ISSN 1473-9348 Volume 4 Issue 4 September/October 2004

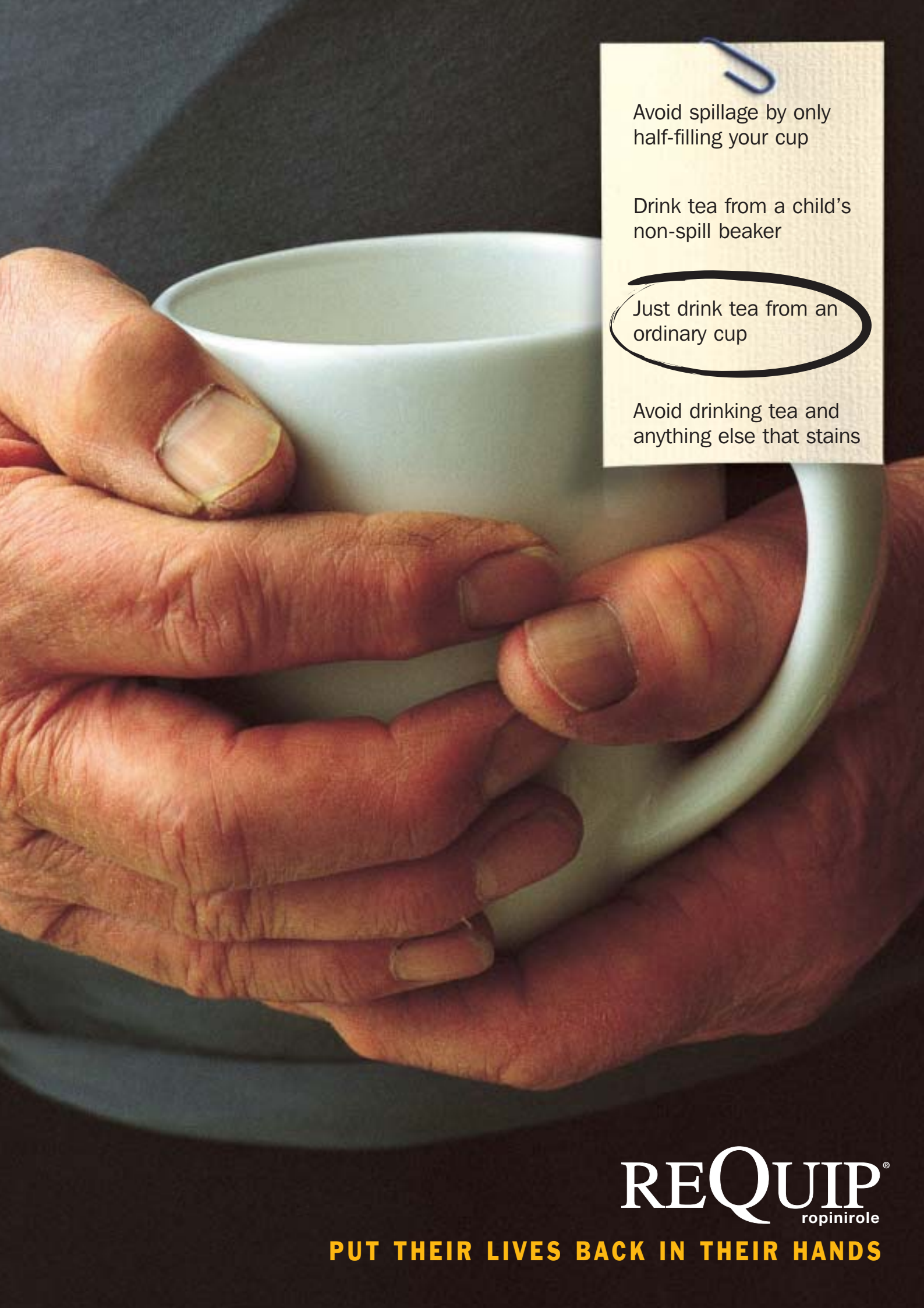
ACNR

Advances in Clinical Neuroscience & Rehabilitation

journal reviews • events • management topic • industry news • rehabilitation topic

Review Articles: The Genetics of Stroke; The Current Status of Carotid Artery Angioplasty and Stenting
Management Topic: How I Manage Supratentorial Meningiomas
Rehabilitation Article: Musculoskeletal Complications of Neurological Conditions

www.acnr.co.uk


Avoid spillage by only half-filling your cup
Drink tea from a child's non-spill beaker
Just drink tea from an ordinary cup
Avoid drinking tea and anything else that stains
REQUIP®
ropinirole
PUT THEIR LIVES BACK IN THEIR HANDS

Editorial Board and contributors

Roger Barker is co-editor in chief of Advances in Clinical Neuroscience & Rehabilitation (ACNR), and is Honorary Consultant in Neurology at The Cambridge Centre for Brain Repair. He trained in neurology at Cambridge and at the National Hospital in London. His main area of research is into neurodegenerative and movement disorders, in particular parkinson's and Huntington's disease. He is also the university lecturer in Neurology at Cambridge where he continues to develop his clinical research into these diseases along with his basic research into brain repair using neural transplants.

Alasdair Coles is co-editor of ACNR. He has recently been appointed to the new position of University Lecturer in Neuroimmunology at Cambridge University. He works on experimental immunological therapies in multiple sclerosis.

Stephen Kirker is the editor of the Rehabilitation section of ACNR and Consultant in Rehabilitation Medicine in Addenbrooke's NHS Trust, Cambridge. He graduated from Trinity College, Dublin in 1985 and trained in neurology in Dublin, London and Edinburgh before moving to rehabilitation in Cambridge and Norwich. His main research has been into postural responses after stroke. His particular interests are in prosthetics, orthotics, gait training and neurorehabilitation.

David J Burn is the editor of our conference news section and Consultant and Reader in Neurology at the Regional Neurosciences Centre, Newcastle upon Tyne. He qualified from Oxford University and Newcastle upon Tyne Medical School in 1985. His MD was in the functional imaging of parkinsonism. He runs Movement Disorders clinics in Newcastle upon Tyne and Sunderland. Research interests include progressive supranuclear palsy and dementia with Lewy bodies. He is also involved in several drugs studies for Parkinson's Disease.

Andrew Larner is the editor of our Book Review Section. He is a Consultant Neurologist at the Walton Centre for Neurology and Neurosurgery in Liverpool, with a particular interest in dementia and cognitive disorders. He is also an Honorary Apothecaries' Lecturer in the History of Medicine at the University of Liverpool.

Alastair Wilkins is Specialist Registrar in Neurology in East Anglia. He trained in Cambridge, Sheffield and London, and has just finished a PhD investigating potential mechanisms of axon loss in multiple sclerosis.

International editorial liaison committee

Professor Riccardo Soffietti, Italy: Professor Soffietti is Chairman of the Neuro-Oncology Service, Dept of Neuroscience and Oncology, University and S. Giovanni Battista Hospital, Torino, Italy. He is President of the Italian Association of Neuro-Oncology, member of the Panel of Neuro-Oncology of the EFNS and EORTC Brain Tumour Group, and Founding member of the EANO (European Association for Neuro-Oncology). He has written more than 300 scientific papers.

Professor Klaus Berek, Austria: Since 1999, Dr Berek has been Head of the Neurological Department of the KH Kufstein in Austria. He is a member of the Austrian Societies of Neurology, Clinical Neurophysiology, Neurological and Neurosurgical Intensive Care Medicine, Internal and General Intensive Care Medicine, Ulrasound in Medicine, and the ENS.

Professor Hermann Stefan, Germany: Professor Stefan trained in neurology, psychiatry, neuropathology, and epileptology at the University Bonn. He is Professor of Neurology/Epileptology in the Department of Neurology, University Erlangen-Nürnberg, and specialises in the treatment of epilepsies, especially difficult to treat types of epilepsy and presurgical evaluation, including Magnetic source imaging (MEG/EEG) and MR-Spectroscopy.

Professor Nils Erik Gilhus, Norway: Professor Gilhus has been Professor of Neurology at the University of Bergen and Haukeland University Hospital since 1987. He is Research Dean at the medical faculty, and Chairman for the Research Committee of the Norwegian Medical Association. He chairs the scientist panel of neuroimmunology, European Federation of Neurological Societies (EFNS), is a member of the EFNS scientific committee, the World Federation of Neurorehabilitation council, and the European School of Neuroimmunology board. His main research interests are in neuroimmunology and neurorehabilitation.

contents

september/october 2004

Cover picture.
Cover picture compliments of Siemens Medical Solutions. See page 47 for more details.

Features

Additional web content

Extra journal reviews, including an in-depth review of 'Computer Technology to support the Treatment of Aphasia' by Professor Pam Enderby, see www.acnr.co.uk/journals.htm

Regulars

ACNR is published by Whitehouse Publishing, 7 Alderbank Terrace, Edinburgh EH11 1SX.
Tel. 0131 477 2335/07989 470278, **Fax.** 0131 313 1110 **E-Mail.** AdvancesinCNR@aol.com
Publisher: Rachael Hansford **Design & Production:** Barbara Newton
Printed by: Stephens & George Magazines, Tel. 01685 388888.


Female : 16
Partial Epilepsy with Secondarily Generalised Tonic-Clonic seizures
If she was your daughter how would you treat her?
Lamictal™
lamotrigine

This issue of ACNR brings two review articles on related topics – one on the genetics of stroke and the other on carotid artery angioplasty and stenting.

Hugh Markus and Steve Bevan in their article on the genetics of stroke present a marvellous account on single gene disorders associated with stroke (e.g. Notch 3 and CADASIL) whilst also engaging in the much thornier issue of the role of genetic factors in sporadic stroke. This raises many issues, which are not unique to stroke, but are common to multifactorial disorders – namely proving causality and true aetiological risk in studies showing a degree of genetic association. This review is therefore a wonderful distillation of this complex field whilst also providing some very useful summary information, including a great table summarising the rare single gene disorders associated with stroke.

Continuing the theme, Hans-Peter Haring and colleagues in Austria discuss the current status of interventional carotid artery procedures such as stenting and angioplasty. This is an emerging area, although the origins of these procedures go back almost 20 years. In their article the authors critically evaluate this field including completed as well as ongoing clinical trials using these different approaches and how they compare to carotid endartectomy. This field is therefore an exciting area and we are fortunate to have such an authorative account of this controversial field.

It is also worth highlighting that in this issue we have the first in our "Controversies" series, which also has a stroke flavour. Paul Syme presents his approach to the diagnosis and treatment of small vessel occlusive disease using transcranial doppler ultrasonography. Do let us know what you think about this controversy, as we hope to publish responses to articles such as this one in future issues of ACNR.

The second topic in our management series on Neurosurgery tackles meningiomas. This relatively common brain tumour can present in a variety of ways and poses a number of challenges to the clinician. This includes questions on whether to operate (as they are typically slow growing) as well as how to operate given their often large size and location in some cases (e.g. para-saggital region). Anne Moore reviews her practice and delivers a beautifully clear and balanced discussion of these issues with a plethora of radiological illustrations.

In our neuropathology feature, Susan Robinson and William Stewart discuss meningitis and cerebral abscesses. This article combines clinical practice with neuropathological findings highlighting the dialogue that has to exist between these two disciplines of neuroscience. In particular the authors lay out the common causes of meningitis and how this can vary with immune status, and provide a wealth of highly informative figures to illustrate the points they make. Thus, in the tradition of this journal, their article speaks across specialities to allow for all of us to adopt a more integrated approach to our clinical practice and neuroscientific understanding.

Our terrific cognitive primer on spatial neglect - by Andrew Parton and Masud Husain - is well-crafted, in line with the excellent articles we have had in this series. Andrew and Masud begin with an account on diagnosis, including useful bedside tests before discussing the anatomy of the phenomena and finally its management – an area that can be a major problem in the rehabilitation of patients with this problem. En route the authors entertain us with an interesting discussion on the cognitive basis for neglect - whether it is due to deficits in attention, spatial mapping or movement initiation.

We also have a special article from the International Parkinson's disease Non-motor symptom scale development group detailing a new questionnaire that seeks to explore the extent and range of non motor symptoms in this common condition. This is an important area, as we often think of Parkinson's disease (PD) in motor terms without any consideration to the range of other deficits that occur, reflecting the diffuse pathology of this condition. A better method of accessing this information is important, not only to raise awareness but to help plan therapy including new experimental approaches.

In the rehabilitation article, Rory O'Connor discusses musculoskeletal complications of neurological conditions that can occur as part of the original insult as well as secondary to neurological disability. This is clearly a very important area, as it is all too easy to see every complaint in a patient through one pair of diagnostic spectacles – the frozen shoulder to a rheumatologist being a radiculopathy in the eyes of a neurologist. The article addresses these issues, as well as how best to manage them pharmacologically and with physiotherapy. This well written account is clearly based on extensive experience and as such is immediately accessible and useful to all involved in this area of neurological practice.

The web site contains all the previous back issues of the journal along with illustrative case reports, and this will include a new one on meningitis by Alastair Wilkins, as well as additional reviews and conference reports. Do keep the feedback coming, and let us know if you are interested in becoming a journal reviewer.

Roger Barker, Co-editor
E-Mail.AdvancesinCNR@aol.com

For some, epilepsy still means being out of control. LYRICA is a new and effective 1st choice adjunctive therapy for adults with partial seizures.[1–3]

LYRICA has demonstrated that up to 50% of refractory patients have at least 50% fewer seizures at 12 weeks.[1]

In addition, in patients treated with LYRICA in open-label studies for 12 months, 6% remained seizure-free.[4]

Bringing stability, taking control

So, with no known pharmacokinetic drug interactions,* simple dosing, and a favourable tolerability profile,[5] LYRICA is a rational next step when monotherapy is insufficient, enabling you to bring control to partial seizures.

*Despite no PK interactions, LYRICA appears to be additive in the impairment of cognitive and gross motor function when co-administered with oxycodone. LYRICA may potentiate the effect of lorazepam and ethanol[5]

New

LYRICA®

PREGABALIN

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 Genetics of Stroke

Stroke is not a single disease, but rather describes a syndrome of different processes all resulting in focal cerebral damage due to disruption of cerebral blood flow. Although the different processes share some obvious risk factors, they have different conventional and genetic risk factor profiles. Most strokes appear to be sporadic, with no obvious patterns of Mendelian inheritance. A minority can be ascribed to a monogenic cause, but genetic factors do also appear to be important in the remainder. There is considerable evidence from twin studies [1,2], family history studies[3,4] and animal models[5,6] that sporadic stroke is due in part to genetic influences. Rather than being due to a highly penetrant single gene disorder however, common sporadic strokes are thought to arise as a consequence of polygenic or multifactorial influences whereby multiple genes each exert a small influence or risk on phenotype, with individuals showing different combinations of genetic and environmental influences. This presents novel challenges in gene identification, not only due to the small effect size of each genetic influence, but also due to the incomplete penetrance and population stratification that these genetic factors may display. However, recent research suggests that these challenges may not be insurmountable.

Single gene disorders in stroke

When referring to stroke, a distinction must be made between isolated stroke in which there are no additional physical characteristics, and conditions in which stroke is just one feature of a multi-system disorder. CADASIL, or cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, is the only form of isolated stroke to display familial patterns of inheritance in which the responsible gene has been identified[7]. There are also several single gene disorders in which stroke is a secondary presenting feature in which genes have been identified and areas of linkage mapped, as detailed in table 1.

CADASIL usually presents with at least one of four manifestations, namely lacunar stroke and TIA, cognitive deficits, migraine with aura, and psychiatric disturbance, usually depression, which may precede the onset of stroke (30%). The disease most commonly presents in the 40s but can present from the 20s to 70s. MRI scans show characteristic changes with a combination of lacunar infarcts and white matter high signal or leukoaraiosis.(figure 1). The latter often involves the anterior temporal pole and external capsule. Diagnosis can be made by gene screening or skin biopsy for the characteristic granular osmiophilic material[8].

CADASIL has been shown to be due to highly stereotyped mutations in the Notch3 gene[9], a large transmembrane receptor involved in cell fate decisions during embryogenesis and promotion of vascular smooth muscle cell survival[10]. Mutations in Notch3 leading to CADASIL all disrupt highly conserved cysteine residues. As a consequence the usual number of six residues is converted to an odd number, resulting in abnormal multimerisation of Notch3 and possibly aberrant cell signalling. The phenotype is variable even within families and to date, despite more than 50 different mutations having been reported, no clear genotype-phenotype correlations have emerged.

Genetics of common stroke

The two stalwarts of genetic analysis for multifactorial stroke remain candidate gene studies and family based linkage studies. Many candidate gene studies have been performed in stroke[11], although most have proved inconclusive as a consequence of low power, insufficient sample size, population stratification, poor phenotyping of cases, and failure to appreciate the heterogeneity of stroke[12]. More recently these limitations have been increasingly recognised, resulting in improved experimental design and appropriately powered study design and with collaborative ventures to strengthen future research.

Despite the lack of families available to aid stroke research, the most recent and exciting discovery in the field has come from such an approach – the identification of a gene that appears to confer an increased risk of ischaemic stroke, and specifically of cardioembolic and large vessel stroke subtypes[13]. The gene identified, phosphodiesterase 4D (PDE4D) is a regulator of cyclic AMP levels[14], and is proposed to control the level of smooth muscle proliferation and immune function in vessels thereby leading to increased or decreased atherosclerosis and hence ischaemic stroke risk. Although causative mutations within PDE4D have yet to be identified, evidence of altered expression has been shown, with ischaemic stroke patients showing significantly reduced mRNA levels of PDE4D isoforms D1, D2 and D5[13]. The mechanism by which this change exerts its effects and predisposes to stroke is currently unclear, due in part to the very recent identification of this gene, and in part to

Steve Bevan is Lecturer in Stroke Genetics at St George's Hospital Medical School. He was previously a Senior Post Doctoral Fellow at the Institute of Cancer Research, Sutton, London, UK, and has a PhD in Molecular Genetics from the University of London.

Hugh Markus is Professor of Neurology at St George's Hospital Medical School. He was previously Senior Lecturer and then Reader in Neurology at Guy's, Kings and St Thomas' School of Medicine, London. He qualified from Cambridge and Oxford Universities, and trained in Neurology in London.

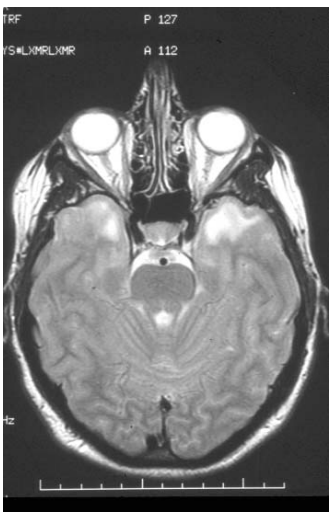


Figure 1. Characteristic MRI finding in a patient with CADASIL. On this FLAIR sequence high signal (leukoaraiosis) can be seen in the white matter and characteristic involvement of the anterior temporal pole is present (arrowed). (copyright with author-HM).

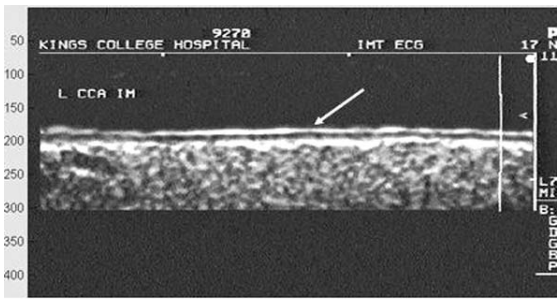
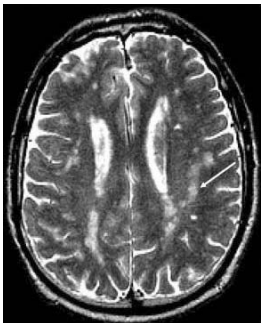
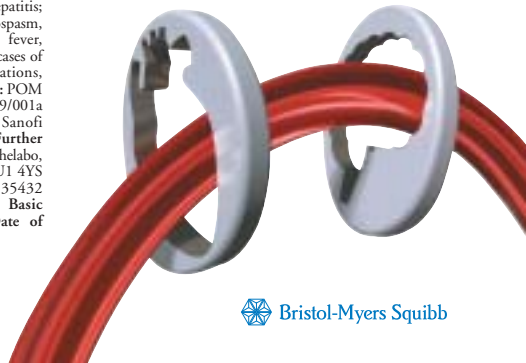


Figure 2. Intermediates phenotypes used in stroke genetic research. A. Common carotid artery intima-media thickness on the posterior wall of the artery. IMT (arrowed) includes the inner bright line and the dark line deep to this. B. White matter hyperintensities (one arrowed) on a T2 weighted MRI scan. Recent data[16] suggest that confluent WMH progress and appear to represent small vessel cerebrovascular disease. (copyright with author-HM).



PLAVIX Prescribing Information.
Presentation: Round, pink, film coated tablets containing 75mg clopidogrel (as the bisulphate). **Indication:** Reduction of atherothrombotic events in patients with a history of symptomatic atherosclerotic disease defined by ischaemic stroke (from 7 days until less than 6 months), myocardial infarction (from a few days until less than 35 days) or established peripheral arterial disease, and, in combination with aspirin, in patients with unstable angina (UA) or non-ST-elevation MI (NSTEMI). **Dosage:** Adults and elderly: 75mg as a single daily dose. In patients with UA/NSTEMI: single 300mg loading dose, followed by 75mg daily (with aspirin 75-100mg/day); clinical trial data support use up to 12 months (maximum benefit at 3 months). Children and adolescents: Not recommended under 18 years. **Contraindications:** Hypersensitivity to clopidogrel or excipients; severe liver impairment; active pathological bleeding; breast-feeding. **Warnings:** Due to the risk of bleeding and haematological disorders, blood cell count determination should be conducted where suspected clinical symptoms suggestive of bleeding arise during treatment; monitor for signs of bleeding, especially during the first weeks of treatment and after invasive cardiac procedures or surgery; caution in patients with lesions likely to bleed, particularly gastrointestinal and intraocular; renal impairment; hepatic disease. Discontinue therapy 7 days prior to surgery. Not recommended during pregnancy. **Drug Interactions:** Not recommended with warfarin. Caution when used with aspirin (although combination used together for up to one year in the CURE study), NSAIDs, heparin, thrombolytics, glycoprotein IIb/IIIa inhibitors. **Side Effects:** Haematological disorders: very rare cases of thrombotic thrombocytopenic purpura, severe thrombocytopenia, neutropenia, agranulocytosis, anaemia and aplastic anaemia / pancytopenia; Haemorrhagic disorders: serious bleeding such as skin bleeding, bruising, haemarthrosis, haematoma, eye bleeding, epistaxis, respiratory tract bleeding, haematuria and intracranial, gastrointestinal and retroperitoneal haemorrhage and haemorrhage of operative wound. Significantly increased risk of major/minor bleeding when used with aspirin (dose dependent); Gastrointestinal disorders: diarrhoea, very rare reports of colitis and pancreatitis; Urinary/hepatic disorders: very rare cases of renal disorders, abnormal creatinine levels, abnormal liver function tests/hepatitis; Allergic disorders: skin reactions, bronchospasm, angioedema, anaphylactoid reactions, fever, arthralgia and arthritis; Others: very rare cases of taste disorders, confusion, hallucinations, vasculitis and hypotension. **Legal category:** POM **Product Licence Number:** EU/1/98/069/001a **Marketing authorisation Holder:** Sanofi Pharma Bristol-Myers Squibb SNC **Further information is available from:** Sanofi-Synthelabo, One Onslow Street, Guildford, Surrey GU1 4YS **Tel:** 01483 505515 **Fax:** 01483 535432 **Website:** www.sanofi-synthelabo.co.uk **Basic NHS Price:** £35.31 for 28 tablets **Date of preparation:** September 2003.

Reference: 1. The Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Eng J Med* 2001; **345**: 494-502.
PLA03/140



sanofi~synthelabo

Bristol-Myers Squibb

Disorder	Gene	Mechanism of Action	Type of Stroke
CADASIL – cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy	Notch3	Pure stroke syndrome affecting small cerebral vessels	Small vessel
CARASIL – cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy	Unknown	Pure stroke syndrome affecting small cerebral vessels	Small vessel
CRV & HERNS – cerebro-retinal vasculopathy and hereditary endotheliopathy with retinopathy, nephropathy and stroke	Linkage to 3p21.1-21.3	Microangiopathy of the brain in combination with vascular retinopathy	Small Vessel
MoyaMoya disease	Linkage to 3p24.2-26, and 17q	Spontaneous occlusion of basal intracerebral arteries	Large intracranial vessel disease
Ehlers-Danlos syndrome type IV	Collagen 3AI	Collagen disorder, 10% of patients show neurovascular complications	Large vessel disease
Marfan Syndrome	Fibrillin	Musculoskeletal disorder 4% show neurovascular complications	Large vessel disease
Pseudoxanthoma Elasticum	ABCC6	Connective tissue disorder with high prevelance of cardiovascular complications	Large vessel disease
Fabry disease	/ galactosidase A leading to damaged vascular endothelial cells	Lysosomal enzyme deficiency disease	Large and small vessel
Sickle Cell Disease	Haemoglobin S	Stroke, TIA or neurological complications present in up to 25% of cases	Large and small vessel disease
HHT – Hereditary hemorrhagic telangiectasia	Endoglin and ALK1	Vascular dysplasia with variable expressivity leading to venous malformations	Embolic stroke

Table 1. Rare single gene disorders with stroke as a primary or significant secondary clinical characteristic. Although multiple genes have been identified, the low frequency of these conditions in the general population means their clinical significance is limited.

the complexity of its downstream pathway and the multitude of effects cAMP exerts on a cell as a secondary messenger.

The PDE4D gene contributes to only a minority of strokes, and its association with stroke needs to be replicated in other independent populations. Nevertheless its identification is 'proof of principal' that taking the genetic approach to understanding and eventually treating stroke is sound.

Intermediate phenotypes

Stroke involves a series of pathophysiological processes often occurring over many years. Each may be influenced by a number of different genes. One way of studying a simplified system in which fewer genes may be involved is the use of intermediate phenotypes, or stages, in the disease process. Two are being widely used in stroke genetics, namely carotid artery intima-media thickness (IMT) and plaque quantified by ultrasound as an intermediate phenotype for large vessel disease stroke[14], and white matter hyperintensities on MRI as an intermediate phenotype for small vessel disease stroke (Figure 2)[15]. Both have been shown to have a significant genetic component in twin and family studies. Their use has emphasised the importance of gene-environment interactions, which should be taken into account in study design[16]. The study of intermediate phenotypes allows larger populations to be collected with relative ease, but suffers from the effects of phenocopy and heterogeneity in that the phenotype may be due to variable factors and not all of the cohort will go

on to display future stroke events. Despite this the use of intermediate phenotypes remains of importance, not least because it allows the use of a more statistically powerful continuous variable rather than a dichotomous presence or absence variable. It also overcomes the problems of covert disease whereby a control in a case-control study may have subclinical cerebrovascular disease.

Conclusions

The genetics of multifactorial disease remains a complex area. Yet recent advances in the identification of PDE4D and the confirmation that the genetic component of diseases such as stroke can be found give hope to the idea that, little by little, we may understand how our genetic makeup and our environment interact to cause stroke. Such advances will require large collaborative studies with rigorous design and phenotyping.

