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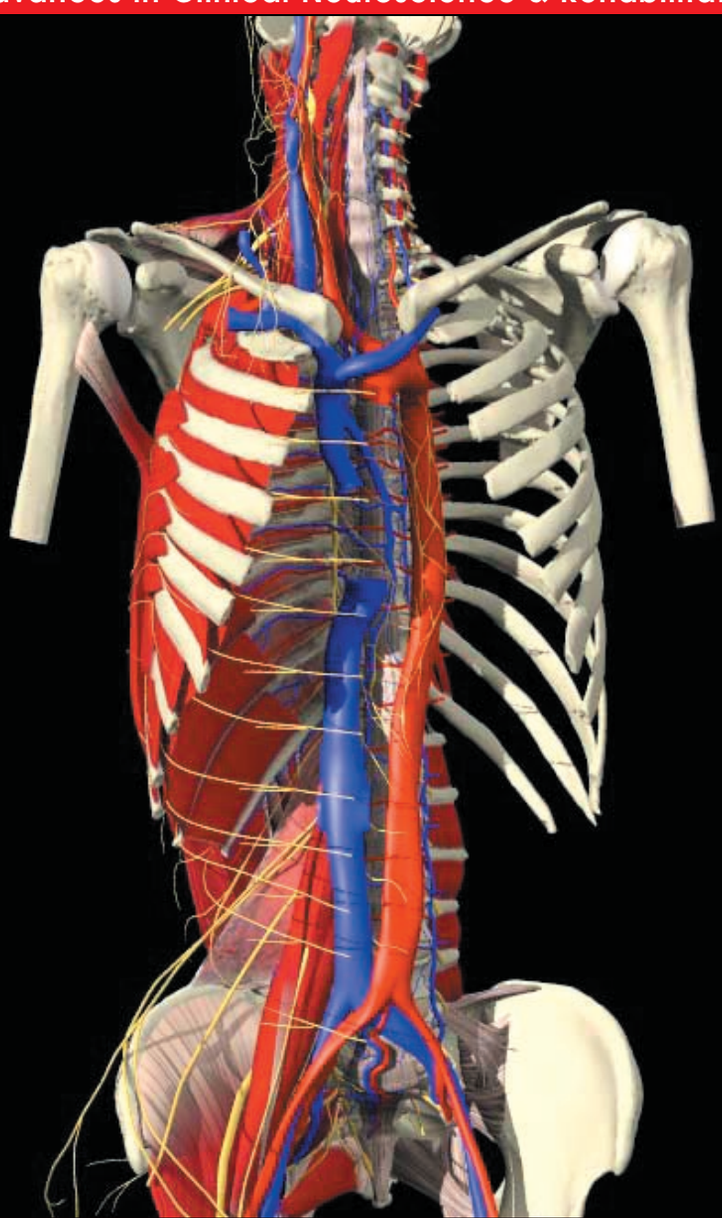


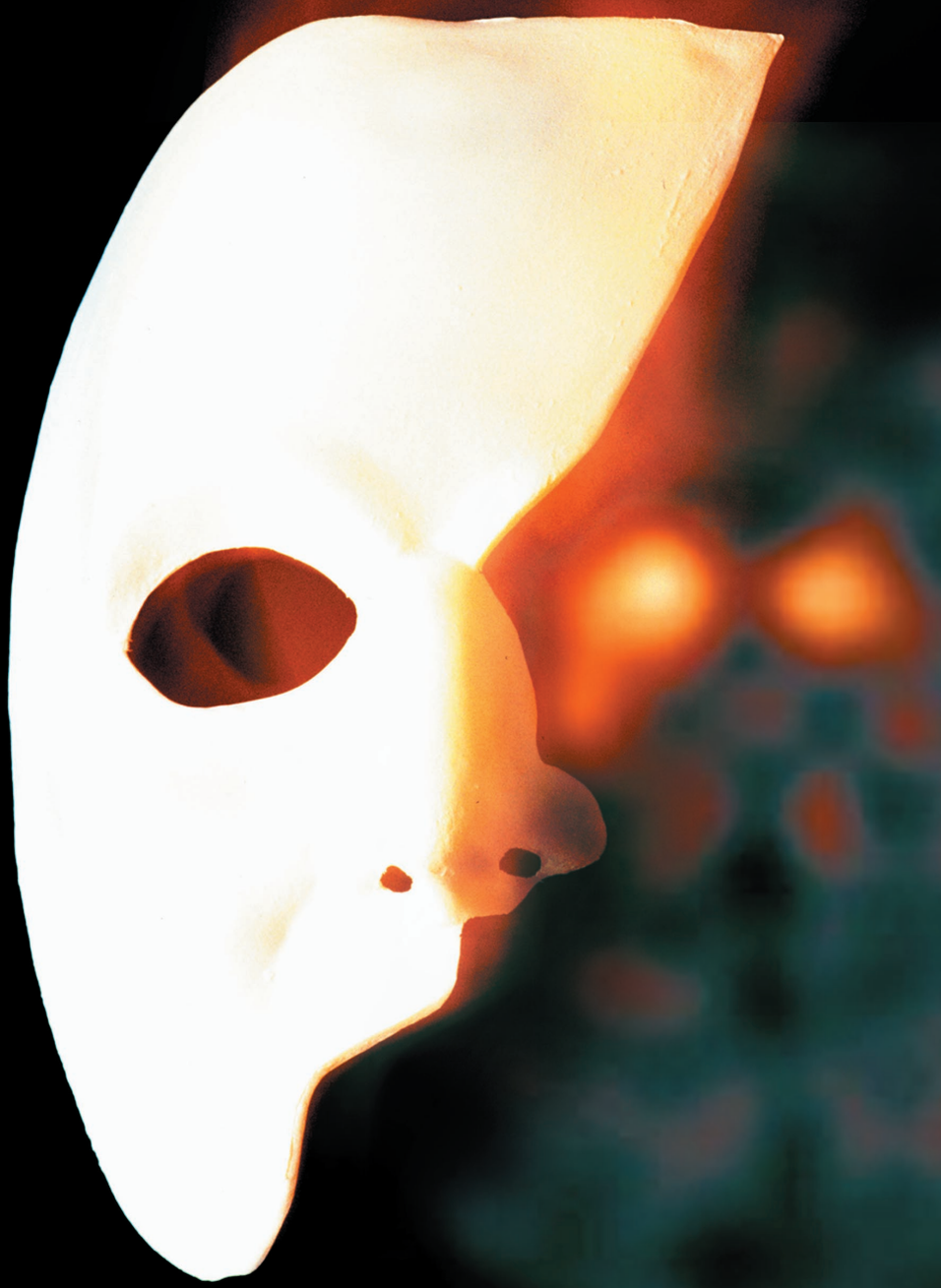
journal reviews • events • management topic • industry news • rehabilitation topic

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

THE TRUTH BEHIND THE MASK



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Date of preparation: February 2001

[1] Benamer H et al. Accurate differentiation of Parkinsonism and Essential Tremor using visual assessment of ^{123}I-FP-CIT SPECT imaging: the ^{123}I-FP-CIT Study Group. Movement Disorders 2000;15:503-510.

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contents

march/april 2002

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 backbenches 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 all 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 a 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.

Roger Barker
AdvancesCNR@aol.com

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Elderly

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Contra-indications

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Special warnings and precautions

Subcutaneous use only. One or more of vasodilatation, chest pain, dyspnoea, palpitations or tachycardia may occur within minutes after injection. These generally resolve spontaneously after a short time. If severe, treat symptomatically. Caution in patients with pre-existing cardiac disorders. Review such patients regularly. Rarely, convulsions and/or anaphylactic or allergic reactions. Rarely, hypersensitivity (bronchospasm, anaphylaxis or urticaria). If severe, treat appropriately and discontinue Copaxone.

Interactions

No formal evaluation. Increased incidence of injection-site reactions with concurrent corticosteroids. Theoretical potential to affect distribution of protein-bound drugs, therefore concomitant use of these should be monitored.

Pregnancy and lactation

Safety in pregnancy not established. Consider if expected benefit outweighs risk to foetus. No data on excretion in human milk.

Undesirable effects

Injection-site reactions (particularly hypersensitivity, pain, mass, inflammation, oedema) are common and usually mild. An immediate post-injection reaction (one or more of vasodilatation, chest pain, dyspnoea, palpitation, tachycardia) was reported at least once in controlled trials by 47% on Copaxone and 29% on placebo. Asthenia, nausea, hypertonia, headache infrequently. Rarely, anaphylactoid or allergic reactions and convulsions. Rarely, shifts in white blood cell counts and level of SGOT, no evidence of clinical significance.

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28 vials of Copaxone plus 28 ampoules of water for injection: £510.14. Copaxone administration package, including syringes and needles supplied free of charge.

