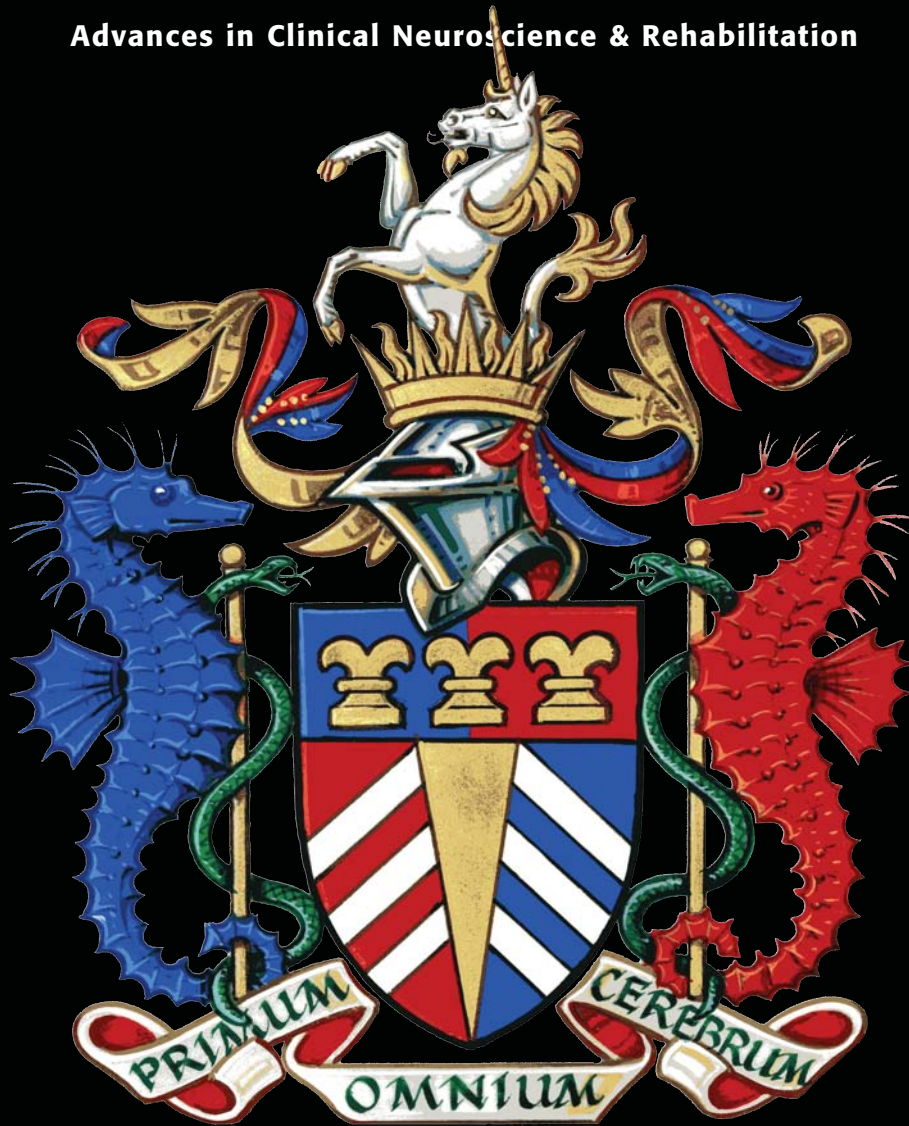


ACNR

Advances in Clinical Neuroscience & Rehabilitation



Mark Wardle and Neil Robertson

Progressive Late-Onset Cerebellar Ataxia

Edward Wild and Sarah Tabrizi

Genetic Causes of Dementia

Martin Coleman and Adrian Owen

Functional Imaging and the Vegetative State



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For some reason, I always get anxious that I am missing some obvious or treatable diagnosis when diagnosing patients with cerebellar syndromes. In this issue of ACNR we have a fantastic review by Mark Wardle and Neil Robertson on how to approach the patient with progressive late-onset cerebellar ataxia. This review is wonderfully comprehensive but also packed with really helpful comments and strategies. I am sure it will become a standard text that many of us will take to clinic, and by so doing give us greater confidence and structure in our diagnostic attempts in such patients.



The surgical treatment of trigeminal neuralgia is not an uncommon discussion to be had in neurological practice, but what exactly this involves and how the patients do after such procedures is not especially well known by most neurologists (or at least not by me, anyway). It is therefore particularly useful to have such an expert as Hugh Coakham take us through this topic, highlighting that “microvascular decompression is now established as a safe and effective treatment for trigeminal neuralgia in patients where medication has failed. Our objective, patient orientated review has indicated that this procedure should be offered earlier and preferably as first line treatment before any injection therapy which can adversely affect the operative success rate”.

In the second of our neurogenetics series Ed Wild and Sarah Tabrizi summarise the current position with respect to genetic causes of dementia and which genes are worth testing for, in which patient. This is a succinct informative account with very useful summary tables and clear messages to be taken to the clinic.

Neuropathology returns in this issue, with a new series again kindly edited by Professor Roy Weller. In the first of the series, Rahul Phadke and Janice Holton take us through the clinical features and diagnosis of inflammatory myopathies, including the pathology of such disorders as revealed by muscle biopsy. This beautifully clear review continues the tradition of excellence that characterised the first series of such articles, and succeeds in distilling out the key factors in these disorders.

In the last issue of ACNR a case report of a patient in a vegetative state and Cushing’s disease was described, and the ethical dilemmas of their management discussed. In this issue, Martin Coleman and colleagues enlighten us on how functional imaging has modified our assessment and interpretation of such patients. They discuss how patients with clinically defined vegetative states actually retain the capacity to process complex sensory stimuli which can only be seen by recording activation patterns on functional scans. This highlights how advances in imaging can impact on the definition of what was previously only diagnosed using cruder, less sophisticated clinical and electrophysiological methods.

In our Drugs in Neurology series, sponsored on this occasion by Schwarz-Pharma, we have an article by Donald Grossett on the use of the rotigotine transdermal patch in patients with advanced Parkinson’s disease. This article highlights the efficacy of this therapy, and complements the article we published in the ACNR last year on this drug.

In the patient perspective, Helen Thomas tells the story of her hereditary sensory motor peripheral neuropathy. She highlights her sense of isolation by the medical profession, and the support offered her by friends and family and her amazing self-reliance. Perhaps though the most revealing and moving part of the account is the judgements cast on her by those around her, unfamiliar with the condition and its manifestations. It is all so easy to undermine individuals with neurological disease by casual ill informed comments and to underestimate the impact of disease on one’s life.

Finally, I have always regarded the journal as having an intimacy and eclectic mix that makes it different to other journals, and it owes much of this to those who help set it up. I would therefore like to dedicate this issue to the memory of someone who taught me an awful lot about these aspects of life - Imogen Rose Barker, our 15-year-old daughter who was sadly knocked down and killed on the 24th February 2007.

Roger Barker, Co-Editor,
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Roger Barker is co-editor of ACNR, and is Honorary Consultant in Neurology at The Cambridge Centre for Brain Repair. His main area of research is into neurodegenerative and movement disorders, in particular parkinson's and Huntington's disease. He is also the university lecturer in Neurology at Cambridge where he continues to develop his clinical research into these diseases along with his basic research into brain repair using neural transplants.



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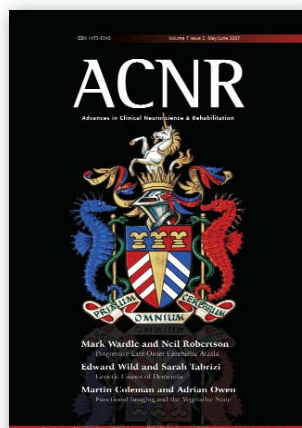
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Cover picture illustrates the new Coat of Arms of the Association of British Neurologists, granted in 2007 as part of their 75th anniversary celebrations.

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Adjunctive therapy for partial onset seizures with or without secondary generalisation in adults and children from 4 years of age and for myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy. *Infusion:* an alternative for patients when oral administration is temporarily not feasible. **Dosage and Administration:** *Oral solution* should be diluted prior to use. *Infusion:* Keppra concentrate must be diluted in at least 100 ml of a compatible diluent and administered intravenously as a 15-minute infusion.

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Progressive Late-Onset Cerebellar Ataxia

Ataxia is a term used to describe a condition characterised by disordered or incoordinate movement and is commonly caused by diseases affecting the cerebellum and its connections within the central nervous system (CNS). Ataxia caused by cerebellar dysfunction is a dominant feature in a wide spectrum of overlapping heterogeneous clinical disorders¹ and may also be mimicked by a variety of isolated or combined neurological deficits, including loss of muscular strength, altered tone, diminished sensation or the intrusion of involuntary movements.

Ataxia may present either as a pure cerebellar syndrome or associated with significant cognitive, pyramidal, extrapyramidal, sensory and autonomic dysfunction, and can also be the presenting feature of a more widespread neurodegenerative disorder. It is therefore not surprising that the investigation of cerebellar ataxia often poses considerable diagnostic challenges for the treating physician, and has been made increasingly complex by advances in molecular genetics and immunology that allow access to a bewildering array of novel investigations.

Extent of the problem

Cerebellar ataxia is not a rare condition: Hospital Episode Statistics (HES) for England and Wales (2005/6) suggest admission figures similar to disorders such as myasthenia gravis, idiopathic intracranial hypertension and bacterial meningitis, and three times that of Huntington's disease (HD) (<http://www.hesonline.nhs.uk>). However, these statistics are likely to significantly underestimate the true extent of the problem as cerebellar disease frequently occurs as a feature of other primary neurological disorders such as multiple sclerosis (MS), stroke and CNS tumours. Accurate epidemiological statistics for incidence and prevalence are scarce and highly variable largely as a result of ascertainment bias, differing inclusion criteria, variable aetiological classification and founder effects. Contemporary estimates of the prevalence of autosomal dominant cerebellar ataxia (ADCA) in the UK lie between 0.31–8.0/100,000²⁻⁴ and 1.2–41.0/100,000 worldwide.⁵⁻⁷

Prevalence estimates for sporadic idiopathic late-onset cerebellar ataxia are limited, but a minimum prevalence of 10.8/100,000 has been suggested for the UK.³ These data

suggest there are at least 10,000 cases of familial and sporadic late-onset cerebellar ataxia (LOCA) in the UK alone, with the majority of both familial and sporadic cases having no defined aetiology.

Diagnostic strategy

For many patients, especially those with an acute or subacute presentation of ataxia, initial investigations will readily identify an acquired cause (Table 1) such as chronic alcoholism, MS, remote malignancy (paraneoplastic cerebellar degeneration), vitamin deficiency, toxins or hypothyroidism.⁸ Adult patients with a more progressive disease course of more than one year, particularly if associated with few discriminatory signs on neuroimaging, commonly present the most challenging clinical scenario. They require careful initial and subsequent clinical assessment of frequently complex clinical features which may change over time. This necessitates a practical diagnostic and management strategy, focusing on the early identification of potentially reversible causes and demands a logical approach to more specialised investigations (Table 2).

The most important discriminating factors in the history and examination of this group of patients with late onset cerebellar ataxia (LOCA) are family history, age of onset, rate and pattern of development of symptoms, a comprehensive drug and alcohol history, past medical history and the presence of other associated symptoms and signs.

Is there a family history?

A dominant family history is the single most important factor predicting the chance of successfully diagnosing a genetic cause of cerebellar ataxia. Analysis of the common spinocerebellar mutations results in a positive identification in 39–64% of dominant and 11–38% of non-dominant families, but only 1–19% of sporadic late-onset cases.⁹⁻¹³

The inherited ataxias are a broad heterogeneous group, and can manifest in childhood, adolescence or adulthood with widely variable clinical features, even within the same family. They may be inherited in an autosomal recessive, autosomal dominant (ADCA), X-linked or mitochondrial inheritance pattern, but prevalence estimates are limited and sensitive to founder effects resulting



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Table 1: Aetiology of cerebellar ataxia. Adapted from reference 34.

<p>Acute (hours to days)</p> <p><i>Intoxication (alcohol, lithium, barbiturates)</i></p> <p><i>Acute viral cerebellitis</i></p> <p><i>Post-infection syndrome</i></p> <p><i>Vascular (e.g. cerebellar infarction, haemorrhage)</i></p> <p><i>Infectious (e.g. cerebellar abscess, Whipple's)</i></p>	<p>Subacute (days to weeks)</p> <p><i>Intoxication (mercury, solvents, petrol, glue, cytotoxic agents)</i></p> <p><i>Alcoholic cerebellar degeneration</i></p> <p><i>Nutritional / malabsorption (vitamin B1, vitamin B12)</i></p> <p><i>Posterior fossa tumour (e.g. cerebellar glioma, metastases)</i></p> <p><i>Multiple sclerosis</i></p> <p><i>Hydrocephalus</i></p> <p><i>Foramen magnum compression</i></p> <p><i>AIDS-related multi-focal leukoencephalopathy</i></p> <p><i>Miller-Fisher syndrome</i></p> <p><i>Lyme disease</i></p>
<p>Chronic (months to years)</p> <p><i>Intoxication (phenytoin toxicity)</i></p> <p><i>Paraneoplastic cerebellar syndrome</i></p> <p><i>'Gluten ataxia'</i></p> <p><i>Vitamin E deficiency (inherited or acquired)</i></p> <p><i>Hypothyroidism</i></p> <p><i>Tabes dorsalis</i></p> <p><i>Creutzfeld-Jacob disease</i></p> <p><i>Rubella panencephalitis</i></p> <p><i>Previous vascular lesion or demyelination</i></p> <p><i>Congenital lesion</i></p> <p><i>Inherited ataxias</i></p> <p><i>'Idiopathic'/degenerative ataxias</i></p>	<p>Episodic ataxia</p> <p><i>Intoxication</i></p> <p><i>Multiple sclerosis</i></p> <p><i>Transient ischaemic attacks</i></p> <p><i>Foramen magnum compression</i></p> <p><i>Intermittent hydrocephalus (e.g. cysticercosis, colloid cyst)</i></p> <p><i>Dominant episodic ataxia (e.g. EA1, EA2 etc.)</i></p> <p><i>Inherited metabolic ataxias</i></p>

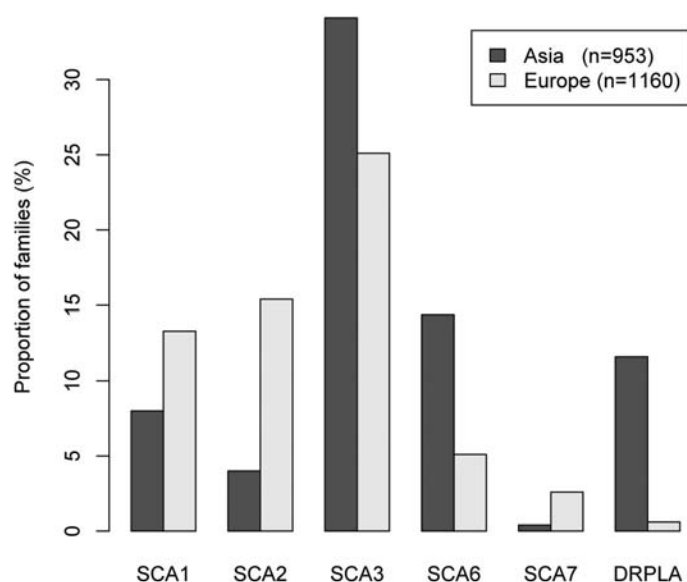


Figure 1: Aggregated data showing ethnic differences in SCA subtype frequency among families with ADCA.

in variable frequencies of the different subtypes both geographically and ethnically. SCA1, SCA2 and SCA3 are the commonest cause of ADCA in Caucasian families, but SCA3, SCA6 and DRPLA are more common in Asian populations (Figure 1).

A clinical classification of autosomal dominant cerebellar ataxia (ADCA) was introduced by Harding in 1982,¹⁴ with a division into ADCA I, II and III based on the presence of extracerebellar features, a pigmentary retinopathy or a pure cerebellar syndrome respectively. Whilst this classification is still useful in clinical characterisation and can help with an increasing choice of diagnostic tests, it has now been superseded by a genetic classification based on the underlying genetic disorder (Table 3). Most of the SCA mutations identified to date are dynamic repeat expansions and many, but not all, are expanded triplet repeats. The majority are CAG repeats encoding a poly-

lutamine track in the resulting protein leading to abnormal protein conformation; others are either untranslated repeats, deletions or missense mutations. The five main pathogenetic mechanisms of inherited ataxias are abnormal protein folding (e.g. SCA1), mitochondrial (e.g. Friedreich's ataxia), defective DNA repair (e.g. ataxia telangiectasia), channelopathies (e.g. EA1) and metabolic (e.g. inherited vitamin E deficiency).¹⁵

Which genetic tests?

NHS laboratories across the UK commonly perform SCA1, SCA2, SCA3, SCA6 and usually SCA7 in response to a generic 'SCA screen' request. Other investigations such as SCA12, SCA17, DRPLA, and Friedreich's are available but usually must be specifically requested. Research laboratories may offer additional tests (Table 3) if the clinical circumstances are appropriate. The choice of diagnostic tests should be guided by local knowledge of the common ataxia families, an insight into the prevalence of common SCA subtypes (Figure 1) within the ethnic group, and the presence of suggestive extracerebellar features (Table 4). However, phenotypic variability and overlap make clinical diagnosis difficult, and in most cases, screening for a range of diseases is necessary.

If there is a strong dominant family history, it is appropriate to screen for SCA1, SCA2, SCA3, SCA6 and SCA7 as part of first-line investigations. An important clue to the presence of a dominantly inherited trinucleotide repeat (TNR) disorder is anticipation, resulting in increasing severity and earlier age of onset through generations. However, even in sporadic cases, a routine screen is recommended since the presence of a dominant family history may be hidden by reduced penetrance (e.g. SCA17), marked anticipation (most notable in SCA7) or false paternity.

In sporadic cases, or if there is a history of consanguinity or affected siblings, testing for Friedreich's ataxia (FA) is essential. FA is the most common recessive cause of spinocerebellar ataxia, and traditionally this clinical diagnosis was limited to patients with an onset below the age of 25 with

Table 3: Summary of the SCA mutations. Adapted from reference 35. The designation SCA9 is reserved and has not been used.

† These tests may be available in research laboratories.

SCA subtype	Gene/protein	Phenotype	Mutation
Diagnostic test commonly available in clinical practice			
SCA1	ATXN1/Ataxin 1	ADCA I	CAG repeat
SCA2	ATXN2/Ataxin 2	ADCA I	CAG repeat
SCA3	ATXN3/Ataxin 3	ADCA I	CAG repeat
SCA6	CACNA1A/CACNA1A	ADCA III	CAG repeat
SCA7	ATXN7/Ataxin 7	ADCA II	CAG repeat
SCA12	PPP2R2B/PPP2R2B	ADCA I	CAG repeat
SCA17	TBP/TBP	ADCA I	CAG repeat
DRPLA	ATN1/Atraphin 1	ADCA I	CAG repeat
Test not available routinely †			
SCA5	SPTBN2/ β -III spectrin	ADCA III	Deletion/missense
SCA8	KLHL1A/Kelch-like 1	ADCA I	CTG repeat
SCA10	ATXN10/Ataxin 10	ADCA I	ATTCT repeat
SCA13	KCNK3/KCNK3	ADCA I	Missense
SCA14	PRKCG/PRKCG- γ	ADCA III	Missense
SCA27	FGF14/FGF14	ADCA I	Missense
EA1	KCNA1/K ⁺ channel	EA	Missense
EA2	CACNA1A/PQ-type Ca ²⁺ + α -1A	EA	Missense
EA5	CACNB4/Ca ²⁺ channel β 4	EA	Missense
EA6	SCL1A3	EA/Migraine	Missense
Gene not yet identified or published			
ADCA I: SCA11†, SCA15, SCA16 and SCA26.			
ADCA III: SCA4, SCA18, SCA19, SCA20, SCA21, SCA22, SCA23, SCA24, SCA25, SCA27 and SCA28			
Episodic: EA3, EA4			

Table 2: Diagnostic strategy in late-onset cerebellar ataxia

First-line investigations

Magnetic resonance (MR) imaging of brain
Chest radiography
Electrocardiogram
Vitamin B1, B12
Thyroid function tests
Serum VDRL

Second-line investigations

Lumbar puncture (inc. oligoclonal bands, VDRL)
Genetic investigations – see Table 4
Anti-neuronal antibodies – see Table 6
Nerve conduction studies and electromyography

Investigations with specific indications

Serum copper, caeruloplasmin, 24 hour urinary copper
Blood film for acanthocytes
Serum lipids, immunoglobulins
Vitamin E levels
Phytanic acid levels
Very long chain fatty acids
Serum gonadotrophins
Serum hexosaminidase A
 α -fetoprotein
Serum/CSF lactate
Muscle biopsy
Organic acids, ammonia, pyruvate
Anti-gliadin antibodies

Table 4: Genetic investigation of adult-onset cerebellar ataxia. † Feature highly suggestive of diagnosis

Indication	Possible Diagnoses
Recommended routine screen	SCA1, SCA2, SCA3, SCA6, SCA7, FRDA
Pure ataxia	SCA6 †
Slow ocular saccades	SCA1, SCA2†, SCA3, SCA7,
Ophthalmoplegia	SCA1, SCA2, SCA3
Pigmentary maculopathy / retinopathy	SCA7 †, abetalipoproteinaemia
Cognitive impairment	DRPLA†, SCA17 †, HD
Chorea	DRPLA†, SCA17, HD
FA phenotype	FRDA †, vitamin E deficiency, abetalipoproteinaemia, AT
Cataract	Mitochondrial, cerebrotendinous xanthomatosis
Oculomotor apraxia	AT, ataxia with oculomotor apraxia type 1+2
Epilepsy	DRPLA †, SCA10, SCA17, HD, Wilson's disease, mitochondrial, prion disease
Myokymia	SCA3, EA1
Myoclonus	DRPLA, SCA2, SCA3
Peripheral neuropathy	SCA1, SCA2, SCA3, SCA4†, SCA6, SCA12, SCA18 †, SCA22, SCA25 †
Pyramidal signs	SCA1, SCA2, SCA3 †, SCA7, SCA12
Extrapyramidal signs	SCA1, SCA2, SCA3, SCA12, SCA17, SCA21
Dystonia	SCA3, SCA17

progressive ataxia, absent lower-limb reflexes and skeletal abnormalities, often associated with additional non-neurological symptoms such as cardiomyopathy and diabetes mellitus. Since the identification of the expanded intronic TNR (GAA) in the X25 gene (94% of patients),¹⁶ it is now known that the clinical spectrum is broader than that defined by classical criteria, and includes patients with disease onset over the age of 25 with retained tendon reflexes. The remaining 6% of patients are compound heterozygotes with an expanded repeat on one allele, and a point mutation on the other. FA is thought to be due to mitochondrial dysfunction; the gene encodes frataxin, a mitochondrial protein. Even in those patients without the characteristic phenotype, up to 5.2% of patients with sporadic ataxia may have FA and in those below the age of 40 this rises to 21%.^{13,17} Other recessive disorders are listed in Table 5.

SCA1 is highly variable but a pancerebellar syndrome is usually described, with prominent ataxia of gait, limb, speech and eye movements. SCA2 is associated with marked ocular saccadic slowing. SCA3 is the most common subtype (Figure 1) and has a widely variable phenotype. SCA6 is commonly described as a late-onset pure ataxic syndrome. Pigmentary maculopathy and retinopathy is associated with SCA7, but this may be preceded by ataxia by up to 20 years.

There is much controversy regarding SCA8 and testing is not offered routinely since there is low penetrance and expanded repeats are also found in unaffected controls.

A history of psychiatric illness, chorea or dementia should prompt testing for DRPLA (dentatorubral pallidolusian atrophy), SCA17 and HD. DRPLA is a rare autosomal dominant, clinically heterogeneous neurodegenerative disorder, most commonly reported in Japan and rare in Caucasian populations. In Europe and the United States, there have been 153 patients reported in the literature since 1989, segregating in 20 families. However, a pure gait ataxia can precede the other manifestations by up to ten years making diagnosis challenging in the early stages of disease.¹⁸

Discrete episodes of ataxia are associated with the dominantly inherited episodic ataxias, caused by mutations in genes encoding voltage-dependent potassium (e.g. EA1) and calcium (e.g. EA2) channels. Episodes may last minutes in EA1 and hours to days in EA2. Interictal myokymia may be evident clinically and electromyographically in EA1, and some cases of EA2 can have a more progressive course similar to SCA6, to which it is allelic. Genetic testing is not widely available, and since EA2 may be responsive to acetazolamide, a therapeutic trial is warranted if the diagnosis is suspected clinically.

Fragile-X tremor/ataxia syndrome (FXTAS) was first described in 2001 in five elderly men carrying premutation range (55-200) triplet repeats in the FMR1 gene and characterised by a progressive action tremor associated with executive frontal deficits and generalised brain atrophy.¹⁹ Initially thought to affect only men, it has subsequently been described in women albeit in a less severe form.²⁰ FMR1 premutation may account for 3.6–4.2%^{21,22} of cases of sporadic ataxia in male patients older than 50

Table 5: Additional diagnostic possibilities in young adults

Disorder	Gene locus	Diagnostic features
Autosomal recessive disorders		
Friedreich's ataxia	X25-FRDA1 9q13-q21	Hyporeflexia Pyramidal signs Cardiomyopathy
Ataxia telangiectasia	11q22.3	Elevated α -fetoprotein Reduced serum immunoglobulins Telangiectasia, dystonia Predisposition to malignancy
Wilson's disease	13q14.3-q21.1	Reduced caeruloplasmin Elevated 24hr urine copper Kayser-Fleischer ring Hepatosplenomegaly Abnormal basal ganglia on MR
Abetalipoproteinaemia (acanthocytosis)	4q22-q24	Blood film for acanthocytes Serum cholesterol very low Serum beta lipoprotein absent. Pigmentary degeneration of the retina
Inherited vitamin E deficiency Refsum's disease (HMSN IV)	8q13.1-q13.3 10pter-p11.2, 6q22-q24	Reduced vitamin E levels Elevated phytanic acid levels Retinitis pigmentosa Polyneuropathy, sensorineural deafness Ichthyosis
Adrenoleukodystrophy /Adrenomyeloneuropathy	Xq28	Very long chain fatty acids Men (X-linked) Abnormal MRI brain
GM2 gangliosidosis	(multiple)	Reduced serum hexosaminidase A Supranuclear gaze palsy Dystonia
Cerebrotendinous xanthomatosis (Cholestanolysis)	2q33-qter	Elevated serum cholestanol Tendon xanthomata Dementia, cataract
Peripheral neuropathy Hypogonadotropic hypogonadism (Holmes syndrome)		Secondary sexual characteristics Loss of libido / infertility
Mitochondrial and metabolic disorders		Elevated serum / CSF lactate Elevated serum ammonia, pyruvate Muscle biopsy, organic acids Additional neurological sequelae (e.g. stroke, myoclonic epilepsy)



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use of Neupro, discontinue treatment. Avoid exposure to direct sunlight until the skin is healed. If treatment is to be withdrawn, it should be gradually reduced to avoid symptoms of neuroleptic malignant syndrome. Compulsive behaviours and hallucinations have been reported in patients treated with Neupro. Do not administer neuroleptics or dopamine antagonists to patients taking dopamine agonists. Caution is advised when treating patients with severe hepatic impairment, and in patients taking sedating medicines or other depressants in combination with rotigotine. Switching to another dopamine agonist may be beneficial for those patients who are insufficiently controlled by rotigotine. **Undesirable effects:** Very common side effects include nausea, vomiting, somnolence, dizziness and application site reactions. Common side effects include anorexia, hallucinations, sleep attacks, insomnia, abnormal dreams, headache, dyskinesia, lethargy, orthostatic hypotension, hypertension, hiccup, cough, constipation, diarrhoea, dry mouth, dyspepsia, hyperhidrosis, erythema, pruritus, asthenic

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Table 6: Antibodies to neuronal antigens in cerebellar syndromes.
Adapted from references 29, 36.
(VGCC—voltage-gated calcium channel antibodies)

Antibody	Antigen	Typical tumour associated
Anti-Yo	<i>cd62,32</i> (purkinje cytoplasmic)	Gynaecological Breast
Anti-Hu	<i>HuD</i> (neuronal nuclear)	Small cell lung cancer (75-80%) Neuroblastoma
Anti-Ri	<i>Nova1,2</i> (neuronal nuclear)	Breast Small cell lung cancer
Anti-Tr	(purkinje cytoplasmic)	Hodgkin's Lymphoma
Anti-VGCC	VGCC	Small cell lung cancer (>80%)
Anti-GAD	GAD	None
Anti-Ma1	<i>Ma1,2,3</i> (neuronal nucleolar)	Various
Anti-Ma2	<i>Ma2</i> (neuronal nucleolar)	Testis

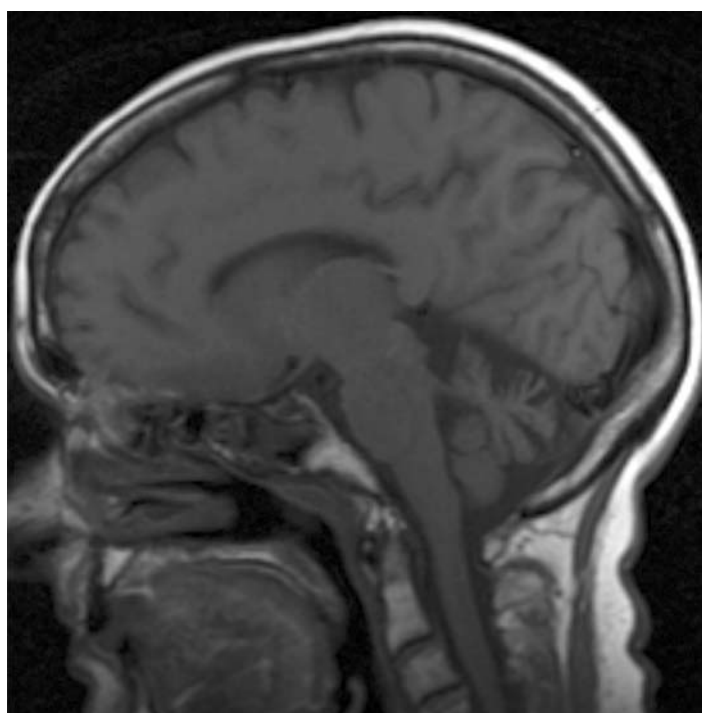


Figure 2: Pure cerebellar atrophy in SCA6.

years. FXTAS should be considered in elderly men, especially in families with grandchildren with Fragile-X or reported learning difficulties.