References

1. Brass LM, Isaacsohn JL, Merikangas KR, Robinette CD. *A study of twins and stroke.* Stroke 1992;23:221-223.
2. Bak S, Gaist D, Sindrup SH, Skytthe A, Christensen K. *Genetic liability in stroke: a long term follow up study of Danish twins.* Stroke 2002;33:769-774.
3. Jousilahti P, Rastenyte D, Tuomilehto J, Sarti C, Vartiainen E. *Parental history of cardiovascular disease and risk of stroke. A prospective follow-up of 14371 middle-aged men and women in Finland.* Stroke 1997;28:1361-1366.
4. Liao D, Myers R, Hunt S, Shahar E, Paton C, Burke G, Province M, Heiss G. *Family history of stroke and stroke risk. the family heart study.* Stroke 1997;28:1908-1912.
5. Jeffs B, Clark JS, Anderson NH, Gratton J, Brosnan MJ, Gauguier D, Reid JL, Macrae IM, Dominiczak AF. *Sensitivity to cerebral ischaemic insult in a rat model of stroke is determined by a single genetic locus.* Nat Gen 1997;16:364-367.
6. Rubattu S, Volpe M, Kreutz R, Ganten U, Lindpaintner K. *Chromosomal mapping of quantitative trait loci contributing to stroke in a rat model of complex human disease.* Nat Gen 1996;13:429-434.
7. Kalaria RN, Low WC, Oakley AE, Slade JY, Ince PG, Morris CM, Mizuno T. *CADASIL and genetics of cerebral ischaemia.* J Neural Transm Suppl 2002;63:75-90.
8. Joutel A, Favrole P, Labauge P, Chabriat H, Lescoat C, Andreux F, Domenga V, Cecillon M, Vahedi K, Ducros A, Cave-Riant F, Bousser MG, Tournier-Lasserve E. *Skin biopsy immunostaining with a Notch3 monoclonal antibody for CADASIL diagnosis.* Lancet 2001;358:2049-2051.
9. Joutel A, Corpechot C, Ducros A, Vahedi K, Chabriat H, Mouton P, Alamowitch S, Domenga V, Cecillion M, Marechal E, Maciazek J, Vayssiere C, Cruaud C, cabanis EA, Ruchoux MM, Weissenbach J, Back JF, Bousser MG, Tournier-Lasserve E. *Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia.* Nature 1996;383:707-710.
10. Wang W, Prince CZ, Mou Y, Pollman MJ. *Notch3 signalling in vascular smooth muscle cells induces c-FLIP expression via ERK/MAPK activation.* J Biol Chem 2002;277:21723-21729.
11. Hassan A, Markus HS. *Genetics and Ischaemic Stroke.* Brain 2000; 123: 1784-1812.
12. Hassan A, Sham P, Markus HS. *Planning genetic studies in human stroke: Sample size estimates based on family history data.* Neurology 2002; 58: 1483-88.
13. Gretarsdottir S, Thorleifsson G, Reynisdottir ST, Manolescu A, Jonsdottir S, Jonsdottir T, Gudmundsdottir T, Bjarnadottir SM, Einarsson OB, Gudjonsdottir HM, Hawkins M, Gudmundsson G, Gudmundsdottir H, Andrason H, Gudmundsdottir AS, Sigurdardottir M, Chou TT, Nahmias J, Goss S, Sveinbjornsdottir S, Vladimarsson EM, Jakobsson F, Agnarsson U, Gudnason V, Thorgeirsson G, Fingerle J, Gurney M, Gudbjartsson D, Frigge ML, Kong A, Stefansson K, Gulcher JR. *The gene encoding phosphodiesterase 4D confers risk of ischaemic stroke.* Nat Gen 2003;353:131-138.
14. Houslay M, Adams D. *PDED4 cAMP phosphodiesterases: modular enzymes that orchestrate signalling crosstalk, desensitisation and compartmentalisation.* Biochem J 2003;370:1-18.
15. O'Leary DH, Polak JF, Kronmal RA, *et al. Carotid artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults.* New Eng J Med 1999; 340:14-22.
16. Schmidt H, Fazekas F, Kostner GM *et al. Angiotensinogen gene promoter haplotype and microangiopathy-related cerebral damage: results of the Austrian Stroke Prevention Study.* Stroke 2001; 32: 405-412.
17. Jerrard-Dunne P, Sitzer M, Risley P, Steckel DA, Buehler A, von Kegler S, Markus HS. *Interleukin-6 promotor polymorphism modulates the effect of alcohol on carotid atherosclerosis: the Carotid Atherosclerosis Progression Study.* Stroke 2003;34:402-7.

Correspondence to:
Dr Steve Bevan, Clinical Neuroscience, St George's Hospital Medical School, Cranmer Terrace, London SW17 ORE.
E-Mail: s.bevan@sghms.ac.uk

The Current Status of Carotid Artery Angioplasty and Stenting

Background

As a result of important landmark studies such as the North American Carotid Endarterectomy trial (NASCET) and the Asymptomatic Carotid Atherosclerotic Study (ACAS), surgical intervention has been found to be beneficial in decreasing the relative risk of morbidity and mortality in patients with significant carotid artery atherosclerotic disease[1–4].

However, carotid endarterectomy still carries a significant perioperative risk. The risk of perioperative stroke from carotid endarterectomy varies from 1.5% to 9% depending on the published series[5,6]. The perioperative stroke and death rate was 7.5% in the European carotid surgery trial (ECST), 5.8% in NASCET and 2.3% in ACAS[1-4,7,8].

Also, the NASCET perioperative stroke and death rate for contralateral occlusions was 14.3%[9]. The risk of cranial nerve palsies occurs in 7.6% to 27% of cases and these results frequently are not recorded as morbidity in surgical publications[5,8,10]. As an alternative to the traditional surgical treatment of carotid artery occlusive disease, there has been much interest in the use of carotid artery stenting (CAS)[7,8,10,11], an area that has a huge amount of political and public scrutiny.

Carotid Stenting - A Review

Mathias, Theron and Kachel were the first to introduce this treatment for cervical carotid artery disease in the early 1980's[12-16] and with the advent of stent technology, interventional management of carotid artery disease began to develop as a practical new technique. Stents provide key improvements compared with angioplasty alone. They also help to decrease restenosis, to prevent dissections and to contain lesion surfaces so reducing the susceptibility for thromboembolism.

When the use of stenting was newly introduced only two peripheral stent systems were available: The balloon-mounted Palmaz-Stent and the Wall-Stent. According to the 1997 world carotid registry of approximately 2041 stents placed, Palmaz-Stents were used in 54% followed by Wall-Stents in 40%[11]. Both systems have advantages and disadvantages. The Palmaz-Stent was of shorter length, required only a two-step-process and had more precise deployment, which allowed it to be placed at the ostium of the internal carotid artery as opposed to the Wall-stent, which was frequently placed across the origin extending into the common carotid artery. However, the major disadvantage of the Palmaz-Stent was the compression and deformability issue.

When Nitinol-Stents became available in 1999, many interventionalists had changed or were in the process of changing from balloon-mounted stents to newer Wall-stents or the Nitinol-stents. In the updated 2000 world registry of 5427 stents placed, Wall-stents were placed in 57% and Palmaz in 33%[17].

Cerebral Protection Devices

Dislodgement of embolic particles during catheter manipulation and stent placement can be disastrous. Various cerebral protection devices including various filters and balloon catheter systems have been developed to prevent dislodgement of embolic particles. These devices are designed to trap, collect and remove particles distal to the lesion.

Currently three types of cerebral protective devices are used. The first type is a microcatheter, such as a Percusurge-Guardwire that has a soft, occlusive balloon catheter at or near the distal tip which is inflated during the procedure.

This balloon catheter system was initially developed and employed by Theron in 1990[12]. The microcatheter is carefully advanced past the carotid lesion and inflated during the procedure. The angioplasty balloon catheter is advanced over the microcatheter and through the guiding catheter. With the microcatheter inflated, embolic debris is aspirated through the guiding catheter.

The second type is a microcatheter or wire with a filter designed to capture and retrieve embolic particles. The third type relies on an occluding guiding catheter and occluding balloon in the external carotid artery, which allows for reverse arterial flow from the targeted internal carotid artery into the guide catheter and than via the femoral vein through a special sheath system.

The filter is designed to be advanced past the lesion in a closed state and then opened during the procedure to collect embolic debris. After the procedure is completed, the filter collapses and the particles are removed from the body.

Both protection devices have advantages and disadvantages. The advantages of the balloon catheter system include the existence of clinical studies in both neurological and coronary systems, the use of soft latex and other materials that minimally damage the artery and a high rate of removal of embolic debris. The disadvantages of the balloon system include occlusion of the entire flow during the procedure in patients who frequently have compromised contralateral carotid artery and collateral flow and inability to evaluate the lesion while the balloon is inflated in the internal carotid artery.

Advantages of an embolic filter device include the ability to provide flow during the procedure while fully expanded and that it does not require flushing.

The disadvantages of the umbrella-type-microfilter-technique include the induction of spasm or damage to the vessel wall, the risk of releasing microparticles and the possibility of draped embolic particles being squeezed out the filter as it is retracted and collapsed.

Current Evidence from Controlled Clinical Trials

Three randomised clinical trials comparing the efficacy of carotid artery stenting and CEA have been conducted. In Europe, the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS) investigators were comparing surgical intervention with angioplasty for treatment of carotid and vertebral occlusive lesions. Among 504 patients randomised primarily to angioplasty alone (only 25% received stents) and considered suitable candidates for CEA, the 30-day disabling stroke and death rates were comparable: 6.3% for CEA and 6.4% for CAS. Phase II is now active and will employ CEA vs. CAS in symptomatic carotid cases[17].

The influence of these recently published data on cases randomised to CEA or CAS may be blunted by the somewhat higher than expected complication rate in the CEA group.

A smaller clinical trial was halted prematurely because of a higher than expected complication rate in the CAS arm of the study[18]. However, concerns have been raised as to the investigators choice of an unacceptably small sample size, inadequate performance of the stenting procedure and unrealistic complications from CAS before the trial was halted.

Alberts *et al.* described the methodology of another randomised clinical trial comparing CAS with CEA in

Univ. Doz. Dr Hans-Peter Haring is currently Head of the Stroke Unit and Neurosonological Laboratory at the Department of Neurology, Landesnervenklinik Wagner Jauregg, Linz, Austria. His research interests are cerebrovascular disease, clinically and experimentally; He is local investigator of various clinical trials (Abestt I & II, Ecass III, DIAS, BRAVO, MATCH., PROFESS, ESPRIT etc).

Dr Johannes Trenkler is Head of the Institute of Radiology, Landes-Nervenklinik Wagner-Jauregg, Linz, Austria. He is also a member of the executive committee of the Austrian Society of Neuroradiology. His main practical and scientific interest is in imaging and endovascular treatment of cerebrovascular diseases.

Professor Franz Thaddäus Aichner is Professor of Neurology and Chair of the Department of Neurology, Wagner-Jauregg Hospital Linz. Austria, and the University Teaching Hospital Innsbruck. He has written over 145 original papers, and edited several scientific books.

219 randomised symptomatic patients[19]. The stated aim of the trial was to determine whether or not CAS was equivalent to CEA in the prevention of ipsilateral stroke, periprocedural death (within 30 days) or vascular death within one year of treatment.

However, this trial was discontinued because of procedural and recruitment difficulties.

Data from this clinical series, however, demonstrated a 30-day stroke and death rate for CEA of 4.5% and for CAS of 12.1% as well as a primary end point rate of 3.6% for CEA and 12.1% for CAS[20]. In an equivalency analysis, this trial did not find that CAS was equivalent to CEA in symptomatic patients. Methodological flaws included limited experience with the procedure by some interventionalists, non uniformity of antiplatelet regimes, absence of supervisions by a designated principal investigator and apparent lack of input to the trialists from an independent cross data monitoring and safety board.

Conclusions regarding the results of these initial clinical trials await further review and do not provide conclusive data. However, as confirmed at a recent consensus conference, CAS can be used to treat extracranial carotid stenosis in selected subsets of patients with periprocedural complications that approach those reported for CEA[21].

Nevertheless, a well designed clinical trial is urgently required, particularly for good risk patients with primary atherosclerotic occlusive disease, if we are to advise our patients about the comparative efficacy of these two new procedures.

Patient Selection

Careful patient selection is critical if the potential benefits of carotid stenting are to be realised. Given the proven efficacy and track record of endarterectomy, carotid stenting will remain an experimental procedure until further data from clinical trials is available. Thus, all reasonable candidates for endarterectomy should either be referred for surgery or enrolled in a clinical trial randomising patients to stenting or surgery. Patients considered to be high risk for surgery should be enrolled in a stent registry, particularly if the patient is asymptomatic. This is important, not only to further define the utility of stenting but also to afford patient's access to the variety of embolic protection devices under investigational protocol. A number of risk factors have been identified that are predictive of embolic complications during carotid stenting. These include advanced age, recent symptoms or large stroke, severe disease of the aortic arch, severe lesion calcification, subtotal occlusion or "string sign", significant lesion – associated thrombus, ostial common carotid disease in conjunction with bifurcation stenosis and significant vessel tortuosity[22,23]. Endovascular therapy for patients exhibiting these risk factors should be avoided if possible, particularly in a physician's experience. All patients should undergo a comprehensive assessment by an independent neurologist both before and after the procedure and during the follow-up period.

Technical Approach and Postprocedural Management

Carotid interventions are optimally performed in a suite having technology with high-resolution imaging capability. Digital subtraction capability is essential, which enables optimisation of imaging at the carotid bifurcation, which is frequently heavily calcified. In addition, adequate imaging of the intracranial circulation requires subtraction. Patient sedatives are administered to avoid obscuring the neurological examination while maintaining patient comfort. For arterial access the femoral route is normally preferred although both the brachial and transradial approaches have been successfully employed[24,25]. Furthermore, equipment developed

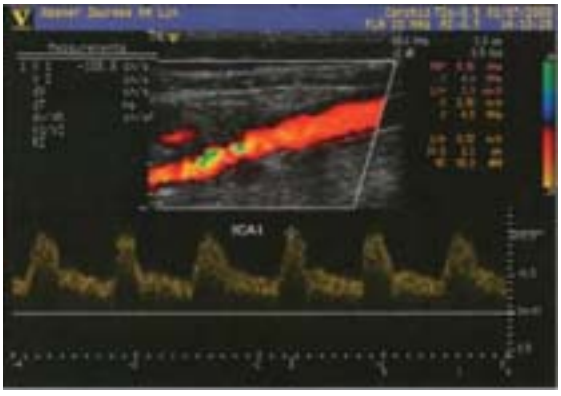


Figure 2: Color coded duplex sonography reveals complete hemodynamic normalisation from high velocity and turbulent jet flow (left) to regular laminar flow after stent insertion (right).

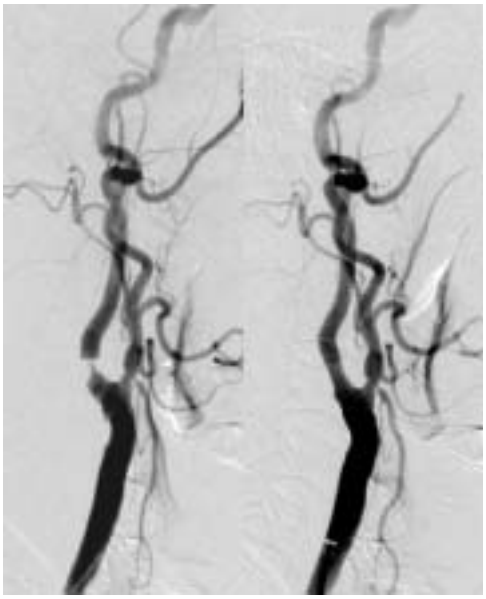


Figure 1: Angiogram of high grade (90%) internal carotid artery stenosis before (left) and after (right) stent application. An Easy Wall Stent has been deployed expanding from the distal common- through the internal carotid artery.

Dr Raffi Topakian has a residency in neurology at the Nervenklinik Wagner-Jauregg Linz, Austria. He has been clinical investigator/local coordinator in various trials and registries, and has special interests in neurological critical care, stroke & cerebrovascular disease, and rehabilitation.

Professor Klaus Berek, Austria: Since 1999, Dr Berek has been Head of the Neurological Department of the KH Kufstein in Austria. He is a member of the Austrian Societies of Neurology, Clinical Neurophysiology, Neurological and Neurosurgical Intensive Care Medicine, Internal and General Intensive Care Medicine, Ulrasound in Medicine, and the ENS.

specifically for carotid stent deployment has been tailored to the femoral approach. Central venous access, although not required, provides a safe root for rapid pacemaker deployment and fluid resuscitation in cases of persistent procedure–related bradycardia and hypotension. Although these events occur with much less frequency then in early experience with carotid stenting, they are all still occasionally observed. Preparing for them in advance may prove to be life-saving.

After femoral access is obtained, heparin is administered to achieve an activated clotting time (ACT) of 300 seconds. This level was primarily based on safety data from coronary intervention and seems thus far to have provided a similar safety profile for carotid intervention[26,27]. Standard prophylactic use of glycoprotein IIbIIIa inhibitors is not generally accepted as in coronary stenting, subgroup analysis of clinical trials of IIbIIIa inhibitors have consistently failed to show benefit in degenerated vein grafts, presumably because of the non platelet nature of distal emboli[28,29]. Furthermore studies suggest that embolic debris freed during carotid intervention also consists primarily of plaque component fragments rather than platelet aggregates and thrombi[30,31]. Recent studies have shown no increased risk of intracranial bleeding when IIbIIIa inhibition is used during coronary intervention[32]. Studies evaluating risk of intracranial haemorrhage in carotid stenting with adjuvant abciximab have shown mixed results[33,34]. No study of IIbIIIa inhibition in carotid intervention has been adequately powered to assess safety or efficacy of this adjunctive pharmacological therapy. Further studies are needed before recommendations can be made.

Sheaths are removed the same day, and post procedure anticoagulation is not routinely administered. Little data is available with regard to stent thrombosis in the carotid circulation, although its incidence appears to be exceedingly rare[35]. Nonetheless, given the proven benefits and excellent safety profile of combination antiplatelet therapy for the prevention of stent thrombosis after coronary intervention and the devastating nature of stent thrombosis should it occur, routine practice has been to treat patients with Aspirin and Clopidogrel for at least four weeks[36-39].

In uncomplicated procedures, the patient may be safely discharged the next day. Surveillance duplex ultrasound scanning should be performed after carotid stenting. The timing and intervals for these examinations is not prescribed, although a typical program might recommend duplex scanning before discharge and then at three, six and twelve months and then annually. Although a negative study is a reliable indicator of patency, the positive predictive value of an abnormal study appears to be poor. Contrast angiography should be performed to examine clinically significant restenosis detected by ultrasound.

Ongoing Clinical Trials

Unlike with PTCA, renal or innominate artery stenting, the Federal Drug Administration (FDA) has required that randomised trials and registries be performed to assess the safety of carotid stenting. The endpoints for the carotid filter are major neurological events such as minor and major strokes and deaths. Currently, two randomised trials are underway in the USA. The carotid revascularisation endarterectomy versus stenting trial (CREST) is a randomised carotid stent placement versus surgical endarterectomy trial that has been recently approved by the FDA. It is currently being initiated and will eventually comprise approximately 40 centres and 2300 patients with symptomatic carotid stenosis. The 2nd randomised trial is SAPPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy), which is studying stent placement with the Angioguard protection device versus endarterectomy in high surgical risk patients. Preliminary results have been presented at the Chicago AHA Meeting in November 2002: 307 patients were randomly assigned to either CAS or CEA. Both symptomatic (≥ 50% ICA stenosis) and asymptomatic (≥ 80% ICA stenosis) patients were eligible when suitable for either technique. A critical inclusion criterion was high surgical risk (NYHA IIIIV, restenosis following CEA, radiation therapy etc.). 156 patients received CAS and the remaining 151 patients underwent CEA. The 30 day incidence of the primary endpoint (death, stroke, myocardial infarction) was significantly lower in the CAS group compared to the surgical group (5.8% vs. 12.6%; p=0.047). The advantage of the stent held true in both symptomatic (4.2% vs. 15.4%; p=0.13) and asymptomatic (6.7% vs. 11.2%; p=0.33) patients. In addition to the randomised group, the SAPPHIRE study enrolled 409 patients into a stent registry. These were patients who required treatment but were felt by their multidisciplinary treatment team, (which included at least one vascular surgeon) to not qualify for CEA. The 30-day primary EP rate for this group was 7.8% and thereby somwhat above the study group (5.8%). This might reflect the fact that significantly more high-risk patients who did not qualify for randomisation were entered onto the registry.

European studies include EVA II, a French study, and SPACE, a German-Austrian trial. The SPACE trial (Stentprotected Percutaneous Angioplasty of the Carotid Artery vs. Endarterectomy) is a randomised multicentre study to compare safety and efficacy of CAS vs. CEA in 450 patients each . Currently, 39 centers in Germany and Austria have randomised 248 CAS and 240 CEA patients. Primary endpoint is the combined 30-day rate of vascular death and ipsilateral stroke.

Table:
Completed and ongoing randomised controlled trials (RCT) comparing safety and efficacy of carotid endarterectomy (CEA) versus carotid artery stenting (CAS).

RCT	STATUS	PUBLICATION	RESULTS
Alberts *et al*	Completed	1997 (20)	CEA superior to CAS
Naylor *et al*	Stopped	1998 (18)	Prematurely halted due to unexpected high complication rate in CAS arm
CAVATAS I	Completed	2001 (17)	CEA and CAS equivalent
CAVATAS II	Ongoing		
CREST	Ongoing		
SAPPHIRE	Ongoing	Preliminary data presented at AHA meeting Chicago 11/2002	CAS superior to CEA in high risk surgical subgroup
EVA II	Ongoing		
SPACE	Ongoing		

References

1. *Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis: North American Symptomatic Carotid Endarterectomy Trial collaborators.* N Engl J Med 1991; 325:445-453

UK ABBREVIATED PRESCRIBING INFORMATION: PROVIGIL® 100mg/200 mg Tablets
Please refer to UK Summary of Product Characteristics (SmPC) before prescribing.
Presentation: White to off-white tablets containing modafinil 100 mg or modafinil 200 mg (debossed with "Provigil" on one side and "100 mg" or "200 mg" on the other). **Indication:** Excessive sleepiness associated with chronic pathological conditions, including narcolepsy, obstructive sleep apnoea/hypopnoea syndrome and moderate to severe chronic shift work sleep disorder. **Dosage:** *Adults: Narcolepsy and Obstructive Sleep Apnoea/Hypopnoea Syndrome:* 200 – 400 mg daily either as two divided doses in the morning and at noon or as a single morning dose according to response; *Shift Work Sleep Disorder:* 200 mg daily taken as a single dose approximately 1 hour prior to the start of the work shift. *Elderly:* treatment should start at 100 mg daily, which may be increased subsequently to the maximum adult daily dose in the absence of renal or hepatic impairment. *Severe renal or hepatic impairment:* Reduce dose by half (100 – 200 mg daily). *Children:* Not recommended. **Contra-indications:** Use in pregnancy and lactation, uncontrolled moderate to severe hypertension, arrhythmia, hypersensitivity to modafinil or any excipients used in Provigil. **Warnings and precautions:** Patients with major anxiety should only receive Provigil treatment in a specialist unit. Sexually active women of child-bearing potential should be established on a contraceptive programme before taking Provigil. Blood pressure and heart rate should be monitored in hypertensive patients. In patients with obstructive sleep apnoea, the underlying condition (and any associated cardiovascular pathology) should be monitored. Patients should be advised that Provigil is not a replacement for sleep and good sleep hygiene should be maintained. Provigil is not recommended in patients with a history of left ventricular hypertrophy, cor pulmonale, or in patients who have experienced mitral valve prolapse syndrome when previously receiving CNS stimulants. This syndrome may present with ischaemic ECG changes, chest pain or arrhythmia. Studies of modafinil have demonstrated a low potential for dependence, although the possibility of this occurring with long - term use cannot be entirely excluded. Provigil tablets contain lactose and therefore should not be used in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption. **Drug interactions:** Modafinil is known to induce CYP3A4/5 (and to a lesser extent, other) enzymes and so may cause clinically significant effects on other drugs metabolised via the same pathways. The effectiveness of oral contraceptives may be impaired through this mechanism. When these are used for contraception, a product containing at least 50 mcg ethinylestradiol should be taken. Certain tricyclic antidepressants and selective serotonin reuptake inhibitors are largely metabolised by CYP2D6. In patients deficient in CYP2D6 (approximately 10% of the Caucasian population) a normally ancillary metabolic pathway involving CYP2C19 becomes more important. As modafinil may inhibit CYP2C19 lower doses of antidepressants may be required in such patients. Care should also be observed with co-administration of other drugs with a narrow therapeutic window, such as anticonvulsant or anticoagulant drugs. **Side effects:** *Very common (>10%)* – headache. *Common (>1%)* – nervousness, insomnia, anxiety, dizziness, somnolence, depression, abnormal thinking, confusion, paraesthesia, blurred vision, nausea, dry mouth, diarrhoea, decreased appetite, dyspepsia, constipation, tachycardia, palpitation, vasodilatation, asthenia, chest pain, abdominal pain and abnormal liver function tests. Dose related increases in alkaline phosphatase and gamma glutamyl transferase have been observed. (See SmPC for uncommon side effects). **Basic NHS cost:** Pack of 30 blister packed 100 mg tablets: £60.00. Pack of 30 blister packed 200 mg tablets: £120.00 **Marketing authorisation numbers:** PL16260/0001 Provigil 100 mg Tablets, PL 16260/0002 Provigil 200 mg Tablets. **Marketing authorisation holder:** Cephalon UK Limited. **Legal category:** POM. **Date of preparation:** March 2004. Provigil and Cephalon are registered trademarks. Full prescribing information, including SmPC, is available from **Cephalon UK Limited**, 11/13 Frederick Sanger Road, Surrey Research Park, Guildford, Surrey UK GU2 7YD, Medical Information Freefone 0800 783 4869 (ukmedinfo@cephalon.com). PRO809/Mar 04

Cephalon
deliver more>

2. *Asymptomatic Carotid Atherosclerosis Study Group. Endarterectomy for asymptomatic carotid artery stenosis.* JAMA 1995; 273:1421-1428
3. Clinical Advisory:*Carotid endarterectomy for patients with asymptomatic internal carotid artery stenosis.* J Neurologic Sci 1995;129:76-77
4. Clinical Advisory:*Carotid endarterectomy for patients with asymptomatic internal carotid artery stenosis.* Stroke 25:2523-2524
5. Lusby RJ, Wylie EJ: *Complications of carotid endarterectomy.* Surg Clin North Am 1994; 63:1293-1301
6. Zarins CK: Carotid endarterectomy: *The gold standard.* J Endovasc Surg 1996;3:10-15
7. Diethrich EB : Indications for carotid stenting: *A preview of the potential derived them from early clinical experience.* J Endovasc Surg 1996;3:132-139
8. Yadav JS, Roubin GS, King P, *et al*: *Angioplasty and stenting for restenosis after carotid endarterectomy.* Stroke 1997;27:2075-2079
9. Gasecki AP, Elliasziw M, Ferguson GG, *et al*: *Long-term prognosis and effect of endarterectomy in patients with symptomatic severe carotid stenosis and contralateral carotid stenosis or occlusion: Results from NASCET.* J Neurosurg 1995;83:778-782
10. Diethrich EB: Cerebrovascular disease therapy: *The past, the present, and the future.* J Endovasc Surg 1996;3:7-9
11. Wholey MH, Wholey M, Bergeron P, *et al*: Current global status of carotid artery stent placement. Cath Cardiovasc Diagn 1998;44:1-6
12. Theron J, Courtheroux P, Alachkar, *et al*: *New triple coaxial catheter systems for carotid angioplasty with cerebral protection.* Am J Neuroradiol 1990;11: 867-874
13. Mathias KD, Jaeger MJ, Sahl. H: *Internal carotid stents-PTA: 7 Year experience,* Cardiovasc Intervent Radiol 1997;20:1-46 (abstr)
14. Kachel R, Basche St, Heerklotz I, *et al*: *Percutaneous transluminal angioplasty (PTA) of supra-aortic arteries especially the internal carotid artery.* Neuroradiology 1991;33:191-194
15. Wholey MH Wholey M, Mathias K, *et al*: *Global experience in cervical carotid artery stent placement.* Cathet Cardiovasc Interv 2000;50:160-167
16. Theron JG, Payelle GG, Coskun, 0, *et al*: *Carotid artery stenosis: Treatment with protected balloon angioplasty and stent placement.* Radiology 1996;201:627-636
17. Brown MM, Rogers J, Bland JM, *et al*: *Endovascular versus surgical treatment in patients with carotid stenosis in the carotid and vertebral artery transluminal angioplasty study (CAVATAS): A randomised trial.* Lancet 2001;357:1729-1737
18. Naylor AR, Bolia A, Abbott RJ, *et al*: *Randomised study of carotid angioplasty and stenting versus carotid endarterectomy. A stopped trial.* J Vasc Surg 1998 ;28:326-334
19. Alberts MJ, McCann R, Smith TP, *et al*: *A randomised trial: Carotid stenting versus endarterectomy in patients with symptomatic carotid stenosis, study designs.* J Neurovasc Dis 1997;228-234
20. Alberts MJ: *Results of a multicenter prospective randomised trial of carotid artery stenting vs. carotid endarterectomy.* Stroke 2001; 32:325-d.
21. Veith FJ, Amor M, Ohki T, *et al*: *Current status of carotid bifurcation angioplasty and stenting based on a consensus of opinion leaders.* J Vasc Surg 33:S111-S116, 2001
22. Mathur A, Roubin G, lyer S, *et al*: *Predictors of stroke complicating carotid artery stenting.* Circulation 1998;7:1239-1245
23. Vitek J, Roubin G, AI-Mubarek, *et al*: *Carotid artery stenting: Technical considerations.* Am J Neuroradiol 2000;21:1736-1743
24. AI-Mubarak N, Vitek J, lyer S, *et al*: *Carotid stenting with distal-balloon-protection via the transbrachial approach: A case report.*
25. Castriota F, Cremonesi A, Manetti R, *et al*: *Carotid stenting using radial artery access.* J Endovasc Surg 1999;6:385-386
26. Ferguson J, Dougherty K, Gaos C, *et al*: *Relation between procedural activated coagulation time and the outcome after percutaneous translminal coronary angioplasty.* J Am Coll Cardiol 1994;23:1061
27. Chew D, Bhatt D, Lancoff A, *et al*: *Defining the optimal activated clotting time during percutaneous coronary intervention: Aggregate results from 6 randomised, controlled trials.* Circulation 2001;103:961-966
28. Ellis S, Lincoff A, Miller D, *et al*: *Reduction in complications of angioplasty with abciximab occurs largely independently of baseline lesion morphology. EPIC and EPILOG investigators. Evaluation of 7E3 for the prevention of ischemic complications. Evaluation of PTCA to improve long-term outcome with abciximab GPIIbIIIa receptor blockade.* J Am Coll Cardiol 1998;32:1619-1623
29. Webb J, Carere, R, Virmani R, *et al*: *Retrieval and analysis of particulate debris after saphenous vein graft intervention.* J Am Coll Cardiol 1999;34:468-475
30. Martin J, Pache J, Treggiari-Venzi M, *et al*: *Role of the distal balloon protection technique in the prevention of cerebral embolic events during carotid stent placement.* Stroke 2001; 32:479-484
31. Ohki T, Roubin G, Veith F, *et al*: *Efficacy of a filter device in the prevention of embolic events during carotid angioplasty and stenting: An ex vivo analysis.* J Vasc Surg 1999 ;30:1034-1044
32. Akkerhuis K, Deckers J, Lincoff A, *et al*: *Risk of stroke associated with abciximab among patients undergoing percutaneous coronary intervention.* JAMA 286:78-82, 2001
33. Kapadia S, Bajzer C, Ziada K, *et al*: *Initial experience of platelet glycoprotein lib/IIIa inhibition with abciximab during carotid stenting: A safe and elfective adjunctive therapy.* Stroke 2001;32:2328-2332
34. Qureshi A, Suri M, Ali Z, *et al*: *Carotid angioplasty and stent placement: A prospective analysis of perioperative complications and impact of intravenously administered abciximab.* Neurosurgery 2002;50:466-473
35. Roubin G, New G, lyer S, *et al*: *Intermediate and late clinical outcomes of carotid artery stenting in patients with symptomatic and asymptomatic carotid artery stenosis.* Circulation 2001;103:532-537
36. Leon M, Baim D, Popma J, *et al*: *A clinical trial comparing three anti-thrombotic drug regimens after coronary artery stenting.* New Engl J Med 1998; 338:1665-1671
37. Cutlip D, Baim D, Ho K, *et al*: *Stent thrombosis in the modern era: A pooled analysis of multicenter coronary stent trials.* Circulation 2001;103:1967-1971
38. Bertrand M, Hans Jurgen R, Urban P, *et al*: *Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: The clopidogrel aspirin stent international cooperative study (CLASSICS).* Circulation 2000;1-2:624-629
39. Mehta S, Yusuf S, Peters R, *et al*: *Effects of-pretreatment with Clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: The PCI-CURE study.* Lancet 2001;358:527-533

Correspondence to:
Hans – Peter Haring, MD
Dept. Neurology,
Landesnervenklinik
Wagner Jauregg Weg 15,
A-4020 Linz
Austria.
E-Mail:
hanspeter.haring@gespag.at

Spatial Neglect

Spatial neglect is a common syndrome following stroke, most frequently of the right hemisphere. Up to two-thirds of acute right-hemisphere stroke patients demonstrate signs of contralesional neglect, failing to be aware of objects or people to their left in extrapersonal space. For example, when searching through a visual scene patients with left neglect tend to look at elements on the right only (Fig. 1). The syndrome may also involve 'personal' space, with patients neglecting their own contralesional body parts. Importantly, many patients are unaware they have these problems (anosognosia). Perhaps unsurprisingly, therefore, enduring neglect is a poor prognostic indicator for functional independence following stroke.