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Gillian Hall contributes our Muscle Management Feature. She is a Consultant Neurologist 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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Relapses, progression, inflammation and neuro degeneration in multiple sclerosis: a changing view

Author

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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.[1,2] Progression in MS is classically defined as the continual worsening of symptoms and signs for a minimum of six or 12 months.[1-3] 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.[1,4]

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.[5] 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.[6-7] 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.[8]

Progression and neurodegeneration

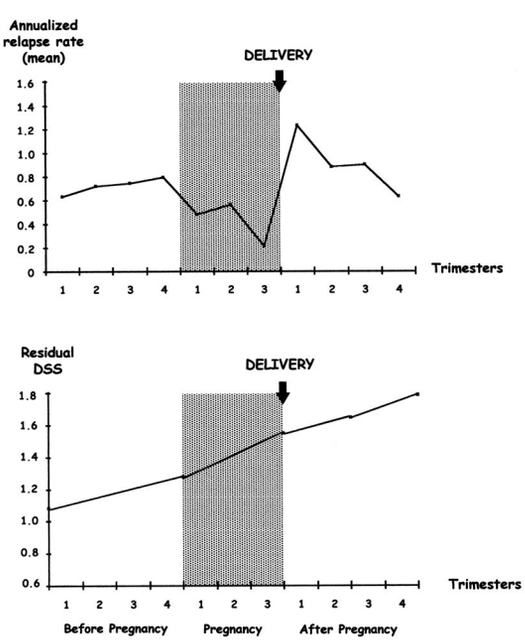
There is increasing evidence that progression is the clinical counterpart of chronic diffuse neurodegeneration. Multifocal inflammatory lesions are not the final story in MS. Pioneer neurologists used to classify MS within neurodegenerative disorders.[9] This has been revived with modern pathological studies[10] and, even more strikingly, with modern imaging techniques. Whole brain and spinal cord atrophy has been well-documented with conventional MRI.[11,12] The NAWM on conventional MRI in fact shows structural abnormalities. Its magnetisation transfer ratio is decreased[13] whereas its anisotropy is reduced and its diffusity is increased[14] in comparison to normal controls. Biochemically, it shows a reduction of the neuronal marker N-acetyl aspartate concentration.[15] Functionally, a given task to be performed involves extraneuronal pathways in comparison to normal brain, as shown by functional MRI.[16] Several of these abnormalities progress throughout the entire course of the disease. For instance, brain atrophy can be observed in the early years of the disease,[17] but also at any stage of the disease.[18] The rate of progression of brain atrophy seems to be rather constant, around 0.8 % per year, i.e. over twice as much as that of control subjects.[17,18] It remains to be shown that this is also true with the other techniques and that there is some parallel between the rate of neurodegeneration and the rate of clinical progression.

The interplay: a dissociation between relapses and progression ?

What are the rules of the game for these two players? The classical view is to consider that MS 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.[19-21] 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,[17] such an effect has not been observed for secondary progressive MS.[22]

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

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

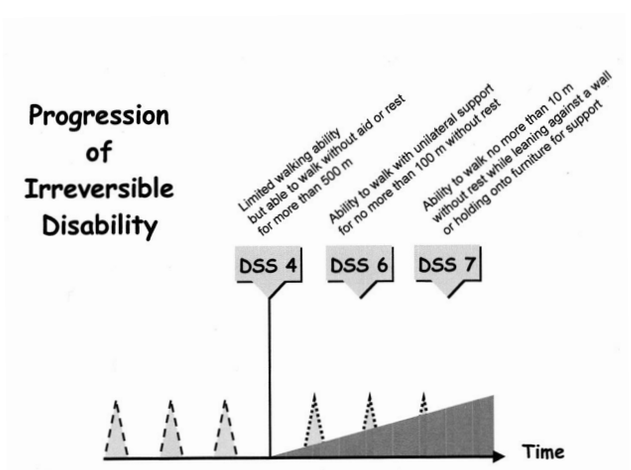
suppression of clinical and MRI activity. In spite of this, progression of clinical disability and cerebral atrophy still occurs.[23,24] Similar observations can be gathered with mitoxantrone (personal observations).

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.[25] 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.[26] Progression of irreversible disability from the assignment of a score of 4 on the DSS Kurtzke scale[27] 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 in comparison to the cases without (Figure 2).

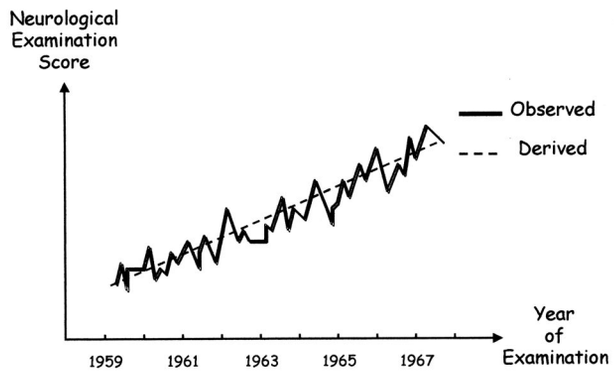
All these observations give some credit to the fact that relapses do not essentially influence irreversible disability in the long term in MS. They are consistent with what has been shown at the individual level in the 70's.[28] By performing **serial quantitative neurological examinations** over several 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 of 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 Confavreux *et al,* Ref 26).



From: NEJM 1998; 339:289

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 enoughfor 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 developped.[30] In this respect, strategies for remyelination by using autologous stem cells,[31] autologous olfactory ensheathing cells,[32] or in situ quiescent premyelinating oligodendrocytes[33] are all very promising.

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Molecular characterisation of motor neuron disorders

Author

Professor Karen Morrison took up the Chair in Neurology at the University of Birmingham in 1999. She trained in molecular genetics at Yale University and the University of Oxford, working on both SMA and ALS. She combines laboratory research on molecular mechanisms in neurodegenerative disorders with clinical work neurology at the Queen Elizabeth Hospital, Birmingham.

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 suggests a genetic contribution of 38-85% in apparently sporadic ALS.[4] Experience from ALS clinics 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.[5]

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 Scandivanian 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.[6] 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'.[2] 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.[5]

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-q22 respectively. 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 (NFH).[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.[8] 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*.[9] 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-

Disease	Mode of inheritance	Chromosomal location	Protein affected
Sporadic ALS	-	-	*
Familial ALS			
ALS1	AD	21q22.1	SOD-1
ALS 18q	AD	18q21	-
Familial ALS with with dementia	AD	9q21-22	-
Familial ALS with dementia and parkinsons	AD	17q21	Tau
ALS X-linked	XL	Xp11-Xq12	-
Juvenile type 1, ALS5	AR	15q15-22	-
Juvenile type 2	AR	-	-
Juvenile type 3, ALS2	AR	2q33	alsin
Juvenile, ALS4	AD	9q34	-
SMA			
SMA Type I	AR,	5q13	SMN
	rarely X-linked	-	-
Type II	AR	5q13	SMN
Type III	AR	5q13	SMN
Type IV	AR	5q13	SMN
	AD	-	-
	X-linked	-	-
Distal SMA			
dHMN-II	AD	12q24.3	-
dHMN-V	AD	7p15	-
dHMN-VI	AR	11q13-21	-
dHMN-VII	AD	2q14	-
dHMN-Jerash type	AR	9p21.1-p12	-
Kennedy's disease	X-linked	Xq21-22	androgen receptor

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 neuronopathy, 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).[5,10,12] As yet no gene defects in distal SMA have been identified.

Kennedy's disease/Spinal bulbar muscular atrophy (SBMA)

SBMA is primarily a disease of the motor nerves of the spinal cord and brain stem, although sensory nerves of the dorsal root ganglia are also involved. The underlying genetic defect is an expansion of a polyglutamine tract within the coding region of the X-chromosome encoded androgen receptor.[13] The importance of mentioning SBMA in this short review is that, now that molecular diagnosis is possible, cases of Kennedy's that would previously have carried an 'ALS label' can be distinguished, with implications for prognosis (milder progression than ALS) and genetic counselling (X-linked recessive disease). 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.

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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, dystrophinopathies). 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 palmotyl 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 McArdle's disease reflects the normal transition of cell energy generation from stored glycogen to lipid. Acid alpha-glycosidase (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 channelopathies (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 (Gutron'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, S1 radiculopathy and following poliomyelitis.

Specific pattern of muscle wasting.

For example, wasting of 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

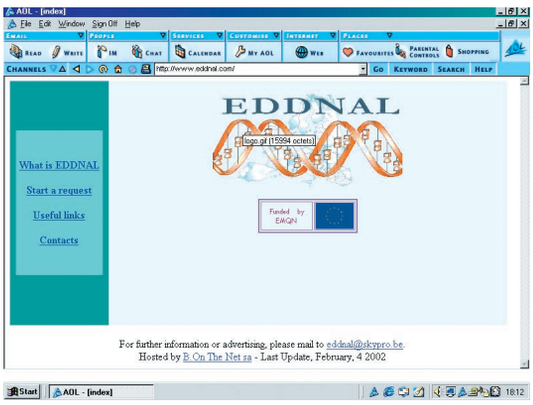
In addition to a full examination of muscle strength:

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)?