Age of onset and disease progression

In young adults (<40 years), there are a wide range of important, potentially reversible or treatable diagnostic possibilities that should not be missed (Table 5). Fortunately, these diagnoses are normally suspected because of the presence of characteristic extracerebellar features. While an early onset is normally associated with autosomal recessive disorders, it does not preclude the presence of a dominantly inherited disorder and they should be considered in both sporadic and familial cases. The term 'idiopathic' late-onset cerebellar ataxia²³ is a diagnosis of exclusion. However, there is considerable overlap with other neurodegenerative disorders and within five years 29–33% of cases will meet diagnostic criteria for possible or probable multiple system atrophy (MSA).^{8,24} The main features of MSA comprise autonomic failure, parkinsonism, cerebellar ataxia and pyramidal signs in any combination, with two major subtypes distinguished: MSA-P (80%) and MSA-C (20%) with parkinsonian or cerebellar features dominating respectively,²⁵ but ultimate confirmation of diagnosis is pathological. Patients with MSA have a poor prognosis and accumulate greater disability, remaining ambulant for a median of six years, and surviving only seven to nine years. This contrasts to those with a pure cerebellar syndrome whose median survival is over 20 years.^{24,26,27} In patients over the age of 50, a rapidly progressive disease course should prompt re-evaluation for MSA.

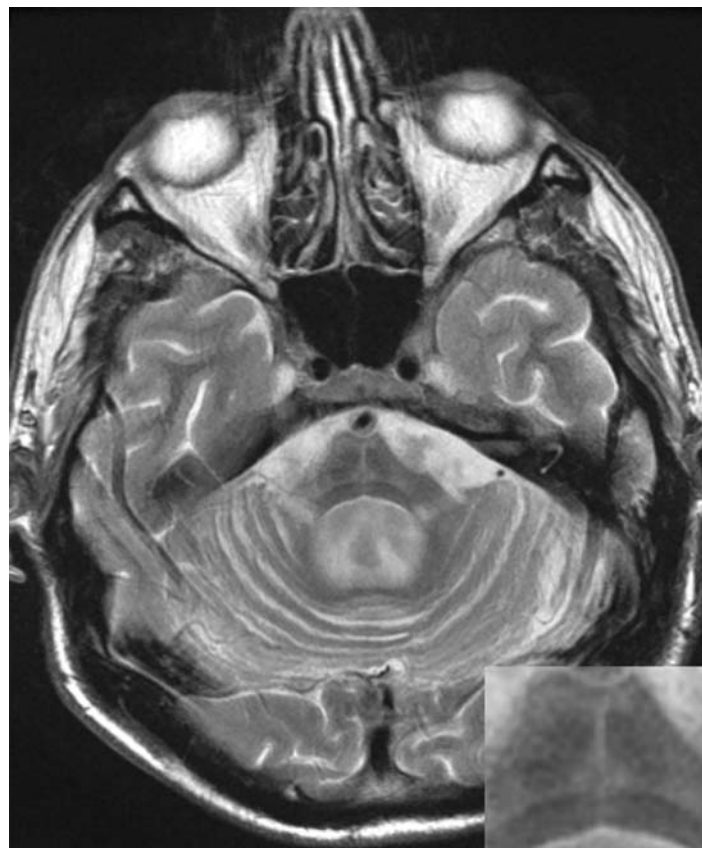


Figure 3: 'Hot cross bun' sign in multiple system atrophy.

Is imaging helpful?

Magnetic resonance imaging is essential in the diagnostic work-up of patients presenting with late-onset cerebellar ataxia. The most important benefit is the exclusion of an acquired cause, but it can also provide clues to other causes of sporadic and familial ataxia. There are three clear patterns of radiological abnormality:

- spinal atrophy,
- cortical cerebellar atrophy (CCA) and
- olivopontocerebellar atrophy (OPCA).

FA is characteristically associated with cervical spinal cord atrophy. CCA is found in the pure cerebellar syndromes (e.g. SCA6 - Figure 2) whereas OPCA is found in those with prominent extracerebellar features. There is considerable overlap between all the SCAs and imaging cannot be used for diagnostic purposes alone.

In MSA, cranial MR imaging may show non-specific OPCA, as well as putamen, caudate and basal ganglia atrophy. Signal hyperintensities in the pons and middle cerebellar peduncles may be seen on T2-weighted images to give rise to 'the hot cross bun sign' (Figure 3) but such changes are also found in some patients with proven SCA.²⁸ The presence of widespread brainstem, caudate and putamen atrophy in patients presenting with cerebellar ataxia should raise the suspicion of MSA and predict a guarded prognosis.

What about immunological ataxia?

In subacute disease, up to 5% of cases may be associated with anti-neuronal antibodies (Table 6) and their presence should initiate a search for an occult neoplasm.²⁹ Paraneoplastic cerebellar degeneration may present months or even years before the appearance of the underlying tumour, but its significance in chronic disease is unclear.

There remains considerable controversy regarding the presence and significance of auto-antibodies in chronic progressive cerebellar ataxia. Antibodies to glutamic acid decarboxylase (GAD) are well described in patients with type I diabetes mellitus and stiff-person syndrome, but it has been suggested that anti-GAD antibodies may play a pathogenic role in cerebellar ataxia³⁰ and even be responsive to immunosuppressive therapy.³¹ Controversially, anti-glial antibodies have been implicated in the pathogenesis of some sporadic cases of cerebellar ataxia in patients without gluten enteropathy.³² The presence of such antibodies may reflect a high prevalence

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of auto-immunity within this population but more research is needed before any definitive conclusions can be made regarding the pathogenic role of these antibodies in sporadic ataxia.

Management

Early and accurate diagnosis is invaluable in guiding treatment, and providing patient counselling and support. However, in up to 80% of cases, even after extensive investigation, no definitive diagnosis is made. The diagnostic label 'idiopathic cerebellar ataxia' is unsatisfactory for both clinician and patient and in this group, longitudinal follow-up is essential to monitor progress and identify new symptoms and signs that may point to a previously neglected diagnosis. In symptomatic ataxia, management must be guided by the underlying cause, but all patients and their families need ongoing support. Local and national patient support organisations such as Ataxia UK (<http://www.ataxia.org.uk/>) can provide patient information leaflets, telephone advice lines and facilitate the creation of local patient groups.

Patients will also benefit from multidisciplinary care. In patients with FA, orthopaedic input

may be required for skeletal deformities and early referral to a cardiologist is essential for management of cardiomyopathy. In all forms of spinocerebellar ataxia, patients may benefit from physiotherapy to reduce spasticity, improve mobility and to provide walking aids. Speech and language assessment is essential for those with communication and/or swallowing difficulties. Urinary difficulties commonly occur as a result of spasticity or autonomic failure, and have a considerable impact on quality of life for both the patient and their carer. Desmopressin spray may help nocturnal polyuria, anticholinergics such as oxybutynin may reduce detrusor instability and urgency, and intermittent or permanent urinary catheterisation may be required if there is incomplete bladder emptying.

In up to a third of patients with possible or probable MSA, symptoms of bradykinesia may respond to levodopa but its effect may decline within years, and use may be limited by autonomic and dyskinetic side-effects.³³ Autonomic failure is frequently difficult to manage, but if disabling patients should avoid aggravating factors such as large meals, straining at toilet, alco-

hol and drugs, and are sometimes helped by the use of elastic stockings, head-up tilt of the bed at night, increased salt intake and fludrocortisone. The diagnosis of an inherited condition requires careful counselling for both patient and family, and referral to clinical genetics is usually appropriate. At present, there are no disease modifying therapies available for the inherited ataxias.

Summary

- Adult-onset progressive cerebellar ataxia frequently poses diagnostic difficulties
- A proven genetic aetiology may be identified in half of all dominant families but only 1 in 10 sporadic cases.
- Genetic investigation of sporadic disease should include SCA1, SCA2, SCA3, SCA6, SCA7 and Friedreich's ataxia.
- Application of additional genetic tests in familial disease should be guided by local knowledge of ataxia families and the presence of extracerebellar features.
- Patients should be followed up for diagnostic, treatment and supportive purposes, ideally in a specialist ataxia clinic.

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References

- Harding AE. *The hereditary ataxias and related disorders*. Churchill Livingstone, New York, 1984.
- Koeppen AH, Hans MB, Shepherd DI, Best PV. *Adult-onset hereditary ataxia in Scotland*. Arch Neurol 1977;34(10):611-8.
- Muzaimi MB, Thomas J, Palmer-Smith S, Rosser L, Harper PS, Wiles CM, Ravine D, Robertson NP. *Population based study of late onset cerebellar ataxia in south east Wales*. J Neurol Neurosurg Psychiatry 2004;75(8):1129-34.
- Craig K, Keers SM, Archibald K, Curtis A, Chinnery PF. *Molecular epidemiology of spinocerebellar ataxia type 6*. Ann Neurol 2004;55(5):752-5.
- Brignolio F, Leone M, Tribolo A, Rosso MG, Meineri P, Schiffer D. *Prevalence of hereditary ataxias and paraplegias in the province of Torino, Italy*. Ital J Neurol Sci 1986;7(4):431-5.
- Polo JM, Calleja J, Combarros O, Berciano J. *Hereditary ataxias and paraplegias in Cantabria, Spain. An epidemiological and clinical study*. Brain 1991;114(Pt 2):855-66.
- Orozco G, Estrada R, Perry TL, Araña J, Fernandez R, Gonzalez-Quevedo A, Galarraga J, Hansen S. *Dominantly inherited olivopontocerebellar atrophy from eastern Cuba*. Clinical, neuropathological, and biochemical findings. J Neurol Sci 1989;93(1):37-50.
- Abele M, Burk K, Schols L, Schwartz S, Besenthal I, Dichgans J, Zuhlke C, Riess O, Klockgether T. *The aetiology of sporadic adult-onset ataxia*. Brain 2002;125(Pt5):961-8.
- Juvonen V, Hietala M, Kairisto V, Savontaus ML. *The occurrence of dominant spinocerebellar ataxias among 251 Finnish ataxia patients and the role of predisposing large normal alleles in a genetically isolated population*. Acta Neurol Scand 2005;111(3):154-62.
- Takano H, Cancel G, Ikeuchi T, Lorenzetti D, Mawad R, Stevanin G, Didierjean O, Dürr A, Oyake M, Shimohata T, Sasaki R, Koide R, Igarashi S, Hayashi S, Takiyama Y, Nishizawa M, Tanaka H, Zoghbi H, Brice A, Tsuji S. *Close associations between prevalences of dominantly inherited spinocerebellar ataxias with CAG-repeat expansions and frequencies of 20 large normal CAG alleles in Japanese and Caucasian populations*. Am J Hum Genet 1998;63(4):1060-6.
- Pujana MA, Corral J, Gratacòs M, Combarros O, Berciano J, Genis D, Banchs I, Estivill X, Volpini V. *Spinocerebellar ataxias in Spanish patients: genetic analysis of familial and sporadic cases*. The Ataxia Study Group. Hum Genet 1999;104(6):516-22.
- Maruyama H, Izumi Y, Morino H, Oda M, Toji H, Nakamura S, Kawakami H. *Difference in disease-free survival curve and regional distribution according to subtype of spinocerebellar ataxia: a study of 1,286 Japanese patients*. Am J Med Genet 2002;114(5):578-83.
- Schols L, Szymanski S, Peters S, Przuntek H, Epplen JT, Hardt C, Riess O. *Genetic background of apparently idiopathic sporadic cerebellar ataxia*. Hum Genet 2000;107(2):132-7.
- Harding AE. *The clinical features and classification of the late onset autosomal dominant cerebellar ataxias. A study of 11 families, including descendants of the 'the Drew family of Walworth'*. Brain 1982;105(Pt1):1-28.
- De Michele G, Coppola G, Coccozza S, Filla A. *A pathogenetic classification of hereditary ataxias: is the time ripe?* J Neurol 2004;251(8):913-22.
- Campuzano V, Montermini L, Molto MD, Pianese L, Cossette M, Cavalcanti F, Monros E, Rodius F, Duclou F, Monticelli A, Zara F, Canizares J, Koutnikova H, Bidichandani SI, Gellera C, Brice A, Trouillas P, De Michele G, Filla A, De Frutos R, Palau F, Patel PI, Di Donato S, Mandel JL, Coccozza S, Koenig M, Pandolfo M. *Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion*. Science 1996;271(5254):1423-7.
- Moseley ML, Benzow KA, Schut LJ, Bird TD, Gomez CM, Barkhaus PE, Blindauer KA, Labuda M, Pandolfo M, Koob MD, Ranum LP. *Incidence of dominant spinocerebellar and Friedreich triplet repeats among 361 ataxia families*. Neurology 1998;51(6):1666-71.
- Yabe I, Sasaki H, Kikuchi S, Nonaka M, Moriwaka F, Tashiro K. *Late onset ataxia phenotype in dentatorubropallidolysian atrophy (DRPLA)*. J Neurol 2002;249(4):432-6.
- Hagerman RJ, Leechey M, Heinrichs W, Tassone F, Wilson R, Hills J, Grigsby J, Gage B, Hagerman PJ. *Intention tremor, parkinsonism, and generalized brain atrophy in male carriers of fragile X*. Neurology 2001;57(1):127-30.
- Hagerman RJ, Leavitt BR, Farzin F, Jacquemont S, Greco CM, Brunberg JA, Tassone F, Hessel D, Harris SW, Zhang L, Jardini T, Gane LW, Ferranti J, Ruiz L, Leechey MA, Grigsby J, Hagerman PJ. *Fragile-X-associated tremor/ataxia syndrome (FXTAS) in females with the FMR1 premutation*. Am J Hum Genet 2004;74(5):1051-6.
- Van Esch H, Dom R, Bex D, Salden I, Caeckebeke J, Wibail A, Borghgraef M, Leguis E, Frys JP, Matthijs G. *Screening for FMR-1 premutations in 122 older Flemish males presenting with ataxia*. Eur J Hum Genet 2005;13(1):121-3.
- Brussino A, Gellera C, Saluto A, Mariotti C, Arduino C, Castellotti B, Camerlingo M, de Angelis V, Orsi L, Tosca P, Migone N, Taroni F, Brusco A. *FMR1 gene premutation is a frequent genetic cause of late-onset sporadic cerebellar ataxia*. Neurology 2005;64(1):145-7.
- Harding AE. *'Idiopathic' late onset cerebellar ataxia. A clinical and genetic study of 36 cases*. J Neurol Sci 1981;51(2):259-71.
- Gilman S, Little R, Johanns J, Heumann M, Kluijn KJ, Junk L, Koeppe RA, An H. *Evolution of sporadic olivopontocerebellar atrophy into multiple system atrophy*. Neurology 2000;55(4):527-32.
- Wenning GK, Colosimo C, Geser F, Poewe W. *Multiple system atrophy*. Lancet Neurol 2004;3(2):93-103.
- Klockgether T, Ludtke R, Kramer B, Abele M, Burk K, Schols L, Riess O, Laccone F, Boesch S, Lopes-Cendes I, Brice A, Inzelberg R, Zilber N, Dichgans J. *The natural history of degenerative ataxia: a retrospective study in 466 patients*. Brain 1998;121(Pt4):589-600.
- Watanabe H, Saito Y, Terao S, Ando T, Kachi T, Mukai E, Aiba I, Abe Y, Tamakoshi A, Doyu M, Hirayama M, Sobue G. *Progression and prognosis in multiple system atrophy: an analysis of 230 Japanese patients*. Brain 2002;125(Pt5):1070-83.
- Bürk K, Skalej M, Dichgans J. *Pontine MRI hyperintensities ('the cross sign') are not pathognomonic for multiple system atrophy (MSA)*. Mov Disord 2001;16(3):535.
- Trivedi R, Mundanthanam G, Amyes E, Lang B, Vincent A. *Autoantibody screening in subacute cerebellar ataxia*. Lancet 2000;356(9229):565-6.
- Honnorat J, Saiz A, Giometto B, Vincent A, Brieva L, de Andres C, Maestre J, Fabien N, Vighetto A, Casamitjana R, Thivolet C, Tavolato B, Antoine J, Trouillas P, Graus F. *Cerebellar ataxia with anti-glutamic acid decarboxylase antibodies: study of 14 patients*. Arch Neurol 2001;58(2):225-30.
- Lauria G, Pareyson D, Pitzolu MG, Bazzigaluppi E. *Excellent response to steroid treatment in anti-GAD cerebellar ataxia*. Lancet Neurol 2003;2:634-5.
- Hadjivassiliou M, Grunewald RA, Chattopadhyay AK, Davies-Jones GA, Gibson A, Jarratt JA, Kandler RH, Lobo A, Powell T, Smith CM. *Clinical, radiological, neurophysiological, and neuropathological characteristics of gluten ataxia*. Lancet 1998;352(9140):1582-5.
- Wenning GK, Tison F, Ben Shlomo Y, Daniel SE, Quinn NP. *Multiple system atrophy: a review of 203 pathologically proven cases*. Mov Disord 1997;12(2):133-47.
- Wood NW, Harding AE. *Neurology in Clinical Practice: Ataxic disorders*, vol. I, chap. 24, 309-317. Butterworth-Heinemann, third ed., 2000.
- Dueñas AM, Goold R, Giunti P. *Molecular pathogenesis of spinocerebellar ataxias*. Brain 2006;129(Pt6):1357-70.
- Sutton I, Winer JB. *The immunopathogenesis of paraneoplastic neurological syndromes*. Clin Sci (Lond) 2002;102(5):475-86.

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References:

1. Galetta SL, et al. *Arch Intern Med*, 2002; 162: 2161–2169.
2. Polman CH, et al. *NEJM* 2006; 354(9): 899–910.
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Infections: Other opportunistic infections have been reported with use of TYSABRI®. If an opportunistic infection is suspected, dosing with TYSABRI® is to be suspended until such infection can be excluded through further evaluation. **Hypersensitivity:** Hypersensitivity reactions have been associated with TYSABRI®, including serious systemic reactions. These reactions usually occur during the infusion or up to 1 hour after completion of infusion. If a hypersensitivity reaction occurs TYSABRI® must be permanently discontinued. **Immunogenicity:** In the case of disease exacerbations or infusion related events the presence of antibodies should be evaluated. Treatment should be discontinued if persistent antibodies develop. **Stopping Therapy:** If therapy is discontinued be aware that TYSABRI® has pharmacodynamic effects for up to 12 weeks. **Pregnancy and lactation:** If patients become pregnant while taking TYSABRI®, discontinuation of TYSABRI® should be considered. Patients receiving TYSABRI® should not breastfeed their infant. **General:** Physicians must discuss the benefits and risks of TYSABRI® therapy with the patient and provide them with a Patient Alert Card. Patients should be instructed that if they develop any infection they should inform their physician that they are being treated with TYSABRI®. **Drug interaction:** Combination with beta-interferons or glatiramer acetate is contraindicated. The safety and efficacy of TYSABRI® in combination with other immunosuppressive and antineoplastic therapies have not been fully established. Concurrent use of these agents with TYSABRI® may increase the risk of infections including opportunistic infections. No formal interaction studies have been conducted with TYSABRI® in humans. **Undesirable Effects:** The most commonly reported symptoms are: **Infections and infestations:** Urinary tract infection, nasopharyngitis. **Immune system disorders:** urticaria. **Nervous system disorders:** headache, dizziness. **Gastrointestinal disorders:** vomiting, nausea. **Musculoskeletal and connective tissue disorder:** arthralgia. **General disorders and administration site conditions:** rigors, pyrexia, fatigue. Other less common events include: hypersensitivity reactions, infusion reactions, PML, other opportunistic infections, immunogenicity. For further information regarding adverse events please refer to the Summary of Product Characteristics. **Legal Classification:** POM. **Pack size:** 1 vial/pack. **NHS Price:** UK: £1130/vial, Ireland: €1636.85/vial. **Package Quantities:** 300 mg/15 ml. **Product Licence Number:** EU/1/06/346/001. **Product Licence Holder:** Elan Pharma International Ltd., Monksland, Athlone, County Westmeath, Ireland. **Date of last revision of Prescribing Information:** August 2006. Please refer to the Summary of Product Characteristics for further information.

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Genetic Causes of Dementia

Dementia is a syndrome encompassing many intellectual domains that can be broadly defined as an overall decline in intellectual function, including difficulties with language, simple calculations, planning and judgment, motor skills as well as loss of memory. A genetic cause is identified in only a minority of patients, but patients and their family members are frequently concerned about the possible genetic basis of dementia and potential risk to relatives. This article reviews the main genetic causes of dementia. These are summarised in Table 1.

Genetic testing for dementia is a relatively young field and the consensus of expert guidance is that genetic testing should not be used routinely in diagnosis but that, where appropriate, patients should be referred to specialist centres for genetic counselling.¹

Alzheimer's disease

Alzheimer's disease (AD) is the commonest cause of dementia, typically causing progressive impairment of episodic memory with more general intellectual decline such as impaired judgment, decision-making, and orientation. Pathologically, AD is characterised by beta-amyloid neuritic plaques, intraneuronal neurofibrillary tangles and amyloid angiopathy. About 25% of patients with AD have one or more first-degree relatives with the disease. Early-onset AD (EOAD), arising before the age of 60, accounts for about 3% of cases.² In contrast to AD as a whole, about 60% of EOAD is familial, with 13% of

EOAD cases showing autosomal dominant inheritance.² The clinical characteristics of familial and non-familial AD appear to be identical.³

Familial early-onset AD

Three single genes, PSEN1, PSEN2 and APP, are responsible for the majority of cases of early-onset autosomal dominant AD (Table 2). PSEN1 and PSEN2 encode the proteins presenilin-1 and presenilin-2 respectively, while APP encodes the amyloid beta precursor protein. The three proteins are closely involved in AD pathogenesis: presenilins form the catalytic core of the gamma-secretase enzyme complex that produces amyloid beta from amyloid precursor protein. Mutations in PSEN1, PSEN2 and APP increase the relative quantity of the most pathogenic form of amyloid beta, A β -42.⁴

Mutations in PSEN1 account for about 65% of familial EOAD cases. Causative mutations are essentially fully penetrant by age 70; 90% of individuals undergo disease onset before the age of 60 and the mean age of onset is 35 with relatively rapid progression.² While the identification of a causative mutation in an affected patient is sufficient to make the diagnosis, counselling of unaffected individuals is more difficult. Ideally, an affected family member should be tested first to confirm the mutation in the family. Testing of presymptomatic individuals only predicts an individual's lifetime risk of developing AD but cannot predict age of onset, severity, type of symptoms or rate of progression.⁵



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Sarah J Tabrizi, MRCP PhD*, studied biochemistry and medicine at Edinburgh University, then trained in neurology at the National Hospital for Neurology and Neurosurgery and the Royal Free Hospital. She did her PhD, as an MRC Clinical Training Fellow at UCL studying mitochondrial dysfunction, excitotoxicity and oxidative stress in neurodegeneration. She then undertook further research as a DH National Clinician Scientist, and she is now a tenured Clinical Senior Lecturer in the Department of Neurodegenerative Disease at UCL Institute of Neurology. Her clinical and research interests are in neurogenetics, particularly Huntington's disease, and basic cellular mechanisms of neurodegeneration focusing on protein misfolding disorders.

Table 1: Genetic causes of dementia.

Disorder	Gene (protein)	Clinical test available
Alzheimer's disease	<i>PSEN1</i> (presenilin-1)	•
	<i>PSEN2</i> (presenilin-2)	•
	<i>APP</i> (amyloid precursor protein)	•
	<i>ApoE</i> (apolipoprotein E)	
Frontotemporal dementia	<i>MAPT</i> (tau)	•
	<i>PGRN</i> (progranulin)	
	<i>VCP</i> (valosin-containing protein)	
	<i>CHMP2B</i> (chromatin-modifying protein 2B)	
Huntington's disease	<i>IT15</i> (huntingtin)	•
Familial prion disease	<i>PRNP</i> (prion protein)	•
CADASIL	<i>Notch3</i> (notch 3)	•
FBD	<i>BRI</i> (integral membrane protein 2B)	

Table 2: Genetic causes of familial early-onset Alzheimer's disease (EOAD). Familial EOAD accounts for less than 0.5% of all AD.

Gene	Percentage of familial cases	Mean age at onset	Comments
<i>PSEN1</i>	65%	35	Rapid progression. Fully penetrant by age 70.
<i>PSEN2</i>	<2%	55	Slower progression. 95% penetrance.
<i>APP</i>	Mutation	51	May show vascular pathology.
	Duplication	8%	Strong association with cerebral amyloid angiopathy.

Abbreviations

AD - Alzheimer's disease • CADASIL - Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy • CJD - Creutzfeldt-Jakob disease • EOAD - Early-onset Alzheimer's disease • FBD - Familial British dementia with angiod angiopathy • FTD - Frontotemporal dementia • fvFTD - frontal-variant frontotemporal dementia • HD - Huntington's disease • LOAD - Late-onset Alzheimer's disease • PrP - Prion protein

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Table 3: Genetic causes of frontotemporal dementia (FTD). Autosomal dominant cases account for 10-40% of FTD.

Gene	Percentage of autosomal dominant cases	Comments
<i>MAPT</i>	18%	<i>Tau-positive cases. Associated with frontal variant or Parkinsonism.</i>
<i>PGRN</i>	23%	<i>Tau-negative cases with TDP-43 protein inclusions.</i>
<i>VCP</i>	Rare	<i>Inclusion body myopathy, Paget's disease and FTD</i>
<i>CHMP2B</i>	Rare	<i>Danish pedigree</i>
<i>Chromosome 9 loci</i>	<i>Unknown</i>	<i>FTD with motor neurone disease</i>

Mutations in *PSEN2* are rare, accounting for less than 2% of cases of familial EOAD. Age at onset tends to be later than in *PSEN1*-associated AD, with a mean of 55 years. Disease duration is longer and there is more clinical overlap with the sporadic form of AD. Penetrance is nearly complete (95%) but there have been reports of individuals unaffected over the age of 80.⁶ *PSEN2* testing is available clinically, but counselling should warn that the onset is even more variable than for *PSEN1* mutations.

APP mutations account for around 15% of familial EOAD cases. Clinical genetic testing is not available for APP mutations but may be performed on a research basis. The mean age at onset is 51 years.² Though most cases of AD associated with APP mutations are typical, there may be amyloid angiopathy causing vascular features such as white matter infarcts.⁷ As well as within-gene mutations, APP duplications have recently been found to cause early-onset AD with vascular features. Such duplications, which appear to account for about 8% of autosomal dominant EOAD, are not detected by mutation screening and must be sought specifically.⁸

Late-onset AD

Symptoms of AD begin after the age of 60 in about 97% of cases. Late-onset (LOAD) is referred to as AD type 2. Familial clustering is found in about 25% of cases of (LOAD), although only a small fraction are caused by *PSEN1*, *PSEN2* and APP mutations making population genetic testing inadvisable.¹ Only one genetic locus, ApoE- ϵ 4, has been consistently shown to be associated with age-at-onset in LOAD. Between 34 and 65% of individuals with AD carry at least one copy of the ApoE- ϵ 4 allele (rather than ϵ 2 or ϵ 3), which is present in only about 25% of the population. Most subjects homozygous for the ApoE- ϵ 4 allele will develop AD by the age of 80, while 26-50% of heterozygotes will develop AD. The presence of the ApoE- ϵ 4 allele is moderately specific for AD and a strong predictor of a diagnosis of AD in a subject with memory impairment. However, the risk of the ApoE- ϵ 4 allele remains relative and open to distressing

misinterpretation and it is advised that testing, though clinically available, should not be used in asymptomatic individuals.

Frontotemporal dementia

Frontotemporal dementia (FTD) is the second commonest cause of early-onset dementia after AD. It is a neurodegenerative illness encompassing three clinical syndromes characterised by behavioural and language disturbance: frontal-variant FTD (fvFTD), progressive non-fluent aphasia and semantic dementia. There is also clinical overlap between FTD and corticobasal degeneration, progressive supranuclear palsy and motor neurone disease. Pathologically, FTD usually causes intracellular inclusions that either are composed of tau protein or are tau-negative, ubiquitin-positive.

Thirty to fifty percent of FTD patients have a positive family history, with autosomal dominant inheritance in 10-40%. About 18% of those with autosomal dominant inheritance are found to have mutations in the *MAPT* gene encoding tau protein.⁹ Clinical testing for *MAPT* mutations is available. Most cases of FTD due to mutations affecting tau result in either fvFTD or FTD with parkinsonism; primary language impairment is unusual in such cases.¹⁰ Genetic causes of FTD are summarised in Table 3.

Mutations in the *PGRN* gene, encoding progranulin, were recently described as a cause of ubiquitin-positive FTD.¹¹ Interestingly, the intracellular inclusions in progranulin-mutation cases of FTD contain not progranulin, but TDP-43, a protein involved in transcriptional regulation. The link between progranulin and TDP-43 is not yet known.¹² Genetic testing for progranulin mutations is not available clinically, but early analyses suggest that progranulin mutations are common in FTD, accounting for about 10% of cases overall, and 23% of those with a positive family history.¹³

Several other genetic loci have been implicated in rare subtypes of FTD but cannot yet be tested for clinically. Inclusion body myopathy associated with Paget's disease of bone and frontotemporal dementia is caused

by mutations in *VCP*; mutations in *CHMP2B* have been found in a large Danish FTD pedigree; and FTD with motor neurone disease has been linked to two separate loci on chromosome 9.¹⁴

Huntington's disease

Huntington's disease (HD) is a fully penetrant autosomal dominant disorder caused by CAG triplet repeat expansions in the gene encoding the huntingtin protein. It classically produces a triad of chorea, dementia and behavioural disturbance, but the phenotype is highly variable and cognitive changes can precede the movement disorder by several years. The dementia of HD is usually of the subcortical-frontal type, with impulsivity, irritability and poor planning but normal memory. The behavioural phenotype encompasses depression, anxiety, irritability and psychosis.¹⁵ HD genetic testing is widely available and should be accompanied by detailed genetic counselling.

Familial prion disease

Familial prion diseases are caused by mutations in the *PRNP* gene encoding the prion protein (PrP). Abnormal PrP promotes the conversion of normal PrP to the pathological form, resulting in aggregation and spongiform neurodegeneration. The vast majority of prion disease (about 80%) is sporadic, namely sporadic Creutzfeldt-Jakob disease (CJD). Acquired forms (variant CJD) are rarer. About 10-15% of prion disease is familial.

Familial prion diseases were traditionally classified into three forms: Gerstmann–Straussler–Scheinker syndrome is characterised by slowly progressive ataxia followed by dementia; fatal familial insomnia causes insomnia, hallucinations, autonomic dysfunction and motor impairment; and familial CJD causes rapidly progressive dementia, myoclonus and electroencephalographic abnormalities. These clinical categories are increasingly replaced by the general term 'familial prion disease', with specific mutations identified by genetic testing. Over 30 different *PRNP* mutations have been described: some cause specific phenotypes,

Patients with genetic dementia represent a small fraction of the total dementia caseload, but possible genetic risk causes great concern among patients and relatives

others a broad range of abnormalities.¹⁶ PRNP gene sequencing is available clinically.

Inherited vascular dementias

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is caused by mutations in Notch3. It is the most common genetic cause of stroke and produces progressive dementia with stepwise deteriorations, particularly in executive function, with onset in the 30s-60s. Dementia often precedes other symptoms of stroke and 30-40% of subjects also have migraine headaches. Magnetic resonance imaging invariably reveals white matter T2 hyperintensities and lacunar infarcts.

