant parkinsonism with with pleomorphic pathology.

NEURON

2004;44:601-7.

Paisan-Ruiz C, Jain S, Evans EW, Gilks WP, Simon J, van der Brug M, de Munain AL, Aparicio S, Gil AM, Khan N, Johnson J, Martinez JR, Nicholl D, Carrera IM, Pena AS, de Silva R, Lees A, Marti-Masso JF, Perez-Tur J, Wood NW, Singleton AB.

Cloning of the gene containing mutations that cause PARK8-Linked parkinsonism.

NEURON

2004;44:595-600.

DEMENTIA: The nosology of Hippocampal Sclerosis Dementia

These two papers and associated editorial represent an important contribution to the evolving nosology of neurodegeneration. In recent years, progress in the fields of molecular genetics, immunohistochemistry and neuropsychology has resulted in a move away from such bland expressions as senile and pre-senile dementia. In their place a bewildering array of terms derived from the various scientific disciplines which overlap one another to varying degrees. The concept of frontotemporal dementia (FTD) encompasses a particularly challenging area of nosology. As a minimum, all cases of FTD have the signature of focal cotrical atrophy with neuronal loss, and all have characteristic higher function deficits in the domains of behaviour and/or language, in keeping with a frontal and/or temporal distribution to the atrophy. Hippocampal sclerosis dementia (HSD) is a recently described disease of unknown aetiology and pathogenesis. Cases show neuronal loss in the hippocampus, similar in appearance to mesial temporal sclerosis but in an older age-group and without a history of seizures. Nearby isocortical areas may also show neuronal loss. Parallel studies reported in Neurology last month examined 18 cases of HSD. Various comparisons were also made to groups with other neurodegenerative diseases, namely motor neuron disease (MND) inclusion dementia, Alzheimer's disease (AD) and conventionally-diagnosed FTD. The first is a detailed pathological study. The key finding is that immunohistochemical preparations show 11 of the 18 cases to have cytoplasmic ubiquitin positive inclusions located in the granule cells of the hippocampal dentate gyrus. Such inclusions are well described in motor neuron disease (MND) and FTD with clinical MND; they also occur in the absence of clinical MND in, so-called, MND-inclusion dementia. Comparison of the HSD cases with a further series of MND-inclusion dementia cases also showed similar patterns of atrophy in the two groups. The remaining 7 cases are compared with the entity of dementia lacking distinctive histopathology (DLDH). DLDH, like MND, falls within the pathological spectrum of FTD. No tau-containing lesions are identified on immunohistochemistry in the 18 cases; HSD is therefore differentiated from AD, as well as from the FTD-tauopathies (cases with Pick bodies or with the astrocytic tau pathology of the parkinsonian FTD syndromes). Furthermore, whilst a group of DLDH cases was recently shown to have abnormally low levels of soluble brain tau, tau levels in HSD were no different from controls. The second paper is a clin-

