Review Articles: Relapses, progression, inflammation and neuro degeneration in multiple sclerosis: a changing view
Molecular characterisation of motor neuron disorders

Rehabilitation Article: The use of electrical stimulation for correction of dropped foot in subjects with upper motor neuron lesions

Management Topic: Muscle disease: history, examination and investigation
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ACNR has now completed its first year and seems to have met with some success, judging by the comments that have been fed back to us. Obviously we are always keen to improve the journal, so do keep sending us your ideas and feedback. In this edition we have two review articles as usual. An excellent account of the molecular genetics of motor neuron diseases, an area that has undergone something of a revolution in the last 5 or so years. Sadly the identification of genetic defects in these conditions has not lead to major advances in pathogenesis or treatment but hopefully will in the near future. We also have our first international author, Professor Christian Confavreux. We are very honoured to be able to include the reviews of such distinguished overseas neurologists and I am very grateful for his article which explores the relative roles of inflammation and degeneration in the development of disability in MS. In this respect the recent developments on prescribing beta interferon have provided much food for thought, and Alastair Wilkins has distilled out the major issues and implications of the NICE decision.

We also have in this issue the first of the new series by Gillian Hall on muscle disease, following on from the excellent series by Mark Manford on epilepsy. Mark has now retired to the back-benches to spend more time with his journal reviews! This first article by Gillian takes us through the key issues in assessing the patient with muscle disease, and is enormously helpful to those of us who see these patients outside specialist clinics. It is often too easy to just send the patient for a serum CPK, EMG and muscle biopsy without really thinking through the possibilities that may be hidden in the history and nuances of the examination.

In the rehabilitation section we have a most interesting article by Paul Taylor on the use of electrical stimulators for foot drop in upper motor neuron lesions. This, I must say, is something I knew nothing about and having read this article is something I will be keen to try in the next patient I have with problems of this nature.

Furthermore although it is hard to believe, there is yet another new section appearing for the first time in this edition - historical neurology and neuroscience. Andrew Larner provides some intriguing insights into the neurological descriptions to be found in the writings of Charles Dickens. A most enjoyable read, and especially of interest to those involved in setting neurological quizzes. If you would like to contribute to this section, then do let Andrew know.

Finally we have our usual regular articles. A beautiful account of the anatomy of the venous sinuses with radiological images for illustration by Alasdair Coles and Justin Cross. Indeed such is the quality of some of these anatomy primers, that they even made it in to the local Christmas quiz last December in the round on great medical artists! Oh yes, I should say, Dr Coles actually set the quiz.

To conclude, we have our usual smattering of book, journal and conference reviews. Happy reading.
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Dosage and administration
Store Copaxone in refrigerator (2° to 8°C). May store in refrigerator controlled trials by 47% on Copaxone and 29% on placebo. Asthenia, dyspnoea, palpitation, tachycardia) was reported at least once in

Editorial Board and regular 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 and contributes our Anatomy Primer. He is a Wellcome Advanced Fellow working on experimental immunological therapies in multiple sclerosis, based at the Dunn School of Pathology in Oxford and Department of Neurology in Cambridge.

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 prophesics, orthotics, gait training and neurorehabilitation.

David J Burn is the editor of our conference news section and Consultant and Senior Lecturer 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 Neuroligist 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.

Niall Pender is a member of the editorial board. He is a Neuropsychologist and Clinical Leader of the Neuro-behavioural Rehabilitation Unit at the Royal Hospital for Neuro-disability, London. He is also Neuropsychologist to the Huntington’s Disease Unit at the Royal Hospital. In addition he is an Honorary Lecturer in Psychology at the Institute of Psychiatry, King’s College. Following degrees in Psychology and Neuropsychology he completed his training in Clinical Psychology at the Institute of Psychiatry. His research interests include cognition in Huntington’s disease, behaviour management in brain injury rehabiliation, memory, and visual impairments after brain injury.

Justin Cross is a Consultant Neuroradiologist at Addenbrooke’s Hospital, Cambridge. He trained in neuroradiology in Cambridge and Toronto. Current research interests include the imaging of paediatric brain tumours and the use of web-based media for neuroanatomy teaching. He is a supervisor in neuroanatomy at Peterhouse, Cambridge.

Gillian Hall contributes our Muscle Management Feature. She is a Consultant Neuroligist working between The Western General Hospital, Edinburgh and Forth Valley. She trained in Glasgow, Oxford and Cambridge and has a particular interest in diseases of muscle.
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The clinical course of multiple sclerosis (MS) is characterised by an interplay between relapses and progression. Relapses are defined as the occurrence, the recurrence, or the worsening of symptoms of neurological dysfunction that last more than 24 hours, that stabilise or eventually resolve either partially or completely, and that occur 30 days at least after the onset of the preceding relapse. Progression in MS is classically defined as the continual worsening of symptoms and signs for a minimum of six or 12 months. As soon as progression has started, it may reach some plateaus but, usually, never stops. Relapses and remissions may evolve independently of progression, which are features of the relapsing-remitting phase of MS. Progression may evolve with or without superimposed relapses. It may follow a relapsing-remitting phase, which is a feature of the secondary progressive forms of MS.

Relapses and inflammation

There is good evidence that relapses are the clinical counterpart of acute focal inflammation of the central nervous system. For instance, the loss of visual function in acute optic neuritis is associated with an abnormal visual evoked response (VER), reflecting the nerve conduction block, and a gadolinium-enhancing lesion on optic nerve MRI, reflecting the focal blood-brain-barrier breakdown. The recovery of visual function during clinical remission is associated with the restoration of the VER and the cessation of the gadolinium-enhancement on MRI. Serial MRI scanning of the brain has demonstrated that this inflammatory process is much more active than could be expected from the relapse rate. For an average of one clinical relapse every other year, there is an average of ten new MRI lesions: “MS never sleeps”. Relapses may improve only partially or not at all. Similarly, focal inflammation can lead to focal destruction with demyelination, astrocytic gliosis and, more importantly, axonal transection. But inflammation also has some beneficial effects, the most natural evidence being that remission is the rule following a relapse. Some experimental data have also shown a neuroprotective effect of inflammation.

Progression and neurodegeneration

There is increasing evidence that progression is the clinical counterpart of chronic diffuse neurodegeneration. Multifocal inflammatory lesions are not the final story in MS. Pioneer neurologists used to classify MS within neurodegenerative disorders. This has been revived with modern pathological studies and, even more strikingly, with modern imaging techniques. Whole brain and spinal cord atrophy has been well-documented with conventional MRI. The NAWM on conventional MRI is an organ-specific auto-immune disease, i.e. that inflammation is the cause of the neurodegeneration. The succession of relapses eventually leads to accumulation of disability and clinical progression could result from infraclinical relapses. A series of recent observations tend to challenge this classical concept. Beta Interferons are the most widely used drugs among the presently approved disease-modifying drugs. Their effects in MS are well-known, owing to a number of appropriately designed and conducted phase III trials. Results are remarkably consistent. Interferons lead to a 30% reduction in the relapse rate and to a more than 50% reduction in conventional MRI activity. Despite this strong effect on inflammation, the effect of interferons on disability is only marginal and possibly relapse-reduction driven. Furthermore, although interferons have a protective effect on progressive cerebral atrophy in relapsing-remitting MS, such an effect has not been observed for secondary progressive MS.

Campath-1H is a humanised monoclonal antibody, probably the most powerful lymphocyte-depleting antibody. Its administration to MS patients with a very active disease in terms of frequency of relapses, accumulation of disability and MRI activity, results in a profound and prolonged lymphopenia, and the

Relapses, progression, inflammation and neurodegeneration in multiple sclerosis: a changing view

Professor Christian Confavreux is Head of the Department of Neurology A, Hôpital Neurologique, Lyon, France. He is a member of INSERM U433 “Experimental Neurobiology and Physiological Pathology”, as well as head of the EDMUR (European Database for Multiple Sclerosis) Co-ordinating Centre in Lyon. Professor Confavreux is project-leader of the Lyon Multiple Sclerosis Cohort, and also head of NEURO-BIOTEC, Hospices Civils de Lyon and Institut Fédératif des Neurosciences de Lyon. INSERM U433 (Hôpital Neurologique)

Figure 1: Evolution of the relapse rate and the residual DSS before, during and after pregnancy (From Confavreux et al, Ref 25).

From: NEJM 1998; 339:285-91

Review Article
suppression of clinical and MRI activity. In spite of this, progression of clinical disability and cerebral atrophy still occurs.25,26 Similar observations can be gathered with mitoxantrone (personal observations).

Pregnancy is a natural experience which has proven to be very informative in MS. The relapse rate decreases dramatically during pregnancy, notably during the third trimester, where it is reduced by 60% in comparison to the rate observed during the pre-pregnancy year. This is far more than what is obtained with interferons and glatiramer acetate. In contrast, the three-month post-partum period is characterised by a 60% increase in the relapse rate in comparison to the same period of reference. Thereafter, the relapse rate stabilises towards the reference period rate.27 Despite these dramatic changes in the frequency of relapses, progression of disability goes on, seemingly unaffected throughout this period (Figure 1).

Presumably, the most striking results come from the study of the natural history of MS in the Lyon MS Cohort.28 Progression of irreversible disability from the assignment of a score of 4 on the DSS Kurtsze scale27 to the assignment of a score of 6 or 7 is unaffected by the presence or the absence of superimposed relapses before the progressive phase of MS. The same observation is true regarding the presence or the absence of superimposed relapses during the progressive phase, either primary or secondary. Surprisingly, for some intervals in secondary-progressive MS, notably time from assignment of a score of 4 to a score of 7, or from a score of 6 to a score of 7, the progression of disability is slower in the cases with superimposed relapses than in the cases without superimposed relapses (Figure 2).

All these observations give some credit to the fact that relapses do not essentially influence irreversible disability in the long term in MS. They are consistent with what has been shown at the individual level in the 70’s.29 By performing serial quantitative neurological examinations over several years, it appeared in the majority of MS patients that progression of neurological abnormalities was following, after regression analysis, a linear curve or a curvilinear curve (exponential, parabolic,…) but with a small inflexion only, even in the cases with a relapsing-remitting course or with superimposed relapses during the progressive phase of the disease (Figure 3).

**Figure 2**: Schematic representation of the progression of irreversible disability from the assignment of a score 4 to the assignment of a score of 6 or 7. The rate of progression of irreversible disability is essentially not affected by the presence or the absence of superimposed relapses before the progressive phase of MS or during it (From Contavelux et al, Ref 26).

**Figure 3**: Evolution of the neurological examination score with the progress of the disease in a given patient with MS (From Fog and Linnemann, Ref 28).

**What are the consequences of this apparent relapse / progression dissociation?**

Consequences of this paradox are many. For instance, some authors are ready to consider that instead of being an autoimmune disease with secondary neurodegeneration, MS is a primary neurodegenerative disease with secondary autoimmunisation.29 Major consequences lie at the therapeutic level. Inflammation and neurodegeneration seem independent enough for both to be addressed specifically in MS patients. When inflammation has its clinical counterpart, i.e. the relapses, it deserves a specific treatment. A number of first line and second line approved immuno-active drugs are currently available for that purpose. It must be kept in mind however that even with powerful agents such as Campath-1H or mitoxantrone, this strategy essentially does not prevent neurodegeneration. In other words, it remains to be proven that these immuno-active drugs are to be administered as early as possible when the disease starts, in order to prevent future disability. Major efforts in the forthcoming years are therefore to be concentrated on the second player. Powerful tools for protecting the central nervous system from degenerating and for repairing it are to be developed.30 In this respect, strategies for remyelination by using autologous stem cells,31 autologous olfactory ensheathing cells,32 or in situ quiescent premelinating oligodendrocytes33 are all very promising.

**References**


Correspondence Address

Christian Confavreux, MD. Professor of Neurology, Head of Department, INSERM U433. Service de Neurologie A and EDMUS Coordinating Centre, Hôpital Neurologique, Lyon, France.
E-Mail: christian.confavreux@chu-lyon.fr

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Molecular characterisation of motor neuron disorders

Several disorders have as their main site of pathology the cell bodies or axons of motor nerves. In this short article the main genetic abnormalities associated with clinical syndromes affecting motor nerves will be reviewed (see Table 1).

ALS - the most common adult motor neuron disorder

Amyotrophic lateral sclerosis, ALS, (also known as ‘motor neuron disease’ in the UK) is the commonest motor neuron disorder of adults, affecting 4 - 6 per 100,000 individuals. Subtypes such as progressive bulbar palsy, progressive muscular atrophy and primary lateral sclerosis are defined on the basis of the predominance of upper or lower motor neuron involvement and on the distribution of weakness. The prognosis in ALS is poor; with a median survival from diagnosis of less than two years. More prolonged survival is sometimes seen and is more likely the earlier the age of disease onset and in the predominantly spinal forms of the disease. Studies on the association of the apolipoprotein E allele APOE e4 and severity or duration of ALS have yielded conflicting results.1

Some of the proposed causes of ALS are summarised in Box 1.2 Key theories include abnormalities in neurofilaments, oxidative damage, and glutamate excitotoxicity. An interesting recent paper reported that ALS symptoms and neuropathology can be produced in mice bearing a deletion in the promoter region of the vascular endothelial growth factor gene, VEGF.3 This deletion, encompassing the ‘hypoxia response element’, prevents increased VEGF expression during hypoxia. It is suggested that VEGF is either directly trophic to motor nerves or increases the oxygen available to them via increasing blood flow. The hypothesis that ALS may arise due to an altered response to hypoxia is attractive, given that the disorder has an onset in middle life and that motor neurons have high metabolic demands, which might render them selectively vulnerable to such an insult.

