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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION



Included
with this issue:
**The Year in
Parkinson's
disease 2010**

In this issue

David Beeson

– Congenital Myasthenic Syndromes

Sinéad Murphy, Mary Reilly

– Amyloid neuropathies

Rehabilitation – Jose G Romano

– Rehabilitation of Hemianopic Visual Field Defects

Neurosurgery – Sally-Ann Price, Stephen Price, Peter Whitfield

– Low-grade Gliomas

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diagnosed patients

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Prescribing information (Please refer to the Summary of Product Characteristics (SmPC) before prescribing) **Presentation:** Tablets containing 1mg rasagiline (as the mesilate). **Indication:** Treatment of idiopathic Parkinson's disease as monotherapy or as adjunct to levodopa in patients with end of dose fluctuations. **Dosage and administration:** Oral, 1mg once daily taken with or without food and with or without levodopa. **Elderly:** No change in dosage required. **Children and adolescents (<18 years):** Not recommended. **Patients with renal impairment:** No change in dosage required. **Patients with hepatic impairment:** Predominant hepatic metabolism. Do not use in patients with severe impairment. Avoid use in patients with moderate impairment. Use with caution in patients with mild impairment and stop if progresses to moderate. **Overdose:** Symptoms reported following rasagiline overdose (3-100mg) included dysphoria, hypomania, hypertensive crisis and serotonin syndrome. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Do not use in patients with severe hepatic impairment. Co-administration of other monoamine oxidase (MAO) inhibitors is contraindicated due to risk of hypertensive crises. Concomitant pethidine treatment is contraindicated. Allow at least 14 days off rasagiline before using other MAO inhibitors or pethidine. **Special warnings and precautions:** Administer antidepressants with caution as serious adverse reactions have been reported with concomitant use of selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs), tricyclic and tetracyclic antidepressants, and MAO inhibitors. Cases of serotonin syndrome have been reported post-

marketing in patients treated concomitantly with antidepressants/SNRIs and rasagiline. Avoid concomitant use with fluoxetine or fluvoxamine. Leave at least five weeks between discontinuation of fluoxetine and initiation of treatment with rasagiline. Leave at least 14 days between discontinuation of rasagiline and initiation of treatment with fluoxetine or fluvoxamine. Administer potent CYP1A2 inhibitors with caution. Co-administration with dextromethorphan or sympathomimetics not recommended. Avoid use in patients with moderate hepatic impairment. Use caution in patients with mild hepatic impairment. Use with caution in pregnancy or lactation. There is an increased risk of skin cancer in Parkinson's disease, not associated with any particular drug. Suspicious skin lesions require specialist evaluation. Cases of elevated blood pressure have been reported in the post-marketing period, including rare cases of hypertensive crisis associated with the ingestion of unknown amounts of tyramine. **Undesirable effects in clinical trials:** **Monotherapy:** >1%: headache, influenza, skin carcinoma, leucopenia, allergy, depression, hallucinations, conjunctivitis, vertigo, angina pectoris, rhinitis, flatulence, dermatitis, musculoskeletal pain, neck pain, arthritis, urinary urgency, fever, malaise. <1%: decreased appetite, cerebrovascular accident, myocardial infarction, vesiculobullous rash. **Adjunct therapy:** >1%: dyskinesia, decreased appetite, hallucinations, abnormal dreams, dystonia, carpal tunnel syndrome, balance disorder, orthostatic hypotension, abdominal pain, constipation, nausea and vomiting, dry mouth, rash, arthralgia, neck pain, decreased weight, fall. <1%: skin melanoma, confusion, cerebrovascular accident, angina pectoris. **Please refer to the SmPC for the rates of adverse events.** **Basic NHS Price:**

Azilect® (tablets) 1mg x 28 £70.72 **Legal category:** POM **Marketing Authorisation Number:** 1mg tablets (28 pack size) EU/1/04/304/003 **Marketing Authorisation Holder:** Teva Pharma GmbH, Kandelstr 10, D-79199 Kirchzarten Germany **Date last revised:** September 2010. **Further information available from:** Lundbeck Limited, Lundbeck House, Caldecotte Lake Business Park, Caldecotte, Milton Keynes, MK7 8LG

Adverse events should be reported.
Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Teva Pharmaceuticals Ltd on telephone number: 01296 719768.

References:

1. Olanow CW, Rascol O, Hauser R et al. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. *N Engl J Med* 2009; 361: 1268-1278.
2. Stocchi F, Brooks DJ, Melamed E, et al. Effect of rasagiline on severity of OFF in Parkinson's disease. Poster presented at the 58th American Academy of Neurology Annual Meeting, San Diego, California, USA. 2006.
3. Azilect Summary of Product Characteristics. October 2010.

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Professor Hermann Stefan, Germany: Professor of Neurology /Epileptology in the Department of Neurology, University Erlangen-Nürnberg.

Professor Nils Erik Gilhus, Norway: Professor of Neurology at the University of Bergen and Haukeland University Hospital.

Award for Professor Maguire

Professor Eleanor Maguire, Senior Research Fellow in the Wellcome Trust Centre for Neuroimaging, has been awarded the 2011 Feldberg Foundation prize, to facilitate the exchange of scientific knowledge between German and British scientists.

The Feldberg Foundation, a registered German charity, was established in 1961 by Professor Wilhelm Feldberg, CBE, FRS, with the aim of promoting scientific contact between Germany and the UK, particularly between researchers working in the area of physiology, pharmacology and related topics. Each year the foundation awards two prizes, worth €20,000 each, to two scientists, one German and one British.



For more information contact www.ion.ucl.ac.uk

MS myelin repair research set to continue

The MS Society has announced that funding for the second stage of multiple sclerosis research into myelin repair, is to be conducted at the MS Society Cambridge Centre for Myelin Repair. Key results from the first stage of the research were published in the journal *Nature Neuroscience* in December 2010 and found damage to myelin – which results in MS symptoms and long term disability – could be reversed in rats with an MS-like condition.

The groundbreaking findings were led by Professor Robin Franklin and his team at the Cambridge Centre for Myelin Repair, based at the University of Cambridge, who worked in collaboration with scientists based at the MS Society Edinburgh Centre for Translational Research.

The MS Society has committed more than £2 million over the next five years to fund the second stage of the research, which includes plans for a clinical trial. Having found a possible treatment to reverse damage to myelin, the team in Cambridge will now look at:

- testing this potential treatment for its effectiveness and dosage levels
- safety aspects of the potential treatment
- building on recent advances in myelin repair research, making it possible to identify more potential MS treatments in the future

The next stage of the project is due to start in April 2011.

For more information contact the MS Society: T. +44 (0)20 8438 0782
www.mssociety.org.uk/research.

MS Society: Best MS Research of the Year

This category recognises a world class, UK-based MS research project or a researcher, active within MS research in any field, either of which will be of significant benefit to people affected by MS. The judges will be looking for research outcomes and impact as well as good use of resources and budget. In terms of researcher they will be looking for enthusiasm, dedication, details of the individual's objectives and achievements, and indication that they show great promise for the future in MS research.

For more details visit:
www.mssociety.org.uk/about_us/about_our_society/ms_awards/index.html

World's First Basic Research Institute for Childhood Neurological Diseases Opens

Texas Children's Hospital has officially opened the Jan and Dan Duncan Neurological Research Institute (NRI), the world's first basic research institute dedicated to childhood neurological diseases. The NRI aims to increase the pace of discoveries by pioneering a multidisciplinary research approach to the challenge of understanding brain development and function. Because many childhood neurological disorders share common symptoms and characteristics, NRI investigators will work across a spectrum of diseases.

For more information visit: www.nri.texaschildrens.org.



Image: Peter Fraser

*You can't get away from MS,
but you can get away for the day.*

MS can make simple, everyday tasks difficult or impossible. Adding Sativex to existing spasticity treatment can improve symptoms like stiffness and spasm, helping to make daily life easier for people with MS.

Another small victory for Sativex

Instead of leaving the Sativex prescribing information at the foot of the page, we've put it where you can't miss it. Please take a look. After all, these are the crucial details that will help you decide if Sativex can help your MS patients.

Sativex® Oromucosal Spray Prescribing Information (refer to full Summary of Product Characteristics (SmPC) before prescribing). Presentation: 1mL contains: 38-44mg and 35-42mg of two extracts from *Cannabis sativa* L., (Cannabis leaf and flower) corresponding to 27mg delta-9-tetrahydrocannabinol (THC) and 25mg cannabidiol (CBD). Each 100 microlitre spray contains: 2.7mg THC and 2.5mg CBD. **Indication(s):** as add-on treatment, for symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy. **Posology and method of administration:** oromucosal use only. Treatment must be initiated and supervised by a physician with specialist expertise in MS. Direct spray at different sites on the oromucosal surface, changing site for each use of product. May take up to 2 weeks to find optimal dose, review response after 4 weeks of treatment. Re-evaluate long term treatment periodically.