The web site of EDDNAL allows you to source availability of specific tests.



Reflexes

Deep tendon reflexes will be diminished in the presence of significant muscle wasting and weakness, however, areflexia suggests a neuropathy or presynaptic neuromuscular problem (Lambert Eaton Myaesthenic Syndrome).

Sensation

Should be normal unless there is an associated neuropathy. Conditions in which both myopathy and neuropathy are seen include mitochondrial disorders, IBM and alcohol induced disease.

Systemic Examination

Eyes

Cataracts are found in myotonic dystrophy. A retinopathy may be a feature of several dystrophies including MD and FSHMD. In FSHMD retinal vascular change is present in the majority of patients but an exudative retinopathy is only seen in more severely affected individuals. Retinitis pigmentosa or extraocular ophthalmoplegia may be seen in some mitochondrial cytopathies.

Ears

Hearing loss can be found in mitochondrial cytopathies and FSHMD. In the latter this is usually only severe in infantile cases.

Respiratory

Many chronic progressive muscle disorders will affect the muscles of respiration in their later stages. However, some primary muscle conditions can present with respiratory failure and should be considered: acid maltase deficiency, nemaline myopathy.

Cardiac

As mentioned above, muscle disease may affect either the myocardium itself resulting in a cardiomyopathy or the conducting system causing the potential for arrhythmias. Are there signs of cardiac enlargement or failure? Is the patient in sinus rhythm?

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

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

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The concept of Functional Electrical Stimulation (FES) was put forward by Liberson[1, 2] 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.

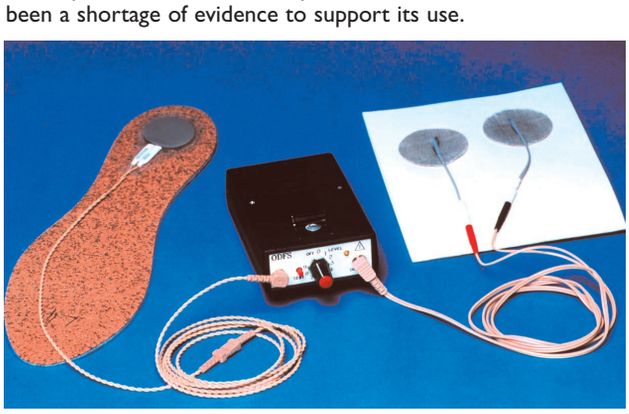

Figure 1. The ODFS III

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 the 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 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[3, 4, 5]. 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-

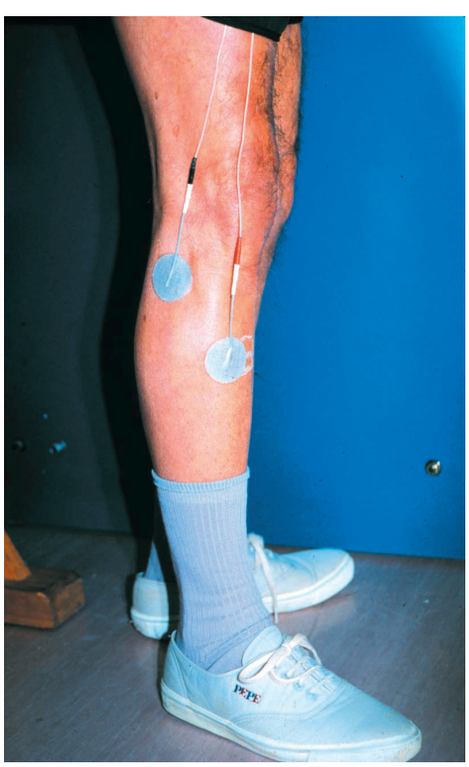

Figure 2. Standard Electrode Positions

ment in quality of life. Cost benefit analysis showed that use of the device gave a QALY (quality adjusted life years) gain over the control group of 0.042, indicating that the use of the device met the requirements for a treatment within the NHS. The trial 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[6]. 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 courses for clinicians who wished to use the device.

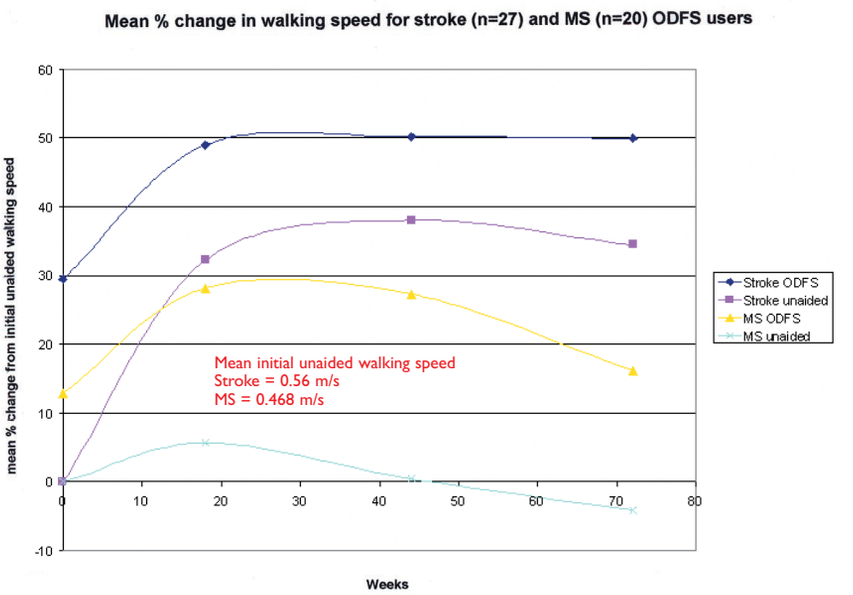

Figure 3.

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 doses 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 clinic 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[7]. 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[8] *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[9]. 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(sd ±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[10]. 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[11]. 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"[12].

Future developments

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

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[13].

Preliminary investigations suggest that the ODFS may be applied in cases of Parkinson's Syndrome to help initiate gait and prevent freezing[14].

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 wheel chair, 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

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Sharing the risk of multiple sclerosis

Author

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

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 ß-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 along side 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 to tackling this issue and, although a new initiative, the scheme may well act as a blueprint for the provision of 'NICE-negative' drugs in the future. The NICE guidelines for ß-interferon state, 'The Department of Health and manufacturers are invited to consider what actions could be taken, jointly, to enable any of the four medicines…to be secured for patients…in a manner which could be considered cost effective.' From this has arisen the idea of 'risk-sharing', meaning that if a drug is not as effective for the patient as expected benefits would predict, the cost of the drug is lowered. Thus drug costs are directly linked to clinical benefit. The proposed scheme will mean that patients will be thoroughly assessed at regular intervals for the duration of treatment. 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 ß-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.

> "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."

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 ß-interferon to the NHS.

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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 100-200mg/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 25-50mg every 1-2 weeks until optimal response. Usual maintenance dose 100 to 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/day in 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 400mg/day given in two divided doses. *Children aged 2-12 years:* To be dosed on a mg/kg basis until the adult recommended titration 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 0.3mg/kg every 1-2 weeks until optimal response. Usual maintenance dose is 1 to 5mg/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 0.6mg/kg bodyweight/day given in two divided doses for two weeks, followed by 1.2mg/kg/day 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 5-15mg/kg/day given in two divided doses. Weight of child should be monitored and dose adjusted as appropriate. If calculated dose is 1-2mg/day then 2mg may be taken on alternate days for the first two weeks. *Dose Escalation:* 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. *Elderly patients:* 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 concomitant 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, drowsiness, and insomnia. Other adverse experiences have included diplopia, blurred vision, conjunctivitis, GI disturbances, irritability/aggression, 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.

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Further information is available from **GlaxoSmithKline UK Limited**, Stockley Park West, Uxbridge, Middlesex UB11 1BT.

Note: If changes in AED medication are to be made they should be completed before conception.* The UK Pregnancy Register (0800 389 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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*Crawford P *et al*. Seizure 1999; **8**: 201-217.

LAM/DPS/02/977 - MWL February 2002

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.[1] 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, hypersomnolence, 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.[2] (Cosnett, reviewing sleep disorders in Dickens's works,[3] suggests that Joe in fact has a diencephalic tumour or suffers the consequences of a head injury; he identifies Mr Willet in *Barnaby Rudge* (1841) as a possible case of obstructive sleep apnoea syndrome.)

Other characters, of possible neurological significance, may be identified in Dickens's oeuvre. Although there are dangers associated with making such inferences (anachronism, hegemonism), nonetheless they may give some insights into the history of neurology since the accuracy of the descriptions (as judged retrospectively) prompts 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 diseases, identified several "Dickensian diagnoses".[4] For example, Sir Leicester Dedlock (*Bleak 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 conceivably be essential tremor. The villagers who witness 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 (*Bleak 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 wilful legs", diagnosed by Brain as an ataxic gait.[4] Perkin has mentioned a number of other Dickensian characters with apparent gait disturbances, without proferring diagnoses.[5] Perhaps Sairey Gamp's difficulties (*Martin Chuzzlewit*) result from her partiality to gin.