What of the environment versus genetic debate in the causation of ALS? Data from twin studies suggest a genetic contribution of 38-85% in apparently sporadic ALS.4 Experience from twin studies suggests that between 5 and 10% of all ALS patients will have a family history of the disorder, most usually compatible with autosomal dominant inheritance.2

Genetics of autosomal dominant familial ALS, FALS

Mutations in Cu/Zn superoxide-dismutase, SOD-1, a chromosome 21q gene encoding an enzyme that protects cells from free-radical damage, are found in one fifth of autosomal dominant FALS cases. To date over 95 different mutations have been described, including point mutations, insertions, deletions and truncating mutations (see http://www.alsod.org). The D90A mutation is unique amongst FALS SOD-1 mutations as it behaves both as a dominant mutation (reported in several populations) and as a recessive mutation in the Scandinavian population. Various explanations for this have been proposed, including that of the haplotype of recessive Scandinavian families harbouring an ALS protective factor such that homozygosity of the mutant SOD-1 is required for the phenotype of motor neuron degeneration to develop.5 Much evidence, including the crucial observation that mice overexpressing human FALS mutant SOD-1 develop an ALS-like phenotype while SOD-1 knock out mice do not, points to mutant SOD-1 causing disease by a toxic ‘gain-of-function’.6 The precise mechanism whereby mutant SOD-1 causes motor neuron death however remains uncertain (see Box 2).

Genetic linkage studies are ongoing to try to determine the abnormal genes in the remaining 80% of FALS cases not harbouring SOD-1 mutations. A recent report details a novel locus on chromosome 18q, determined in a large European kindred with classical autosomal dominant ALS.7 Other reports of linkage have been in kindreds with phenotypes distinct from classical ALS. For example, a dominant form of juvenile ALS (ALS4) has been mapped to chromosome 9q34, and autosomal dominant ALS with frontotemporal dementia (ALS-FTD) has been mapped to 9q21-22. Mutations in the Tau gene have been found in kindreds with ALS with frontotemporal dementia and Parkinsonism.8

Genetic studies in autosomal recessive ALS

Two rare types of autosomal recessive ALS, juvenile ALS type 3 (ALS2) and juvenile ALS type 1 (ALS5) have been mapped to chromosomes 2q33 and 15q15-22 respectively.9 ALS2 was originally reported in a large consanguineous Tunisian family, with a phenotype of upper motor neuron features in the limbs and face and distal amyotrophy. Last year mutations in ALS2, encoding the protein ‘alsin’, a GTPase regulator, were found in 4 such ALS2 families from Saudi Arabia, Kuwait and Tunisia (reviewed in 2). The phenotype in these families ranged from a milder primary lateral sclerosis variant to an ALS phenotype.

Genetic studies in sporadic ALS

Some 2% of apparently sporadic ALS cases harbour mutations in SOD-1, while approximately 1% have deletions in the gene encoding the heavy neurofilament subunit (NFL).4 The major gene that is mutated in spinal muscular atrophy, SMN1 (see below), is not mutated in ALS, although one study suggests that

Box 1 Possible causes of ALS

- Toxins
- Environmental – lead, mercury, manganese, aluminium
- Excitatory amino acids e.g. L-BMAA, L-BOAA
- Intrinsic – excitatory amino acids e.g. glutamate
- Free radicals and oxidative species
- Altered axonal transport
- Altered trophic factor support
- Autoimmune factors e.g. antibodies to L-type voltage-gated Ca2+ channels
- Viruses e.g. enteroviruses or retroviruses
- Altered cellular responses to hypoxia

Box 2 Possible mechanisms of FALS mutant SOD-1 motor nerve damage

- Abnormal copper- or zinc-mediated chemistry
- Abnormal protein misfolding/aggregation
- Free radical damage due to aberrant SOD-1 substrates
- Impaired glutamate homeostasis
- Defects in slow axonal transport
- Primary damage to astrocytes
deletions in the copy gene, SMN2 (see below), are a risk factor for the progressive muscular atrophy variant. Several association studies report the frequency of certain polymorphisms in various genes to be different in ALS cases compared to controls (e.g., in APEX, in Mn-SOD) but none of these has been shown to have clear functional effects to implicate them in disease pathogenesis.

Spinal muscular atrophy (SMA)
The spinal muscular atrophies are another group of motor system disorders with pathology specifically targeted to lower motor neuron cell bodies in the anterior horn of the spinal cord and brain stem motor nuclei. Unlike ALS, most cases of SMA are inherited and have onset in infancy and childhood. The most common variant, childhood onset proximal SMA (SMA Types I, II and III) is inherited as an autosomal recessive trait and is caused by mutations in the survival motor neuron gene SMN1, encoded on chromosome 5q13. SMN1 is present within a duplicated chromosomal region, and the severity of the phenotype resulting from homozygous mutations in SMN1 is modified by the number of copies of the upstream duplicated gene SMN2. Studies of the SMN protein and its interactors show it functions to regulate RNA expression, and the pathological mechanism in SMA is thought to involve an inability to splice pre-messenger RNA in motor neurons.

The adult-onset SMAs (SMA Type IV) are a genetically heterogeneous group of disorders. Generally the disease is milder than in the childhood forms of disease, although significant mor-

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<th>Disease</th>
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Table 1 Genetics of motor neuron diseases

* SOD-1, NFH mutations identified in 1-2% of cases

Abbreviations: ALS - amyotrophic lateral sclerosis, SMA - spinal muscular atrophy, AD - autosomal dominant, AR - autosomal recessive, XL - X-linked, SOD-1 - superoxide dismutase 1, NFH - neurofilament heavy chain polypeptide

Data in Table 1 from Refs 5,10,12 and website http://www.neuro.wustl.edu/neuromuscular/synmot.html
bidity can result. SMN1 mutations are found in approximately 30% of adult-onset cases compatible with autosomal recessive inheritance, with the latest age at onset of weakness reported being greater than 70 years.10,11 Autosomal dominant inheritance has been suggested in around 30% of adult SMA cases.

Distal SMA, also termed distal hereditary motor neuronopa-thy, dHMN, or ‘spinal Charcot-Marie-Tooth Disease’, accounts for about 10% of cases of Charcot-Marie-Tooth disease.12 Subgroups are defined on the basis of clinical criteria and mode of inheritance and several chromosomal linkages have now been determined, most usually in single large pedigrees (see Box 1).13,13 It is noted that carrier females of the expansion can show signs of bulbar weakness or cramps in later life (and many such carriers show chronic denervation on neurophysiological examination).14

Summary

This brief overview has mentioned the main known genetic abnormalities underlying motor neuron disorders. The clinical benefits of the identification of these gene defects are now being seen in improved diagnosis and advice on prognosis, and in genetic counselling. As yet this increased genetic knowledge has not resulted in new effective therapies, and it is to this end that research efforts are now focused.

Correspondence Address

Professor Karen E Morrison, Department of Neurology, The Medical School, University of Birmingham, Edgbaston, Birmingham B15 2TT. E-Mail k.morrison@bham.ac.uk

References

Muscle disease: history, examination and investigation

Gillian Hall

Introduction

As in all neurology, good clinical evaluation is the key to diagnosis of muscle disease. An accurate history and careful examination allows directed investigation and appropriate use of expensive or invasive tests such as genetic analysis or muscle biopsy.

History

Most commonly a patient will complain of muscle weakness, wasting or pain. Does this appear to be focal or generalised? If focal, are there specific complaints? For example, difficulty getting out of a bath or reaching to high cupboards suggesting proximal weakness or difficulty using aerosols suggesting weakness of the long finger flexors (flexion of the distal phalanx; flexor digitorum profundus) as seen in inclusion body myositis (IBM).

Duration of history

Does the patient have an acquired condition or has it been present from birth (congenital or hereditary)? Some dystrophic processes can progress gradually, the patient dismissing earlier symptoms as ‘poor at sports’. The following may give useful clues:

- Reduced tone (‘floppy baby’), breathing or feeding problems at birth
- Delayed motor milestones
- Less sporty than class mates at school

Hereditary disease

Rarely the patient may offer a consistent, positive family history aiding diagnosis. However, in autosomal recessive or x-linked conditions the parents may not know that they carry the gene for a particular disease. Myotonic dystrophy (MD), a so-called ‘triplet repeat’ disease, can demonstrate anticipation and therefore previous generations may remain undiagnosed having had only minor myopathic changes (ptosis or typical facies) or non-muscular complications of the disease such as cataracts or frontal balding. Sudden death of an undiagnosed family member might signify a disturbance of cardiac rhythm (MD, dys-trophinopathies). Prolonged and assisted labour, although not uncommon, might point to muscle disease in the mother.

Metabolic disease

Consider disorders of glycogen and lipid metabolism and of mitochondrial function.

- Muscle pain and cramps on exercise and myoglobinuria after more severe exercise are suggestive of a failure of energy delivery to the muscle. Symptoms after only a matter of minutes are more suggestive of abnormal glycogen metabolism (myophosphorylase deficiency; McArdles Disease) whereas disorders of lipid metabolism tend to present with pain after more prolonged exercise. In the latter case the pain is more severe and prolonged. Patients with problems in lipid metabolism (carnitine palmitoyl transferase deficiency) may have naturally developed into sprinters avoiding long distance events. They may also carry a ‘candy bar’ as a source of instant energy. The second wind phenomenon described in McArdles disease affects the normal transition of cell energy generation from stored glycogen to lipid. Acid alpha-glycerosidase (acid maltase) deficiency (Pompe’s Disease), another glycogen storage disease, may present with a progressive myopathy in association with other organ involvement. Myopathy may also be the presenting feature of a mitochondrial cytopathy. Other things to look out for include a history of seizures, deafness, night blindness (retinitis pigmentosa) and diabetes mellitus. The patient may be of short stature.

Inflammatory muscle disease

Polymyositis, dermatomyositis and sporadic IBM are all regarded as inflammatory disease of muscle. However, unlike the others, IBM does not respond clinically to immunosuppression suggesting that the inflammation is a secondary phenomenon.

Patients with both polymyositis and dermatomyositis may complain of both weakness and muscle pain or tenderness. In dermatomyositis they will also have developed the characteristic rash (see below).

IBM is usually painless. The long finger flexors and quadriceps are involved early (see above).

Myotonia

Clinical myotonia, slow relaxation of contracted muscle, is a feature of MD and certain channnelopathies (hyperkalaemic periodic paralysis and myotonia congenita). It is a symptom about which patients seldom complain. They may simply describe stiffness. It may be demonstrated on clinical and/or electrophysiological examination (see below).

Respiratory and cardiac history

Many muscle diseases can affect both respiratory and cardiac muscle as well as the cardiac conducting system. Ask about shortness of breath, chest pain and palpitations as well as any family history of sudden death (see above).

It is imperative that those known to be affected with a condition that affects the cardiac conducting system (eg MD) have regular ECG screening. Some congenital myopathies such as nemaline myopathy may have gone undetected and present with respiratory failure in the teens. In those conditions with more insidious respiratory failure it is important to consider this, detect it early and, where appropriate, offer nocturnal home ventilatory support.

Examination

Neurological examination

General observation

Weight. Baseline for future indicator of loss of muscle bulk.

Rash. Dermatomyositis is associated with a typical heliotropic rash of the eyelids and cheeks and erythematous, indurated rash on extensor surface of elbows, and knuckles (Gottron’s patches). Fasciculations are a sign of active denervation rather than primary muscle disease. Calf hypertrophy. This is usually a nonspecific pointer to a dystrophic process but has been described in other conditions, SI radiculopathy and following poliomyelitis.

Specific pattern of muscle wasting.

For example, wasting of the facial muscles, scapular fixators and biceps and triceps but with sparing of deltoid suggests fascioscapulohumeral dystrophy (FSHMD). Winging of the scapulae secondary to weakness of the scapular fixators is also seen in other conditions including certain Limb Girdle muscular dystrophies.

Power

In addition to a full examination of muscle strength:

- Is there proximal weakness?
- Can the patient rise from a chair without using his/her arms?
- Can the patient squat and stand up without performing a Gower’s manoeuvre? Is the patient able to lift his arms above his head?
- Is there a specific pattern of weakness (see above; specific pattern of wasting)?
Serum creatine kinase (CK).

Investigations
Serum creatine kinase (CK).

This is a non-specific marker of muscle damage. While there may be a significant rise with active or rapidly progressive disease (polymyositis, dermatomyositis and more severe dystrophies) a modest rise can be seen in non pathological situations; following trauma, excessive exercise or an injection, in black males, carriers of certain X-linked or recessive conditions etc. Some drugs cause a subclinical myopathy, for example statins. CK may be normal in slowly progressive muscle conditions such as MD.

Genetic Studies
The genetic basis of more and more muscle disorders is being uncovered, allowing accurate diagnosis. While testing for some disorders is available routinely, others are only available on a research basis. The European Directory of DNA Laboratories web site (www.eddnal.com) is an excellent place to locate where a specific test can be done. Genetic testing can, however, be time consuming and expensive. Furthermore, in some cases the results are not as black and white as one might expect and care must be taken in interpretation of the results. For all these reasons genetic testing is not a screening test and should be employed with discrimination.

Electrophysiology
EMG
EMG may demonstrate myopathic motor units in the case of myopathy or dystrophy and can help differentiate between focal and generalised conditions. The presence of spontaneous activity associated with myopathic units is suggestive of active inflammatory or necrotic disease. True myotonic discharges are seen in myotonic dystrophy and proximal myotonic myopathy (PROMM) and certain channelopathies (see above). Pseudomyotonia is a less specific finding. Single fibre EMG (SFEMG) can be used to evaluate neuromuscular transmission.

NCS
A subclinical neuropathy is a feature of certain muscle conditions (see above). Repetitive nerve stimulation in conjunction with SFEMG gives further information on neuromuscular junction function.

Imaging
Muscle imaging is not widely used in the UK but there are certain situations in which it can be very useful. Muscle inflammation or oedema is seen as diffuse high signal on T2 weighted MR images. It is therefore possible to identify subacute injury (infarction or denervation) in a particular muscle. It is also useful in focal disease to characterise the distribution of involved musculature and identify an appropriate muscle for biopsy.

Muscle Biopsy
For conditions in which genetic diagnosis is not possible, biopsy may be the definitive diagnostic procedure. Through routine and specialised stains, immunocytochemistry and electron microscopy much information can be gathered. It is possible to diagnose inflammatory, metabolic, congenital myopathic and dystrophic conditions amongst others (see further reading below).