Adults: titration period necessary; number/timing of sprays will vary between patients. Number of sprays increased daily according to SmPC table, up to maximum of 12 sprays per day with minimum 15 minutes between sprays. **Children and adolescents:** not recommended. **Elderly:** no specific studies but CNS side effects may be more likely (see Warnings and precautions) **Significant hepatic or renal impairment:** no specific studies but effects of Sativex may be exaggerated or prolonged. Frequent clinical evaluation recommended. **Contra-indications:** hypersensitivity to cannabinoids or excipients. Breast feeding. Known/suspected history or family history of schizophrenia/other psychotic illness. History of severe personality disorder/other significant psychiatric disorder other than depression due to underlying condition. **Warnings and precautions:** not recommended in patients with serious cardiovascular disease. Caution in patients with history of epilepsy/recurrent seizures. THC and CBD are metabolised in the liver. Several THC metabolites may be psychoactive. Contains approx. 50% v/v ethanol. Risk of falls if spasticity/muscle strength no longer sufficient to maintain posture/gait. CNS side effects e.g. dizziness, somnolence could impact personal safety, e.g. hot food and drink preparation. Theoretical risk of additive effect with muscle-relaxing agents, not seen in clinical trials but warn patients risk of falls may increase. No effect seen on fertility but cannabinoids shown to affect spermatogenesis in animals. Female patients of child-bearing potential/male patients with a partner of child-bearing potential should use reliable contraception. Patients with a history of substance abuse may be more prone to abuse Sativex. Withdrawal symptoms following abrupt withdrawal of long-term Sativex are likely to be limited to transient disturbances of sleep, emotion or appetite. No increase in daily dosage observed in long-term use; self-reported levels of 'intoxication' low; dependence on Sativex unlikely. **Interactions:** no clinically apparent

drug-drug interactions seen. Co-administration with food results in mean increase in C_{max} , AUC and half-life (increase less than between-subject variability in these parameters). Concomitant ketoconazole increases C_{max} and AUC of THC (and primary metabolite) and CBD. Increase less than between-subject variability. Risk of additive sedation and muscle relaxing effects with hypnotics, sedatives and drugs with sedating effects. **Pregnancy and lactation:** do not use in pregnancy unless benefit outweighs potential risks. Do not use if breast feeding. Insufficient experience of effects on reproduction - use reliable contraception during therapy and for 3 months after discontinuation. **Effects on ability to drive and use machines:** do not drive, operate machinery or engage in any hazardous activity if experiencing significant CNS side effects; warn patients may cause loss of consciousness. **Side effects:** very common - dizziness, fatigue; common - anorexia, decreased or increased appetite, depression, disorientation, dissociation, euphoria, amnesia, balance disorder, disturbance in attention, dysarthria, dysgeusia, lethargy, memory impairment, somnolence, blurred vision, vertigo, constipation, diarrhoea, dry mouth, glossodynia, mouth ulceration, nausea, oral discomfort/pain, vomiting, application site pain, asthenia, feeling abnormal/ drunk, malaise, fall; uncommon - hallucination, illusion, paranoia, suicidal ideation, delusional perception, syncope, palpitations, tachycardia, hypertension, pharyngitis, throat irritation, upper abdominal pain, oral mucosal disorders e.g. discolouration, exfoliation, stomatitis, tooth discolouration, application site irritation; unknown frequency - psychiatric symptoms e.g. anxiety and mood changes, transient psychotic reactions, possible leukoplakia (unconfirmed): inspect oral mucosa regularly in long term use.

Prescribers should consult the SmPC for further information on side effects. **Overdose:** symptomatic and supportive treatment required. **Special precautions for storage:** refrigerate (2 to 8°C); once opened refrigeration is unnecessary but do not store above 25°C. **Legal Category:** POM **Package quantities and basic NHS costs:** 3 x 10mL £375.00. **MA holder:** GW Pharma Ltd, Porton Down Science Park, Salisbury, Wiltshire SP4 0JQ **MA number(s):** PL 18024/0009 **Further information available from:** Bayer Schering Pharma, Bayer plc, Bayer House, Strawberry Hill, Newbury, Berkshire RG14 1JA United Kingdom. Telephone: 01635 563000. **Date of preparation:** March 2010.

Sativex® is a registered trademark of GW Pharma Ltd.



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delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)

Congenital myasthenia whilst being rare is nevertheless an important condition which can also tell us much about the structural assembly of the neuromuscular junction or synapse. David Beeson in his lovely review takes us through the major mutations underlying these conditions and how they interact across the pre- and postsynaptic membranes to cause myasthenia. He concludes with a useful discussion on how these conditions can be treated, and where the field is next looking for breakthroughs.

Amyloidosis describes the abnormal deposition of insoluble protein fibrils in a beta-pleated sheet configuration and causes a range of problems in different organs including peripheral nerves (both autonomic and sensorimotor). In their excellent short review Sinéad Murphy and Mary Reilly discuss the acquired and inherited amyloidoses and how they affect the nervous system as well as other organs. This learned account describes not only the clinical features, but the investigation and management of these relatively rare patients as well as taking a peek into the therapeutic future.

Jose Romano in his article for the rehabilitation series takes us through how one can help patients with visual field defects. Often these occur in the context of acute events and then recover, but a significant number of people are left with deficits and this article discusses ways around helping such people compensate for these problems.

If you misread "deer" for "beer" what does that actually mean, how could it come about? Roberto Cubelli and Sergio Della Sala in their article tell us why neuropsychologists are needed and how they can help in the assessment and management of patients with cognitive deficits. This is a thought provoking account which is very helpful, especially to those who look at the neuropsychometric report as something written in a foreign, and not especially useful, language, which tells us nothing beyond what we already know from the scan findings!

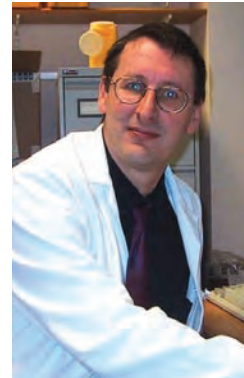
Andrew Larner in his continuing series on Neurological Literature takes Sherlock Holmes as his subject and his involvement with cases of neurological interest. He considers a number of cases including headaches, syncope, catalepsy and in one case he even leaves it up to us to make the diagnoses.

In our Neurosurgery series, Sally-Ann Price and colleagues discuss low grade gliomas, which can present something of a management issue. This is because one has to decide how to best treat them and/or follow their progression, as ultimately they all tend to become more malignant as they accrue genetic abnormalities. This includes a discussion on how to best stage the glioma before considering their optimal treatment and prognosis and concludes with a perspective on the therapeutic future for these tumours.

Heather Angus-Leppan shares the concerns of many over planned changes to the NHS and how this will impact on Neurological clinical practice. This article highlights some of the many contradictions that exist in our current health care service and the increasing confusion that this will cause GPs as they try to balance their accounts with clinical care.

Thrombolysis for stroke is now a widely available treatment, the introduction of which has implications for neurology trainees as Rose Bosnell and Chrissie Burness discuss in their contribution to the ABNT section of ACNR.

Finally we have our usual series of reviews. Sadly though, I have to announce that both Andrew Larner and David Burn have decided to step down as Book review and Conference review editors respectively. They have done this job for 10 years with great energy and purpose, and I would like to thank them on your behalf for all that they have done to make this part of ACNR such a great success. Rhys Davies has kindly taken over as the new Book Review editor, and we are currently seeking to fill the Conference reviews editorship position. Please feel free to contact me with your nominations for this role, or to volunteer yourself. ♦



Roger Barker, Co-Editor.

*Roger Barker, Co-Editor,
Email. Rachael@acnr.co.uk*

Life with epilepsy can be much more than just a gap between seizures

It's hard to live life to the full if part of you is always expecting the next seizure. VIMPAT® is an anti-epileptic drug with an innovative mode of action.^{1,2} In clinical trials, VIMPAT® has shown improved seizure control when added to first and second generation AEDs.³ Prescribe VIMPAT® when you want your patients to look forward with the confidence of additional seizure control.^{1,3}


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PRESCRIBING INFORMATION (Please consult the Summary of Product Characteristics (SPC) before prescribing.) **Vimpat® Lacosamide Active Ingredient:** Tablets: lacosamide 50 mg, 100 mg, 150 mg and 200 mg. Syrup: lacosamide 15 mg/ml. **Solution for infusion:** lacosamide 10 mg/ml. **Indication:** Vimpat is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older. **Dosage and Administration:** Adults and adolescents from 16 years: Recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after 1 week. Maximum daily dose of 400 mg (in two 200 mg doses). **Solution for infusion:** Infused over a period of 15 to 60 minutes twice daily. Can be administered i.v. without further dilution. **Elderly:** No dose reduction necessary. Age associated decreased renal clearance with an increase in AUC levels should be considered. **Paediatric patients:** Not recommended. **Patients with renal impairment:** No dose adjustment necessary in mild and moderate renal impairment. Dose adjustment is recommended for patients with severe renal impairment and patients with end-stage renal disease (see SPC). Dose titration should be performed with caution. **Patients with hepatic impairment:** No dose adjustment needed in mild to moderate impairment. In accordance with current clinical practice, if Vimpat has to be discontinued, it is recommended this be done gradually (e.g. taper the daily dose by 200 mg/week). **Contraindications, Warnings, etc:** Contraindications:

Hypersensitivity to lacosamide or to any of the excipients. Known second- or third-degree atrioventricular block. In addition for tablets, hypersensitivity to peanuts or soya. **Precautions:** Lacosamide has been associated with dizziness. Use with caution in patients with known conduction problems, severe cardiac disease or in elderly. Excipients in the syrup may cause allergic reactions (possibly delayed), should not be taken by those with fructose intolerance and may be harmful to patients with phenylketonuria. Monitor patients for signs of suicidal ideation and behaviours. Advise patients and carers to seek medical advice should such signs emerge. **Interactions:** Prolongations in PR interval with lacosamide have been observed in clinical studies. Use with caution in patients treated with products associated with PR prolongation and those treated with class I antiarrhythmic drugs. Strong enzyme inducers such as rifampicin or St John's Wort may moderately reduce the systemic exposure of lacosamide. No significant effect on plasma concentrations of carbamazepine and valproic acid. Lacosamide plasma concentrations were not affected by carbamazepine and valproic acid. No clinically relevant interaction with ethinylestradiol and levonorgestrel. No effect on pharmacokinetics of digoxin. **Pregnancy and Lactation:** Should not be used during pregnancy. For precautionary measures, breast feeding should be discontinued during treatment with lacosamide. **Driving etc.:** Patients are advised not to drive a car or operate other potentially hazardous machinery until they are familiar with the effects of Vimpat on their ability to perform such activities. **Adverse Effects:** Very common (≥10%): Dizziness, headache, diplopia, nausea. Common (between 1%-10%): Depression, balance disorder, abnormal coordination,

memory impairment, cognitive disorder, somnolence, tremor, nystagmus, blurred vision, vertigo, vomiting, constipation, flatulence, pruritus, gait disturbance, asthenia, fatigue, fall, skin laceration. Adverse reactions associated with PR prolongation may occur. Consult SPC in relation to other side effects. **Pharmaceutical Precautions:** Tablets: None. Syrup: Do not store above 30°C. Use within 4 weeks of first opening. **Solution for infusion:** Do not store above 25°C. Use immediately. **Legal Category:** POM. **Marketing Authorisation Number(s):** 50 mg x 14 tabs: EU/1/08/470/001; 100 mg x 14 tabs: EU/1/08/470/004; 100 mg x 56 tabs: EU/1/08/470/005; 150 mg x 14 tabs: EU/1/08/470/007; 150 mg x 56 tabs: EU/1/08/470/008; 200 mg x 56 tabs: EU/1/08/470/011; Syrup (15 mg/ml) x 200 ml: EU/1/08/470/014; Solution for Infusion (10 mg/ml) x 20 ml: EU/1/08/470/016. **NHS Cost:** 50 mg x 14 tabs: £10.81; 100 mg x 14 tabs: £21.62; 100 mg x 56 tabs: £86.50; 150 mg x 14 tabs: £32.44; 150 mg x 56 tabs: £129.74; 200 mg x 56 tabs: £144.16; Syrup (15 mg/ml) x 200 ml: £38.61; Solution for Infusion (10 mg/ml) x 20 ml: £29.70. **Marketing Authorisation Holder:** UCB Pharma SA, Allée de la Recherche 60, B-1070 Bruxelles, Belgium. **Further information is available from:** UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire, SL1 3WE. Tel: 01753 534655. Fax: 01753 536632. Email: medicalinformationuk@ucb.com. **Date of Revision:** 01/2010 (10VPE0010). Vimpat is a registered trademark. **References:** 1. Vimpat Summary of Product Characteristics, 2010. 2. Beyreuther BK et al. CNS Drug Rev 2007; 13(1): 21-42. 3. UCB Data on file. **Date of preparation:** June 2010. 10VPE0137



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CONTENTS

MARCH/APRIL 2011

03 Awards & Appointments

06 From the Editor...

Review Article

10 Congenital Myasthenic Syndromes
David Beeson

Review Article

16 Amyloid neuropathies
Sinéad Murphy, Mary Reilly

Neuroliterature

20 Sherlock Holmes and Neurology
Andrew Larner

Book Reviews

23 Long-Term Management of Dementia;
Motor Neuron Disease. A Practical Manual

Neurosurgery

24 Low-grade Gliomas
Sally-Ann Price, Stephen Price, Peter Whitfield

Rehabilitation Article

31 Rehabilitation of Hemianopic Visual Field Defects
Jose G Romano

Association of British Neurologists

34 NHS 'Reforms': Right Care or Destruction?
Heather Angus-Leppan

Association of British Neurologists Trainees

35 Neurology Trainees Thrombolysis Survey
Rose Bosnell, Chrissie Burness

Clinical Dilemmas in Neuropsychiatry

36 The Purposes of Neuropsychological Assessment and How to Achieve Them
Roberto Cubelli, Sergio Della Sala

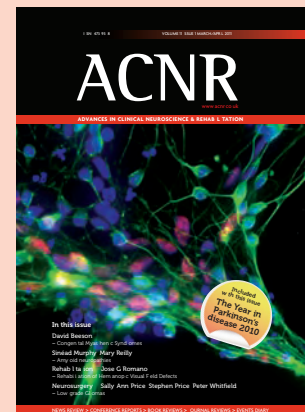
Regulars

38 Events Diary

39 Conference News

47 Journal Reviews

51 News Review



Cover picture: Motor neurons derived from human iPSC cells, courtesy of Prof Siddharthan Chandran, Bilada Bilican and Andrea Serio, University of Edinburgh.

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Congenital Myasthenic Syndromes



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Over the last 15 years there has been a rapid advance of our understanding of the congenital myasthenic syndromes (CMS).¹ These are disorders of neuromuscular transmission characterised by fatiguable muscle weakness that is usually apparent at birth, but presentation is not uncommon in early childhood, adolescence or adulthood.

There is wide variation in disease severity even for patients that harbour the same mutations, but the clinical features often reflect the underlying disease mechanism, thus careful clinical examination can often provide clear pointers both to the syndrome and the particular gene involved. To date, mutations in at least 12 different genes have been shown to cause CMS, although for two genes, *SCN4A* and *LAMB2*, there has only been a single case report. In the UK population the known CMS genes account for around 80% of clinically definite cases and it is likely that mutations at further, and as yet unidentified, gene loci are responsible for the remaining 20%. Analysis of the genetically confirmed cases diagnosed through the Oxford CMS service (Table 1) shows that acetylcholine receptor (AChR) deficiency due to mutations in the ϵ -subunit (*CHRNE*) is the most common of the CMS but that also mutations in *RAPSN* and *DOK7* make up major components of the total.

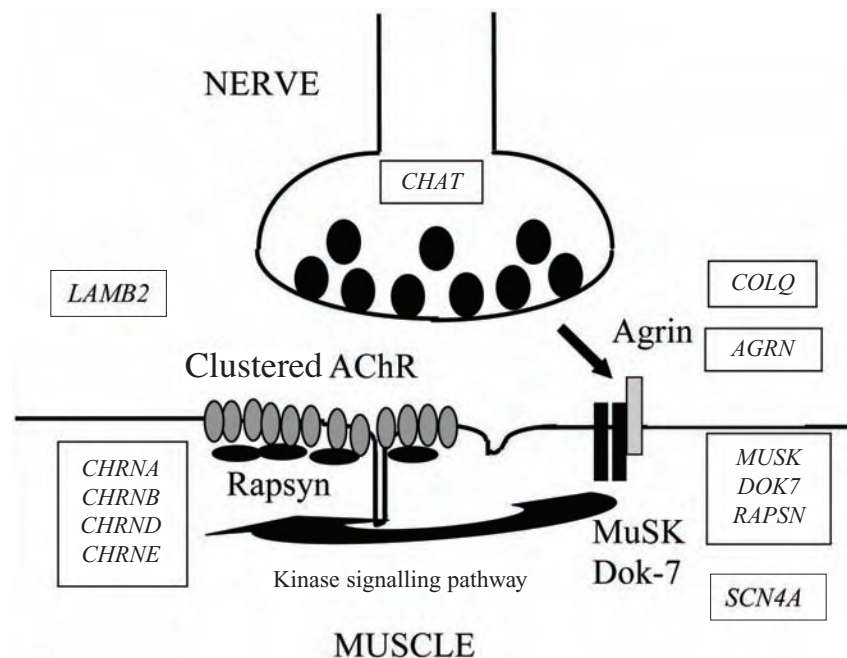
Previously it was postulated that aberrant function of a number of proteins in the

Table 1: Frequency of the different forms of congenital myasthenic syndromes in studies in Oxford.