Clinical genetic testing identifies mutations in 90% of affected individuals. Skin biopsy, to look for small vessel abnormalities, is reserved for gene-negative cases.¹⁷

Familial British dementia with amyloid angiopathy (FBD) also produces vascular dementia but with progressive spastic tetraparesis and cerebellar ataxia. It is caused by mutations in the BRI gene. Clinical genetic testing is not available but it causes abnormal MRI findings typical of vascular dementia.

Conclusion

Dementia is a significant and increasing problem in neurology. Patients with dementia with a clearly identifiable genetic cause represent a

small fraction of the total dementia caseload, but possible genetic risk causes great concern among patients and relatives. In the coming years, we can expect clinical genetic tests to become available for the genes discussed, as well as the discovery of further causative and modifying genes in dementia.

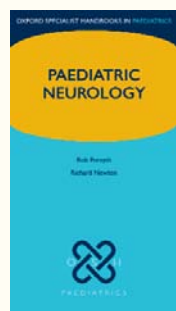
Knowledge of the genes causing the common dementia syndromes, their relative frequencies and the associated clinical pictures is useful in evaluating patients with dementia.

The consensus of expert advice is that genetic testing should be avoided if a given diagnosis is unlikely on clinical grounds and, where performed, should always be preceded by detailed, expert genetic counselling.¹

References

- Knopman DS, DeKosky ST, Cummings JL, et al. *Practice parameter: Diagnosis of dementia (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology*. Neurology 2001;56:1143-53.
- Campion D, Dumanchin C, Hannequin D, et al. *Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum*. Am J Hum Genet 1999;65:664-70.
- Haupt M, Kurz A, Pollmann S, Romero B. *Alzheimer's disease: identical phenotype of familial and non-familial cases*. J Neurol 1992;239:248-50.
- Brunkan AL, Goate AM. *Presenilin function and gamma-secretase activity*. J Neurochem 2005;93:769-92.
- Bertram L, Tanzi RE. *The current status of Alzheimer's disease genetics: what do we tell the patients?* Pharmacol Res 2004;50:385-96.
- Bird TD, Levy-Lahad E, Poorkaj P, et al. *Wide range in age of onset for chromosome 1-related familial Alzheimer's disease*. Ann Neurol 1996;40:932-6.
- Raux G, Guyant-Marechal L, Martin C, et al. *Molecular diagnosis of autosomal dominant early onset Alzheimer's disease: an update*. J Med Genet 2005;42:793-5.
- Rovelet-Lecrux A, Hannequin D, Raux G, et al. *APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy*. Nat Genet 2006;38:24-6.
- Goldman JS, Farmer JM, Wood EM, et al. *Comparison of family histories in FTL2 subtypes and related tauopathies*. Neurology 2005;65:1817-9.
- Baba Y, Tsuboi Y, Baker MC, et al. *The effect of tau genotype on clinical features in FTDP-17*. Parkinsonism & Related Disorders 2005;11:205-8.
- Baker M, Mackenzie IR, Pickering-Brown SM, et al. *Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17*. Nature 2006;442:916-19.
- Neumann M, Sampathu DM, Kwong LK, et al. *Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis*. Science 2006;314:130-3.
- Gass J, Cannon A, Mackenzie IR, et al. *Mutations in progranulin are a major cause of ubiquitin-positive frontotemporal lobar degeneration*. Hum Mol Genet 2006;15:2988-3001.
- Talbot K, Ansorge O. *Recent advances in the genetics of amyotrophic lateral sclerosis and frontotemporal dementia: common pathways in neurodegenerative disease*. Hum Mol Genet 2006;15 Spec No 2:R182-187.
- Bates G, Harper PS, Jones L, eds. *Huntington's Disease, Third ed*. Oxford: Oxford University Press, 2002.
- Mead S. *Prion disease genetics*. Eur J Hum Genet 2006;14:273-81.
- Amberla K, Waljas M, Tuominen S, et al. *Insidious Cognitive Decline in CADASIL*. Stroke 2004;35:1598-1602.

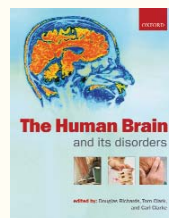
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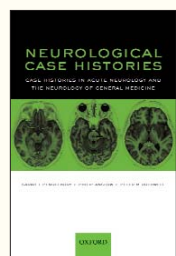


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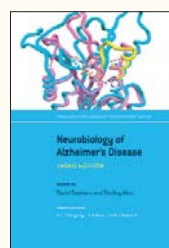
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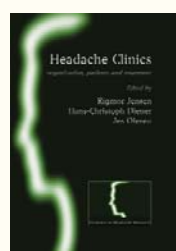
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The Surgical Treatment of Trigeminal Neuralgia

Whilst drug therapy remains the first line of treatment for trigeminal neuralgia (TN), many patients do not achieve sufficient pain relief or suffer from side-effects. Furthermore, increasing numbers of patients are questioning the safety of long term medication. For these cases modern surgical treatments offer a safe and effective option with emphasis on microvascular decompression, a procedure which is reconstructive rather than destructive.

Prior to the late 1970s surgical approaches were not without risk or side-effects. The standard approaches then were neuro-destructive, consisting of Gasserian ganglion alcohol injection, percutaneous radiofrequency thermocoagulation (RFL) and fractional section of the sensory root – now known as partial sensory rhizotomy (PSR), carried out via a posterior fossa approach in the retro-mastoid region.¹

By contrast, the early 1980s saw the introduction of non-destructive procedures; retrogasserian glycerol injection² and microvascular decompression³. Microvascular decompression (MVD) has not only resulted in improved results but has led to a better understanding of the pathophysiology of TN. Importantly, the non-destructive procedures do not usually cause facial numbness.

There is still a place for RFL, glycerol injections and PSR which will be described. However the good results and safety of MVD indicate that this procedure should no longer be thought of as a last resort.

The injection techniques have a 50% recurrence rate at one to seven years depending on technique used and are now used in treating patients unfit for open surgery due to co-morbidity or age.

Radiofrequency lesion or thermocoagulation (RFL)

Under brief general anaesthetic (GA) a needle electrode is passed through the foramen ovale under x-ray control and is adjusted until the tip lies just behind the ganglion within the sensory rootlets. A series of heat lesions are then made which result in variable sensory loss depending on the lesion intensity. Sensory loss is the common side effect, but corneal anaesthesia and dysaesthesia can occur, with pain relief lasting for five to seven years on average. RFL is generally used in patients with pain involving maxillary and mandibular divisions since attempts to treat ophthalmic TN are either unsuccessful or result in loss of corneal sensation

Retrogasserian glycerol injection

This technique is similar to RFL but after needle insertion the patient is repositioned with the head inclined downwards and a small amount of glycerol is injected into Meckel's cave around the sensory rootlets. The result is 'milder' than RFL with only a minimal risk of numbness or dysaesthesia but there is a shorter period of pain relief, 50% recurrence of neuralgia at one year in the author's experience.

Glycerol injection is ideal for treating ophthalmic TN when microsurgery is not possible. It is also useful as emergency treatment for severe cases whilst planning for MVD.

Patho-physiology

Neurovascular compression (NVC) is found in about 90% of TN cases who are not suffering from multiple sclerosis or have a causative lesion eg tumour, cyst or AVM. Jannetta pioneered the MVD operation in 1966 and hypothesised that the compression caused localised demyelination and this led to ephaptic transmission which results in the electric shock-like paroxysms of pain.^{3,4} This theory was first proved by nerve biopsy studies in Bristol⁵ and later confirmed by others.^{6,7} However, there remains a small group of patients (about 10%) where no NVC exists and the cause of neural-

gia in these cases remains unexplained. Some of these represent the initial symptom of multiple sclerosis (MS) despite the MRI being normal (personal observation).

Microvascular decompression

Investigations

Imaging is necessary to detect a possible structural lesion or underlying MS. Also the presence of NVC can now be detected with high accuracy using appropriate MRI sequences.^{8,9} Though NVC at the pontine root entry zone (REZ) is the commonest finding, NVC anywhere along the cysternal path of the nerve must be taken seriously and dealt with.⁴

Pre-operative consent

On the basis of results from the Frenchay Hospital/BUPA Hospital database patients are advised that there has been no mortality or serious neurological morbidity and that the commonest complications are CSF leak, unilateral hearing loss and dysaesthesia, all with less than 2% incidence.¹⁰ In cases when no NVC appears on the MRI the patients are asked if they wish the surgeon to proceed to a PSR if there is no convincing NVC found at surgery. In the light of our follow-up studies reported here they are counselled about the risks and benefits of a PSR. This does not apply to patients with ophthalmic division TN (V1) which is unlikely to respond to a PSR. However fortunately the majority of patients with V1 TN have neurovascular compression and can be treated with MVD (personal observation).



Professor Coakham qualified at UCH London then trained in neurosurgery at the Guys-Maudsley Unit and was a fellow at Massachusetts General Hospital, Boston, USA. He was appointed as consultant to Frenchay Hospital and awarded the first Personal Chair in Neurosurgery by the University of Bristol. He developed an early interest in surgery of the skull base and cranial nerves. In the UK he has pioneered microvascular decompression for trigeminal neuralgia, hemifacial spasm and glossopharyngeal neuralgia. He has been involved in new operative approaches for skull base tumours and has taught on skull base dissection courses in the UK and USA. Neurophysiological intraoperative monitoring and hearing preservation in vestibular schwannoma surgery have been a particular interest.

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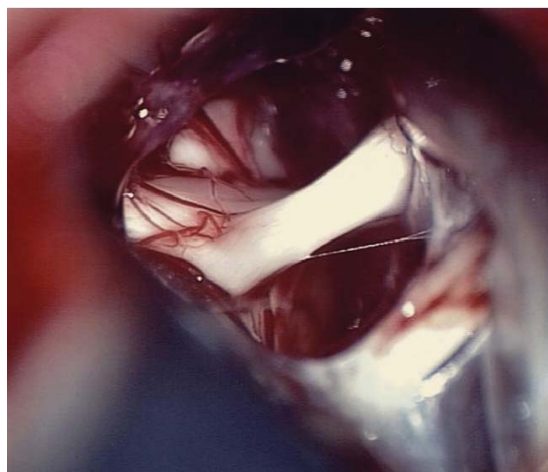
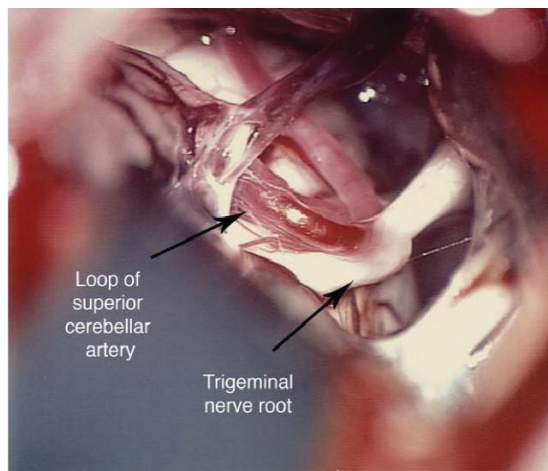


Figure 1a (top): Compression of the right trigeminal sensory root by a loop of the superior cerebellar artery.

Figure 1b (bottom): The artery has been fixed to the tentorium by a teflon wool sling resulting in total decompression. Note that the appearance of the nerve has already returned to normal.

Abbreviations

TN - trigeminal neuralgia
RFL - radiofrequency thermocoagulation
PSR - partial sensory rhizotomy
MVD - microvascular decompression
NVC - neurovascular compression
MS - multiple sclerosis
AVM - arteriovenous malformation

Support group for patients:

Trigeminal Neuralgia
Association UK,
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Bromley, BR2 9XS, UK.
T. 020 8462 2478.
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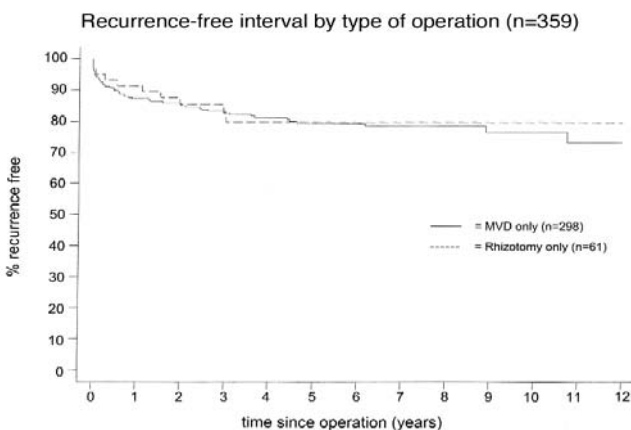


Figure 2: A Kaplan-Meier plot showing neuralgia cure to be close to 80% at 12-year follow-up of 359 cases. Results of MVD and PSR are almost identical.

Microvascular Decompression - Procedure

Under GA a keyhole retromastoid craniotomy is performed and the upper cerebellopontine angle is entered. Sufficient retraction is necessary to visualise the whole intracysternal nerve root since compression can occur anywhere. Occasionally neuro-endoscopy is helpful, especially if the petrous bone anatomy is anomalous.¹¹ The commonest compressive vessel is a loop of medially placed superior cerebellar artery (Figure 1) but in about 25% of cases multiple vessels are responsible and all must be carefully identified and dealt with.⁴ Veins are diathermied and divided, arteries are dissected free of neural contact. Following Jannetta's technique, many surgeons then interpose a pledget of Teflon wool between artery and nerve.⁴ Following the teaching of Fukushima¹² we prefer to carry out a 'total decompression' using sling retraction in which small Teflon tapes and Tisseel glue are used to tether the offending vessel to a distant structure, either the tentorium or dura.¹³

Headache and nausea may occur for 12 to 24 hours but rapid recovery usually follows with the average discharge being on the third post-operative day. Many patients are fully recovered in about one month.

Partial Sensory Rhizotomy - Procedure

The approach is identical to MVD but when no NVC is present a 50% to 75% incision is made in the caudal part of the root entry zone. This sounds radical but it has long been observed

that subsequent sensory loss is less than would be expected and total anaesthesia of the lower face is rare.¹⁴ In our own patient survey only 48% reported numbness.¹⁵

Long-term results of MVD and PSR

These results were analysed by the surgical team as an observational study. The same patient data was then independently analysed by means of a separate patient survey.

Observational study

The Frenchay Hospital/BUPA Hospital results were prospectively entered on to a database managed by two nurse practitioners over a 15-year period. Annual mail or telephone follow-up was carried out. Results are shown as a Kaplan-Meier plot in Figure 2 which demonstrates a 5-year cure rate of 80% falling slightly by 12 years.¹⁰

Patients surveyed by questionnaire

For the first time to our knowledge, the surgical database was transferred (with patient consent) to an independent group led by Prof JM Zakrzewska, Physician in Oral Medicine specializing in facial pain, St Barts and the London Hospitals. All patients were sent a detailed questionnaire and results analysed according to operative procedure and whether or not previous intervention had occurred (designated 'primary' and 'non-primary').¹⁵ This patient-orientated study revealed an overall 5-year cure rate of 79%, better for primary cases (84%) and worse for non

Table 1: Patients' views on their surgical outcomes after microvascular decompression or partial sensory rhizotomy.

Primary group = no previous invasive therapy.
Non-primary group = previous therapy by glycerol injection, RFL or peripheral nerve block. (Reference 15)

	Primary group		Non-primary group	
	MVD	PSR	MVD	PSR
Satisfaction with current situation	96%	75%	76%	64%
Would have preferred earlier surgery	78%	65%	71%	52%
Result better than expected	82%	60%	59%	52%
Would have same surgery again	80%	59%	66%	52%
Would have drug therapy again	2%	0%	0%	0%

primary cases (70%). 96% of primary MVD patients were satisfied with results as opposed to 64% of non primary patients who required PSR. Most patients answered that they should have had the surgery sooner and that the results exceeded their expectations. Drug therapy was surprisingly unpopular, however this was a selected group that had failed on medication and therefore been referred for surgery (Table 1).

Finally, it should be pointed out that this study confirms other reports that patients who have previously received ablative/destructive treatment do not respond so well to MVD.^{16,17} Obviously patients who are too elderly, unfit or reluctant to undergo open surgery would be offered Gasserian injections either with glycerol or radiofrequency thermocoagulation.

Conclusion

MVD is now established as a safe and effective treatment for TN in patients where medication has failed. Our objective, patient-orientated review has indicated that MVD should be offered earlier and preferably as first-line treatment before any injection therapy which can adversely affect the operative success rate. Partial sensory rhizotomy still remains a good back-up procedure for those patients without vascular compression and gives a long-term cure rate similar to MVD. Meticulous surgical technique is essential and experience helps; it has been confirmed that surgeons performing high numbers of MVD procedures achieve better results.¹⁸

References

- Surgical Treatment of trigeminal neuralgia. Editorial. BMJ 1977; Vol 2: pt 6089.
- Hakanson S. Trigeminal neuralgia treated by the injection of glycerol into the trigeminal cistern. Neurosurgery 1981;9:638-46.
- Jannetta PJ. Arterial compression of the trigeminal nerve at the pons in patients with trigeminal neuralgia. Journal Neurosurgery 1967;26:159-62.
- McLaughlin MR, Jannetta PJ, Clyde BL, Subach BR, Comey CH, Resnick DK. Microvascular decompression of cranial nerves: lessons learned after 4400 operations. Journal Neurosurgery 1999;90:1-8.
- Hilton DA, Love S, Gradidge T and Coakham HB. Pathological findings associated with trigeminal neuralgia caused by vascular compression. Neurosurgery 1994;35:299-303.
- Rappaport ZH, Gorvin-Lippman R, Devor M. An electron-microscope analysis of biopsy samples taken during MVD surgery. Stereotact. Func. Neurosurgery 1997;68:182-6.
- Love S, Coakham HB. Trigeminal neuralgia - pathology and pathogenesis. Brain 2001;124:2347-60.
- Meany JFM, Eldridge PR, Dunn LI, Nixon TE, Whitehouse GH, Miles JB. Demonstration of neurovascular compression in trigeminal neuralgia with magnetic resonance imaging. Journal of Neurosurgery 1995;83:799-855.
- Patel NK, Aquilina K, Clarke Y, Renowden SA, Coakham HB. How accurate is magnetic resonance angiography in predicting neurovascular compression in patients with trigeminal neuralgia? A prospective, single-blinded comparative study. British Journal Neurosurgery 2003;17:60-4.
- Coakham HB, Plaha P, Clarke Y, Zakrzewska. Microsurgical treatment of trigeminal neuralgia: long term follow up of surgical results and patient satisfaction. British Journal Neurosurgery 2004;18:43.
- Shenouda EF and Coakham HB. Management of petrous endostosis in posterior fossa procedures for trigeminal neuralgia. Neurosurgery 2007;60(ONS suppl 1):ONS - 63-ONS - 69.
- Fukushima T. Microvascular decompression for hemifacial spasm and trigeminal neuralgia: results in 4000 cases. Journal Neurology, Neurosurgery, Psychiatry 1990;53:811.
- Coakham HB. The microsurgical treatment of trigeminal neuralgia, hemifacial spasm and glossopharyngeal neuralgia. In Cranial Base Surgery Eds. Robertson JT, Coakham HB, Robertson JH. pp 543-564. Churchill Livingstone, London, Edinburgh, New York.
- Hussein M, Wilson LA, Illingworth R. Patterns of sensory loss following fractional posterior fossa fifth nerve section. Journal Neurosurgery, Psychiatry 1982;45:786-90.
- Zakrzewska JM, Lopez BC, Kim SE, Coakham HB. Patient reports of satisfaction after microvascular decompression and partial sensory rhizotomy for trigeminal neuralgia. Neurosurgery 2005;56:1304-12.
- Barba D and Alskane JF. Success of microvascular decompression with and without prior surgical therapy. Journal Neurosurgery 1984;60:104-7.
- Mendoza N and Illingworth RD. Trigeminal neuralgia treated by microvascular decompression: a long-term follow-up study. British Journal Neurosurgery 1995;9:13-19.
- Kalkanis SN, Eskander EN, Carter BS, Barker FG. Microvascular decompression surgery in the United States, 1996-2000: mortality rates, morbidity rates and the effects of hospital and surgeon volumes. Neurosurgery 2003;52:1251-61.

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The Lancet Handbook of Treatment in Neurology

There can be few book reviewers so dedicated to their art that they do not experience a slight decline in spirits on learning that their Book Review Editor has sent them an offering edited by a recent president of the ABN, whose authors include former colleagues and friends, some of whom still smart from sporting defeats. Here goes. This wee book is great! Firstly, it is small, weighing only 499g and would fit into a 'white coat' pocket or one of those redundant pouches in the freebie conference hold-all that transports the laptop and may just convince any nearby eagle eyed postgraduate education budget manager that you actually went. Secondly, it has a bendy plastic cover, more resilient than paper, more flexible than hard back, and coffee-resistant. It can be cleaned with a wet cloth!

The title represents a gleeful and hopefully final nail in the coffin of the time-expired perception of neurology as a 'diagnose and adios' speciality, a perception that needs burying both to encourage recruitment of future neurologists and to help treat patients with 'incurable' diseases.

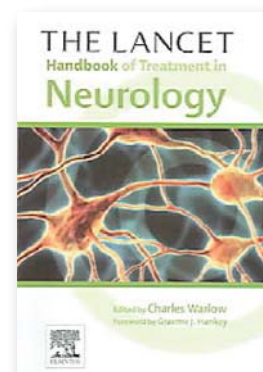
So to the contents. Nineteen chapters penned by renowned authors covering the traditional subjects with some welcome relative newcomers. "Emotional disorders, functional somatic disorders and psychoses" (all in 16 pages); "Neuropathic pain" (14 pages); "Neurogenic pelvic organ dysfunction" (20 pages) and "Anaesthesia for patients with neurological disease" (7 pages) all provide a

useful start point for those unfamiliar with or seeking refreshers in such areas.

The style is clearly laid out with an emphasis on therapeutics, but bullet points on definitions, epidemiology, pathology, and prognosis abound and so they should, since a book comprising pure treatment regimes alone would be pretty indigestible. Treatment is so much more than writing a prescription and non-pharmacological therapy is generously summarised.

The drug treatment schedules themselves are clear and specific and one is left in no doubt when such edicts are based on less than concrete evidence. Adverse effects of recommended treatments and monitoring requirements add considerably to the utility of the text. What this book is not is a source for in-depth exploration of neurology for either the inquisitive youngster or the more seasoned campaigner tasked with postgraduate neurology teaching or lecturing. What it represents is a concentrated source of hard practical therapeutic information spanning the vast breadth of our subject which will be invaluable to those whose job plan still leaves time to see the occasional patient.

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County Hospital, Lincoln, UK.*



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Published by: Elsevier
ISBN: 0080446507 / 9780080446509
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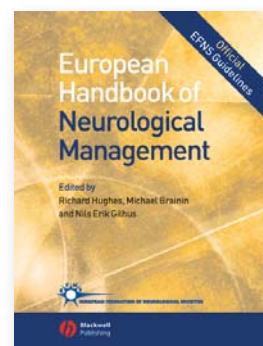
European Handbook of Neurological Management

Launched at the EFNS Meeting held in Glasgow in September 2006, this volume brings together the deliberations of EFNS Task Forces, 44 in all, appointed to examine particular diagnostic and therapeutic issues in neurology. Some of these 'Official EFNS Guidelines' have been previously published or are available on the EFNS website, others have been the theme of sessions at previous EFNS Meetings (e.g. Alzheimer's disease and dementia in Athens in 2005). Topics covered range from those which fall within the purview of practically all neurologists (e.g. headache, Parkinson's disease) to the frankly *recherché* which few will be called upon to manage (e.g. neurological complications of liver transplantation, fatty acid mitochondrial disorders). Chapters vary in size from less than ten (e.g. cerebral vasculitis) to more than 30 pages (e.g. stroke), but all use a common framework for the classification of evidence (4 classes: I-IV) and the rating of recommendations (3 levels: A-C), as defined in Brainin et al. (Eur J Neurol 2004; 11: 577-81) and also in chapter 3 of this volume, Task Force members reaching consensus by an iterative method. Where evidence was lacking but consensus was clear, 'Good Practice Points' have been stated. Most reports include evidence published up to 2004, some earlier, some later. The title page heading of 'First edition' clearly anticipates the updating of these guidelines over time.

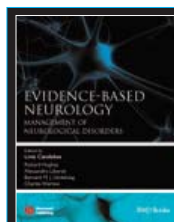
Neurologists may be equivocal in their response to 'guidelines': they may attract or repel, possibly in equal measure, depending on whether uniformity of clinical practice is seen as a highly-desirable blessing or an autonomy-undermining curse. Although I have not systematically examined this, it is my impression that Good Practice Points outnumber A-C recommendations in this book, reflecting the lack of evidence underpinning neurological practice in many areas. This upshot of the work of many of the Task Forces may act as a strong stimulus for further research.

The book is attractive and well-produced (few typographical errors, of which my favourite was the observation, p. 315, that PEG for enteral nutrition in ALS is "wildly available"), but who will buy this book? In an age of subspecialisation, much of the contents may not be immediately relevant to the day-to-day work of individual practitioners, reducing the incentive to purchase, perhaps the more so in light of the provisional nature of many of the guidelines. Trainees may be attracted by the short overviews and definitions of certain syndromes, but this is not a comprehensive textbook of neurology and moreover it does not come cheap. Clearly, however, every departmental library should have a copy for reference.

AJ Larner, WCNN, Liverpool, UK.



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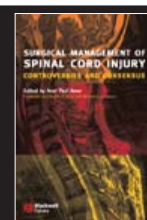
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Pathology and Biology of Inflammatory Myopathies

The idiopathic inflammatory myopathies (IIMs) are an important heterogeneous group of potentially treatable acquired disorders. On the basis of clinical, histological and immuno-pathogenic features, three distinct subsets are recognised: dermatomyositis (DM), polymyositis (PM) and sporadic inclusion-body myositis (IBM). An accurate diagnosis is important, given the potential toxicity associated with the immunotherapy used to treat these disorders. A wide array of histochemical and immunocytochemical stains are used to investigate cases. This review outlines the clinical features, pathology and recent advances in the pathogenesis and treatment of IIMs, with a special emphasis on the role of muscle biopsy in their diagnosis and management.

Clinical features and laboratory investigations

There are differences in the clinical features of the three major forms of inflammatory myopathy (Table 1). A clinical diagnosis of an inflammatory myopathy is confirmed by serological tests, electromyography and a muscle biopsy. Autoantibodies are found in up to 20% of patients in PM and DM but are unusual in IBM (Table 2). With the possible exception of anti-Jo-1, none of the autoantibodies have sufficient sensitivity or specificity to be of diagnostic value. Autoantibodies in IBM are unusual. They are not associated with muscular dystrophies or metabolic myopathies, although their presence should not automatically exclude these diagnoses.¹ The most sensitive muscle enzyme assay is creatine kinase (CK), which is increased up to 50 times in active disease. In IBM, CK is more mildly elevated. Enzyme activity can be normal in some patients with active PM and IBM, even in the presence of inflammatory changes found on biopsy and therefore

should not be relied upon solely for diagnostic purposes. Needle electromyographic findings in idiopathic inflammatory myopathies are not specific and are useful only insofar as they confirm an active myopathic process.

Muscle biopsy

A definitive diagnosis of idiopathic inflammatory myopathies requires a muscle biopsy. The criteria as originally proposed by Bohan and Peter in 1975² have been more recently modified to include histological differences between PM, DM and IBM.³

Technical considerations

The biopsy should ideally be performed before commencing treatment. Where the distribution of weakness is proximal, a moderately affected proximal muscle that is also easily accessible, such as the quadriceps (vastus lateralis) or the biceps can be selected. There are advantages in limiting the biopsies to these muscles as their normal distribution of fibre sizes and fibre types is well recognised. A muscle that is severely atrophied or has been subjected to electromyography should not be biopsied. Open biopsy or needle biopsy may be performed, the latter are smaller but are often adequate for diagnostic purposes. Sufficient tissue must be obtained for light microscopic, histochemical, immunohistochemical, electron microscopic and biochemical evaluation. All histological, histochemical and immunohistochemical studies are best demonstrated on unfixed material.