Conclusion
As stated at the outset, careful attention to history, examination and investigation is key to efficient and correct diagnosis. Of course, one must be familiar with a condition in order to tease out the relevant history, elicit the salient signs and arrange the appropriate tests. Hopefully this article provides a framework on which to hang further knowledge.

Further Reading

Correspondence Address
Gillian Hall, Western General Hospital, Crewe Road, Edinburgh EH4 2XU. E-mail ghall@skull.dcn.ed.ac.uk
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:
Date of Preparation: February 2002

Mestinon is the most widely prescribed 1st-line treatment for Myasthenia Gravis (MG) for four very good reasons:

- **Rapid onset**
- **Highly effective**
- **Smooth action**
- **Predictable**

So prescribe Mestinon in MG and watch the smile return to your patients’ faces.

Because every Myasthenia Gravis patient is individual.
The use of electrical stimulation for correction of dropped foot in subjects with upper motor neuron lesions

The concept of Functional Electrical Stimulation (FES) was put forward by Liberson in 1960 when he and his team produced the first electrical stimulation device for the correction of dropped foot due to an upper motor neuron lesion. His concept was that by applying electrical stimulation to paralysed muscles, functional movement could be produced, providing the user with a useful orthotic device. Liberson’s device was a portable neuromuscular stimulator which produced pulses of between 20 and 250µs at a frequency of 30-100Hz and current amplitudes of up to 90mA. Stimulation was timed using a switch placed under the heel of the affected side. When weight was taken from the switch, stimulation was delivered to carbon rubber electrodes placed over the common peroneal nerve as it passes over the head of fibula, causing dorsiflexion. Liberson reported that the gait of hemiplegics was significantly improved by use of the device and that on several occasions users acquired the ability of voluntary dorsiflexion for short periods after its use. Since that time several groups have developed similar systems and the devices have received some clinical use, most notably in the former Yugoslavia. However, until recently, the technique has not been widely used in the UK and there has been a shortage of evidence to support its use.

The Odstock Dropped Foot Stimulator (ODFS) (figure 1) is a single channel, foot switch triggered stimulator designed to elicit dorsiflexion and eversion of the foot by stimulation of the common peroneal nerve, (max. amplitude 100mA, 350µs pulse, 40 Hz). It is a development of the device first described by Liberson. Skin-surface electrodes are placed, typically, over the common peroneal nerve as it passes over the head of fibula and the motor point of tibialis anterior (figure 2). If greater knee flexion is required, the indifferent electrode can be placed over the common peroneal nerve as it passes through the popliteal fossa, eliciting a withdrawal reflex. The rise and fall of the stimulation envelope can be adjusted to prevent a sudden contraction, which might induce a stretch reflex in the calf muscles. There is also a facility to add an extension to the stimulation envelope after heel strike which mimics the natural activity of the anterior tibialis muscle which contracts eccentrically lowering the foot to the ground. The Odstock 2 Channel Stimulator (O2CHS) is a version of the ODFS allowing the correction of bilateral dropped foot controlled by a single foot switch.

By provision of dorsiflexion and eversion, the foot clears the ground in the swing phase more easily. This reduces the effort of gait, reducing compensatory activities such as hip hitching and circumduction. Reduction in effort will lead to a reduction of associated reactions and result in a general lowering of tone. Contraction of the tibialis anterior muscle and the hamstrings via the withdrawal reflex may, by reciprocal inhibition, reduce antagonist activity leading to a more normal modulation of tone in gait. Repeated use of the stimulator may then lead to a pattern of "normal" walking being relearned centrally and long term potentiation of the required pattern of synapses may lead to a reinforcement of this pattern of walking. However, a more immediate benefit from the orthotic use of the device is that walking is easier and safer and therefore confidence will improve leading to an extension of mobility range and an overall improvement in quality of life.

The ODFS was the subject of a randomised controlled trial in which 32 stroke patients who had a stroke for in excess of 6 months were allocated to a treatment group or a control group. The treatment group used the device and also received 12 sessions of physiotherapy in the first month, while the control group who received the same contact time only received physiotherapy. After three months of use the treatment group showed a statistically significant increase in walking speed of 16% and a reduction in the Physiological Cost Index (PCI) of 29% when the stimulator was used while no changes were seen in the control group. No significant ‘carry-over’ effect was seen although a trend was present. Users of the ODFS showed a continuing reduction in quadriceps spasticity measured using the Wartenberg Pendulum Drop Test, which was only seen in the control group while physiotherapy continued. The treatment group also showed a reduction in the Hospital Anxiety and Depression index suggesting an improve-
development and evaluation

West Regional Health Authority

results together with case series data from subjects who had multiple sclerosis were presented to the South and West Regional Health Authority Development and Evaluation Committee. After examining this and evidence from other groups, the committee recommended the ODFS for use in the UK’s National Health Service for patients with upper motor neuron lesions.

Following the trial and some publicity in a national newspaper, there was some considerable demand for treatment and it was therefore decided to set up a clinical service. As previously mentioned the idea of FES is not new and it was our opinion that the reason for its poor take up into clinical practice was for several reasons. Firstly, initial devices had been unreliable with poor technical back up. Secondly, the clinical techniques for its successful application have been poorly documented and practitioners received no training in its use. Thirdly, it was plain from our clinical experience that regular follow up was required to ensure continued effective use of the device. The first problem we hoped we had solved by using new technology and careful design based on considerable clinical experience. The second problem was tackled by writing a detailed clinical manual and by running a regular two day training course for clinicians who wished to use the device.

To satisfy the need for follow up the following clinical model has been adopted. Patients are first seen at an assessment clinic. Subjects are suitable for treatment if they have a dropped foot due to an upper motor neuron lesion and are able to walk at least a few metres with appropriate aids or assistance. The following are contraindications; fixed contractures of the ankle, poorly controlled epilepsy (there is some anecdotal evidence of symptoms being exacerbated by electrical stimulation) and poor skin condition in the area of the electrodes. The effect of the stimulation is not known in pregnancy and pacemaker users are assessed by a cardiologist to ensure the ODFS does not interfere with the pacemaker. The stimulator is tried and if gait can be improved, the patient is recommended for treatment.

The ODFS is fitted over two clinical sessions on consecutive days. On the first day the user is taught how to apply the device while on the second day their ability to do so is assessed and further training given if necessary. If appropriate, carers are also instructed in its use. If the patient has severe calf spasticity it has been found useful to use an exercise stimulator for a period of about an hour a day for one month. By using a stimulator with a slow rising edge ramp, calf spasticity can be reduced and range of motion increased. A recent pilot study has shown that botulinum toxin may also be beneficial in such cases. Follow up is made at 6 weeks, 18 weeks, 45 weeks and 72 weeks from first use and then yearly for as long as the device is used. If users experience problems they are encouraged to contact the clinic so advice can be given, equipment repaired or extra clinic sessions arranged if necessary.

Following the establishment of a clinical service, it was decided to continue recording the main outcome measures of walking speed and PCI that had been recorded in the RCT. While increased walking speed was not highlighted as a significant reason for continued use of the ODFS, it has been shown by Wade et al. to be representative of overall gait function. An audit of these parameters over the first 18 weeks of use confirmed the results of the original RCT and also showed a significant carryover effect i.e. an improvement in walking ability when not using the stimulator, in a group of 111 stroke subjects. Overall, users walked 27% faster when they used the device with a carryover effect of 14%. In a subgroup of 27 ODFS users walking speed both with and without the device was observed to improve over the first 18 weeks and thereafter remain unchanged (figure 3). As the ODFS users were an average of 5.4(s.d ±10.7) years post stroke this supports the hypothesis that the carryover observed was due to use of the stimulator rather than natural recovery following the stroke. In a group of 78 MS subjects, users walked 20% faster when using the device. However no carryover effect was observed. In a subgroup of 20 MS users, this improved walking speed with the device was shown to also peaks at 18 weeks with no significant change from initial values after that time. 18 MS users of the bilateral dropped foot stimulator showed a 48% increase in walking speed at 18 weeks but again no significant carryover effect although a strong trend was observed.

A questionnaire survey indicated that the most common reasons for using the ODFS were that it reduced the effort of walking, reduced tripping and improved confidence. Compliance was 92% at 18 weeks and 86% at 1 year. In the year 2000 the device was recommended by the Royal College of Physicians in their publication "National clinical guidelines on stroke".

Future developments

While the ODFS has been shown to improve gait by correction of dropped foot, problems often remain with movement of

Figure 3.
other joints, in particular the knee and hip. The O2CHS can be used to add a second channel of stimulation. Hip extension in the stance phase can be improved by stimulation of the gluteus maximus while hip abduction can be improved by stimulation of the gluteus medius. Knee flexion can be improved by stimulation of the hamstrings at terminal stance and initial swing while the same muscle can be used to control knee hyperextension at initial floor contact. The calf muscles can be stimulated to improve push off and triceps can be stimulated to improve arm swing and therefore balance while walking in patients with significant associated reaction in the upper limb. Preliminary investigations suggest that the ODFS may be applied in cases of Parkinson’s Syndrome to help initiate gait and prevent freezing.

Conclusion
It has been demonstrated by RCT that the ODFS can improve the mobility of people who have a dropped foot following stroke. A clinical service has been successfully set up and these techniques successfully transferred to other centres. Audit of these services has confirmed the RCT results and further indicated that mobility can be improved in people with multiple sclerosis. Use of the bilateral system in MS can delay final dependence on a wheelchair, providing a means of access where a chair cannot be used. Compliance of both devices is high suggesting that they are well accepted and provide a useful benefit to their users.

For further information, please visit our web site: www.salisburyfes.com

References
6. See our web page www.salisburyfes.com
Sharing the risk of multiple sclerosis

The provision of disease modifying treatments for patients with multiple sclerosis has taken another turn along the treacherous NHS funding path. The National Institute of Clinical Excellence (NICE; www.nice.org.uk), set up to provide patients, health professionals and the public with authoritative, robust and reliable guidelines on current best practice, has published its final guidelines. Not unexpectedly after several years of studying the problem, the decision is that neither β-interferon nor glatiramer acetate are cost effective on clinical grounds for the treatment of multiple sclerosis. Undoubtedly anticipating a storm of protest over this decision, the Department of Health has come up with a new scheme of ‘risk-sharing’ by which the drugs should be available to all those patients in England and Wales who meet the criteria of eligibility determined by the Association of British Neurologists (www.theabn.org).

The problem, as usual, is money. NICE functions to give scientifically based guidance on cost-effectiveness of a variety of treatments. Most people now agree that in a financially limited health service there have to be assessments of drug effectiveness and there has to be a pecuniary figure for each treatment (usually cost per quality adjusted life year (QALY) which the service can finance. Then whatever the cost per QALY, a drug is either used or not used. However, controversy will always exist when monetary values are placed alongside a patient’s quality of life. It is one thing to set values to cost effectiveness thresholds and another to be a patient suffering from a particular disease, or a clinician struggling to keep a disease at bay. Patients and patient groups, quite justifiably, will argue that more money should be available for their treatment. The problem is compounded in the case of multiple sclerosis, a disease for which few other therapies exist. In reality, NICE and the Department of Health are always likely to run into these problems when assessing drug costs in terms of quality of life measures, when the decision is not to fund a particular therapy.

The only real alternative therefore appears to be addressing the question of drug costs. The new proposals instituted by the Department of Health go some way towards tackling the issue of drug costs, and the scheme may well act as a blueprint for the provision of ‘NICE-negative’ drugs in the future.

“The new proposals instituted by the Department of Health go some way towards tackling the issue of drug costs, and the scheme may well act as a blueprint for the provision of ‘NICE-negative’ drugs in the future.”

Importantly, under the scheme the initial cost of the drugs have fallen to between £6,000 and £9,000, compared to previous figures of between £7,000 and £12,000. Due to ‘risk-sharing’ these costs may fall further. The estimated yearly bill for β-interferon and glatiramer acetate will be £50m, and it is thought that between 7,500 and 9,000 patients (approximately 15% of all patients with multiple sclerosis) will be eligible for treatment under ABN guidelines.

Whilst ‘risk-sharing’ seems highly logical and may provide some answers to the problems of high-cost drugs, several quarters have raised concerns over the implementation of the scheme. The ABN has for a long time advocated the use of disease modifying treatments in multiple sclerosis for all patients meeting set criteria, but notably has foreseen problems with the new scheme. They point out that up to 30,000 patients will have to be assessed within the next 18 months for eligibility, which in itself is a reasonably lengthy procedure. On top of this, annual assessments of patients on treatment will require time and resources to be taken from an already stretched service. The ABN has called for additional infrastructure support from the Department of Health in order to institute the scheme and prevent it from compromising other services provided by neurologists. The idea of linking clinical effectiveness to drug cost on the face of things seems an ideal solution to the ever-expanding problem of high-cost drug provision. However, the institution of change may require large amounts of money and a reorganisation of existing services. It remains to be seen in the long run whether ‘risk-sharing’ will actually significantly lower the cost of β-interferon to the NHS.

Correspondence Address
Alastair Wilkins,
Department of Neurology, Addenbrooks Hospital, Hills Road,
Cambridge, CB2 2PY
E-mail: aw255@cam.ac.uk

24th Advanced Clinical Neurology Course
26 - 28 March 2002 - University of Edinburgh

Topics will include: muscle, stroke, peripheral nerve, a CPC, some political issues. The course is aimed at trainee neurologists but others are very welcome.

It is supported by the Guarantors of Brain.

Course fee, including accommodation and all meals £250.

Further details from Professor Charles Warlow, Department of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh EH4 2X. Phone 0131 537 2082. email cpw@skull.dcn.ed.ac.uk
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Lamictal™
Epilepsy treatment with women in mind
Lamictal (lamotrigine)

**Brief Prescribing Information.** Presentation: Pale yellow tablets containing 25mg, 50mg, 100mg and 200mg lamotrigine, and white dispersible/cheviable tablets containing 2mg, 5mg, 10mg and 15mg lamotrigine.