Lord Brain also mentions Dickens's descriptions of the sequelae 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*.[4] 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 be 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 writhings have suggested a generalised dystonia, Mr Creakle the schoolmaster may have a spasmodic dysphonia,[8] and the sleepy waiter at the Golden Cross Inn (chapter 19) restless legs syndrome.[3,8] 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.[9] 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.[10] 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.[9]

A few passages give insight into nineteenth century attempts at neurorehabilitation, rudimentary though these were. Most famous perhaps is the little crutch used by Tiny Tim Cratchitt 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 climbing the dust heaps in search of Mr Boffin's buried treasure. Captain Cuttle, in *Dombey and Son*, has "a hook instead of a hand attached to his right wrist" which conveniently doubles as a toasting-fork (chapter 49), and is illustrated being thus used by "Phiz" (Hablot K Browne). Curiously, two other illustrations of Captain Cuttle clearly show the hook on the left hand! A remarkable account of a wheeled chair, used by Mr Omer to facilitate his failing mobility, is to be found in *David Copperfield* (chapter 51): this easy chair on wheels "runs as light as a feather, and tracks as true as a mail-coach".

Orwell contends that Dickens sees human beings with the most intense vividness yet, as a caricaturist, with a narrowness of vision; the mark of his writing is seen as the unnecessary detail.[11] These may be the very qualities which permit us to see some of his characters "like pictures", "fixed like painted miniatures",[11] and hence in certain cases as exemplars of neurological diseases.

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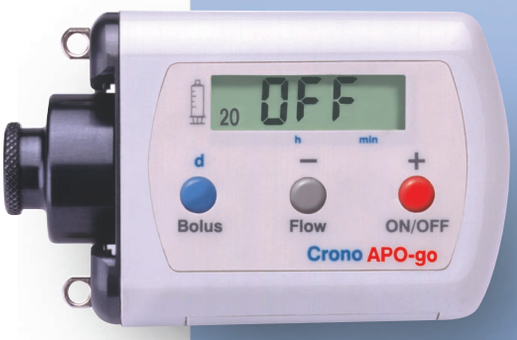
- Continuous waking day dopaminergic stimulation with APO-go® reset the threshold for dyskinesias and led to a pronounced reduction in their frequency[1]
- APO-go® should be considered in all patients before stereotactic neurosurgical intervention[2,3]
- For some patients APO-go® may exacerbate neuropsychiatric symptoms although there is clinical evidence that in patients with previous oral drug-related neuropsychiatric problems, APO-go® led to the reduction or abolition of these complications in all cases[4]



CE 0476

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

1 Colzi A, Turner K, Lees AJ, J Neurology, Neurosurgery and Psychiatry, 1998
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

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ABRIDGED PRESCRIBING INFORMATION

Consult Summary of Product Characteristics before prescribing.

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 initiation of therapy in elderly and/or debilitated patients. Since apomorphine may produce hypotension, care should be exercised in patients with cardiac disease or who are taking vasoactive drugs, particularly when pre-existing postural hypotension is present. Neuropsychiatric disturbances 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 £37.96 – 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.API.V1

APG.AD.V2A4

An invitation to the ABN Spring Meeting

3-5 April 2002, Oxford, UK

Your Association needs you!

David Bateman is Consultant Neurologist at the RUH, Bath and Honorary Secretary of the ABN, responsible for organising ABN meetings.

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'.

Magdalen Bridge, Oxford

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!

Bodleian library

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

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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. *CNS:* 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 seizures. New seizures should be treated with appropriate anti-convulsant therapy prior to resuming AVONEX®. *Pregnancy and lactation:* See Contraindications. Fertile women should take appropriate contraceptive measures. *General:* 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 corticosteroids or ACTH can be given during relapses. Caution should be exercised 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 ache, fever, chills, asthenia, headache, and nausea. Other less common events include: *Body as a whole:* anorexia, hypersensitivity reactions, severe allergic reactions, syncope episode. *Skin and appendages:* alopecia, injection site reaction, pruritus, rash, urticaria. *Digestive system:* diarrhoea, hepatitis, liver function test abnormalities, vomiting. *Cardiovascular system:* arrhythmia, cardiomyopathy, congestive heart failure, chest pain, palpitations, tachycardia, vasodilation. *Haematologic system:* thrombocytopenia. *Reproductive system:* metrorrhagia and/or menorrhagia. *Nervous system:* anxiety, dizziness, insomnia, paresthesia, seizures, depression, suicide and transient neurological symptoms that mimic MS exacerbations may occur following injections. *Musculo-skeletal system:* arthralgia, pain, hypertonia and/or severe muscular weakness. *Respiratory system:* dyspnoea. Autoimmune disorders, central nervous system disorders and laboratory abnormalities have been reported with interferons. Rare cases of arthritis, and hypo- and hyperthyroidism, confusion, emotional lability and psychosis have been reported with AVONEX®. **Preclinical safety:** Fertility and developmental studies with Interferon beta-1a in Rhesus monkeys show anovulatory and abortifacient effects at high doses. No teratogenic effects or effects on foetal development were observed. **Legal Classification:** POM. **Package Quantities and Cost:** 1 box containing four trays. Each tray contains a 3 ml glass vial with BIO-SET device containing a 30µg dose of Interferon beta-1a per vial, a 1ml pre-filled glass syringe of solvent and one needle. **UK:** £697, **Ireland:** available through the High Tech Scheme. **Product Licence Number:** EU/1/97/033/002. **Product Licence Holder:** Biogen France SA., 55 Avenue des Champs Pierreux, 92012 Nanterre-France. **Date document drawn up/revised:** 3 December 2001. **Date of preparation:** February 2002. 2002/3-AV-GBR-1554-2004/3.

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 acetyl choline receptor alpha 4 sub unit 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 onto 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 sub unit gene mutations (SCN1B; chromosome 19q 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.

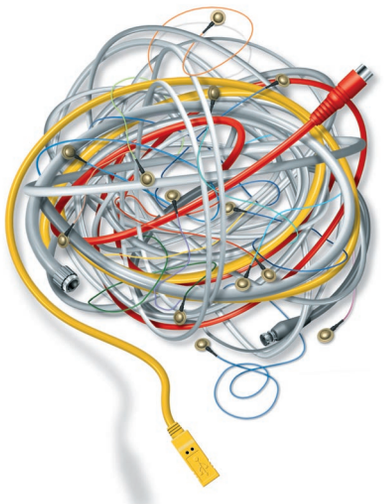
Once again this was a very worthwhile meeting for anyone interested in epilepsy.

Steve Wroe, Ipswich

View abstracts at http://www.aesnet.org/

The next annual meeting will take place 6-11 December, 2002 in Seattle, US.

ADJUNCTIVE THERAPY FOR PARTIAL SEIZURES IN ADULTS



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- Highly effective: up to 4 out of 10 refractory patients had ≥50% partial seizure reduction[1,2,3]
- Excellent tolerability, discontinuation rates not significantly different from placebo[4,5]
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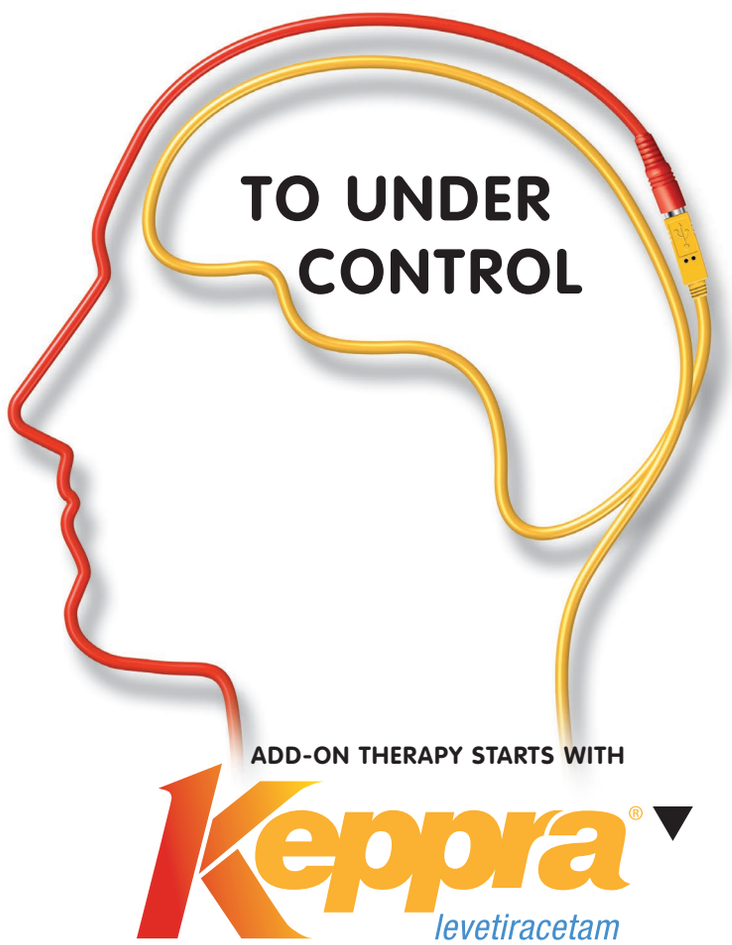
- Therapeutic starting dose (500mg bd)