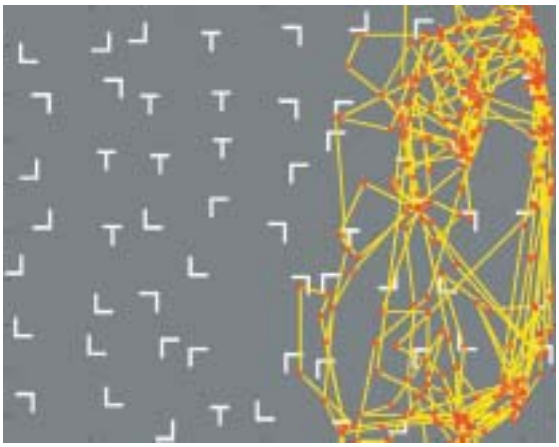


Figure 1. Measurement of the eye-movements during search for letter Ts among Ls of a typical patient with left neglect reveals a tendency to repeatedly fixate items on the right while ignoring those on the left.

Diagnosis

Severe neglect may often be diagnosed by simple observation, e.g. patients who turn their head and eyes to their extreme right and never spontaneously gaze to the left, even though leftward eye movements are intact on formal testing. In most cases, however, specific bedside assessments are required to identify neglect. Furthermore, it is important to quantify the severity of neglect in order to track patients' progress in an acute stroke unit, or in response to rehabilitation. A number of simple and rapid tests have been developed for the assessment of neglect[1, 2]. We recommend, where possible, using several of these because there is considerable variability in the tests that patients fail (probably reflecting differences in the exact nature of the underlying cognitive deficits):

- *Cancellation tasks* (Fig. 2) involve patients searching for and marking with a pen target items on a sheet of paper. Right-hemisphere neglect patients often start on the right side of the page (whereas control subjects who read left-to-right usually start on the left), and omit targets on the left of the page. The most sensitive tests have a high density of targets as well as irrelevant distracter items. Cancellation tests are the *single* most sensitive bedside test and should wherever possible be included in any test battery[2].
- In *line bisection tasks* patients mark where they perceive to be the midpoint of a long (18-20 cm) horizontal line on a sheet of paper. Neglect patients, especially those with right posterior lesions, often deviate considerably to the right of the true midpoint.
- *Object copying* (Fig. 3) and *drawing a clock face* are commonly used but they are relatively insensitive when used alone, difficult to score in a graded manner and also affected by constructional apraxia.
- When asked to *report ten objects* around the room neglect patients may predominantly choose items from the ipsilesional side of space.
- Tests of *personal neglect* include asking the patient to mime combing their hair, shaving or making-up their face. Right-hemisphere patients often fail to groom the left side of their face on such tasks, as well as in daily life.

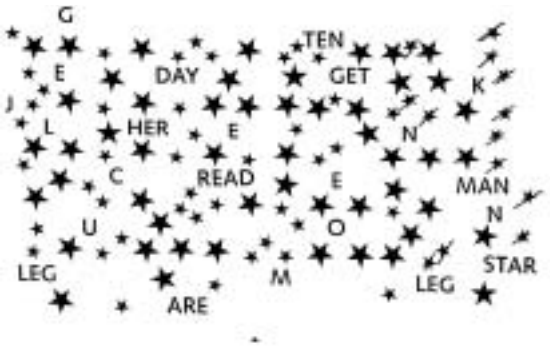


Figure 2. In a clinical cancellation task a neglect patient tends to cross out only those targets (small stars) on the right of the page.

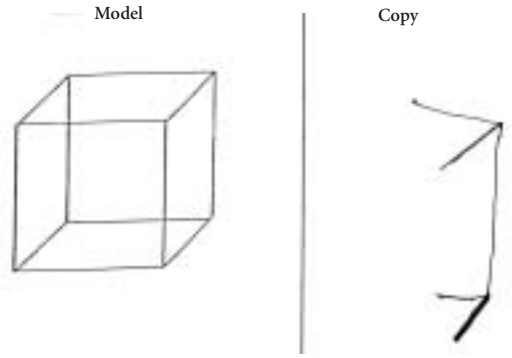


Figure 3. When copying a model line drawing of a cube neglect patients may omit leftward features.

Anatomy of neglect

Most neglect patients have suffered large right-hemisphere MCA strokes but the syndrome has been more specifically associated with damage to the following regions (Fig. 4):

- The right inferior parietal lobe (IPL) or nearby temporo-parietal junction (TPJ), considered the 'classical' cortical sites[3].
- The right inferior frontal lobe, which tends to lead to more transient neglect[4].
- Subcortical ischaemic lesions in the territory of the right MCA involving the basal ganglia or thalamus, although this may be due to diaschisis or hypoperfusion in overlying parietal and frontal regions[5].
- Large posterior cerebral artery (PCA) territory strokes extending from occipital to medial temporal lobe. It remains to be determined whether neglect following such extensive PCA infarction is in fact due to parietal diaschisis, or is a separate disorder distinguished by unique underlying component deficits.

Cognitive deficits underlying neglect

Many different cognitive deficits, either in isolation or combination, are considered to contribute to the neglect syndrome. The following important spatially lateralised

Andrew Parton is Post-Doctoral Research Associate in the Department of Visual Neuroscience at Imperial College London, Charing Cross Hospital. His research interests are the cognitive neuroscience of attention, eye movements and spatial representation.

Masud Husain is Wellcome Trust Senior Fellow and Reader in Neurology at Imperial College London, Charing Cross Hospital. He has a special interest in disorders of visuospatial cognition and attention.

Figure 1 reproduced from "Impaired spatial working memory across saccades contributes to abnormal search in parietal neglect. Brain 2001;124(Pt 5):941-52." by permission of Oxford University Press.

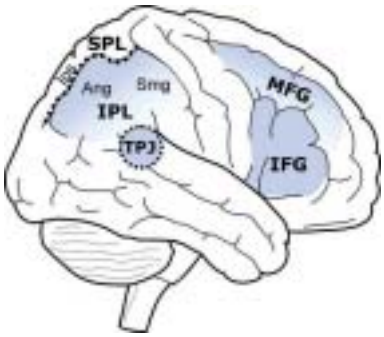


Figure 4. Cortical right hemisphere brain regions associated with neglect include the angular (Ang) and supramarginal (Smg) gyri of the inferior parietal lobe (IPL), the temporo-parietal junction (TPJ), and the inferior (IFG) and middle frontal (MFG) gyri. Additionally, the diagram also shows the superior parietal lobe (SPL) and intraparietal sulcus (IPS).

components (worse to the left in right-hemisphere patients) have been proposed to underlie neglect:

- A deficit in directing attention to the left – due either to a graded bias in directing attention rightwards[6], items on the right invariably 'winning' over objects to the left in the competition for attentional selection[7], or a difficulty in disengaging attention and shifting it leftward[8].
- An impaired representation of space - which may occur in multiple frames of reference (e.g. retinotopic, head-centred, trunk-centred) or be specific to near or far space[9].
- A directional motor impairment, with patients experiencing difficulty in initiating or programming leftward movements[10].

In addition to these lateralised impairments (worse to the left following right-hemisphere stroke), it is increasingly becoming apparent that the neglect syndrome also consists of *non-spatially lateralised* deficits, involving both sides of space. Different patients may suffer different combinations of lateralised and non-lateralised deficits, depending upon the precise location and extent of their lesions. Furthermore, the severity of a patient's neglect may be determined by the interaction between their lateralised and non-lateralised impairments, which could help to explain why some patients recover poorly[11]. Non-spatially lateralised components of neglect include:

- Impairments in sustained attention[12]
- A bias to local features in the visual scene[13]
- A deficit in spatial working memory[14]
- Prolonged time-course of visual processing[15]

Treatment and Rehabilitation

Initial attempts to rehabilitate neglect encouraged patients to direct their gaze towards contralesional space. But although these approaches showed some success in reducing neglect within a particular task (e.g. in reading, by cueing patients to find a red line marked on the left margin), patients typically demonstrated little generalisation of their improved scanning behaviour to tasks outside of the training environment[16]. Unfortunately, many neglect patients are often unaware of their deficit and in complex real-world environments, cues to remind them to look left (e.g. red lines) are not readily available.

Recently researchers have attempted to develop techniques that produce an automatic change in behaviour, without relying on patients adopting a new control strategy to look leftwards. The most promising of these approaches involves *prism adaptation*, using lenses that induce a rightward horizontal displacement of patients' visual fields[17]. Recent studies have suggested that the after-effects of simple prism adaptation treatment may result in a long lasting amelioration of neglect that generalises across a wide range of deficits[18]. Further work is required to understand the mechanisms underlying such improvement, and to establish the extent of its effectiveness. Other research is being directed towards drug treatments for specific cognitive deficits underlying the neglect syndrome.

Acknowledgment

Our research programme is funded by The Wellcome Trust.

References

1. Parton A, Malhotra P, Husain, M. *Hemispatial Neglect.* J Neurol Neurosurg Psychiatry 2004;75:13–21.
2. Azouvi P, *et al. Sensitivity of clinical and behavioural tests of spatial neglect after right hemisphere stroke.* J Neurol Neurosurg Psychiatry 2002;73(2): 160-6.
3. Vallar G. *The anatomical basis of spatial hemineglect in humans in Unilateral neglect: clinical and experimental studies.* Robertson IH, Marshall JC, Editors. Hove: Lawrence Erlbaum, 1993:27-59.
4. Husain M, Kennard C. *Distractor-dependent frontal neglect.* Neuropsychologia 1997;35(6):829-41.
5. Hillis AE *et al. Subcortical aphasia and neglect in acute stroke: the role of cortical hypoperfusion.* Brain 2002;125(Pt 5):1094-104.
6. Kinsbourne M. *Orientational bias model of unilateral neglect: Evidence from attentional gradients within hemispace, in Unilateral neglect: Clinical and Experimental Studies.* Robertson IH, Marshall JC, Editors. Hove: Lawrence Erlbaum 1993:63-86.
7. Duncan J, Humphreys G, Ward R. *Competitive brain activity in visual attention.* Current Opinion in Neurobiology 1997;7:255-261.
8. Losier BJ, Klein RM. *A review of the evidence for a disengage deficit following parietal lobe damage.* Neurosci Biobehav Rev 2001; 25(1):1-13.
9. Karnath HO. *Spatial orientation and the representation of space with parietal lobe lesions.* Philos Trans R Soc Lond B Biol Sci 1997;352(1360): 1411-9.
10. Heilman KM *et al. Directional hypokinesia: prolonged reaction times for leftward movements in patients with right hemisphere lesions and neglect.* Neurology 1985; 35:855-859.
11. Husain M, Rorden C. *Non-spatially lateralized mechanisms in hemispatial neglect.* Nat Rev Neurosci 2003;4(1):26-36.
12. Robertson IH *et al. Auditory sustained attention is a marker of unilateral spatial neglect.* Neuropsychologia 1997;35(12):1527-32.
13. Robertson LC, Lamb MR, Knight RT. *Effects of lesions of temporal-parietal junction on perceptual and attentional processing in humans.* Journal of Neuroscience 1988;8:3757-3769.
14. Husain M *et al. Impaired spatial working memory across saccades contributes to abnormal search in parietal neglect.* Brain 2001;124(Pt 5):941-52.
15. Husain M *et al. Abnormal temporal dynamics of visual attention in spatial neglect patients.* Nature 1997; 385(6612):154-6.
16. Robertson IH, Marshall JC, *Unilateral Neglect: Clinical and Experimental Studies.* Hove: Lawrence Erlbaum, 1993.
17. Rossetti Y *et al. Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect.* Nature 1998; 395(6698):166-9.
18. Frassinetti F *et al. Long-lasting amelioration of visuospatial neglect by prism adaptation.* Brain 2002;125(Pt 3):608-23.

Correspondence to:
Department of Visual Neuroscience
Division of Neuroscience & Psychological Medicine
Imperial College School of Medicine
Charing Cross Hospital
Fulham Palace Road
London W6 8RF
E-Mail: a.parton@imperial.ac.uk or m.husain@imperial.ac.uk

DR. ALOIS ALZHEIMER

BEFORE HIM,
THE DISEASE DIDN'T HAVE A NAME

BEFORE ARICEPT,
IT DIDN'T HAVE A REALISTIC TREATMENT

Aricept®
donepezil hydrochloride

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.

Eisai Pfizer

A577-ARI236-12-02

Can We Improve The Holistic Assessment of Parkinson's Disease?

The development of a non-motor symptom questionnaire and scale for Parkinson's disease

K Ray Chaudhuri[1], **A H V Schapira**[2], **P Martinez-Martin**[3], **R Brown**[4], **W Koller**[5], **K Sethi**[6] and **D MacMahon**[7] on behalf of the International Parkinson's Disease Non-Motor Symptom Scale Development Group*

* Other members of the PD Non-Motor Symptoms Scale Development Group: Professor Paulo Barone; Ms Annette Bowron; Ms Alison Forbes; Professor Chris Goetz; Ms Linda Kelly; Dr Graeme Macphee; Prof. Per Odin; Prof. Warren Olanow; Dr William Ondo; Dr David Rye; Professor Fabrizio Stocchi; Ms Sue Thomas; Dr Adrian Williams

[1]Kings Colleges Hospital, University Hospital Lewisham, Guy's, King's St.Thomas' School of Biomedical Sciences and Kings College London.
[2]Royal Free Hospital Medical School and National Hospital for Neurology Neurosurgery, Queen Square, London.
[3]Area of Applied Epidemiology, National Center for Epidemiology, ISCIII, Madrid, Spain
[4]Institute of Psychiatry, London
[5]Medical College of Georgia, USA
[6]Mount Sinai School of Medicine, New York, USA
[7]Royal Cornwall NHS Trust, Devon, UK

It is nearly 200 years since James Parkinson described the key motor symptoms of Parkinson's disease (PD) in his classic Essay on the Shaking Palsy.[1] He also drew attention to the non-motor symptoms experienced by his patients which, in contrast to the motor features, still remain under-recognised and under-treated.

The importance of non-motor symptoms in PD

In people with PD, progressive degeneration of the dopamine-producing cells in the brain combines with loss in the noradrenergic, cholinergic and serotoninergic systems to produce a wide range of clinical features. Motor symptoms (Table 1) are well recognised in PD, but numerous studies have also identified a wide range of non-motor symptoms.

The non-motor symptoms in PD range from cognitive and psychiatric problems such as apathy, depression, anxiety disorders and hallucinations to sleep disorders, sexual dysfunction, bowel problems and dribbling of saliva. In a recent survey of 163 consecutive patients attending a PD clinic, problems with balance, sleep disturbance, memory failure or confusional episodes, and dribbling of saliva were rated as the most disabling symptoms ahead of the motor features of PD such as bradykinesia and tremor.[2] Importantly, most of the non-motor symptom complex of PD is more likely to be seen at the primary care level, as patients and hospital specialists more often confine discussion to the management of motor symptoms and motor complications such as dyskinesias.

It is increasingly clear that non-motor symptoms have a dramatic effect on the lives of both PD patients and caregivers.[3] Depression and daytime somnolence are common in PD and have been shown to have an adverse effect on health-related quality of life.[3-6] Although the economic implications in relation to hospital and societal cost of treating PD have not been comprehensively evaluated, individual non-motor symptoms such as falls, dementia and hallucinations are now recognised as some of the major reasons for admission to institutional care. In the UK, total annual direct costs for patients living in full-time institutional care were recently estimated at £19,338 compared with £4189 for those being cared for at home.[7]

Non-motor symptoms of PD also contribute to the burden of hidden costs, in the form of informal care and lost productivity.[8] These costs may be substantial, particularly when we consider that PD patients frequently live on a fixed income from pension or benefits, and that the family caregiver is often an elderly spouse. Early and accurate identification and appropriate management of the nature and severity of non-motor symptoms in PD will aid the holistic care of this progressive neurodegenerative illness, improve the quality of life of patient and carer, and contribute to limiting the financial impact of PD. Precedents for the success of such a strategy are available from other chronic, progressive neurological disorders.[9]

Lack of awareness of non-motor symptoms in PD

Non-motor symptoms of PD are not well recognised in clinical practice, either in primary and secondary care. Depression, anxiety, fatigue and sleep disturbance are among the most troubling symptoms for PD patients, but during routine consultations, Shulman *et al* reported that patients with these symptoms are not identified by neurologists in over 50% of consultations and sleep disturbance in particular is not recognised in over 40% of patients.[10] There is also lack of awareness of the considerable disability associated with non-motor symptoms among general practitioners who refer few of their PD patients for speech, occupational or physio-therapy[11]. In clinical trial studies, PD patients generally report satisfaction with their hospital and general practice care, and this likely reflects their and their family caregivers' own lack of awareness that PD was responsible for many of their symptoms. As a result, patients are unlikely to report non-motor symptoms unless health professionals ask specifically. In a recent pilot questionnaire study (L Kelly 2004, Personal Observation), members of the UK Parkinson's Disease Society were asked to describe symptoms experienced during the previous 24 hours. Pain, tremor, and fatigue were most often mentioned spontaneously, but when specific enquiry was made patients were more likely to report non-motor symptoms such as depression, anxiety and sleep disturbance.

The assessment of non-motor symptoms of PD

Interest is growing in the evidence-based treatment of non-motor symptoms, but in part its success will depend not just on the identification but also on the quantification of the effects of treatment on patients' baseline disability. This must involve the use of validated assessment, but symptom-specific instruments may not be relevant to people with PD. For example, the prevalence of depression in PD varies depending on whether diagnostic criteria such as Diagnostic & Statistical Manual (DSM)-IV, rating scales or clinical diagnosis are used in the evaluation.[11]

Existing PD-specific rating scales largely concentrate on motor symptoms. Recently, this issue has been recognised by the Movement Disorder Society, and a revised version of the Unified Parkinson's Disease Rating Scale (UPDRS)—the most frequently used instrument in


Doug MacMahon


William C. Koller


Pablo Martinez-Martin


K Ray Chaudhuri


Anthony Schapira


Kapil D Sethi is


Richard Brown

Biographical information on the authors and other members of the Non-Motor Symptoms Scale Development Group can be found at www.acnr.co.uk/pdfs/volume4issue4/v4i4nmsbios.pdf

clinical research and practice—will include some screening questions on non-motor symptoms. There will also be an official appendix that includes other, more detailed, and optionally used scales to determine severity of these impairments (Movement Disorder Society Task Force 2003).[12] Individual aspects of non-motor disability in PD are included in some other current initiatives, most notably the Scales for Outcomes in Parkinson's disease (SCOPA) project.[13,14] There is, however, no single scale that enables a comprehensive assessment of the range of non-motor symptoms that occur in PD. Although ambitious, the development of such an instrument would undoubtedly improve our assessment of PD patients, facilitate research into non-motor symptoms and help to improve individualised delivery of care.

Against this background, an international, multidisciplinary group of experts including nursing and patient group representatives have developed the first non-motor symptom assessment questionnaire and scale. The group was conscious that such an assessment tool should be able to quantify symptoms ranging from anxiety to bowel problems and at the same time be practical, reliable, validated, responsive to treatment or interventions, and interpretable in different languages.

As the awareness for the range of non-motor symptoms is low, the group developed a 30-item screening questionnaire to be used by the patient/caregiver while waiting to be seen in clinic (Fig 1). This instrument will not provide an overall score of disability; instead, it is designed to draw attention to the presence of non-motor symptoms, and to prompt health professionals to initiate further investigation and suitable treatment. A pilot study using the screening questionnaire has been completed in the UK, USA, Germany and Italy. The initial results show a wide range of non-motor symptoms in people with PD from all disease stages compared to healthy controls.[13] Interestingly many such symptoms had never been revealed to their clinicians by patients and were only declared when the questionnaire was administered.

In contrast to the questionnaire, the PD non-motor scale is divided into nine major domains containing 33 questions (Fig 2). The questions were devised after detailed literature review, expert experience and evaluation of the screening questionnaire pilot study. The scale is aimed to be a practical and quantitative scale that encompasses the non-motor symptoms experienced by people with PD. It is envisaged that health professionals will administer the scale, and patients' responses will enable quantification of symptoms based on a multiple of severity (from zero to three) and frequency scores (from one to four). The scale is simple to administer and is intended for use in both primary and secondary care.

Following completion of this pilot, a major international study is now planned for validation of the scale . We hope that this will become an integral part of the assessment of patients and contribute to the comprehensive, modern management of patients with PD.

Table 1. Motor symptoms in Parkinson's disease

Primary motor symptoms
Tremor at rest
Rigidity
Bradykinesia
Loss of postural reflexes
Additional motor symptoms/signs
Dysphagia
'Freezing' (inability to initiate movement)
Gait disturbances (slow, shuffling gait; difficulty turning)
Hypomimia (mask-like face)
Hypophonia (decrease in volume and clarity of speech)
Micrographia (small, illegible handwriting)
Sialorrhea (drooling)
Stooped axial posture

Conclusion

Effective alleviation of symptoms is especially important for patients with a chronic, progressive, incurable illness such as PD, but non-motor symptoms have been comparatively neglected. Once validated, the non-motor symptoms questionnaire and scale should help to raise awareness of these issues among both health professionals and patients, and promote the holistic assessment and treatment of these disabling and distressing symptoms.

Acknowledgements

We are grateful to Pfizer Corporation for an educational grant to support this venture. Aakshay Gulati, Frauke Stegie, Vandana Dhawan, Susanne Tluk, Joanna Estelita, Mario Ganau, Catherine Meilak for data collection, recruitment of controls, maintaining database. Sue Lyon for dissemination of NMS meeting minutes.

References

1. Parkinson J. *An Essay on the Shaking Palsy.* London 1817
2. Gulati A, Forbes A, Stegie F, *et al. A clinical observational study of pattern and occurrence of non-motor symptoms in Parkinson's disease.* Presented at Movement Disorders Congress, Rome, June 2004. Mov Disord 2004; 19 (Supp 9): S406 (P1187)
3. Clarke C E, Zobkiw R M, Gullaksen E. *Quality of life and care in Parkinson's disease.* Br J Clin Pract 1995; 49 (6): 288-93
4. Hobson P, Holden A, Meara J. *Measuring the impact of Parkinson's disease with the Parkinson's Disease Quality of Life questionnaire.* Age Ageing 1999; 28 (4): 341-6
5. Karlsen K H, Larsen J P, Tandberg E, *et al. Influence of clinical and demographic variables on quality of life in patients with Parkinson's disease.* J Neurol Neurosurg Psychiatry 1999; 66:431–5
6. Global Parkinson's Disease Survey Steering Committee. *Factors impacting on quality of life in Parkinson's disease: results from an international survey.* Mov Disord 2002; 17 (1): 60-7
7. Findley L, Aujla M A, Bain P G, *et al Direct economic impact of Parkinson's disease: a research survey in the United Kingdom.* Mov Disord 2003; 18 (10): 1139-45
8. Whetten-Goldstein K, Sloan F, Kulas E, *et al. The burden of Parkinson's disease on society, family, and the individual.* J Am Geriatr Soc 1997;45 (7): 844-9
9. Bosanquet N, May J, Johnson N. *Alzheimer's disease in the United Kingdom. Burden of disease and future care.* Health Policy Review Paper No. 12. London: Health Policy Unit, Imperial College School of Medicine 1998
10. Shulman L M, Taback R L, Rabinstein AA, Weiner W J. *Non-recognition of depression and other non-motor symptoms in Parkinson's disease.* Parkinsonism Relat Disord 2002; 8 (3): 193-7
11. Slaughter J R, Slaughter K A, Nichols D, *et al. Prevalence, clinical manifestations, etiology, and treatment of depression in Parkinson's disease.* J Neuropsychiatry Clin Neurosci 2001; 13 (2): 187-96
12. Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease. *The Unified Parkinson's Disease Rating Scale (UPDRS): status and recommendations.* Mov Disord 2003; 18 (7): 738-50
13. Ramaker C, Marinus J, Stiggelbout A M, Van Hilten B J. *Systematic evaluation of rating scales for impairment and disability in Parkinson's disease.* Mov Disord 2002; 17 (5): 867-76
14. Marinus J, Visser M, Martinez-Martin P, *et al. A short psychosocial questionnaire for patients with Parkinson's disease: the SCOPA-PS.* J Clin Epidemiol 2003; 56 (1): 61-7.

Correspondence to:
Movement Disorders Unit
9th Floor Ruskin Wing
King's College Hospital
Denmark Hill
London SE5 9RS
Telephone: 020 7346 8336
Fax : 020 8333 3093
E-Mail:
ray.chaudhuri@uhl.nhs.uk

Figure 1: The Non motor symptoms screening questionnaire:

NMS SCREENING QUESTIONNAIRE

Name . . . . . Date . . . . . .