Pathological features

Although the underlying pathogenesis in PM, DM and IBM is different, they have several pathological features in



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Table 1: Clinical features in inflammatory myopathies

	DM	PM	IBM
Age	Children (juvenile DM) and adults	Adults, mainly after the second decade	Adults, mainly over 50 years
Sex	Females > Males	Females > Males	Males >> Females
Onset	Subacute (several weeks), can be acute	Subacute (typically over months)	Chronic (over years)
Muscle involvement	Weakness proximal, symmetric, non-selective	Weakness proximal, symmetric, non-selective	Weakness asymmetric, typically involves quadriceps and long finger flexors first
Skin rash	Characteristically present, rarely transient or absent	Absent	Absent
Extramuscular manifestations	Joint contractures, subcutaneous calcinosis and ischaemic bowel disease in juvenile DM. Increased association with malignancy in adults	Cardiac involvement and interstitial lung disease particularly associated with anti-Jo-1 antibody	Infrequent
Association with connective tissue disease	Up to 12% with scleroderma and mixed connective tissue disease	5-8% with lupus, less commonly Sjögren's and rheumatoid arthritis	Infrequent
Response to treatment	Yes	Yes	Progressive disease with poor response to treatment

Table 2: Autoantibodies in inflammatory myopathies

Autoantibody	Characteristics	Associations
anti-Jo-1	anti-histidyl-tRNA synthetase antibody (80% of all anti-synthetases)	interstitial lung disease in PM/DM
anti-Mi-2	anti-signal recognition particle (nuclear helicase)	10-15% of DM and PM
anti-polymyositis-Scl	anti-signal recognition particle (nuclear complex)	DM with scleroderma
anti-KL6	anti-signal recognition particle (mucin-like glycoprotein)	interstitial lung disease in PM/DM
anti-nRNP	anti-nuclear ribonucleoprotein	Overlap with mixed connective tissue disease

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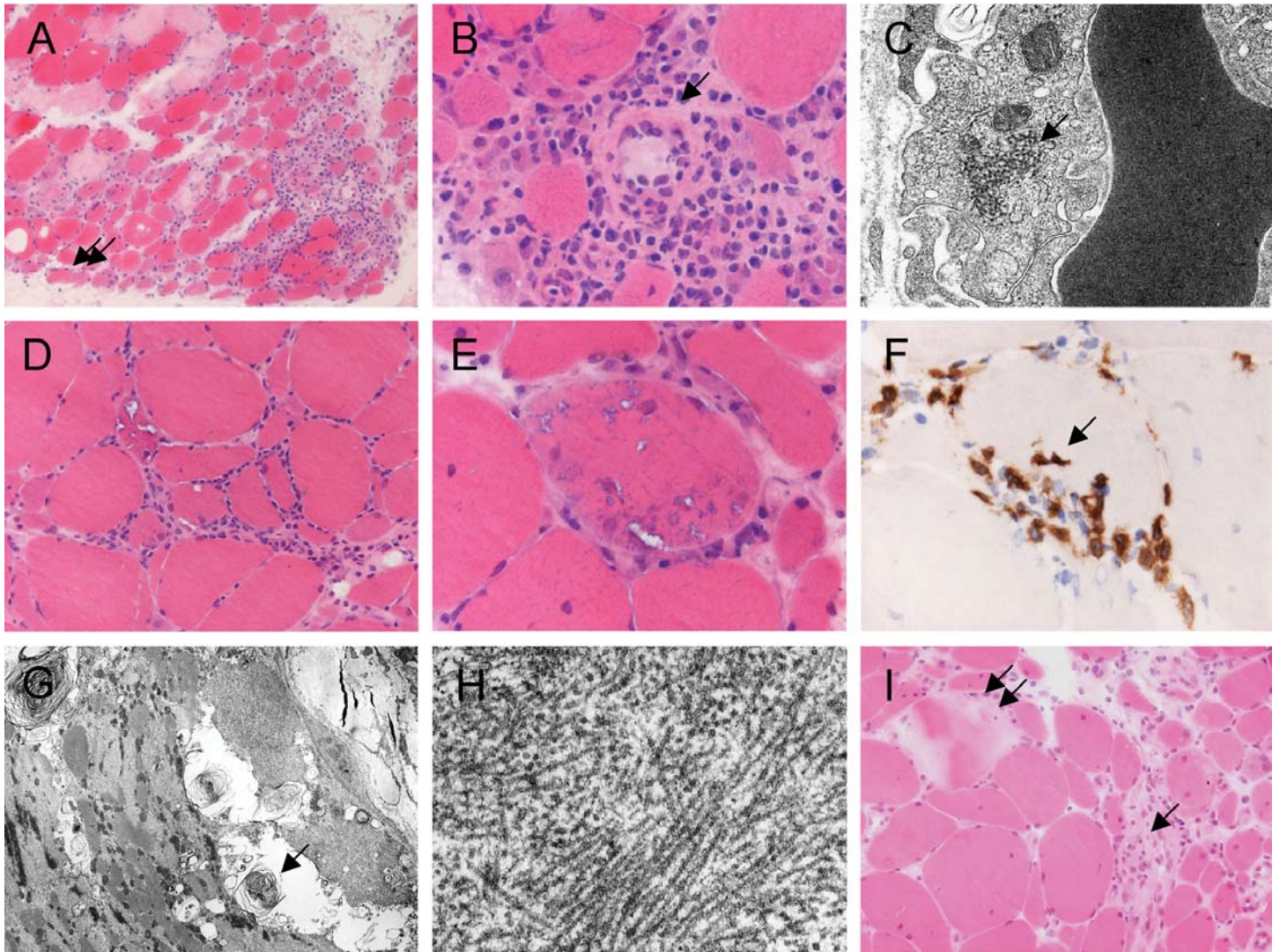


Figure 1: In DM, the atrophy is characteristically perifascicular (double arrows), (A). Inflammation is more often perivascular (arrow), (B) and may extend into the endomysium. Ultrastructural examination shows tubuloreticular inclusions in the endoplasmic reticulum of

vascular endothelial cells (arrow) (C). In IBM, scattered fibres contain single or multiple rimmed vacuoles containing basophilic granules (D), (E). There is partial invasion of intact fibres by cytotoxic CD8 T cells (F). On ultrastructural examination, the basophilic granules correspond to

membranous whorls (arrow) (G). Abnormal filamentous inclusions 12-18 nanometres in diameter are seen in the nucleus and cytoplasm (H). In polymyositis, fibre necrosis (double arrows) and endomysial inflammation is characteristic (single arrow) (I).

common. In all IIMs variation in fibre diameters is often seen, but hypertrophy is less pronounced compared to the muscular dystrophies. Large group atrophy and fibre type grouping is absent. Scattered necrotic fibres are common.

Features of DM include perifascicular atrophy (Figure 1), defined as atrophy involving six or more fibres out of ten along one edge of a fasciculus and not exclusive to type IIB fibres.⁴ Focal infarction may also occur. Regenerating fibres may surround necrotic fibres in basophilic cuffs, a feature rarely seen in the muscular dystrophies. In DM, the inflammation is usually in the perimysium, centered on the vessels and less often in the endomysium (Figure 1). Vasculitis may occur. B lymphocytes are as common as T lymphocytes around vessels and much less common within the fascicles. The T cell CD4/CD8 ratio is highest in perivascular and lowest in endomysial sites. There is upregulation of MHC class 1 antigens on the muscle fibres. The capillaries may show deposition of immune complexes and the terminal complement membrane attack complex C5b-9 (MAC). The capillary density may also be reduced. Electron microscopic examination in DM may show tubuloreticular structures

in the endoplasmic reticulum of vascular endothelial cells (Figure 1). Although not specific, this finding provides useful supportive evidence for a diagnosis of DM.⁵

In IBM, scattered fibres contain single or multiple vacuoles termed 'rimmed vacuoles' characterised by small central or peripheral basophilic granules (Figure 1). Such vacuoles may contain round or oval eosinophilic and congophilic masses. The vacuoles may show discrete granular acid phosphatase activity. Ragged red fibres in excess of those expected for age may be seen. Several proteins, including A β , APP, ubiquitin, phosphorylated tau, α -synuclein, prion protein, presenilin-1, apolipoprotein E and survival motor neuron protein, have been shown to be associated with the vacuoles.⁶ Ultrastructural examination demonstrates that the basophilic granules in the vacuoles correspond to membranous whorls (Figure 1) which are associated with abnormal filaments 12-18 nanometers in diameter (Figure 1). Such filaments may also be seen in the nucleus.

In PM and IBM, inflammation is prominent in the endomysium and comprises lymphocytes and macrophages. T lymphocytes account for

two-thirds of the endomysial infiltrates and of these, a majority are CD8 cells. Sparse B cells may be seen around the perimysial vessels. An important feature seen in PM and IBM and absent in DM is the partial invasion of non-necrotic fibres by CD8 cells (Figure 1).⁷ In normal muscle MHC class 1 antigens can only be detected on the blood vessels while in IIMs, there is generalised expression of MHC class 1 antigens on the sarcolemma and also within necrotic fibres.⁸ The term 'CD8/MHC 1 complex' is used to define the primary inflammation in PM and IBM i.e. infiltration of histologically intact muscle fibres expressing MHC class 1 antigens by cytotoxic CD8 T cells.⁷ The major histological features in IIMs are summarised in Table 3.

Differential diagnosis

There are several potential pitfalls in biopsy interpretation which may lead to misdiagnosis. Demonstration of primary inflammation i.e. the CD8/MHC 1 complex is essential, as it is important in the pathogenesis of PM and IBM. MHC class 1 upregulation may be seen even in the absence of inflammation and should be routinely sought. Inflammatory changes may be associ-

Table 3: Pathological features in inflammatory myopathies

Histological features	DM	PM	IBM
Hypertrophy	Not pronounced	Not pronounced	Not pronounced
Atrophic fibres	Perifascicular, especially juvenile DM, no group atrophy	Scattered, no group atrophy	Scattered, no group atrophy
Necrosis	Scattered, may involve groups (infarcts)	Scattered	Scattered
Fibre type grouping	Absent	Absent	Absent
Rimmed vacuoles	Absent	Absent	Characteristic. basophilic granules in the vacuoles are congophilic, may stain for A β and other proteins
Inflammation	Mainly perifascicular, perivascular with prominent B cells, CD4 > CD8	Perifascicular and endomysial, mainly T cells, CD8 >> CD4	Perifascicular and endomysial, mainly T cells, CD8 >> CD4
Partial invasion of non-necrotic fibres by CD8+ T cells	Absent	Characteristically present	Characteristically present
Upregulation of MHC I antigens on muscle fibres	Present	Widespread	Widespread

ated with muscular dystrophies, including Duchenne and Becker muscular dystrophy, fascioscapulothoracic dystrophy, limb girdle muscular dystrophy type 2B and congenital muscular dystrophy with primary merosin deficiency.⁹ Appropriate immunohistochemical staining should be performed to assess reduced sarcolemmal expression of proteins associated with muscular dystrophies. Inflammation may also be associated with toxic, necrotising and metabolic myopathies. Paraffin embedded muscle tissue is not suitable for the diagnosis of IBM as rimmed vacuoles are indiscernible. In some cases, inflammation may be patchy, resulting in sampling problems and repeat biopsy from a different site may be considered to confirm the diagnosis. Rimmed vacuoles may also be seen in a number of conditions including myofibrillar myopathies and oculopharyngeal muscular dystrophy and these must be considered in the differential diagnosis of IBM.

Immunopathogenesis

The specific target antigens initiating self-sensitisation in the IIMs remain unknown. In DM, the primary antigenic target is thought to be the endothelium of the endomysial capillaries. The predominant lymphocytes are B cells and CD4 T cells, consistent with a humoral immune response. Activation of complement leads to formation and deposition of the membrane attack complex C5b-9 on the endothelial cells. This results in lysis, intravascular thrombosis and capillary necrosis. Depletion of the capillary bed causes ischaemia, muscle necrosis and microinfarcts, endofascicular hypoperfusion and finally perifascicular atrophy.¹⁰ Cytokines and chemokines related to complement activation are released, upregulating adhesion molecules (VCAM-1, ICAM-1) on the endothelial cells. These in turn facilitate binding of T cells and macrophages via integrins and their egress into the perimysial and endomysial spaces.

In PM and IBM, CD8 T cells invade the MHC 1 expressing muscle fibres. There is evidence for clonal expansion of the autoinvasive T cells being driven by specific antigens.¹¹ The transmigration of activated T cells and adhesion to the muscle fibre is facilitated by cytokines (IL-1b and TNF- α), chemokines, adhesion molecules and metalloproteinases. Dendritic cells have been

identified in the endomysial infiltrates of PM (and DM), although their role in antigen presentation remains unclear.¹² Recent work on the pathogenesis of sporadic IBM suggests that abnormal accumulations of APP and A β , associated with the ageing cellular muscle fibre environment are key pathogenic events.¹³ Abnormalities of the APP processing machinery may occur and there may be preferential accumulation of the more toxic A β 42 in IBM muscle fibres.¹⁴ Endoplasmic reticulum stress, in the form of upregulation of chaperone proteins, suggests that unfolded/misfolded proteins may participate in the pathogenic cascade.¹⁵ Recent studies have demonstrated strong A β -reactive and HLA-restricted T-cell responses against the immunogenic A β 42 peptide in the elderly.¹⁵ It remains unclear whether A β can also serve as antigen, processed by the MHC class 1 expressing muscle fibres in sporadic IBM, leading to antigen-specific T cell activation.

Treatment

Current immunosuppressive therapies in PM and DM include high dose corticosteroids, azathioprine, intravenous immunoglobulins and cyclophosphamide. IBM does not respond well to immunosuppressants. Recent experimental approaches include the use of monoclonal antibodies against T cell regulatory pathways, costimulatory molecules, adhesion molecules, cytokines or B cells.¹⁵ More specific immunotherapies await the identification of the specific target antigens against which the immune response is directed.

Conclusion

The IIMs are an important group of potentially treatable autoimmune diseases. IBM has a progressive course leading to severe disability and does not respond well to treatment. The differential diagnosis is potentially large and muscle biopsy is a crucial diagnostic test recommended before commencing therapy. Demonstration of primary inflammation (CD8/MHC 1 complex) is important and is central to the pathogenesis of PM and IBM. Neither the inflammatory changes nor rimmed vacuoles in IBM are entirely specific findings. Detailed histochemical and immunohistochemical studies, supplemented by biochemical and electron microscopic investiga-

tions will help to exclude other diseases that may mimic IIMs. These include the muscular dystrophies, metabolic myopathies including mitochondrial myopathy, toxic and necrotising myopathies. Biopsies without well defined morphological abnormalities present the greatest difficulties and a close clinicopathological correlation is essential to reach a correct diagnosis.

References

- Faunauchi M, Nozaki Y, Yoo BS, et al. A case of limb-girdle muscular dystrophy with serum anti-nuclear antibody which lead to a mistaken diagnosis of polymyositis. *Clin Exp Rheumatol* 2002;20:707-8.
- Bohan A, Peter JB. *Polymyositis and dermatomyositis*. *N Eng J Med* 1975;292:344-7.
- Dalakas MC. *Polymyositis, dermatomyositis and inclusion-body myositis*. *N Eng J Med* 1991;325:1487-98.
- Wedderburn LR, Varsani H, Li CKS, et al. *International consensus on a proposed score system for muscle biopsy evaluation in patients with juvenile dermatomyositis: a tool for use in clinical trials*. *Arthritis care and research* 2007 (in press).
- Luu J, Bockus D, Remington F, et al. *Tubuloreticular structures and cylindrical confronting cisternae: A review*. *Human Pathol* 1989;20:617-27.
- Oldfors A, Fyhr IM. *Inclusion body myositis: genetic factors, aberrant protein expression and autoimmunity*. *Curr Opin Rheumatol* 2001;13:469-75.
- Dalakas MC, Hohlfeld R. *Polymyositis and dermatomyositis*. *Lancet* 2003;362:971-82.
- van der Pas J, Hengstman GJ, Ter Laak HJ, et al. *Diagnostic value of MHC class 1 staining in idiopathic inflammatory myopathies*. *J Neurol Neurosurg Psychiatry* 2004;75:136-9.
- Nirmalanathan N, Holton JL, Hanna MG. *Is it really myositis? A consideration of the differential diagnosis*. *Curr Opin Rheumatol* 2004;16:684-91.
- Kissel JT, Mendell JR, Rammohan KW. *Microvascular deposition of complement membrane attack complex in dermatomyositis*. *N Eng J Med* 1986;314:324-9.
- Bender A, Ernst N, Iglesias A, et al. *T cell receptor repertoire in polymyositis: clonal expansion of autoaggressive CD8 T cells*. *J Exp Med* 1995;181:1863-8.
- Page G, Chevrel G, Miossec P. *Anatomic localization of immature and mature dendritic cell subsets in dermatomyositis and polymyositis*. *Arthritis Rheum* 2004;50:199-208.
- Askanas V, Engel WK. *Molecular pathology and pathogenesis of inclusion-body myositis*. *Microscopy Research and Technique* 2005;67:114-20.
- Askanas V, Engel WK. *Proposed pathogenic cascade of inclusion-body myositis: importance of amyloid- β , misfolded proteins, predisposing genes, and aging*. *Curr Opin Rheumatol* 2003;15:737-44.
- Dalakas MC. *Inflammatory disorders of muscle: progress in polymyositis, dermatomyositis and inclusion body myositis*. *Curr Opin Neurol* 2004;17:561-7.



mother: 365 days a year
ms patient: 15 minutes every friday

AVONEX[®]
(interferon beta-1a)

efficacy that lasts

Prescribing information: AVONEX®

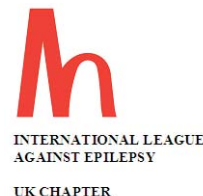
Presentations: Lyophilised powder for injection for IM administration containing a 30µg dose (6 million IU) of Interferon beta-1a per vial. Solution for injection in a pre-filled syringe of 0.5ml for IM administration containing 30µg dose (6 million IU) of Interferon beta-1a. **Indications:** For the treatment of ambulatory patients with relapsing multiple sclerosis characterised by at least 2 recurrent attacks of neurologic dysfunction (relapses) over the preceding 3-year period without evidence of continuous progression between relapses. AVONEX® slows the progression of disability and decreases the frequency of relapses. AVONEX® is also indicated for the treatment of patients who have experienced a single demyelinating event with an active inflammatory process if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis (see SPC for further information). Treatment should be discontinued in patients who develop chronic progressive multiple sclerosis. **Dosage and Administration:** The recommended dosage of AVONEX® in the treatment of relapsing MS is 30µg injected IM once a week. AVONEX® lyophilised powder presentation should be reconstituted with the solvent supplied. Treatment should be initiated under supervision of a physician experienced in the treatment of the disease. An antipyretic analgesic is advised to decrease the flu-like symptoms associated with AVONEX® administration. AVONEX® should not be used in children. **Contraindications:** initiation of treatment in pregnancy. Patients with a history of hypersensitivity to natural or recombinant interferon beta or any of the excipients. Patients with current severe depression disorders and/or suicidal ideation. **Precautions:** CNS: AVONEX® should be used with caution in patients with previous or current depressive disorders, in particular to those with antecedents of suicidal ideation. Depression and suicidal ideation are known to occur in increased frequency in the multiple sclerosis population in association with interferon use. Patients treated with AVONEX® should be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physician. AVONEX® should be administered with caution to patients with a history of seizures, to those receiving treatment with anti-epileptics, particularly if their epilepsy is not adequately controlled with anti-epileptics. **Pregnancy and lactation:** Initiation of treatment is contraindicated during pregnancy. Women of child bearing potential should take appropriate contraceptive measures. If the patient becomes pregnant or plans to become pregnant while taking Avonex, discontinuation of therapy should be considered. **General:** AVONEX® should be used with caution in patients with cardiac disease, severe renal or hepatic failure or severe myelosuppression, and these patients should be closely monitored. Routine periodic blood chemistry and haematology tests are recommended during treatment with AVONEX®. Laboratory abnormalities may also occur which do not usually require treatment. **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 medicinal products with a narrow therapeutic index and dependent on hepatic cytochrome P450 for clearance. **Side Effects:** The most commonly reported symptoms are of the flu-like syndrome: muscle ache, fever, chills, asthenia, headache and nausea. Other less common events include: **Body as a whole:** anorexia, hypersensitivity reactions, weight loss, weight gain, severe allergic reactions (anaphylactic reactions or anaphylactic shock), syncope. **Skin and appendages:** alopecia, angioneurotic oedema, injection site reaction including pain, pruritus, rash, urticaria. **Digestive system:** diarrhoea, hepatitis, liver function test abnormalities, vomiting. **Cardiovascular system:** chest pain, palpitations, tachycardia, and vasodilatation and rarely arrhythmia, cardiomyopathy, congestive heart failure. **Haematological system:** thrombocytopenia and rare cases of pancytopenia. **Reproductive system:** metrorrhagia and/or menorrhagia. **Nervous system:** anxiety, dizziness, insomnia, paraesthesia, seizures, depression, suicide (see Precautions). Transient neurological symptoms that mimic MS exacerbations may occur following injections. **Musculoskeletal system:** arthralgia, pain, transient hypertension 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, hypothyroidism, lupus erythematosus syndrome, confusion, emotional lability, psychosis, migraine and very rare cases of autoimmune hepatitis have been reported with AVONEX®. For further information regarding adverse events please refer to the Summary of Product Characteristics. **Preclinical Safety:** Fertility and developmental studies with a related form of 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. **Pack Size and UK NHS Price:** Box containing four injections £654. Reimbursed through High Tech Scheme in Ireland. **Package Quantities:** Lyophilised Powder: 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 1 ml pre-filled glass syringe of solvent and one needle. Pre-filled Syringe: 1 box containing four trays. Each tray contains a 1 ml pre-filled syringe made of glass containing 0.5 ml of solution (30µg dose of Interferon beta-1a) and one needle. **Product Licence Numbers:** EU/1/97/033/002-003. **Product Licence Holder:** Biogen Idec Ltd., 5 Roxborough Way, Foundation Park, Maidenhead, Berkshire SL6 3UD, United Kingdom. Date of last revision of Prescribing Information: September 2006. Please refer to the Summary of Product Characteristics for further information.

Information about adverse event reporting can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Biogen Idec Ltd., on 08000 286639.

Date of preparation: February 2007

AVO-GBR-20561

PREVIEW: The ILAE UK Chapter 2007 Annual Scientific Meeting



The ILAE UK Chapter 2007 Annual Scientific Meeting will be held on 10th-12th October at the De Vere Grand Harbour Hotel, West Quay Road, Southampton, Hampshire.

The De Vere is an elegant five star property with a waterside location and excellent road, rail and air links with the rest of the UK. We are also offering lower cost alternative accommodation at the Holiday Inn, situated across the road from the De Vere. Both hotels have excellent leisure club facilities free to hotel guests.

The Council of the UK Chapter of the International League Against Epilepsy would like to invite abstracts of no more than 400 words. Abstracts can be related to any aspect of epilepsy (basic science abstracts should be submitted to the basic science abstract section). The best two abstracts will be invited for platform presentation at the Annual Scientific Meeting. Deadline is June 30th, 2007.

The Council also invite entries for the following 2007 Awards.

Gowers' Young Physician Award (£1000):

A dissertation on any aspect of epilepsy. Entrants must be no older than 35 years on 31st December 2007

Gowers' Medical Student Awards x 2 (£500 each)

A dissertation on any aspect of epilepsy, including case histories of a patient personally observed by the student. Entrants must be bona fide medical students

Gowers' Combined Nursing & Health Professional Award (£1,000)

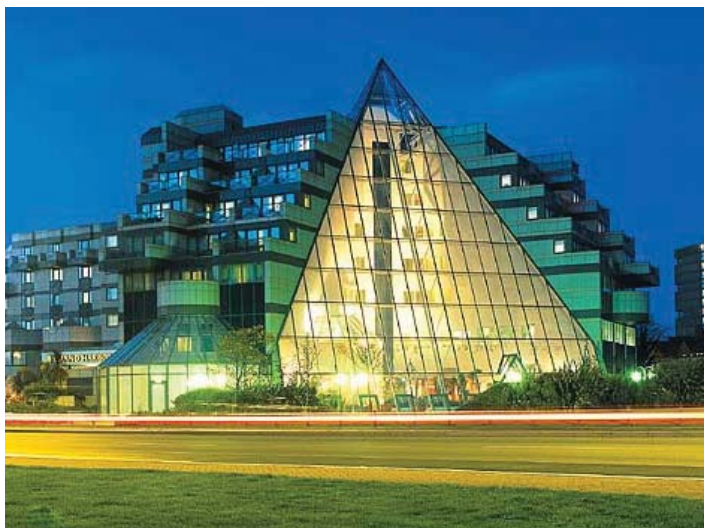
A dissertation on any aspect of epilepsy, by a member of the nursing profession or recognised health profession related to epilepsy care.

Closing Date 30th June 2007. Entries must be from within the UK, in English and not more than 5000 words. Prizes will be presented at the Annual Meeting. Accommodation and travel expenses for the award winners will be met by the ILAE UK Chapter.

Young Basic Scientific Investigator Award (£1,000)

The award is open to any UK basic scientist or health professional employed at lecturer level or below (or NHS equivalent) and working in the field of basic science research (non-clinical) in epilepsy. Entrants must be 40 years or under on 31st December.

For more information on the Annual Meeting or the Awards, see www.ilae-uk.org.uk/ASM.html or www.conference2k.com



PREVIEW: The SMI Group's 8th Annual Pain Therapeutic Conference

Crowne Plaza Hotel, London, UK, 11-12 June 2007.

Sponsored by: CRS Group, ICON Development Solutions, Lectus Therapeutics Ltd, Medeval Limited, Mallinckrodt & MD Biosciences.
Supported by: DrugResearcher.com, Neuro Drug Focus, CNS Drug News, Pharma Times & World Pharmaceutical Frontiers.

As pharmaceutical companies continually strive to find new and evolving ways to combat neuropathic and neurological pain, The SMI Group's 8th Annual Pain Therapeutics Conference once again showcases the new advances within the pharmaceutical industry.

Listen to case studies on novel targets for effective pain relief such as ion channels, CB2 receptors and the purinergic cascade, and explore revolutionary strategies for confronting neuropathic pain.

Senior representatives from the top ten Pharma Companies together with those from pharmaceutical companies that specialise in pain medication will deliver a series of specialised presentations detailing the discoveries and advances they have made over the last 12 months.

The continual success of The SMI Group's Pain Therapeutics Conference stands as proof of its reputation as the leading conference in the field. With this years promising to be the most successful, attendance is compulsory in order to keep abreast of developments in this ever-evolving industry.

This is an exceptional occasion to hear presentations from the industry's decision-making experts:

- Dr James Sullivan, Divisional Vice President, Neuroscience Discovery, Abbott Laboratories

- Dr Linda Surh, Director, CEDD Global Regulatory Affairs, GlaxoSmithKline
- Dr Shimon Amselem, Vice President, Pharmaceutical Development, Pharmos Ltd
- Dr Phil Skolnick, Executive Vice President and Chief Scientific Officer, DOV Pharmaceutical Inc
- Dr Alyson Fox, Global Head, Gastrointestinal Disease Area, Novartis
- Professor Theo Meert, Senior Research Fellow, Therapeutics Area Leader & Biology Head, CNS, Pain & Neurology, Johnson & Johnson
- Dr Liza Leventhal, Principal Research Scientist 1, Neuroscience Discovery Research, Wyeth
- Dr Steve England, Associate Research Fellow, Discovery Biology, Pfizer
- Dr John Connell, Director, Clinical Pharmacodynamics & Project Management, Icon Development Solutions
- Dr Emanuele Sher, Research Advisor, Pain/Migraine Team, Eli Lilly and Company
- Roland Kozlowski, Chief Executive Officer, Lectus Therapeutics

Benefits of Attending:

- **GROUNDBREAKING NEW TARGETS** for effective pain relief
- **SUCCESSFUL AND NOVEL** approaches to neuropathic and neurological pain

- **NEW AND EVOLVING ANALGESICS** in development
- **THE RELEVANCE** of translational pharmacology to neurological pain

PLUS AN ASSOCIATED HALF-DAY POST-CONFERENCE EXECUTIVE BRIEFING

The Critical Path for the Discovery of New Pain Therapeutics
13th June 2007

In association with NeuroKnowledge & Pharmidex

For more information, please visit our website at:

www.smi-online.co.uk/2007pain2.asp
To register contact Andrew Hinton on
Tel: +44 (0) 20 7827 6722 or
ahinton@smi-online.co.uk

Sponsorship and Exhibition Opportunities:

There are still a number of linked sponsorship and promotional opportunities available for this event. To discuss these or any other opportunities please contact **Martin Cawte** on Tel: +44 (0) 20 7827 6728 or mcawte@smi-online.co.uk.

Mention ACNR to be eligible for a 10% discount on the conference fee.

PREVIEW: 1st International Symposium on Basal Ganglia Speech Disorders and Deep Brain Stimulation

Institute of Neurology, Queen Square, London, UK, 2&3 July 2007.

Fluent articulation is probably man's most complex motor skill. It involves the co-ordinated use of approximately 100 muscles, such that speech sounds are produced at a rate of 15 per second.

Basal ganglia dysfunction can affect the smooth coordination of these muscles with a variable presentation of hypokinesia or hyperkinesia. The majority of people with Parkinson's disease and dystonia present with speech impairment at some stage of the disease process. Speech impairment can lead to both social isolation and direct disadvantages in employment.

There is a wide variability of the perceptual characteristics of basal ganglia speech disorders with lack of strong relationship with the limb motor disability.

This variable presentation of basal ganglia speech impairment responds poorly to otherwise effective medical and surgical management.

Speech is therefore an area of great interest both for research and clinical practice.

The development of basal ganglia stimula-



tion procedures gave rise to a renewed interest in the role of basal ganglia in speech motor control. Speech has a variable and often negative response to deep brain stimulation despite beneficial effects in limb motor control.

This area of neurological study remains relatively new and as such it presents many opportunities for the advancement of both research and patient care.

The aim of this first symposium is to focus

on speech problems following deep brain stimulation for Parkinson's disease, dystonia, Tourette syndrome and essential tremor.

The symposium will bring together a unique group of the world's most prominent researchers and practitioners in the field of neurological studies and speech, with emphasis on video /audio presentations and discussion.

Topics include: variability of basal ganglia speech disorders; measuring speech in movement disorders; deep brain stimulation: overview of the surgical procedure and post-operative management; speech and swallowing outcome following deep brain stimulation for Parkinson's disease and dystonia; imaging and neurophysiology in basal ganglia speech disorders; treatment of speech disorders following deep brain stimulation.

For further information visit:

www.ion.ucl.ac.uk/education/dbs.html

Neuroscience for Clinicians 14 & Brain Repair Spring School 2007

Cambridge, UK, 10-12 April 2007

A joint meeting of Neurosciences for Clinicians 14 and the Cambridge Centre for Brain Repair Spring School has been held in Cambridge recently. The focus of the conference this year was on demyelination, remyelination, progenitor biology and axon regeneration.

The first section of the conference was on 'Stem cells and progenitors'. W Richardson from the University College London presented his study on tracking oligodendrocyte progenitors, subventricular zone (SVZ) stem cells and their progeny in the adult mouse brain. With Cre-lox fate mapping techniques in transgenic mice, he showed that the adult oligodendrocyte progenitors (OPCs), which are widely distributed in the forebrain, are capable of a continuous generation of new oligodendrocytes in the white matter of adult brain. He also showed that the stem cells found in the adult SVZ are heterogenous, both in terms of their origins and their fates in the olfactory bulbs. The talk of T Ben-Hur then shed light on the effect of transplantation of neural stem cells on attenuating inflammatory process in multiple sclerosis (MS) models. Transplantation of neurospheres attenuated brain inflammation in the acute experimental autoimmune encephalomyelitis model of MS and reduced the degree of demyelination and axonal pathology in the chronic model. W Blakemore from the University of Cambridge then discussed the significance of the acute inflammatory response in initiating myelination from the remyelination-competent OPCs that repopulate the demyelinated area in MS lesions.

The conference next turned its attention to various other aspects on demyelination, remyelination and axon glial interactions. In this session, speakers discussed the latest advances in our understanding of the mechanisms on various myelin-related diseases and models. Their talks suggested that apart from studying the actual myelination/demyelination



by oligodendrocytes and Schwann cells, cross-talk between different cell types through gap junctions, internodal lengths and even the organelles in myelin-forming glia are important for the proper function of myelin. S Scherer from the University of Pennsylvania showed that mutations on various connexins cause mal-function and mal-formation of gap junctions on the myelin, which eventually leads to demyelination. P Brophy from the University of Edinburgh then demonstrated that the absence of Cajal bands on Schwann cells in periaxin null mice leads to a striking decrease in longitudinal growth of myelin. The effect of shorter internodal length is reflected in their conduction velocity with the conduction velocity decreasing from about 20ms⁻¹ to 10ms⁻¹. Furthermore a study by KA Nave from the Max Planck Institute demonstrated progressive axonal loss in both the PLP null mutants and Pex 5 conditional mouse. As PLP null mutants lacks NAD⁺ dependent regulatory enzymes and the Pex5 conditional mouse lacks functional peroxisomes, the axonal loss found in these models highlights the possible importance of sub-cellular organelles in axonal maintenance.

One of the highlights of the conference was the clinical session in which J Fawcett and J Somerfield introduced two patients, one with MS and the other with spinal cord injury. While both patients talked about their person-

al experiences in identifying the disease or the cause of the injury, the patient suffering from MS shared her view on how an ongoing clinical trial improved her life significantly. The patient with spinal cord injury expressed his opinion about the correct and positive attitude in maintaining a comparatively normal life. These interviews with patients do help the more basic neuroscientists to identify the key problems which patients are facing everyday and to understand the importance of good communication with patients in order to help improve their quality of life.