Syndrome	Kinships
AChR deficiency (<i>CHRNE</i>)	114
AChR deficiency (<i>RAPSN</i>)	63
CMS with proximal weakness (<i>DOK7</i>)	62
Slow channel (<i>CHRNA/B/D/E</i>)	25
Fast channel (<i>CHRNA/D/E</i>)	14
AChE deficiency (<i>COLQ</i>)	15
Presynaptic (<i>CHAT</i>)	8

agrin/muscle-specific kinase (MuSK) pathway (outlined in Figure 1) which determines the formation and stability of the neuromuscular synapse could underlie disorders of neuromuscular transmission.² In this pathway agrin is released from the presynaptic nerve terminal and activates MuSK via the low density lipoprotein-related receptor 4 (LRP4). Activation of the cytoplasmic kinase domain of MuSK is amplified by Dok-7 and through kinase signalling results in the developmental specialisation and maintenance of the postsynaptic apparatus. An important component of this process is the aggregation of the AChR in the postsynaptic membrane beneath the motor nerve terminal

Figure 1: Diagram illustrating the 'core pathway' that is responsible for forming and maintaining the neuromuscular synapse. MuSK, Muscle-specific tyrosine kinase; Dok-7, downstream of kinase 7; LRP4, low density lipoprotein receptor-related protein 4; rapsyn, receptor associated protein of the synapse. Genes that have been associated with CMS are shown boxed.



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through interaction with AChR-clustering protein Rapsyn. With the exception of LRP4, mutations in each of these components have now been reported to underlie CMS.

Mutations in the AChR subunits

Mutations of the AChR are still found to be the most common cause of the CMS. They can be subdivided into AChR deficiency syndromes in which defective neuromuscular transmission is caused by a reduction in the number of receptors on the postsynaptic membrane, and syndromes involving ion channel function (the slow channel and fast channel syndromes) in which the abnormalities lie in the length of time that the channels are activated. The slow channel syndromes are due to gain of function mutations that prolong the ion channel activations and thus show dominant inheritance, whereas the fast channel mutations cause a loss of function due to abnormally brief channel activations and show recessive inheritance.¹ In most cases of fast channel syndromes the 'fast channel' mutation is accompanied by a second 'loss of function' mutation such as a null mutation of the AChR ϵ -subunit.¹ The great majority of mutations that cause the recessive AChR deficiency syndromes are located at the CHRNE locus with many causing a frameshift in the translation that leads to a non-functioning ϵ -subunit. In these cases residual expression of the foetal form of the AChR in which the γ subunit replaces the ϵ -subunit within the AChR pentamer, allows for survival of the patient, albeit with reduced AChR numbers at the endplates.

Mutations of the AChR clustering pathway

The DOK-7 synaptopathy

The two most common gene loci for CMS in this pathway are *DOK7* and *RAPSN*, each of which underlie about 20% of cases seen in the UK. *Dok7* binds to MuSK, and through mechanisms that have not yet been fully elucidated is thought to amplify the signalling from MuSK that governs both the formation of the neuromuscular synapse and also maintaining its structure once formed. Mice with *DOK7* 'knocked out' die at birth due to respiratory failure which underlines the vital role played by this protein.³ The syndrome caused by *DOK7* mutations is characterised by a limb-girdle pattern of muscle weakness with proximal muscles usually more affected than distal.⁴ Children most frequently have normal

initial motor milestones but then will develop a waddling gait and have frequent falls shortly after learning to walk. Ptosis is often present and both stridor and respiratory problems may occur at birth or in early infancy, but eye movements are minimally affected if at all. In many of the older cases wasting of the tongue is observed. Bulbar problems often develop later than limb weakness. Fluctuation in symptoms is common, and in many cases a previous diagnosis of unspecified congenital myopathy has previously been suggested. As with other CMS there is remarkable variation in disease severity. Patients may have symptoms at birth, or in some cases onset only occurs in adolescence or later.⁵

Studies of motor endplate muscle biopsies from patients harbouring mutations in the *DOK7* gene found that the endplates were small but the crucial endplate proteins were present at normal density and the AChR had normal kinetic properties. Thus, it appears that the *DOK7* mutations impair both the maturation and the maintenance of normal synaptic structure and so has been termed a synaptopathy.⁴ It may be that remodelling of the endplate structures continues to occur on an ongoing basis when the *DOK7* mutations are present.⁶ The reasons why the disorder has its predominant effect on proximal muscle groups have yet to be determined.

Mutations in RAPSN

The final steps in the aggregation of AChR at the motor endplates are thought to involve interaction with the clustering protein *Rapsyn*. Mutations in this protein cause a deficiency of AChR at the endplate.⁷ Onset of symptoms is usually at birth, 'early onset', although occasional 'late onset' cases presenting from early adulthood through to middle age have been reported. Early onset cases are frequently associated with hypotonia, marked bulbar dysfunction often necessitating nasogastric feeding, and may require assisted ventilation. Mild facial malformation, a high arched palate and joint contractures of hands and ankles are common. In childhood the course of disease is associated with severe exacerbations often presenting with life-threatening respiratory failure. Patients tend to improve over time and in many cases in adulthood disability is minimal. Weakness of ankle dorsiflexion tends to be maintained into adult life and may provide a clue for diagnosis.⁸

The overwhelming majority of patients harbour the missense mutation N88K on at least one allele, suggesting an original founder

mutation. In cell culture experiments, rapsyn-N88K was able to mediate agrin-induced AChR clusters but these clusters were found to be less stable than clusters formed with wild type rapsyn. Thus, it may be that in patients with the N88K mutation AChR deficiency is due to instability of the endplate rapsyn-N88K/AChR clusters. Not all patients with AChR deficiency harbour N88K. Rare cases have been reported where patients have other mutations in the coding region that result in partially functional rapsyn and a number of cases have been identified with mutations in the promoter region of the *RAPSN* gene. Of interest is a missense mutation in the AChR δ -subunit gene, δ E381K, that does not affect AChR function but rather impairs rapsyn-induced AChR clustering.⁹ The patient phenotype bears the hallmarks of a 'rapsyn deficiency' rather than an AChR-subunit deficiency and so may shed light on the molecular basis for AChR-rapsyn interaction.

Additional genes in the clustering pathway

Two other key proteins in this pathway, MuSK¹⁰ and agrin,¹¹ have also been shown to harbour mutations that can cause CMS. Mutations in these two genes are far less common than in *DOK7* and *RAPSN* and so, as yet, it is difficult to get a common phenotypic picture. However, it does appear that they share some of the features of CMS due to *DOK7* mutations rather than CMS due to *RAPSN* mutation which is consistent with the conjunction of agrin, musk and DOK-7 within the clustering pathway.

Treatment choice depends on molecular mechanism

An understanding of the molecular mechanisms that underlie each of the different types of CMS enables treatments to be tailored to the individual. In CMS where mutations reduce active signal transmission such as AChR deficiency, the fast channel syndrome, *RAPSN* CMS or *CHAT* CMS patients respond to cholinesterase inhibitors or increased neurotransmitter release of 3,4-diaminopyridine (3,4-DAP). However, for *CHAT* mutations activity-dependent weakness is thought to result from the inability to re-synthesise ACh sufficiently fast to fully replenish the pre-synaptic vesicles. If this is correct then 3,4-DAP should be used with caution since it could potentially exacerbate depletion of the pre-synaptic ACh.

For the slow channel syndrome the prolonged ion channel activations can be

An understanding of the molecular mechanisms that underlies each of the different types of CMS enables treatments to be tailored to the individual



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REVIEW ARTICLE

curtailed by drugs that block the AChR ion channel when in an open state, so called 'open channel' blockers. Both fluoxetine and quinidine sulphate have been used successfully, though both can have side effects.¹²

For reasons not yet clearly understood ephedrine or salbutamol (which work in a similar way as β 2-adrenergic receptor agonists) are proving to be effective for the forms of CMS that affect MuSK signalling. Thus *DOK7* CMS responds well to this treatment¹³ and in the few reported cases of mutations in *MuSK* and *agrin* these drugs appear to be similarly beneficial. Finally, patients with mutations in *COLQ* that underlie a deficiency of acetylcholinesterase at the motor endplate also show a beneficial response to ephedrine. Of note, there are reports that *ColQ* may interact with MuSK at the neuromuscular junction. It may be that stimulation of β 2-adrenergic receptors is able to partially stabilise the endplate region for patients with either *DOK7* or *COLQ* mutations. By contrast with the almost immediate response seen for cholinesterase inhibitors, the beneficial effects of ephedrine and salbutamol tend to build over a period of time and improvement may continue for up to six months after starting treatment.