DYSPORT® PRESCRIBING INFORMATION
Presentation: Vials of 500 units of *Clostridium botulinum* type A toxin-haemagglutinin complex. **Indications:** The treatment of focal spasticity, including: arm symptoms associated with focal spasticity in conjunction with physiotherapy in adults; and dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, 2 years of age or older. Spasmodic torticollis, blepharospasm and hemifacial spasm in adults. **Administration:** Dysport should only be injected by specialists who have had administration training. Blepharospasm and hemifacial spasm, reconstitute 500 units in 2.5ml normal saline. Spasmodic torticollis and focal spasticity, reconstitute in 1ml. **The units of Dysport are specific to the preparation and are not interchangeable with other preparations of botulinum toxin. Posology:** The dose should be lowered for patients with low muscle mass or in whom the suggested dose may result in excessive weakness. See SPC for recommendations. **Arm spasticity:** The recommended dose is 1,000 units in total, distributed among the most active arm muscles; biceps brachii (300-400 units); flexor digitorum profundus (150 units); flexor digitorum superficialis (150-250 units); flexor carpi ulnaris (150 units); flexor carpi radialis (150 units). Sites of injection should be guided by standard EMG locations, although actual sites will be determined by palpation. All muscles should be injected at one site, except for the biceps which should be injected at two sites. **Paediatric cerebral palsy:** Starting dose is 20 units/kg body weight given intramuscularly as a divided dose between calf muscles. Subsequently the dose may be titrated between 10 and 30 units/kg body weight, depending on response. If only one calf is affected, the dose should be halved. The maximum dose administered must not exceed 1,000 units/patient. Injections may be repeated approximately every 16 weeks or as required to maintain response, but not more frequently than every 12 weeks. **Spasmodic torticollis:** The initial recommended dose is 500 units given intramuscularly as a divided dose to the two or three most active neck muscles, which will likely include splenius capitis and sternomastoid. The split amongst muscles will vary according to the type of torticollis diagnosed. Doses within the range 250-1,000 units are recommended. Injections should be repeated approximately every 12 weeks or as required to prevent recurrence of symptoms. **Blepharospasm and hemifacial spasm:** The initial recommended dose is 120 units per affected eye; injections are given subcutaneously, medially and laterally into the junction between the preseptal and orbital parts of both the upper and lower orbicularis oculi muscles of each eye. Injections should be repeated approximately every 12 weeks or as required to prevent recurrence of symptoms. Subsequently the dose may be reduced to 80 units per eye and then to 60 units by omitting the medial lower lid injection. **Contra-indications:** Dysport is contraindicated in individuals with known hypersensitivity to any component of Dysport. **Warnings and precautions:** Dysport should be administered with caution to patients with existing swallowing or breathing difficulties or with subclinical or clinical evidence of marked defective neuromuscular transmission. Careful consideration should be given to the use of Dysport in patients with a history of allergic reaction to a product containing botulinum toxin type A or in patients with prolonged bleeding times, infection or inflammation at the proposed injection site. Dysport contains a small amount of human albumin. The risk of transmission of viral infection cannot be excluded with absolute certainty following the use of human blood products. Antibody formation to botulinum toxin has been noted rarely in patients receiving Dysport. **Interactions:** Drugs affecting neuromuscular transmission, eg. aminoglycoside antibiotics, should be used with caution. **Pregnancy and lactation:** Safety in this patient group has not been demonstrated. Dysport should not be used unless clearly necessary. **Side effects:** Side effects may occur due to deep or misplaced injections of Dysport temporarily paralysing other nearby muscle groups. In general, adverse events reported in clinical trials included: *common:* generalised weakness, fatigue, flu-like syndrome, pain/bruising at injection site; *uncommon:* itching; *rare:* neuralgic amyotrophy, skin rashes. **Arm spasticity:** *common:* dysphagia, arm muscle weakness, accidental injury/falls. **Paediatric cerebral palsy:** *common:* diarrhoea, vomiting, leg muscle weakness, urinary incontinence, abnormal gait, accidental injury due to falling. **Spasmodic torticollis:** *very common:* dysphagia; *common:* dysphonia, neck muscle weakness; *uncommon:* headache, diplopia, blurred vision, dry mouth; *rare:* respiratory disorders. **Blepharospasm and hemifacial spasm:** *very common:* ptosis; *common:* facial muscle weakness, diplopia, dry eyes, tearing, eyelid oedema; *uncommon:* facial nerve paresis; *rare:* entropion, ophthalmoplegia. **Overdose:** Respiratory support may be required where excessive doses cause paralysis of respiratory muscles. There is no specific antidote; antitoxin should not be expected to be beneficial and general supportive care is advised. **Pharmaceutical precautions:** Unopened vials must be maintained at temperatures between 2°C and 8°C. Reconstituted Dysport may be stored in a refrigerator (2-8°C) for up to 8 hours prior to use. Dysport should not be frozen. **NHS Cost:** £329.48 per pack of two 500 unit vials. **POM:** PL 6958/0005. **MA Holder:** Ipsen Ltd, 190 Bath Road, Slough, Berkshire, SL1 3XE. **Date of preparation of PI:** October 2004. 2701. Dysport® is a registered trademark. **Date of preparation:** October 2004. 2708.