The final session of the conference focused on the repair of central nervous system (CNS) circuitry. By studying GAP-43 on Purkinje cells, F Rossi showed that over-expression of GAP-43 in these cells enhances their plasticity and allows neurite outgrowth even in the presence of inhibitory signals. The expression level of the receptors did not decrease in the presence of these inhibitory molecules. Further experiments using an injury model revealed that there is an accumulation of GAP-43 at sites where myelin retracts and new processes sprout on the Purkinje axon. L Schnell and D Pearse later discussed the various possible ways in repairing CNS injury. L Schnell spoke about how anti-NogoA antibodies help in neutralising the inhibitory properties of Nogo-A, therefore enhancing CNS regeneration in various animal models whilst D Pearse gave a very comprehensive review on the transplantation of Schwann cells on various spinal cord injury (SCI) models. He compared and discussed the results between acute and chronic SCI, complete and incomplete SCI and also thoracic and cervical SCI, using a combination of biological/pharmacological molecules. Finally, J Steve concluded the session by presenting various aspects and challenges which neuroscientists will have to consider if they are to translate their research findings into clinical practice.

Dr Jessica Kwok, Cambridge, UK.

Are you attending any of these meetings?

Would you like to write a short report for ACNR?

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

- BSRM: Rehab today and tomorrow
- 16th European Stroke Conference Glasgow
- MS Frontiers
- European Neurological Society
- From Science to Practice, Multidisciplinary care in PD
- 11th International Congress of PD & Movement Disorders, Istanbul
- International Headache Society Congress Stockholm
- 27th International Epilepsy Congress, Singapore
- 11th EFNS, Brussels
- 1st World Congress on Controversies in Neurology, Berlin
- World Congress on Huntington's Disease, Dresden
- ECTRIMS (MS) - Prague
- International Psychogeriatric Association Meeting, Osaka

Association of British Neurologists Spring Meeting

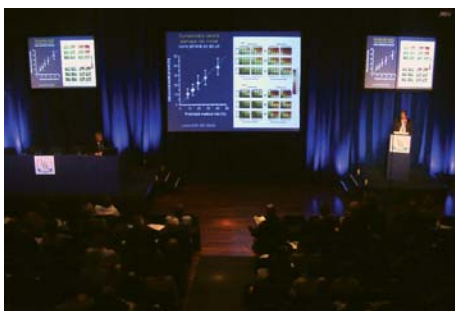
Cambridge, UK, 11-13 April 2007

For its 75th anniversary meeting, the Association of British Neurologists chose to meet in Cambridge. And a surprisingly lively affair it turned out to be.

My personal highlight was a magisterial account of the history and science of spinal cord injury by James Fawcett. He took us from the trenches of WWI to the current Nogo trials (which we have reported on before in ACNR). He dwelt in-between on the character of Sir Ludwig Guttmann, who single-handedly transformed Stoke Mandeville Hospital from sleepy DGH to the prestigious spinal injuries unit it is today. His secret, it seems, was to rigorously manage the bladder symptoms and pressure sores of his patients, which were considered at the time (and now?) to be the province of the nurses. George Hyslop's talk on Alzheimer's was as good, I understand from those whose clinical work I was left to do that afternoon.

The history of twentieth century British neurology was the one session arranged by the local organiser, Alastair Compston. Perhaps the biggest treat was a film of a patient with Wilson's disease, and other movement disorders, made by Kinnear Wilson himself. The great man appeared in one of the clips; identified as such by his son, a retired stooped scholar of ancient languages, who rose from the front row of the meeting to warm applause. Semir Zeki popped up, rather randomly in this historical section, to answer whether neuroscience had explained the brain or beauty with a resounding No, to little surprise. And the rest of the afternoon was spent indulging in warm anecdotes of our great predecessors. And then the grand unveiling of the ABN's Coat of Arms, presented by a Knight-Herald, or some such. Congratulations to Colin Mumford of Edinburgh for persisting with this project on the ABN's behalf.

I have written before of my frustration with recent ABN meetings. There seems to be a significant anti-academic wing amongst the abstract selectors. This was again apparent at the Cambridge meeting. In two and a half days, there was time for only 19 open platform presentations (why so few?). As at least 129 abstracts were submitted, those selected for an



oral presentation would be expected to be of the highest quality. And some were.... But not the talk on Google neurology or the audit of a DGH neurologist's work. Why did these take precedence over the following fantastic posters?

- A meta-analysis of 33 studies of secondary prevention of cervical artery dissection (unclear whether anticoagulation of antiplatelets better) [Menon, St George's].
- A study of excessive sleepiness of 843 patients with Parkinson's disease (23% scored in the narcolepsy range) [Malone, Exeter].
- A review of 84 consecutive cases of non-traumatic myelopathy from Tanzania (neoplasia and TB top the list interestingly) [Murphy, Kilimanjaro Christian Medical Centre].
- A prevalence study of the congenital myasthenic syndromes in the UK (210 found, of whom the investigators could identify 131 gene defects) [Lashley, Oxford].
- A five-year study of 126 patients with Parkinson's, which showed that subsequent cognitive decline could be predicted from baseline on the basis of a specific (MAPT) genotype and performance in verbal fluency and pentagon copying. [Williams-Gray, Cambridge].

By the last afternoon, I was beginning to think that the ABN had become a club for nostalgic reminiscences or discussing service development, rather than a community of thinkers keen to discover and provoke. But then came the debate. The motion, proposed some months ago in all innocence, was that "Modernising medical careers is good for patients, trainees

and the practice of neurology". But just a few weeks before the ABN meeting, the Medical Training Application Service had fallen apart, leaving young doctors stranded, and making national headlines. Chris Clough, who was proposing the motion, found it impossible to persuade the meeting that MTAS and MMC were not the same thing. So he locked his jaw and took the punches as Alastair Compston whipped up a preconditioned crowd, with great showmanship, to a near-unanimous (bar 4) vote against. A few days after the meeting, we all received this email from the ABN council.

At its annual general meeting on 11th April 2007 the Association of British Neurologists agreed that its aim was 'to improve the health and well being of people with neurological disorders by advancing the knowledge and practice of neurology in the British Isles'.

At a separate meeting of members and trainees during the Spring meeting, and by an overwhelming majority, members expressed their view that this aim could not be achieved by the exclusion of speciality-ready trainees from competing in an equal fashion with other applicants for ST3 posts as part of the MTAS selection process. In particular, trainees were of the view that they would prefer to be re-interviewed in open competition rather than proceed with a perceived flawed selection based on round one of the MTAS process.

The Association, through its Officers and Council, supports this position and recommends that any member who feels unable to participate in the existing appointments process because of this inequity should not do so.

For the first time, I felt that an ABN meeting achieved something significant. Concerned members were prepared to be awkward for the sake of young doctors and the subject. Bravo.

Alasdair Coles, Cambridge, UK.

The Autumn Meeting of the ABN will be held at the QE11 Conference Centre, London, 14-16 November, 2007.



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for a list of all our training events.

Training Events for Health and Social Care Professionals

Pain Management in Rehabilitation • 26th Jun 07
Posture and Balance in Neurological Conditions – Upper Limb Qualified staff • 26th and 27th Sept 07
10th Annual Advanced Rehabilitation Course • 3 days
Epilepsy Management in Neurological Rehabilitation • 26th Sept 2007
Neurological Rehabilitation in Primary Care • 27th Sept 2007
Multiple Sclerosis and the National Standards Framework • 28th Sept 2007
Exploring Gait as it relates to Posture and Balance for Qualified Therapists • 18th Oct 07

Posture and Balance in Neurological Conditions – Lower Limb Qualified staff • 15th Nov & 16th Nov 07
Epilepsy study day • 29th Nov 07
Parkinson Plus study day • Tbc Oct 07
Exploring Gait as it relates to Posture and Balance for qualified therapists • 23rd Jan 08
Neurological Upper Limb for Occupational Therapists • 30th Jan 08
Head Injury Conference: The Claiming Culture • 11th Mar 08
Motor Neurone Disease study day • 28th Mar 08



Clinical update: epilepsy in adults and adolescents

Thursday 28 June in Manchester

- All that shakes is not epilepsy
- When to treat?
- Sudden unexpected death in epilepsy
- Non-epileptic attack disorder
- Epilepsy and Society (*to include employment, driving regulations & legal implications for childcare and education*)
- When drugs fail – selection for surgery

Pathways to work: promoting a life in work

Friday 13 July in London

- Returning people with mental health problems to work
- Tackling psychological and social determinants of health illness, disability and work-incapacity
- From symptoms to disability

To view current speakers or to book online, please visit www.rsm.ac.uk/diary or contact Primrose on 0207 290 2965



The Institute of Neurology, Queen Square

Basal Ganglia Speech Disorders and Deep Brain Stimulation



**1st International Symposium
2nd and 3rd July 2007**



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- Basal Ganglia and speech disorders.
- Measuring speech: the challenge of movement disorders.
- Deep brain stimulation: overview of the surgical procedure and post-operative management.
- Speech and swallowing outcome following deep brain stimulation for Parkinson's Disease and Dystonia.
- Imaging and neurophysiology in basal ganglia speech disorders.
- Treatment for speech disorders following deep brain stimulation.

Who should attend:

Neurosurgeons, Neurologists Neurophysiologists, Neuropsychologists, Neuroscientists, Speech & Language Therapists, specialist nurses and other health professionals with a specialist interest on speech in movement disorders.

FEE: £120 for two days - £80 for one day

For an application form please contact:
j.reynolds@ion.ucl.ac.uk

For further information:

e.tripoliti@ion.ucl.ac.uk
Elina Tripoliti, Sobell Department,
Unit of Functional Neurosurgery, box 146,
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ANNUAL SCIENTIFIC MEETING 10TH-12TH OCTOBER 2007

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- Cortical Dysplasias
- Neurostimulation for Epilepsy
- Encephalopathies
- Epilepsy and Society
- Researching Epilepsy - The Future

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The SMi Group presents the 8th Annual...



Pain Therapeutics Conference

11th & 12th June 2007, The Crowne Plaza Hotel - The City, London

Confirmed Speakers:

- Dr James Sullivan, Divisional Vice President, Neuroscience Discovery, Abbott Laboratories
- Dr Linda Surh, Director, CEDD Global Regulatory Affairs, GlaxoSmithKline
- Dr Keith Bley, Senior Vice President, Nonclinical R&D, NeurogesX Inc
- Dr Shimon Amsalem, Vice President, Pharmaceutical Development, Pharmos Ltd
- Dr Phil Skolnick, Executive Vice President and Chief Scientific Officer, DOV Pharmaceutical Inc
- Dr Alyson Fox, Global Head, Gastrointestinal Disease Area, Novartis
- Roland Kozlowski, Chief Executive Officer, Lectus Therapeutics
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2007

May

Therapists in MS Study Day - "Mind Matters in MS"

9 May, 2007, UK
www.mstrust.org.uk/tims,
T. 01462 476704,
E. Education@mstrust.org.uk

Visual Perceptual Dysfunction and brain injury, Part 2

9-11 May, 2007; London, UK
W. www.brainretraining.co.uk
E. enquiries@brainretraining.co.uk

Brain Development 2007

10 May, 2007; London, UK
W. www.abcam.com/brain2007

EFNS Academy for Young Neurologists 8th Course

10-13 May, 2007; Staré Splyav, Czech Republic
E. efns@fmkv.cz or pragueoffice@efns.org
T/F. +420 2 6716 35 63

UCL Short Course Epilepsy

14 May, 2007; London, UK
Jean Reynolds
T. 020 7829 8740
F. 020 7278 5069
E. J.Reynolds@ion.ucl.ac.uk
W. www.ion.ucl.ac.uk

International Conference on Diagnosis & Treatment in Pediatric Neurology

14-17 May, 2007; Warsaw, Poland
E. neuroped2008@firstclass.com.pl
W. http://www.neuroped2008.pl

UCL Short Course Neuro-ophthalmology

15 May, 2007; London, UK
Jean Reynolds
T. 020 7829 8740
F. 020 7278 5069
E. J.Reynolds@ion.ucl.ac.uk
W. www.ion.ucl.ac.uk

UCL Short Course Movement Disorders

16 May, 2007; London, UK
Jean Reynolds
T. 020 7829 8740
F. 020 7278 5069
E. J.Reynolds@ion.ucl.ac.uk
W. www.ion.ucl.ac.uk

Liverpool Advances in Neurology Symposium 2007

16 May, 2007; Liverpool, UK
Pam Bessant,
T. 0151 529 5460
F. 0151 529 5465
E. p.bessant@liv.ac.uk

UCL Short Course Statistical Parametric Mapping

17, 18 & 19 May, 2007; London, UK
Jean Reynolds
T. 020 7829 8740
F. 020 7278 5069
E. J.Reynolds@ion.ucl.ac.uk
W. www.ion.ucl.ac.uk

Primary Care Neurology Society 2007 Conference

17 May, 2007; Birmingham, UK
W. www.p-cns.org.uk

4th International Hydrocephalus Workshop

17-20 May, 2007; Rhodes, Greece
E. hydrocephalus@artion.com.gr
T. +30 2310 250928
F. +30 2310 277964

2nd course in EMG/NCS for non-specialists

18 May, 2007; Birmingham, UK
Dr A M Purves,
T. 07770987762
E. apurves@dsl.pipex.com

UCL Short Course Neuromuscular Disease

21 May, 2007; London, UK
Jean Reynolds
T. 020 7829 8740
F. 020 7278 5069
E. J.Reynolds@ion.ucl.ac.uk
W. www.ion.ucl.ac.uk

Rehabilitation Medicine Today and Tomorrow: Service models for specialist rehabilitation in hospitals and communities

22 May, 2007; London, UK
Sandy Weatherhead, BSRM,
E. admin@bsrm.co.uk
T. 01992 638865
W. www.bsrm.co.uk

UCL Short Course Stroke

22 May, 2007; London, UK
Jean Reynolds
T. 020 7829 8740
F. 020 7278 5069
E. J.Reynolds@ion.ucl.ac.uk
W. www.ion.ucl.ac.uk

Multiple Sclerosis Trust Masterclass for MS Specialist Nurses

22 May, 2007; London, UK
W. www.mstrust.org.uk
T. 01462 476704
E. Education@mstrust.org.uk

PD MED Collaborators' Meeting 2007

22-23 May, 2007; Birmingham, UK
Tom Boodell,
T. 0121 687 2315
E. t.boodell@bham.ac.uk

UCL Short Course Neuropathology

23 May, 2007; London, UK
Jean Reynolds
T. 020 7829 8740
F. 020 7278 5069
E. J.Reynolds@ion.ucl.ac.uk
W. www.ion.ucl.ac.uk

BISWG Annual General Meeting

23 May, 2007; Birmingham, UK
Patti Simonson
T/F. 0208 780 4530
E. psimonson@rhn.org.uk

UCL Short Course Neuropsychiatry

24 May, 2007; London, UK
Jean Reynolds
T. 020 7829 8740
F. 020 7278 5069
E. J.Reynolds@ion.ucl.ac.uk
W. www.ion.ucl.ac.uk

Kerr in the Community - Delivering for Epilepsy

24 May, 2007; Edinburgh, UK
Craig Gover,
T. 0141 427 4911
E. cglover@epilepsyscotland.org.uk

2nd Biennial Vocational Outcomes in Traumatic Brain Injury Conference

24-26 May, 2007; Vancouver, BC Canada
E. sljproductions@telus.net
W. www.tbicvancouver.com

UCL Short Course Multiple Sclerosis

25 May, 2007; London, UK
Jean Reynolds
T. 020 7829 8740
F. 020 7278 5069
E. J.Reynolds@ion.ucl.ac.uk
W. www.ion.ucl.ac.uk

8th European Neuro-Ophthalmology Society Meeting

26-29 May, 2007; Istanbul
Pinar Aydin O'dwyer
E. Aydinp@Eunos2007.Org
W. www.Eunos2007.Org

12th Meeting of the European Society of Neurology and Cerebral Hemodynamics

26-29 May, 2007; Budapest, Hungary
W. www.esnch.org/

1st Migrating Course on Epilepsy

27 May-3 June, 2007; Babe, Serbia
E. epi.savezliga@eunet.yu
W. www.epilepsy-academy.org,
www.info-yulac.co.yu, www.ilae-epilepsy.org

The 29th Advanced Clinical Neurology Course

28-30 May, 2007; Edinburgh, UK
E. Judi.clarke@ed.ac.uk

XVI European Stroke Congress

29 May-1 June, 2007; Glasgow, UK
E. info@stroke.org.uk

Consortium of Multiple Sclerosis Centers (CMSC)

30 May - 3 June, 2007; Washington DC, USA
E. info@mcsare.org

4th Dubrovnik International Conference On Multiple Sclerosis

30 May-2 June, 2007; Dubrovnik, Croatia
E. zpetelin@mef.hr
W. www.multipia.hr

59th Annual Congress Of The Scandinavian Neurosurgical Society

31 May-3 June, 2007; Helsinki, Finland
E. goran.blomstedt@hus.fi
W. www.eventnordic.fi/congreszon/sns2007/

June

BISWG 'Thinking out of the Box - Good Practice in Joint Working'

1 June, 2007; Paisley, Scotland
Fen Parry
T. 01315 376853
E. fen.parry@edinburgh.gov.uk or
mhairi.mckay@ipct.scot.nhs.uk

39th International Danube Symposium for Neurological Sciences and Continuing Education in conjunction with the 1st International Congress on ADHD

2-5 June, 2007; Wurzburg, Germany
W. www.danube-wuerzburg.de or
www.adhd-wuerzburg.de

1st International Congress on ADHD: From Childhood to Adult Disease

3-7 June, 2007; Wurzburg, Germany
E. peter.riederer@mail.uni-wuerzburg.de

11th International Congress of Parkinson's Disease and Movement Disorders

3-7 June, 2007; Istanbul, Turkey
W. www.movementdisorders.org/meetings/index.shtml

Multiple Sclerosis Trust Study Day in MS - Focus on Health Professionals in the Residential Environment

5 June, 2007; UK
W. www.mstrust.org.uk
T. 01462 476704
E. Education@mstrust.org.uk

Kuopio Stroke Symposium

6-8 June, 2007; Kuopio, Finland
E. jukka.jolkkonen@uku.fi
W. www.uku.fi/stroke2007

Perfusion and reperfusion of the brain - RSM Clinical Neurosciences Section

7 June, 2007; London, UK
T. 020 7290 2984/2982
F. 020 7290 2989
E. cns@rsm.ac.uk

2nd International Congress on Neuropathic Pain

7-10 June 2007; Berlin, Germany
T. +41 22 908 0488
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E. neuropain@kenes.com
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4th World Congress of the International Society of Physical Medicine and Rehabilitation

10-14 June, 2007; Seoul, Korea
E. isprm2007@intercom.co.kr
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E. marketingdept@smi-online.co.uk

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International Workshop Erlangen: Prediction of Outcome

15-16 June, 2007; Erlangen, Germany
Prof. Dr. H. Stefan,
E. hermann.stefan@neuro.imed.uni-erlangen.de
E. +49 9131 85364689
W. www.epilepsiezentrum-erlangen.de

17th Meeting of the European Neurological Society

16-20 June, 2007; Rhodes, Greece
W. www.ensinfo.com
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Advances in Neurorehabilitation Part of The Festival of International Conferences on Caregiving, Disability, Aging and Technology (FICCDAT)

16-19 June, 2007; Toronto, Canada
E. catherine@smartmove.ca
W. www.ficdat.ca

7th World Congress on Brain Injury

17-21 June, 2007; Jerusalem, Israel
W. www.kenes.com/ibia07/

International Society for Stem Cell Research Meeting

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International Society for Stem Cell Research,
T. +847-509-1944
F. +847-480-9282
E. isscr@isscr.org

2nd Neurorehabilitation Panamerican Congress

18-20 June, 2007; Buenos Aires, Argentina
E. dfelder@ineba.net
W. www.ineba.net

Canadian Neurological Sciences Federation (CNSF) 42nd Annual Scientific Meeting

19-22 June, 2007; Alberta, Canada
W. www.cnsf.org

Pain and the Brain

20th June, 2007; Bristol, UK
W. www.physiouk.co.uk
T/F. 020 8394 0400

9th International Conference of the Baltic Child Neurology Association

20-23 June, 2007; Vilnius, Lithuania
T. +37052120003
F. +370522120013
E. cna@bcna2007.com
W. www.bcna2007.com

Joint Meeting of WFNR and EMN

22-24 June, 2007; Fuggi, Italy
E. fservade@ausl-cesena.emr.it
W. www.emn.cc

Understanding and treating cognitive problems after brain injury

22-23 June, 2007; London, UK
www.brainretraining.co.uk
E. enquiries@brainretraining.co.uk

Epileptology : Comprehensive Review and Practical Exercises

June 24-26, 2007; Cleveland, USA
W. www.ClevelandclinimedEd/Epileptology07

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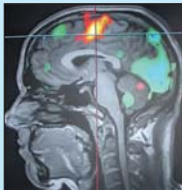
13th Congress of the International Headache Society

28 June-1 July 2007; Stockholm, Sweden
W. www.ihc2007.org/
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July

1st International Symposium on Basal Ganglia Speech Disorders and Deep Brain Stimulation

2-3 July, 2007; London, UK
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Pain and the Brain Evening Lectures



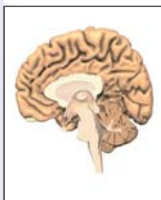
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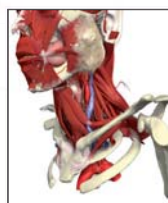
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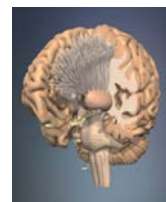
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Potential of the Rotigotine Transdermal Patch for Patients with Advanced Parkinson's Disease

The symptomatic burden of Parkinson's disease (PD) can be managed effectively for long periods, although no disease-modifying treatments have been developed. The clinical diagnosis of PD is based on the presence of cardinal motor features, which include tremor at rest, rigidity, bradykinesia and postural instability.¹ The initial motor symptoms of PD have been attributed primarily to dopamine deficiency arising from degeneration of the substantia nigra.²

Early motor symptoms of PD can be controlled by dopamine agonists or levodopa. Dopamine agonists are often used as a first-line option because they delay the onset of motor fluctuations and dyskinesia associated with prolonged levodopa use;¹ however, the attenuation of disease-related symptoms tends to be less pronounced with dopamine agonists than with levodopa. As PD progresses, symptom control with dopamine agonist monotherapy inevitably diminishes to a point where treatment with levodopa becomes a necessity.¹

Parkinson's disease: a progressive condition

It is now recognised that, in addition to degeneration of the nigrostriatal dopaminergic pathway, a variety of neuronal systems are involved in PD.² PD is associated with progressive loss of monoaminergic and cholinergic neurons, initially at the level of the brainstem, but later involving subcortical and cortical regions. Dysfunction of non-dopaminergic cells is thought to play a role in development of non-motor symptoms,³ including autonomic dysfunction, cognitive and psychiatric changes, sensory symptoms and sleep disturbances.^{4,5} Although these non-motor symptoms can occur at an early stage, they tend to dominate the clinical picture in advanced PD and are a major contributor to disability and impaired quality of life.⁴

Advanced PD is also characterised by development of motor complications associated with long-term

dopaminergic therapy. These motor complications typically begin with minor motor fluctuations, often after four to five years of therapy, and progress to significant dyskinesia and akinetic periods after 10–15 years.^{6,7} Pulsatile stimulation of dopamine receptors is thought to play a significant role in this process,⁸ leading to the hypothesis that continuous dopaminergic stimulation (CDS), such as through treatment with the rotigotine transdermal patch, may ameliorate or prevent development of motor complications.⁹

The rotigotine transdermal patch

Rotigotine is a non-ergolinic dopamine agonist with a receptor profile similar to that of dopamine¹⁰ and is formulated in a once-daily transdermal patch that provides continuous, uniform release over 24 hours.¹¹ The clinical studies of the rotigotine transdermal patch in early PD,^{12,13} which reported efficacy with good tolerability, were reviewed previously in *Advances in Clinical Neuroscience and Rehabilitation*.¹⁴ These results provided the basis for approval of the transdermal rotigotine patch for use in early PD. More recently, the rotigotine transdermal patch was approved for the treatment of idiopathic PD, either with or without concomitant levodopa therapy. When used in combination with levodopa, the transdermal patch can be used to deliver rotigotine doses of up to 16mg/24 hours.

Clinical studies of rotigotine in advanced PD

The efficacy and tolerability of the rotigotine transdermal patch were compared with placebo in a phase III trial in 351 patients with advanced PD.^{15,16} Patients were randomised to receive transdermal rotigotine 8 or 12mg/24 hours, or placebo, with titration to the randomised dose over a four-week period followed by a four-week maintenance phase. Both doses of transdermal rotigotine resulted in statistically significant decreases from baseline in absolute 'off' time compared with placebo (Figure 1). These decreases in 'off' time were associated with an increase in 'on without troublesome dyskinesia' time (Figure 2). Though there was a greater reduction in 'off' time for the 8mg/day rotigotine group compared to the 12mg/day group, this difference was not significant in a post hoc analysis. In fact, the apparent increase in treatment effect with 8mg/day became evident during the titration phase when daily rotigotine intake was the same for each group (Figure 2).¹⁶

Further evidence of the efficacy of the transdermal rotigotine patch was provided by a phase III placebo- and pramipexole-controlled trial in which 604 patients with advanced PD were randomised to rotigotine, pramipexole or placebo in a ratio of 2:2:1.¹⁷ Rotigotine doses were titrated weekly in 2mg/24 hours increments to an optimal response or a maximum dose of 16mg/24 hours. Patients receiving pramipexole were titrated weekly to an optimal response or a maximum dose of 4.5mg/day (expressed as the salt formulation of pramipexole; base equivalent 3.3mg/day). Patients



Dr Donald Grosset is Consultant Neurologist at the Southern General Hospital and Honorary Senior Lecturer at the University of Glasgow. His ongoing clinical and research interests are in Parkinson's disease and movement disorders. He is director of the Regional Movement Disorder Clinic, a co-founder of the Glasgow Movement Disorder Group, and also runs the Regional Dystonia Clinic. In Parkinson's disease his research is currently focused on diagnostic techniques for Parkinson's disease and therapeutic compliance. Novel approaches to prevention and management of fluctuations and dyskinesia are being explored. These clinical treatment angles reflect his dual training in clinical pharmacology and neurology.

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Glasgow G51 4TF, UK.
Tel: +44 141 201 2486
Fax: +44 141 201 2510
Email: d.grosset@clinmed.gla.ac.uk

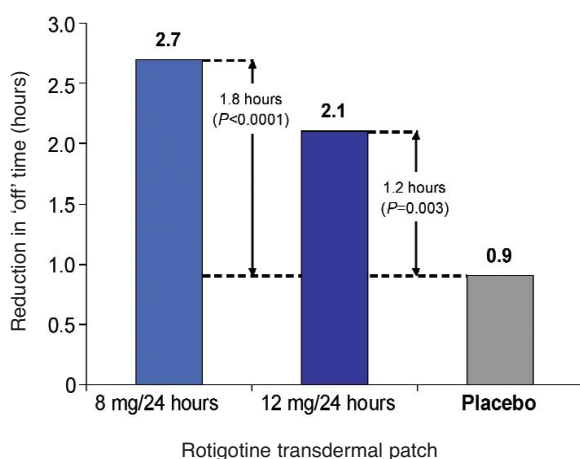


Figure 1: Reduction in 'off' time between baseline and the end of the maintenance phase in a phase III placebo-controlled trial in patients with advanced Parkinson's disease.

Prescribing information
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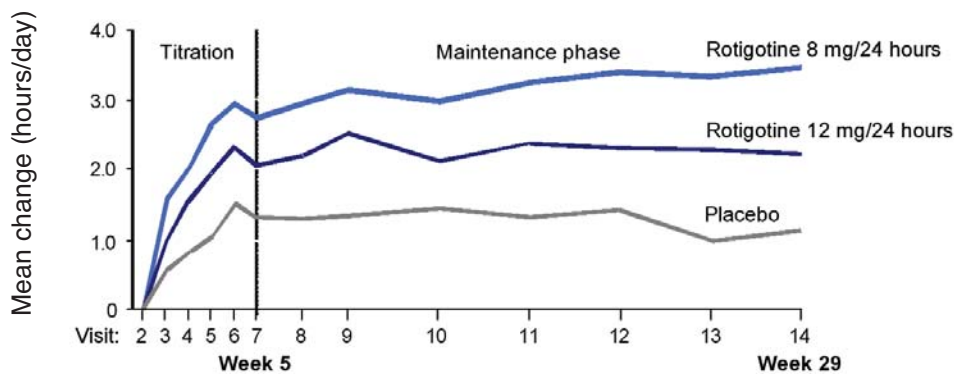


Figure 2: Increase in 'on without troublesome dyskinesia' time between baseline and the end of the maintenance phase in a phase III placebo-controlled trial in patients with advanced Parkinson's disease.

receiving the rotigotine transdermal patch or pramipexole had a significant decrease in 'off' time from baseline (Figure 3) and an increase in time spent 'on without troublesome dyskinesia' (rotigotine +2.8 hours/day, pramipexole +2.7 hours/day and placebo +1.4 hours/day). The transdermal rotigotine patch was non-inferior to pramipexole for reduction in 'off' time and, in addition, was associated with an increase in time spent 'on without troublesome dyskinesia'. The results from both phase III trials of the transdermal rotigotine patch in advanced PD provide a helpful indication of the type and rate of adverse events which occur with this treatment. In the phase III placebo-controlled trial, the most frequent adverse events were application-site reactions (rotigotine 41% vs placebo 13%), somnolence (31% vs 27%), nausea (24% vs 18%), dizziness (19% vs 15%), dyskinesia (15% vs 7%) and oedema (11% vs 1%).¹⁵ These events are typical of those in patients with PD or who are treated with other dopaminergic drugs or alternative transdermal systems.¹⁵ In the placebo- and pramipexole-controlled trial, adverse events occurred with similar frequency in each of the active treatment groups, with the exception of psychiatric adverse events, which were more frequent with pramipexole (21.3%) than rotigotine (14.6%) or placebo (11.1%), and application-site reactions, which were more frequent with rotigotine (20.5%) than pramipexole (8.4%) or placebo (10.1%).¹⁷

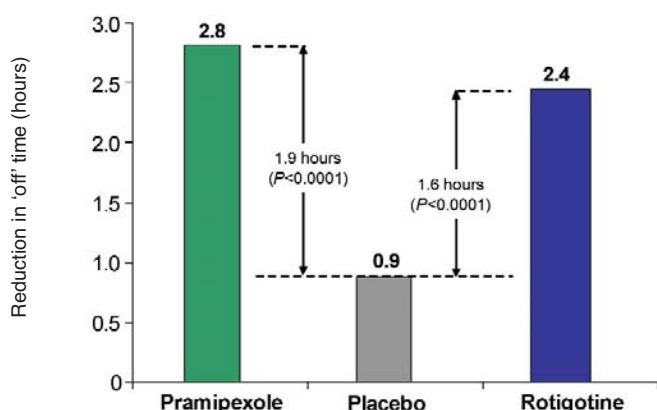


Figure 3: Reduction in 'off' time between baseline and the end of the maintenance phase in a phase III placebo- and pramipexole-controlled trial in patients with advanced Parkinson's disease.