NON-MOVEMENT PROBLEMS IN PARKINSON'S

The movement symptoms of Parkinson's are well known. However, other problems can also occur as part of the condition or its treatment. It is important that the doctor knows about these, particularly if they are troublesome for you.

A range of problems are listed below. Please tick the box 'Yes' if you have experienced it during the past month. If you are uncertain tick the box marked 'Not sure'. The doctor or nurse may ask you some questions to help decide. If you have not experienced the problem in the past month tick the 'No' box. You should tick 'No' even if you have had the problem in the past but not in the past month.

Have you experienced any of the following in the last month?	***Yes***	***Not sure***	***No***
1. Dribbling saliva during the daytime	❒	❒	❒
2. Loss or change in your ability to taste or smell	❒	❒	❒
3. Difficulty swallowing food or drink or problems with choking	❒	❒	❒
4. Vomiting or feelings of sickness (nausea)	❒	❒	❒
5. Constipation (less than 3 bowel movements a week) or having to strain to pass a stool (feces)	❒	❒	❒
6. Bowel (fecal) incontinence	❒	❒	❒
7. Feeling that your bowel emptying is incomplete after having been to the toilet	❒	❒	❒
8. A sense of urgency to pass urine that makes you rush to the toilet	❒	❒	❒
9. Getting up regularly at night to pass urine	❒	❒	❒
10. Unexplained pains (not due to known conditions such as arthritis)	❒	❒	❒
11. Unexplained change in weight (not due to change in diet)	❒	❒	❒
12. Problems remembering things that have happened recently, or forgetting to do things	❒	❒	❒
13. Loss of interest in what is happening around you or in doing things	❒	❒	❒
14. Seeing or hearing things that you know or are told are not there	❒	❒	❒
15. Difficulty concentrating or staying focussed	❒	❒	❒
16. Feeling sad, 'low' or 'blue'	❒	❒	❒
17. Feeling anxious, frightened or panicky	❒	❒	❒
18. Feeling less interested in sex or more interested in sex	❒	❒	❒
19. Finding it difficult to have sex when you try	❒	❒	❒
20. Feeling lightheaded, dizzy or weak when standing from sitting or lying	❒	❒	❒
21. Falling	❒	❒	❒
22. Finding it difficult to stay awake during activities such as working, driving or eating	❒	❒	❒
23. Difficulty getting to sleep at night or staying asleep at night	❒	❒	❒
24. Intense, vivid dreams or frightening dreams	❒	❒	❒
25. Talking or moving about in your sleep as if you are 'acting out' a dream	❒	❒	❒
26. Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move	❒	❒	❒
27. Swelling of your legs	❒	❒	❒
28. Excessive sweating	❒	❒	❒
29. Double vision	❒	❒	❒
30. Believing things are happening to you that other people say are not true	❒	❒	❒

Continuous control

Twenty-four hour symptom control – one dose a day

Cabaser®
CABERGOLINE
The once-daily dopamine agonist

As adjuvant therapy to levodopa

CABASER® (CABERGOLINE). Abbreviated Prescribing Information. Before prescribing see Summary of Product Characteristics. **Presentation:** Cabaser tablets: Containing 1, 2 or 4 mg cabergoline. **Uses:** The treatment of symptoms of Parkinson's disease, as adjuvant therapy to levodopa plus dopa-decarboxylase inhibitor, in patients affected by 'on-off' mobility problems with daily fluctuations in motor performance. Improvement of motor deficit has been demonstrated while permitting a substantial decrease in L-dopa dose. **Dosage and Administration:** Adults and elderly patients: The recommended therapeutic dosage is 2-6 mg/day as adjuvant therapy to levodopa, given as a single daily oral dose. Dose should be titrated slowly against efficacy and tolerability. A starting dose of 1 mg daily is recommended; the dosage of concurrent levodopa may be gradually decreased, while the dose of Cabaser is increased. In view of the long half-life of the compound, the dose may be increased in gradual weekly or bi-weekly intervals by increments of 0.5-1.0 mg, up to optimal doses. Use in Children: not recommended. **Contra-indications:** Hypersensitivity to any ergot alkaloid. Warnings: In patients with severe hepatic insufficiency the dose should be reduced accordingly. Cabaser is an ergot derivative. Fibrotic reactions have occurred after prolonged usage of ergot derivatives. Patients with a history of such disorders should not be treated with Cabaser. Renal insufficiency has not been shown to modify Cabaser kinetics. Caution is advised in patients suffering from severe cardiovascular disease, Raynaud's syndrome, peptic ulcer, gastrointestinal bleeding or a history of major psychotic illness. In cases of unexplained high ESR, or emergence of respiratory symptoms, a chest X-ray is recommended to exclude pleural effusion/fibrosis. Symptomatic hypotension can occur following administration of Cabaser: particular attention should be paid when administering Cabaser concomitantly with other drugs known to lower blood pressure. Cabaser has been associated with somnolence and, uncommonly, sudden sleep onset. Patients who have experienced somnolence and/or an episode of sudden onset of sleep must refrain from driving or operating machines, until such recurrent episodes and somnolence have resolved. Furthermore a reduction of dosage or termination of therapy may be considered. **Drug Interactions:** No pharmacokinetic interaction with levodopa or selegiline has been observed in clinical studies in Parkinsonian patients. Concomitant use of other ergot alkaloids with Cabaser is not recommended. Cabaser should not be administered concurrently with drugs which have dopamine antagonist activity since these might reduce Cabaser's efficacy. Cabaser should not be used in association with macrolide antibiotics since systemic bioavailability of Cabaser and adverse effects could increase. The effects of alcohol on overall tolerability of Cabaser are currently unknown. **Pregnancy and Lactation:** Based on limited clinical experience, cabergoline does not appear to be associated with an increased risk of abortion, premature delivery, multiple pregnancy or congenital abnormalities. As a precautionary measure, it is recommended that women seeking pregnancy discontinue Cabaser one month before intended conception, in order to prevent possible foetal exposure to the drug. If conception occurs during therapy, treatment is to be discontinued as soon as pregnancy is confirmed. Do not use in nursing mothers as lactation may be inhibited; no information on the excretion of cabergoline in maternal milk in humans is available. **Undesirable Effects:** Events most frequently reported in clinical studies were dyskinesia, hyperkinesia, hallucinations or confusion. Other events include nausea, vomiting, dyspepsia and gastritis, as well as dizziness and hypotension. Symptomatic pleural effusion/fibrosis has been reported with a frequency <2%; in these cases discontinuation of Cabaser is expected to lead to immediate improvement of symptoms. Cabaser has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes. In view of Cabaser's pharmacological class, other reported events include angina (reported in 1%), erythromelalgia (0.4%) and peripheral oedema (6%). CNS events are more common in the elderly. **Overdose:** No incidences reported in the proposed indication. Symptoms of overdose are likely to be related to dopaminergic activity. **Legal Category:** POM. **Basic NHS Cost:** 20x1mg £75.45; 20x2mg £75.45; 16x4mg £75.84 all bottles. **Product Licence Numbers:** CABASER 1mg: PL0022/0169, CABASER 2mg PL0022/0170, CABASER 4mg: PL0022/0171. **Product Licence Holder:** Pharmacia Laboratories Limited, Davy Avenue, Milton Keynes, MK5 8PH, United Kingdom. **Date of Preparation:** January 2003.

Fig 2: NON-MOTOR SYMPTOM ASSESSMENT SCALE FOR PARKINSON'S DISEASE

Symptoms assessed over the last month.
Each symptom scored with respect to:

Severity:
0 = None
1 = Mild: symptoms present but causes little distress or disturbance to patient
2 = Moderate: some distress or disturbance to patient
3 = Severe: major source of distress or disturbance to patient

Frequency:
1 = Rarely < 1/wk
2 = Often 1/wk
3 = Frequent, several times
4 = Very frequent, daily or all the time

Total score expressed as multiplication of severity and frequency.
Domains will be weighted differentially.
Yes/No answers are not included in final frequency x severity calculation.
(Bracketed text in questions within the scale is included as an explanatory aid).

Domain 1: Gastrointestinal tract
1. Does the patient dribble saliva during the day?
2. Does the patient have difficulty in swallowing?
3. Does the patient ever have a sensation of nausea or does he or she vomit (Do you ever feel that you may be sick? Do you ever vomit?)
4. Does the patient suffer from constipation? (Bowel action less than three times weekly)
5. Does the patient have to strain to pass a stool? (Do you need to take laxatives of any sort other than healthy diet)?
6. Does the patient have altered sensation in the lower bowel? (Unsatisfactory voiding)
7. Does the patient suffer from faecal incontinence? (Leaking, involuntary defecation)

Domain 2: Pain
8. Does the patient suffer from pain not explained by other known conditions?
9. Is it related to intake of drugs and is it relieved by antiparkinson drugs? Yes/No

Domain 3: Urinary
10. Does the patient have difficulty holding urine? (Urgency)
11. Does the patient have to void within 2 hrs of last voiding? (Frequency)
12. Does the patient have to get up regularly at night to pass urine? (Nocturia)

Domain 4: Cardiovascular including falls
13. Does the patient experience lightheadedness, dizziness, weakness or pain in shoulders on standing from sitting or lying position?
14. Does the patient fall because of fainting or blacking out?

Domain 5: Sexual function
15. Does the patient have altered interest in sex? (Very much increased or decreased)
16. Does the patient have problems in becoming sexually aroused?

Domain 6: Sleep/fatigue
17. Does the patient doze off or fall asleep unintentionally during daytime activities? (For example, during conversation, during mealtimes, or while watching television or reading?)
18. Does fatigue (tiredness) or lack of energy (not slowness) limit the patient's daytime activities?
19. Does the patient have difficulties falling or staying asleep?
20. Is the patient aware or has he or she been told about talking during sleep or moving about as if acting out a dream?
21. Does the patient experience an urge to move the legs or restlessness in the legs that improves with movement when he or she is sitting or lying down inactive?

Domain 7: Hallucinations/delusions
22. Does the patient indicate that he or she sees things that are not there?
23. Does the patient have beliefs that you know are not true? (For example, about being harmed, being robbed or being unfaithful?)

Domain 8: Apathy/attention/memory
24. Has the patient lost interest in his or her surroundings?
25. Has the patient lost interest in doing things or lack motivation to start new activities?
26. Does the patient look dazed or unaware of what is going on? (Not just when drowsy or falling asleep)
27. Does the patient have problems sustaining concentration during activities? (For example, reading or having a conversation)
28. Does the patient forget things that he or she has been told a short time ago or events that happened in the last few days?
29. Does the patient forget to do things? (For example, take tablets or turn off domestic appliances)

Domain 9: Depression/anxiety/anhedonia
30. Does the patient feel nervous, worried or frightened for no apparent reason?
31. Does the patient seem sad or depressed or has he or she reported such feelings?
32. Does the patient have flat mood without the normal 'highs' and 'lows'?
33. Does the patient have difficulty in experiencing pleasure from usual activities or report that they lack pleasure?

More Information

We welcome centres that would like to pilot the screening questionnaire and take part in the validation study of the NMS scale in the UK.

Please contact:
NMS Co-ordinator Alison.forbes@uhl.nhs.uk
Or call 020 8333 3030 ext 8060 or 020 7346 8336

MIRAPEXIN™ (pramipexole) Abbreviated Prescribing Information. Before prescribing see Summary of Product Characteristics. **Presentation:** Mirapexin 0.088mg, Mirapexin 0.18mg and Mirapexin 0.7mg tablets containing 0.125mg, 0.25mg and 1mg respectively of pramipexole salt (dihydrochloride monohydrate). **Uses:** 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:* The daily dosage is administered orally with water in equally divided doses three times per day. *Initial treatment:* Titration of dose from 0.264mg base (0.375mg of salt) per day, doubling the dose every 5-7 days, to a daily dose of 1.08mg base (1.5mg salt). If a further dose increase is necessary the daily dose should be increased by 0.54mg base (0.75mg salt) at weekly intervals up to a maximum dose of 3.3mg base (4.5mg salt) per day. NB The incidence of somnolence is increased at doses higher than 1.5mg (salt)/day. *Maintenance treatment:* The individual dose should be in the range from 0.264mg base (0.375mg salt) to a maximum of 3.3mg base (4.5mg salt) per day. It is recommended that the dosage of levodopa is reduced during both the escalation and the maintenance treatment with Mirapexin, dependent upon individual response. *Treatment discontinuation:* Abrupt discontinuation of dopaminergic therapy can lead to the development of neuroleptic malignant syndrome. Therefore, pramipexole should be tapered off at a rate of 0.54mg of base (0.75mg of salt) per day until the daily dose has been reduced to 0.54mg of base (0.75mg of salt). Thereafter, the dose should be reduced by 0.264mg of base (0.375mg of salt) per day. *Renal impairment:* Consult the Summary of Product Characteristics for information on revised dosage schedules. *Hepatic impairment:* Dose adjustment in patients with hepatic failure is probably not necessary. **Children:** Not recommended. **Contra-indications, Warnings etc.: Contra-indications:** Hypersensitivity to pramipexole or any other component of the product. **Warnings:** In patients with renal impairment a reduced dose is recommended (see above). Hallucinations are a known side-effect of treatment with dopamine agonists and levodopa. Patients should be informed that (mostly visual) hallucinations can occur. Mirapexin has been associated with somnolence and, uncommonly, sudden sleep onset. Patients who have experienced somnolence and/or an episode of sudden onset of sleep must refrain from driving or operating machines, until such recurrent episodes and somnolence have resolved. Futhermore a reduction of dosage or termination of therapy may be considered. In advanced Parkinson's disease, in combination with levodopa, dyskinesias can occur during the initial titration of Mirapexin. If they occur, the dose of levodopa should be decreased. Patients with psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks. Ophthalmologic monitoring is recommended at regular intervals 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. Reduction of the pramipexole dose should be considered when these drugs are administered concomitantly with Mirapexin. While increasing the dose of Mirapexin it is recommended that the dosage of levodopa is reduced and the dosage of other anti-Parkinsonian medication is kept constant. Due to possible additive effects, caution is advised when patients are co-prescribed Mirapexin with other sedating medication or alcohol. Co-administration of antipsychotic drugs with pramipexole should be avoided. **Pregnancy and Lactation:** The effect on pregnancy and lactation has not been investigated in humans. Therefore, Mirapexin should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Similarly, Mirapexin should not be used during breast-feeding. **Undesirable Effects:** Nausea, constipation, somnolence, insomnia, hallucinations, dizziness and peripheral oedema occurred more often than with placebo. More frequent adverse reactions in combination with levodopa were dyskinesias. These adverse events tend to decrease or disappear with continued therapy. Hypotension may occur at the beginning of treatment in some patients, especially if Mirapexin is titrated too fast. Mirapexin 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/emetic measures may be required. **Basic NHS Cost:** 0.088mg x 30 £10.00, 0.18mg x 30 £20.00, 0.18mg x 100 £66.67, 0.7mg x 30 £63.67, 0.7mg x 100 £212.24. **Legal Category:** POM. **Marketing Authorisation Holder:** Pharmacia Enterprises S.A., 6, Circuit de la Foire Internationale, L-1347 Luxembourg, G.D. Luxembourg. **Marketing Authorisation Number:** Mirapexin 0.088mg x 30 tablets EU/1/97/051/001; Mirapexin 0.18mg x 30 tablets EU/1/97/051/003; Mirapexin 0.18mg x 100 tablets EU/1/97/051/004; Mirapexin 0.7mg x 30 tablets EU/1/97/051/005; Mirapexin 0.7mg x 100 tablets EU/1/97/051/006. Further information is available from Pharmacia Ltd, Davy Avenue, Milton Keynes, MK5 8PH, UK. Tel: 01908 661101. **Date of preparation:** April 2003.

References: 1. Shannon KM, Bennett JP Jr, Friedman JH *et al.* Neurology 1997; 49: 724-728. 2. Barone P, Bressman S. Poster presented at 53rd Annual American Academy of Neurology; May 5-11, 2001 Philadelphia, Pa. 3. Parkinson's Study Group. JAMA 2000: Vol 284, No.15: 1931-1938.

Pfizer

Initiating therapy with Mirapexin quickly and effectively controls the symptoms of Parkinson's disease.[1]

Using Mirapexin as initial therapy can delay the introduction of levodopa for at least four years[2] and help to delay the troublesome motor complications associated with long-term levodopa use.[3]

Mirapexin™
pramipexole

Act today for an active tomorrow

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

Catatonia: A Clinician's Guide to Diagnosis and Treatment

Edited by: M Fink, MA Taylor
ISBN: 0-521-82226-2
Publisher: Cambridge University Press, 2003
Price: £50.00

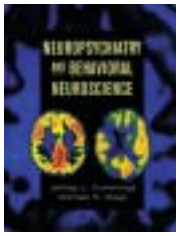
First delineated by Karl Kahlbaum in 1874, catatonia is a syndrome of motor dysregulation characterised by mutism, characteristic posturing (catalepsy, waxy flexibility), repetitive speech, negativitism, and imitative movements. In this monograph, two American neuropsychiatrists draw together their own extensive experience of the condition with that of the published literature. They detail the history, clinical features, differential diagnosis, treatments (old and new), and possible neurobiological substrates of the syndrome, which they observe to be common in acute psychiatric practice. The text is leavened with over 50 illustrative patient vignettes.

A number of themes emerge. The classification of catatonia as a subtype of schizophrenia, initially by Kraepelin and latterly perpetuated in successive editions of the *Diagnostic and Statistical Manual* (DSM) of the American Psychiatric Association, is criticised as being too narrow. Most catatonic patients in fact suffer from a mood disorder; neurological and general medical disorders may also manifest catatonia. Suggestions for an alternative classification of catatonia as a syndrome, in accordance with these observations, are made, possibly in hopes of inclusion in DSM-V. There is strong advocacy for treatment of catatonia with lorazepam, followed, if unsuccessful, by ECT. There is trenchant criticism of the legal barriers causing delay of ECT in certain localities. Neuroleptic malignant syndrome (NMS), which may have causes other than treatment with neuroleptic drugs (e.g. withdrawal of dopaminergic therapies), is subsumed within the category of "malignant catatonia" (MC), as is the serotonin syndrome. Suggested treatment of MC/NMS is with benzodiazepines and ECT, as for other causes of catatonia, rather than with dantrolene and/or bromocriptine.

I found this book an interesting read, providing some insights into the often obscure territory lying in the borderland between neurology and psychiatry. Characterisation of catatonia as a syndrome with many possible causes is certainly appropriate, presumably reflecting a common neurobiological substrate, irrespective of the underlying disease process (and whether that is arbitrarily categorised as neurological or psychiatric). However, as a neurologically trained practitioner, I was not receptive to the suggestion that stiff-person syndrome and locked-in syndrome might be amenable to the same treatments as catatonia because of their clinical similarity (109), nor that echophenomena are specific catatonic features (116). Also, I suspect that evidence-based practitioners will be less than convinced by the assurance that the reported efficacy of lorazepam and ECT is not solely due to a "misleading selection of clinical vignettes" (193): I cannot recall any reference to randomised controlled trials of treatment. If the therapeutic effects are large, small trials should have adequate power to demonstrate this.

AJ Larner; Cognitive Function Clinic, WCNN, Liverpool

Neuropsychiatry and Behavioral Neuroscience



Edited by: JL Cummings, MS Mega
Publisher: Oxford University Press, 2003
ISBN: 0-19-513858-9
Price: £75.00

The authors open their textbook by stating that they aim to integrate a current review of the two disciplines of behavioural neurology and biological psychiatry in a single volume. This may seem to be a more than reasonable project and, as the first author is both a professor of neurology and psychiatry and the second a neuroimager, one that should be eminently achievable; however, the book largely fails on two counts. Firstly, at only 414 pages long, it is just too short to be able to deliver on its promise to "… link the recent explosion of new information from neurochemistry, neuroanatomy, genetics, neuropharmacology, neuropathology, and neuroimaging to the clinical descriptions", especially as a further aim is to include therapeutics. Thus Alzheimer's disease is allocated only three sides, and, while we all recognise that the familial forms of this disease are rare, there is no mention of Apo E or the presenilin genes in either text or index. Stroke receives even less attention with therapy dealt with in only one paragraph which is limited to clot-busting drugs and aspirin; there is no mention of rehabilitation - cognitive or otherwise.

The second flaw is a more philosophical and indeed personal one. It has been lamented that Neurology and Psychiatry (surely two sides of the same coin) have drifted apart to each others' detriment and need to be reunited immediately in order to share mutually enlightening discoveries about brain function. After all, most psychiatrists would accept that the mind is an emergent property of brain function, and all neurologists have at least a passing interest in disorders of the brain. The problem is that the 'common ground' argument is perhaps most true for neuroscience research (especially neuroimaging), and least true for clinical practice. Neurologists (even behavioural ones) and Psychiatrists just don't see the same type of patients and thus it does not necessarily follow that a clinically orientated textbook designed for both will be useful to either (for more on this debate see: Leon Eisenburg in Neurology Today 2002; 2(5):p.4).

Trying to mix the immiscible leads to a few jarring moments: the treatment of neuropsychiatric disorders is discussed before the principles of neuropsychiatry are laid down; apraxia and acalculia are dealt with in the chapter on speech and language disorders; traumatic brain injury and CNS infections pop-up in the chapter on focal brain disorders. But there are parts of the text where this approach reaps rewards. The chapters on memory disorders and hallucinations both start with clear definitions and then move neatly between 'psychiatric' and 'neurological' causes for these difficult and complex symptoms which often confront clinicians on ward consults or in the out-patient clinic. The former chapter also has a good summary of the more recent functional imaging work on memory encoding and storage. Other hidden gems include the best taxonomic system for the classification of aphasic syndromes that I've come across in a textbook and a nice comparison between the disordered speech output seen in Wernicke's aphasia and schizophrenia. The selection and quality of illustrations is high throughout.

This textbook is probably best dipped into by neurologists who want to know a little bit more about psychiatry, and psychiatrists who want to know a little bit more about neurology; but until neurologists start treating psychoses and psychiatrists start thrombolising stroke, any clinically based text aimed at both specialists is going to appear uneven in both scope and detail.

AP Leff, National Hospital, Queen Square, London

Cerebrovascular Ultrasound in Stroke Prevention and Treatment

Edited by: Andrei V Alexandrov
Publisher: Blackwell Futura, 2003
ISBN: 1405103817
Price: £110 (Quote ACNR to receive special price of £80)

This book has been produced by an international team of contributors, edited at the University of Texas and is aimed at three types of individuals: beginners to learn the basics of ultrasound testing, advanced users to learn differential diagnosis and clinicians involved in treating stroke patients. The text is packed full of useful practical information and has excellent illustrations and TCD images. However, the content is not basic and beginners wishing to start TCD would be advised to read simpler texts prior to this book. It is divided into five parts: Part I-*How to perform ultrasound tests* covers both extracranial and intracranial ultrasound examination with an emphasis on standardisation for carotid duplex. The techniques for carrying out single-gated spectra (TCD), power-motion Doppler (M-mode) and transcranial colour duplex imaging (TCCS) are outlined in a simple and clear manner. The advantages of M-mode (easier window-finding) and TCCS (identifying anomalies of the circle of Willis) for the beginner are emphasised but the caveat for both M-mode and TCCS is spectral resolution and it is acknowledged that experienced operators will still use single-gated TCD. Part II-*Haemodynamic principles* is a "heavy" section but will be of particular interest to anyone working in the intensive care/surgical setting. The chapter on practical models of cerebral haemodynamics importantly emphasises spectral waveform recognition rather than the usual emphasis on velocity. Part III-*Criteria for interpretation.* is an excellent section covering diagnostic and validation criteria for carotid stenosis, carotid and vertebral artery dissection and occlusion, intracerebral arterial vasospasm, embolism detection, with a good description of the TIBI ultrasound classification for large vessel occlusion. Part IV–*Ultrasound in stroke prevention and treatment* covers ultrasound findings of specific diseases including sickle cell disease, cardiovascular risk, secondary stroke prevention, acute ischaemic stroke, subarachnoid haemorrhage. The chapter on ischaemic stroke discusses the potential therapeutic use of TCD and is well worth reading. Part V–*Select clinical applications and clinical vignettes* includes an interesting collection of anecdotal vascular cases covering areas which can give diagnostic difficulty. The exciting parts of this book have to be the emphasis on the potential therapeutic use of diagnostic TCD and the focus on waveform analysis rather than velocity measurements. This opens up TCD as a bedside tool, which will hopefully mean that more clinicians will start using this powerful technique.

Dr Paul Syme, NHS Borders/University of Edinburgh

Peaks and troughs of levodopa therapy have put limits on patient function.

When symptoms develop due to shortening of levodopa/DDCI dose effectiveness switch to Stalevo and stay in control.[1,2]

New STALEVO

ORION PHARMA

Stalevo (levodopa / carbidopa / entacapone) Brief Prescribing Information Indication: Treatment of patients with Parkinson's disease and end-of-dose motor fluctuations not stabilised on levodopa/dopa decarboxylase (DDC) inhibitor treatment. **Dosage and administration:** Orally with or without food. One tablet contains one treatment dose and may only be administered as whole tablets. Optimum daily dosage must be determined by careful titration of levodopa in each patient preferably using one of the three tablet strengths. Patients receiving less than 70-100mg carbidopa a day are more likely to experience nausea and vomiting. The maximum Stalevo dose is 10 tablets per day. Usually Stalevo is to be used in patients who are currently treated with corresponding doses of standard release levodopa/DDC inhibitor and entacapone. See SPC for details of how to transfer these patients and those not currently treated with entacapone. *Children and adolescents:* Not recommended. *Elderly:* No dosage adjustment required. *Mild to moderate hepatic impairment, severe renal impairment (including dialysis):* Caution advised. **Contraindications:** Hypersensitivity to active substances or excipients. Severe hepatic impairment. Narrow-angle glaucoma. Pheochromocytoma. Concomitant use of non-selective monoamine oxidase inhibitors (e.g. phenelzine, tranylcypromine). Concomitant use of a selective MAO-A inhibitor and a selective MAO-B inhibitor. Previous history of Neuroleptic Malignant Syndrome (NMS) and/or non-traumatic rhabdomyolysis. **Warnings and precautions:** Not recommended for treatment of drug-induced extrapyramidal reactions. Administer with caution to: patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or history of peptic ulcer disease or of convulsions, or past or current psychosis; patients receiving concomitant antipsychotics with dopamine receptor-blocking properties, particularly D2 receptor antagonists; patients receiving other medicinal products which may cause orthostatic hypotension. In patients with a history of myocardial infarction who have residual atrial nodal, or ventricular arrhythmias, monitor cardiac function carefully during initial dosage adjustments. Monitor all patients for the development of mental changes, depression with suicidal tendencies, and other serious antisocial behaviour. Patients with chronic wide-angle glaucoma may be treated with Stalevo with caution, provided the intra-ocular pressure is well controlled and the patient is monitored carefully. Caution when driving or operating machines. Doses of other antiparkinsonian treatments may need to be adjusted when Stalevo is substituted for a patient currently not treated with entacapone. Rhabdomyolysis secondary to severe dyskinesias or NMS has been observed rarely in patients with Parkinson's disease. Therefore, any abrupt dosage reduction or withdrawal of levodopa should be carefully observed, particularly in patients who are also receiving neuroleptics. Periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function is recommended during extended therapy. **Undesirable effects:** *Levodopa / carbidopa* – Most common: dyskinesias including choreiform, dystonic and other involuntary movements, nausea. Also mental changes, depression, cognitive dysfunction. Less frequently: irregular heart rhythm and/or palpitations, orthostatic hypotensive episodes, bradykinetic episodes (the 'on-off' phenomenon), anorexia, vomiting, dizziness, and somnolence. *Entacapone* – Most frequently relate to increased dopaminergic activity, or to gastrointestinal symptoms. Very common: dyskinesias, nausea and urine discolouration. Common: insomnia, hallucination, confusion and paroniria, Parkinsonism aggravated, dizziness, dystonia, hyperkinesias, diarrhoea, abdominal pain, dry mouth constipation, vomiting, fatigue, increased sweating and falls. See SPC for details of laboratory abnormalities, uncommon and rare events. **Legal category:** POM. **Presentations, basic NHS costs and marketing authorization numbers:** Stalevo 50mg/12.5mg/200mg, 30 tablet bottle £24.00, 100 tablet bottle £80.00, MA numbers: EU/1/03/260/002-003; Stalevo 100mg/25mg/200mg, 30 tablet bottle £24.00, 100 tablet bottle £80.00, MA numbers: EU/1/03/260/006-007; Stalevo 150mg/37.5mg/200mg, 30 tablet bottle £24.00, 100 tablet bottle £80.00 MA numbers: EU/1/03/260/010-011. **Distributed in the UK by:** Orion Pharma (UK) Ltd. Leat House, Overbridge Square, Hambridge Lane, Newbury, Berkshire, RG14 5UX, England. **In Ireland information is available from:** Orion Pharma (Ireland) Ltd, c/o Allphar Services Ltd, Belgard Road, Tallaght, Dublin 24. Tel 01-4041600. Fax: 01-4041699. Full prescribing information is available on request. Stalevo is a registered trademark. Updated November 2003.