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ical study with blinded, retrospective survey of records for the cases diagnosed with HSD, AD or one of the recognised FTD-spectrum pathologies. The key finding here is that the behavioural profile of HSD cases far more closely resembles that of FTD than AD. Unfortunately, limited information is available on language difficulties, which might also produce a contrast between FTD-type cases and AD. Such limitations are, of course, inherent in retrospective studies. Interestingly, memory symptoms are present in almost all cases of HSD, AD and FTD, casting doubt on the usefulness of memory symptoms to differentiate these diseases. Much remains to be clarified in the nosology of FTD. These studies strongly suggest that the majority of cases labelled as HSD may usefully be considered under the rubric of FTD as cases of MND-inclusion dementia. Some cases of HSD, however, seem to defy further labelling at present. These may provisionally be grouped alongside DLDH, on the assumption that DLDH is a heterogeneous grouping that awaits further subcategorisation. - ***RD***

Hatanpaa KJ, Blass DM, Pletnikova O, Crain BJ, Bigio EH, Hedreen JC, White CL 3rd, Troncoso JC.
Most cases of dementia with hippocampal sclerosis may represent frontotemporal dementia.
NEUROLOGY
2004;63(3):538-42.

Blass DM, Hatanpaa KJ, Brandt J, Rao V, Steinberg M, Troncoso JC, Rabins PV.
Dementia in hippocampal sclerosis resembles frontotemporal dementia more than Alzheimer disease.
NEUROLOGY
2004;63(3):492-7.

PARKINSON'S DISEASE: Gaucher's disease mutations and parkinsonism

In this very simple study from Israel, the glucocerebrosidase gene was screened for six common gene mutations in 99 Ashkenazi Jewish patients with Parkinson's disease and 1543 controls. Remarkably the authors discovered that 31% of the Parkinson's disease group carried mutations (almost all were heterozygous) compared to just 6% of controls. The authors concluded that heterozygous mutations in this gene predisposed to Parkinson's disease in the Ashkenazi Jews and that the clinical phenotype in these patients was indistinguishable from idiopathic Parkinson's disease, with the exception of a slightly earlier age of onset. Homozygous mutations in the glucocerebrosidase gene have long been known to cause Gaucher's disease, a glycolipid storage disorder characterised by the cellular accumulation of glucocerebrosidase. Although Gaucher's disease has rarely been associated with atypical parkinsonism, it is currently difficult to provide a plausible biological explanation for this finding. The authors postulate that this may be from aberrant protein degradation resulting from reduced cellular glucocerebrosidase activity and/or the accumulation of glucocerebroside. However, this hypothesis is very preliminary and untested. Clinicians have got used to considering a genetic explanation for young onset Parkinson's disease. This paper, and the recent discovery of PARK8 mutations, provides further evidence that even the late onset "idiopathic" Parkinson's disease phenotype has a major inheritable component. - ***DH***

Aharon-Peretz J, Rosenbaum H, Gershoni-Baruch R.
Mutations in the glucocerebrosidase gene and Parkinson's disease in Ashkenazi Jews.
NEW ENGLAND JOURNAL OF MEDICINE
2004;351:1972-7.