Summary

Disorders of neuromuscular transmission can be caused by impaired function in a series of different proteins, some of which have still not been identified. Defects are present both in proteins associated with the signal transfer itself and in proteins that govern synaptic structure. The disorders can be partially mitigated with treatments, but the challenge remains to make these both more specific and more effective. ♦

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for allele HLA-B*1502 in individuals of Han Chinese and Thai origin as this has been shown to be strongly associated with the risk of developing Stevens-Johnson syndrome (SJS) when treated with carbamazepine. Examine serum sodium levels in patients with pre-existing renal disease or who are treated with medicinal products which may lead to hyponatraemia or if clinical signs of hyponatraemia occur. Discontinue if clinically relevant hyponatraemia develops. Do not use in primary generalised seizures. Prolongations in PR interval have been observed. Caution in patients with medical conditions or when taking concomitant medicinal products associated with PR prolongation. Monitor for signs of suicidal ideation and behaviours. **Drug interactions:** Has an inducing effect on the metabolism of medicinal products mainly eliminated by CYP3A4 or UDP-glucuronyl transferases, therefore the dose of these products may need to be increased when used concomitantly with Zebinix. May take 2 to 3 weeks to reach the new level of enzyme activity when initiating, discontinuing or changing dose, therefore take time delay into account when using with other medicines that require dose adjustment. Interactions can arise when co-administering high doses with medicinal products that are mainly metabolised by CYP2C19. Carbamazepine: Zebinix dose may need to be increased if used concomitantly with carbamazepine. Concomitant treatment with carbamazepine increased the risk of the diplopia, abnormal coordination and dizziness. An increase in other adverse reactions cannot be excluded. Phenytoin: An increase of Zebinix dose and a decrease of phenytoin dose may be required. Lamotrigine and topiramate: No dose adjustments are required. Valproate and levetiracetam: Concomitant administration appeared not to affect the exposure to eslicarbazepine but has not been verified by conventional interaction studies. Oral contraceptives: Interacts with the oral contraceptive. Simvastatin: An increase of the simvastatin dose may be required when used concomitantly with Zebinix. Warfarin: Can decrease exposure to S-warfarin. No effects on R-warfarin

or coagulation. Monitoring of INR should be performed in the first weeks after initiation or ending concomitant treatment. Digoxin: no effect. MAOIs: an interaction between eslicarbazepine acetate and MAOIs is theoretically possible. **Side effects:** Adverse reactions were usually mild to moderate in intensity and occurred predominantly during the first weeks of treatment with Zebinix. Refer to SPC for all side effects. Very common effects (≥1/10): dizziness, somnolence. Common effects (≥1/100, <1/10): Headache, abnormal coordination, disturbance in attention, tremor, diplopia, vision blurred, vertigo, nausea, vomiting, diarrhoea, rash, fatigue, gait disturbance. Serious side effects: hypersensitivity, hyponatraemia, dehydration, grand mal convulsion, ocular hyperaemia, palpitations, bradycardia, hypertension, hypotension, epistaxis, liver disorder, drug toxicity, poisoning. Some rare adverse reactions such as bone marrow depression, anaphylactic reactions, severe cutaneous reactions (e.g. Stevens-Johnson Syndrome), systemic lupus erythematosus or serious cardiac arrhythmias did not occur during clinical studies. However, they have been reported with oxcarbazepine and their occurrence during treatment with Zebinix cannot be excluded. **Legal category:** POM. **Basic UK NHS cost:** Zebinix 800 mg; pack of 30 £154.20. **Marketing authorisation numbers:** EU/1/09/514/012-020. **Marketing authorisation holder:** Bial-Portela & C^a, S.A. À Av. da Siderurgia Nacional 4745-457 S. Mamede do Coronado – Portugal. **Further information from:** Eisai Limited, European Knowledge Centre, Mosquito Way, Hatfield, Herts, AL10 9SN, UK. **Date of preparation:** December 2010

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Amyloid neuropathies



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Amyloidosis is a heterogeneous disease with many different clinical manifestations, occurring as a result of the deposition of insoluble protein fibrils which disrupt normal tissue structure. Over 25 proteins have been described that form amyloid, but only some are deposited in peripheral nerves. Progressive neuropathy is a common feature of familial amyloid polyneuropathy (FAP) and monoclonal immunoglobulin light-chain (AL) amyloidosis. Neuropathy is not a major feature of reactive AA amyloidosis, β 2-microglobulin amyloidosis or other types of amyloidosis. For classification of systemic amyloidosis, see Table.

Monoclonal immunoglobulin light-chain (AL) amyloidosis

This is the most common form of systemic amyloidosis. All patients have an underlying clonal B-cell dyscrasia; 10-20% meet criteria for multiple myeloma. Fibrils are derived from the variable region of lambda light chains in 75% and kappa chains in the remainder.

Clinical features

The mean age of onset is 65 years; AL amyloidosis rarely presents before 40 years. Two-thirds of patients are male.¹ Macroglossia and periorbital ecchymoses are pathognomonic but occur in a minority of patients. Other clinical features include carpal tunnel syndrome (CTS), sensory-motor axonal neuropathy with autonomic involvement, nephropathy and cardiomyopathy.² Symptoms of peripheral neuropathy typically start with small fibre symptoms such as unpleasant sensory symptoms including pain; progressive sensory loss and motor weakness occur later. Autonomic symptoms include nausea and vomiting, nocturnal diarrhoea, postural lightheadedness and erectile dysfunction.³ Non-specific systemic features such as fatigue and weight loss are common.

Differential diagnosis

Small fibre neuropathies are a common reason for referral to neurologists; often idiopathic, the most frequent association is with abnormal glucose metabolism including diabetes and impaired glucose tolerance. These symptoms may be indistinguishable from the early symptoms of amyloid neuropathy. The symptoms which should alert the neurologist to a possible diagnosis of amyloid include autonomic symptoms, new cardiac symptoms, the presence of a paraprotein or the rapid progression of the neuropathy to involve large fibres. If there is a family history of cardiomyopathy, pacemaker insertion or neuropathy, inherited amyloid neuropathy should be considered (see below).

Diagnosis

Biopsy

A tissue diagnosis is essential in all forms of amyloidosis. Rectal or abdominal fat biopsy may be performed; however, in a patient presenting with neuropathy nerve biopsy is often performed directly. Because of the patchy nature of amyloid, a negative

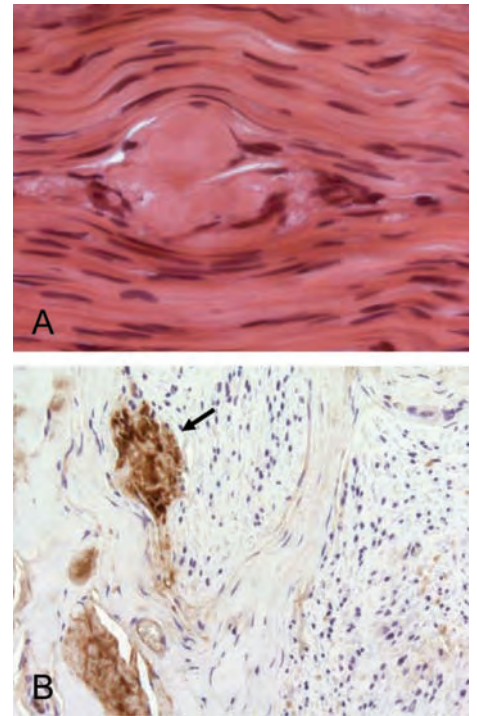


Figure: Sural nerve biopsy of a patient with IgM lambda light chain amyloidosis. (A) Longitudinal section of sural nerve demonstrating deposition of amyloid causing structural displacement of the nerve fibres (H&E stain). (B) Immunohistochemical staining demonstrates the presence of Ig lambda light chains in the endoneurium (arrow). (Figures kindly supplied by Prof S Brandner).

biopsy does not rule out amyloidosis. If clinical suspicion is high, repeat nerve biopsy or biopsy of another affected tissue should be undertaken. Histological examination after Congo red staining demonstrates green birefringence when viewed under polarised light. Immunohistochemical staining confirms the presence of λ or κ light chains (Figure) but is not 100% sensitive.