**Uses:** Monotherapy. Not recommended in children under 12 years. Adults and children over 12 years for partial epilepsy with or without secondarily generalised tonic-clonic seizures and in primary generalised tonic-clonic seizures. **Add-on therapy:** Adults and children over 2 years for partial epilepsy with or without secondary generalised tonic-clonic seizures and in primary generalised tonic-clonic seizures. Seizures associated with Lennox-Gastaut syndrome.

**Dosage and Administration:** Initial dose and subsequent dose escalation should not be exceeded to minimise the risk of rash. Monotherapy. Initial dose is 25mg daily for two weeks, followed by 50mg daily for two weeks. Dose should be increased by a maximum of 50-100mg every 1-2 weeks until optimal response. Usual maintenance dose is 100-240mg/day in one dose, or two divided doses. **Add-on therapy:** Adults and Children over 12 years. To sodium valproate with or without any other antiepileptic drug (AED), initial dose 25mg every alternate day for two weeks, followed by 25mg/day for two weeks. Dose should be increased by 25-30mg every 1-2 weeks until optimal response. Usual maintenance dose is 100-200mg/day in one dose, or two divided doses. To enzyme inducing AEDs with or without other AEDs (but NOT valproate), initial dose is 50mg daily for two weeks, followed by 100mg daily for two divided doses for two weeks. Dose should be increased by 100mg every 1-2 weeks until optimal response. Usual maintenance dose is 200 to 800mg/day in two divided doses. **Children aged 2-12 years:** To be dosed on a mg/kg basis until the adult recommended initiation dose is reached. Add-on to sodium valproate with or without any other AED, initial dose is 0.15mg/kg bodyweight/day given once a day for two weeks, followed by 0.3mg/kg/day given once a day for two weeks. Dose should then be increased by a maximum of 0.5mg/kg every 1-2 weeks until optimal response. Usual maintenance dose is 1 to 3mg/kg/day given in one dose, or two divided doses. Add-on to enzyme-inducing AEDs with or without other AEDs (but NOT valproate) is 0.5mg/kg bodyweight/day given in two divided doses for two weeks, followed by 1.2mg/kg daily for two weeks given in two divided doses. Dose should then be increased by a maximum of 1.2mg/kg every 1-2 weeks until optimal response. Usual maintenance dose is 3-5mg/kg/day given in two divided doses. Weight of child should be monitored and dose adjusted as appropriate. If calculated dose is 1-mg/day then 2mg may be taken on alternate days for the first two weeks. **Dose Evolution:** Starter packs covering the first four weeks treatment are available for adults and children over 12 years. When the pharmacokinetic interaction of any AED with Lamictal is unknown the dose escalation for Lamictal and concurrent sodium valproate should be used with extreme caution. No dose adjustment required.

**Contra-indications:** Hypersensitivity to lamotrigine.

**Precautions:** Adverse skin reactions, mostly mild and self-limiting, may occur generally during the first 8 weeks of treatment. Rarely, serious, potentially life-threatening rashes including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. Patients should be promptly evaluated and Lamictal withdrawn unless the rash is clearly not drug related. High initial dose, exceeding the recommended dose escalation rate, and concurrent use of sodium valproate have been associated with an increased risk of rash. Patients who acutely develop symptoms suggestive of hypersensitivity such as rash, fever, lymphadenopathy, facial oedema, blood and liver abnormalities, flu-like symptoms, drowsiness or worsening seizure control, should be evaluated immediately and Lamictal discontinued if an alternative aetiology cannot be established. **Hepatic impairment:** Dose reductions recommended.

**Withdrawal:** Avoid abrupt withdrawal, except for safety reasons. **Pregnancy:** Lamictal was not carcinomaigenic, mutagenic, teratogenic or shown to impair fertility in animal studies. There are insufficient data available on the use of Lamictal in human pregnancy to evaluate its safety. Lamictal should not be used during pregnancy unless, in the opinion of the physician, the potential benefits of treatment to the mother outweigh any possible risk to the developing foetus. **Driving:** As with all AEDs, the individual response should be considered.

**Interactions:** Antiepileptic drugs which alter certain metabolising enzymes in the liver affect the pharmacokinetics of Lamictal (see Dosage and Administration). This is also important during AED withdrawal.

**Side and Adverse Effects:** With monotherapy: headache, tiredness, rash, nausea, dizziness, tiredness, and insomnia. Other adverse experiences have included dizziness, blurred vision, agitation, confusion, hallucinations and haematological abnormalities. Also movement disorders such as tics, unsteadiness, ataxia, nystagmus and tremor. Severe skin reactions including SJS and TEN have occurred rarely, with or without secondarily generalised tonic-clonic seizures. Seizures associated with Lennox-Gastaut syndrome. **Adverse skin reactions, mostly mild and self-limiting,** may occur generally during the first 8 weeks of treatment. Rarely, serious, potentially life-threatening rashes including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. Patients should be promptly evaluated and Lamictal withdrawn unless the rash is clearly not drug related. High initial dose, exceeding the recommended dose escalation rate, and concurrent use of sodium valproate have been associated with an increased risk of rash. Patients who acutely develop symptoms suggestive of hypersensitivity such as rash, fever, lymphadenopathy, facial oedema, blood and liver abnormalities, flu-like symptoms, drowsiness or worsening seizure control, should be evaluated immediately and Lamictal discontinued if an alternative aetiology cannot be established. **Hepatic impairment:** Dose reductions recommended.

**Withdrawal:** Avoid abrupt withdrawal, except for safety reasons. **Pregnancy:** Lamictal was not carcinogenic, mutagenic, teratogenic or shown to impair fertility in animal studies. There are insufficient data available on the use of Lamictal in human pregnancy to evaluate its safety. Lamictal should not be used during pregnancy unless, in the opinion of the physician, the potential benefits of treatment to the mother outweigh any possible risk to the developing foetus. **Driving:** As with all AEDs, the individual response should be considered.

**Interactions:** Antiepileptic drugs which alter certain metabolising enzymes in the liver affect the pharmacokinetics of Lamictal (see Dosage and Administration). This is also important during AED withdrawal.

**Side and Adverse Effects:** With monotherapy: headache, tiredness, rash, nausea, dizziness, tiredness, and insomnia. Other adverse experiences have included dizziness, blurred vision, agitation, confusion, hallucinations and haematological abnormalities. Also movement disorders such as tics, unsteadiness, ataxia, nystagmus and tremor. Severe skin reactions including SJS and TEN have occurred rarely, with or without signs of hypersensitivity syndrome. Elevations of liver function tests and rare reports of hepatic dysfunction. **Legal category:** PO2.

**Basic NHS costs:** £16.45 for Monotherapy Starter Pack of 42 x 25mg tablets (PL0003/0272); £27.98 for Non-Valproate Starter Pack of 42 x 25mg tablets (PL0003/0275); £28.25 for Valproate Starter Pack of 21 x 25mg tablets (PL0003/0272). £64.37 for 56 x 100mg tablets (PL0003/0272); £110.42 for 56 x 200mg tablets (PL0003/0272). £21.95 for pack of 56 x 25mg tablets (PL0003/0272); £37.51 for pack of 56 x 50mg tablets (PL0003/0272). £87.75 for pack of 56 x 100mg tablets (PL0003/0272). £121.95 for pack of 56 x 200mg dispersible tablets (PL0003/0272). £64.57 for pack of 56 x 100mg dispersible tablets (PL0003/0272). £21.95 for pack of 56 x 200mg dispersible tablets (PL0003/0272).

**Product Licence Holder:** The Wellcome Foundation Ltd, Middlesex UB8 1NN. Lamictal is a Trade mark of the GlaxoSmithKline Group of Companies. Further information is available from GlaxoSmithKline UK Limited, Stockley Park West, Uxbridge, Middlesex UB11 8TJ. **Note:** If changes in AED medication are to be made they should be completed before conception.* The UK Pregnancy Register (0800 340 1248) is collecting prospective data on the effects of all AEDs in pregnancy. Please phone for information or to register a patient.


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Charles Dickens, Qua Neurologist

Andrew Larner

It is well recognised that acute observers of nature may record medical conditions, unwittingly or not, sometimes prior to their description (and hence legitimation) by members of the medical professions. A number of examples of relevance to neurology are evident in the work of painters. Likewise, in the writings of non-medical authors, subsequent medical readers have felt able to discern accounts corresponding to conditions recognised clinically. Perhaps nowhere is this more evident than in the works of Charles Dickens, famed for his close observation of the human condition.

The classic example is that of Joe the fat boy, in the Posthumous Papers of the Pickwick Club (1837), whose obesity, ruddy complexion, hyperventilation, and dropsy prompted use of the term “Pickwickian syndrome” to describe similar cases, only more recently superseded by “obstructive sleep apnoea syndrome.” Dickens’s powers of observation, in respect of this case, have been claimed to exceed those of his physician contemporaries.1 (Cosnett, reviewing sleep disorders in Dickens’s works,2 suggests that Joe is a sleep diagnostically mute, being symptomatically prone to the belief that they are based on observation of actual patients. (We have no difficulties accepting this premise when viewing the work of painters.) Here I review previous relevant publications, and suggest some further cases of possible interest.

Lord Brain, famed for his textbooks of neurological diagnosis and dissection, identified several “Dickensian dysgraphics.” For example, Sir Leicester Dedlock (Black House, 1853), William Dorrit (Little Dorrit, 1857), and Mrs Skewton (Dombey and Son, 1848) are all adjudged to suffer cerebrovascular accidents. We would perhaps not be quite so ready to ascribe Mrs Skewton’s head tremor, evident before her stroke, to “cerebral arteriosclerosis,” other than as a diagnosis of exclusion (“senile tremor”). The tremor of Mr Dolls (Our Mutual Friend, 1865) may simply reflect alcohol withdrawal but might be regarded as an essential tremor. Betty Higden’s blackout (Our Mutual Friend, book 3, chapter 8) are uncertain whether she has suffered a faint or a fit, a familiar enough diagnostic dilemma even today. The old lady’s rapid recovery and flight from the scene suggest it was a syncopal event. An epileptic seizure is the likely cause of death of Anthony Chuzzlewit (Martin Chuzzlewit, 1844).4 Grandfather Smallweed’s need to be carried everywhere (Black House) is ascribed to paraplegia, likewise Mrs Clennam’s confinement to her room (Little Dorrit). She, however, makes a most startling recovery from apparently lost neurological function, getting up and running from the house when confronted with alarming news. Cousin Feenix (Dombey and Son) is described as “meaning to go in a straight line, but turning off sideways by reason of his wiffl legs,” diagnosed by Brain as an ataxic gait.5 Perkin has mentioned a number of other Dickensian characters with apparent gait disturbances, without professing diagnoses.6 Perhaps Sairey Gamp’s difficulties (Martin Chuzzlewit) result from her partiality to gin.

Lord Brain also mentions Dickens’s descriptions of the sequence of head injury, as in Mrs Joe Gargery (Great Expectations, 1861) and Eugene Wrayburn (Our Mutual Friend), Cases of “mental defectives” are also in evidence, such as Maggy (Little Dorrit), and the title character of Barnaby Rudge. Exactly what diagnosis one might apply to these individuals with learning disability is uncertain, but it has been argued that Rudge has autism.6

Mrs Gradgrind (Hard Times, 1854) famously fails to locate her pain any more precisely than “somewhere in the room,” which has been taken as an example of the difficulty of locating pain of visceral origin, so familiar in clinical practice. For this description Dickens earns the chastisement of Oliver Sacks, who informs us that “one cannot have a pain except in oneself.”7

The field of movement disorders might be expected to provide a rich source of materials for a novelist as observant as Dickens. In David Copperfield (1850), Uriah Heep’s writings have suggested a generalised dystonia, Mr Creakle the schoolmaster may have a spasmodic dyshisia,8 and the sleepy waiter at the Golden Cross Inn (chapter 19) restless legs syndrome.9 Cosnett has suggested that two characters in Little Dorrit are worthy of note in this context: the description of Jeremiah Flintwinch is highly suggestive of spasmodic torticollis, and Mr Pancks manifests features concordant with those of Gilles de la Tourette syndrome.10 To this list one might perhaps add Frederick Dorrit, uncle of the title character of Little Dorrit, who is described (chapter 8) as “stooped a good deal,” turning round in a “slow, stiff, stooping manner,” and speaking with a “weak and quavering voice,” features which might be construed as parkinsonism. A clearer description of parkinsonism, with an accompanying eye movement disorder, highly suggestive of progressive supranuclear palsy, has been identified in The Lazy Tour of Two Idle Apprentices (1857), written jointly by Dickens and his friend Wilkie Collins.11 This latter account predates by more than 100 years the eponymous description of Steele et al. (1964). Likewise Mr Pancks predates Gilles de la Tourette’s (1885) description.12

A few passages give insight into nineteenth century attempts at neurorehabilitation, noteworthy though these were. Most famous perhaps is the little crutch used by Tiny Tim Cratchit in A Christmas Carol (1843); his limbs are also supported by an “iron frame.” Jenny Wren, the dolls’ dressmaker in Our Mutual Friend, also uses a crutch. Prostheses are also in evidence: the wooden leg of Silas Wegg (Our Mutual Friend) is illustrated by Marcus Stone as little more than a stump (book 3, chapters 7 and 14) which proves a significant hindrance when the protagonist is running with his crutch. The classic example is that of Joe the fat boy, in the Pickwick Club (1842); his limbs are also supported by an “iron frame.”

Orwell contends that Dickens sees human beings with the most intense vividly yet, as a caricaturist, with a narrowness of vision; the mark of his writing is seen as the unnecessary detail.7 These are perhaps the very qualities which permit us to see some of his characters “like pictures,” “fixed like painted miniatures,”6 and hence in certain cases as exemplars of neurological diseases.

References

Correspondence Address
Andrew J Larner, Walton Centre for Neurology and Neurosurgery Lower Lane, Fazakerley, Liverpool L9 7LJ, U.K.
E.mail: larner-a@wcwn-tr.nwest.nhs.uk
Continuous waking day dopaminergic stimulation with APO-go® reset the threshold for dyskinesias and led to a pronounced reduction in their frequency

APO-go® should be considered in all patients before stereotactic neurosurgical intervention.