PRION DISEASE: EEG periodic complexes in the diagnosis of sporadic CJD

What role do periodic complexes on the EEG play in the diagnosis of sporadic Creutzfeldt-Jakob disease (sCJD)? How are periodic complexes defined? In 1996, the group from the German CJD surveillance study published (Ann Neurol 1996;53:162-166) EEG criteria for typical periodic complexes, viz.: strictly periodic potentials, duration 100-600 ms, intercomplex interval 500-2000 ms and at least 5 repetitive intervals with a duration difference of < 500 ms (to rule out semiperiodic, or pseudoperiodic, complexes). Now the utility of these criteria has been examined in a larger data set. EEGs were examined from 206 patients with autopsy-confirmed diagnoses (sCJD = 150; non CJD = 56). The EEG assessment was performed blind to all clinical and investigation data. 64% (96/150) sCJD cases had typical periodic complexes; false positive rate was 9% (5/56). Of these five, the diagnoses were Alzheimer's disease in 4 and multiple cerebral infarctions in 1. In only one of these 5 did clinical criteria also suggest a diagnosis of sCJD. The sensitivity and specificity of the EEG criteria for the diagnosis of sCJD were 64% and 91% respectively, with positive and negative predictive values of 95% and 49% respectively. (For those who prefer to digest such data in the form of likelihood ratios, these are LR(+) = 7.1, moderate change in pre-test to post-test probability; and LR(-) = 0.39, small change.) Combining both EEG and clinical diagnostic criteria, the sensitivity, specificity, positive and negative predictive values were 63%, 98%, 99%, and 49% respectively. Hence these EEG criteria are very specific and have high diagnostic value. Their widespread adoption should be encouraged. This may avoid the occasional instance of a patient without sCJD requiring post-mortem with full prion precautions when atypical periodic complexes are recorded on an EEG; we have had 2 such instances in patients with dementia with Lewy bodies (Eur J Neurol 2004;11:838-841). - ***AJL***

Steinhoff B, Zerr I, Glatting M, Schulz-Shaeffer W, Poser S, Kretzscmar HA.
Diagnostic value of periodic complexes in Creutfeldt-Jakob disease.
ANNALS OF NEUROLOGY
2004;56(5):702-8.

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

Sight Unseen. An Exploration of Conscious and Unconscious Vision

Melvyn A Goodale, A David Milner
Published by: Oxford University Press
ISBN: 0-19-851052-7
Price: £25.00

This slim volume is based on the authors' investigations over a period of 15 years of a patient ("Dee Fletcher") who developed visual form agnosia following a freak accident in which she suffered carbon monoxide poisoning. Specifically, DF has lost certain perceptual abilities, namely identifying shape and form, although she can still perceive colour and the fine detail of surfaces (visual texture), yet her visuomotor ("vision for action") control is strikingly preserved. The neuroanatomical substrate of this pattern of deficits is selective damage to the ventral stream of visual processing, specifically the lateral occipital area, whilst the dorsal stream is left intact (the deficits are the inverse of those seen in patients with optic ataxia).

The authors take DF as the starting point for an exposition on the workings of the two visual systems, originally postulated by Mishkin & Ungerleider, summarizing animal work and functional imaging studies as well as neuropsychology. The conclusions which emerge are that visuomotor control is viewpoint-dependent (egocentric), uses real-world metrics, and has a very short time constant, whereas visual perception is object-based, relational, and has an indefinitely long time constant. Moreover, the workings of the former are not available to consciousness, whereas the latter are (hence the subtitle of the book). Despite these polarities, and the possible implication of Cartesian dualism, nonetheless the two systems interact seamlessly.

It is a fascinating tale and well-told. Although obviously of most appeal to those with an interest in cognitive neurology, this book may nonetheless be read with profit by any neurologist with an interest in how the brain works. The lack of a bibliography of papers referred to in the text is, however, a significant omission.

AJ Larner, Cognitive Function Clinic, WCNN, Liverpool.