Other investigations

Nerve conduction studies (NCS) typically show an axonal length-dependent peripheral neuropathy which is sensory more than motor. There is often superimposed CTS.^{2,3} Electromyography (EMG) may demonstrate acute and chronic denervation with reinnervation. In the early stages of disease, NCS may be normal but quantitative sensory testing may demonstrate a small fibre neuropathy.³

All patients with suspected amyloidosis should have serum and urine protein electrophoresis, immunoglobulins, immunofixation and light chains checked. A monoclonal protein is detectable in the serum or urine in 90%, two-thirds have a light-chain present. However, because monoclonal gammopathies occur not uncommonly in the general population, the detection of a paraprotein in a patient with amyloidosis must be interpreted cautiously; one study found that 10% of patients with suspected AL amyloidosis had an inherited form.⁴ Bone marrow biopsy typically contains a population of monoclonal plasma cells expressing λ or κ light chains. N-terminal



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at risk of metabolic acidosis. If metabolic acidosis develops and persists, consider reducing the dose, discontinuing or alkali treatment. Use with caution in patients treated with carbonic anhydrase inhibitors, e.g. topiramate. Decreased sweating, elevated body temperature and heat stroke have been reported. Patients should maintain hydration and avoid excessive temperatures. Monitor pancreatic lipase and amylase levels in patients taking Zonegran who develop clinical signs and symptoms of pancreatitis, consider discontinuation. In cases of severe muscle pain/weakness with or without fever, assess markers of muscle damage and consider discontinuation. Zonegran 100 mg capsules contain E110. Caution in patients less than 40 kg. In patients with weight loss consider dietary supplement, increased food intake or discontinuation. **Drug interactions:** No clinically relevant pharmacokinetic effects on carbamazepine, lamotrigine, phenytoin, sodium valproate, oral contraceptives (ethinylestradiol or norethisterone). Insufficient data with carbonic anhydrase inhibitors, e.g. topiramate. Zonegran was not affected by lamotrigine or CYP3A4 inhibitors. Caution with drugs which are P-gp substrates. Avoid concomitant administration with drugs causing urolithiasis. Zonisamide is metabolised partly by CYP3A4, N-acetyl-transferases and conjugation with glucuronic acid; therefore caution with substances that can induce or inhibit these enzymes. **Side effects:** Most common adverse reactions in controlled adjunctive-therapy studies were somnolence, dizziness and anorexia. Refer to SPC for all side effects. Very common effects (≥1/10): anorexia, agitation, irritability, confusional state, depression, ataxia, dizziness, memory impairment, somnolence, diplopia, decreased bicarbonate. Common effects (≥1/100, <1/10): ecchymosis, hypersensitivity, affect

lability, anxiety, insomnia, psychotic disorder, bradyphrenia, disturbance in attention, nystagmus, paraesthesia, speech disorder, tremor, abdominal pain, constipation, diarrhoea, dyspepsia, nausea, rash, nephrolithiasis, fatigue, influenza-like illness, pyrexia, weight decreased. Serious effects: pneumonia, suicidal attempt, convulsion, cholecystitis, calculus urinary. Isolated cases of Sudden Unexplained Death in Epilepsy Patients (SUDEP). Post-marketing data suggests patients aged ≥65 years report a higher frequency of Stevens-Johnson syndrome and Drug Induced Hypersensitivity syndrome. **Legal category:** POM. **Basic UK NHS cost:** Zonegran 25 mg: packs of 14 £8.82, Zonegran 50 mg: packs of 56 £47.04, Zonegran 100 mg: packs of 56 £62.72. **Irish price to wholesaler:** Zonegran 25 mg: packs of 14 €9.20, Zonegran 50 mg: packs of 56 €48.78, Zonegran 100 mg: packs of 56 €65.18. **Marketing authorisation numbers:** Zonegran 25 mg 14 capsules: EU/1/04/307/001, Zonegran 50 mg 56 capsules: EU/1/04/307/003, Zonegran 100 mg 56 capsules: EU/1/04/307/004. **Marketing authorisation holder:** Eisai Ltd. **Further information from/Marketed by:** Eisai Ltd, European Knowledge Centre, Mosquito Way, Hatfield, Hertfordshire, AL10 9SN. **Date of preparation:** Jan 2011

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Table 1: Classification of the systemic amyloidoses

	Type	Disease	Phenotype	Protein	
Inherited	Neuropathic	Transthyretin- related FAP	Sensory-motor and autonomic neuropathy, vitreous deposits, CTS, cardiomyopathy	TTR	
		ApoAI-related FAP	Sensory-motor neuropathy, nephropathy, gastric ulcers	Apo AI	
		Gelsolin-related FAP	Cranial neuropathies, corneal lattice dystrophy, CTS	Gelsolin	
	Cerebral	Alzheimer's disease type 1	Dementia	APP	
		Alzheimer's disease type 3	Dementia	Presenilin 1	
		Alzheimer's disease type 4	Dementia	Presenilin 2	
		Hereditary cerebral haemorrhage (Dutch type)	Cerebral haemorrhage	APP	
		Cystatin C amyloidosis (Icelandic type)	Cerebral haemorrhage	Cystatin C	
		Familial British dementia	Dementia, spasticity, ataxia, cataracts	BRI	
		Familial Danish dementia	Dementia, spasticity, ataxia, hearing loss	BRI	
Non-neuropathic	Fibrinogen A α -associated amyloidosis	Nephropathy, petechiae	Fibrinogen A α		
		Lysozyme associated amyloidosis	Nephropathy	Lysozyme	
	Familial Mediterranean fever	Nephropathy, periodic fever, peritonitis	Pyrin		
		Apo AII amyloidosis	Nephropathy, gastrointestinal haemorrhage	Apolipoprotein A-II	
	Acquired	Primary	Monoclonal immunoglobulin light-chain AL amyloidosis	Nephropathy, cardiomyopathy, neuropathy, CTS, hepatomegaly, macroglossia	AL
			Secondary	Reactive AA amyloidosis	Nephropathy, diarrhoea, malabsorption, hepatomegaly
			β 2 microglobulin associated amyloidosis (dialysis associated)	CTS, bone cysts, spondyloarthropathy, pathological fractures	β 2 microglobulin
	Age-related	Senile systemic (cardiac) amyloidosis	Cardiomyopathy, intra-cardiac thrombus	Wild-type TTR	

Abbreviations: TTR = transthyretin; FAP = familial amyloid polyneuropathy; CTS = carpal tunnel syndrome; ApoAI = apolipoprotein AI; APP = amyloid precursor protein; BRI = integral member protein 2B; AL = light chain; AA = serum amyloid A;

pro-brain natriuretic peptide (NT-proBNP) and troponin are useful to screen for cardiac involvement; a staging system using these biomarkers guides prognosis.⁵ Skeletal survey is performed to investigate for myeloma lesions. Renal function is assessed, including measurement of proteinuria. SAP scintigraphy may be performed to demonstrate radiolabelled serum amyloid P. This is useful to monitor visceral amyloid load and response to treatment but does not differentiate between different forms of amyloid. Sensitivity is ~90% for AL amyloid; however, SAP scans do not reliably demonstrate peripheral nerve or cardiac involvement.⁶

Cardiac dysfunction is a major cause of morbidity and mortality. Echocardiography in patients with cardiac amyloid deposition demonstrates thickened ventricular walls and interventricular septum and a granular myocardium. A characteristic finding is preserved wall motion at the left ventricular apex with hypokinesis in basal and midsections.⁷ Electrocardiogram shows low voltage in limb leads and conduction block.

Management

Specific treatment

Several treatment regimens are available to suppress light chain production. High dose

melfalan with autologous stem-cell transplantation (HDM/SCT) is first line in selected patients. Monthly cycles of oral melfalan with dexamethasone may be considered for high risk patients.⁸ Alternatives include bortezomib- or lenalidomide-based options. For patients with single organ involvement solid organ transplantation may be used.⁹

Supportive management

Management of patients with amyloidosis requires a multi-disciplinary approach. Wearing pressure stockings and judicious use of drugs like midodrine and fludrocortisone may help orthostasis. Eating small meals often helps nausea and anti-diarrhoeal medication may be required. Drugs for erectile dysfunction may be appropriate in some cases. Cardiac pacing may be required for arrhythmia. Medication for neuropathic pain is frequently required.

Prognosis

Survival is variable depending on organ involvement; the presence of congestive cardiac failure at diagnosis significantly reduces survival.^{5,10} Survival has been significantly improved by the use of chemotherapy and SCT, with complete response rates ranging from 32-79% and responders surviving >4 years.⁹

Inherited amyloid neuropathies

Transthyretin (TTR)-related FAP

TTR-related FAP is the commonest form of inherited amyloid neuropathy. TTR is a protein which transports thyroxine and retinol; circulating as a tetramer of four identical non-covalently associated subunits. The liver is the major producer of TTR; however, small amounts are synthesised by the retina and choroid plexus.

Genetics of TTR-related FAP

Over 100 mutations have been described in the TTR gene associated with TTR-related FAP. TTR-related FAP is dominantly inherited; however, variable penetrance means that patients may not have an obvious family history. The same mutation has different penetrance and age at onset in different populations. The most common mutation, Val30Met, presents in the second/third decade in Portuguese patients with a high penetrance,¹¹ but presents later (sixth decade) in Swedish patients with lower penetrance.¹² In patients with Irish ancestry, the Thr60Ala mutation is the most prevalent; presenting in the sixth/seventh decade.¹³ Recessive mutations have been described in TTR, without a more severe clinical phenotype.

Clinical features

CTS is often the initial symptom and may predate other symptoms by many years. Patients subsequently develop a small-fibre neuropathic syndrome with prominent pain which progresses relatively rapidly. As the disease progresses pain gives way to numbness, and large fibre involvement becomes apparent with a progressive sensory-motor neuropathy. Autonomic dysfunction including orthostatic hypotension, alternating diarrhoea and constipation, urinary incontinence and impotence are prominent later symptoms. Diarrhoea also results from amyloid deposition in the gastrointestinal tract. Cardiac involvement is common. Other features include vitreous deposits and, less commonly, nephropathy and leptomeningeal involvement. Cachexia is a common late feature of the disease. Mean survival in untreated patients is approximately 10 years from symptom onset.