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APO-go® showed no loss of therapeutic effect after 5 years.

2 O'Sullivan JD, Lees AJ, Hospital Medicine, 1999
3 Giron LT, Koller WC, Drug Safety, 1996
4 Ellis C et al, Parkinsonism & Related Disorders, 1997
5 Colosimo C et al, Clinical Neuropharmacology, 1994

Abridged Prescribing Information

Uses
The treatment of disabling motor fluctuations in Parkinson’s disease which persist after treatment with levodopa and/or other dopamine agonists.

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

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

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

Interactions
Neuroleptic drugs may have an antagonistic effect if used with apomorphine. Apomorphine may potentiate the antihypertensive effect of antihypertensive and cardioactive drugs.

Precautions
Use with caution in patients with renal, pulmonary or cardiovascular disease, or who are prone to nausea and vomiting. Extra caution is recommended during inauguration of therapy in elderly and/or debilitated patients. Since apomorphine may produce hypotension, care should be exercised in patients with cardiac disease or who are taking vasoactive drugs, particularly when pre-existing postural hypotension is present. Neuropsychiatric disturbances associated with Parkinson’s disease may be exacerbated by APO-go, but APO-go may also improve the symptoms of such disturbances.

Side Effects
Local induration and nodules at the sites of subcutaneous injection leading to erythema, tenderness, induration, and (rarely) ulceration. Drug-induced dyskinesias during “on” periods can be severe, and in a few patients may result in cessation of therapy. Postural hypotension is seen infrequently and is usually transient. Transient sedation following each dose of apomorphine may occur at the start of therapy, but this usually resolves after a few weeks of treatment. Nausea and vomiting may occur, particularly when APO-go treatment is initiated, usually as a result of the omission of domperidone. Transient mild confusion and visual hallucinations have occurred during apomorphine therapy, and neuropsychiatric disturbances may be exacerbated by apomorphine; however, APO-go may also improve the symptoms of such disturbances. The use of apomorphine HCl in conjunction with levodopa treatment may cause Coombs’ positive haemolytic anaemia. Eosinophilia has occurred in only a few patients during treatment with apomorphine HCl.

Presentation and Basic NHS Cost: APO-go Ampoules contain apomorphine hydrochloride; 10mg/ml, as follows: 20mg in 2ml – basic NHS cost £17.96 – per carton of 5 ampoules. 50mg in 5ml – basic NHS cost £76.16 – per carton of 5 ampoules.

Marketing Authorisation Number: PL 05928/0020
Legal Category: POM.

Date of Last Review: September 2000.
Version Number: APG.APV1
Your Association needs you!

The Spring meeting of the Association of British Neurologists, kindly organised by Dr M Donaghy, will take place in Oxford from 3-5th April. Watch out for these key features:

The meeting will begin with a symposium on treating neuromuscular disease. A variety of topics will be discussed, including:

- Guillain-Barré syndrome
- Vasculitic neuropathy
- Chronic inflammatory demyelinating polyneuropathy
- Multifocal motor neuropathy
- Motor neurone diseases, myasthenias and neuromyotonias
- Inflammatory neuropathies.

After the symposium, there will be a meeting of the MS Database User Group.

The final session of the first day is a satellite symposium “Developments in Parkinson’s disease: Imaging and Autopsy Studies,” with Professors Lees and Brookes and Dr Burn. Professor Lees will be talking on clinical diagnostic accuracy based on pathology studies, Professor Brookes on neuroimaging in Parkinson’s disease, and Dr Burn on Lewy Body Dementia.

The next two days consist of platform presentations - grouped by topic - as well as invited guest lectures. Baroness Greenfield will give a talk on ‘The Private Life of the Brain’ and Dr Charlton on ‘Neuroendocrinology, reproduction, your nose, and sex’.

For the first time, due to the record number of excellent abstracts, there will also be parallel sessions on each day.

The morning session of day two will focus on Parkinson’s disease and movement disorders. This is followed by two parallel sessions. The first, on multiple sclerosis, considers topics such as: the natural history of multiple sclerosis; the predictive value of brain lesion load in determining brain atrophy; the effect of beta interferon on progression of axonal injury; and validation of the McDonald criteria in patients with clinically isolated syndromes. The other parallel session will be on Parkinson’s disease and movement disorders, with talks by Drs Pal, Silverdale, Filipovic and Frima.

In the afternoon, there will be parallel sessions on epilepsy & dementia, and multiple sclerosis. A general neurology session will look at 10 year survival data from the Scottish MND register, and there will also be a session on neurological and cognitive dysfunction in ‘never-encephalopathic’ patients awaiting liver transplantation.

Finally the afternoon ends with a poster session with refreshments!

Beta interferon and the DoH risk sharing scheme – breakfast meeting

For early risers, there is a breakfast meeting at 7.30am on 5th April, to give an update on Beta Interferon and the Department of Health risk sharing scheme. More information about this can be found on pages 19 and 39 of this magazine.

The final day’s morning session will concentrate on vascular disease, followed by parallel sessions on General Neurology and Epilepsy. The afternoon has parallel sessions once again in General Neurology, and Muscle Disease.

There will be plenty of time for socialising, with a drinks reception in the Museum of Natural History followed by dinner in Keeble College. We are sure that this will be an enjoyable and exciting meeting. Please come! Test yourself on the CPC. Have fun and get some CME points the easy way!

David Bateman, Bath
Preclinical safety: Fertility and developmental studies with interferon beta-1a in rhesus monkeys show no serious adverse effects on early development, with no observed teratogenic effects on the developing embryo. No teratogenic effects or effects on fetal or neonatal development were observed.


Indications: For the treatment of relapsing-remitting multiple sclerosis. No clinical criteria that would predict response to AVONEX® have been identified. Dosage and Administration: 30 mcg injected (1 ml solution) IM once a week. AVONEX® should be reconstituted with the solvent supplied. Treatment should be initiated under supervision of a physician experienced in the treatment of the disease. An antipyretic analgesic is advised to decrease the flu-like symptoms associated with AVONEX® administration. AVONEX® should not be used in children.

Contraindications: Hypersensitivity to interferon beta or human albumin; pregnant patients; nursing mothers; patients with severe depressive disorders and/or suicidal ideation; epileptic patients not adequately controlled by treatment. Precautions: The most common adverse events associated with interferon beta are symptoms of the flu-like syndrome, usually most prominent at therapy initiation and decreasing in frequency and severity with continued treatment. Colds AVONEX® should be used with caution in patients with depression and/or suicidal ideation. Patients exhibiting depression should be closely monitored, treated appropriately, and cessation of AVONEX® considered. AVONEX® should be used cautiously in patients with pre-existing infections. Normal infections should be treated with appropriate anti-infective therapy prior to resuming AVONEX®. Pregnancy and Lactation: See Contraindications. Females should take contraceptive precautions. AVONEX® should be used with caution in patients with cardiac disease, severe renal or hepatic failure or severe myelosuppression, and the patients should be closely monitored. Routine periodic blood chemistry and haematology tests are recommended during treatment with AVONEX®. Certain laboratory abnormalities may also occur which do not usually require treatment. Serum neutralising antibodies against AVONEX® may develop. Drug Interactions: No formal interaction studies have been conducted with AVONEX® in humans. Clinical studies indicate that concomitant use of AVONEX® with medical products with a narrow therapeutic index and dependent on hepatic cytochrome P450 for clearance is contraindicated in combining AVONEX® with medical products with a narrow therapeutic index and dependent on hepatic cytochrome P450 for clearance.

Side Effects: The most commonly reported symptoms of the flu syndrome are muscle aches, fever, chills, headache and nausea. Other less common events include: Body as a whole: asthenia, hyperventilation, severe allergic reactions, syncope, episodes. Skin and appendages: alopecia, injection site reaction, pruritus, severe allergic reactions, syncope. Skin and appendages: rash, urticaria. Digestive system: nausea, vomiting. Respiratory system: chest pain, palpitations, tachycardia, vasodilation. Cardiovascular system: arrhythmia, cardiomyopathy, congestive heart failure. Endocrine system: diabetes, hyper- and hypothyroidism, confusion, emotional disorders and laboratory abnormalities have been reported with interferons. Rare cases of arthritis, myalgia, and myasthenia gravis have been reported with AVONEX®. Preclinical safety: Fertility and development studies with interferon beta-1a in rhesus monkeys show no serious adverse effects at high doses. No teratogenic effects or effects on fetal or neonatal development were observed.
American Epilepsy Society Annual Meeting
30 November - 5 December 2001, Philadelphia, USA

The American Epilepsy Society meets each year in early December, usually alternating East and West Coast venues. Unseasonably warm weather in Philadelphia contributed to another enjoyable opportunity to meet old friends, catch up on some recent advances in the basic sciences relating to epilepsy and observe trends in North American clinical practice.

The complexities of seizure pathogenesis and epilepsy genetics have delayed the impact of the molecular biology revolution on epilepsy practice compared to some other areas of clinical neurology. The immediate future lies in the genetics of neurodevelopmental dysfunction and a better understanding at the molecular level of neurotransmitter receptors and ion channels.

Epilepsy occurs in the majority of patients with more severe cortical dysplasias including the lissencephaly syndromes and tuberous sclerosis. More subtle malformations account for significant numbers of other patients and the genetic defects underlying several of these have become evident over the last 10 years. LIS-1 (less memorably renamed PAFH1B1) gene mutations associate with lissencephaly, epilepsy, mental retardation and facial dysmorphism (Miller-Dieker syndrome). Disruption of post mitotic migration of neural cells from the ventricular zone to the cortical surface also occurs in filamin 1 (FLN1; chromosome Xq28) and doublecortin (DCX; chromosome Xq22) gene mutations. These exhibit sexual dimorphism. DCX protein interacts with microtubules of the neuronal cytoskeleton important for neuronal migration. Gene mutation in males is associated with (X linked) lissencephaly, but in females subcortical band heterotopia (SBH) occurs. Subcortical bands are separated from normal overlying cortex which may in fact be the site of seizure generation. In tuberous sclerosis abnormal hamartin (TSC1 gene) and tuberin (TSC2 gene) protein formation probably affects cell proliferation. Seizures arise from focal cortical dysplasia evident as tubers containing dysplastic neurones, astrocytosis and giant cells. Most recently 2 separate reelin protein gene (RELN; chromosome 7Q22) mutations have been described in families with autosomal recessive forms of lissencephaly.

Autosomal dominant frontal lobe epilepsy (ADFLE) was the first epilepsy syndrome linked to an ion channel disorder. Mutations in the neuronal nicotinic acetylcholine receptor alpha 4 subunit gene (CHRNA4) in some families leads to ligand gated calcium channel dysfunction. This alters inhibitory and excitatory neurotransmitter release and presumably plays a role in the pathogenesis of seizures through this mechanism. Voltage gated potassium and sodium channels are implicated in other epilepsy syndromes but for the most part these exhibit genetic heterogeneity imposing some diagnostic limitations in clinical practice. Benign familial neonatal convulsions (BFNC) presents with frequent tonic/clonic seizures on the second or third day of life. This autosomal dominant disorder has a high penetrance but fits usually stop by 4 months of age. Only a minority of patients go on to have seizures as adults. Separate voltage gated potassium channel gene (KCNQ2; chromosome 20 and KCNQ3; chromosome 8) mutations have been identified in this condition. Generalised epilepsy with febrile seizures plus (GEFS+) is another early onset epilepsy syndrome. In this case separate sodium channel subunit gene mutations (SCN1B; chromosome 1q and SCN1A; chromosome 2q) are implicated. Most recently mutations of the GABA A receptor gene (GABRG2) have also been identified in 2 separate families with this disorder.

Once again this was a very worthwhile meeting for anyone interested in epilepsy.

Steve Wroe, Ipswich

View abstracts at http://www.aesnet.org/
The next annual meeting will take place 6-11 December, 2002 in Seattle, US.

The National Centre for Young People with Epilepsy

Epilepsy is the world’s most common severe neurological condition. One in 130 of the UK population has epilepsy – around 350,000 at any one time, of whom some 75,000 are children and young people.

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**Keppra** Prescribing Information:

**Presentation:** Keppra 250 mg, 500 mg and 1,000 mg film-coated tablets containing 250 mg, 500 mg and 1,000 mg levetiracetam respectively.

**Uses:** Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in patients with epilepsy.

**Dosage and administration:**
- **Adults and adolescents older than 16 years:** The initial therapeutic dose is 500 mg twice daily which can be started on the first day of treatment. Depending upon clinical response and tolerance the dose can be increased up to 1,500 mg twice daily. Dose changes can be made in 500 mg twice daily increments or decrements every two to four weeks.
- **Elderly:** Adjustment of the dose is recommended in elderly patients with compromised renal function.
- **Children (under 16 years):** Not recommended.
- **Patients with renal impairment:** Adjust dose according to creatinine clearance as advised in SPC.
- **Patients with hepatic impairment:** No dose adjustment with mild to moderate hepatic impairment. In patients with severe hepatic impairment and creatinine clearance <70 ml/min a 50% reduction of the daily maintenance dose is recommended.

**Contraindications:** Hypersensitivity to levetiracetam, other pyrrolidone derivatives or excipients.

**Warnings and special precautions for use:** If discontinuing treatment reduce dose gradually as advised in SPC. Patients with hepatic impairment: No dose adjustment with mild to moderate hepatic impairment. In patients with severe hepatic impairment and creatinine clearance <70 ml/min a 50% reduction of the daily maintenance dose is recommended.

**Interactions:** Keppra did not affect serum concentrations of phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin or primidone. Drugs excreted by active tubular secretion could reduce the renal clearance of the metabolite. Levetiracetam 1,000 mg daily did not affect the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel) or levels of luteinizing hormone or progesterone. Levetiracetam 2,000 mg daily did not affect the pharmacokinetics of digoxin and warfarin and prothrombin times were not modified. Pregnancy and lactation: Should not be used during pregnancy unless clearly necessary. Breast-feeding not recommended.