Clinical Neurology Version 1.0

Edited by: David Nicholl
CD-ROM
Published by: Churchill Livingstone
ISBN: 0443060193
Price: £89.99

Few will dispute the assertion that junior doctors have little understanding of neurology. That this situation should persist despite the plethora of short introductory textbooks published in recent years will hopefully be taken as evidence that the best way to convey neurological knowledge is not to simplify and to abridge, but to present it in a way that makes its richness and complexity engross rather than perplex. And it may well be – the nature of clinical neurology being so intensely practical – that if this is a very difficult thing to do in a book it may be slightly easier in a multimedia production.

The idea behind this CD-ROM, then, is commendable, although the authors aim to be illustrative rather than comprehensive*. The disc contains good-quality video clips of over 60 neurological cases accompanied by short notes relevant to the diagnosis, the odd table, and in some instances one or two radiological images. The cases are organised into 12 chapters more or less logically (narcolepsy and functional weakness come under neurological emergencies), and span across most of neurology. In tutorial mode the clips are presented side by side with reasonably useful brief general notes about the condition depicted; in presentation mode they can be selected from a menu in any order and displayed on their own. The cases are well chosen and representative, and the clips show, unusually, not only the examination but also long sequences of the patients' history. In fact, the video space devoted to the history is often greater than that devoted to what are generally somewhat cursory examinations. (Students of internuclear ophthalmoplegia, for example, will be led into thinking it is a disorder of pursuit rather than saccades).

Medical students and those who have to teach them will probably find this CD-ROM a valuable, if expensive, collection of illustrative cases. Whether this is also true of MRCP candidates and neurological trainees is harder to answer. Despite the editor's assertion that he was inspired by Patten's *Neurological Differential Diagnosis* there is no adequate attempt to demonstrate the clinical thinking that leads to the diagnosis in each case. Indeed the notes are often very general and sometimes do not even refer to the signs demonstrated on the videos (spectacularly so in the patient with midbrain stroke). Where a differential diagnosis is provided it is rarely pointed out which particular clinical feature favours one diagnosis over another. What neurological trainees (and even medical students) really need is to be taught how to make a diagnosis, not how to recognise someone else's. Until we find a good way to do that, incompetence in neurology amongst junior doctors is likely to persist.

*They may have started off with different intentions: the cd cover is entitled 'Clinical Neurology', but the software itself qualifies it as 'Essential Clinical Neurology'.

Parashkev Nachev, Imperial College London (Charing Cross Campus).

Developmental Neuropathology

Editors: Jeffrey A Golden, Brian N. Harding
Publisher: International Society of Neuropathology, 2004
ISBN: 3-9522313-2-0
Price: Book 85 dollars, CD 45 US dollars

This book is simply outstanding.
Developmental neuropathology, a previous Cinderella specialty, has been illuminated by recent strides in molecular genetics, neuro-imaging and developmental biology. The result is demonstrated in this text. It uses a multidisciplinary approach to further our understanding of malformations, perinatal acquired pathology, sudden infant death syndrome, autism, metabolic and infectious diseases. I would have enjoyed in addition, a chapter on the macroscopy and developmental stages of the normal developing brain and the controversial area of non-accidental injury, but these are minor points.

The book has about 400 pages and 150 beautiful colour illustrations. Its 63 chapters were written by more than 50 international experts. To my knowledge this resource is not available elsewhere.

Each entity is defined and the clinical data, genetic influences, pathophysiology, macroscopy, microscopy and therapeutical approaches are presented. This format is similar to the previous in this excellent series of books which cover Brain tumours, Muscle diseases and Neurodegenerative diseases.

Finally, although I think this will become a fixture on every neuropathologists' and paediatric pathologists' shelf, I do feel it has wider appeal. In particular paediatric neurologists and neuroscientists involved in research would find it useful. After all if you can understand the child, perhaps knowledge of the man the will follow.

Dr Reena Kurian, Western General Hospital, Edinburgh.