The potential of the rotigotine transdermal patch in advanced PD

A recent change to the marketing authorization now allows rotigotine to be used in combination with levodopa at doses up to 16mg/24 hours, which means that patients who progress from early to advanced PD can continue to receive treatment in combination with levodopa, even if they require high dopamine agonist doses.

The rotigotine transdermal patch has been shown to provide effective control of some non-motor symptoms in patients with advanced PD. These non-motor symptoms include sleep disturbances, which may arise as a consequence of degeneration of central sleep

regulation centres in the brainstem and thalamocortical pathways.⁴ Long-acting dopamine agonists (such as the rotigotine transdermal patch and the ergot-derived dopamine agonist cabergoline) may provide relief for patients with sleep disturbances.^{18,19,20} Furthermore, as noted above, the phase III placebo- and pramipexole-controlled study showed that treatment with the rotigotine transdermal patch was associated with a decreased probability of waking up in an 'off' state and an increased likelihood of waking up 'on without dyskinesia'.¹⁷ A single-arm study in PD patients with unsatisfactory control of early-morning motor impairment showed that the rotigotine transdermal patch had positive effects on motor and non-motor variables, including nocturnal akinesia, dystonia and cramps score, Epworth Sleepiness Scale, and number of nocturias.²¹ In addition to improving motor and non-motor symptoms, transdermal rotigotine might reduce the number of pills that the patient with dysphagia has to take.

Data from experimental models shows that continuous rotigotine delivery provides CDS. In freely moving non-parkinsonian rats, subcutaneous injection of an oily crystalline rotigotine suspension, which mimics the kinetics of transdermal administration, increased locomotor activity throughout a 48-hour period and led to stable extracellular dopamine levels.²² These findings were supported by a study in marmosets, which showed that continuous rotigotine administration resulted in good locomotor activity and improved motor disability throughout the day.²³

The potential for CDS to reverse levodopa-induced motor complications has been demonstrated in studies of continuous infusions of apomorphine,^{24,25,26,27,28} intrajejunal carbidopa/levodopa²⁹ and lisuride.³⁰ However, continuous infusions are expensive and impractical for large numbers of patients.⁹ Therefore, the rotigotine transdermal patch may provide a convenient means of delivering CDS without the need for continuous infusion. In addition to improving motor complications, CDS may also have the potential to alleviate sleep disturbances, prevent the development of gastrointestinal dysfunction and reduce the risk of developing psychosis or behavioural disturbances.⁹ These possible benefits require investigation in large, well-designed clinical trials.

Summary

Delivery of CDS with the rotigotine transdermal patch may have the potential to alleviate motor complications and has been shown to significantly reduce 'off' time in clinical trials in advanced PD. Advanced PD is characterised by motor complications associated with long-term dopaminergic therapy. The available evidence suggests that the rotigotine transdermal patch is a valuable addition to the therapeutic options for patients with advanced PD.

References

- Nutt JG, Wooten GF. *Clinical practice. Diagnosis and initial management of Parkinson's disease*. N Engl J Med 2005;353:1021-7.
- Braak H, Ghebremedhin E, Rub U, et al. *Stages in the development of Parkinson's disease-related pathology*. Cell Tissue Res 2004;318:121-34.
- Ahlskog JE. *Challenging conventional wisdom: the etiologic role of dopamine oxidative stress in Parkinson's disease*. Mov Disord 2005;20:271-82.
- Chaudhuri KR, Healy DG, Schapira AH. *Non-motor symptoms of Parkinson's disease: diagnosis and management*. Lancet Neurol 2006;5:235-45.
- Samii A, Nutt JG, Ransom BR. *Parkinson's disease*. Lancet 2004;363:1783-93.
- Marsden CD, Parkes JD. *Success and problems of long-term levodopa therapy in Parkinson's disease*. Lancet 1977;1:345-9.
- Rajput AH, Fenton ME, Birdi S, et al. *Clinical-pathological study of levodopa complications*. Mov Disord 2002;17:289-96.
- Olanow CW, Obeso JA, Stocchi F. *Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications*. Lancet Neurol 2006;5:677-87.
- Giladi N, Steiger M. *Constant dopaminergic stimulation by transdermal delivery of dopaminergic drugs: a new treatment paradigm in Parkinson's disease*. Eur J Neurol 2007; in press.
- Scheller D. *Extended receptor profile of rotigotine, a non-ergolinic dopamine agonist being investigated in Parkinson's disease*. Mov Disord 2006;21 (Suppl 13):S1-S159.
- Braun M, Cawello W, Poole K, et al. *Steady-state pharmacokinetics of rotigotine in patients with early-stage Parkinson's disease*. Eur J Neurol 2005;12:37.
- Parkinson Study Group. *A controlled trial of rotigotine monotherapy in early Parkinson's disease*. Arch Neurol 2003;60:1721-8.
- Watts RL, Jankovic J, Waters C, et al. *Randomized, blind, controlled trial of transdermal rotigotine in early Parkinson disease*. Neurology 2007;68:272-6.
- Grosset D. *The rotigotine transdermal patch may provide continuous dopaminergic stimulation in early-stage Parkinson's disease*. Advances in Clinical Neuroscience and Rehabilitation 2006;6:32-4.
- LeWitt PA, Nausieda PA, Chang F, et al. *Rotigotine transdermal system as adjunctive therapy to levodopa in patients with advanced-stage Parkinson's disease. Results of a randomized, double-blind, placebo-controlled, multicenter, multinational trial [abstract]*. J Neurol Sci 2005;238:S353.
- LeWitt PA, Lyons KE, Pahwa R. *Advanced Parkinson disease treated with rotigotine transdermal system: PREFER Study*. Neurology 2007;68:1262-7.
- Poewe W, Giladi N, Boothman B, et al. *Rotigotine transdermal system in patients with advanced-stage Parkinson's disease as adjunctive therapy to levodopa: results of a placebo- and pramipexole-controlled trial*. Mov Disord 2006;21:548.
- Chaudhuri KR, Bhattacharya K, Porter MC. *The use of cabergoline in nocturnal parkinsonian disabilities causing sleep disruption: a parallel study with controlled-release levodopa*. Eur J Neurol 1999;6(5):11-15.
- Reuter I, Ellis CM, Ray CK. *Nocturnal subcutaneous apomorphine infusion in Parkinson's disease and restless legs syndrome*. Acta Neurol Scand 1999;100:163-7.
- Rinne UK, Bracco F, Chouza C, et al. *Early treatment of Parkinson's disease with cabergoline delays the onset of motor complications. Results of a double-blind levodopa controlled trial*. The PKDS009 Study Group. Drugs 1998;55 Suppl 1:23-30.
- Giladi N, Mair KJ, Badenhorst F, et al. *Effects of rotigotine transdermal patch on early morning motor function, sleep quality, and daytime sleepiness in patients with idiopathic Parkinson's disease. Results of a multicenter, multinational trial*. Eur J Neurol 2007, in press.
- Scheller D, Kehr J. *Evidence for continuous dopamine receptor stimulation by rotigotine in freely moving rats using a continuous delivery system*. Parkinsonism and Related Disorders 2005;11 (Suppl 2):PS002-02.
- Scheller D, Rose S, Smith L, et al. *Comparison of continuous vs pulsatile administration of rotigotine in a monkey model of Parkinson's disease*. Presented at the World Parkinson Congress, Washington, DC, USA, 22-26 February 2006.
- Colzi A, Turner K, Lees AJ. *Continuous subcutaneous waking day apomorphine in the long term treatment of levodopa induced interdose dyskinesias in Parkinson's disease*. J Neurol Neurosurg Psychiatry 1998;64:573-6.
- Kanovsky P, Kubova D, Bares M, et al. *Levodopa-induced dyskinesias and continuous subcutaneous infusions of apomorphine: results of a two-year, prospective follow-up*. Mov Disord 2002;17:188-91.
- Katzschlager R, Hughes A, Evans A, et al. *Continuous subcutaneous apomorphine therapy improves dyskinesias in Parkinson's disease: a prospective study using single-dose challenges*. Mov Disord 2005;20:151-7.
- Manson AJ, Turner K, Lees AJ. *Apomorphine monotherapy in the treatment of refractory motor complications of Parkinson's disease: long-term follow-up study of 64 patients*. Mov Disord 2002;17:1235-41.
- Stibe CM, Lees AJ, Kempster PA, et al. *Subcutaneous apomorphine in parkinsonian on-off oscillations*. Lancet 1988;1:403-6.
- Nyholm D, Askmark H, Gomes-Trolin C, et al. *Optimizing levodopa pharmacokinetics: intestinal infusion versus oral sustained-release tablets*. Clin Neuropharmacol 2003;26:156-63.
- Stocchi F, Ruggieri S, Vacca L, et al. *Prospective randomized trial of lisuride infusion versus oral levodopa in patients with Parkinson's disease*. Brain 2002;125:2058-66.

Neupro® Rotigotine

Prescribing Information

Presentation: Neupro® is a thin, matrix-type square transdermal patch.

Neupro 2 mg/24 h transdermal patch: Releases 2 mg rotigotine over 24 hours. 10cm² patch contains 4.5 mg rotigotine.

Neupro 4 mg/24 h transdermal patch: Releases 4 mg rotigotine over 24 hours. 20cm² patch contains 9.0 mg rotigotine.

Neupro 6 mg/24 h transdermal patch: Releases 6 mg rotigotine over 24 hours. 30cm² patch contains 13.5 mg rotigotine.

Neupro 8 mg/24 h transdermal patch: Releases 8 mg rotigotine over 24 hours. 40cm² patch contains 18.0 mg rotigotine.

Indications: To treat the signs and symptoms of idiopathic Parkinson's disease, either with or without concomitant levodopa therapy.

Dosage: Neupro is applied to the skin once a day. The patch remains on the skin for 24 hours and will then be replaced by a new one at a different application site. In monotherapy, treatment is initiated with a single daily dose of 2 mg/24 h. Dose increased by 2 mg/24 h each week (e.g. 2 mg/24h in Week 1, 4 mg/24 h in Week 2, 6 mg/24 h in Week 3 and 8 mg/24 h in Week 4), until an effective dose is reached. Maximal dose is 8 mg/24 h. In combination with levodopa, treatment initiation is at 4 mg/24 h and increased weekly in 2 mg increments, up to a maximum dose of 16 mg.

Contraindications: Hypersensitivity to rotigotine or to any

of the excipients. Neupro should be removed prior to Magnetic Resonance Imaging (MRI) or cardioversion to avoid burns.

Warnings and Precautions: External heat should not be applied to the patch. Dopamine agonists are known to cause hypotension, and monitoring of blood pressure is recommended. Where somnolence or sudden sleep onset occurs, or where there is persistent, spreading or serious skin rash at the application site, consider dose reduction or termination of therapy. Rotate the site of patch application to minimise the risk of skin reactions. In case of generalised skin reaction associated with use of Neupro, discontinue treatment. Avoid exposure to direct sunlight until the skin is healed. If treatment is to be withdrawn, it should be gradually reduced to avoid symptoms of neuroleptic malignant syndrome.

Compulsive behaviours and hallucinations have been reported in patients treated with Neupro. Do not administer neuroleptics or dopamine antagonists to patients taking dopamine agonists. Caution is advised when treating patients with severe hepatic impairment, and in patients taking sedating medicines or other depressants in combination with rotigotine. Switching to another dopamine agonist may be beneficial for those patients who are insufficiently controlled by rotigotine.

Undesirable effects: Very common side effects include nausea, vomiting, somnolence, dizziness and application site reactions. Common side effects include anorexia, hallucinations, sleep attacks, insomnia, abnormal dreams, headache, dyskinesia, lethargy, orthostatic hypotension, hypertension, hiccup, cough, constipation, diarrhoea, dry

mouth, dyspepsia, hyperhidrosis, erythema, pruritus, asthenic conditions and peripheral oedema. Uncommonly, syncope, loss of consciousness, visual disturbances, or hypotension may occur. Rarely, psychotic disorders, increased libido or convulsion may occur.

Basic NHS Cost: Starter Pack: £110.34

2 mg Continuation Pack of 28 patches: £77.24

4 mg Continuation Pack of 28 patches: £88.28

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Date of preparation: December 2006 (NEU3898)

Neupro® is a registered trademark.

Prescribers should consult the Summary of Product Characteristics for the full information on side-effects, warnings and precautions.

Information about adverse event reporting can be found at www.yellowcard.gov.uk. Adverse events should be reported to the Drug Safety department at SCHWARZ PHARMA Limited (UK) on 01923 684 100 or drugsafety@schwarzpharma.co.uk.

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Functional Imaging and the Vegetative State

The vegetative state (VS) is one of a number of conditions of impaired consciousness (coma, vegetative state, minimally conscious state) resulting from either traumatic or non-traumatic neurological damage. In contrast to many neurological conditions the VS is defined by the behaviours exhibited by patients rather than a common underlying pathology. Consequently the clinical diagnosis is made on the basis of prolonged and extensive, but critically subjective, observations of a patient's behaviour in response to sensory and cognitive stimulation. To fulfil the diagnostic criteria a patient must (1) demonstrate no evidence of awareness of self or environment, (2) demonstrate no evidence of sustained, reproducible, purposeful or voluntary response to visual, auditory, tactile or noxious stimuli, and (3) demonstrate no evidence of language comprehension or expression.^{1,2} The VS typically follows the acute comatose period in which the patient demonstrates no wakefulness (eye opening/sleep wake cycles) or response to command. This period typically lasts two to four weeks after the initial insult before the patient either regains consciousness or progresses to the vegetative or minimally conscious state. The minimally conscious state describes a spectrum of impairment.³ At the lowest boundary and earliest sign of emergence from the vegetative state, a patient demonstrates visual fixation and/or evidence of tracking objects or people. At the upper boundary before emergence to a fully conscious but severely disabled state, the patient demonstrates inconsistent but reproducible response to command. Emergence to the severely disabled condition reflects consistent and reproducible communication either via movement or speech.

Pathophysiology, prevalence and prognosis

Although defined by the exhibited behaviour, post mortem work has identified three crude pathophysiological presentations in VS: (1) damage predominantly to subcortical brainstem structures with an intact cerebral cortex, (2) damage predominantly to cortico-cortical con-

nections with a relatively preserved brainstem, and (3) damage to both the brainstem and cerebral cortex.⁴ In reality, patients meeting the diagnostic criteria for the VS are extremely heterogeneous. Although precise figures for the incidence of this condition are not available, estimates have suggested up to 14 persons per million in the UK and 46 persons per million in the USA could exist in this condition one month post ictus.⁵ It is also thought that three times this figure could exist in the minimally conscious state; each patient requiring 24 hour high dependency care, which is predominantly met by the private sector. Although diagnosis does not take place until at least six weeks post presentation, decisions about long-term prognosis and in some cases withdrawal of nutrition and hydration can not be made until at least six months post non-traumatic and 12 months post traumatic brain injury. Although prognosis following non-traumatic brain injury is very poor, for those with traumatic brain injuries, up to 20% are estimated to recover consciousness within six months.⁵

Clinical assessment

A diagnosis of vegetative state is typically made by two independent doctors supported by the observations of all persons in regular contact with the patient, including family members. Observations are typically performed over a minimum period of six weeks at different times of the day and when the patient is in different postural positions or taking part in stimulatory activities. Behaviours are typically recorded using a range of purpose built scales such as the Sensory Modality Assessment and Rehabilitation Technique⁶ (SMART), the JFK Coma Recovery Scale⁷ or the Wessex Head Injury Matrix⁸ (WHIM). However, the interpretation and subsequent decision as to whether the patient demonstrates awareness of self or environment and/or purposeful response to sensory or cognitive stimulation is purely based on the subjective observation of the assessors. Critically, this approach relies upon the patient being capable of making



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Adrian Owen, PhD is senior scientist and assistant director of the MRC Cognition and Brain Sciences Unit in Cambridge. He currently uses functional imaging (fMRI, PET and MEG) and neuropsychological assessments to investigate brain injured patients. Specific areas of interest include localisation of function within the human frontostriatal system, cognitive deficits in patients with Parkinson's disease and detecting residual cognitive function in patients with impaired consciousness.



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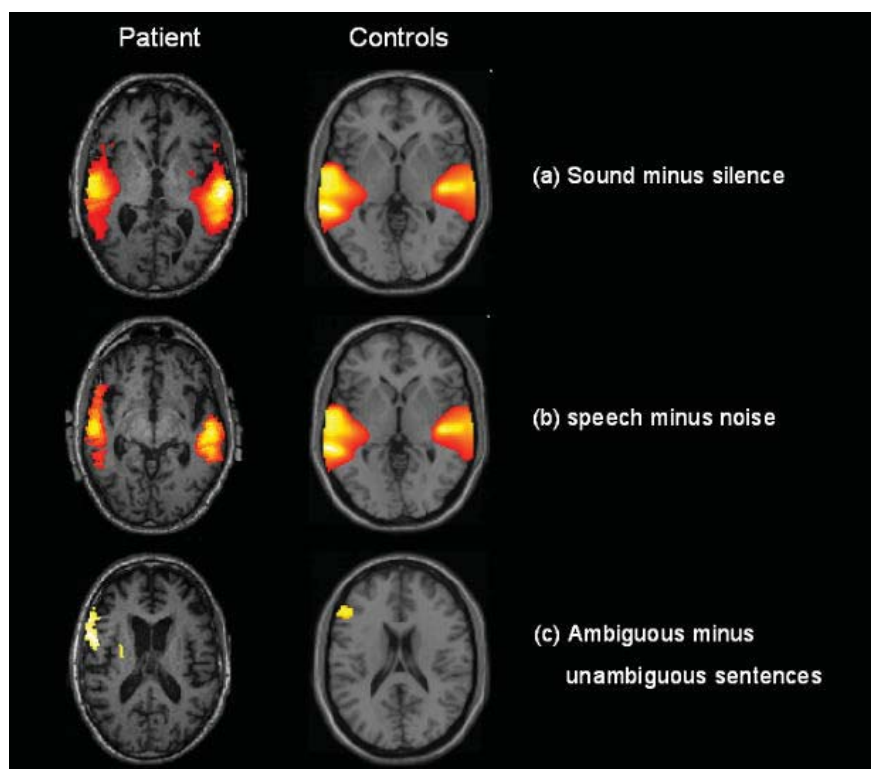


Figure 1: Auditory activations from a single patient meeting the behavioural criteria for the vegetative state and from a group of 12 healthy volunteers: (a) Large bilateral temporal activation can be seen to hearing sound versus silence, (b) intelligible speech minus signal correlated noise, in the superior and inferior temporal lobe, and (c) discrete left inferior frontal activation can be seen to hearing sentences with ambiguous versus unambiguous content. All results are thresholded at FDR $p < .05$, corrected for multiple comparisons.

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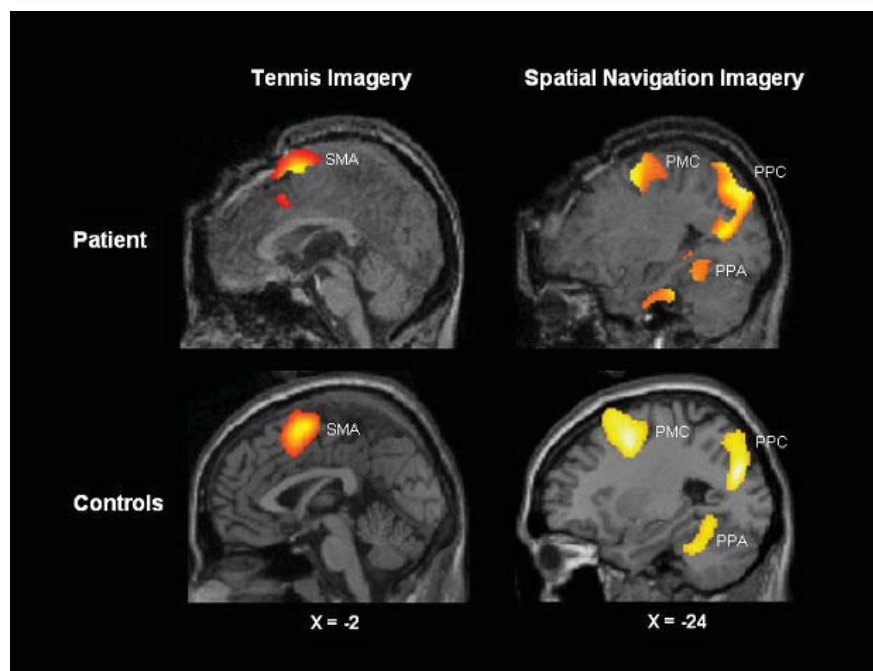


Figure 2: Supplementary motor area (SMA) activity in the comparison between tennis imagery and rest in both a VS patient and in a group of 12 healthy volunteers. Parahippocampal gyrus (PPA), posterior parietal-lobe (PPC) and lateral premotor cortex (PMC) activity in the comparison between imagining moving around a house and rest in both the patient and in the same group of volunteers. All results are thresholded at FDR $p < .05$, corrected for multiple comparisons.

an overt motor behaviour (movement or speech) to signal awareness and willingness to respond. However, a large number of patients progressing to the vegetative state also suffer complex peripheral nervous system changes. Many have extensive contractures, limited range of movement and muscle wastage preventing sufficient motor output to respond to command. Consequently, this difficulty is thought to be one of several contributing to the reported high rate of misdiagnosis.⁹

Emerging objective tools to aid the clinical assessment

Since 1998 work using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) has slowly facilitated a change in attitude to and understanding of this complex condition. Although by definition a vegetative patient should demonstrate no sustained or purposeful response to sensory or cognitive stimuli, a number of imaging studies have demonstrated 'islands' of preserved cerebral function in a small number of patients otherwise behaviourally unresponsive.^{10,11,12,13} Founded on the belief that the assessment of patients should require no overt action on the part of the patient, functional imaging has the ability to tap discrete covert cognitive processes – something the behavioural observation of a patient is entirely unable to do. In 1998 a landmark paper by Menon and colleagues identified preserved face processing in a VS patient behaviourally unresponsive to command. This was later expanded to auditory processing of intelligible versus unintelligible sound¹² and more recently to speech comprehension.¹³ Indeed, Owen and colleagues have developed and subsequently advocated a hierarchical approach to the assessment of these patients using functional neuroimaging.¹³ Having established the integrity of sensory pathways using electro-

physiology, a number of paradigms using PET and fMRI are used to tap the residual cognitive function of the patients. In the auditory domain the group have developed a paradigm to determine whether (a) the patient is able to detect sound versus silence, (b) is able to discriminate speech from non speech, and (c) retrieve semantic information in order to comprehend sentences with ambiguous content (Figure 1). Although this paradigm is able to determine whether a patient is able to comprehend language, it does not tell us definitively whether the patient is aware of the information presented to them. To address this issue Owen and colleagues have recently developed an fMRI paradigm where the participant is asked to imagine playing tennis or moving around the rooms of their home.¹⁴ In this scenario the subject is asked to create a vivid mental picture of the movement associated with hitting a ball with a racket and critically to maintain this picture for 30 seconds until told to relax. This request is then repeated five times and alternated with an equal number of rest periods. Therefore, in performing this task the participant not only demonstrates understanding of the command to perform the mental imagery task, but also the will and therefore awareness of the command to actually perform the task. To date four patients meeting the international criteria defining the vegetative state have been asked to perform these tasks. Two of these patients (one unpublished) have not only demonstrated appropriate activation consistent with retrieving semantic information to comprehend speech, but have also demonstrated cerebral activation consistent with volunteers asked to perform the mental imagery tasks (Figure 2). This has further suggested that despite negative behavioural markers a small subset of VS patients do in fact retain awareness of self and environment.

Conclusion

Despite the emerging and promising utility of functional imaging in this area there are a number of very important caveats. Firstly, only positive findings on functional imaging can be interpreted since false negatives are known to occur in conscious and healthy volunteers. Secondly, even if a negative finding is observed it is impossible to exclude the fact that at another time or in another cognitive task a patient might respond. Indeed, only a limited number of functional imaging paradigms currently exist to tap specific cognitive networks – for instance we know very little about whether these patients are able to learn or feel emotions. This work will undoubtedly continue over the coming years, but what is certain is that functional imaging is likely to play an increasingly important part in the accurate assessment of patients with impaired consciousness following brain injury.

References

- Royal College of Physicians. *The vegetative state: Guidance on diagnosis and management*. London: Royal College of Physicians, 2003.
- Multi-Society Task Force on PVS. *Medical aspects of the vegetative state (in two parts)*. New England Journal of Medicine. 1994;330:1499-508, 1572-9.
- Giardino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, Kelly JP, Rosenberg JH, Whyte J, Zafonte RD & Zasler ND. *The minimally conscious state: Definition and diagnostic criteria*. Neurology. 2002;58:349-53.
- Kinney HC & Samuels MA. *Neuropathology of the persistent vegetative state: a review*. Journal of Neuropathology and Experimental Neurology. 1994;53:548-58.
- Jennett B. *Thirty years of the vegetative state: clinical, ethical and legal problems*. In Laureys S (Ed). Progress in Brain Research: The boundaries of consciousness; Neurobiology and neuropathology. 2005;150:537-43.
- Gill-Thwaites H & Munday R. *The Sensory Modality Assessment and Rehabilitation Technique (SMART): A comprehensive and integrated assessment and treatment protocol for the vegetative state and minimally responsive patient*. Neuropsychological Rehabilitation. 1996;9:305-20.
- Giardino JT, Kalmar K & Whyte J. *The JFK Coma Recovery Scale – revised: Measurement characteristics and diagnostic utility*. Archives of Physical Medicine and Rehabilitation. 2004;85(12):2020-9.
- Shiel A, Horn SA, Wilson BA, Watson MJ, Campbell M & McLellan DL. *The Wessex Head Injury Matrix (WHIM) main scale: A preliminary report on a scale to assess and monitor patient recovery after severe head injury*. Clinical Rehabilitation. 2002;14(4):408-16.9. Andrews K, Murphy L, Munday R & Littlewood C. *Misdiagnosis of the vegetative state*. British Medical Journal. 1996;313:13-16.
- Menon DK, Owen AM, Williams EJ, Minhas PS, Allen CMC, Boniface SJ & Pickard JD. *Cortical processing in the persistent vegetative state*. Lancet. 1998;352:200.
- Schiff N, Ribary U, Moreno DR, Beattie B, Kronberg E, Blasberg R, Giacino J, McCagg C, Fins JJ, Llinas R & Plum F. *Residual cerebral activity and behavioural fragments can remain in the persistently vegetative brain*. Brain. 2002;125:1210-34.
- Owen AM, Menon DK, Johnsrude IS, Bor D, Scott SK, Manly T, Williams EJ, Mummery C & Pickard JD. *Detecting residual cognitive function in persistent vegetative state*. Neurocase 2002;8:394-403.
- Owen AM, Coleman MR, Menon DK, Johnsrude IS, Rodd JM, Davis MH, Taylor K & Pickard JD. *Residual auditory function in persistent vegetative state: A combined PET and fMRI study*. Neuropsychological Rehabilitation. 2005;15(3/4):290-306.
- Owen AM, Coleman MR, Boly M, Davis MH, Laureys S & Pickard JD. *Detecting awareness in the vegetative state*. Science. 2006;313:1402.

Living with Charcot-Marie-Tooth Disease

I was born with Charcot-Marie-Tooth Disease (CMT) also known as hereditary motor and sensory neuropathy and peroneal muscular atrophy. Diagnosis is a matter of luck as most GPs do not recognise the disease. I was diagnosed in my early twenties by Dr PK Thomas at the Royal Orthopaedic Hospital in London. Diagnosis in childhood would be ideal, as muscles can be strengthened as much as possible to try to manage the illness and avoid unnecessary injuries.

I had a genetic test in the nineties that showed that it was CMT type 1a, the most common type. It is a dominant gene, common to both sexes and each child of an affected parent has a 50% chance of inheriting it. In my case, my father had the gene (unbeknown to him) and two of his three children inherited it. My sister, the only one of us to have children, has also passed it on to two of her three daughters.

The disease is progressive and affects the peripheral nerves by damaging the myelin sheath and slowing down the messages to the muscles. This has a negative effect on sensory information and muscle function in the hands, forearms, lower legs and feet.

“This can lead to foot bone abnormalities such as high arches and hammer toes, foot-drop walking gait, scoliosis (curvature of the spine), muscle cramping, problems with balance and hand functions, and the loss of some normal reflexes. It can produce chronic pain and fatigue, and in rare instances it may cause severe disability, but it is not life-threatening and does not affect life expectancy. Despite being the most common inherited neurological disease in the world – it affects approximately 1 in 25000 of the global population – CMT is not widely understood.” *Charcot-Marie-Tooth Disease, A Practical Guide*, compiled by CMT International, UK in 2000.

I have the results of motor conduction velocity tests taken by Dr PK Thomas in the late sixties. He included the results in a paper he published: “Hereditary motor and sensory polyneuropathy (peroneal muscular atrophy)” – in 1974 By PK Thomas and colleagues and these are listed in Table 1.

Table 1: Motor nerve conduction velocity (ms-1)

	<i>Median (hands)</i>	<i>Peroneal (feet)</i>	<i>Age</i>
My father	26	13	65
Helen (me)	10	14	22
Leslie (sister)	27	19	23
Anna (niece, 1998)	16.5	24.5	24
(My niece’s tests were taken in Finland)			

After the diagnosis, I was told that nothing could be done, so I had no more contact with neurologists from my early twenties until my fifties. I had no further information until I discovered CMT International/UK (<http://www.cmt.org.uk>), an organisation started in

Canada in the late 80s by CMT sufferers to offer support, information and practical advice to fellow sufferers.

I started walking unsupported quite late and always had trouble picking up my feet. This gradually got worse and resulted in totally drop feet. I experimented with boots until I was able to find some that were light enough and supportive enough to help me to walk (tying the laces very tightly). I have torn ligaments in both feet many times. After a failed tendon transplant, my left foot was fixed in position and I wore an elastic bandage on my right foot until I discovered Silicone Ankle Foot Orthosis (SAFOs) (see below).

In the 90s the local surgical appliances people made me some plastic orthotics. These were totally useless and very painful and were termed “crass” by a foot specialist I showed them to.

Circulation to the extremities is a problem. My feet were often icy cold, but for the last two years I have been taking Tamoxifen for breast cancer. This now causes uncomfortable menopausal symptoms such as hot flushes, night sweats and burning hot feet.

Having no muscles in your feet to lift them up and stop your ankles from twisting makes them very floppy, bony and lacking in padding. The toes also curve and big toes can fracture because they can turn under. I see a chiropodist regularly to deal with callouses and toe problems and wear jelly inserts and toe padding to keep the toes straighter.

The thing that has helped me most was the discovery of SAFOs, that are made by Dorset Orthopaedics (<http://www.dorset-ortho.co.uk>). These are silicone orthoses that look like boots with the toes and heel cut out. They are wonderful supports for drop feet while being soft enough for fragile feet. The down side is the cost, which is very high, circa £650 per foot*, and trips down to Dorset for the fittings. I tried to get funding for them but was turned down.