ADD-ON THERAPY STARTS WITH

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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. **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. **Driving, etc:** Caution recommended when performing skilled tasks, *e.g.* driving vehicles or operating machinery. **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 (between 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. **Basic NHS cost:** 250 mg x 60 tablets: £27.00. 500 mg x 60 tablets: £49.50. 1,000 mg x 60 tablets: £94.50.
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:
1. Shorvon S et al. Pooled efficacy and safety data of levetiracetam (LEV) used as adjunctive therapy in patients with partial onset seizures. *Epilepsia* 1999;40,S7:76,abstract B.01.
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SIMPLIFYING SEIZURE CONTROL

If you would like your event listed in the next issue, send details to: Rachael Hansford on Fax: 0131 3131110 or E-Mail: AdvancesinCNR@aol.com by April 8th, 2002.

2002

March

British Society of Clinical Neurophysiology Scientific Meeting
8 March, 2002; Liverpool, UK
E. secretariat@bscn.org.uk

Brain Awareness Week 2002
12-17 March, 2002; UK
Elaine Snell,
Tel. 020 7738 0424,
E. elaine.snell@which.net

Multiple Sclerosis - from Science to Society
14 March, 2002; Aylesbury, UK
Tel. 020 8438 0818,
Fax. 020 8438 0877,
E. pcrossman@mssociety.org.uk

Advance Course In Infant Imaging of The European Society of Magnetic Resonance in Neuropediatrics
14-16 March, 2002; London, UK
E. Ernst.Martin@kispi.unizh.ch

RSM - Neuro-Epidemiology
21 March, 2002; London, UK
RSM, Tel. 020 7290 2984,
E. fleur.raggatt@rsm.ac.uk

Degeneration and Regeneration of the Nervous System
21-24 March, 2002; St Moritz, Switzerland
Joachim Weis, Division of Neuropathology, Institute of Pathology,
Fax. 0041 31 632 9872,
Tel.0041 31 632 3210,
E. joachim.weis@pathology.unibe.ch

Neurology for Neuroscientists
26-27 March, Oxford, UK
Prof J B Clark,
Tel. 0207 837 3611 x 4201,
Fax. 0207 833 1016,
E. nneurosc@ion.ucl.ac.uk

23rd Advanced Clinical Neurology Course
26-28 March, 2002; Edinburgh, UK
Tel. 0131 537 2082,
Fax. 0131 332 7886,
E. jcc@skull.dcn.ed.ac.uk

April

ABN Spring Meeting
3-5 April, 2002; Oxford, UK
Susan Tann, ABN,
Tel. 020 7405 4060,
Fax. 020 7405 4070,
E. abn@abnoffice.demon.co.uk

3rd World Congress in Neurological Rehabilitation
3-6 April, 2002; Venice, Italy
Aristea,
Tel. 0039 06 844 98364,
Fax. 0039 06 844 98332,
E. neurorehab2002@aristea.com

7th International Geneva / Springfield Symposium on Advances in Alzheimer Therapy
3-6 April, 2002; Geneva, Switzerland
Fax. 39-0-763-344-880,
E. bshelow@siumed.edu

International Neurotrauma Symposium
13-16 April, 2002; Doha, Qatar
Fax. +974 439 2260,
E. Neurosurgery@hmc.org.qa

54th Annual Meeting of the American Academy of Neurology
13-20 April, 2002; Denver, USA
Tel. 001 651 695 1940,
Fax. 001 651 695 2791

RSM - Sherrington Memorial Lecture
15 April, 2002; London, UK
RSM, Tel. 020 7290 2984,
E. fleur.raggatt@rsm.ac.uk

Innovation & Disability - Nursing Challenges of the 21st Century
18 April, 2002; London, UK
Tel. 020 8780 4500, ext 5236

International Meeting on Neuro-Psycho Endocrinology
19-20 April, 2002; Rome, Italy
Fax. 39-630-122-53,
E. md1964@mclink.it

2nd International Meeting in Neuromuscular Rehabilitation
22-23 April, 2002; London, UK
Tel. 020 7829 8692/020 7813 8394,
Fax. 020 7831 6902,
E. courses@ich.ucl.ac.uk

5th European Parkinson's Disease Association Conference
22-24 April, 2002; Jerusalem, Israel
Lizzie Graham, Tel 0207 932 1304,
Fax. 0207 233 9226,
E. lgraham@parkinsons.org.uk

British Neuropsychological Society Spring Meeting
24-25 April, 2002; London, UK
Tel. 0161 275 3401,
www.hop.man.ac.uk/bns

1st Mediterranean Congress of Neurology
26-28 April, 2002; Limassol, Cyprus
Tel. 00357 5 749919,
Fax. 00357 5 749744,
E. conwise@cytanet.com.cy

May

RSM - Advances in Management of Epilepsy
2 May, 2002; London, UK RSM, Tel. 020 7290 2984, E. fleur.raggatt@rsm.ac.uk

3rd Neurological Cooperation Workshop
2-7 May, 2002; Trest, Czech Republic
Tel. +420 2 67 16 28 14,
Fax. +420 2 67 16 23 77,
E. efns@fnkv.cz

8th European Congress on Epilepsy and Society
3-6 May, 2002; Seville, Spain
Tel. 00353 145 0302,
Fax. 00353 1 409 7814

XIV International Neuro-Ophthalmology Society Meeting
5-8 May, 2002; Buenos Aires, Argentina
Fax. 0054 11 4331 0223,
E. Inos2002@congresosint.com.ar

International Workshop Parkinsonism & Dementia
9-11 May, 2002; Istanbul, Turkey
Tel. ++90 212 293 93 08,
Fax. +90 212 244 12 33,
E. events@vistatourism.com

Sensory Impairment - A Challenge for Rehabilitation
10 May, 2002; Perth, UK
Karen Girvan, Tel. 0141 620 0068,
E. karengirvanSSR@aol.com

6th Congress of the European Society for Clinical Neuropharmacology (ESCNP)
14-18 May, 2002; Budapest, Hungary
Tel. 0036 1 311 6687, Fax. 0036 1 383 7918, E. Motesz@elender.hu

PDSNA 2002 Conference
20-21 May, 2002; Nottingham, UK
E. Sandra.Christou@leedsth.nhs.uk

7th Meeting of the European Society of Neurosonology and Cerebral Hemodynamics
26-28 May, 2002; Bern, Switzerland
Tel. 0041 41 767 34 49,
Fax. 0041 41 767 34 00, E. Neurosonology2002@jacch.jnj.com

Cholinesterase Inhibitors: The Evidence Base
28 May, 2002; London, UK
Tel. 020 7290 2984,
E. geriatrics@rsm.ac.uk

13th European Congress of Physical Medicine & Rehabilitation
28-31 May, 2002; Brighton, UK
Melanie Ramsdell, Concorde Services.
Tel. 020 8743 3106,
www.bsrm.co.uk/ec2002

33rd Scandinavian Neurology Congress
29 May-1 June, 2002; Reykjavik, Iceland
Tel. 00354 585 3900,
Fax. 00354 585 3901,
E. Congress@congress.is,
www.congress.is

11th European Stroke Conference
29 May-1 June, 2002; Geneva, Switzerland
Tel. 0041 22 33 99 624, Fax. 0041 22 33 99 621, E. Esc@mci-group.com

June

European Course in Neuroradiology
1-5 June, 2002; Cambridge, UK
Wendy Taylor, Tel. 0718 377 660, Fax. 0712 785 122, E. W.Taylor@ion.ucl.ac.uk

6th European Congress of Clinical Gerontology
June 2002; Moscow, Russia
Prof L B Lazebnik, E. Lazebnik@aha.ru

16th Congress of the European Sleep Research Society
3-7 June, 2002; Reykjavik
Iceland Tel. 35 45 10 20 40, Fax. 35 45 10 20 49, E. esrs2002@vortex.is

RSM - Advances in treatment of movement disorders
6 June, 2002; London, UK
RSM, Tel. 020 7290 2984,
E. fleur.raggatt@rsm.ac.uk

10th International Symposium on Paediatric Neuro-Oncology
9-12 June, 2002; London, UK
Meeting Makers, Jordanhill Campus, 76 Southbrae Drive, Glasgow, G13 1PP.
E. helen@meetingmakers.co.uk