Visions of Science 2004

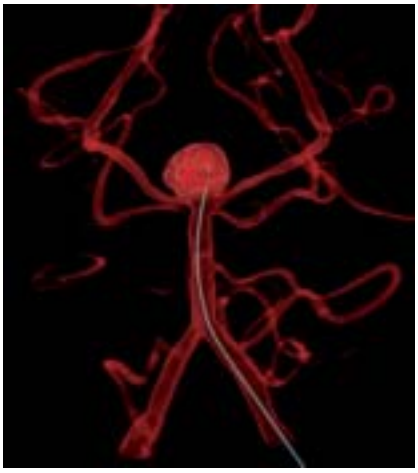
Dr Peter Keston, a neuroradiologist from the Centre for Interventional Neuroradiology of Edinburgh, was awarded first prize at the Visions of Science Awards Ceremony recently. He created his image for the Medicine & Life Award using Siemens Medical Solutions imaging equipment.

The image 'Hanging by a thread' was created to help patients understand their condition and treatment. The image shows a 'berry' aneurysm at the base of the brain. In order to block blood flow inside the aneurysm, we see the platinum wire coiled up inside the berry.

The brain arteries were imaged with Siemens AXIOM Artis bi-plane neuro-angiography equipment and the images were then manipulated with Inspace volume rendering software on the Siemens Leonardo workstation. The wire was imaged by Fuji Finepix 4900 digital camera.

Visions of Science was set up by Novartis, in association with The Daily Telegraph and supported by the Science Photo Library. Novartis Pharmaceuticals produces sets of the winning images, which tour science and arts centres in the UK. See www.visions-of-science.co.uk for details.

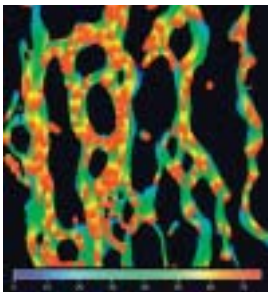
For more information about Siemens Medical Solutions, Tel: 01344 396317 or see www.siemens.co.uk/medical



Novartis/Daily Telegraph Visions of Science 2004 was awarded to Dr Peter Keston, a neuroradiologist from the Centre for Interventional Neuroradiology of Edinburgh, who used the AXIOM Artis BA imaging equipment from Siemens Medical Solutions.

World's Fastest Confocal Microscope

Carl Zeiss has launched a dedicated live cell imaging system capable of collecting up to 120 full frame images per second, said to be 20 times faster than any other confocal system. Called LSM 5 LIVE, the new instrument's combination of high speed, image quality and sensitivity provides exclusive insights to the cell's highly transient and dynamic events. It is suited to studies at the forefront of live cell imaging, such as the movement of individual intracellular molecules or measuring the dynamics of the cytoskeleton during such processes as cell adhesion, cell motility and cell signalling. The LSM 5 LIVE captures events of the order of microseconds.



Motion of erythroblasts during one heartbeat cycle in 8-day old mouse embryo. GFP expression, colour-coded projection over time, recorded at 88 frames per second. Specimen: Dr. Mary Dickinson, Biological Imaging Centre, Caltech Pasadena, USA.

The speed, resolving power and sensitivity are driven by a completely new optical concept specially tailored for studies on living specimens. The light beam is shaped into laser light of rectangular cross section and focused precisely on the colour-independent AchroGate beam splitter. According to Carl Zeiss this guarantees virtually 100% excitation efficiency and emission yield at all wavelengths to deliver maximum performance even on thick or weakly fluorescent specimens. An ultra-fast CCD line detector picks up the shaped laser light to allow parallel imaging of 512 pixels with high quantum yield.

For further information contact Aubrey Lambert, Carl Zeiss UK, Tel: 01707 871233, Fax: 01707 871287, Email: a.lambert@zeiss.co.uk

Quick Magnification Switching and Slide Marking

Users of Nikon's Eclipse 50i and 55i microscopes can now switch between 10x and 40x magnifications during cytological screening at the flick of a switch. This follows the introduction of a compact and retrofittable cytodiagnosic unit with a motorised mechanism for changing between magnifications. The new "Ergo-View" one-touch nosepiece and objective changeover system also includes an easy-to-use slide marking function. This permits areas of interest to be marked while still observing the specimen, and removes the need to rotate the nosepiece, giving a further important boost to work efficiency.