New Stalevo® ▼
levodopa, carbidopa, entacapone

Enhance the benefits of levodopa

References
1. Larsen JP *et al. Eur J Neur* 2003;**10**:137-146.
2. Rinne UK *et al. Neurology* 1998;**51**:1309-1314.

Date of preparation:
December 2003
STA1016

Detection of Small Vessel Knock using Transcranial Doppler Ultrasonography - Implications for the Ischaemic Penumbra and the Treatment of Small Vessel Occlusive Stroke

Paul Syme is Consultant Physician (Lead Stroke Physician), Borders General Hospital and Part-time Senior Lecturer, Department of Geriatrics, University of Edinburgh. He is the principal investigator of the Scottish Borders Stroke study. He was formerly an MRC Clinical Scientist, University of Oxford, quantifying NMR spectroscopy (Professors David Grahame-Smith and Sir George Radda) and an MRC French Exchange Fellow, University of Nice (Dr Jacques Pouysségur).

The ischaemic penumbra has been defined in a variety of ways, but the most clinically relevant definition is that portion of the ischaemic territory that is still potentially salvageable, if an appropriate treatment is given.[1] Following large vessel occlusion, the benefit of revascularisation is time-dependent with penumbral tissue present in a significant proportion of cases around 3-6 hours but rarely up to 48 hours.[2] Transcranial Doppler ultrasonography (TCD) has recently been shown to increase revascularisation in association with recombinant tissue plasminogen activator (tPA) within 3 hours of middle cerebral artery occlusive stroke but no clear clinical benefit was identified.[3] However, the time-dependence for beneficial revascularisation following small vessel occlusion (SVD) of the brain, which is the commonest form of ischaemic stroke, is unknown. Here, I would like to report a new Transcranial Doppler ultrasonography (TCD) finding in ischaemic stroke due to SVD which I have named "small vessel knock" (SVK). I will show preliminary evidence that SVK is the ultrasound finding of SVD and that targeted insonation, using only diagnostic ultrasound of 2 Mhz (EZ Dop, DWL elektronische), can recanalise SVD resulting in clinical recovery over a considerable time window.

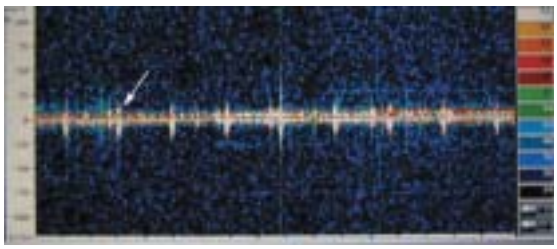
"Knock" is the name given to the TCD finding of a high intensity thump-like sound occurring at peak systole and has been found in circulatory arrest due to brain death[4] (see figure 1a) and traumatic brain injury.[5] It has been proposed that this is due to reflected sound from vessel wall motion.[5] However, I have found similar knock in association with middle cerebral artery occlusion (see Figure 1b). SVK is also associated with peak systole and is found in the ±300 Hz range of the spectrum, which is automatically "filtered-out" by most TCD machines. It is often obscured by the signal obtained from the main supplying artery and has a characteristic high-intensity, low-velocity systolic wave often associated with a reversed diastolic wave (Figures 2 to 4). The diastolic component is likely to be due to aortic valve closure since it coincides with the second heart sound on auscultation. SVK closely resembles the systolic and diastolic knock found in extracranial internal carotid artery occlusion just proximal to the flow void area (see figure 1c)[6]. Figure 2 shows that SVK results from occlusion of a small perforating artery. Targeted insonation results in changes to the SVK signal within a few minutes (broadens and changes in intensity) revealing a small vessel waveform. Clinical improvement is associated with either full arterial opening or the appearance of a black area of low intensity in the high intensity systolic SVK signal (an "SVK insonation window"). I have found SVK in association with MRI-negative stroke-like deficits[7] and in both anterior and posterior circulation stroke. As examples, I will now briefly discuss 3 cases of SVK-positive posterior circulation stroke. Video evidence of complete clinical recovery associated with SVK opening during insonation can be seen in Case 3.[8]

Cases:

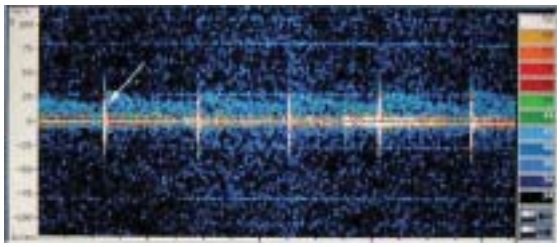
Case 1. (Figure 3) is a 67 year old man who presented with sudden onset of left face, arm and leg weakness with mild dysarthria. A T2-weighted MRI slice through the pons showed a hyperintensity signal consistent with an infarct. TCD performed 12 hours post-onset showed an abnormal high intensity low velocity signal occurring at peak systole with an inverted signal during diastole, to the right of the main basilar artery, at a depth of 103 mm. Continuous insonation improved flow (not shown) but did not result in any recovery.

Case 2 (Figure 4) is a 44 year old woman with a 7 week history of intermittent, left sided weakness, dizziness and mild paraesthesia. The figure shows two FLAIR MRI slices, one with left basal ganglia hyperintensity signals

Figure 1. Shows knock in association with (a) cerebral death (b) Left MCA occlusion and (c) Right internal carotid artery occlusion.



(a) Knock (arrow) in the Right middle cerebral artery of a 40 year old woman with brain death following a right internal carotid artery dissection



(b) Knock (arrow) associated with a Left MCA occlusion in a 40 year old man with dysphasia and dense hemiplegia, 48 hours post-hip surgery. A patent foramen ovale was identified.

(c) Right internal carotid artery occlusion with systolic knock (arrow) followed by vessel wall motion due to aortic valve closure in a 53 year old with a large Right MCA infarct. This patient also had knock in the Right middle cerebral artery, increased velocity in the Left anterior cerebral artery and flow reversal in the Right ophthalmic artery.

Don't just prescribe Mestinon: personalise it!

Mestinon®
pyridostigmine bromide

Personalised therapy

Because every Myasthenia Gravis patient is individual

To get the most out of Mestinon, the most widely prescribed 1st-line treatment for Myasthenia Gravis (MG)[1,2,3,] **it has to be taken at frequent intervals:**

- ***A half-life of 3-4 hours means that a dose frequency of around every 4 hrs is necessary for continuous cover***
- ***Frequency may be increased to every 3 hrs when awake[4]***
- ***Dosage should be tailored to the needs of the patient***

Don't just prescribe Mestinon: personalise it. Make sure every patient gets the most out of Mestinon – 5-6 times a day!

Prescribing Information:

Presentation: Each tablet contains 62.5mg pyridostigmine bromide (equivalent to 60.0mg of the base). **Indications:** Myasthenia Gravis, paralytic ileus and post-operative urinary retention. **Dosage and Administration:** *Myasthenia Gravis – Adults* – Doses of 30 to 120mg are given at intervals throughout the day. The total daily dose is usually in the range of 5-20 tablets. *Children* – Children under 6 years old should receive an initial dose of half a tablet (30mg) of Mestinon; children 6-12 years old should receive one tablet (60mg). Dosage should be increased gradually, in increments of 15-30mg daily, until maximum improvement is obtained. Total daily requirements are usually in the range of 30-360mg. The requirement for Mestinon is usually markedly decreased after thymectomy or when additional therapy is given. When relatively large doses of Mestinon are taken by myasthenic patients, it may be necessary to give atropine or other anticholinergic drugs to counteract the muscarinic effects. It should be noted that the slower gastro-intestinal motility caused by these drugs may affect the absorption of Mestinon. In all patients the possibility of "cholinergic crisis", due to overdose of Mestinon, and its differentiation from "myasthenic crisis" due to increased severity of the disease, must be borne in mind. *Other indications: Adults* – The usual dose is 1 to 4 tablets (60-240mg). *Children* – 15-60mg.The frequency of these doses may be varied according to the needs of the patient. *Elderly* – No specific dosage recommendations. **Contra-indications, Warnings etc:** *Contra-indications* – Gastro-intestinal or urinary obstruction, known hypersensitivity to the drug and to bromides. Extreme caution is required when administering Mestinon to patients with bronchial asthma. *Warnings* – care should also be taken in patients with bradycardia, recent coronary occlusion, hypotension, vagotonia, peptic ulcer, epilepsy or Parkinsonism. Lower doses may be required in patients with renal disease. *Use in pregnancy:* The safety of Mestinon during pregnancy or lactation has not been established. Experience with Mestinon in pregnant patients with Myasthenia Gravis has revealed no untoward effects. Negligible amounts of Mestinon are excreted in breast milk but due regard should be paid to possible effects on the breast-feeding infant. *Side effects:* These may include nausea and vomiting, increased salivation, diarrhoea and abdominal cramps. *Drug interactions* – None known. **Pharmaceutical Precautions:** *Storage* – Recommend maximum storage temperature 25ºC. Protect from light and moisture. **Legal Category:** POM. **Package Quantities:** Amber glass bottles with aluminium screw caps and desiccant, containing 200 tablets. **Basic NHS Price:** £50.15. **Product Licence Number:** PL 15142/0006. **Product Licence Holder:** ICN Pharmaceuticals Ltd, Cedarwood, Chineham Business Park, Crockford Lane, Basingstoke, Hampshire. RG24 8WD.

References:

1. Sharma KR. Myasthenia Gravis: a critical review. *IM Intern Med* 1996; August: 47-69
2. Drachman DB. Myasthenia Gravis. *N Eng J Med* 1994; **330:** 1797-1810
3. Buckley C. Diagnosis and treatment of Myasthenia Gravis. *Prescriber* 2000; **11**(Issue 22); 107-113
4. Vincent A and Drachman DB. Myasthenia Gravis. *Neuromuscular disorders* 2001; **11:** 159-188

Date of Preparation: May 2003

VP006/0504

VALEANT Pharmaceuticals Ltd.

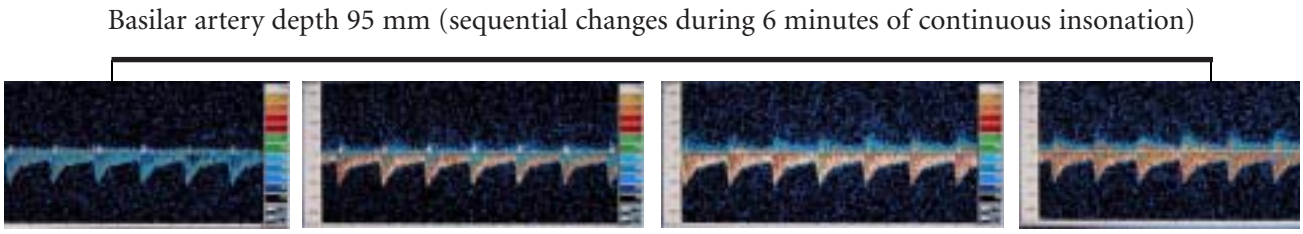


Figure 2. Shows SVK (white triangles) occurring at peak systole. During insonation the SVK disappears (left to right) to reveal a small vessel waveform. This patient had trigeminal neuropathy for 6 weeks prior to insonation. Sensation returned on opening the SVK signal.

Case 1.

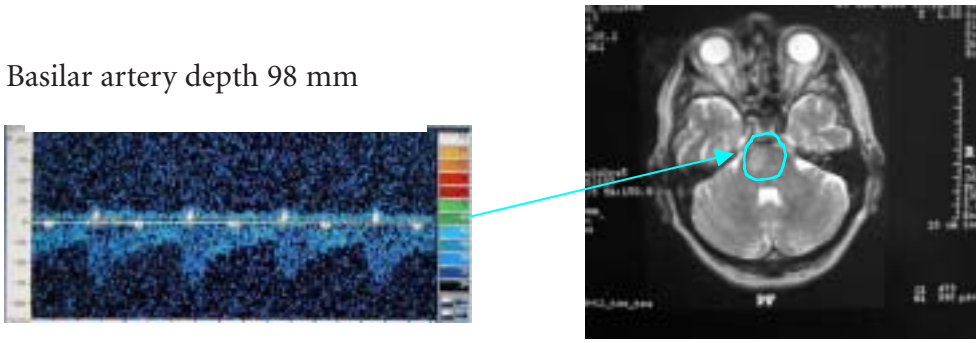


Figure 3. SVK (white triangles) seen in spectra obtained from the basilar artery (Left). This was associated with a hyperintense area in the right paramedian area of the Pons on T2-weighted MRI (Right)

Case 2.

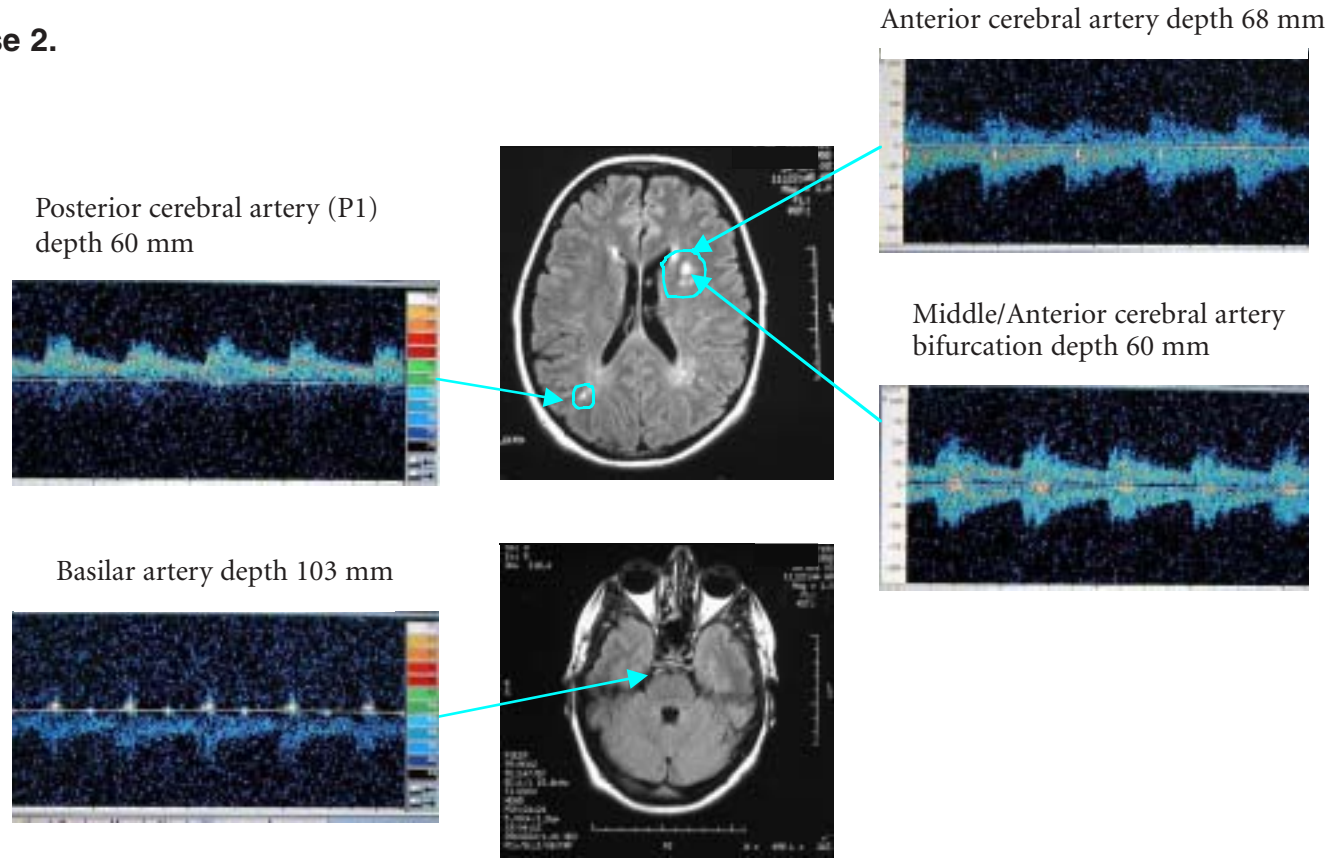


Figure 4. Knock is shown at peak systole in the anterior cerebral artery (top right) and Posterior cerebral artery (top left). A bruit was found at the MCA/ACA junction (middle right). This was associated with hyperintense areas on FLAIR MRI (middle top). SVK was found in the Basilar (bottom left). The brain stem was normal (middle bottom).

consistent with small vessel occlusive disease (SVD). These signals were associated with knock in the left anterior cerebral artery (ACA), the posterior cerebral artery and a bruit at the ACA/middle cerebral artery junction. This patient also had SVK to the right of the basilar artery as per Case 1 with a normal brain-stem image on MRI. Prior to insonation she had been symptomatic for over 48 hours. Continuous insonation of the basilar SVK improved flow and relieved her symptoms. Recovery occurred on arterial opening.

Case 3[8] is a 58 year old woman with known hypertension and hyperlipidaemia with a strong family history of ischaemic heart disease who presented with sudden onset of right hemisensory loss, tinnitus, vertigo and mild right hemiplegia. She was examined at 21 hours post-onset and then again at 26 hours post-onset (24 hour cut-off for the WHO definition of stroke) with no change in her signs or symptoms. SVK was then identified at 72 mm through the transforaminal window and this opened during targeted insonation. This was associated with immediate and full clinical recovery. This patient was CT and MRI negative. For a 'Quicktime' movie clip, see rtsp://pilton.ucs.ed.ac.uk:554/gmed/psyme/newtreat.mov[8]
NB. You will need a minimum 256k connection to view this 98mb clip.

Conclusions and implications:
These cases serve to illustrate that TCD can detect SVD in the form of "small vessel knock" in patients who have either MRI positive or negative[7,9] stroke-like deficits. If the MRI and CT scans are negative, targeted SVK insonation consistently results in small vessel recanalisation and clinical recovery over an extensive therapeutic window. This discovery provides evidence that salvageable brain tissue in the ischaemic penumbra of SVD can be found over a much larger time period than that following large vessel occlusion. This may explain the difference in clinical benefit following recanalisation between large[3] and small vessel occlusion. It is possible that the ischaemic penumbra for SVD may last as long as the collateral blood flow persists. It is also possible, that variations in the degree of collateral flow could mean that SVK will be found in a spectrum of disease ranging from asymptomatic occlusion (excellent collateral flow) through transient ischaemia, to salvageable stroke (Cases 2 & 3) and finally to established permanent stroke (poor collateral flow, MRI and CT positive) (Case 1).

The mechanism by which ultrasound induces SVK recanalisation is unknown but has to be either a direct physical action on the clot[10,11] or indirectly via the endothelium. The low power and higher frequency used here with diagnostic TCD favours the latter mechanism. Ultrasound produces cellular shear stress by cavitation[12] and it has also been shown that minimal endothelial shear stress results in the release of both endogenous tPA[13] and nitric oxide[14] from endothelium. Thus, targeted insonation may simulate flow stress resulting in vasodilatation, endogenous thrombolysis and recanalisation. Clinical recovery occurs if salvageable brain tissue still exists distal to the site of occlusion and is likely to depend on both the size of the ischaemic area and collateral blood flow. Targeted SVK insonation is also likely to be important since non-targeted ultrasound could redirect collateral blood flow away from the ischaemic area by vasodilating arteries supplying non-ischaemic areas. This is analogous to the paradoxical fall in cerebral blood flow ipsilateral to a critically stenosed carotid artery when contralateral arteries are dilated during CO^2 inhalation.

Randomised control trials are now needed to confirm these findings, to optimise treatment and to answer some of the above hypotheses. However, this discovery offers the exciting possibility of an effective, non-invasive, safe treatment for all SVD stroke, including vascular dementia, which can be provided over a considerable time window.

Conflict of interest: A patent has been applied for the targeted ultrasound treatment of small vessel occlusive disease with an exclusive licence to the NHS.

References

1. Fisher M. *The ischemic penumbra: Identification, evolution and treatment concepts.* Cerebrovasc Dis. 2004;17 Suppl 1:1-6.
2. Donnan GA, Howells DW, Markus R, Toni D, Davis SM. *Can the time window for administration of thrombolytics in stroke be increased?* CNS Drugs. 2003;17:995-1011.
3. Alexandrov AV, Demchuk AM, Burgin WS, Robinson DJ, Grotta JC. *Ultrasound-enhanced thrombolysis for acute ischemic stroke: Phase I. Findings of the clotbust trial.* J Neuroimaging. 2004;14:113-117.
4. Wijdicks EF. *The diagnosis of brain death.* N Engl J Med. 2001;344:1215-1221.
5. Alexandrov A. *Practical models of cerebral haemodynamics and waveform recognition. In: Alexandrov A, ed.* Cerebrovascular ultrasound in stroke prevention and treatment. Blackwell Publishing; 2004:62-78.
6. Alexandrov A, Neumyer MM. *Diagnostic criteria for cerebrovascular ultrasound. In: Alexandrov A, ed.* Cerebrovascular ultrasound in stroke prevention and treatment. Blackwell Publishing; 2004:81-129.
7. Syme PD. *Transcranial doppler ultrasonography detection of small vessel knock in patients with MRI-negative stroke-like deficits.* 5th World Stroke Congress. 2004:141.
   http://www.geriatric.med.ed.ac.uk/paul_syme.htm
8. Syme PD. *A case of hemianaesthesia.* 2004.
   rtsp://pilton.ucs.ed.ac.uk:554/gmed/psyme/newtreat.mov[8]
9. Ay H, Buonanno FS, Rordorf G, Schaefer PW, Schwamm LH, Wu O, Gonzalez RG, Yamada K, Sorensen GA, Koroshetz WJ. *Normal diffusion-weighted MRI during stroke-like deficits.* Neurology. 1999;52:1784-1792.
10. Francis CW, Onundarson PT, Cartensen EL, Blinc A, Meltzer RS, Schwartz K, Marder VJ. *Enhancement of fibrinolysis in vitro by ultrasound.* J Clin Invest. 1992;90:2063-2068.
11. Behrens S, Daffertshofer M, Speigel D, Hennerici M. *Low-frequency, low-intensity ultrasound accelerates thrombolysis through the skull.* Ultrasound in Medicine & Biology. 1999;25:269-273.
12. Tegeler CH, Ratanakorn D. *Physics and principles. In: Babikian VL, Weschsler LR, eds.* Transcranial doppler ultrasonography. Butterworth-Heinemann; 1999.
13. Diamond SL, Eskin SG, McIntire LV. *Fluid flow stimulates tissue plasminogen activator secretion by cultured human endothelial cells.* Science. 1989;243:1483-1485.
14. Ozawa N, Shichiri M, Iwashina M, Fukai N, Yoshimoto T, Hirata Y. *Laminar shear stress up-regulates inducible nitric oxide synthase in the endothelium.* Hypertens Res. 2004;27:93-99.

Correspondence to:
Dr Paul Syme
Borders General Hospital
Melrose, Roxburghshire
Scotland TD6 9BD
Email:
paul.syme@borders.scot.nhs.uk
or
p.d.syme@btinternet.com

Musculoskeletal Complications of Neurological Conditions

Dr Rory O'Connor is a Rehabilitation Consultant in the Leeds Teaching Hospitals NHS Trust, with an interest in neurological rehabilitation. He trained in the National Rehabilitation and Beaumont Hospitals in Dublin, and was a Research Fellow in the Institute of Neurology in London. His research interests include outcome measurement in rehabilitation and quality of life after neurological injury.

Introduction

Physically disabling neurological conditions can result in secondary musculoskeletal complications that limit patients' activities even further. These secondary complications can develop at any stage after the onset of a neurological illness, and the ability of clinicians to recognise and treat these complications will improve patients' functioning. Rehabilitation physicians have traditionally come from a neurological or rheumatological background, and current training in rehabilitation medicine includes rotations in both neurology and rheumatology. Rehabilitation physicians are therefore well placed to assess and treat patients with neurological conditions who have developed secondary musculoskeletal complications.

The impairments caused by neurological conditions can result in direct degenerative complications in skeletal and soft tissues. Complications may also arise secondarily to the neurological condition or its treatment. As trauma is a common cause of neurological deficits, patients who have sustained trauma often present with concomitant musculoskeletal injuries. Finally, the sudden onset of neurological symptoms may herald an underlying rheumatological condition.

Direct Degenerative Complications

Musculoskeletal problems can be a direct consequence of the neurological condition resulting from decreased or increased muscle activity around a joint. For instance, imbalance of the muscles of the rotator cuff in patients with stroke can contribute to post-stroke shoulder pain[1]. The condition is more common in patients who had degenerative shoulder conditions prior to their stroke. Post-stroke shoulder pain is, however, multifactorial and its treatment requires a concerted multidisciplinary and multimodality approach that is beyond the scope of this article.

Neck and shoulder pain can also be a feature of a spinal cord injury (SCI)[2]. This is typically seen in mid-cervical lesions where spasticity in the trapezii muscles elevate the shoulders without opposition from antagonists, the so-called "coat-hanger" syndrome. This painful condition is generally preventable by early upper limb passive range of movement exercises and judicious use of anti-spasticity medications.

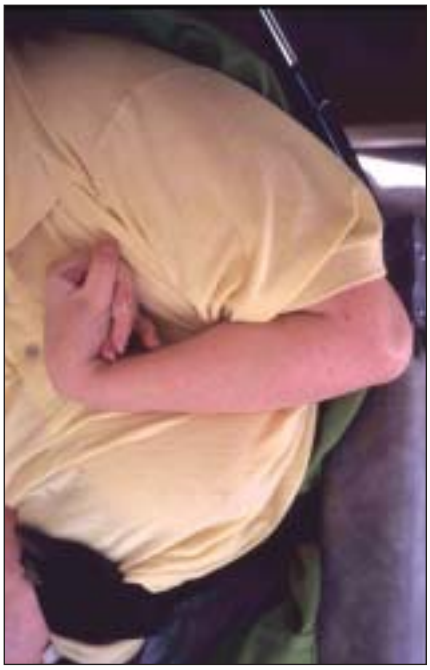


Figure 1. Wrist dislocation secondary to traumatic brain injury induced muscle spasticity.

Neurological conditions also result in patients putting extra stress across upper limb joints, which are not designed to take body weight. Intra-articular pressure in the shoulders can be as much as five times body weight when transferring from chair to chair, for example. Appropriate transferring technique with the use of a transfer board can alleviate these pressures and prevent further complications.

Intense upper limb muscle spasticity, as seen in traumatic brain injury (TBI), for instance, is frequently associated with wrist joint dislocation (figure 1). Treatment involves management of pain and spasticity by appropriate splinting, therapy and medication.

Wrist problems can also occur when patients use wheelchairs or crutches for mobility. Prolonged wrist extension when holding the handle of an elbow crutch or gripping a wheelchair rim can result in carpal tunnel syndrome. Indeed, the advice of SCI teams to patients in the past was to relieve pressure on their ischial tuberosities by pushing up on their wheelchair rims every 15 minutes. This resulted in a generation of SCI patients with iatrogenic carpal tunnel syndrome. Management is similar to that in idiopathic carpal tunnel syndrome, with rest, splinting and steroid injection as appropriate. If operative management is required it is necessary to arrange alternative mobility aids for patients, such as powered wheelchairs, while they are recovering from the surgery.

The widespread increased spasticity and dystonic movements associated with cerebral palsy frequently result in degenerative joint disease[3,4]. As a further complication, asymmetrical development of the spine in patients with hemiplegia or diplegia produces scoliosis, which can progress onto myelopathy[5,6]. For adults with cerebral palsy, joint pain is a common limiting factor with 67% to 84% of patients reporting large joint pain. Early detection and treatment of spinal and large joint degeneration particularly during growth spurts can reduce the degenerative complications associated with cerebral palsy.

It is not all bad news however, there is well-documented evidence of reduction in rheumatoid arthritis, osteoarthritis, gout and scleroderma in the parts of the body affected by neurological impairments[7–9]. The complex neuroendocrine basis of these conditions can be altered by neurological conditions resulting in reduced joint inflammation.