6th European Headache Congress
17-22 June, 2002; Istanbul, Turkey
Flap Tourism & Organisation, Cinnah Cad. Tel. 0090 312 4420700,
E. Flaptour@flaptour.com.tr

BSCN Paediatric Theme Meeting
21 June, 2002; Oxford, UK
E. secretariat@bscn.org.uk

ENS 2002
22-26 June, 2002; Berlin, Germany
Tel. +41 61 686 77 11,
Fax. +41 61 686 77 88,
E. info@akm.ch

7th Euroacademia Multidisciplinaria Neurotraumatologica Congress
26-29 June, 2002; Newcastle upon Tyne, UK
Tel. 0191 273 88 11 22 999,
E. emn2002@ncl.ac.uk

July

7th Cycle: First Course of the Brain
Wendy Taylor, Tel. 0207 837 7660,
Fax. 0207 278 5122,
E. W.Taylor@ion.ucl.ac.uk / r.jager@ion.ucl.ac.uk

ABN one-day joint meeting with RCP
4 July, 2002; London, UK
Susan Tann, ABN, Tel. 020 7405 4060,
Fax. 020 7405 4070,
E. abn@abnoffice.demon.co.uk

INSTITUTE OF NEUROLOGY

in association with
THE NATIONAL HOSPITAL FOR NEUROLOGY AND NEUROSURGERY
Queen Square, London WC1

SHORT COURSES

13-24 May 2002

Epilepsy ***(13 May)***
Neuroinflammation ***(14 May)***
Dementia ***(15 May)***
Stroke ***(16 May)***
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; £340 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
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Email: J.Reynolds@ion.ucl.ac.uk

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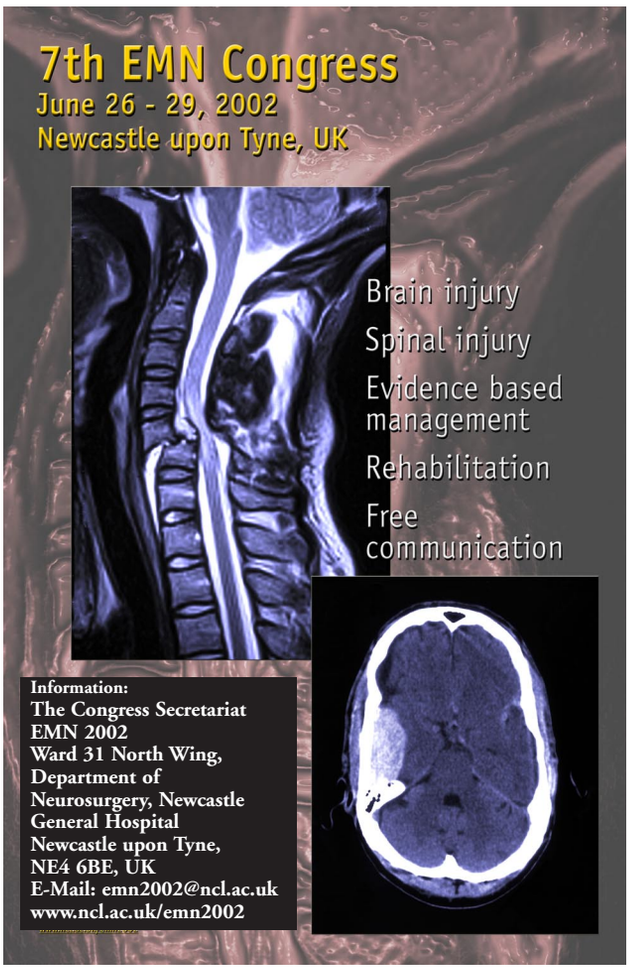


MS Frontiers

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 Altmann, 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 Woodroofe

Expert panel

Dr Coles, Prof Ebers, Dr Ford, Dr Giovannoni, Dr Glickman, Prof Jessen, Prof Matthews, Ms Porter, Dr Ray, Prof Reynolds, Prof Robinson, Prof Scolding, Prof Thompson

Who should attend?

- All healthcare professionals with an interest in MS, in every discipline
- 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: pcrossman@mssociety.org.uk
Multiple Sclerosis Society – Registered Charity Number 207495

Dural venous sinuses and the deep cerebral veins

Alasdair Coles and Justin Cross

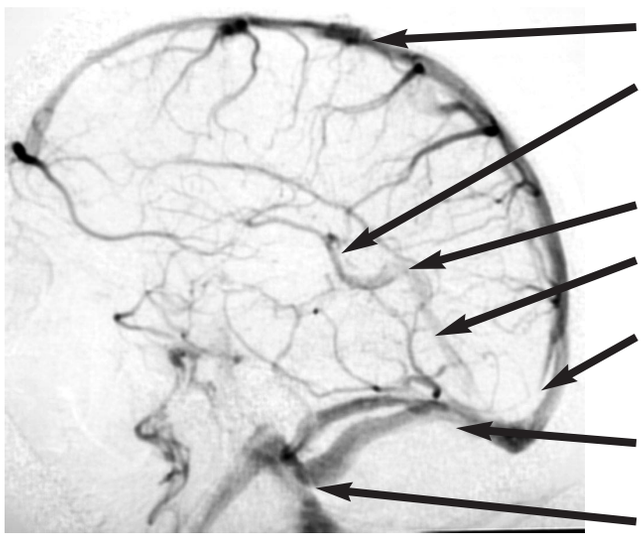
Anatomy

Dural venous sinuses

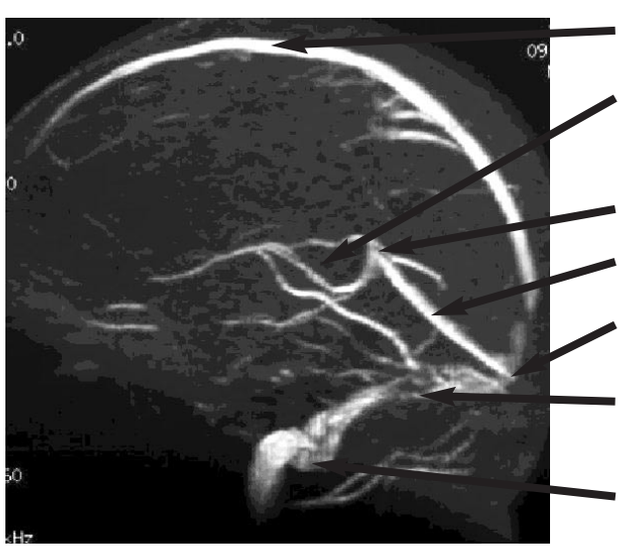
These are endothelium-lined channels which lie between the outer (periosteal) and inner (meningeal) layers of the dura mater. They collect blood from superficial and deep cerebral veins, meninges and calvarium and are connected via emissary veins to the extracranial venous system.

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 formaen 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 c**avernous 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 form the superior and inferior ophthalmic veins and pterygoid plexus and drain vua the petrosal sinuses and clival venous plexus.

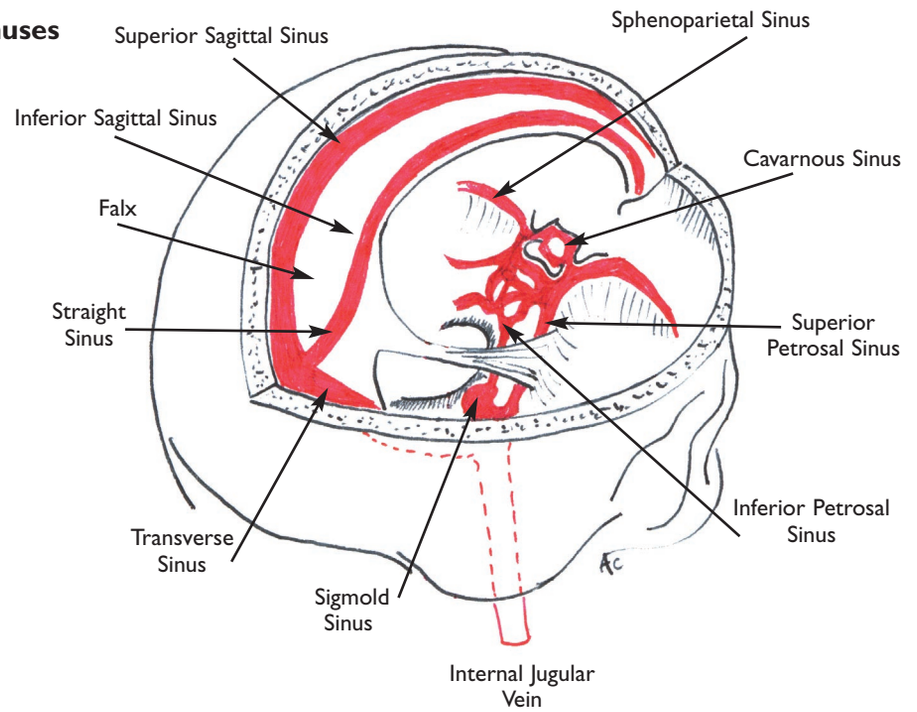
"Magnetic" resonance venogram



"Digital" substraction angiogram



Dural venous sinuses



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 anastamotic 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 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.