With the Ergo-View fitted on the Eclipse 55i, users can perform observations at a constant brightness as the intensity of the LED illumination automatically adjusts with changes in magnification. This approach is ideal for bright field applications, overcoming excessive heat and colour temperature changes that occur with halogen light sources when changing from high to low intensity. The digital LED illumination provides a bright, homogenous distribution across the whole field of view for optimal viewing and digital imaging.

For more information Email: discover@nikon.co.uk

Dysport® Now Licensed To Treat Focal Spasticity Of The Arm

Dysport® (Clostridium botulinum type A toxin–haemagglutinin complex), manufactured by Ipsen Ltd, is now licensed for the treatment of arm symptoms associated with focal spasticity in conjunction with physiotherapy.

Muscle spasticity causes significant physical problems in some stroke patients. Stroke is the largest single cause of severe disability in England and Wales, and an estimated 20% of stroke patients with spasticity require specific treatment for their condition.

Dysport is a local muscle relaxant, which is injected into the affected muscles significantly reducing spasticity, improving arm function and reducing disability and carer burden when used as part of a rehabilitation programme. Dysport is presented as a convenient treatment pack and is simple to administer by intramuscular injection. It should be used as part of a rehabilitation programme involving physical therapy and patients should experience a clinical improvement in their spasticity within two weeks of treatment.

For further product information contact Ipsen on Tel: 01753 627777.

New APO-go® Pre-Filled Syringe

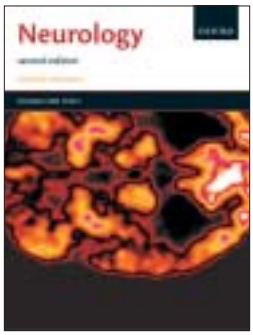
Britannia Pharmaceuticals Limited has launched a new presentation in the APO-go range; the APO-go 5mg/ml Pre-filled Syringe (PFS).

The PFS has been designed for use with infusion devices, including the APO-go Pump. It is a product which eliminates the need for patients or carers to break open glass ampoules, removing the risk of cuts from broken ampoules and reducing sharp-stick injuries. It will dramatically reduce the time spent setting up infusion devices for APO-go users. The pre-dilution also minimises the risk of dilution error and spillage and contamination risks are reduced. The PFS will benefit patients and carers, and also has cost benefits for the NHS.

Britannia Pharmaceuticals believe the Pre-filled Syringe is the most convenient method for apomorphine infusion patients and its use conforms to best pharmaceutical practice.

For further information, please contact the APO-go Helpline 01737 781414.

Neurology - An Oxford Core Text



Second Edition, Michael Donaghy, ISBN 0-19-852636-9

Oxford University Press are publishing Neurology - An Oxford Core Text in January 2005. This 224 page paperback book with around 200 photographs and line illustrations, is highly recommended reading for medical undergraduates. It introduces the major neurological diseases; deals with weakness, visual symptoms, headaches, blackouts and stroke; covers the general principles of history-taking; gives practical advice on how to perform simple neurological examinations; has detailed instructions on examination in particular clinical circumstances; includes 24 detailed case histories and is highly illustrated with clinical photos and line diagrams.