ApoA1-related FAP

ApoA1 is the main protein in high-density lipoprotein, secreted by the liver and intestine, and catabolised by the kidneys. The classical presentation of ApoA1-related FAP is with proteinuria and hypertension with slow progression of renal failure. Patients often have extensive visceral amyloid deposits with hepatosplenomegaly. A sensory-motor neuropathy with autonomic involvement may occur. There is a high incidence of nephropathy and gastric ulcers.

Gelsolin-related FAP

Gelsolin-related FAP occurs as a result of mutant gelsolin fragments being deposited as amyloid fibrils. Although originally and still most commonly described in Finland, it has subsequently been reported in European, American and Japanese families. The clinical features are of corneal lattice dystrophy producing corneal clouding (often the first sign of disease in the fourth decade), cutis laxa and cranial neuropathies. Facial weakness occurs, affecting the forehead first. Cranial nerves VIII, IX and XII are involved later with development of bulbar weakness. CTS is common; although peripheral neuropathy may occur it is not a prominent feature and is predominantly sensory. Autonomic dysfunction rarely occurs.

Diagnosis

Neurophysiology

TTR- and ApoA1-related FAP typically demonstrate a length-dependent sensory-motor axonal neuropathy although in TTR-related FAP patchy slowing of motor conduction can be seen leading in some instances to an erroneous diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).¹⁴ In gelsolin-related FAP NCS may be normal other than showing evidence of CTS or mild reduction in sensory amplitudes; however, EMG may show denervation in facial and bulbar muscles.

Biopsy

Nerve biopsy is often used in patients presenting with a neuropathy to obtain a tissue diagnosis although, as for AL amyloidosis, other tissues including rectum, abdominal fat or heart can be biopsied. The histopathological features of FAP on nerve biopsy are similar to AL amyloidosis, with amyloid deposited in the endoneurium, epineurium and surrounding vessels. Immunolabelling with specific antibodies should be performed to confirm the amyloid type.

Genetic testing

Direct DNA sequencing of the relevant gene should be performed. Predictive testing of family members and prenatal or pre-implantation genetic diagnoses are possible.

Other findings

SAP scintigraphy has a much lower sensitivity (48%) for FAP than for AA or AL amyloid.⁶ Gadolinium-enhanced MRI of the brain and cord should be performed if leptomeningeal amyloidosis is suspected. Ophthalmological assessment should be performed to look for evidence of lattice corneal dystrophy in gelsolin-related FAP and for vitreous deposits in TTR-related FAP.

Treatment

General measures

Supportive management, including management of neuropathic pain and cardiac complications, with multi-disciplinary input as for AL amyloidosis is appropriate for patients with FAP. Carpal tunnel release may be appropriate

for symptomatic CTS; if necessary, the flexor retinaculum may be biopsied perioperatively to confirm the presence of amyloid. Vitrectomy may be performed for vitreous deposits.

Specific treatment

The only specific treatment for TTR-related FAP is orthotopic liver transplantation to remove the source of abnormal TTR production. Severe peripheral neuropathy and significant autonomic neuropathy are relative contraindications and many patients (especially older patients) are too unwell to tolerate major surgery by the time of diagnosis. Patients with the Val30Met mutation benefit most from liver transplantation. With non-Val30Met TTR mutations, especially Thr60Ala, cardiomyopathy may progress rapidly after liver transplantation due to continued deposition of wild-type TTR on mutant TTR already laid down; patients with these mutations who have evidence of cardiomyopathy are generally not offered liver transplantation. Because the liver is otherwise healthy, the removed liver may be transplanted into a patient with end-stage liver disease (domino liver transplant).

Patients with ApoA1-related FAP may be offered kidney or combined heart and kidney transplant as end-stage renal failure is usually the predominant feature. Liver transplantation has been performed in occasional patients with some success.¹⁵ There is no specific therapy for gelsolin-related FAP other than corneal transplant for lattice dystrophy; plastic surgery may be required for facial weakness.

Future directions

Advances have been made in understanding the pathogenesis and improving outcome for patients with amyloidoses. Trials are underway of medications that inhibit fibrillogenesis and enhance regression of SAP as well as that of a chimeric antibody which enhances clearance of amyloid fibrils. Several trials are ongoing comparing different chemotherapeutic/SCT regimens for treatment of AL amyloidosis. Diflunisal, a drug that stabilises amyloid precursor protein, is already used by patients with TTR-related FAP not suitable for liver transplant (evidence of efficacy awaited). Publication of reports on a similar drug, tafamidis, is awaited. ♦

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Neurological literature: Sherlock Holmes and Neurology

Much has been written and committed to film, both motion picture and television, on the subject of Sherlock Holmes and it is not my intention to weary the reader with a further long exposition on Holmesian methods of deduction (recently adduced to the service of evidence-based medicine¹), but merely to point out a few possible encounters of the great man with subjects of neurological interest as attested to in the canon.² Of course, some of these may reflect upon the medical experiences of his creator, Dr Arthur Conan Doyle (1869-1930), or his mentor and the so-called forerunner of Sherlock Holmes, Dr Joseph Bell (1837-1911),³ or even possibly of the writer of the stories, Dr John H. Watson, MD, a veteran of Afghanistan who sometimes observes people with a "surgical eye" (1041). Some Holmesian examples of neurological illness have previously been documented by Westmoreland & Key.⁴

Headache and facial pain

Conan Doyle suffered from neuralgia from boyhood, apparently so much so that the editors of his collected letters omit examples for "fear of exhausting the reader's patience".⁵ In a fictionalised account of parts of Conan Doyle's life, Jean Leckie, the woman who was to become his second wife, is said to suffer from migraines.⁶ It might therefore be anticipated that headache and/or neuralgia would feature in Holmes's experiences, but Westmoreland & Key make no mention of headache, unless it be adumbrated by their category of "simulated condition".

In fact, only four references to headache have been noted (269,463,839,1115), two of which at least are certainly spurious, being used as excuses: for example, in *The Adventure of the Speckled Band*, Holmes advises Miss Stoner to confine herself to her room on the pretence of a headache in order to facilitate giving a nocturnal signal which is material to the apprehension of the criminal (269). McMurdo in *The Valley of Fear* develops headache as a consequence of excessive drink (839).

Altered states of consciousness

There are plenty of examples of "brain fever" and/or delirium. An episode of the former is central to the plot of *The Naval Treaty*, and an episode also occurs in *The Adventure of the Cardboard Box*. Delirium is mentioned on several occasions (e.g. 56,759,797), rather than the once alluded to by Westmoreland & Key,⁴ often in the context of fever. Most celebratedly, Holmes himself



Sherlock Holmes by Sidney Paget (1860-1908).

feigns delirium, sufficient to deceive even the medical gaze of Watson, to ensnare the criminal in *The Adventure of the Dying Detective* (935). Syncopal episodes are also encountered (929), for example, two in quick succession in *The Adventure of the Devil's Foot*:

...the doctor was as white as a sheet. Indeed, he fell into a chair in a sort of faint...(959)
She had fainted with horror upon entering the room...and seeing that dreadful company around the table (959).

Both these phenomena are occasioned by seeing two brothers, "the senses stricken clean out of them" (957), and their dead sister. The brothers are described as "demented" (957), apparently acutely, necessitating transfer to an asylum (959).

A toxic cause is eventually found responsible for all these events.

Movement disorders

In *The Sign of Four*, Thaddeus Sholto is reported thus:

He writhed his hands together as he stood, and his features were in a perpetual jerk – now smiling, now scowling, but never for an instance in repose (100).
Mr Thaddeus Sholto ... sat twitching on his luxurious settee (105).

In addition to these apparently involuntary movements, Sholto has a peculiar physiognomy: he is a "small man with a very high head, a bristle of red hair all round the fringe of it, and a bald shining scalp...In spite of his obtrusive baldness he gave the impression of youth" (100).

It would be interesting to know if his identical twin brother, Bartholomew, had a similar movement disorder, but he is only encountered in



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RRMS: relapsing–remitting multiple sclerosis. DMD: disease-modifying drug. sc: subcutaneous. tiw: three times weekly. im: intramuscular. qw: once weekly.