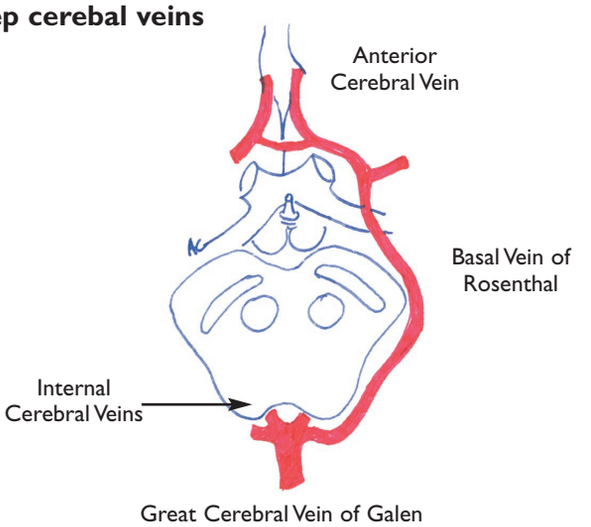
Asymmetric jugular bulbs - complete symmetry is very rare.

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.

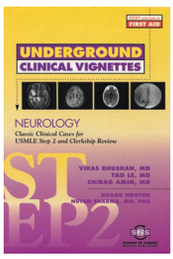
Magnetic resonance techniques exploit signal generated from flowing blood. Phase contrast and time of flight imaging are both routinely used in the examination of the intracranial veins. A disadvantage of this technique is the relatively long acquisition times (6-7 minutes). A common artefact associated 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.

Deep cerebal veins



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



Author: V Bhushan *et al.*
Published by: S2S Medical Publishing, distributed by Blackwell Science
Pages: 103
ISBN No: 0632048271
Price: £12.50

If you are a (normal) medical student who is confused, even terrified, by the obscure world of neurology, a book which opens 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.

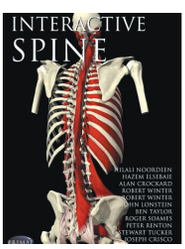
The authors present 52 'supra-prototypical cases in a cohesive and memorable clinical picture'. The material is well chosen and spans the breadth of clinical neurology. Each vignette comes in the form of a grand-round presentation pared down to the important positive features which makes for a snappy read. Unfortunately, the order of the cases is determined by classification and the alphabet rather than clinical importance, so eponymous genetic 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 glioblastoma multiforme 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 (eg 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



Published by: Primal Pictures
ISBN No: 1-902470-32-X
Price: £176.25

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 ligaments?)

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 Horner's syndrome. But these are footling objections. Any neurologist wishing better to understand the complexities of the cranio-cervical junction, the intervertebral foramina and the neck muscles and have enormous fun on the way should buy this CD.

Alasdair Coles, Cambridge

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 a 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.

LM Björklund *et al.* (2002) Proceedings National Academy of Sciences (USA) Jan (epub ahead of print)

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. - ***AJL***

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

Geschwind DH, Robidoux J, Alarcón M *et al.* (2001) ANN.NEUROL. 50(6): 741-746

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

dominant AD. However, as its name implies, HCHWA-D most frequently manifests clinically with lobar cerebral haemorrhages, although dementia may develop in some patients. CAA is a much commoner condition than HCHWA-D, which increases in prevalence with age in both demented and non-demented individuals. However, the precise relationship of CAA to dementia is uncertain because most demented cases show associated neuritic plaques and neurofibrillary tangles. Because these latter findings are very rare in HCHWA-D, this condition permits investigation of the relation between CAA and dementia.

Of 19 HCHWA-D patients, 8 developed dementia, 11 did not. The demented patients had a higher CAA load in the frontal cortex, quantified by computerised morphometry, and more vessel wall thickening. This relationship was independent of neurofibrillary pathology, plaque density, and age. The mechanism of dementia is not certain: small cerebral haemorrhages and infarcts seem the likeliest explanation but HCHWA-D may on occasion present with dementia in the absence of a history of stroke or focal radiological lesions. Neuronal loss and white matter change may also contribute to dementia. This study suggests that if extensive, CAA is sufficient to cause dementia in HCHWA-D, findings which may have implications for AD and other dementias associated with CAA. ***- AJL***

Natté R, Maat-Schieman MLC, Haan J, Bornebroek M, Roos RAC, van Duinen SG. (2001)
Dementia in hereditary cerebral hemorrhage with amyloidosis-Dutch type is associated with cerebral amyloid angiopathy but is independent of plaques and neurofibrillary tangles.
ANN.NEUROL.
50(6): 765-772

EPILEPSY

★★★ RECOMMENDED

What drug next for refractory epilepsy?

Harry Potter fans will remember the Hogwarts school sorting hat, which when placed on each pupil's head, magically chooses the school house they will enter. I have an antiepileptic drug (AED) hat. This is placed on the head of each patient with refractory, focal epilepsy in order to choose their next drug. I believe this is as likely to choose the right drug as any other method yet devised. Each of us has anecdotes of cure of "refractory" cases in our practices, but why did we choose that drug?

This study looks at the expression of drug resistance proteins, which have been identified in cancer patients and act as drug transporters. They are known to transport some AED. The proteins MDR1 and MRP were studied in the resected tissue from patients with refractory epilepsy due to hippocampal sclerosis (HS), dysembryoplastic neuroepithelial tumour (DNT) and focal cortical dysplasia (FCD). MRP1 was expressed in all DNT tissue, in 5 of 8 HS cases and all FCD cases. In some FCD cases the protein was associated with dysplastic neurones and in all the other cases with reactive astrocytes. MDR1 was seen in fewer cases. In no case were these proteins expressed in adjacent, normal neuronal tissue also resected. These proteins are not known to be expressed in normal CNS tissue. It seems therefore, that these proteins are not simply expressed because of exposure to AED but are an abnormal response restricted to epileptic tissue.

The authors have explored a mechanism whereby tissue may become resistant to AED. One day we may be able to predict whose epilepsy will be resistant to each drug, but I suspect my hat will remain valid for some years to come; the Hogwarts hat is 700 years old I believe. ***- MM***

SM Sisodiya, W-R Lin, BN Harding, Thom M (2002).
Drug resistant epilepsy: expression of drug resistance proteins in common causes of refractory epilepsy.
BRAIN
125:22-31.

Drug withdrawal in epilepsy

The best drug withdrawal study to date is the MRC study[1]. 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 likely to be less well educated, have a normal EEG, have shorter disease duration, have longer remission prior to 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.

1. Medical Research Council Antiepileptic Drug Withdrawal Study Group (1991). Randomised study of antiepileptic drug withdrawal in patients in remission. *Lancet 337*:1175-80.

- MM

Specchio LM, Tramacere L, A La Neve, Beghi E. (2002).
Discontinuing antiepileptic drugs in patients who are seizure-free on monotherapy.
J NEUROL NEUROSURG PSYCHIAT. 72:22-25

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 arteriosclerotic 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 some 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

★★★ RECOMMENDED

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' 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 melatonin 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 neurones, 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 peripheral and central nervous system.***-AJL***

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 agrypnia.
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 Fujii, Mian Li, Bashar Lutfi, Joan Kyhos, and Beverley McElroy (2001)
High-dose intravenous immunoglobulin for stiff person syndrome. NEJM 345:1870-6

PERIPHERAL NERVE

★★★ RECOMMENDED

Life after steroids in neuromuscular disease?