**Undesirable effects:** The most commonly reported undesirable effects are somnolence, asthenia and dizziness. In the pooled safety analysis there was no clear dose-response relationship but incidence and severity of the central nervous system related undesirable effects decreased over time. Incidence of undesirable effects considered to be at least possibly related in controlled clinical studies: Very common (>10%): asthenia and somnolence. Common (1%–10%): accidental injury, headache, anorexia, diarrhoea, dyspepsia, nausea, amnesia, ataxia, convulsion, depression, dizziness, emotional lability, hostility, insomnia, nervousness, tremor, vertigo, rash and diplopia.

**Legal category:** POM. Marketing Authorisation numbers: 250 mg x 60 tablets: EU/1/00/146/004. 500 mg x 60 tablets: EU/1/00/146/010. 1,000 mg x 60 tablets: EU/1/00/146/024.

**Further information is available from:** UCB Pharma Ltd., 3 George Street, Watford, Herts WD18 0UH. Tel: 01923 – 211811 or e-mail medicaluk@ucb-group.com

**Date of Preparation:** October 2001.

**References:**
5. Data on file, UCB Pharma Ltd.
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SHORT COURSES
13-24 May 2002
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Dementia (15 May)
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Statistical Parametric Mapping (17 and 18 May)
Behavioural Neurology (20 May)
Movement Disorders (21 May)
Neurorehabilitation (22 May)
Structural Imaging of the Brain (23 May)
Neuromuscular Disease (24 May)

Course fee £175 per day (£150 per day for clinical trainees; £125 per day student rate and for attendance on 5 or more days; £40 for the SPM course) to include refreshments.

For further details please contact:
The Assistant Secretary for Students, Institute of Neurology National Hospital for Neurology and Neurosurgery
Queen Square, London WC1N 3BG
Tel: 020 7829 8740. Fax: 020 7278 5069
Email: J.Reynolds@ion.ucl.ac.uk

The Institute of Neurology promotes teaching and research of the highest quality in neurology and the neurosciences.

MS Frontiers
Venue: The Birmingham Metropole Hotel, NEC
Date: Thursday 16th May 2002
Time: 9:00 – 17.00

Aims of the conference
• To promote research funded by the MS Society
• To discuss current MS research issues and themes
• To identify challenges for the future

Speakers
Dr Altman, Dr Amor, Dr Barnett, Prof Blakemore,
Dr Boggild, Prof Brophy, Prof Compston, Dr Diemel,
Prof ffrench-Constant, Mr Freeman, Dr Hobart,
Prof Morgan, Prof Perry, Ms Petty, Prof Thompson,
Ms Willer, Prof Woodroffe

Who should attend?
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• MS researchers – in basic and applied science
• People affected by MS

Fees
£95.00 for healthcare professionals - £70.00 for students
£20.00 for PwMS who are waged - £10.00 for unwaged
(this includes lunch and refreshments)

For programmes and booking forms please contact:
The Conference Team, MS National Centre, 372 Edgware Road, London, NW2 6ND
Telephone: 020 8438 0818 Fax: 020 8438 0877 Email: acrossman@msociety.org.uk

Multiple Sclerosis Society – Registered Charity Number 207495
Anatomy

Dural venous sinuses

These are endothelium-lined channels which lie between the outer (periosteal) and inner (meningeal) layers of the dura mater. They collect blood from superficial and deep cerebral veins, meninges and calvarium and are connected via emissary veins to the extracranial venous system.

The superior sagittal sinus originates near the crista galli where it communicates with facial and nasal veins. It passes in the midline between the cerebral convexities and terminates by joining with the straight sinus to form the torcular herophili at the internal occipital protuberance. The inferior sagittal sinus is a small channel in the inferior free edge of the falx. It terminates at the falcotentorial apex when it joins the vein of Galen to form the straight sinus. The straight sinus lies within the confluence of the falx and the tentorium cerebelli receiving vermian and hemispheric tributaries. It terminates at the torcular, frequently joining the left transverse sinus.

The torcular is formed by the union of the superior sagittal sinus, straight sinus and transverse sinuses. This confluence of sinuses is frequently asymmetric and shows numerous variations. The transverse sinuses (lateral sinuses) are contained within the junction of the tentorium with the calvarium. They curve from the torcular to the posterior petrous bones at which point they receive the superior petrosal sinus and turn inferomedially to become the sigmoid sinuses. The sigmoid sinuses pass in a gentle S-shaped curve along the posterior petrous face to reach the jugular foramina at which point they become the internal jugular veins.

The occipital sinus is a small, variable channel that passes from the foramen magnum to the torcular. The superior petrosal sinus extends from the cavernous sinus to the jugular bulb in the free margin of the tentorium. The inferior petrosal sinus shows marked anatomical variability lying in a groove between the petrous apex and the clivus. The petrosal sinuses drain blood from the cavernous sinus, pterygoid plexus, vertebral and clival plexuses as well as from the cerebellum and brainstem. The cavernous sinuses lie on either side of the body of the sphenoid. They receive blood from the superior and inferior ophthalmic veins and pterygoid plexus and drain via the petrosal sinuses and clival venous plexus.
**Imaging techniques**

The gold standard of examination remains cerebral angiography. Selective catheterisation of the internal carotid artery and injection of 6-10 mls of iodinated contrast medium is followed by a rapid series digital subtraction acquisitions. This provides the highest spatial resolution currently available.

Magnetic resonance techniques exploit signal generated from flowing blood. Phase contrast and time of flight imaging are both routinely used in the examination of the intracranial veins. A disadvantage of this technique is the relatively long acquisition times (6-7 minutes). A common artefact associated with magnetic resonance venography is lack of sensitivity to flow in the plane of acquisition. For example, on an axial acquisition, flow in the horizontal portion of the transverse sinus may be incorrectly depicted as absent.

**Cerebral veins**

The superficial cerebral veins are divided into superior, middle and inferior groups. The superior anastomotic vein (of Trolard) courses from the sylvian fissure to the mid cerebral convexity. It connects the superficial middle cerebral vein with the superior sagittal sinus. The superficial middle cerebral vein runs along the Sylvian fissure, curving anteriorly over the temporal tip passing medially into the cavernous sinus. It anastomoses with the deep cerebral veins partly via the basal veins. The inferior anastomotic vein (of Labbe) courses over the temporal lobe along the occipitotemporal sulcus and connects the superficial middle cerebral vein with the transverse sinus.

The deep cerebral veins drain the deep cerebral white matter and basal ganglia. A number of small medullary veins originate 1-2 cm deep to the cortical surface and drain into subependymal veins that course along the lateral ventricular walls. The small subependymal veins merge into the more important septal, thalamostriate and internal cerebral veins. Two other important deep veins are the basal veins (of Rosenthal) and the great vein of Galen. The basal veins arise within the Sylvian fissure from the junction of anterior and deep middle cerebral veins. They course around the midbrain receiving the lateral mesencephalic veins to join the internal cerebral veins at the vein of Galen.

**Normal variants**

Absent anterior superior sagittal sinus (rare) - in this situation, the posterior SSS is formed by the junction of superficial draining veins and the vein of Trolard.

Direct termination of the superior sagittal sinus into a transverse sinus (3-5%) - this is more common on the right, with the straight sinus running into the left transverse sinus.

Absence or hypoplasia of part of a transverse sinus (5-50%) - this may be confused with thrombotic occlusion.

Asymmetric jugular bulbs - complete symmetry is very rare.
If you would like to review books for ACNR, please contact Andrew Larner, Book Review Editor, c/o AdvancesinCNR@aol.com

Underground Clinical Vignettes: Neurology - classic clinical cases

If you are a (normal) medical student who is confused, even terrified, by the obscure world of neurology, a book which apes with Friedreich’s ataxia is probably not for you. On the other hand, SHOs in the third month of neurology training who feel their only achievements have been acquiring competence in lumbar punctures and organising urgent CT scans might be very interested.

The authors present 52 ‘supra-prototypical cases in a cohesive and memorable clinical picture’. The material is well chosen and spans the breadth of clinical neurology. Each vignette comes in the form of a grand-round presentation pared down to the important features which makes for a snappy read. Unfortunately, the order of the cases is determined by classification and the alphabet rather than clinical importance, so eponymic syndromes come first and headaches come last.

My main criticism is that this ‘Student to Student’ book has clearly not been written by neurologists. The biggest resulting deficiency is that it doesn’t really teach: reading this book won’t help students put together new clinical findings. For example, they may begin word-associating early morning headaches with giant cell arteritis and multifomate but will not learn that the underlying problem is of raised intracranial pressure. For the same reason, while the quality of information is generally very good, there are a few errors ranging from the amusing (e.g. ‘pseudobulbar effect’) to the serious (e.g. phenobarbital ahead of carbamazepine in the treatment of primary generalised epilepsy).

This book is written with US medical students in mind. I think it is better suited for people who already have some knowledge and experience of clinical neurology. It is not a primary neurology text. SHOs preparing for MRCP will find it easily digestible. Teachers will find good clinical material here. I would even recommend it as a refresher for any research trainee returning to the real world of clinical neurology.

Wojtek Rakowicz, Cambridge

The Interactive Spine

The anatomy of the spine is complex, as anyone trying to understand serial axial spinal MRI slices will tell you. The subject is ripe for a lucid and authoritative analysis, which this CD – wonderfully and enjoyably – provides. The viewer can toy with images from nineteen different spinal regions: moving and rotating them, then peeling back as many as 20 layers from surface landmarks to bone, as though dissecting. Pointing at any structure brings up a textbox with a brisk anatomical description. There is also a sequence of co-registered anatomical and magnetic resonance images where, very helpfully, selecting an object on one highlights its equivalent on the other, again with accompanying text. In these sections it is not always possible to zoom sufficiently to get a really good view of individual nerves, which are perhaps the least well shown of all the structures. However, there is a further section of static images, again annotated, of more CT and MRI scans, cadaver slices and dissections, some pathological pictures and a few clinical plates. These can be zoomed down to the last pixel. They can also be compiled into a slide show. There are some brief videos showing the surface anatomy and action of some muscles around the spine. Finally, there are two self-evaluation tools: a dry multiple-choice questionnaire and a flexible quiz incorporating images, which is much more fun. (Could you find the obliquus capitis superior? Or the superior costotransverse ligament?)

This CD has been produced with the spinal surgeon in mind. Its authors consist of an anatomist from Leeds and neuro-orthopaedic surgeons from The Royal National Orthopaedic Hospital, Stanmore; Great Ormond Street; Queen Square; and the Twin Cities Spinal Centre, Minneapolis. The lack of neurological input is clear. There is no anatomy of the spinal cord tracts, the Brown-Sequard syndrome is vaguely attributed to a hemisection of the cord, with no further explanation, and brachial plexus trauma is given as a cause of Homer’s syndrome. But these are fooling objections. Any neurologist wishing better to understand the complexities of the crano-cervical junction, the intervertebral foramina and the neck muscles and have enormous fun on the way should buy this CD.

Alasdair Coles, Cambridge

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The second edition of this convenient reference book covers a wide spectrum of the presenting complaints and neurological disorders encountered in daily practice. All chapters have been thoroughly revised to include the latest therapeutics and all of the contributing authors are well established clinicians and educators. The book has been written in a concise and user friendly outline format with an emphasis on diagnosis and treatment.

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EDITOR’S CHOICE

Making dopamine cells out of ES cells

The attraction of using embryonic stem cells to repair the brain is related to their potential ability to proliferate and differentiate into specific neuronal populations, such as dopaminergic neurons. To date much of the work has been spent on getting the ES cells to turn into any type of neuron, and not proliferate uncontrollably into teratomas. This paper, which has gained much attention from the press, claims to be able to produce dopaminergic neurons from a mouse ES cell line which can ameliorate behavioural deficits in an animal model of Parkinson’s disease. The trick in this study was to transplant low numbers of cells, namely 2000-4000 in total, compared to the 500,000 to 1,000,000 that are normally implanted in this model system when primary embryonic neural tissue is used. By using such low numbers of cells, the risk of teratoma was reduced but importantly not removed altogether with 5 out of 25 developing teratomas. Furthermore another 6 out of 25 had no surviving graft, which despite the use of cyclosporin A may relate to rejection given it was a mouse to rat xenograft paradigm. In those rats with grafts, dopamine cells were found at 16 weeks post implantation and this was associated with a reduction in drug induced rotation at 9 weeks. The latter is a test known to be sensitive to dopamine levels in the striatum. Why there is a difference between the timing of the behavioural testing and the histological analysis is not made clear, but one does wonder what happened to the behaviour of these animals in the intervening 7 weeks. This study therefore shows it is possible to get some useful dopamine cells out of mouse ES cells, but the system is still too unreliable for any clinical application, despite claims, by some, to the contrary - RAB

Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model.


DEMENTIA

RECOMMENDED

Dementia: ageing or development?

Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) is a highly penetrant dominantly-inherited disorder associated with mutations in the gene encoding the microtubule-associated protein tau. The identification of mutation carriers permits presymptomatic testing of cognitive function, many years before expected disease onset. Asymptomatic members of a large French-Canadian kindred known to carry the P301L tau mutation (Nasreddine et al., Ann. Neurol. 1999; 45: 704-715) underwent neuropsychological evaluation and mutation screening. Of 16 non-demented individuals in one generation, 10 were found to be heterozygous P301L mutation carriers, 6 had no mutation. The two groups were similar in mean age (31 +/- 8.0 vs. 37 +/- 5.0 years); age range (17-46 vs. 27-42), gender, and educational level. The mutation carriers were impaired in tasks testing frontal-executive and attentional functions (e.g. verbal fluency, Wisconsin Card Sorting Test categories completed, Stroop interference, WAIS-R similarities and digit span subtests, Trails B) compared to those without tau mutations. However, verbal and spatial memory, language, and visuomotor constructive abilities were preserved in the mutation carriers. Hence their deficits mirrored those seen at the onset of clinical disease, but many years before the expected onset (57-63 years in this family).