For more information please visit www.oup.co.uk/best.textbooks/medicine/

If you teach neurology and would like to receive a free inspection copy of this book, Tel: 01536 741068, or Email: inspectioncopies.europe@oup.com

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BEFORE ARICEPT,
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CONTINUING COMMITMENT TO ALZHEIMER'S

ABBREVIATED PRESCRIBING INFORMATION
ARICEPT® (donepezil hydrochloride)
Please refer to the SmPC before prescribing ARICEPT 5 mg or ARICEPT 10 mg. **Indication:** Symptomatic treatment of mild to moderately severe Alzheimer's dementia. **Dose and administration:** ***Adults/elderly;*** 5 mg daily which may be increased to 10 mg once daily after at least one month. No dose adjustment necessary for patients with renal impairment. Dose escalation, according to tolerability, should be performed in patients with mild to moderate hepatic impairment. ***Children;*** Not recommended. **Contra-Indications:** ***Pregnancy.*** Hypersensitivity to donepezil, piperidine derivatives or any excipients used in ARICEPT. ***Lactation:*** Excretion into breast milk unknown. Women on donepezil should not breast feed. **Warnings and Precautions:** Initiation and supervision by a physician with experience of Alzheimer's dementia. A caregiver should be available to monitor compliance. Regular monitoring to ensure continued therapeutic benefit, consider discontinuation when evidence of a therapeutic effect ceases. Exaggeration of succinylcholine-type muscle relaxation. Avoid concurrent use of anticholinesterases, cholinergic agonists, cholinergic antagonists. Possibility of vagotonic effect on the heart which may be particularly important with "sick sinus syndrome", and supraventricular conduction conditions. There have been reports of syncope and seizures - in such patients the possibility of heart block or long sinusal pauses should be considered. Careful monitoring of patients at risk of ulcer disease including those receiving NSAIDs. Cholinomimetics may cause bladder outflow obstruction. Seizures occur in Alzheimer's disease and cholinomimetics have the potential to cause seizures and they may also have the potential to exacerbate or induce extrapyramidal symptoms. Care in patients suffering asthma and obstructive pulmonary disease. As with all Alzheimer's patients, routine evaluation of ability to drive/operate machinery. No data available for patients with severe hepatic impairment. **Drug Interactions:** Experience of use with concomitant medications is limited, consider possibility of as yet unknown interactions. Interaction possible with inhibitors or inducers of Cytochrome P450; use such combinations with care. Possible synergistic activity with succinylcholine-type muscle relaxants, beta-blockers, cholinergic or anticholinergic agents. **Side effects:** Most commonly diarrhoea, muscle cramps, fatigue, nausea, vomiting, and insomnia. Common effects (>1/100, <1/10): common cold, anorexia, hallucinations, agitation, aggressive behaviour, syncope, dizziness, insomnia, diarrhoea, vomiting, nausea, abdominal disturbance, rash, pruritis, muscle cramps, urinary incontinence, headache, fatigue, pain, accident. Uncommon effects (>1/1,000, <1/100): seizure, bradycardia, gastrointestinal haemorrhage, gastric & duodenal ulcers, minor increases in serum creatine kinase. Rare (>1/10,000, <1/1,000): extrapyramidal symptoms, sino-atrial block, atrioventricular block, liver dysfunction including hepatitis. **Presentation and basic NHS cost:** Blister packed in strips of 14. ARICEPT 5 mg; white, film coated tablets marked 5 and Aricept, packs of 28 £68.32. ARICEPT 10 mg; yellow, film coated tablets marked 10 and Aricept, packs of 28 £95.76. **Marketing authorisation numbers:** ARICEPT 5 mg; PL 10555/0006. ARICEPT 10 mg; PL 10555/0007. **Marketing authorisation holder:** Eisai Ltd. **Further Information from/Marketed by:** Eisai Ltd, Hammersmith International Centre, 3 Shortlands, London, W6 8EE and Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS. **Legal category:** POM
Date of preparation: January 2002.

References: 1. Gauthier S, Feldman H, Hecker J, *et al. Curr Med Res Opin* 2002; **18** (6): 347-354. **2.** Holmes C, Wilkinson D, Dean C, *et al. Neurology* 2004; **63**: 214-219. **3.** Cummings JL, Donohue JA, Brooks RL. *Am J Geriatr Psychiatry* 2000; **8:2:** 134-140.

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