Immune-mediated neuromuscular diseases are not the only conditions in neurology in need of modulating therapies other than oral 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 a backdrop to a couple of case reports that offer us glimpses into 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

conditions who appear to be doing badly. - ***WR***

Rivner M; Bedlack R, Sanders D (2002)
Steroid treatment for myasthenia gravis
MUSCLE AND NERVE 25: 115-121
Evoli A, di Schino C, Marsili F, Punzi C (2002)
Successful treatment of myasthenia gravis with tacrolimus.
MUSCLE AND NERVE 25: 111-114
Schneider C, Gold R, Schafers M, Toyka K (2002)
Mycophenolate mofetil in the therapy of polymyositis associated with a polyautoimmune syndrome.
MUSCLE AND NERVE 25: 286-288

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 controlled 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 standard 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 prognos-

tic signs during treatment. Clearly that is another study waiting to be conducted. **– *ADW***

Sander A M, Roebuck T M, Struchen M A, Sherer M, High W M Jr (2001)
Long-term maintenance of gains obtained in postacute rehabilitation by persons with traumatic brain injury.
JOURNAL OF HEAD TRAUMA REHABILITATION
16: 4: 356-373

STEM CELLS

★★★ RECOMMENDED

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 pluripotential 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. **- *RAB***

In vitro differentiation of transplantable neural precursors from human embryonic stem cells
Zhang S-C *et al.* (2001) Nature Biotech. 19:1129-1133
Neural progenitors from human embryonic stem cells
Reubinoff BE *et al* (2001) NATURE BIOTECH.
19: 1134-1140

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 Downs syndrome, which may underlie some of their cognitive abnormalities. **- *TH***

Sabine Bahn, Michael Mimmick, Margaret Ryan, Maeve Caldwell, Eric Jauniaux, Michael Starkey, Clive Svendsen and Piers Emson (2002)
Neuronal traget genes of the neuron-restricter silencer factor in neurospheres derived from fetuses with Down's syndrome: a gene expression study.
LANCET
359: 310-315

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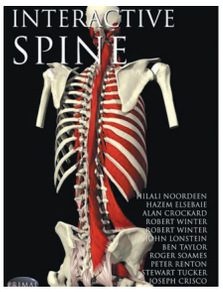

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For a review of this CD, see page 32.

Brain damage, behaviour and cognition

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The books in the Brain Damage, Behaviour and Cognition Series present comprehensive, up-to-date overviews of current research, and will be of particular interest to those working with the brain-damaged.

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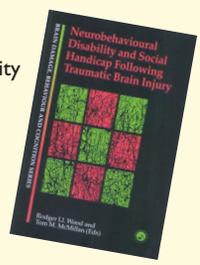
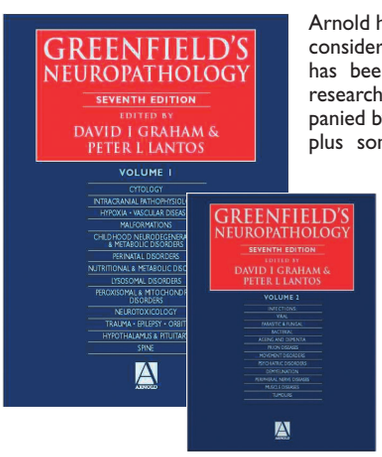


New edition of Greenfield's Neuropathology



Arnold has published the 7th edition of Greenfield's Neuropathology. "Long considered the world's leading neuropathology reference, this new edition has been greatly revised and contains a wealth of new material and research. And, for the first time, the new edition of Greenfield's is accompanied by a CD ROM, containing all the illustrations from the 2-volume set, plus some extras - over 2000 in total! Greenfield's Neuropathology Illustrated is a unique and comprehensive atlas of neuropathology," says the publisher.

INTRODUCTORY OFFERS

Greenfield's Neuropathology, 7th ed and Greenfield's Neuropathology Illustrated are available to purchase separately or as a set. Order now and save up to £80. **Please note: offers end on publication date - 1st June 2002**.

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CONFERENCE AMENDMENT

EPDA
EUROPEAN PARKINSON'S DISEASE ASSOCIATION

Working in Harmony - the team approach

THE Fifth European Parkinson's Disease Association Conference, 18 - 20 August 2002, Jerusalem, Israel

It is with regret that the EPDA has to announce that this conference will not be taking place due to the current situation in Jerusalem, Israel.

However, to celebrate the EPDA's 10th Anniversary, a two-day multidisciplinary conference will be held at The Grand Union Hotel, Ljubljana, Slovenia, 30-31 May 2002.

For more information, contact the EPDA Liaison/Project Manager, 4 Golding Road, Sevenoaks, Kent TN13 3NJ. Tel/Fax: 01732 457683, Mobile: 07787554856, e-mail. Lizzie@epda.demon.co.uk, www.epda.eu.com, www.epdaconferences.org

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.

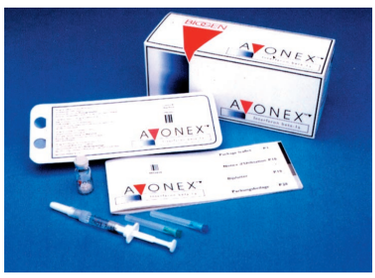
Previous imaging restrictions are now a thing of the past: large-volume imaging did not allow for thin slices, and longer acquisition times resulted in degraded image quality due to motion artifacts. With the Somatom Sensation 16, Siemens Medical Solutions have succeeded in combining volume, speed, and 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.

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.

CARE dose, one of the components of CARE (Combined Applications to Reduce Exposure), an initiative of Med to 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

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.

Dr Martin Toal, Medical 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 extensive clinical experience, and we have no doubt that this scheme will confirm the benefits to UK patients".

The DOH has set a start date of May 2002 for the commencement of the scheme, and an 18 month period for its completion. This will present considerable logistical challenges for many MS clinics.

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_Toal@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.

Multiple Sclerosis Trust
opening the door to information education and research

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 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.

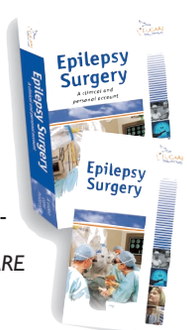
The scheme will be co-ordinated by a research department, and the MS Trust will be working with the DOH to recruit this team. An advertisement concerning applications for this appointment will appear shortly.

For people with MS it is going to take some time for the neurology centres across the UK to set up the systems to administer this scheme, but it is hoped that all centres will be operating by May 2002. Resources are going to be an issue and the MS Trust will be monitoring the situation to ensure that the scheme is put into place across the UK. The fact that it does have statutory backing is clearly important in this context.

An information sheet on the scheme can be obtained by ringing the MS Trust on 01462 4767000 or sending an e-mail to info@mstrust.org.uk

Epilepsy surgery - A clinical and personal account

This new educational pack includes a video programme for professionals which runs for approximately 20 minutes, and an accompanying 20 page booklet written by Specialist Epilepsy Counsellor Sue Usiskin which answers the common questions asked by people being offered epilepsy surgery.



In the programme, a multi disciplinary team discusses the assessment of risk associated with epilepsy surgery against the risks for people who continue having seizures. It also includes a personal view of a patient who gives insight into what it is like to live with uncontrolled epilepsy and then to be considered for surgical treatment.

It expounds quality of life issues from both the medical and personal perspective and so gives a holistic view of surgical assessment issues.

For further information, or to order a copy of the pack contact Jill Putman at EUCARE (UK Branch), UCB Pharma Ltd, UCB House, 3 George Street, Watford, Hertfordshire, WD18 OUH. Tel: 01923 211811, e-mail: eucare-uk@ucb-group.com

Mestinon for the treatment of Myasthenia Gravis

Mestinon is prescribed for the treatment of Myasthenia Gravis (MG). MG is an autoimmune disorder of the neuromuscular junction (NMJ) caused by circulating antibodies to skeletal muscle protein, usually acetylcholine receptors (AChR). The defining feature is fatiguable muscle weakness, which is often debilitating and sometimes fatal.

MG usually develops in adults and the prevalence is 1:10-20,000.[1,2] In 60-70% of patients, the presenting feature is ocular weakness causing ptosis or diplopia or both.

Mestinon is the first-line drug for most MG patients.[1] It competitively blocks acetylcholinesterase at the neuromuscular junction and, thus, increases the functional concentration of ACh.

Mestinon's effect begins within 30 minutes, peaks at around 2 hours, and gradually declines thereafter. (Ref-Drachman). Duration of action is 3 to 5 hours.[1] To gain the greatest therapeutic benefit the dosage regimen should be tailored to the response of the patient and reviewed frequently, as inter-patient variability in plasma concentrations after taking Mestinon can be great.

With prompt and correct management, more than 85% of patients regain normal function, almost regardless of age.[1]

References

1. Hart I, Myasthenia Gravis the essentials; Eurocommunica Publication
2. Drachman DB, Myasthenia Gravis

For further information please contact ICN Pharmaceuticals Ltd, Cedarwood, Chineham Business Park, Crockford Lane, Basingstoke, Hants. RG24 8WD e-mail: icnpharm.com

PD symposium at the ABN

Amersham Health will be running a satellite symposium at the Association of British Neurologists meeting in Oxford on Thursday 3rd April. The symposium, entitled, **Developments in Parkinson's; Imaging and Autopsy Studies**, will commence at 17.45 at the Examination Halls, University of Oxford.

The meeting will be chaired by Dr Donald Grosset, with presentations from Professor Andrew Lees, Professor David Brooks and Dr David Burn. We look forward to seeing you at the meeting and afterwards for dinner at Exeter College.

If you would like any information about Datscan or the meeting, please contact Zillah Moore on 01494 798697.

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to go to the toilet.

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Please refer to the Summary of Product Characteristics before prescribing. **Presentation** 'Requip' Tablets, PL 10592/0085, 0087-0089, 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 3mg/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 domperidone. 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; symptomatic 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. **Overdosage** No incidences 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

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Date of preparation: February 2002

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