I started dislocating my left knee-cap from the age of nine, and the right one from the age of 14. My father and sister also had/have dislocating knee problems. My knees became so lax that they sometimes dislocated in the action of sitting down and both were operated on in my twenties. One operation was successful for almost thirty years, but the other knee dislocated so badly a few years later that the tendon snapped and my knee-cap rose at least an inch higher up the leg. It is now kept in place with an elastic support.

I developed osteo-arthritis in both knees from the age of 30. I occasionally had them drained and had cortisone injections. Eventually I became very immobile and was in a lot of pain. I am allergic to anti-inflammatories and aspirin, so I relied on ice-packs and paracetamol. I later had two arthroscopies and a new right knee when I was about 56. By that time my leg was totally unstable and I could hardly stand.

Because of all the dislocations and operations there is a lot of scar tissue, which prevents me from bending the new knee much. I have to be very careful not to trip, especially as my right knee doesn’t bend much and my toes



Helen Thomas

*At that time, the cheaper Safo Walk was not available.

Diagnosis in childhood would be ideal, as muscles can be strengthened as much as possible to try to manage the illness and avoid unnecessary injuries

often catch on uneven surfaces.

My hands have always been weak, unlocking doors can be difficult and I have a thick, very light penholder for writing as I find gripping pens very tiring. My little fingers on both hands are beginning to be floppy.

My shoulders have been problematic for some time. The tendons are stretched and the shoulders are unstable. I sleep with a small cushion at night to keep them in the right position. I have had cortisone injections in both shoulder joints. Walking with a crutch also affects my left shoulder and hand, due to strains and shocks and vibrations. I am exploring the internet for better ones, but anti-shock crutches tend to be too heavy.

CMT patients seem to be left to their own devices to find suitable footwear, foot supports etc. I would welcome more practical help for this condition, which has no treatment at present. I have also arranged for private physiotherapy and hydrotherapy, which have both been very helpful (but expensive).

Being disabled from early childhood with an inherited condition has emotional and psycho-

logical effects. Of course some social activities such as sports and long walks have always been out of the question. You learn to dress to disguise the problem, to boost your confidence, attract the opposite sex and to get accepted at job interviews. I made the painful decision not to have children, as the genetic test did not exist at the time.

Here are some quotes from different stages of my life:

- "You should be in a Special School" School Matron at boarding school (after a dislocation).
- "Pick up your feet, X asked me if you'd had polio" and "Why don't you be more careful" (after a dislocation), my worried father.
- "The way she walks is a very bad example to the children" overheard when I was doing teaching practice.
- "We'd like to offer you the job, but please don't wear those boots."
- "I'd like to marry someone just like you, but without the leg problems."
- "I don't approve of people like you adding to

the genetic pool." Gynaecologist I'd visited for period pain.

- "Lots of people are much worse off than you." Registrar on the ward after an orthopaedic operation, in answer to a neurological question he didn't understand.

Actually I've been lucky and have a good life, thanks to the support of my husband and friends. I want to live and enjoy my life despite having been born with CMT. I don't think it's a good idea to be obsessed by one's illnesses. However, it is important to get practical help to live a normal life and to get up to date information on treatment, as it becomes available.

I have been very fortunate in being able to afford to experiment with footwear and to have had the chance to buy SAFOs, and pay for physiotherapy. I am concerned about my future when I will no longer be able to afford these things.

The tendency seems to be for doctors to disregard CMT. I wonder how fellow sufferers manage without the emotional and financial support I have received.



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EDITOR'S CHOICE

EPILEPSY: The SANAD Study

I don't know if it is because it was sponsored by NHS R+D but this study has been subject to as many leaks as a confidential memo from Ruth Turner at No.10. It is however good to see the paper in print and its two arms between them merited 27 pages of the *Lancet*, which is a measure of their clinical importance; this study should alter clinical practice.

Study Design. Patients were divided into two groups. In the first group were those diagnosed by their clinicians as having focal epilepsy. This group was randomised to carbamazepine (standard drug), gabapentin, topiramate, lamotrigine or oxcarbazepine. There were 378 patients in each arm of this group, except oxcarbazepine, which was a late addition to the study and where there were only 210 patients. The second group of patients were those in whom either the clinician made a confident diagnosis of idiopathic generalised epilepsy (IGE) or they were not sure, for example, patients with tonic clonic seizures and no focal features clinically or on investigation. These patients were randomised to valproate (standard drug), lamotrigine or topiramate, with 239 patients in each group. There were two primary outcome measures; the time from randomisation to treatment failure, for whatever reason and the time from randomisation to the achievement of a one year seizure remission. Secondary outcome measures included the time to first seizure and the incidence of clinically important adverse events. In both arms of the study, early withdrawal was more commonly due to adverse effects and later withdrawal to lack of efficacy – it stands to reason that you don't know a drug isn't working until you have tried it for a while. Quality of life assessments were performed on a subset of patients and cost-effectiveness was also assessed, using the assumption that patients were treated with the cheapest available preparation, which presumably means generic preparations, where available.

Results for focal epilepsy. It was quite clear that treatment failures were most likely with gabapentin and topiramate. In the case of gabapentin, seizure control was 20% less likely than with carbamazepine and with topiramate 4-8%, depending on the time period; both these results were significant. Time to two year remission was also significantly worse with these two drugs. Gabapentin was however, better tolerated than carbamazepine and topiramate was roughly equally tolerated to carbamazepine. For lamotrigine total treatment failures were 12% less than carbamazepine in the first year, 8% in the second year and 6% in the third year. Treatment failures for adverse events were 10-11% less for lamotrigine in each of the six years of the study, which was significant throughout. Part of this was related to the very high rate of rash, which accounted for 37 out of 177 treatment failures for carbamazepine and 22 out of 155 treatment failures for lamotrigine. This begs the question of how large the differences are if the patient does not have an allergic rash to the drug. Since most allergic rashes are in the first year, it seems likely that the later adverse events, which are still significantly in favour of lamotrigine, reflect other events. Carbamazepine was the least likely to cause treatment failure as a result of lack of efficacy, although the difference from lamotrigine was not significant and was biggest in the first year, perhaps related to the slower dose titration of lamotrigine. The numbers of patients taking oxcarbazepine were smaller and so the results are less statistically robust, but they suggest that this drug may be roughly equivalent to carbamazepine, with slightly less efficacy and slightly fewer adverse effects. On the basis of efficacy data, therefore, lamotrigine emerges as first line treatment for most patients with focal epilepsy with carbamazepine and oxcarbazepine as reasonable alternatives, and topiramate and especially gabapentin as also-rans. Using the lowest available cost of drugs, lamotrigine gave cost-effective benefit.

Results for general epilepsy. Sixty-three percent could be diagnosed with a specific IGE syndrome. The others had unclassifiable epilepsy. Treatment failures for topiramate were 11-14% worse than for valproate for the first five years of the study, which was highly significant. Eight to ten percent of this was attributable to adverse events and 4-6% to inadequate seizure control. Lamotrigine withdrawals were 5-10% more than valproate throughout the

study and it was slightly better tolerated but withdrawal due to lack of efficacy was 7-15% more common throughout, which was highly significant. In an intention-to-treat analysis valproate was also the favoured drug in terms of achieving a one year remission, but this is an underestimate of the difference between the drugs. If you delve into the web tables of the study you will see that many patients switched to valproate after failing with lamotrigine or topiramate, so what patients were actually taking when they achieved a one year remission was valproate 196 patients, lamotrigine 135 patients and topiramate 111 patients, with a sprinkling of other drugs, and 19 on polytherapy. The authors found that the differences between valproate and the other drugs were greater when the analysis was restricted to those with an established diagnosis of IGE, suggesting that the others had a different diagnosis. Valproate was a clear winner over lamotrigine and topiramate in generalised epilepsy. So in male patients the decision is easy. What about in women of childbearing age? Results from the Belfast epilepsy and pregnancy register¹ suggests that high dose lamotrigine may cause problems with comparable frequency to valproate (*reviewed in ACNR vol 5, issue 6*). Will this swing practice back to valproate? What about those patients with unclassified epilepsy: valproate was better for those too. What was their diagnosis? Was it focal epilepsy? If so, should valproate have been in the focal epilepsy arm of the study? Only one study² comparing valproate and carbamazepine is sufficiently large to analyse alone and it showed that carbamazepine was better for time to first seizure but there was no difference in seizure-freedom at 12 months. So is it that valproate is good for generalised epilepsy and not for focal epilepsy or is it that it is so good at generalised epilepsy that we biased humans are relatively disappointed with it in focal epilepsy and actually it is as good as anything else? Marson et al undertook a meta-analysis of studies comparing valproate and carbamazepine³ and in their recommendations to the Cochrane database concluded: "We have found some evidence to support the policy of using carbamazepine as the first treatment of choice in partial epilepsies, but no evidence to support the choice of valproate in generalised epilepsies, but confidence intervals are too wide to confirm equivalence. Misclassification of people with epilepsy may have confounded our results, and has important implications for the design and conduct of future trials." Clearly the SANAD study throws into sharp relief the inadequacy of previous studies in giving basic answers and we need to question the assumptions on which our traditional treatment choices are based.

This study provides clinically useful answers, arguably for the first time in comparing different drugs in the treatment of epilepsy and it confirms some clinicians' impressions but also throws up some surprises and provokes questions. It should make us appreciate more clearly than ever that most AED drug studies are designed to get a drug to market (a good thing) but are not sufficiently robust to alter clinical practice. The standard pre-marketing study uses the test of getting half of a refractory group of epilepsy patients to be half seizure-free for a few months. Whilst this is a different group of patients from those above, the SANAD study clearly shows us that these short studies are really only useful for assessing adverse effects and as proof of principle for efficacy. Efficacy is a long term outcome and is the main determinant of quality of life for our patients – they may stop a drug because of adverse effects, but they won't be happy until they are taking one that works long-term. Comparisons between drugs had previously relied largely on number needed to treat comparisons of premarketing studies, with different designs. These had shown that gabapentin had a large NNT, consistent with its lack of efficacy in SANAD but that topiramate had a low NNT, different from SANAD. It is true that there have been studies comparing lamotrigine with carbamazepine, which roughly came out with the same answer as this one. So when the reps come and ask you what order you use drugs in and why you haven't changed, insist on a head-to-head study and that they put their money where their mouth is and fund SANAD 2.

For the mechanistic clinicians, there is the interesting conclusion that lamotrigine really is the drug of choice for focal epilepsy. This squares with its predominant mechanism of action as a sodium channel blocker alongside carbamazepine, oxcarbazepine and phenytoin. In the choice of polytherapies

Journal reviewers

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Roger Barker, Cambridge Centre for Brain Repair;
Alasdair Coles, Cambridge University;

Andrew Larner, Walton Centre, Liverpool;
Mark Manford, Addenbrooke's Hospital, Cambridge and Bedford Hospitals;
Wendy Phillips, Addenbrooke's Hospital, Cambridge;
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Ailie Turton, University of Bristol.

too, this will add force to the arguments that mechanism of action (where we know it) can predict logical therapy combinations. Certainly, along with those drugs it has a propensity to make myoclonus worse. However, I expect Glaxo-Smith-Kline will not be dissatisfied with the outcome of this study.

The SANAD study showed cost-effectiveness of lamotrigine using the cheapest preparations available. What would the analysis have concluded if proprietary lamictal™ had been used? I suggest we have a duty to revisit the arguments of generic versus proprietary treatments; we can no longer think of ourselves exclusively as our patients' champions – our treatment choices impact on the health care available to others and we have a social responsibility to consider these. Decisions regarding the choice of proprietary versus generic drugs should be based on evidence. We all have anecdotal patients who have run into problems with generic AEDs but is this a reason always to prescribe branded medications? How about a study where we allocate patients to proprietary or generic drugs and for those on generics, plough the savings back into other aspects of epilepsy patient care? This is the true comparative study between generics and proprietary medication. Most likely it will remain a thought experiment but with the exception of phenytoin, I have little doubt where the QOLY's will lie. - **MRAM**

Marson AG for the SANAD study group.

The SANAD study for the effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial.

LANCET

2007;369:1016-26.

1. Morrow JJ, Russell A, Guthrie E et al. *Malformation risks of anti-epileptic drugs in pregnancy: a prospective study from the UK epilepsy and pregnancy register.* JNNP 2006;77:193-8.
2. Mattson RH, Cramer JA and Collins JF. *A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults: the Department of Veterans Affairs Epilepsy Cooperative Study No 264 group.* NEJM 1992;327:765-71.
3. Marson AG et al. *Carbamazepine versus valproate monotherapy for epilepsy: a meta-analysis.* Epilepsia 2002 May;43(5):505-13.

MULTIPLE SCLEROSIS: a new gene discovered for multiple sclerosis

The genetics of multiple sclerosis have been difficult to crack. For thirty years or so, we have known multiple sclerosis is associated with some HLA alleles, like many autoimmune diseases. In particular, in most populations, owning DRB1*1501, and perhaps DRB1*0301, increases your risk of getting multiple sclerosis. This is one variant of the genes which construct the 'class II' molecule which sits on the antigen-presenting cell, awaiting a passing T-cell. Since those landmark papers in the 1970s, there have been many thousands of DNA donations by patients, several genome screens, some key international collaborations and many millions of pounds spent to find the additional genetic cause of multiple sclerosis; but to no avail – until now. Finally, the increasing technological and analytical sophistication and vaster DNA banks have thrown up a novel gene underlying multiple sclerosis. This paper, presented by Stephen Sawcer in the Annals for the International Multiple Sclerosis Genetics Consortium, describes a filou pastry approach to HLA genetics... The starting database was DNA from 930 'trios' (people affected by multiple sclerosis and their parents), as well as from 721 other people with multiple sclerosis (presumably 'solos!'). But this was gradually whittled away as first people with DRB1*1501 and then with DRB1*0301 were excluded. With some SNPs here, some microsatellites there, and a lot of overheated PCR machines and computers... out emerged the result: people who have the HLA-C*05 allele are slightly protected against getting multiple sclerosis.

Now that is truly fascinating, because HLA-C produces proteins which act as ligands for immunoglobulin-like receptors on killer cells, a rather curious group of immune cells which are part of the innate immune response, which kicks in rapidly with infections based on recognising generic motifs on bacteria and viruses. 'Natural killer' and 'killer T cells' have yet to find an established role in the pathogenesis of multiple sclerosis. No doubt, someone is beavering away as I write this, working out exactly what is going on in the hope of harnessing the protective effect of HLA-C*05 for therapeutic gain. - **AJC**

Yeo TW, De Jager PL, Gregory SG, Barcellos LF, Walton A, Goris A, Fenoglio C, Ban M, Taylor CJ, Goodman RS, Walsh E, Wolfish CS, Horton R, Traherne J, Beck S, Trowsdale J, Caillier SJ, Iverson AJ, Green T, Pobywajlo S, Lander ES, Pericak-Vance MA, Haines JL, Daly MJ, Oksenberg JR, Hauser SL, Compston A, Hafler DA, Rioux JD, Sawcer S.

A second major histocompatibility complex susceptibility locus for multiple sclerosis.

ANNALS OF NEUROLOGY

2007;61(3):228-36.

HUNTINGTON'S DISEASE: What is it the cause of Huntington's disease?

Huntington's disease is a disorder that is currently attracting a great deal of attention. Whilst the genetic defect of Huntington's disease is well known to be mutant huntingtin, exactly how this interferes with cellular function is currently poorly understood. Joel Perlmutter and colleagues in this recent paper in PNAS has looked at this in vivo, building on the previous post mortem data suggesting that there are oxidative phosphorylation abnormalities in this condition. In this study they took patients with genetically proven HD and age matched controls and used positron emission tomography to look at changes in cerebral oxygen and glucose metabolism. They reported that there was a significant abnormality in the striatum, characteristic of defects in mitochondrial oxidative phosphorylation. This is not that surprising perhaps, except that the abnormalities in the mitochondrial electron transport system may be mediated by astrocytes; thus implying that the neuronal pathology of HD may be secondary to a primary defect in astrocytes! This is an interesting study and obviously raises questions as to how neurons and astrocytes interact in normal brain behaviour and disease. A second paper on Huntington's disease raises interesting questions about what triplet repeat size mediates disease pathogenesis. In this case report in 'Movement disorders', Joseph Jankovic and team report on a patient who developed pathologically proven Huntington's disease with a CAG repeat of only 29. This patient, had clinical manifestations of the disease, and went on to have an autopsy that confirmed the pathology of this condition. Whilst this is only a single case report it does raise interesting issues as to what other factors drive the pathology in HD as only 70% of the variance can be explained by the CAG repeat length. Certainly in this case the patient had clinical and pathological evidence of the disease whilst having what appeared to be a normal CAG repeat length. Exactly what is going on in this case is far from clear but obviously raises many questions about what interacts with the polyglutamine region of the huntingtin protein and how this causes cellular dysfunction and neuronal death and clinical manifestations of the condition. - **RAB**

Powers WJ, Videen TO, Markham J, McGee-Minnich L, Antenor-Dorsey JV, Hershey T, Perlmutter JS.

Selective defect of in vivo glycolysis in early Huntington's disease striatum.

PROC NATL ACAD SCI U S A

2007;104:2945-9.

Kenney C, Powell S, Jankovic J.

Autopsy-proven Huntington's disease with 29 trinucleotide repeats.

MOVEMENT DISORDERS

2007; 22;127-130.

EPILEPSY: Sudden unexplained death

Like all meta-analyses this paper is only as good as its sources and, in this area, quality is very variable, with the definition of SUDEP and case ascertainment being particular difficulties. Papers were included if they met the author's criteria for quality: of 120 papers relating to SUDEP, only 27 fulfilled the authors' criteria for analysis. Those factors previously suspected of conferring a risk of SUDEP were analysed with respect to these papers, including demography, seizure type, associated psychiatric morbidity, treatment and circumstances at time of death. Those which conveyed the greatest risk of SUDEP were: young age (15-30), male sex, the presence of generalised tonic clonic seizures and being in bed. Seizure frequency was not a high risk factor which is surprising but it may be that some patients with low risk seizure types, such as simple partial seizures, had high seizure frequencies. Weak risk factors included prone position, subtherapeutic drug levels, being in the bedroom and sleeping. Why being in bed should carry a high risk but being asleep a low risk is not clear – what were those patients doing? - **MRAM**

Monté CPJA, Arends JBAM, Tan IY, Aldenkramp AP, Limburg M, de Krom.
Sudden unexplained death in epilepsy patients: risk factors. A systematic review.

SEIZURE

2007;16:1-7.

STROKE: Hereditary multi-infarct dementia of Swedish type

When CADASIL was first described as such (Tournier-Lasserre et al., Nature Genetics 1993;3:256-9.), it was noted that prior descriptions of familial disorders characterised by multiple brain infarcts and dementia might also be cases of CADASIL, specifically a Swedish pedigree described under the rubric of 'Hereditary multi-infarct dementia' (Sourander & Wälinder, Acta

Neuropathol 1977;39:247-54.) and a British pedigree described as ‘chronic familial vascular encephalopathy’ (Stevens et al., Lancet 1977;i:1364-5.). In this paper, these families have been subjected to further clinical, neuroradiological, neuropathological and neurogenetic analysis to establish their precise diagnoses. However, beyond the bald statement that patients had “moderate to severe cognitive impairment” no neuropsychological assessment was reported. The British family was found to have a mutation (R141C) in the NOTCH3 gene, confirming the diagnosis of CADASIL. In the Swedish family however, sequencing of the entire 8091 base pair exonic sequence of NOTCH3 identified no pathogenic mutations; nor were there any mutations in the APP gene. Moreover limited haplotype analysis showed no linkage to NOTCH3. Histological analysis of skin biopsy showed no granular osmiophilic material in association with muscle cells, nor was it seen in the brain. Absence of NOTCH3 N-terminal fragment accumulation in the walls of the brain microvasculature was noted on immunocytochemistry of Swedish brain. Hence Swedish MID is not CADASIL, but a novel small vessel disease. -*AJL*
Low WC, Junna M, Borjesson-Hanson A, Morris CM, Moss TH, Stevens DL, St Clair D, Mizuno T, Zhang WW, Mykkanen K, Wahlstrom J, Andersen O, Kalimo H, Viitanen M, Kalaria RN.

Hereditary multi-infarct dementia of the Swedish type is a novel disorder different from NOTCH3 causing CADASIL.

BRAIN

2007;130(2):357-67.

NEUROGENESIS: a happy event or not?

Of late there has been a great deal of interest in the possibility that anti depressants work by increasing neurogenesis in the dentate gyrus of the hippocampus. In a recent paper in PNAS Jennifer Warner-Schmidt and Ronald Duman advance further our understanding of this by suggesting that vascular endothelial growth factor (VEGF) is important in mediating the effects of anti depressants on cell proliferation. Using a number of different strategies they demonstrate that anti depressants can increase hippocampal VEGF expression. They then go on to show that this is responsible for the cell proliferation and mediates the behavioural responses to chronic anti depressant treatment. This is important as anti depressants have traditionally been thought to work by upregulating noradrenaline and serotonin neurotransmission at the synapse. Perhaps changes at the serotonin and noradrenaline synapses mediate changes in VEGF. How this produces an anti depressant effect is still to be worked out but clearly this provides interesting new data on the mechanism of action of anti depressant drugs. In a second paper in the same issue of PNAS, Michael Saxe and colleagues have also attempted to look at hippocampal neurogenesis but this time looking at its effects on behaviour. What they demonstrate is that hippocampal neurogenesis can have different effects on different cognitive tasks depending on the exact paradigm used. The early work by Shors et al suggested that hippocampal neurogenesis was critical for contextual fear conditioning, whereas others have felt it has more to do with spatial learning. In this study the group show young neurons generated through the neurogenic process can have a negative influence on specific forms of working memory. They therefore conclude that a “strategy ... aimed at stimulating hippocampal neurogenesis to elicit antidepressant or pro-cognitive effects will need to strike a fine balance between restoring function and avoiding the potential or negative consequences of an excess in neurogenesis”. It is clear that fine tuning hippocampal neurogenesis is not straightforward and there is the potential that negative outcomes could arise if the system is not properly regulated or manipulated. - *RAB*

Warner-Schmidt JL, Duman RS.

VEGF is an essential mediator of the neurogenic and behavioral actions of antidepressants.

PROC NATL ACAD SCI U S A

2007;104:4647-52.

Saxe MD, Malleret G, Vronskaya S, Mendez I, Garcia AD, Sofroniew MV, Kandel ER, Hen R.

Paradoxical influence of hippocampal neurogenesis of working memory.

PROC NATL ACAD SCI U S A

2007;104:4642-6.

EPILEPSY: in intellectually disabled patients

It is easy to become demoralised when faced with patients with severe disability and awful epilepsy. So here is a study you can view as a ray of hope or a justification of therapeutic nihilism. It is a retrospective, observational study of 550 patients so the usual caveats of this design apply. Seventy-two percent had mild to moderate learning disability and patients were divided into categories according to seizure frequency: seizure-free; >1/year; >1/month; >1/week and >1/day. Moving up to the next best category over the 10 year period of observation was

described as improved and moving up by two categories as strongly improved. In this cohort, 156 patients were seizure-free at the outset and 84% remained seizure-free at ten years. Of those in whom seizures returned, fifteen had >1/year, nine >1/month and one >1/day. Fifty-five percent of patients with seizures were improved (15% strongly improved). This was similar, whether or not patients had a medication change. The greatest improvement was seen in those with the most frequent seizures, perhaps suggesting a natural regression to the mean. There was no relationship between either epilepsy type or degree of intellectual disability and the improvement in epilepsy. Since case ascertainment was retrospective, it is possible that a particular group may have suffered a higher mortality and been selected out of the study – that it’s impossible to determine. The authors go on to discuss different therapeutic regimens. They identified 78 different drug combinations but clearly any conclusions about relative merits – which actually occupies over half the results and discussion – is deeply suspect. So the bottom line is that on balance patients will improve over time, but it is usually nothing to do with anything done by their physician. - *MRAM*

Huber B, Hauser I, Horstmann V, Jokeit G, Liem S, May T, Meinert T, Robertson E, Schorlemmer H, Wagner, W, Seidel M.

Long term course of epilepsy in a large cohort of intellectually disabled patients.

SEIZURE

2007;16:35-42.

REHABILITATION: Robot better than physio...

It is accepted nowadays that task specific repetitive training is beneficial for improving recovery of function after stroke. This is largely based on the results of a high quality meta-analysis of the intensity of treatment that concluded that at least a 16-hour difference in treatment time between experimental and control groups provided in the first six months after stroke is needed to obtain small but significant differences in independence in activities of daily living (ADL) (Kwakkel et al. Stroke 2004;35:2529-36.) This is a lot of extra practice to provide within the constraints of the resources for rehabilitation in the UK. And even if time for extra face-to-face therapy was available therapists often display a low boredom threshold when supervising practice so that the number of repetitions of single tasks would likely remain low. One way to increase repetitive practice is to use assisted technology. This has been demonstrated very successfully in a single blind multicentre RCT of walking training using a mechanical gait-trainer and harness to support the patient. Early treadmill systems with body weight support required lots of effort from one or more therapists to assist in limb positioning during the exercise. Patients using the new mechanical gait trainer were able to practice alone or with a little assistance at first so it has the potential for greater intensity of practice.

Pohl et al have shown the potential in their trial in which 155 stroke patients who needed help to walk, were randomly allocated either to physiotherapy and the gait trainer, or to physiotherapy only. The experimental group received 20 minutes practice in the gait trainer in addition to 25 minutes of physiotherapy that concentrated on standing and walking. The control group received 45 minutes of the standing and walking physiotherapy intervention. The treatments were given five days a week for four weeks. The results were very impressive: At the end of the treatment period 41 of 77 patients in the gait trainer augmented therapy group were walking independently compared with only 17 of the 78 physiotherapy only group. These large differences between groups were also evident in the Barthel (ADL) scores. What’s more the effects were long lasting: at the six month follow up there were 30% more independent walkers in the gait trainer group (54/77) than in the physiotherapy only group (28/78).

The investigators did not count the number of steps made in the physiotherapy only group, but based on the therapists’ estimates of the distances covered, it is thought that patients in the control group rarely exceeded 150-200 steps during their 45 minute sessions. The patients in the gait trainer group practiced between 800 and 1200 steps at each session in addition to the steps taken in their 25 minutes of physiotherapy. It seems likely that the superior outcomes of the experimental group were due to the intensity of practice. It is scandalous that patients are not able to fulfill their potential in our rehabilitation services. Every rehabilitation unit should invest in an electromechanical gait trainer. - *AJT*

Pohl M, Werner C, Holzgraefe M, Kroczeck G, Mehrholz J, Wingendorf I, Hölig G, Koch R, Hesse S.

Repetitive locomotor training and physiotherapy improve walking and basic activities of daily living after stroke: a single blind, randomized multicentre trial (Deutsche GangtrainerStudie, DEGAS).

CLINICAL REHABILITATION

2007;21:17-27.

PARKINSONIAN SYNDROMES: Can the accuracy of diagnosis be improved?

The importance of saccadic eye movements in neurological conditions such as Parkinson's disease has been repeatedly illustrated by various groups over the past decade. PD patients typically present with difficulties in initiating movements which are then executed slowly, especially when these movements are sequential, repetitive or simultaneous. Rivaud-Pechaux et al investigated prosaccades (saccades towards a visual target) and antisaccades (saccades away from a visual target) in three groups of patients with parkinsonian syndromes; Parkinson's disease, corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) as well as in a control group. The authors' primary goal was to demonstrate that in patients with different patterns of neurodegeneration, performances in pro and antisaccades could significantly differ according to the task design. The groups consisted of 12 PSP patients (8 male and 4 female), 8 CBD patients (4 male and 4 female) and 15 PD patients. The control group was made up of 10 individuals with no history of neurological or psychiatric disorders and on no medication. Eye movement recordings were made using a horizontal electro-oculography with red and green LEDs subtending a visual angle of 0.18° and luminance of 5 cd/m². Each recording session did not exceed 40 minutes. The authors used single tasks and mixed tasks of both pro- and antisaccades. CBD patients exhibited the greatest deficits; pro and antisaccade latencies were markedly increased in both single and mixed tasks. When the single tasks were compared with the control group, an increased prosaccade latency was observed in the CBD group only and antisaccade latency was significantly longer in CBD patients than in PSP. For the mixed trials, an increased prosaccade latency was found in the CBD group only and increased antisaccades in both CBD and PSP groups. When compared with the control group, a higher prosaccade error rate was observed in the CBD group and the PD group which was not the case in the PSP group. The authors were not able to define precisely the neural structures involved in oculomotor mixing tasks. However, it pinpointed the profound deficits present in CBD and the different patterns in PSP and PD patients. Thus, such studies may help not only in diagnosing PD and PD plus conditions but may also provide unique insights into decision making processes especially those involved in the control of movement. - CA

Rivaud-Pechoux S, Vidailhet M, Brandel JP, Gaymard B.

Mixing pro and antisaccades in patients with parkinsonian syndromes.

BRAIN

2007;130(Pt 1):256-64.

EPILEPSY: Move over Hughlings Jackson

Like most British neurologists I think of John Hughlings Jackson as the father of modern epileptology; the pictures with a long white beard invest him with the appropriate gravitas to be patriarch of the specialty. But this article suggests that he may have to move over or at least share his pedestal with a relative unknown; a whipper-snapper who worked at Guy's Hospital and in a few short years, from 1869-1874, wrote his ideas on epilepsy before he suddenly dropped dead at the age of 33 in a carriage with his wife at his side. At least he had the decency to have a double-barrelled surname so as not to further debase the history books. Dickson said: "there is ample reason to believe that the seat of intellectual impressions is the surface of the brain" and went on to describe the subtle cognitive phenomena of partial seizures. Taking these two statements together he clearly suggested that focal epilepsy arose from the cerebral cortex and seems to have been the first to move away from the idea of the brainstem as their source. He believed that an alteration in cortical activity produced a release of the striatum, producing the motor activity of grand mal and thus was the first to consider the possibility of a release phenomenon as part of epileptic seizures, a concept later borrowed by Hughlings Jackson. It is clear that the two men knew each other as they had consulted over patients. He also believed in cerebral localisation of function. In 1870 Thompson gave a clear description of Jacksonian (Thompsonian?) seizure progression and in 1872 he wrote: "if the spot on the surface which becomes the seat of the affection should be a centre presiding over a ganglion controlling muscular movement, convulsion or movement in the muscles so deprived of control will occur; but if, on the other hand the spot on the surface not be associated with ganglia controlling muscles, muscular manifestations cannot occur". Perhaps on reflection, the term Jacksonian should be kept, as the poor man not only described the seizures more or less contemporaneously with Dickson but also had the misfortune to see his beloved wife suffer from them before her death in 1876. - MRAM

Eadie M.

The epileptology of John Thompson Dickson (1841-1874).

EPILEPSIA

2007;48:23-30.