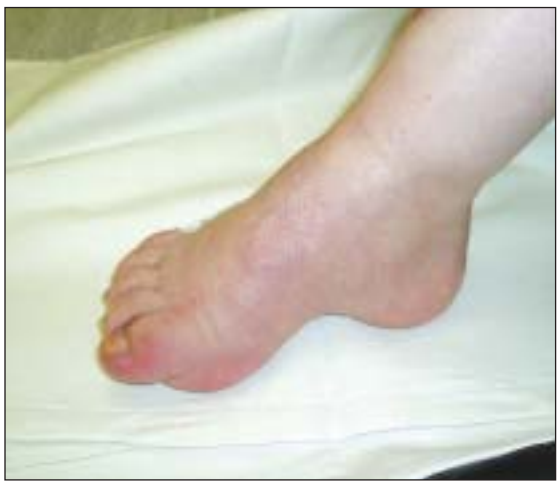


Figure 2. Ankle, tarsal and metatarsal neuropathic joints in a patient with diabetes mellitus.

Secondary to Neurological Injury

A wide range of secondary musculoskeletal problems can occur due to the neurological impairments caused by the original neurological condition. The prototypical condition in this respect is the neuropathic or Charcot joint. This is seen most commonly in the UK in patients with diabetic neuropathy, who develop neuropathic tarsal, metatarsal and ankle joints (figure 2)[10]. Upper limb neuropathic joints are seen in patients with syringomyelia. Worldwide, neurosyphilis and leprosy are also common causes of neuropathic joints. The aetiology of the joint destruction is due to repeated trauma to the anaesthetic limb, which is not protected by nociceptive and propioceptive mechanisms. Neuropathic joints are swollen and unstable, with relatively less pain than might be expected, although rarely pain free as commonly reported. Radiologically, subchondral lucencies are the earliest signs, progressing to microfractures, articular irregularities and increased uptake on the delayed phase of an isotope bone scan. Treatment is, generally, prevention of the neuropathy and orthotic protection of the neuropathic joint. More recently, bisphosphonates have been demonstrated to be useful in the amelioration of joint destruction and pain[11].

Another bone disease directly related to the patient's neurological condition is heterotopic ossification (HO). This is a condition of uncertain aetiology characterised by an imbalance between bone formation and resorption. New bone is laid down, generally in the soft tissues surrounding a large joint, within the area of impaired neurology. For patients with paraplegia, it is mainly in the hips and knees, but for patients with tetraplegia, the shoulders and elbows can also be involved (figure 3). The incidence of heterotopic ossification in spinal cord injury is 20% to 30% within two to five months of injury[12]. The diagnosis is established by a combination of raised bone specific alkaline phosphotase and increased uptake on isotope bone scan[13]. However, these tests are rarely entirely sensitive or specific, and ultrasonography, computed tomography or magnetic resonance imaging have all been demonstrated to be useful in the early detection of HO (figure 4)[14]. Treatment is conservative in the first instance with early immobilisation of the joint and high dose non-steroidal anti-inflammatory drugs. Bisphosphonates have also been reported to be useful and my current treatment preference is oral alendronate, weekly for six months. If these measures are unsuccessful, surgery followed by radiotherapy may be required to release an ossified joint[15].

Impairments of muscle function may result in muscle changes including muscle contractures, fibrosis and atrophy. Changes will also occur in tendons, ligaments and joint capsules. Contractures affect 9% of patients with SCI and are increased by spasticity, concomitant TBI, pressure sores and delay in transfer for rehabilitation[16]. Prevention includes proper positioning, therapy and splinting in conjunction with spasticity management. Treatment has largely been unsuccessful, with surgical release of contracted muscles being the only effective therapy.

Musculoskeletal infections are also more common in patients with neurological conditions. Osteomyelitis and septic arthritis have been reported in up to 13% of patients following SCI. Some of these infections have been related to overlying pressure sores. For patients with TBI, increased muscle spasticity, unexplained pyrexias and decreased cognitive ability can be indicators of underlying bone or joint sepsis.

Osteoporosis is another musculoskeletal complication that can be directly attributable to the immobilisation caused by neurological impairments. High doses of steroids used for immunosuppression, may also be implicated in bone loss. For patients with SCI, bone mass is reduced to 70% of normal within six months of injury. The bone loss is principally from the femoral shafts, which may be injured in subsequent minor falls or trauma. Whilst fractures that occur concomitantly with a SCI are best treated operatively, fractures in patients with established SCI and osteoporosis should be managed conservatively[2].

Associated with Neurological Injury

Musculoskeletal injuries that occurred at the same time as the neurological lesion, in patients injured as a result of trauma, may complicate a patient's recovery. Thirty to forty percent of patients with TBI will have sustained musculoskeletal injuries, including spinal column injuries, at the time of the original injury. Long bone fractures are present in 20% of patients with traumatic SCI. Secondary injuries may also occur as a result of seizures or falls in patients with impaired balance. Bony healing is relatively unaffected in patients with neurological injuries; however, closed operative reduction of fractures is the preferred method of treatment as it reduces barriers to rehabilitation. For instance, self-propulsion in a wheelchair can be achieved much earlier without the encumbrance of an external fixator on a fractured radius and ulna. Bone healing is relatively unaffected early after neurological impairment; however, callus formation may be over-exuberant due to heterotopic ossification, impairing joint mobility if the fracture site is close to a joint.

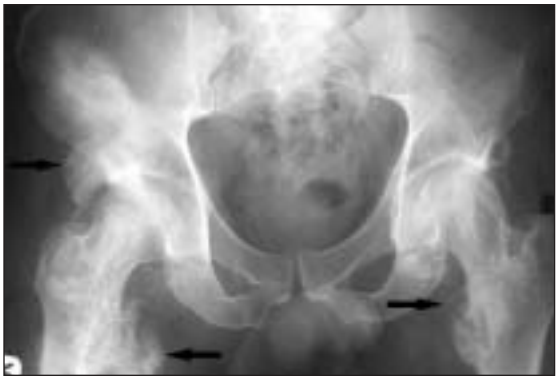


Figure 3. Heterotopic ossification seen on a pelvic radiograph of a 40 year old man with T4 paraplegia. Arrows indicate ossification at both hips and right iliac crest.

Figure 4. Computed tomography of the pelvis demonstrating ossification in the iliopsoas muscles bilaterally.

Correspondence to:
Rory O'Connor MB DCH MRCP
National Demonstration Centre in Rehabilitation
Leeds Teaching Hospitals NHS Trust
Leeds LS7 4SA
Tel: 0113 392 4900
Fax: 0113 392 4942
E-Mail:
Rory.O'Connor@leedsth.nhs.uk

Rheumatological Neurology

Finally, a patient presenting with neurological symptoms may be found to have an underlying musculoskeletal condition. Not only does rheumatoid arthritis (RA) result in significant musculoskeletal disability, it is also one of the commonest causes of secondary neurological impairment[17]. There is an increased risk of ischaemic stroke, which can be explained by a combination of increased diastolic blood pressure, and increased fibrinogen levels and plasma viscosity[18]. This is in addition to the effect of the antiphospholipid syndrome, which commonly accompanies rheumatological conditions. RA is also associated with neurological entrapment syndromes, ranging from atlanto-axial subluxation (approximately 5% of patients with RA)[19] to compressive neuropathies at the elbow and wrist.

Ankylosing spondylitis (AS) can be a direct cause of a compressive myelopathy. Patients with AS are also at increased risk of SCI following minor trauma. AS may be a contributory factor in cerebral ischaemia, particularly posterior circulation infarcts, if the vertebral arteries are compromised by spondolytic bone.

Marfan's syndrome can present with a similar range of neurological impairments. Aortic valve disease will predispose patients to cerebral ischaemia, while aortic dissection can result in paraplegia at T4, if the cord's vascular supply is compromised.

Conclusion

The impact of musculoskeletal problems on the function of patients with neurological conditions must be appreciated and treated. With the majority of musculoskeletal problems, preventative strategies, which are key components of the multidisciplinary rehabilitation programme, are most effective. Treatments must focus on improving patients' function and preventing secondary disability.

Acknowledgements

I am grateful for the comments of my colleagues Drs Bipin Bhakta and Vera Neumann. I would also like to thank Dr Brian McGlone who provided the radiographs.

References

1 Jackson D, Turner-Stokes L, Khatoon A, Stern H, Knight L, O'Connell A. *Development of an integrated care pathway for the management of hemiplegic shoulder pain.* Disabil Rehabil 2002;24:390-398.
2. Goldstein B. *Musculoskeletal conditions after spinal cord injury.* Phys Med Rehabil Clin N Am 2000;11:91-108.
3. Hodgkinson I, Jindrich ML, Duhaut P, Vadot JP, Metton G, Berard C. *Hip pain in 234 non-ambulatory adolescents and young adults with cerebral palsy: a cross-sectional multicentre study.* Dev Med Child Neurol 2001;43:806-808.
4. Gajdosik CG, Cicirello N. *Secondary conditions of the musculoskeletal system in adolescents and adults with cerebral palsy.* Phys Occup Ther Pediatr 2001;21:49-68.
5. Levine RA, Rosenbaum AE, Waltz JM, Scheinberg LC. *Cervical spondylosis and dyskinesias.* Neurology 1970;20:1194-1199.
6. Ko HY, Park-Ko I. *Spinal cord injury secondary to cervical disc herniation in ambulatory patients with cerebral palsy.* Spinal Cord 1998;36:288-292.
7. Sethi S, Sequeira W. *Sparing effect of hemiplegia on scleroderma.* Ann Rheum Dis 1990;49:999-1000.
8. Baerwald CG, Panayi GS. *Neurohumoral mechanisms in rheumatoid arthritis.* Scand J Rheumatol 1997;26:1-3.
9. Needs CJ, Webb J, Tyndall A. *Paralysis and unilateral arthritis: is the association established?* Clin Rheumatol 1985;4:176-80.
10. Sinha S, Munichoodappa CS, Kozak GP. *Neuro-arthropathy (Charcot joints) in diabetes mellitus (clinical study of 101 cases).* Medicine 1972;51:191-210.
11. Selby PL, Young MJ, Boulton AJ. *Bisphosphonates: a new treatment for diabetic Charcot neuroarthropathy?* Diabet Med 1994;11:28-31.
12. Subbarao JV, Garrison SJ. *Heterotopic ossification: diagnosis and management, current concepts and controversies.* J Spinal Cord Med 1999;22:273-283.
13. Chantraine A, Nusgens B, Lapiere CM. *Biochemical analysis of heterotopic ossification in spinal cord injury patients.* Paraplegia 1995;33:398-401.
14. Ledermann HP, Schweitzer ME, Morrison WB. *Pelvic heterotopic ossification: MR imaging characteristics.* Radiology 2002;222:189-195.
15. McAuliffe JA, Wolfson AH. *Early excision of heterotopic ossification about the elbow followed by radiation therapy.* J Bone Joint Surg Am 1997;79:749-755.
16. Dalyan M, Sherman A, Cardenas DD. *Factors associated with contractures in acute spinal cord injury.* Spinal Cord 1998;36:405-8.
17. McEntegart A, Capell HA, Creran D, Rumley A, Woodward M, Lowe GD. *Cardiovascular risk factors, including thrombotic variables, in a population with rheumatoid arthritis.* Rheumatology 2001;40:640-4.
18. del Rincon ID, Williams K, Stern MP, Freeman GL, Escalante A. *High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors.* Arthritis Rheum 2001;44:2737-45.
19. Riise T, Jacobsen BK, Gran JT. *High mortality in patients with rheumatoid arthritis and atlantoaxial subluxation.* J Rheumatol 2001;28:2425-9.

Medtronic

SYNCHROMED® II

PROGRAMMABLE INFUSION SYSTEM

The Next Generation for your intrathecal baclofen infusion patients - Smaller, Simpler, Smarter

For further information, contact Clive Woodard, UK Manager at clive.woodard@medtronic.com

How I Manage Supratentorial Meningiomas

Anne Moore is a Consultant Neurosurgeon at the South West Neurosurgery Centre, Derriford Hospital, Plymouth, UK. She qualified from the Royal London Hospital, London, and trained in neurosurgery at Atkinson Morley's Hospital, the National Hospital for Neurology and Neurosurgery and Great Ormond Street Hospital, London. She spent 11 years as a Consultant at Atkinson Morley's Hospital before moving to the West Country. Her special interest is in anterior skull base surgery.

Meningiomas comprise 15 – 20% of all symptomatic intracranial neoplasms. They are more common in women, where some are hormonally sensitive. Predisposing factors also include neurofibromatosis and radiation exposure, e.g. childhood leukaemias and in these cases, the tumours are likely to occur earlier, be multiple and behave in a more aggressive manner. However the vast majority of meningiomas are benign (WHO Grade 1); only 5% are atypical (Grade 2) and 1% malignant (Grade 3).

Presentation

Meningiomas may present with focal neurological deficits depending on their site of origin, or with seizures and it is unusual for the first presenting symptoms to be related to raised intracranial pressure. Tumours affecting the skull base may present with proptosis (see fig.1) or visual disturbance due to orbital involvement. Increasingly, meningiomas present as an incidental finding, discovered after a scan for an unrelated problem.

Investigations

The initial scan is often a CT, showing a homogeneously enhancing mass with a dural base and a variable degree of surrounding oedema (see fig.2). CT scanning can be useful in showing the degree of calcification of the tumour and delineating the bony anatomy, particularly in meningiomas of the skull base. MRI scanning gives more information regarding the three dimensional anatomy of the tumour and involvement of adjacent neuro-vascular structures (see fig.3), especially dural venous sinuses. In these cases angiography may help to define the involvement of major arteries and the patency of dural venous sinuses (see fig.4), and also allows embolisation of the tumour preoperatively in order to diminish operative blood loss.

Observation

A 'watch and wait' policy is often the most appropriate, particularly where the meningioma has been an incidental finding, as studies have shown that two thirds do not progress over time - although follow up periods were short in this study[1].

Some patients find the knowledge of their intracranial tumour too stressful and choose surgery. In older patients with no or minimal neurological deficits, who present with a single seizure, it may be appropriate to treat with anticonvulsants and to scan annually. Certain meningiomas, especially those of the central skull base, may appear alarmingly large on the scan while causing only minimal symptoms (see fig.5). For these, surgery carries not inconsiderable risks of morbidity and the tumour may progress very slowly. Hydroxyurea has been used to treat patients with those tumours deemed inoperable, but although results are encouraging, the numbers studied are small[2]. Some patients choose conservative management initially and this is not unreasonable as long as the tumour has little surrounding oedema or mass effect.

Surgery

Surgery can offer a chance of cure as well as improvement in neurological deficits. However, there is a recurrence rate of approaching 10% even after seemingly complete excision. The rate of recurrence depends on the extent of tumour resection and the removal or coagulation of the associated dura (see table 1). Skull vault meningiomas are more easily removed completely than those of the skull base and recurrence rates reflect this.

In order to achieve total excision, surgery must completely expose the tumour and its dural origin with minimal brain retraction. The patient should be treated preoperatively with Dexamethasone (16mg daily) and brain relaxation may be aided by Mannitol and drainage of cerebrospinal fluid.

In terms of the surgery itself, some advocate elective non-dominant frontal lobectomy for large olfactory groove meningiomas in order to avoid excessive brain retraction whilst skull base approaches e.g. orbito-fronto-zygomatic, aid access by decreasing the operative working distance. Early devascularisation of the tumour by obliteration of the feeding arteries is helpful, followed by internal decompression and extracapsular dissection to minimise damage to the surrounding brain. Early identification of cranial nerves and major arteries allows their preservation and if possible, no veins are sacrificed. Although it is said to be acceptable to sacrifice the anterior third of the superior sagittal sinus, even in this region venous infarction may occur. Only if the sinus is completely occluded by collateral tumour, and there are therefore collateral venous drainage channels, may it be resected. Otherwise the tumour must be resected from the sinus dura as far as possible and its origin coagulated.

Follow Up

Follow up depends on the completeness of excision and the histology of the tumour. Benign tumours have a 5

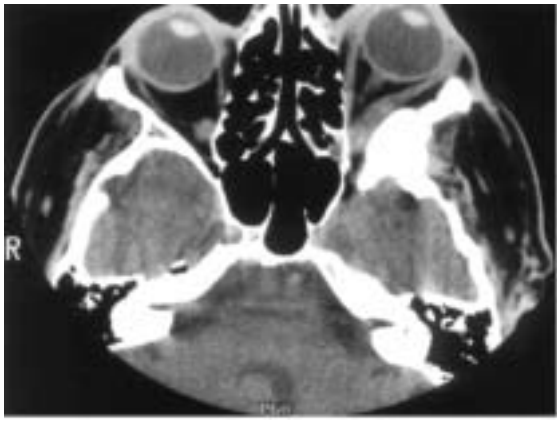


Figure 1. Hyperostotic meningioma of the left sphenoid wing causing proptosis.

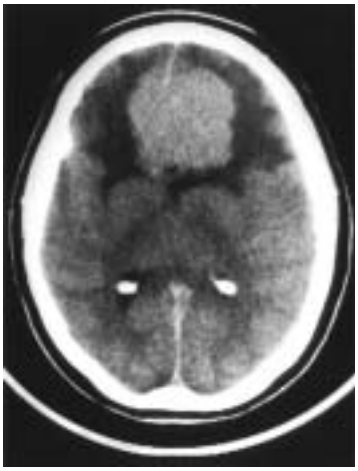


Figure 2. Post-contrast CT head scan showing a large enhancing falcine meningioma with considerable surrounding oedema in the frontal lobes.

year recurrence rate of 3% whereas that for atypical tumours is 38%, and anaplastic/malignant, 78%[4]. Malignant meningiomas should have adjuvant radiotherapy and this is probably also true for incompletely excised atypical meningiomas, although there is little conclusive evidence for this. For the rest, a baseline MRI scan should be followed by further annual scans, at least initially. Any sign of recurrence/progression is an indication for radiotherapy, either conventional or stereotactic radiotherapy. Both have shown control rates approaching 95%. 'Control' implies 'alive with disease' and this is certainly true of many patients with skull base meningiomas. Although most learn to live with the condition, it can be very stressful as recurrence can mean further surgery despite radiotherapy and an essentially benign tumour can still prove to be a fatal condition.

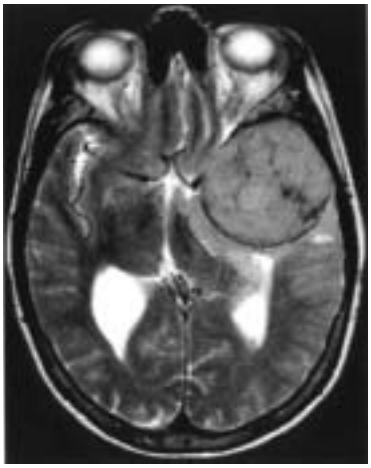


Figure 3. T2 weighted MRI scan showing a large left temporal fossa meningioma. Note the proximity of the proximal middle cerebral artery on the medial aspect of the tumour.

Table 1

Simpson grading and recurrence rate.[3]

Grade	Tumour Resection	Recurrence Rate
I	Macroscopically complete removal of dura, bone	9%
II	Macroscopically complete removal, dural coagulation	19%
III	Complete tumour resection, dura not coagulated	29%
IV	Partial removal	44%
V	Simple decompression	

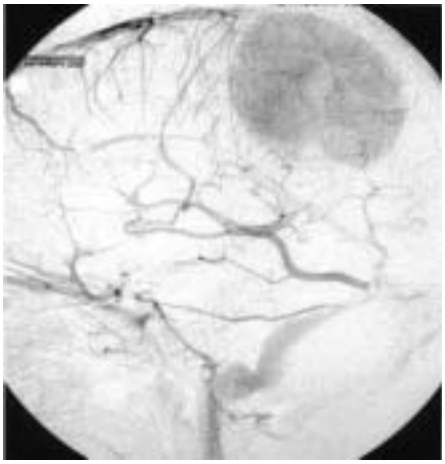


Figure 4. Venous phase of lateral carotid angiogram. The tumour blush from this large parasagittal meningioma is obvious. Obstruction of the superior sagittal sinus is recognised due to minimal distal flow. The venous drainage has been diverted via deep cerebral veins to the sigmoid sinus.

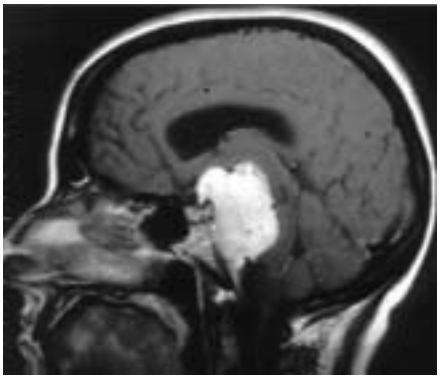


Figure 5. A very large petroclival meningioma causing severe compression of the brainstem.

References

1. Kuratsu JI, Kochi M, Ushio Y. *Incidence and clinical features of asymptomatic meningiomas.* J Neurosurg 2000; 92:766-70.
2. Mason WP, Gentili F, Macdonald DR, Hariharan S, Cruz CR, Abrey LE. *Stabilization of disease progression by hydroxyurea in patients with recurrent or unresectable meningioma.* J Neurosurg 2002; 97(2):341-6.
3. Simpson D. *The recurrence of intracranial meningiomas after surgical treatment.* J Neurol Neurosurg Psychiat 1957; 20: 22-39.
4. Jaaskelainen J, Haltia M, Servo A. *Atypical and anaplastic meningiomas: radiology, surgery, radiotherapy and outcome.* Surg Neurol 1986; 25: 233-42.

Correspondence to:
Anne Moore BSc FRCS
Consultant Neurosurgeon
South West Neurosurgery Centre
Derriford Hospital
Plymouth
PL6 8DH
Tel: 01752 517518
Fax: 01752 763395
E-Mail:
Anne.Moore@phnt.swest.nhs.uk

Inflammatory diseases of the CNS II: Meningitis and cerebral abscess

Dr Susan Robinson is a consultant neuropathologist in Glasgow. Previously she worked as a consultant neuropathologist at King's College Hospital in London.

Dr William Stewart is a Specialist Registrar in Neuropathology in the Institute of Neurological Sciences in Glasgow. His current research interests include risk factors for neurodegenerative disease.

Introduction

Infections of the leptomeninges and subarachnoid space may arise as a consequence of viral, bacterial or fungal pathogens (table). Typically, organisms gain entry to the CNS through haematogenous spread from a systemic source of sepsis or through direct spread from the skull or as a complication of a surgical procedure. In this the second of a series of articles on the neuropathology of Inflammatory Diseases of the CNS we provide an overview of the approach to the neuropathological assessment of meningitis, illustrated with examples of the common abnormalities which may be encountered.

Background Circumstances

A vital component in the pathology assessment of any case is a review of all pertinent, clinical information. Thus, where meningitis is suspected clinically, information regarding the symptoms at presentation, intercurrent illnesses, immune status, prior medical history, results of all investigations and management of the acute presentation (particularly any antimicrobial therapy employed) should, ideally, be available to the reporting pathologist. This information then guides not only the appropriate course of further investigations but will also inform the health and safety procedures which should be employed in the mortuary and/or laboratory.

As noted, meningitis generally arises as a consequence of the direct or haematogenous spread of an organism to the CNS. Thus, in making as full an assessment as possible at autopsy it is preferable to perform a complete, 'unlimited' examination whereby all the major body cavities and organs are examined. However, if consent for an unlimited procedure cannot be obtained, it is still possible to perform a limited examination such as cranial cavity and contents only. Even in such limited examinations substantial information pertaining to the illness and its response to therapy can be obtained. Given this, where autopsy examination is desirable, it is often of value to discuss the case with a local pathologist prior to seeking consent from the next of kin. Common to all assessments of the brain in meningitis are a macroscopic inspection of the whole organ in situ, sampling of CSF/ tissue for culture, sectioning of the organ for further macroscopic examination (preferably after a suitable period of fixation) and sampling for histology.

Pathology

With these comments in mind regarding the general approach to autopsy examination in a case of suspected meningitis, we will now consider the typical patterns of pathology encountered and the common causative organisms involved.

Aseptic Meningitis

Aseptic meningitis describes a characteristically short-lived illness marked by headache, photophobia and neck stiffness. Typically, examination of CSF reveals a cellular specimen with the predominant cell type being lymphocytes, though in the early stages polymorphs may be present. In the great majority of cases (80% or more) the causative organism is a non-polio enterovirus though a number of other agents including a wide range of viruses, bacteria and drug reactions have been implicated[1,2]. Whilst CNS involvement is typically benign, occasional cases do appear at autopsy as a consequence of systemic manifestations of the pathogen (usually viral) such as myocarditis with associated arrhythmia and sudden death. Where described the pathology is of a normal or minimally swollen brain to naked eye examination. On histological inspection a mild lymphocytic infiltrate in the meninges and superficial perivascular spaces is typical.

Purulent (Acute Bacterial) Meningitis

A variety of bacterial species may give rise to purulent meningitis with the likely causative organism influenced by the age of the patient and their immune status (table). As such, in immunocompetent adults the commonest causative organisms identified are *Streptococcus pneumoniae, Neisseria meningitidis and Haemophilus influenzae B*[3]. These share a number of characteristics that contribute to both their incidence and their pathogenicity. They are commensal bacteria which are frequently isolated in samples from the nasopharynx of asymptomatic carriers. Furthermore, these organisms have a polysaccharide capsule that renders them resistant to macrophage digestion. Finally, they are capable of releasing a number of proinflammatory products which stimulate cytokine production and release from nearby endothelial cells and macrophages. This latter process culminates in the release of potent chemoattractants

Table: Common organisms associated with meningitis

Aseptic meningitis	
	non-polio enteroviruses, Herpes simplex virus 2, mumps, human immunodeficiency virus
Purulent meningitis	
Neonates	*group B streptococci, Escherichia coli, Klebsiella species, Listeria monocytogenes*
Adults	*Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitidis*
Granulomatous	
	Mycobacterium tuberculosis
Immune compromised	
	above + fungal (Cryptococcus neoformans, Candida species, Aspergillus)

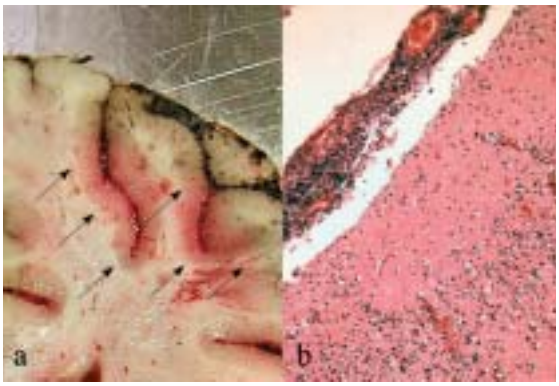


Figure 1: Purulent meningitis
(a) Coronal section of a cerebral hemisphere in a case of proven streptococcal meningitis in which, at autopsy, there was evidence of meningeal thrombophlebitis and superficial cortical infarction (arrows). (b) Microscopy shows a florid meningeal inflammatory cell infiltrate (H&E).

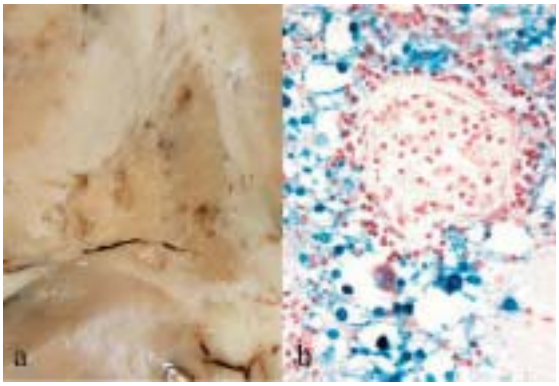


Figure 3: Cryptococcal Meningitis
(a) Coronal section through the basal ganglia showing the typical cysts. (b) The organisms are readily identified on histological section by staining for their mucopolysaccharide capsule (Alcian blue).

resulting in the migration of numerous neutrophil polymorphs to the region of infection, a characteristic feature of pyogenic infections. On cytological examination of CSF, there is, as might be expected, a florid neutrophil leukocytosis.

At autopsy the brain may appear diffusely swollen as a consequence both of oedema and hydrocephalus. Reflecting the dura reveals congested meningeal vessels and a typically purulent exudate within the subarachnoid space the distribution and nature of which may suggest the likely causative organism. Thus where *Strep. pneumoniae* is the pathogen the exudate often has a greenish hue and is more marked over the convexities whereas with many other organisms the exudate may be yellow and more marked basally. On sectioning the brain extension of infection to the ventricles (ventriculitis) may be present together with evidence of the complications of a pyogenic infection such as superficial cortical infarction (fig. 1a), meningeal thrombophlebitis and obstructive hydrocephalus. Histological examination in the early stages of the disease reveals a typically florid neutrophil infiltrate within the meninges with little extension along the penetrating cortical vessels (fig. 1b). With time this infiltrate may become more mixed (including lymphocytes and plasma cells). In many cases, whilst Gram staining of sections may be performed, prior treatment with antimicrobial agents can impair histological detection of organisms.