Although it is possible that these findings are family- and mutation-specific, they do raise intriguing questions. Since the deficits observed showed no correlation with age they seem to represent baseline function, suggesting that certain brain areas are more vulnerable due to reduced reserve, hence explaining the focal clinical presentation. Hence it seems that FTDP-17 has a neurodevelopmental component. Such an observation challenges the long-held notion of dementia as exclusively a disorder of brain ageing. However, it tallies with the observation of subtle cognitive impairments long before diagnosis in other dementias, such as sporadic Alzheimer's disease (see ACNR 2001; 1(2): 27). A long preclinical phase in dementing disorders has profound implications for treatment trials.

Dementia and neurodevelopmental predisposition: cognitive dysfunction in presymptomatic subjects precedes dementia by decades in frontotemporal dementia.


Cerebral amyloid angiopathy as a pathological substrate of dementia

Hereditary cerebral haemorrhage with amyloidosis-Dutch type (HCHWA-D) is an autosomal dominant condition characterised pathologically by cerebral amyloid angiopathy (CAA). Although an extremely rare condition, it has attracted much attention because of its potential relevance to Alzheimer’s disease (AD), since it is caused by a mutation at codon 693 of the amyloid precursor protein (APP) gene; other mutations within the APP gene are deterministic for autosomal...
Drug resistant epilepsy: expression of drug resistance proteins in common causes of refractory epilepsy.

**BRAIN**


**Drug withdrawal in epilepsy**

The best drug withdrawal study to date is the MRC study. This study has a slightly different design, in that the 330 patients were not randomised but chose either to withdraw drugs (225 patients) or stay on therapy (105 patients).Patients who opted for withdrawal were less likely to be well educated, have a normal EEG, have shorter disease duration, have longer remission before withdrawal and less likely to previously experienced relapses. Nevertheless findings were remarkably similar to the MRC study: around half of drug withdrawal patients relapsed in two years compared to 20% of those continuing treatment. Factors predisposing to seizure recurrence were duration of active disease 2-10 years, shorter remission before withdrawal (risk ratio 2.6 if duration 2 years compared to more than 5 years) and an abnormal psychiatric examination (relative risk 2.1). There was no difference between focal and generalised epilepsy syndromes. These data will reinforce the advice currently given to patients.


**MOVEMENT DISORDERS**

Diagnosing vascular parkinsonism

Diagnosing parkinsonism due to a vascular lesion is not a straightforward task. Indeed for many of us, it is not always easy to differentiate genuine extra-pyramidal symptoms and signs, from the stiffness or slowing caused by ageing and joint disease. Distinguishing “Parkinson’s disease” from secondary causes of parkinsonism, including vascular parkinsonism (VP) represents a further challenge.

Many elderly people have evidence of subcortical ischaemia on a CT or MRI scan, so the presence of ischaemic features on scans, is not necessarily a reliable way to distinguish patients with VP, from patients with idiopathic Parkinson’s disease as idiopathic neuro-degeneration may co-exist with arteriolarcerotic disease.

This review discusses the limited specificity of any clinical or radiological feature to accurately predict a diagnosis of VP, when compared with post mortem confirmed disease, and recommends criteria for “possible” and “probable” VP. It appears that there is also variability in the location of lesions capable of causing VP, with 1 in 5 patients having basal ganglia or brainstem lacunes, and others having frontal white matter lesions. From this review of the published studies on VP, it appears that the disorder can be responsible for between 3 and 6% of all cases of parkinsonism seen in outpatient clinics. Patients with VP will therefore be intermittently seen by most neurologists, and the diagnosis should always be considered in patients with parkinsonism especially if pyramidal signs or dementia are present.

From a practical point of view, it is commonly believed that patients with VP will not respond to dopaminergic replacement therapy. That appears to be untrue, and adequate trials...
of dopaminergic replacement ought to be performed before concluding that a patient with suspected VP does not need such treatment. Obviously, vascular risk factors should still be addressed in all patients with cerebrovascular disease, regardless of dopaminergic responsiveness. – TF Foltynie T, Barker R, Brayne C (2002).

Vascular Parkinsonism: A Review of the Precision and Frequency of the Diagnosis Neuroepidemiology 21:1-1-7

NEURO-AUTOIMMUNITY

The expanding spectrum of autoimmunity: sleep and autonomic disorders

In 1890, Morvan described a syndrome of myokymia, muscle pain, hyperhidrosis, severe insomnia and hallucinations, which later became known as Morvan’s fibrillary chorea. Since myokymia, now more appropriately termed neuromyotonia (Isaacs’s syndrome), has been shown to be associated with autoantibodies directed against presynaptic voltage-gated potassium channels (VGKC), it was logical to look for these antibodies in Morvan’s syndrome, which may be characterised as neuromyotonia with CNS involvement.

Liguori et al. report an elderly man with a syndrome affecting the nervous system at several levels: peripheral (neuromyotonia), autonomic (cardiac arrhythmia, urinary incontinence, hyperhidrosis, excessive lacrimation and salivation) and central (spatial and temporal disorientation, hallucinations, insomnia with complex nocturnal behaviours), in association with consistent and marked elevations of serum VGKC antibodies. CSF showed oligoclonal bands but no VGKC antibodies. Neurohormonal investigations showed elevated noradrenaline and cortisol, with reduced melanotin and prolactin and absence of their normal circadian rhythms, a profile identical to that seen in fatal familial insomnia, an inherited prion disorder. Clinical and neurophysiological improvement was seen after plasma exchanges. The patient then died and pathological studies showed binding of VGKC antibodies to brain neurons, for example in the hippocampus. An adenocarcinoma of the lung was also found.

Batocchi et al. report a similar case, a patient with multiple cranial nerve palsies, total insomnia (agrypnia), and respiratory crises from central breathing depression with dysautonomia. The overlap with Morvan’s syndrome did not extend to neuromyotonia, and antibodies to VGKC were not found, although antibodies against GABA-ergic synapses were detected in serum and CSF, as were CSF oligoclonal bands. This patient also improved clinically after plasma exchanges. These cases implicate autoantibodies in the pathogenesis of sleep and autonomic nervous system disorders, in addition to their already established place in other disorders of the nervous system at several levels: peripheral (neuromyotonia), autonomic (cardiac arrhythmia, urinary incontinence, hyperhidrosis, excessive lacrimation and salivation) and central (spatial and temporal disorientation, hallucinations, insomnia with complex nocturnal behaviours), in association with consistent and marked elevations of serum VGKC antibodies. CSF showed oligoclonal bands but no VGKC antibodies. Neurohormonal investigations showed elevated noradrenaline and cortisol, with reduced melanotin and prolactin and absence of their normal circadian rhythms, a profile identical to that seen in fatal familial insomnia, an inherited prion disorder. Clinical and neurophysiological improvement was seen after plasma exchanges. The patient then died and pathological studies showed binding of VGKC antibodies to brain neurons, for example in the hippocampus. An adenocarcinoma of the lung was also found.

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Liguori R, Vincent A, Clover L et al. (2001)

Morvan’s syndrome: peripheral and central nervous system and cardiac involvement with antibodies to voltage-gated potassium channels. BRAIN 124(12):2417-2426

Batocchi AP, Della Marca G, Mirabella M et al. (2001)

Relapsing-remitting autoimmune apragnia. ANN.NEUROL. 50(5):668-671

Immunoglobulin therapy in stiff person syndrome

Although Stiff-person syndrome is a relatively rare movement disorder, it is a fascinating disease because its proposed pathogenesis is probably directly related to the antibody to the enzyme GAD65 (Glutamic acid Decarboxylase). This antibody is then thought to lower the levels of the inhibitory neurotransmitter GABA leading to the continuous firing of motor units producing the hallmark feature of stiffness. Therapy with diazepam is helpful but limited and therefore alternative therapies have been sought. Previous case reports have demonstrated a benefit with using intravenous immunoglobulin therapy, however it is an expensive form of therapy and a positive randomised double blind cross over study is valuable in justifying its use in the modern NHS. This study involved 16 patients who were randomised to receive placebo or iv immunoglobulin once a month at 2g per kilogram body mass divided in two equal doses for a total of three months with a washout period of one month followed by the cross over arm of the study for the same duration. Baseline and monthly assessments were undertaken using a stiffness distribution rating scale and sensitivity rating scale. Anti GAD antibody titres were measured monthly. There was a significant benefit on the stiffness and sensitivity rating, which lasted from 6 weeks to a year after stopping treatment. There was an impressive effect of the washout period with most of the patients returning towards their baseline ratings if they received active treatment first. The anti-GAD titres mirrored the treatment but did not fully correlate with the disease severity. Patients were also asked to try to predict which limb of the study they thought they were in based on their symptoms and most were readily able to correctly identify their treatment. In terms of quality of life there was an overall improvement with easier walking, fewer falls and ability to undertake work-related and home tasks. This study provides compelling evidence that iv immunoglobulin therapy is a valid form of treatment for Stiff-person syndrome. –TH Marinos C Dalakas, Mavis Fuji, Mian Li, Bashar Lufti, Joan Kyhos, and Beverley McElroy (2001)

High-dose intravenous immunoglobulin for stiff person syndrome. NEJM 343:1870-6

PERIPHERAL NERVE

Life after steroids in neuromuscular disease?

Immune-mediated neuromuscular diseases are not the only conditions in neurology in need of modulating therapies other than corticosteroids, but they can be particularly amenable to assessing treatment outcomes by both clinical and laboratory criteria. A useful discussion about the current role of steroids in the treatment of myasthenia gravis provides an overview of the possible therapeutic future.

Mycophenolate mofetil and tacrolimus both appear to act by suppressing the proliferation of activated T cells. Mycophenolate mofetil has a mechanistic, therapeutic and side-effect profile that is similar to azathioprine. It has already been shown to be of benefit in patients with myasthenia gravis and is used here in the treatment of azathioprine- and cyclophosphamide-resistant polymyositis. A positive outcome was demonstrated by clinical and laboratory (CK, EMG) criteria.

Tacrolimus has an established track record in transplantation as an alternative to cyclosporine with which it appears to share a mechanism of action. It is now administered to a patient with myasthenia gravis in whom azathioprine was contraindicated and cyclosporine treatment failed. Outcome was assessed by the remission of generalised symptoms and signs. The lesson from both reports is that there is now even less room for therapeutic nihilism in patients with treatable...

REHABILITATION

Stand up, sit down, on both legs – training to prevent falls after stroke

Falling is a major cause of morbidity, hospitalisation and mortality and fear in the elderly. For stroke patients with poor sensation and motor control the risk of falling is especially great. A rehabilitation group in Taiwan have developed an intensive training programme for stroke patients to improve symmetrical body weight distribution in standing and in standing up and sitting down. They have designed and built a standing biofeedback trainer which allows the patient to practice making postural adjustments as they carry out arm exercises on a table in front of them. The training programme comprised 30 minutes practice on this apparatus per day and then 15 minutes practice of standing up and sitting down from an adjustable chair that was placed in front of the trainer. Feedback about postural symmetry was given in both standing and the sit to stand to sit tasks.

The training programme was tested for effectiveness in a randomised control trial of 54 in-patients who were between 2 and 4 months post stroke. The control group received a standard rehabilitation programme including therapeutic exercise and the training group received the same programme plus the standing and sit to stand training but this was substituted for the therapeutic exercise. The protocol was performed 5 days a week for 3 weeks. Rate of rise in force during sit to stand, body weight distribution and sway were measured before the period of training and at a 6 months follow up appointment. In addition the number of falls occurring between the completion of training and 6 months were recorded.

The control and treatment groups were well matched at the start of the trial. Significant improvements in all the performance measures were found in the training group. The change in rate of rise in force during sit to stand was particularly impressive. There was no significant change in any of the control group measures. The proportion of patients in the control group who had fallen by the time of the follow up was more than twice that of the training group.

The training programme appears to be successful in reducing falls in this vulnerable group. It would be useful to determine the value of each part of the training since it is not clear what contribution of each training task was to decreasing the risk of falling. The programme was intensive, the 50 minutes a day concentrating on postural control was greater than the reported average time spent in physiotherapy and occupational therapy combined in UK stroke units. However if all of this time was valuable in decreasing the risk of falls then it is important for therapists either to provide it or to be creative in devising ways for patients to practice safely and with accurate feedback in their absence. - AJT Cheng P-T, Wu S-H, Liaw M-Y, Wong AMK, Tang F-T. (2001) Symmetrical body weight distribution training in stroke patients and its effect on fall prevention. ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION 82: 1650-54

Students delivering therapy! – cheap but is it effective?

With a chronic shortage in numbers of qualified therapists in the UK there is a need to consider alternative models of service delivery. For example, Rehabilitation Assistants may provide important additional input where therapy resources are stretched. As yet, though, there are few studies examining the value of this type of input. Arkin’s paper tries to address this by looking at the effectiveness of using undergraduate students to provide a multi-faceted intervention programme with adults with mild-moderate Alzheimer's disease. Seven adults with dementia were each paired with a student who supervised them in a range of activities described as physical exercise, memory training and language stimulation. This intervention lasted for two semesters. Subsequently, the patients were compared on numerous cognitive, mood-related and physical measures with a non-intervention group of (only) four cases. There were general improvements in mood, physical well-being and social interaction, but evidence for a specific effect of student-facilitated interventions was weak. Investigations of this kind are important in rehabilitation and should be supported. Sadly, this particular study suffers from methodological weaknesses (including a small sample) that render the results disappointing. Yet, given that rehabilitation services will continue to rely on assistants and support workers, it really is time that their usefulness was recognised and valued, and that requires a proper evaluation of how they can be used most cost-effectively. - ADW Arkin S M (2001) Alzheimer rehabilitation by students: Interventions and outcomes. NEUROPSYCHOLOGICAL REHABILITATION 11: 3: 273-317

RECOMMENDED

Rehabilitation can produce any lasting benefits, but not for everyone.