MULTIPLE SCLEROSIS: Intravenous stem cells, the new immunotherapy

The great hope of stem cells as therapy is that their capacity for self-renewal and differentiation could be used to repair damaged tissues and restore function. It turns out, though, that this is not how they work in animals with experimental autoimmune encephalomyelitis, an inflammatory disorder of the CNS that poorly models multiple sclerosis in humans. Stefano Pluchino and colleagues in Milan have led the way in this story. Now two other groups have arrived at the same conclusion. Tamir Ben-Hur's team from Hadassah-Hebrew University and Antonio Uccelli's group from Genoa have each studied different stem cells in different situations. Ben-Hur showed that intravenous injection of neural progenitor cells reduced the severity of EAE (the MOG35-55 peptide C57BL/6 mice version) nicely. Uccelli took a slightly different approach: injecting iv bone marrow-derived stem cells into animals with (the SJL/J mice /PLP139-151 version of) EAE. In each case, clinical and pathological disease severity was reduced. The key finding was that both investigators labelled their stem cells with green fluorescent protein and found that... no stem cells were to be found in the brain or spinal cord. Instead, it turns out that these stem cells were treating EAE by downregulating the immune response in the peripheral lymph nodes. The mechanism is not yet worked out fully. But the message is clear: the honeymoon is over and stem cells now have to line up against beta-interferon, Tysabri and the rest as immunotherapies rather than magic healers. I wonder if they will make the cut? - AJC

Gerdoni E, Gallo B, Casazza S, Musio S, Bonanni I, Pedemonte E, Mantegazza R, Frassoni F, Mancardi G, Pedotti R, Uccelli A.

Mesenchymal stem cells effectively modulate pathogenic immune response in experimental autoimmune encephalomyelitis.

ANNALS OF NEUROLOGY

2007 Mar;61(3):219-27.

Einstein O, Fainstein N, Vaknin I, Mizrahi-Kol R, Reihartz E, Grigoriadis N, Lavon I, Baniyash M, Lassmann H, Ben-Hur T.

Neural precursors attenuate autoimmune encephalomyelitis by peripheral immunosuppression.

ANNALS OF NEUROLOGY

2007 Mar;61(3):209-18.

HEADACHE: occipital nerve stimulation

Cluster headache can be horrible. And the chronic form, where over 12 months there is no break of more than a month, is terrible. A proportion of these patients do not respond to medications. In the past, options for them have included just about every sort of lesion of the trigeminal nerve, nervus intermedius or sphenopalatine ganglion. Here, Peter Goadsby's team at Queen Square report their experience of using bilateral occipital nerve stimulation as a treatment over a median of 20 months. Under local, the stimulating wires were placed around the occipital nerves, using induced parasthesiae to confirm correct location; then, under general, the pulse generator was put into an abdominal or subclavicular pocket. The bottom line is that six of eight said their headache was improved and that they would recommend an occipital nerve stimulator to other patients with chronic cluster headache. But there were problems. For instance, a total of eight operations had to be performed after the initial procedure, for electrode migration or the like. And this was an open-label, uncontrolled study..... Nonetheless, this is such a painful condition, any prospect of a useful treatment is worth pursuing.

Burns B, Watkins L, Goadsby PJ.

Treatment of medically intractable cluster headache by occipital nerve stimulation: long-term follow-up of eight patients.

LANCET

2007;369(9567):1099-106.

Calling all Journal Clubs

Would you like to join ACNR's panel of reviewers?
Would your journal club be interested in getting involved, submitting summary and comments on recent papers published in the fields of neurology, neuroscience and rehabilitation?

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Rachael Hansford at ACNR,
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Tel. +44 (0)1747 860168.

2007 Charcot Award: Professor Alastair Compston

Professor Alastair Compston has been awarded the Multiple Sclerosis International Federation's (MSIF) biennial Charcot Award for a lifetime achievement in research into the understanding or treatment of multiple sclerosis.

Professor Compston is Professor of Neurology and Head of the Department of Clinical Neurosciences at the University of Cambridge. Early in his career, Professor Compston studied the genetic epidemiology of MS and the interplay between genes and environmental factors. With others, he characterised the class II HLA association and, in 2001, headed the Genetic Analysis of Multiple Sclerosis in EuropeanS (GAMES) network that was the first to perform a full genome association screen in MS.

In the area of neurobiology, Professor Compston's studies on the mechanisms of



injury and regeneration of oligodendrocytes have made a seminal contribution to the advancement of central nervous system cell repair.

In 1987 he performed the earliest controlled trial showing the efficacy of high dose intravenous methylprednisolone for treating relapses in MS. More recently, one of Professor Compston's major contributions has been in the evaluation of the therapeutic efficacy of CAMPATH-1 in MS with highly promising data in relapsing remitting MS.

Professor Compston has been the clinical lead of the Centre for Brain Repair in Cambridge for over ten years, has authored more than 400 papers, was instrumental in the editing and production of McAlpine's Multiple Sclerosis (1998 & 2005) and is the current editor of the journal Brain.

Med President Erich Reinhardt receives award for his successes in medical engineering

Using modern imaging methods as provided by Siemens Medical Solutions, physicians all over the world are trying to find a cure for diseases like Parkinson's, MS and Alzheimer's. For his extraordinary efforts in this area, Erich Reinhardt, member of the Managing Board of Siemens AG and President and CEO of Siemens Medical Solutions, has been awarded the International Neurobionics Award 2006 by the International Neurobionics Foundation.

Erich R Reinhardt plans to promote young scientists with the €25,000 prize money.

Neurobionics connects neurosciences, biology and applied medical engineering to develop new medical procedures that re-establish



destroyed nerve paths or nerve contacts after illnesses or accidents. The International Neurobionics Foundation provides financial and conceptual support to projects that help people who are blind, deaf or paralysed to fully or partially

regain their lost sense or mobility through the use of modern microchip implantation.

Erich R Reinhardt has been honoured with the international award for his efforts in the area of imaging methods. According to Madjid Samii, President of the Senate of the International Neurobionics Foundation, without these activities the extraordinary recent successes in neurosurgery would not have been possible.

Dot Medical receives Frost & Sullivan Award

Frost & Sullivan, the global growth consulting company, has selected medical device company Medivance Inc, maker of the Arctic Sun® Temperature Management System, as the recipient of its 2006 Product



Differentiation Innovation Award for advancing the European Therapeutic Hypothermia Devices Market.

Medivance designed the Arctic Sun to provide an efficient and precise cooling technology that avoids the risks of invasive approaches to patient temperature management. Clinical evidence suggests that cooling may reduce damage from cardiac arrest, brain injury, stroke, trauma, high fevers and other critical conditions.

The Arctic Sun, distributed and managed in the UK by Dot Medical Ltd, is used in hospi-

tal critical care and emergency departments to precisely control patient temperatures non-invasively. The system was recognised for its role in advancing the practice of therapeutic hypothermia and fever control in Europe. Frost

& Sullivan also cited the Arctic Sun's significantly more efficient control of patient temperature than traditional methods.

Dr Ian Rankin, Managing Director of Dot Medical Ltd, said, "We are absolutely delighted that Medivance are the recipients of this award. Dot Medical has always pioneered innovation in medicine in the UK and the Arctic Sun represents a huge leap forward in the management of therapeutic hypothermia for critical care patients."

For more information visit www.dot-medical.com

2007 Max Planck Research Award: Professor Ray Dolan

Professor Ray Dolan, Director of the Wellcome Trust Centre for Neuroimaging at UCL, is the 2007 recipient of the Max Planck Research Award for his work in neuromodulation and behaviour.



Professor Dolan, Professor of Neuropsychiatry at UCL, is one of the pioneers of modern neurobehavioural research, which uses neuroimaging to examine high-level cognitive processes in the brain and their interaction with emotions and behaviour.

The Alexander von Humboldt Foundation and the Max Planck Society grants the award each year to one international and one German scientist who have achieved international recognition and who are expected to continue to produce outstanding academic achievements through international collaboration with the assistance of the award.

The German Federal Ministry for Education and Research funds both the international and German awards, which are worth €750,000 each. Professor Dolan plans to use the prize money to investigate, together with colleagues in Germany, the neurochemical mechanisms underlying emotional learning and decision making in humans.

We would like to publish more awards and appointments in future issues of ACNR. If you know of someone who should be considered for this feature, please send details to Rachael@acnr.co.uk

Sponsorship opportunities for young MS researchers to work in another country

For further information about the

Multiple Sclerosis International Federation (MSIF)

Du Pré Grants

and

Du Pré Fellowship

go to www.msif.org/en/research/awards or contact Zoe Burr at zoe@msif.org

Du Pré Grants nominations due: 30 July

Du Pré Fellowship nominations due: 30 July

www.msif.org  multiple sclerosis international federation

Flexibility and performance for live cell imaging microscopy

Carl Zeiss UK has launched a new inverted research microscope system in the UK developed to enhance the investigation of processes in living cells. The Axio Observer incorporates a host of features found for the first time on this class of instrument. These advances make it possible not only to observe processes in living cells in unparalleled detail but also to manipulate those processes and analyse the resulting changes.

New, thermally-insulated, high-performance objectives may be specified from the Carl Zeiss LCI Plan-Neofluar and Plan-Apochromat ranges.

Combined with a temperature sensor that is integrated into the culture vessel, the new objectives ensure that the required temperature is controlled accurately and reliably. Users may also specify the innovative LD Plan-Neofluar 20x and 40x phase contrast objectives, which combine positive and negative phase contrast in a single objective to deliver optimum contrasting of all object structures with a single objective.

A range of stackable incubation components has also been designed especially for the Axio Observer. These flex-free devices keep temper-



The Axio Observer microscope provides optimum flexibility for live cell imaging and research.

atures under maximum control while maintaining a clear, unobstructed workspace. Filter sets enable up to 70% higher excitation intensity and up to 50% shorter exposure times while the fast-change 6-position reflector turret enables rapid switching of the filter sets and wavelength during an experiment. All these components are automatically recognised by the Axio Observer's ACR (Automatic Component Recognition) function and integrated into the system configuration.

For more information
E. a.lambert@zeiss.co.uk

The first Molecular Imaging Centre in the UAE

Mubadala Development and Siemens Medical Solutions have agreed on a 16.7 million EUR contract to build and operate a Molecular Imaging Centre (MIC) in Abu Dhabi. This will mean that newest cutting-edge diagnostic technology is then available to patients in this region, mainly providing diagnostic services for oncology, cardiology and neurology. Expected to open in summer 2008, the facility will be the first of its kind in the region.

The centre will be fully equipped with state-of-the-art medical diagnostic equipment for anatomic and functional diagnosis. These include a Siemens PET/CT (a hybrid combining Positron Emission Tomography, PET and Computed Tomography, CT) diagnostic system and a Cyclotron radioisotope delivery system. Images from the PET/CT scanner can be acquired twice as fast as with a traditional separate PET and CT scan – with no loss in the image quality. A comprehensive IT infrastructure powered by the syngo software, developed by Siemens, will allow for seamless data and image integration and exchange across all parts of the MIC and with other clinics worldwide.

For more information contact Siemens on
Tel. +44 (0)1344 396000,
E. medmarketing.med.gb@siemens.com

Stratech Scientific distribute research products from rPeptide



Stratech Scientific now distribute research products (recombinant peptides and proteins, antibodies, reagents) from rPeptide; the market leader in providing products for Alzheimer's and Parkinson's disease research.

rPeptide's proprietary expression platform produces recombinant beta-amyloid (the only company to produce all six isoforms without tags), recombinant synuclein proteins and recombinant tau proteins.

rPeptide also provides a range of custom services from molecular biology, protein expression/purification, to C13 and N15 uniform labelling of peptides and proteins.

For more information about rPeptide and its products, please visit www.stratech.co.uk/rpeptide or Tel. +44 (0)1638 782600.

Betaferon® (interferon beta-1b) goes compact

People using Betaferon® (interferon beta-1b) lie at the heart of the change in the application system being introduced by Schering.

Betaferon will be supplied in compact single-use packs which contain everything needed to make up the solution. In addition, the new application system will come with the needle pre-attached to the vial adapter which means fewer steps in the constitution of Betaferon.

The subcutaneous injection will be administered using the thinnest needle (30G) available in treatment of multiple sclerosis (MS).

The previous autoinjector used with Betaferon has also had a face lift to catch up with the latest advances in technology. BETAJECT Lite, the new autoinjector, has been developed recognising users' changing needs during the course of the condition and will help make injecting easier. The new technology facilitates individual administration of the



drug to hard-to-reach locations and is especially useful for those people who have a fear of injecting themselves, as it injects the needle out of sight into the chosen injection site.

"The new administration system is a very welcome innovation," comments Alex Bracegirdle, MS specialist nurse liaison at Schering. "Having tried the new system myself, it is very convenient and thanks to clear labelling and colour coding it is also user friendly, especially for those who may experience visual disturbances. I am confident that it will be welcomed by Betaferon users and will help them get the best out of their treatment."

People using Betaferon will be trained by their MS specialist nurse and will also be able to benefit from the support offered by the BETAPLUS® nurses, who run a 24/7 support programme for Betaferon users. To register Tel. +44 (0)845 600 1212 or log on to www.betaplus.co.uk

The ABN Coat of Arms

The Association of British Neurologists celebrates its 75th anniversary in 2007. As part of the celebrations, the President and Council decided to petition the College of Arms in London for a grant of heraldic arms. Dr Colin Mumford was nominated by Council to be the representative of the Association in dealings with the heraldic authorities.

The Arms were granted on the 18th January 2007, with the full heraldic achievement including arms, crest and supporters, as well as a badge for the Association. The heraldic description or 'blazon' of arms is traditionally given in a rather archaic unpunctuated mixture of English and Norman French, such that red is designated 'gules', blue as 'azure', green as 'vert', with silver and gold becoming 'argent' and 'or' respectively.

The ABN's new arms are described thus:
 "Per pale gules and azure three chevrons argent over all a pile throughout or on a chief per pale azure and gules three chess rooks or"
 The crest is described: "Out of a crown rayonny or a demi unicorn argent armed maned tufted and unglued or" and the badge: "Within an annulet irradiated a chess rook or."



Colin Mumford with the new ABN Banner.



The Association was honoured by the additional approval and granting of supporters for the arms: "On the dexter a hippocampus azure and on the sinister a hippocampus gules each holding with the tail a Rod of Aesculapius or the serpent vert".

There are numerous allusions to the practice of neurology in the symbolism used. The background colours of red, white and blue refer directly to the British Isles. The main 'heraldic charges' take the form of a golden 'pile' or V-shaped device, overlying three chevrons. This gives a diagrammatic representation of the lower end of the spinal cord and cauda equina. In the top of the shield on a 'chief' the colours are reversed, reflecting pyramidal decussation, and the chief is in turn

charged with three heraldic chess rooks, indicating the intellectual complexity sometimes found in neurological practice.

An heraldic beast, the unicorn, forms the crest. In mythical legend the unicorn carried healing powers in its horn. The unicorn in turn emerges from a 'crown rayonny' which is a crown formed of alternating straight and wavy components, making reference to the EEG, alluding to the familiar 'spike and wave' appearance of certain types of epilepsy.

The same geometric pattern is seen in the 'annulet irradiated' surrounding a single chess rook, which forms the badge of the Association.

Supporting the shield are two sea-horses. The heraldic term for the sea-horse is 'hippocampus', giving an immediate reference to the brain, and held by the two sea-horses are snakes climbing a pole, the well-known Rod of Aesculapius, indicating the practice of medicine in general.

The motto is in Latin: 'Primum Omnium Cerebrum', which might be translated in many different ways. 'Above all, the brain' is perhaps the simplest.

For more information contact
 Colin Mumford,
 E. cmumford@staffmail.ed.ac.uk

Carl Zeiss hosts Alzheimer's rediscovered slides on worldwide web

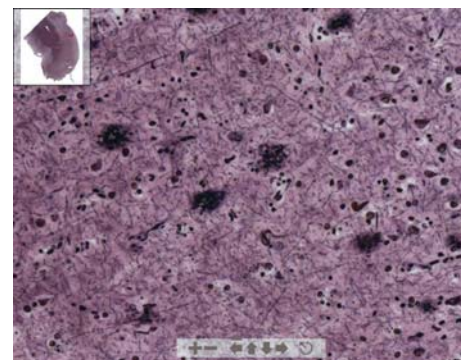
Pathologists from around the world are being offered the opportunity to view in microscopic detail the original research material upon which the discovery of Alzheimer's disease was based, thanks to a website hosted by Carl Zeiss.

In 1906, Alois Alzheimer prepared over 250 slides of human brain tissue from a female patient he had observed closely and published his findings in 1907. That same year he began to treat a male patient and prepared more than 150 slides upon his death in 1910. Both lots of material were re-discovered in basements of the University of Munich after a search organised by Professor Manuel Graeber of Imperial College London. Well preserved and of very high technical quality, all the more than 400 specimens have now been scanned and saved as Virtual Slides using a Zeiss

MIRAX system and are being released to view over the Internet (www.zeiss.de/alzheimer).

Apart from their unique scientific value, the importance of the re-discovery of the slides is that they put an end to lingering doubts about whether Alzheimer's first patient, a 51-year old woman, suffered from a rare metabolic disorder called metachromatic leukodystrophy rather than the disease named after him. However, Graeber says the rediscovered slides show no evidence of this but the cortex does exhibit the two classic pathological signs of Alzheimer's – amyloid plaques and neurofibrillary tangles. Now, thanks to the Zeiss MIRAX digital slide system and the World Wide Web, pathologists will be able to judge for themselves.

For more information E. micro@zeiss.co.uk



Part of Alzheimer's first slide showing the two classic pathological signs of Alzheimer's – amyloid plaques and neurofibrillary tangles.

Digitimer DS5 Stimulator - isolated bipolar computer controlled stimulation



Digitimer announces the launch of the DS5 Bipolar Constant Current Stimulator. The DS5 has been developed in collaboration with Prof Hugh Bostock (Institute of Neurology, London) to facilitate threshold tracking measurements. Although the DS5 has been primarily designed for studies of peripheral nerves, Digitimer hope it will be popular with any researchers who want to safely apply computer controlled constant current stimuli to a subject or patient.

Unlike a traditional 'pulse stimulator', the DS5 produces an isolated constant current stimulus pro-

portional to an input voltage, with the shape of the input waveform describing the stimulus shape. When driven by a suitable computer interface, the DS5 can generate stimuli consisting of sine waves, ramps, square waves or arbitrary waveforms.

The DS5 stimulator has four input voltage ranges, making it widely compatible with other hardware and three stimulus output ranges ($\pm 10\text{mA}$, $\pm 25\text{mA}$ and $\pm 50\text{mA}$).

For more information visit www.digitimer.com or Tel. +44 (0)1707 328347 or E. sales@digitimer.com

Study to investigate 24-hour action and sleep benefits in Parkinson's patients

Parkinson's disease is often regarded as just a motor disease although increasingly it is being recognised that patients also suffer from a number of non-motor symptoms. Among these symptoms are sleep related disturbances such as difficulty getting to sleep and reduced quantity of sleep which can have a significant impact on a patient's quality of life. The frequency and severity of non-motor symptoms has so far been greatly underestimated. Dr Ray Chaudhuri, a Parkinson's expert from the King's College and University Hospital Lewisham in London, estimates that between 50-60 % of Parkinson's patients are affected by sleep problems. Patients may also experience motor problems early in the morning which can have an impact on their ability to start their daily activities. Treating these symptoms with conventional, oral therapies may be difficult since oral therapies require dosing multiple times a day. Neupro® offers a therapeutic option that delivers the active substance over a 24-hour period – thus covering the whole of the day and night with a once-daily application. Neupro® with its active substance rotigotine is a non-ergoline dopamine agonist formulated as a transdermal patch.

The drug is approved both as monotherapy for patients with early-stage Parkinson's disease and in combination with levodopa for the treatment of patients with advanced-stage Parkinson's disease. Studies performed to date indicate that Neupro may be effective at night and in the early morning. "We have conducted rotigotine trials, and the results are very impressive," said Dr Chaudhuri.

These results are now to be corroborated in RECOVER (Randomised Evaluation of the 24-hour-COVERage: Efficacy of Rotigotine), a placebo controlled, double-blind, multi-centre, multinational study. This is the first time that "Sleep and early morning symptoms in Parkinson's patients" have been investigated in a large-scale study. It is also the first time that other, non-motor Parkinson's symptoms are being examined by using a new state-of-the-art diagnostic instrument assessing the full range of non-motor symptoms. The study will enrol more than 330 patients at a ratio of two to one to the rotigotine and the placebo arm, respectively. The principal investigator, Professor Claudia Trenkwalder from the University of Göttingen and Paracelsus-Elena Hospital, Kassel, says that the RECOVER study will include centres in the USA, Europe and Australia.

For more information contact Schwarz Pharma, T. +44 (0)1494 797500.

ABN updates MS guidelines

New guidelines on the use of beta interferon and glatiramer acetate in multiple sclerosis (MS) have recently been published by the ABN, updating guidance last issued in 2001.

It follows the publication of a number of clinical trials^{1,2,3} investigating the use these disease modifying agents in early MS, and the development of new diagnostic criteria⁴ which permit diagnosis of the condition after one clinical episode (clinically isolated syndrome – CIS).

The guidance now includes the option to treat eligible patients with CIS who are diagnosed with MS by the McDonald criteria within one year of presentation.

In addition, patients with active relapsing-remitting disease can now be considered for treatment if there has been a single disabling relapse within the past 12 months – previously, two significant relapses within two years were required.

The full document is available at <http://www.theabn.org/downloads/ABN-MS-Guidelines-2007.pdf>

References

- 1 Kappos et al. *Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes.* Neurology 2006;67:1242-9.
- 2 Jacobs L D et al (2000). *Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis.* The New England Journal of Medicine 2000;343(13):898-904.
- 3 Comi G et al (2000). *Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study.* Lancet 2000;357:1576-82.
- 4 McDonald WI et al. *Recommended diagnostic criteria for Multiple Sclerosis: Guidelines from the international panel on the diagnosis of Multiple Sclerosis.* Ann Neurol 2001;50:121-7.

PRESCRIBING INFORMATION - UK AND IRELAND

Please refer to the Summary of Product Characteristics for further information
REBIF® 8.8 MICROGRAMS AND 22 MICROGRAMS - SOLUTION FOR INJECTION
Interferon beta-1a

Initiation Pack

Presentation Each pre-filled glass syringe contains 8.8 or 22 micrograms of interferon beta-1a in respectively 0.2 or 0.5 ml. **Indication** For the treatment of relapsing multiple sclerosis. Efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapse activity. **Dosage and administration** Treatment should be initiated under supervision of a physician experienced in the treatment of multiple sclerosis. For patients initiating treatment with Rebif®, the dosage recommended for the first month of treatment is 8.8 micrograms three times a week by subcutaneous injection for the first two weeks and 22 micrograms three times a week by subcutaneous injection for the following two weeks. From the fifth week Rebif 44 micrograms should be administered. Limited published data suggest that the safety profile in adolescents from 12 to 16 years of age receiving Rebif 22 micrograms by subcutaneous injection three times per week is similar to that seen in adults. Not to be used in patients under 12 years of age. Evaluate patients at least every second year of treatment period. **Contraindications** History of hypersensitivity to natural or recombinant interferon beta, human albumin, or to any of the excipients; initiation of treatment in pregnancy; current severe depression and/or suicidal ideation. **Precautions** Inform patients of the most common adverse reactions. Symptoms tend to be most prominent at the initiation of therapy and decrease in frequency and severity with continued treatment. Use with caution in patients with previous or current depressive disorders and those with antecedents of suicidal ideation. Patients should be advised to report immediately any symptoms of depression and/or suicidal ideation. Patients exhibiting depression should be monitored closely during therapy and treated appropriately. Cessation of therapy should be considered. Administer with caution to patients with a history of seizures and to those receiving treatment with anti-epileptics, particularly if their epilepsy is not adequately controlled. Patients should use an aseptic injection technique and rotate injection sites to minimise risk of injection site necrosis. Patients with cardiac disease should be closely monitored for worsening of their clinical condition during initiation of therapy. Use with caution in patients with history of significant liver disease, active liver disease, alcohol abuse or increased serum ALT. Serum ALT levels should be monitored prior to the start of therapy, at months 1, 3 and 6 on therapy and periodically thereafter. Stop treatment if icterus or other clinical symptoms of liver dysfunction appear. Treatment has a potential to cause severe liver injury including acute hepatic failure. Laboratory abnormalities are associated with the use of interferons. Liver enzyme and full haematological monitoring are recommended at regular intervals (months 1, 3 and 6 on therapy) and periodically thereafter. New or worsening thyroid abnormalities may occur. Thyroid function testing is recommended at baseline and if abnormal every 6 - 12 months. Administer with caution to and monitor closely patients with severe renal and hepatic failure or patients with severe myelosuppression. Serum neutralising antibodies against interferon beta-1a may develop. The clinical significance of these antibodies has not been fully elucidated but is associated with reduced efficacy. If a patient responds poorly and has neutralising antibodies, reassess treatment. Women of childbearing potential should use effective contraception during treatment. **Side effects** The majority of adverse reactions observed with Interferon beta-1a are usually mild and reversible, and respond well to dose reductions. In case of severe or persistent undesirable effects, the dose of Rebif® may be temporarily lowered or interrupted, at the discretion of the physician. Very common adverse drug reactions (ADRs) are injection site inflammation/reaction, influenza like symptoms, headache, asymptomatic transaminase increase, neutropenia, lymphopenia, leucopenia, thrombocytopenia, anaemia. Common ADRs are injection site pain, myalgia, arthralgia, fatigue, rigors, fever, pruritus, rash, erythematous or maculo-papular rash, diarrhoea, vomiting, nausea, depression and insomnia. Serious AEs are injection site necrosis, hepatitis with or without icterus, severe liver damage, anaphylactic reactions, angioedema, erythema multiforme, erythema multiforme-like skin reactions, seizures, thromboembolic events, suicide attempt. Consult the Summary of Product Characteristics for more information relating to side effects. Additional information is available on request. **Pharmaceutical precautions** Store in a refrigerator at 2°C to 8°C in the original package. Do not freeze. **Legal category** POM **Basic NHS price** Rebif® Initiation Pack containing: Rebif® 8.8 micrograms - solution for injections: 6 pre-filled syringes (0.2 ml) Rebif® 22 micrograms - solution for injections: 6 pre-filled syringes (0.5 ml) £522.24 Prices in Ireland may differ, consult distributors Allphar Services Ltd **Marketing Authorisation Numbers:** EU/1/98/063/007 **Name and Address of Marketing Authorisation Holder** Sero Europe Ltd, 56 Marsh Wall, LONDON E14 9TP **Name and Address of Distributor in UK** Sero Ltd, Bedford Cross, Stanwell Road, Feltham, Middlesex TW14 8NX **Name and Address of Distributor in Ireland** Allphar Services Ltd, Pharmaceutical Agents and Distributors Belgard Road, Tallaght, Dublin 24, Ireland

Date of Preparation: April 2007

Job Bag: REB07-0057

Information about adverse event reporting in the UK can be found at www.yellowcard.gov.uk. In the Republic of Ireland information can be found at www.imb.ie. Adverse events should also be reported to Sero Limited - Tel: +44 (0)20 8818 7373 or email: medinfo.uk@serono.com

Date of Preparation: March 2007

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ABBREVIATED PRESCRIBING INFORMATION

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Please refer to the SmPC before prescribing ARICEPT EVESS 5 mg or ARICEPT EVESS 10 mg. **Indication:** Symptomatic treatment of mild to moderately severe Alzheimer's dementia. **Dose and administration:** Symptomatic treatment of mild to moderately severe Alzheimer's dementia. **Dose and administration:** **Adults/elderly;** 5 mg daily which may be increased to 10 mg once daily after at least one month. Orodispersible tablet which should be placed on the tongue and allowed to disintegrate before swallowing with or without water. Treatment should be initiated and supervised by a physician with experience of Alzheimer's dementia. A caregiver should be available to monitor compliance. Monitor regularly to ensure continued therapeutic benefit, consider discontinuation when evidence of a therapeutic effect ceases. No dose adjustment necessary for patients with renal impairment. Dose escalation, according to tolerability, should be performed in patients with mild to moderate hepatic impairment. **Children;** Not recommended. **Contra-Indications:** Hypersensitivity to donepezil, piperidine derivatives or any excipients used in ARICEPT. **Pregnancy:** Aricept should not be used unless clearly necessary. **Lactation:** Excretion into human breast milk unknown. Women on donepezil should not breast feed. **Warnings and Precautions:** Exaggeration of succinylcholine-type muscle relaxation. Avoid concurrent use of anticholinesterases, cholinergic agonists, cholinergic antagonists. Possibility of vagotonic effect on the heart which may be particularly important with "sick sinus syndrome", and supraventricular conduction conditions. There have been reports of syncope and seizures - in such patients the possibility of heart block or long sinus pauses should be considered. Careful monitoring of patients at risk of ulcer disease including those receiving NSAIDs. Cholinomimetics may cause bladder outflow obstruction. Seizures occur in Alzheimer's disease and cholinomimetics have the potential to cause seizures and they may also have the potential to exacerbate or induce extrapyramidal symptoms. Care in patients suffering from asthma and obstructive pulmonary disease. As with all Alzheimer's patients, ability to drive/operate machinery should be routinely evaluated. No data available for patients with severe

hepatic impairment. **Drug Interactions:** Experience of use with concomitant medications is limited, consider possibility of as yet unknown interactions. Interaction possible with inhibitors or inducers of Cytochrome P450; use such combinations with care. May interfere with anticholinergic agents. Possible synergistic activity with succinylcholine-type muscle relaxants, beta-blockers, cholinergic agents. **Side effects:** Most commonly diarrhoea, muscle cramps, fatigue, nausea, vomiting, and insomnia. Common effects (>1/100, <1/10): common cold, anorexia, hallucinations, agitation, aggressive behaviour, syncope, dizziness, insomnia, diarrhoea, vomiting, nausea, abdominal disturbance, rash, pruritis, muscle cramps, urinary incontinence, headache, fatigue, pain, accident. Uncommon effects (>1/1,000, <1/100): seizure, bradycardia, gastrointestinal haemorrhage, gastric & duodenal ulcers, minor increases in serum creatine kinase. Rare (>1/10,000, <1/1,000): extrapyramidal symptoms, sino-atrial block, atrioventricular block, liver dysfunction including hepatitis. **Presentation and basic NHS cost:** Blister packed in strips of 14. ARICEPT EVESS 5 mg; white, embossed, orodispersible tablets, packs of 28 £63.54. ARICEPT EVESS 10 mg; yellow, embossed, orodispersible tablets, packs of 28 £89.06. **Marketing authorisation numbers:** ARICEPT EVESS 5 mg; PL 10555/0019 ARICEPT EVESS 10 mg; PL 10555/0020. **Marketing authorisation holder:** Eisai Ltd. **Further Information from/Marketed by:** Eisai Ltd, Hammersmith International Centre, 3 Shortlands, London, W6 8EE and Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS. **Legal category:** POM **Date of preparation:** December 2006

Information about adverse event reporting can be found at www.yellowcard.gov.uk
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References: 1. Aricept SmPC 2. Aricept Evess SmPC 3. Rivastigmine SmPC 4. Galantamine SmPC 5. Galantamine XL SmPC 6. Memantine SmPC 7. Data on File Studies 015, 016 and 017 (Eisai Ltd, Pfizer Ltd)

Date of preparation: January 2007
AR1016-AR1984 12-06