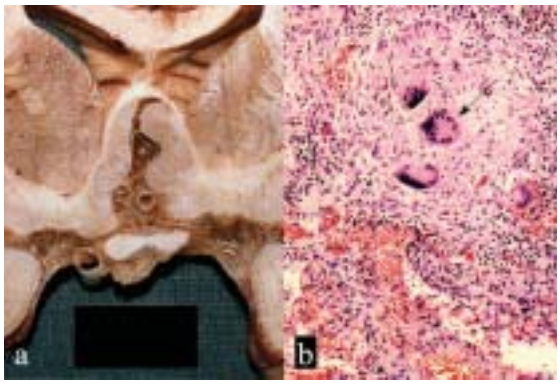


Figure 2: Granulomatous meningitis
(a) Coronal section of the cerebral hemispheres illustrating nodular, gelatinous thickening of the basal meninges. (b) Microscopy typically shows numerous granulomas with a necrotic centre and surrounding epithelioid macrophages. Langhan's giant cells may be present (arrow; H&E; images courtesy Prof. DI Graham).

Granulomatous Meningitis

In common practice granulomatous meningitis in the immunocompetent is most often a consequence of infection with *Mycobacterium tuberculosis* arising as a complication of a primary mycobacterial infection[1,3]. Macroscopically there is a typically nodular, gelatinous exudate more pronounced in the Sylvian fissures and over the base of the brain (fig. 2a). Frequently, evidence of obstruction to flow of CSF with associated hydrocephalus is present. On microscopy a meningeal inflammatory infiltrate consisting of lymphocytes, macrophages and granulomas composed of a central area of necrosis surrounded by epithelioid macrophages and lymphocytes is described (fig. 2b). In contrast to similar lesions which may be encountered elsewhere in the body, Langhan's giant cells can be infrequent in tubercle-related granulomas in the CNS[3]. Staining for acid and alcohol fast bacilli may reveal scattered organisms though, as with purulent meningitis, their detection can be difficult where appropriate therapy was commenced prior to death.

Meningitis in the Immunocompromised

In general the incidence of the commoner organisms associated with purulent and granulomatous meningitis is increased in the immunompromised state[2]. This is typified by the increased risk of pneumococcal infection which follows splenectomy and the increased incidence of tuberculous meningitis with AIDS. In addition, however, a number of other organisms rarely encountered in the immunocompetent may arise. Amongst these are the fungal pathogens of which *Cryptococcus neoformans, Candida albicans,* and *Aspergillus fumigatus* are most commonly associated with meningitis[4]. Cryptococcal meningitis is noteworthy as the commonest mycosis associated with AIDS[5]. On examination of CSF in cryptococcal meningitis the thickly encapsulated yeasts can occasionally be detected on staining the specimen with Indian ink. At autopsy the typical picture is of a pale yellow meningeal exudate over the vertex with multiple, small, mucoid, perivascular, 'soap bubble' cysts within the deep grey matter (fig. 3a). The histological picture varies from a mild meningeal inflammatory cell infiltrate through to a florid, granulomatous reaction with the inflammatory response in part dependent on the immune status of the host. Using appropriate stains the typical encapsulated organisms are readily identified (fig. 3b).

Cerebral Abscess

As with meningitis cerebral abscesses may arise as a consequence of direct spread from an adjacent source of infection or through haematogenous spread from elsewhere. Often the pattern of involvement and aetiological organisms reflect this distinction. Thus where the abscess arises as a consequence of direct spread, for example from a paranasal sinus, the lesion is most often solitary, adjacent to the site of the primary infection and associated with a typical isolate (eg *Streptococcus milleri*). In contrast abscesses of haematogenous origin are often multiple, centred on the grey/white boundary and are most common within the distribution of the middle cerebral artery reflecting their embolic nature. Risk factors associated with such cerebral abscesses include bacterial endocarditis, chronic pulmonary sepsis, cyanotic congenital heart disease and intravenous drug abuse. As such the range of pathogens reflects the source of infection with streptococci and staphylococci most commonly isolated. At autopsy the appearances vary depending on the age of the lesion with early lesions poorly demarcated and associated with focal swelling. As the lesion matures the typical picture develops of a fibrous capsule around a well-demarcated, purulent core.

References

1. Love S, Wiley CA. *Viral diseases.* In: Graham, D.I., Lantos, P.L., eds. Greenfield's Neuropathology vol II. London: Arnold, 2002: 1-105.
2. Love S. *Autopsy approach to infections of the CNS.* In: Love, S., ed. Current topics in pathology 95: Neuropathology. Berlin: Springer, 2001: p1-50
3. Gray F, Alonso, J-M. *Bacterial infections of the central nervous system.* In: Graham, D.I., Lantos, P.L., eds. Greenfield's Neuropathology vol II. London: Arnold, 2002: 151-193
4. Turner G, Scaravelli F. *Parasitic and fungal diseases.* In: Graham, D.I., Lantos, P.L., eds. Greenfield's Neuropathology vol II. London: Arnold, 2002: 107-150.
5. Burns DK, Risser RC, White CL. *The neuropathology of human immunodeficiency virus infection.* The Dallas, Texas experience. Arch Pathol Lab Med 1991, 115: 1112 1124

Correspondence to:
Dr Susan Robinson
Department of Neuropathology
Institute of Neurological Sciences
Southern General Hospital
Glasgow G51 4TF
Tel: (0141) 201-2050
Fax: (0141) 201 2998
E-Mail:
susan.robinson@sgh.scot.nhs.uk

If you would like your event listed in the next issue, send details to: Rachael Hansford on Fax: 0131 3131110 or E-Mail: AdvancesinCNR@aol.com by October 6th, 2004. A bumper version of events is available on our website at www.acnr.co.uk

2004

September

8th Congress of the European Federation of Neurological Societies
4-7 September, 2004; Paris, France
Tel. 0043 1 880 00 270
Fax. 0043 1 88 92 581
E. Headoffice@efns.org

The 8th Triennial Meeting of the International Basal Ganglia Society
5-9 September, 2004; Perthshire, Scotland
Tel. 0131 556 9245
E. katy@in-conference.org.uk

ECTRIMS 2004 - European Congress for Treatment and Research in Multiple Sclerosis
6-9 September, 2004; Vienna, Austria
Fax. +41 61 686 77 88
E. info@akm.ch

9th Annual Meeting of the International Functional Electrical Stimulation Society
6-9 September, 2004; Bournemouth, UK
Tel. 01722 429066
Fax. 01722 425263
www.ifessnet2004.tk
E. i.swain@salisburyfes.com

BSN Annual Meeting - Neuroendocrinology
7-9 September, 2004; Glasgow, UK
E. fran.ebling@nottingham.ac.uk

Microelectrode Techniques for Cell Physiology
8-22 September, 2004; Plymouth, UK
E. dogden@nimr.mrc.ac.uk,
www.ba.ac.uk/education/courses

2004 American Congress of Rehabilitation Scoiety/American Society of Neurorehabilitation
9-12 September, 2004; Florida, US
www.asnr.comr or www.acrm.org

25th Anniversary Conference of Headway, The Brain Injury Association
9-10 September, 2004; Stratford upon Avon, UK E.
eventsandconferences@headway.org.uk

International Pharmaco-EEG Meeting
10-12 September, 2004; Antwerp, Belgium
Fax. +31 412 662 506
E. ge.ruigt@organon.com

7th International Neurotrauma Symposium
12-16 September, 2004; Adelaide, Australia
Tel. +61 8 8379 8222
Fax. +61 8 8379 8177
E. events@plevin.com.au
www.plevin.com.au/ints2004

1st North American / 5th National Conference on Shaken Baby Syndrome
12-15 September, 2004; Montreal, Canada
Fax. 001 801 627 3321
E. sefranks@mindspring.com

British Aphasiology Society Therapy Symposium Conference
13-14 September, 2004; Liverpool, UK
Tel. Alex Stirling on 0151 529 4986
E. alex.striling@thewaltoncentre.nhs.uk

32nd Annual Scientific Meeting of the British Psychophysiology Society
13-15 September, 2004; Manchester, UK
E. Dr D Bentley,
deborah.bentley@man.ac.uk

12th European Symposium - European Society for Neurogastroenterology & Motility
Dr Robin Spiller, Tel. 01159 249 924
Fax. 01159 422 232
E. robin.spiller@nottingham.ac.uk

The British Aphasiology Society Therapy Symposium Conference
13-14 September, 2004; Liverpool, UK
Tel. 0151 529 4986
E. alex.stirling@thewaltoncentre.nhs.uk

9th European Federation of Neurological Societies Congress
17-21 September, 2004; Athens, Greece
Fax. 00 43 1 88 92 581
E. headoffice@efns.org

12th World Congress of Psychophysiology - The Olympics of the Brain
18-23 September, 2004; Thessaloniki, Greece, Fax. 3-0-2 103 301 844
E. olympia@travelplan.gr

Part-time Postgraduate Certifice in Evidence Based Health Care
20 September 2004 - 30 September, 2005. Tel. 01865 286 941, Fax. 01865 286 934 E. cpdhealth@conted.ox.ac.uk

15th Migraine Trust International Symposium
20-23 September, 2004; London, UK
Tel. 02 089 770 011
E. mtis@hamptonmedical.com

II International Congress on Neuroregeneration
20-24 September, 2004; Rio, Brazil
E. icn@congrex.com.br

2nd International Conference on Cognitive Disabilities
21-25 September, 2004; Medellin, Colombia
Fax. +57 42 794 833
E. losalamos@epm.net.co

3rd World Congress World Institute of Pain
21-25 September, 2004; Barcelona, Spain
Fax. 00-34-934-172-279
E. wipcongress@meet2.net

ABN Autumn Scientific Meeting
22-24 September, 2004; Blackpool, UK
Tel. 020 7405 4060
E. abn@abnoffice.demon.co.uk

First International Congress on Neurosciences & Rehabilitation
22-24 September, 2004; Brasilia, Brazil
www.sarah.br

Dutch Rehabilitation Society & British Society of Rehabilitation Medicine
23-24 September, 2004; Edinburgh, UK
Tel. +31 30 2739696 or 01992 638865
E. vra@revalidatiegeneeskunde.nl or admin@bsrm.co.uk

VII Congress of the International Society of Neuroimmunology
28 September-2 October, 2004; Venice, Italy. Tel. 0039 06 519 3499
E. eem@eemservices.com

Evidence-Based Medicine in Neurorehabilitation: 1st European Regional Meeting of the World Federation of Neurorehabilitation
29 September - 2 October, 2004; Zurich, Switzerland
Fax. 00 41 13 861 609
E. caroline.kunz@balgrist.ch

October

Assessment and Management of Children with High Functioning Autism and Asperger Syndrome
1 October, 2004; London, UK
E. courses@ich.ucl.ac.uk

9th ACTRIMS
3 October, 2004; Toronto, Canada
Te. +212 476 0452
E. actrims@nmss.org, www.actrims.org

129th Annual Meeting of the American Neurological Association
3 - 6 October, 2004; Toronto, Canada
Fax. 001 952 545 6073
E. lorijanderson@msn.com

17th Congress of the European Sleep Research Society
5-9 October, 2004; Prague, Czech Republic
Fax. +420 224 261 703
E. esrs@conference.cz

Recent Advances in Brain Injury Rehabilitation
6 October, 2004; London, UK
Tel. 020 8510 7970, Fax. 020 8510 7318

Joint Annual Meeting of ECTRIMS and RIMS
6-10 October, 2004; Vienna, Austria
Fax. +41 61 686 77 88
E. info@akm.ch

16th Meeting European Academy of Childhood Disability (EACD)
7-9 October, 2004; Edinburgh, UK
www.eacd2004.com
Tel. 0131 556 9245, Fax. 0131 556 9638

8th Asian & Oceanian Congress of Child Neurology
7-10 October, 2004; Delhi, India
E. kalra_veena@hotmail.com,
www.8thaoccn2004.com

17th Congress of the European College of Neuropsychopharmacology
9 - 13 October, 2004;
E. secretariat@ecnp.nl

6th Congress of the European Assoication for Neuro-Oncology EANO VI
10-14 October, 2004; Jerusalem, Israel
Fax. 00 972 3 638 4455
E. info@ortra.com

Randomised Controlled Trials
11/13 October, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

Qualitative Research Methods
12/13 October, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

2nd National Brain Injury Conference
13-14 October, 2004; London, UK
Tel. 01763 255609 or
E. kemsley@standrew.co.uk

Ethics in Healthcare
14 October, 2004; Oxford, UK
Tel. 01865 286942
Fax. 01865 286934
E. cpdhealth@conted.ox.ac.uk

Randomised Controlled Trials
15 October, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

20th International Conference of the Alzheimer's Disease International
15 - 17 October, 2004; Kyoto, Japan
Fax. 00 81 75 811 8195
E. adiconference@alzheimer.or.jp

Congress of Neurological Surgeons 54th Annual Meeting
16 - 21 October, 2004; San Francisco, US
Fax. 001 847 240 0804
E. info@1cns.org

Health Status Measurement
18 October, 2004; Oxford, UK
Tel. 01865 286942
Fax. 01865 286934
E. cpdhealth@conted.ox.ac.uk

Randomised Controlled Trials
18/20 October, 2004; Oxford, UK
Tel. 01865 286942
Fax. 01865 286934
E. cpdhealth@conted.ox.ac.uk

Qualitative Research Methods
19/20 October, 2004; Oxford, UK
Tel. 01865 286942
Fax. 01865 286934
E. cpdhealth@conted.ox.ac.uk

BSCN Scientific Meeting: Motor Control & AGM
20-21 October, 2004; UK
E. bscn@secretariat.freeserve.co.uk

3rd International Workshop on the CCN Family of Genes
20-24 October, 2004; St Malo, France
Fax. +33 144 276 043
E. annick.perbal@wanadoo.fr

Beijing International Epilepsy Conference
21-23 October, 2003; Beijing, China
E. shichuoli@yahoo.com,
caepswjz@public.bta.net.cn,
www.epiforum.com

Ethics in Healthcare
21 October, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

Health Status Measurement
21 October, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

Systematic Reviews
22 October, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

Altered Haemodynamics - A new concept in manual therapy
23-24 October, 2004; Manchester, UK
E. ACNRevents@aol.com

34th Annual Meeting of the Society for Neuroscience
23 - 28 October, 2004; San Diego, US
E. info@sfn.org

Mental Dysfunctions in Parkinson's Disease
24 - 27 October, 2004; Salzburg, Austria
Fax. 0847 127 5678
E. PDment2004@kenes.com

Health Status Measurement
25/27 October, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

Qualitative Research Methods
26 October, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

Standardised Assessment in Occupational Therapy with special emphasis on Dementia, Part 1
27-29 October, 2004, London, UK
Tel. 020 7834 3181

Ethics in Healthcare
28 October, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

Systematic Reviews
29 October, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

November

Systematic Reviews
1 November, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

Ethics in Healthcare
2 & 4 November, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

Systematic Reviews
3 November, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

BNS Autumn Meeting: Symposium to commemorate 100 years since the first descriptions of fronto-temporal dementia
3-4 November, 2004; London, UK
Tel. 0115 970 9119
E. georgina.jackson@nottingham.ac.uk

Health Status Measurement
4 November, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

British Orthopaedic Foot Surgery Society: Diabetic Foot & Rheumatoid Foot & Ankle
4-6 November, 2004; Cheshire, UK
Tel. 01257 256248, Fax. 01257 256292
E. uplimb@wrightington.org.uk

Systematic Reviews
5 November, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

2nd International Symposium on Concussion in Sport
5-6 November, 2004; Prague, Czech Republic
Simone Micheletti
Fax. +41 15 622 259
Emicheletti@iihf.com

Ketogenic diets for epilepsy
8 November, 2004; London, UK
E. courses@ich.ucl.ac.uk

Driving With Disabilities
10 November; Leeds, UK
Adele Archer, Tel. 0113 3055086
E. adele.archer@nhs.net

Royal Hospital of Neurodisability Visitors Day for Heatlh Professionals and Funders
18 November, 2004; London, UK
E. chayward@rhn.org.uk

8th Mediterranean Epilepsy Meeting
18-20 November, 2004; Marrakesh, Morocco
Fax. +212 37 77 05 68
E. evenementiel@menara.ma

RCN Rehabilitation & Intermediate Care Nursing Forum: Where are we with intermediate care?
19 November, 2004; London, UK
Sonia Lynch, RCN Events.
Tel. 020 7647 3859
Fax. 020 7647 3411,
E. rehabilitation@rcn.org.uk

Norwegian Neurological Association Annual Scientific Meeting
22-26 November, 2004; Oslo, Norway
E. ragnarstien@hotmail.com

Best Practice in Epilepsy Care
23 November, 2004; Birmingham, UK
Tel. 0113 2108800
E. redgar@epilepsy.org.uk

West of England Seminars in Neurology
25-26 November, 2004; Bovey Castle, Devon, UK
E. cgardnerthrope@doctors.org.uk

Altered Haemodynamics - A new concept in manual therapy
27-28 November, 2004; Manchester, UK
E. ACNRevents@aol.com

December

United in Care - Inaugural Multi-Disciplinary Conference of the British Geriatric Society
1 December, 2004; London, UK
Tel. Sally Bradley on 01248 681 330
E. sbradley@mepltd.co.uk

Eighth International Congress of Parkinson's Disease and Movement Disorders

June 13-17, 2004; Rome, Italy

After the disappointment of Beijing last year, when the Parkinson's disease congress was postponed because of the SARS epidemic, delegates descended upon Rome from all corners of the world, bursting to show their abstracts. Situated in the Palazzo Dei Congressi, a Mussolini-inspired building set apart, it seems, from every hotel in Italy's capital city by at least a long walk or metro ride, the organisation was enthusiastic, if not efficient.

Were their any over-arching themes to emerge from this meeting? There was certainly an emphasis on basic science and its contribution to our understanding of movement disorders. There is an increasing importance attached to the non-motor complications of Parkinson's disease, notably dementia. Therapeutically, the meeting seemed to consolidate knowledge, rather than trail-blaze. With over 1300 posters and eight parallel sessions, together with four plenary sessions, it is impossible to be comprehensive, but some highlights are selected below.

In the first plenary session, Bill Langston (CA, USA) discussed the role of environmental factors in the aetiology of Parkinson's disease (PD), covering smoking and pesticide exposure, in particular. A large NIH-funded agricultural health study should hopefully help to resolve uncertainty over whether PD is associated with an increased risk of pesticide exposure, by comparing rates in applicators with spousal controls. John Hardy (MD, USA) followed with a discussion of genetic causes of PD, in his inimitable thought-provoking style. He covered, amongst other things, the recent discovery of an / -synuclein gene triplication and its link with a PD/dementia with Lewy bodies clinical phenotype. The next speaker (Serge Przedborski, NY, USA) discussed the role of mitochondria, oxidative stress, and inflammation in the pathogenesis of PD. This was a great overview of a complex topic. Potential mechanisms for modulating the glial inflammatory response were discussed, including vaccination strategies, although his conclusion was that the optimal protective strategy of neurones in PD is likely to be a cocktail of agents. Finally, in this session Kevin McNaught (NY, USA) described a new animal model, whereby systemic exposure to proteosomal inhibitors (PSI or epoxomicin) can produce behavioural and pathological features resembling PD, including reduced 11C-CFT binding on PET scanning, loss of nigral neurones and Lewy body-like inclusions. Do all pathogenic roads now point to the ubiquitin-proteosomal system? There is certainly a lot of environmental and genetic data converging on dysfunction of this system in PD.

The afternoon plenary session focused on the basal ganglia pathophysiological model, its contributions and limitations. This was not a session for those predisposed to post-prandial drowsiness. The shortcomings of animal models are recognised (Yanagisawa, Japan), while a number of misconceptions of the current motor loop model were highlighted (Bergman, Israel), including the co-localisation of dopamine receptors, branching of striatal axons, basal ganglia-brainstem, thalamo-striatal and direct cortico-subthalamic nucleus projections. An "action selection model" was proposed, in which dopamine acts to narrow the focus of a chosen action and dyskinesias are associated with an increased "aperture". It is not the level of basal ganglia output but the pattern that is important with a marked excess of synchrony seen in the local field potential in PD, probably linked to akinesia (Brown, UK).

David Williams (London, UK) presented a cogent argument for two distinct clinical phenotypes observed in pathologically proven progressive supranuclear palsy, with immunoblot differences in protein banding pattern to support this notion. Essentially, "Richardson's syndrome" was suggested to represent text-book PSP, with falls, supranuclear gaze palsy and an aggressive disease course, refractory to L-dopa. "PSP-P" was proposed to represent a more benign variant, with great likelihood of L-dopa response, longer disease duration, tremor and asymmetric onset (and thus more likely to be mis-diagnosed). He won a junior award for this work.

A number of posters and speakers (notably Rascol, France and Brotchie, Canada) touched upon potential new agents for dyskinesias that included levetiracetam, adenosine A2A antagonists and sarizotan (a 5HT1A agonist). An excellent parallel session featured updates on dystonia, Huntington's disease, Friedreich's ataxia, psychogenic movement disorders and essential tremor. Unfortunately, from a personal perspective, this clashed with the session on cognitive and behavioural dysfunction in movement disorders. As well as a succinct review of dementia associated with PD, this session also featured lectures on other interesting and frequently less well-covered aspects, notably apathy and motivation, reward and executive function.

Experimental interventional therapeutics for movement disorders (focusing upon PD) were addressed in a plenary session, including gene therapy, stem cells, trophic factors, and transplantation strategies. This was high-powered and exciting stuff. Latest results from the GDNF trial were presented and the use of lentiviral vectors for GDNF delivery proposed (using doxycycline to switch production on and off). In the meantime, the results of a double-blind placebo-controlled multicentre GDNF infusion trial are awaited. Potential pathogenic mechanisms for "off" (runaway) dyskinesias and strategies to optimise success for cell replacement therapy were also considered, amongst other topical themes.

From a surgical perspective, there were numerous posters and a dedicated parallel session. Is the zona incerta (ZI) a better target that the subthalamic nucleus (STN) for deep brain stimulation (DBS) for PD? From a preliminary study of 29 patients conducted in Bristol, UK (Plaha), stimulation of the ZI produced better motor outcomes. Bilateral DBS of the STN can improve motor function and reduce medication requirements for up to four years post-surgery (Liang, Pennsylvania, USA). The outcome of a double-blind multicentre study of bilateral DBS-STN (SPARK study, France) was reported, in which 97 patients in four centres underwent surgery. Mean L-dopa equivalent dose was reduced by 59%. Off medication, motor scores improved by 57% and activities of daily living by 48%. The pre-operative on-medication motor rating score was predictive of the 12-month post-operative motor outcome. In a cohort of 38 patients with advanced PD, DBS of the STN led to benefits in quality of life in both short and long (mean follow up 30.2 months) term follow up (Siderowf, Philadelphia, USA).

And finally, if you suffer from "distressful belching" (actually in the context of neuroacanthocytosis; Cuny, Bordeaux, France), DBS of the internal pallidum might be the treatment of choice, proving the range of conditions that DBS can tackle knows no bounds!

David J Burn and Una Brechany,
Newcastle upon Tyne, UK

The Colosseum, Rome
(Picture courtesy of Dr Naomi M Warren)

For a report on coma and impaired awareness, see the website at www.acnr.co.uk/conferences.htm

"Rage, rage against the dying of the light"*

There's a treatment that could shed light on the desolation of Parkinson's disease.

There's the UK's first and only NMDA antagonist for PD[1,2] which alleviates parkinsonian symptoms.[3-6]

There's a treatment that provides up to 60% reduction in motor fluctuations like dyskinesia,[3-5] while also offering possible neuroprotection.[1,7]

There's Symmetrel – because *"old age should burn and rave at close of day."*

*Taken from: *Do not go gentle into that good night* by Dylan Thomas; published by: Dent.

Symmetrel®
amantadine

The only NMDA antagonist for PD

Abbreviated prescribing information. Symmetrel (amantadine hydrochloride). **Presentation:** Capsules containing 100 mg of amantadine hydrochloride PhEur. Syrup containing 50mg/5ml of amantadine hydrochloride PhEur. **Indications:** Parkinson's disease. **Dosage:** Initially 100mg daily for the first week, increasing to 100mg twice daily. The dose can be titrated against signs and symptoms. Doses exceeding 200mg daily may provide some additional relief, but should not exceed 400mg. The dose should be increased gradually, at intervals of not less than 1 week. Amantadine acts within a few days, but may appear to lose efficacy within a few months of continuous treatment. Its effectiveness may be prolonged by withdrawal for three to four weeks, which seems to restore activity. Any antiparkinson drug already in use should be continued during initial Symmetrel treatment. It may then be possible to reduce the other drug gradually. Symmetrel withdrawal should be gradual, e.g. half the dose at weekly intervals. ***Renal impairment***: Reduce daily dose, or increase the dosage interval (see full prescribing information). **Contra-indications:** Hypersensitivity to amantadine or excipients. Individuals subject to convulsions. A history of gastric ulceration. Severe renal disease. Pregnancy. **Precautions:** Confusional or hallucinatory states or psychiatric disorders. Liver, kidney or cardiovascular disorders. Congestive heart failure. Concurrent administration with anticholinergics, levodopa, neuroleptic medication, drugs or substances (e.g. alcohol) acting on the CNS, combination diuretics (hydrochlorothiazide + potassium sparing diuretics). Withdrawal of amantadine in patients taking neuroleptic agents may cause or aggravate neuroleptic malignant syndrome. Lactation. Driving or operating machinery (blurred vision). **Side effects:** The most commonly reported effects were gastro-intestinal disturbances (anorexia, nausea), CNS effects (loss of concentration, dizziness, agitation, nervousness, depression, insomnia, fatigue, weakness), or myalgia. Side effects after higher doses or chronic use, in addition to above include: Anxiety, elevation of mood, lightheadedness, headache, lethargy, hallucinations, nightmares, ataxia, slurred speech, blurred vision. Confusion, disorientation, psychosis, tremor, dyskinesia, convulsions. Delirium, hypomanic state and mania have been reported but their incidence is not known. Oedema of ankles, livedo reticularis (usually after very high doses or use over many months). Palpitations, orthostatic hypotension. Heart insufficiency/failure. Leucopenia, reversible elevation of liver enzymes. Dry mouth, anorexia, nausea, vomiting, constipation. Diarrhoea. Diaphoresis. Exanthema. Photosensitisation. Corneal lesions, e.g. punctate subepithelial opacities which might be associated with superficial punctate keratitis, corneal epithelial oedema, and markedly reduced visual acuity. Urinary retention, urinary incontinence. **Legal category:** POM. **Product licence number:** Symmetrel Capsules PL16853/0015. Symmetrel Syrup PL16853/0016. **Packs:** Blister packs of 56 capsules. 150ml bottle. **Basic NHS price:** Symmetrel Capsules £15.35. Symmetrel Syrup £5.05. Full prescribing information is available from: Alliance Pharmaceuticals Ltd, Avonbridge House, Bath Road, Chippenham, Wiltshire SN15 2BB, www.alliancepharma.co.uk. **Date of preparation:** September 2003. **References:** 1. Kornhuber J *et al. J Neural Transm* 1994;**43**(Suppl):91-104. 2. Blanchet PJ *et al. Adv Neurol* 2003; **91**:251-257. 3. Verhagen Metman L *et al. Neurology* 1998; **50**(5):1323-1326. 4. Luginger E *et al. Mov Disord* 2000; **15**(5):873-878. 5. Verhagen Metman L *et al. Arch Neurol* 1999; **56**(11):1383-1386. 6. Ruzicka E *et al. J Neural Transm* 2000; **107**(11):1297-1306. 7. Uitti RJ *et al. Neurology* 1996; **46**:1551-1556.

AL/402/08.04/5.0

ALLIANCE

EDITOR'S CHOICE

Neurosteroid therapy for Niemann-Pick Type C

Niemann-Pick type C (NP-C) is an autosomal recessive neurodegenerative lipid storage disorder that presents in childhood. 95% of cases result from mutations in the NPC1 gene that cause defective trafficking of intracellular cholesterol and subsequent lysosomal accumulation of unesterified cholesterol and glycosphingolipids. There is currently no therapy for this devastating disease, which leads to death in adolescence.