When reading long-term outcome or follow-up studies do you ever wonder what has been happening in the intervening period of time that might account for the results? This paper makes a stab at exploring this issue. Although it raises more questions than it answers, it is a worthy attempt to consider a matter too often ignored in other studies. Essentially the authors examined 34 adults with acquired brain injury (50% classified as severe) who had gone through a post-acute rehabilitation programme of between 1-2 years duration. The group were evaluated on two widely-used measures of functional adaptation – the Disability Rating Scale (DRS) and the Community Integration Questionnaire (CIQ). The measures were administered within one year after discharge from the programme, then again after about four years. Results showed that average gains evident on the DRS at discharge from treatment were maintained up to 5 years later. However, nearly a quarter of the sample were more dependent at the first follow-up and this had increased to one-third after four years. On the CIQ there was no significant change in status between discharge from treatment and at either follow-up, but no real decline. Overall, this study is of interest because it confirms that gains made in rehabilitation can be maintained long after formal treatment has ended. However, this is not always the case and effort needs to be focused on supporting those people most vulnerable in the community. Disappointingly, the authors fail to examine their own cases that showed a decline in independence, preferring to speculate on possible causes rather than looking at what has happened to the individuals concerned and determining whether there were any prognostic...
Human embryonic stem cells can differentiate into neurons

There has been a great deal of interest in embryonic stem (ES) cells both at the level of legislation and human cloning and at the scientific level of generating cells for repairing the brain (see Rosser AE. ACNR 1.3 pp6-7). ES cells are pluripotent cells derived typically from the inner cell mass of the preimplantation embryo and as a result can give rise to cells from all three germ layers - endoderm, ectoderm and mesoderm. However in order to be useful these cells must be controlled in terms of their proliferation and differentiation and to date this has been a major limiting factor in their possible clinical application. Two papers have now appeared in Nature Biotechnology that offer some hope that this critical aspect of their behaviour can be regulated using human ES cells. In these papers two groups report that they can isolate cells from cultures of ES cells that have characteristics of partially committed neural precursor cells - cells that can only give rise to neurons, astrocytes and oligodendrocytes. This isolation relied on first dissecting them out of the cultures of cells with a primitive neuroepithelial phenotype and then growing them on in the presence of growth factors known to favour neural stem cell proliferation (FGF2). These cells were then differentiated in culture and gave rise to neurons and astrocytes and a few oligodendrocytes, the proportions of which varied depending on how long they had been grown in vitro. Both groups then transplanted these ES derived neural precursor cells into the neonatal rodent brain - an environment that is permissive for neural development. In both cases these cells were found to have migrated to a number of CNS sites and undergone regionally specific differentiation, although occasional cells were seen without any clear phenotype.

These studies therefore show that it is possible to select neural precursors from human ES cells, although it is not clear whether this is an absolute selection which is clearly critical given the proliferative potential of ES cells. Furthermore it is not clear whether such a migration and differentiation is possible in the adult or damaged CNS, which is again essential if such cells are to be of therapeutic value. So whilst these studies present exciting new data, ES cells still remain a long way off from the clinic from a scientific perspective, quite apart from the ethical issues that surround these cells.

Using stem cells to study disease

One of the aspects of neural stem cell technology which is often ignored is how we can use stem cells as research tools, and this is beautifully demonstrated by Bahn et al, who used neural stems derived from fetuses with Down’s syndrome and compared them with neural stem cells from control fetuses. Using the tremendous expansion potential of neural stem cells, enough cells were generated from the fetal brains to allow mRNA analysis. Using differential display and PCR analysis, mRNA expression from stem cells from Down’s fetuses were compared with those derived from control fetuses to determine which genes were up regulated or down regulated in the former. Strikingly a number of vital genes were down regulated such as SCG10 which is essential for synaptic plasticity, neurite outgrowth, elongation and branching, L1 which is essential for neurite outgrowth and axon bundling, and Synapsin which is required for normal neuronal function. These genes are under the regulation of a control gene REST (repressor element-1 silencing transcription factor) which is essential for the developing nervous system. Genes not under the control of REST were not down regulated suggesting that in Down’s the development of the nervous system is abnormal as a result of specifically abnormal REST function which directly inhibits the expression of SCG10, L1, and Synapsin leading to poor neuronal differentiation and maturation. Underlining this point, the study proceeds to determine the differentiation and maturation potential of the stems cells from both types of fetus by allowing the cells to differentiate in vitro. From the mRNA data it is not surprising that the neural stem cells from the Downs fetuses had significantly less neurogenesis, and the neurons which did develop were dysmorphic with stunted neurite outgrowth. Therefore it would seem that REST controlled genes are essential for allowing neurons to develop and abnormal REST control exists in Down’s syndrome, which may underlie some of their cognitive abnormalities.

Sabine Bahn, Michael Mimmick, Margaret Ryan, Maeva Caldwell, Eric Jauniaux, Michael Starkey, Clive Svendsen and Piers Emson (2002)

Neuronal target genes of the neuron-restrictor silencer factor in neurospheres derived from fetuses with Down’s syndrome: a gene expression study.

LANCET

359: 310-315
Siemens introduces first 16-slice CT scanner

Siemens Medical Solutions believe they are breaking new ground in Computed Tomography with the Somatom Sensation 16 system. As recently as three years ago, the advance from single-slice to multislice detectors set a significant milestone in CT imaging with rotation speeds of under one second. Today, the newest Somatom model is said by Siemens to surpass all previous CT scanners in performance and detail. Somatom Sensation 16 combines 16-slice detector technology with an even faster rotation speed of only 0.4 seconds. This quantum leap will support completely new clinical applications in the future. Additional benefits include further reduced exposure at improved image quality.

With acquisitions of up to 32 slices per second and slices thinner than one millimetre, the breakthrough from 4-slice to 16-slice technology offers many advantages. Previous imaging restrictions are now a thing of the past; large-volume imaging did not allow for thin slices, and longer acquisition times resulted in degraded image quality due to motion artifacts. With the Somatom Sensation 16, Siemens Medical Solutions have succeeded in combining volume, speed, and detailed imaging. For example, high-resolution imaging of the lungs only takes ten seconds, making it easy for older patients to hold their breath during the examination. 

Siemens Medical Solutions have succeeded in combining volume, speed, and detailed imaging. For example, high-resolution imaging of the lungs only takes ten seconds, making it easy for older patients to hold their breath during the examination. Somatom Sensation 16 runs on the workflow-oriented syngo user software with integrated 3D image processing, resulting in short exam times and a high return on investment.

Reduce radiation exposure during X-ray exams, further reduces the radiation dose of the CT examination depending on the anatomy of the patient. As a function of the examination, this application reduces patient exposure by 10 to 50 percent as compared to standard CT examinations.

For more information contact Mike Bell, Siemens Medical Solutions, Tel. 01344 396317, or see http://www.siemensmedical.com

SPECIAL OFFER

Primal Pictures is offering ACNR readers a special offer price of £112.50 plus VAT and a 30-day no risk, money-back guarantee.

For further information contact Primal Pictures Ltd, 2nd Floor, Tennyson House, 159-165 Great Portland Street, London. W1W 5PA. Tel: 020 7637 1010, or visit their web site at www.primalpictures.com

For a review of this CD, see page 32.
Biogen welcomes DOH announcement

Biogen has welcomed the announcement made by the Department of Health (DOH) on February 4th which will enable people with MS in the UK who meet the Association of British Neurologists guidelines to benefit from treatment with Avonex® or one of the other disease modifying treatments.

Director of Biogen said, "Avonex (Interferon Beta-1a) is the most widely used Interferon beta in the world and currently well over 100,000 people are benefiting from its use. The clinical efficacy of Avonex has been confirmed in a number of clinical trials, as well as in many MS clinics.

The DOH scheme allows people with MS to receive the drug on the NHS providing they comply with guidelines set out by the ABN (Association of British Neurologists), and agree to be monitored over an extended period. The scheme will be co-ordinated by a research department, and the MS Trust will be working closely with the DOH to ensure that the necessary structures are in place to enable this initiative to work effectively.

Christine Jones, Chief Executive of the MS Trust said, "We welcome this initiative and are glad that the DOH has provided a solution to what was becoming an intractable problem. At long last people with MS in the UK will have the same opportunities as citizens of other countries. However, sadly, for some people, this announcement will come too late and their disease will have progressed past the point where they are eligible for treatment."

The DOH scheme provides people with MS to receive the drug on the NHS, providing they comply with guidelines set out by the ABN (Association of British Neurologists), and agree to be monitored over an extended period. The scheme will be co-ordinated by a research department, and the MS Trust will be working closely with the DOH to ensure that the necessary structures are in place to enable this initiative to work effectively. Christine Jones, Chief Executive of the MS Trust said, "We welcome this initiative and are glad that the DOH has provided a solution to what was becoming an intractable problem. At long last people with MS in the UK will have the same opportunities as citizens of other countries. However, sadly, for some people, this announcement will come too late and their disease will have progressed past the point where they are eligible for treatment."

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Information for MS Specialists

Biogen has a number of initiatives designed to assist healthcare professionals in overcoming these challenges. For more details please call Dr Martin Toal on 01628 501022 or e-mail at Martin_Tool@biogen.com

MS Trust delighted at launch of DOH risk sharing scheme

The MS Trust has reacted very positively to the announcement by the Department of Health (DOH) of a risk-sharing scheme to make disease modifying drug therapies available to people with MS in the UK. The MS Trust will be working closely with the DOH to ensure that the necessary structures are in place to enable this initiative to work effectively.

Christine Jones, Chief Executive of the MS Trust said, "We welcome this initiative and are glad that the DOH has provided a solution to what was becoming an intractable problem. At long last people with MS in the UK will have the same opportunities as citizens of other countries. However, sadly, for some people, this announcement will come too late and their disease will have progressed past the point where they are eligible for treatment."

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REQUIP (ropinirole) Prescribing Information

Please refer to the Summary of Product Characteristics before prescribing. Presentation
'Requip' Tablets, PL 105925085, 0067-0089, each containing ropinirole hydrochloride equivalent to either 0.25, 1, 2 or 5 mg ropinirole. 0.25 mg tablets – 210 tablets starter pack, £43.12; 1 mg tablets – 84 tablets, £46.20; 2 mg tablets – 84 tablets, £92.40; 5 mg tablets – 84 tablets, £184.80.

Indications
Treatment of idiopathic Parkinson’s disease. May be used alone (without L-dopa) or in addition to L-dopa to control “on-off” fluctuations and permit a reduction in the L-dopa dose.

Dosage
Adults:
Three times a day, with meals. Titrate dose against efficacy and tolerability. Initial dose for 1st week should be 0.25 mg t.i.d., 2nd week 0.5 mg t.i.d., 3rd week 0.75 mg t.i.d., 4th week 1 mg t.i.d. After initial titration, dose may be increased in gradual weekly increments of up to 3 mg/day, until acceptable therapeutic response established. Do not exceed 24 mg/day. Concurrent L-dopa dose may be reduced gradually by around 20%. When switching from another dopamine agonist follow manufacturer’s guidance on discontinuation. Discontinue ropinirole by reducing doses over one week. Renal or hepatic impairment: No change needed in mild to moderate renal impairment. Not studied in severe renal or hepatic impairment – administration not recommended. Elderly: Titrate dose in normal manner.

Children:
Parkinson’s disease does not occur in children – do not give to children.

Contra-indications
Hypersensitivity to ropinirole, pregnancy, lactation and women of child-bearing potential unless using adequate contraception.

Precautions
Caution advised in patients with severe cardiovascular disease and when co-administering with anti-hypertensive and anti-arrhythmic agents. Patients with major psychotic disorders should be treated with dopamine agonists only if potential benefits outweigh the risks. Patients should avoid driving or other potentially dangerous activities, since rarely, sudden onset of sleep has been reported during daily activities. Caution advised when taking other sedating medication or alcohol in combination with ropinirole. If sudden onset of sleep occurs in patients, consider dose reduction or drug withdrawal. Drug interactions Neuroleptics and other centrally active dopamine antagonists may diminish effectiveness of ropinirole – avoid concomitant use. No dosage adjustment needed when co-administering with L-dopa or dopamine. No interaction seen with other Parkinson’s drugs but take care when adding ropinirole to treatment regimen. Extreme somnolence and/or sudden onset of sleep have been reported rarely, occasionally when driving (see ‘Precautions’ and ‘Effects on ability to drive and use machines’).

Drug interactions
Neuroleptics and other centrally active dopamine antagonists may diminish effectiveness of ropinirole – avoid concomitant use. No dosage adjustment needed when co-administering with L-dopa or bromocriptine. No interaction seen with other Parkinson’s disease drugs but take care when adding ropinirole to treatment regimen. Other dopamine agonists may be used with caution. In a study with concurrent digoxin, no interaction seen which would require dosage adjustment. Metabolised by cytochrome P450 enzyme CYP1A2 therefore potential for interaction with substrates or inhibitors of this enzyme – ropinirole dose may need adjustment when these drugs are introduced or withdrawn. Increased plasma levels of ropinirole have been observed with high oestrogen doses. In patients on hormone replacement therapy (HRT) ropinirole treatment may be initiated in normal manner, however, if HRT is stopped or introduced during ropinirole treatment, dosage adjustment may be required. No information on interaction with alcohol – as with other centrally active medications, caution patients against taking ropinirole with alcohol. Pregnancy and lactation Do not use during pregnancy – based on results of animal studies. There have been no studies of ropinirole in human pregnancy. Do not use in nursing mothers as lactation may be inhibited. Adverse reactions In early therapy: nausea, somnolence, leg oedema, abdominal pain, vomiting and syncope. In adjunct therapy: dyskinesia, nausea, hallucinations and confusion. Incidence of postural hypotension (commonly associated with dopamine agonists), was not markedly different from placebo; however, decreases in systolic blood pressure have been noted; asymptomatic hypotension and bradycardia, occasionally severe, may occur. As with another dopamine agonist, extreme somnolence and/or sudden onset of sleep have been reported rarely, occasionally when driving (see ‘Precautions’ and ‘Effects on ability to drive and use machines’). Effects on ability to drive and use machines Patients must be informed not to drive and to avoid other potentially dangerous activities, since rarely, cases of sudden onset of sleep have been reported. If this event occurs, consider dose reduction or drug withdrawal. Overdose No incidents reported. Symptoms of overdose likely to be related to dopaminergic activity. Product License holder SmithKline Beecham plc, Great West Road, Brentford Road, Middlesex, TW8 9BD

Finished yet dear?