There is a naturally occurring mouse model of NP-C with an insertion mutation in the NPC1 gene. This model faithfully replicates the human disease in terms of cholesterol and sphingolipid storage, neuropathology, onset of neurological deficits and early death. These mice are hypoandrogenic and bear under-developed reproductive organs suggesting defective biogenesis from cholesterol. Griffin and colleagues proposed that there may also be defective neurosteroidogenesis in the brains of these mice. Neurosteroids act as anxiolytic and anaesthetic agents via ion-gated neurotransmitter channels. The neurosteroid allopregnanolone is thought to play an important role in neuronal growth, differentiation and survival. On this basis, the group postulated that disrupted neurosteroidogenesis, which putatively results from disordered cholesterol trafficking, contributes to the NP-C phenotype. In addition, they proposed that allopregnanolone treatment would alleviate the condition.

Indeed, in this study NP-C mouse brains contained significantly lower levels of neurosteroid as a result of the progressive reduction in expression and activity of neurosteroidogenic enzymes post-natally. Neonatal allopregnanolone treatment slowed the decline of locomotor functions and motor co-ordination, increased Purkinje and granule cell survival, reduced cortical GM2 and GM3 ganglioside accumulation and doubled the life span in NP-C mice. These actions were mediated via the GABAA receptor. Earlier adminstration of allopregnanolone and continuous treatment regimes proved more effective. The results demonstrate that neurodegeneration in NP-C mice is allopregnanolone dependent. The correlation of improved outcome with earlier administration suggests that allopregnanolone is important in the neurodevelopmental process shortly after birth.

Allopregnanolone represents a promising therapy for the currently incurable NP-C. It increases the life span of NP-C mice to a similar extent compared to N-butyldeoxynojirimycin, a glucosylceramide synthase inhibitor, currently in clinical trials. However, it has yet to be demonstrated that there is defective adrenal or gonadal steroidogenesis in NP-C children and rodent and human patterns of steroidogenesis are different.
- LMS, SJT

Griffin LD, Gong W, Verot L, Mellon S
Niemann-Pick type C disease involves disrupted neurosteroidogenesis and responds to allopregnanolone.
NATURE MEDICINE
2004 10 (7); 704-711

★★★ RECOMMENDED

AUTISM: an autoimmune disease?

Autism is a complex behavioural syndrome that has fascinated the media and public in recent years. This Portuguese group take on the old story of autoimmunity in autism. They studied the serum from 171 patients with autism compared to 54 controls. Their sera were incubated with SDS-Page blots of protein extracts from a single human brain and antibody binding was visualised with anti-human Ig. There were many varying immunoblot relativities amongst the samples, requiring complex statistical processing, but overall there were more for autistic children. One reactivity (called "Section 32") most powerfully distinguished autistic children from controls. This antibody identifies a protein of around 20kDa. The investigators speculated that this might be one of the MBP isoforms; however all attempts to demonstrate that failed.

So children with autism produce more antibodies against brain components than controls, and against one unidentified protein in particular. Fascinating stuff, but what does it mean? Are these antibodies pathogenic? Or responses to neuronal damage? Or even neuro-protective? Only interventional and animal studies can answer these questions. The use of IVIG to treat autism in the late 1990s was deemed largely ineffective, but perhaps we should revisit that. And, I am sure, Susana Silva and colleagues are squirting Section 32 into rodents right now and waiting for the first signs….

What the anti-MMR lobby will make of it all, I dread to think. - *AJC*

Silva SC, Correia C, Fesel C, Barreto M, Coutinho AM, Marques C, Miguel TS, Ataide A, Bento C, Borges L, Oliveira G, Vicente AM.
Autoantibody repertoires to brain tissue in autism nuclear families.
JOURNAL OF NEUROIMMUNOLOGY
2004;152(1-2):176-82

COGNITION: Medial frontal lobe damage and 'Theory of Mind'

This rigorous neuropsychological case-study examines the neural basis of 'theory of mind', a cognitive function currently of great interest. The paper reaches specific conclusions on 'theory of mind' and also provides a useful reminder that, in the localisation of cerebral function, findings from functional imaging and lesion studies must be considered in parallel.

When we explain or predict the behaviour of others by ascribing to them certain beliefs, desires or fears we seem to construct a framework of mental states, i.e. a 'theory of mind'(ToM). The concept of ToM has proven useful in interpreting social difficulties experienced in autism. More recently, tests that tap into ToM function have been found to be informative in cases of frontal lobe damage, particularly frontal-type dementia.

Bird and colleagues describe a case of bilateral anterior cerebral territory infarction, where the damaged anterior parasagittal region bilaterally corresponds to the key region implicated in functional imaging studies of ToM. The surprising finding is that the subject performed within the normal range on four out of five administered ToM tests. The single exception was in a task requiring a judgement on violations of social norms; she judged fewer of the violations to have been embarrassing than did controls. The findings are particularly valuable as the lesion here is well circumscribed. This contrasts with previous cases studied where neuro-axonal injury, seizure-related damage or neurodegeneration are likely to have occurred even in areas where scan appearances were normal. The main limitation is that inferences are being drawn from a single case. For instance, although evidence is offered that the subject's premorbid function was essentially normal, one could argue that her occupation as a teacher would have allowed her to develop superior ToM abilities. The authors do not dwell on the additional complication that ToM, though beguiling as a concept, may well not represent a unitary function.

It is concluded that the antero-medial frontal region, damaged in this case, is not necessary for ToM, although activation of the region in functional studies suggests that it may be sufficient. - *RD*

Bird CM, Castelli F, Malik O, Frith U, and Husain M.
The impact of extensive medial frontal lobe damage on 'Theory of Mind' and cognition.
BRAIN
2004; 127: 914-928

EPILEPSY: Vacuum cleaner reveals a role for circadian genes in epilepsy

The study of a family of transcription factors has inadvertently revealed a link between circadian genes and epilepsy, with the help of a vacuum cleaner.

The PARbZIP protein family consists of three transcription factors DBP, HLF, TEF, the levels of which oscillate according to circadian rhythm. They accumulate at high concentrations in tissues with high amplitude clock gene expression, including the liver and the suprachiasmatic nucleus (SCN; the major mammalian circadian pacemaker). In the brain, the clock gene expression cycles at low amplitude, so that the level of these transcription factors does not fluctuate significantly. Schibler and colleagues were interested in identifying the physiological role of these PARbZIP transcription factors, which have been well conserved throughout mammalian evolution.

Single, double and triple knock-out mice of the three PARbZIP transcription factors were generated and were all anatomically normal and fertile. However, the triple mutant mice died prematurely. The reason for such a dramatic reduction in life span was a mystery until it was noted that the mice died predominantly on Mondays and Thursdays when the animal facility was cleaned. It became clear that the noisy vacuum cleaner was inducing lethal audiogenic seizures in these mice. EEG recordings confirmed this abnormal brain activity and also revealed the susceptibility of the triple mutants to spontaneous generalised tonic-clonic seizures.

The pyridoxal kinase (Pdxk) enzyme is proposed to explain the link between PARbZIP transcription factors and epilepsy. Pdxk was identified by transcriptome profiling as a target gene for the PARbZIP family. It is involved in the conversion of vitamin B6 derivatives to pyridoxal phosphate, a coenzyme important in neurotransmitter homeostasis. Consistent with this finding, Schibler demonstrated down-regulation of Pdxk expression and subsequent reduction in serotonin and dopamine concentrations in the brains of triple knock-out mice. It is widely accepted that such an imbalance in neurotransmitter levels results in epileptic seizures and thus represents a plausible explanation for PARbZIP deficiency in causing epilepsy. This study demonstrates the crucial role the PARbZIP transcription factors play in keeping Pdxk levels within narrow limits in the brain and preventing life-threatening seizures.

This study of triple PARbZIP knock-out mice is clearly of relevance to epilepsy in humans: first, because vitamin B6 deficiency is a known cause of epilepsy. Second, the recessive disease, Unverricht-Lundborg disease (ULD) is caused by mutations in the cystatin B gene, which lies adjacent to Pdxk. The most common mutation causing ULD is a dodecamer expansion in the promoter region. It is therefore conceivable that this mutation also alters Pdxk expression. This mouse is a good model of human disease and may be useful to study pathogenesis and therapeutics - *LMS, SJT*

Gachon F, Fonjallaz P, Damiola F, Gos P, Kodama T, Zakany J, Duboule D, Petit B, Tafti M, Schibler U.
The loss of circadian PARbZIP transcription factors results in epilepsy.
GENES AND DEVELOPMENT
2004 18; 1397- 1412

PAIN: A "hot" neuropathic pain model for fMRI?

People living with nerve damage (neuropathy) can experience painful sensations during transient brushing of the skin e.g. from bed sheets at night or from clothes during movement.

One model of neuropathic pain combines two methods, physical stimulation (heat), and chemical stimulation (topical capsaicin, the active ingredient of chilli pepper) to elicit measurable and reliable areas of "allodynia"- pain induced by an innocuous stimulus. Using this combined model allodynia can be studied for longer than when either method is applied alone. As it is feasible to rekindle allodynia on demand by reapplying heat, it is timely to investigate the model using neuroimaging.

Eleven healthy subjects participated, all right handed. Their left forearm skin was pre-exposed to measured applications of heat and chemical sensitisation. During the functional magnetic resonance imaging (fMRI) experiment, a hand-held brush mechanically stimulated allodynia on the left, and following scanning, sensory testing was used to confirm the allodynia to touch in given areas. The right, untreated, forearm (control site) was compared within the same fMRI brushing paradigm.

Brushing led to different brain activations depending upon whether skin was allodynic or not. Brushing not associated with pain resulted in contralateral S1, PA and insula activation and bilateral S2 activation. Allodynia evoked by brushing resulted in partially overlapping activations, though activation was found in the contralateral inferior frontal cortex (IFC) and was ipsilateral in the insula. "Direct comparison between nonpainful brushing and brush-evoked allodynia revealed significant increases in blood oxygenation level dependent (BOLD) signals in contralateral S1, PA, IFC and bilateral S2/insula during allodynia".

How well does this experimental model simulate neuropathic pain? We do not know. We will learn more by refining the repeatability of such paradigms and examining the effects of existing pharmacological treatments on them. *-LAJ*

Maihöfner C, Schmelz M, Forster C, Neundörfer B, and Handwerker H.
Neural activation during experimental allodynia: a functional magnetic resonance imaging study.
EUROPEAN JOURNAL OF NEUROSCIENCE
2004: 19: 3211-3218, 2004

NEUROIMMUNOLOGY: Lupus in the midbrain

Cerebral lupus is a curious disease. It is not easy to understand the pathogenesis of the common symptoms of cognitive impairment, low mood and poor attention in the face of normal imaging. This study from Canada helps just a little. It focuses on the MRL-lpr animal model of lupus, which has a lpr mutation on chromosome 19 and a defective Fas receptor, leading to failure of deletion of autoreactive T cells. These animals develop florid lupus by three months and are dead three months later. The authors showed that apomorphine injections induce rotational behaviour in these animals, suggesting nigrostriatal damage. Pathologically, there was a loss of TH-positive cells and reduced neuronal survival (demonstrated by increased FJB staining) in the substantia nigra pars compacta. There were no accompanying inflammatory cells, suggesting the mechanism of death was degenerative (and CSF from diseased animals did kill neural progenitor cells in vitro). But immunosuppression of the animals with cyclophosphamide did prevent these changes.

Interesting maybe, but Parkinsonism is an incredibly uncommon feature of lupus (except perhaps in children). However, this animal work begins to resonate when the investigators move on to behavioural tests of their mice. Compared to control animals the MRL-lpr mice showed anhedonia (losing interest for sucrose drinks), reduced motor activity over 30 minutes and

increased "behavioural despair" (spending greater time floating in a no-escape swimming task). Now, that is more like what our patients are telling us. Very unfortunately, the investigators did not examine the effects of immunosuppression on these behaviours, but the implication from the pathology studies would be that they would improve.

So, contrary to prevailing opinion, the cognitive complaints of people with lupus may be due to focal midbrain degeneration and may respond to immunosuppression. All well and good but –if so- why don't we see more Parkinsonism in lupus? Cerebral lupus is a curious disease. *-AJC*

Ballok DA, Earls AM, Krasnik C, Hoffman SA, Sakic B.
Autoimmune-induced damage of the midbrain dopaminergic system in lupus-prone mice.
JOUNRAL OF NEUROIMMUNOLOGY
2004;152(1-2):83-97.

EPILEPSY: Marijuana use…… well would you?

Animal studies have shown a mild antiepileptic effect of cannabinoids although a single trial in humans has been inconclusive. The authors sought to establish the extent of cannabis use in 241 patients in an outpatient database. Only 160 could be contacted and of these 136 had ever used marijuana. Eighteen (13%) were frequent users (48 days in the last year) and 11 (8.1%) were heavy users (more than 182 days in the last year). Four met the DSM-IV criteria for marijuana dependence.

In contrast to use in the general population, the likelihood of using marijuana was not affected by gender or unemployment. It was increased if epilepsy duration was longer and if seizures were frequent. The only statistically significant association was with use of other illicit drugs in the previous year. There was no association with alcohol. 24% of patients believed marijuana benefited their epilepsy.

A question with this kind of study is do patients tell the truth when asked about illegal activities – well would you? Taken at face value a pragmatic line is that use of marijuana in epilepsy probably has little effect either way on epilepsy severity. The most important points here then are the increased use of neurotoxic drugs of abuse in patients who admit to marijuana use and the belief of some patients in the therapeutic benefits of marijuana. - *MRAM*

Gross DW, Hamm J, Ashworth NL, Quigley D.
Marijuana use and epilepsy: prevalence in patients of a tertiary care epilepsy centre.
NEUROLOGY
2004;62:2095-2097.

★★★ RECOMMENDED

PARKINSON'S DISEASE: How on earth does dopamine therapy help?

The management of Parkinson's disease (PD) is complex but most people would agree that dopaminergic therapies are helpful because they stimulate the striatal output neurons through either D1 or D2 receptors. However a recent series of papers suggest that this may only be part of the story.

In the first article from the group of Calabresi, the actions of L-dopa were investigated in the unilateral 6-OHDA rat model of PD. This group, using detailed neurophysiological recordings, found that the actions of L-dopa may be mediated by modification of the glutaminergic corticostriatal projection. In particular they report that the relative glutaminergic hyperactivity that occurs with dopaminergic denervation can be reversed by L-dopa through a presynaptic D2 receptor on the corticostriatal terminals. This study follows up on an earlier report from this group (reported last year – see ACNR 3.3) on the basis of drug induced dyskinesias in PD, and highlights the complex actions of L-dopa therapy in this condition. Indeed this study (as previous) has shown curiously that using an identical lesion and L-dopa dosing regime produces two distinct responses in rats – one group of rats show a therapeutic response, whilst the other show no such benefit owing to the development of dyskinesias. Why such genetically homogenous animals develop such varied responses is unknown, but it may be telling us something about the heterogeneity of treatment response in patients with this condition.

In the other two papers the emphasis shifts to the effects of dopamine therapies on the endogenous neural precursor cell (NPC) found in the subventricular zone (SVZ) of the adult brain. We hypothesised 3 years ago in the Lancet that abnormalities in the endogenous NPC may contribute to the genesis and evolution of neurodegenerative disorders, and these papers go some way to supporting this. In the first of these papers Baker *et al* show that 6-OHDA lesion of the nigrostriatal pathway in adult mice reduces the number of proliferating NPCs in the subventricular zone of the lateral ventricle in the striatum. This observation compliments the data presented in the much more extensive study of Höglinger *et al*. This latter study shows that the midbrain dopaminergic projection includes an innervation to the SVZ, and that manipulation of this innervation alters the kinetics of NPC proliferation. This action is mediated through a D2 receptor, and is such that the loss of dopamine in PD results in reduced SVZ NPC proliferation – the consequences of which are unknown but may contribute to olfactory deficits seen in this condition (albeit given the recent doubts about the existence of the rostral migratory stream in adult humans – see ACNR 4.2).

These articles are therefore thought provoking and raise all sorts of questions about the best management of this common neurological condition, not only about L-dopa but also whether we should be using growth factors and cell replacement strategies. - *RAB*

Picconi B, Centonze D, Rossi S, Bernardi G, Calabresi P.
Therapeutic doses of L-dopa reverse hypersensitivity of corticostriatal D2-dopamine receptors and glutamatergic overactivity in experimental parkinsonism.
BRAIN
2004;127: 1661-1669

Baker SA, Baker KA, Hagg T.
Dopaminergic nigrostriatal projections regulate neural precursor proliferation in the adult mouse subventricular zone.
EUROPEAN JOUNRAL OF NEUROSCIENCE
2004;20:575-579.

Höglinger GU, Rizk P, Muriel MP, Duyckaerts C, Oertel WH, Caille I, Hirsch EC.
Dopamine depletion impairs precursor cell proliferation in Parkinson's disease.
NATURE NEUROSCIENCE.
2004. Epub advanced on line publication.

★★★ RECOMMENDED

REHABILITATION: Cortical reorganisation starts straight away after cerebral ischaemia

One issue for rehabilitation of patients with cerebral infarcts is timing. When is the best time to start rehabilitation? It is not clear whether the potential for beneficial cortical plasticity is greater early after injury or whether there are dangers in starting training early after stroke. Certainly increased excitability of the cortical area surrounding the infarct has been observed in animal models in the early days after a stroke. This has been seen as a sign that there is greater potential for cortical plasticity as a response to brain damage immediately after stroke. However there is also a cautionary school of thought that links the raised excitability to dangerous excitotoxic effects of glutamate released in the ischemic cascade. Now a group in Tokyo have been the first to find rapid plastic changes along with increased excitability in the peri-infarct cortex occurring during the first few hours after lesioning.

Using rats with photochemically induced ischemia in the somatosensory cortex, Fujioka *et al* recorded cortical evoked potentials to single and paired electrical stimuli of the ulnar nerve before and after 1,2,4 and 6 hours following infarction. In addition they mapped the receptive fields in the cortex that corresponded to touch on the forepaw skin using a von Frey hair type probe. The amplitude of evoked potentials demonstrated increased excitability of the peri-infarct area as early as one hour after injury and increased over the observations collected up to six hours. The size of receptive fields in the forepaw also began increasing within one hour of the infarct and kept increasing in correspondence with excitability changes over the subsequent hours.

We are a little way off determining the best biological time for rehabilitation as yet. Certainly many patients are too ill for very active rehabilitation in the early days, let alone hours, after stroke and some are not psychologically ready. But in future maybe this early plasticity could be used to improve outcome for some patients with stroke. - *AJT*

Fujioka H, Kaneko H, Suzuki SS, Mabuchi K.
Hyperexcitability-Associated Rapid Plasticity After a Focal Cerebral Ischemia.
STROKE
2004: 35: e346-e348

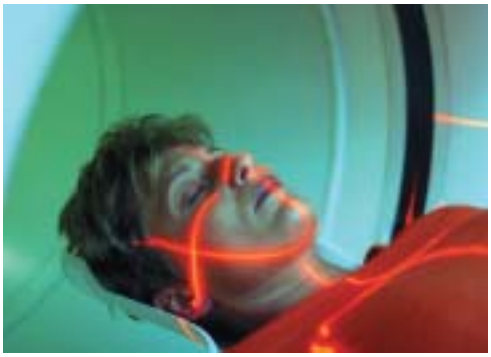
New Class Of PET/CT Scanners

WITH a significant growth in the PET/CT scanner market from two systems operational in 2001 to an expected 400 operational worldwide by the end of 2004, Siemens Medical Solutions have expanded its family of PET/computed tomography (PET/CT) systems to meet the wide ranging clinical demands. The new biograph PET/CT family incorporates an unmatched range of performance options to enhance image quality, resolution and throughput, as well as new information technology solutions for multimodality integration.

Key new features include a high resolution PET option, image quality enhancement, a six-slice CT biograph companion to existing two and 16-slice configurations and further integration into the Siemens Leonardo post processing workplace. The new technological advancements available with the biograph family build upon the ultra-fast Lutetium Oxyorthosilicate (LSO) crystal technology, delivering exceptional image quality in the shortest scanning time possible.

Siemens has incorporated the Leonardo post processing workplace with the nuclear medicine capabilities of the company's esoft package. Strict adherence to the DICOM-standard provides smooth integration into clinical workflows and ensures cross-vendor compatibility with these systems. Automated workflows reduce administrative work and accelerate clinical processes.

For more information contact Siemens on Tel. 01344 396317, or see www.siemens.co.uk/medical



Siemens biograph medical scanner combines anatomical images from computer tomography (CT) with physiological images from positron emission tomography (PET).

The SynchroMed® II System From Medtronic®

For the management of severe complex spasticity delivering intrathecal baclofen therapy (ITB™):

SMALLER: 30% reduction in size for increased patient acceptance; 20% reduction in weight for enhanced patient comfort; Contoured shape for a better fit with the patient's body.

SIMPLER: 20ml and 40ml reservoirs for more therapy options and for up to 59% fewer refills; Reduced number of implant steps; No need to purge or warm the pump; Redesigned and larger refill port and catheter access port for easier access.

SMARTER: "Flex dosing" option to match drug delivery to specific patient needs; Critical therapy data stored in the pump memory; Louder more distinctive alarms;
Estimated Replacement Indicator (ERI) provides estimate of time to replacement;
Personal Therapy Manager (PTM) option to allow the patient to access physician; preprogrammed bolus doses for enhanced therapy delivery.

For further information contact Clive Woodard on clive.woodard@medtronic.com

New Catalogues From Psychology Press

THE New Titles in Clinical and Cognitive Neuropsychology catalogue contains sections on Brain Injury and Neuropsychological Rehabilitation; Cognitive Neuropsychiatry; Cognitive Neuropsychology; Developmental Neuropsychology, and more. The New Titles in Cognitive Psychology catalogue contains sections on Ageing; Attention; Cognitive Neuroscience; Memory; The Psychology of Language and Reading, and more.

To order your free catalogues, please contact Psychology Press Customer Services on 01273 225 025 or by email at customer.services.psychology@psypress.co.uk, specifying which catalogue/s you would like. Visit www.psypress.co.uk for more titles of interest.

Psychology Press
Taylor & Francis Group

PL-EEG Digital EEG System

PULSE Medical are the new distributors of Walter Graphtek digital EEG systems. The PL-EEG system from Walter Graphtek is an advanced and versatile digital EEG system. It offers all these advantages for improved clinical productivity developed both for the Neurological and ENT/Sleep approach:

Choose between three different head-box types to set-up the system you need. (21 + 2 channels, 32 + 3 channels, 32 + 12 channels); Recording and review applications are simple to use whilst providing all of the tools for analysis which are needed in a modern EEG laboratory; An integrated database, coupled with digital archiving, facilitates easy management of the patient's demographic data and the associated recordings; High Resolution Display; Digital video and ambulatory recording available as option.; More dedicated analysis software packages are available.

Pulse Medical also supply a full range of EEG accessories at discounted prices, including Electrode Gel, Nuprep, Ten20 paste, Electrode Caps, Blunted Needles. See www.pulsemedical.co.uk for full details.

For more information contact Pulse Medical Limited, 3000 Cathedral Hill, Guildford, Surrey, GU2 7YB. Tel. 01483 243573, Fax. Fax 01483 243501, E-Mail. sales@pulsemedical.co.uk

PULSE MEDICAL

First Bioresearch Temperature Control For Upright Microscopes

A NEW temperature control chamber has been developed by Solent Scientific to partner BX51 upright research microscopes from Olympus. The system provides environmental control for advanced live cell imaging applications such as time lapse image analysis, low light level microscopy, and cell death and cell motility studies.

Upright microscopes are the most commonly used type, typically offering higher resolution than inverted systems. Nevertheless technical challenges have meant that an environmental control chamber has not previously been available for upright microscopy. Each chamber must be individually designed and calibrated for a particular model of microscope, since different frame shapes and designs will affect the heat transfer characteristics.

The Solent chamber provides the precise environmental control required for optimum cell viability. Changes in focus or light path over time caused by heat expansion are also eliminated – an essential feature for time lapse imaging applications.

For further information contact Orry Dugdale on Tel. 0870 774 7140 or see www.solentsci.com

Going solo

A double-blind, randomised trial has shown that Topamax 100 mg is as effective in various seizure types:

– as carbamazepine when it is predominantly selected for partial-onset seizures[1]

– as valproate when it is predominantly selected for generalised seizures.[1‡]

TOPAMAX®
TOPIRAMATE

BECAUSE LIFE WITHOUT SEIZURES IS SO MUCH BETTER*

*In a double-blind trial in newly diagnosed epilepsy, 49% of patients taking topiramate 100 mg and 63% of children on topiramate were seizure free for the last 6 months of the study[1,2] ‡Topamax is indicated as monotherapy in adults and children aged six years and above with newly diagnosed epilepsy who have generalised tonic-clonic seizures or partial seizures with or without secondarily generalised seizures

TOPAMAX® Abbreviated Prescribing Information. Please read Summary of Product Characteristics before prescribing. Presentation: Tablets: 25, 50, 100, 200 mg topiramate. Sprinkle Capsules: 15, 25, 50 mg topiramate. Uses: Monotherapy: Newly diagnosed epilepsy (age ≥ 6 years): generalised tonic-clonic/partial seizures, with/without secondarily generalised seizures. Adjunctive therapy of seizures: partial, Lennox Gastaut Syndrome and primary generalised tonic-clonic. Conversion from adjunctive to monotherapy: efficacy/safety not demonstrated. Dosage and Administration: Oral: Do not break tablets. Low dose initially; titrate to effect. Renal disease may require dose modification. Monotherapy: Over 16 years: Initial target dose: 100 mg/day (two divided doses; maximum 400 mg/day). Children 6 to 16: Initial target dose: 3 – 6 mg/kg/day (two divided doses). Initiate at 0.5 – 1 mg/kg nightly with weekly or fortnightly increments of 0.5 – 1 mg/kg/day. Doses less than 25 mg/day: Use Topamax Sprinkle Capsules. Adjunctive therapy: Over 16 years: Usually 200-400 mg/day (two divided doses; maximum 800 mg/day). Initiate at 25 mg daily with weekly increments of 25 mg. Children 2 to 16: Approx. 5 - 9 mg/kg/day (two divided doses). Initiate at 25 mg nightly with weekly increments of 1 – 3 mg/kg. Sprinkle Capsules: take whole or sprinkle on small amount (teaspoon) of soft food and swallow immediately. Contra-indications: Hypersensitivity to any component. Precautions and Warnings: Withdraw gradually. Renal impairment delays achievement of steady-state. Caution with hepatic impairment. May cause sedation; so caution if driving or operating machinery. Acute myopia with secondary angle-closure glaucoma reported rarely; symptoms typically occur within 1 month of use and requires discontinuation of Topamax and treatment of symptoms. Increased risk of renal stones. Adequate hydration is very important. Food supplement may be required. Interactions: Possible with phenytoin, carbamazepine, digoxin, oral contraceptives and metformin. Decrease in serum bicarbonate levels. Pregnancy: If benefits outweigh risks. Contraception recommended for women of childbearing potential (oral contraceptives should contain at least 50 µg oestrogen). Lactation: Avoid. Side Effects: Abdominal pain, ataxia, anorexia, anxiety, CNS side effects, diplopia, headache, hypoaesthesia, fatigue, nausea, nystagmus, paraesthesia, weight decrease, agitation, personality disorder, insomnia, increased saliva, hyperkinesia, depression, apathy, leucopenia, psychotic symptoms (such as hallucinations), venous thrombo-embolic events, nephrolithiasis, increases in liver enzymes. Isolated reports of hepatitis and hepatic failure when on multiple medications. Acute myopia with secondary acute-angle closure glaucoma, reduced sweating (mainly in children), metabolic acidosis and suicidal ideation or attempts reported rarely. Bullous skin and mucosal reactions reported very rarely. Pharmaceutical Precautions: Tablets and Sprinkle Capsules: Do not store above 25°C. Keep container tightly closed. Legal Category: POM Package Quantities and Prices: Bottles of 60 tablets. 25 mg (PL0242/0301) = £20.02; 50 mg (PL0242/0302) = £36.17; 100 mg (PL0242/0303) = £64.80; 200 mg (PL0242/0304) = £125.83. Containers of 60 capsules. 15 mg (PL0242/0348) = £16.88, 25 mg (PL0242/0349) = £25.32, 50 mg (PL0242/0350) = £41.60. Product licence holder: Janssen-Cilag Limited, Saunderton, High Wycombe, Buckinghamshire HP14 4HJ, UK. Date of text revision: February 2004. APIVER250204.

References: 1. Privitera MD et al. Acta Neurol Scand 2003; 107: 165-175.
2. Wheless J, Wang S et al. Epilepsia 2001; 42(Suppl 7): (Abstract1.179).

JANSSEN-CILAG Ltd

4794