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Efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapse activity. **Dosage and administration** Initiate under supervision of a physician experienced in the treatment of multiple sclerosis. Administer by subcutaneous injection. Recommended dose: Weeks 1 and 2: 8.8µg three times per week (TIW); weeks 3 and 4: 22µg TIW; week 5 onwards: 44µg TIW (22µg TIW if patients cannot tolerate higher dose). RebiDose pre-filled pen is for single use and should only be used following adequate training of the patient and/or carer. Follow the instructions provided in the package leaflet. Rebif solution for injection in cartridge is for multidose use and should only be used with the RebiSmart autoinjector device following adequate training of the patient and/or carer. Follow the instructions provided with the RebiSmart device. Limited published data suggest that the safety profile in adolescents aged 12–16 years receiving Rebif 22µg TIW is similar to that in adults. Do not use in patients under 12 years of age. Prior to injection and for 24h afterwards, an antipyretic analgesic is advised to decrease flu-like symptoms. Evaluate patients at least every second year of the treatment period. **Contraindications** History of hypersensitivity to natural or recombinant interferon beta, or to any of the excipients; treatment initiation in pregnancy; current severe depression and/or suicidal ideation. **Precautions** Inform patients of most common adverse reactions. Use with caution in patients with previous or current depressive disorders and those with antecedents of suicidal ideation. Advise patients to report immediately any symptoms of depression and/or suicidal ideation. Closely monitor patients exhibiting depression and treat appropriately. Consider cessation of therapy. Administer with caution in patients with a history of seizures and those receiving anti-epileptics, particularly if epilepsy is not adequately controlled. Closely monitor patients with cardiac disease for worsening of their condition during initiation of therapy. Patients should use an aseptic injection technique and rotate injection sites to minimise risk of injection site necrosis. If breaks in skin occur, patients should consult their doctor before continuing injections. If multiple lesions occur, discontinue Rebif until healed. Use with caution in patients with history of significant liver disease, active liver disease, alcohol abuse or increased serum ALT. Monitor serum ALT prior to the start of therapy, at months 1, 3 and 6 and periodically thereafter. Stop treatment if icterus or symptoms of liver dysfunction appear. Treatment has potential to cause severe liver injury including acute hepatic failure. Full haematological monitoring is recommended at months 1, 3 and 6 and periodically thereafter. All monitoring should be more frequent when initiating Rebif 44µg. New or worsening thyroid abnormalities may occur. Thyroid function testing is recommended at baseline and if abnormal every 6–12 months. Use with caution in, and closely monitor patients with, severe renal and hepatic failure or severe myelosuppression. Serum neutralising antibodies may develop and are associated with reduced efficacy. If a patient responds poorly and has neutralising antibodies, reassess treatment. Use with caution in patients receiving medicines with a narrow therapeutic index cleared by cytochrome P450. Women of childbearing potential should use effective contraception. Limited data suggest a possible increased risk of spontaneous abortion. During lactation, either discontinue Rebif or nursing. 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Date of Preparation: August 2010

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death: his “features were set...in a horrible smile, a fixed and unnatural grin” (109). Holmes identifies this as an “extreme contraction, far exceeding the usual rigor mortis” and quizzes Watson as to what “this Hippocratic smile, or risus sardonicus” might suggest about the cause of death.

In *The Greek Interpreter*, a character called Wilson Kemp has involuntary movements:

“...his lips and eyelids were continually twitching like a man with St. Vitus’s dance. I could not help thinking that his strange, catchy little laugh was also a symptom of some nervous malady” (441).

As with Sholto, I leave it to movement disorders experts to diagnose the case!

Catalepsy

Perhaps the most celebrated neurological episode in the Holmes canon occurs in *The Resident Patient*, which features a “Russian Nobleman” reported to have catalepsy who visits Dr Percy Trevelyan, who has a particular interest in this condition. An attack occurs during their consultation, which Trevelyan describes thus to Holmes and Watson:

Suddenly, however, as I sat writing, he ceased to give any answer at all to my inquiries, and on my turning towards him I was shocked to see that he was sitting bolt upright in his chair, staring at me with a perfectly blank and rigid face. He was again in the grip of his mysterious malady (427).

Holmes is unimpressed, later telling Watson: “It is a very easy complaint to imitate. I have done it myself” (430).

Two very distinguished neurologists, Robin Howard and Hugh Willison, have already written a seminal paper on this topic⁷ which renders all further comment superfluous, in which they suggest that the model for Dr Percy Trevelyan was in fact Sir William Gowers (1845–1915), one of the most famous of Queen Square neurologists.⁸

Conclusion

To my reading, it seems that Conan Doyle uses neurological illness in the Sherlock Holmes stories as no more than a convenient literary device. Detailed clinical description, which one might have supposed to be at Conan Doyle’s disposal based on his clinical experience, is not in evidence, precluding detailed retrospective clinical diagnosis (perhaps just as well, some might think).

As for the suggestion of Holmes *qua* neurologist,⁹ one imagines he would be easily capable of acquiring the detailed knowledge required, but I fear that, being a man of his (Victorian) age, he wouldn’t pass the first hurdle into medical school today, based on statements such as this one:

It is of the first importance not to allow your judgement to be biased by personal qualities. A client to me is a mere unit, a factor in a problem. The emotional qualities are antagonistic to clear reasoning (96). ♦

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Long-Term Management of Dementia

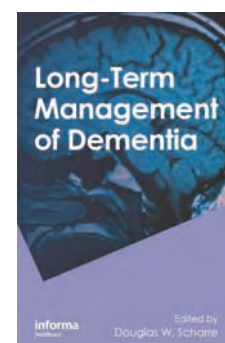
How should dementia best be managed? As the local implementation of the 2009 National Dementia Strategy in England continues to be debated, aided not only by the recent publication by the new government of updated implementation guidance but also, in this period of economic retrenchment, by the QIPPs (Quality Innovation Productivity Prevention) programme, perhaps this US text might provide some helpful insights.

There are chapters on epidemi-

ology (a superb overview), diagnosis, pharmacotherapy of cognition, behaviour management (principally focused on the evidence base for pharmacotherapeutic interventions), management of instrumental and basic activities of daily living, and financial decision making (much wise advice in these chapters), ethical and legal issues, and caregiver stress. There is also a chapter on the role of the primary care physician in dementia management, which seems to envisage a broader role than that

undertaken by UK general practitioners in dementia diagnosis.

Although from the US perspective, much that is written here has transatlantic relevance or resonance. As the broad spectrum of topics covered shows, dementia impacts on all aspects of life in ways which many other conditions do not, and hence devising comprehensive protocols for management which are applicable to all patients at all stages of disease remains a significant, and perhaps ultimately, unanswerable, challenge. ♦



Reviewed by:
AJ Larner, Cognitive Function Clinic, WCNN, Liverpool, UK.

Editor: Scharre DW. Published by: Informa, 2011. ISBN: 9780849338533. Price: £75.00.

Motor Neuron Disease. A Practical Manual

This 200-odd page pocket-sized book provides the reader with a brief overview of different aspects of motor neurone disease (MND).

The first chapter gives a summary of various aspects of the disease, ranging from why 'neuron' is spelt without an 'e' despite the book being written by UK authors, to the epidemiology, neuropathology, and possible mechanisms of the disease. While these topics are understandably not covered in exhaustive detail, it provides MND and non-MND experts with a quick run-through of the salient aspects of the disease.

The second and third chapters are on the diagnosis and natural history of the disease respectively. While the El Escorial criteria for the diagnosis of MND are discussed, there is no mention of the more recently proposed Awaji criteria - a comparison of the differences between these two would have been useful. The authors suggest that 'it would be exceptional to make a diagnosis of MND without performing imaging', which I do not entirely agree with as MND is predominantly a clinical diagnosis, as the authors themselves acknowledge, and can often be confirmed by neurophysiology. The natural history chapter examines the

different disease presentations and phenotypes and is succinctly informative.

The fourth chapter goes into how MND care best involves a multidisciplinary approach and the personnel involved in this process. The next chapter looks at the different measurement methods of MND. The self-administered revised ALS Functional Rating Scale developed by Mitsumoto's group would have been useful to mention as it can be of practical use in MND clinics. I am less certain on the usefulness of the relatively long discussions on the use of neurophysiology and imaging as tools for assessing disease progression as these are not sufficiently well-developed for clinical use at present. The sixth chapter gives a nice overview of the genetics of MND, with several illustrations, the family tree and a table of genetic loci of familial MND.

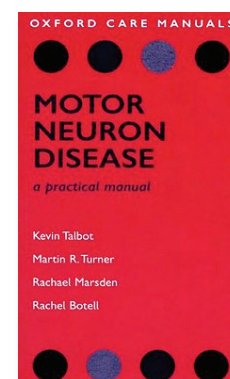
The next five chapters deal with the management of MND, concentrating on potential disease-modifying therapies, symptom management (including respiratory symptoms), nutrition and disability. These chapters go into some detail on the aforementioned issues and provide the reader with quick accessible information, for example the benefits, complications

and timing of starting of artificial nutrition. The information in these chapters is useful for the myriad of different healthcare professionals involved in the care of MND patients, ranging from the doctor to the therapists.

Chapter twelve is a practically useful chapter dealing with end-of-life issues. It highlights the Mental Capacity Act 2005 and the area of advance decisions to refuse treatment which are important in terminally ill patients. Chapter thirteen provides a brief overview on aspects affecting the carers and families of MND sufferers. It provides some useful contact information, including that of the MND Association. There is also an appendix of internet-based sources for patients and professionals.

Chapter fourteen discusses briefly other motor neuron disorders, but in the context of this book being a practical manual of MND is not particularly useful or relevant.

This book is a useful addition to the vast array of neurological books already in the market, not for its size, but for its conciseness. While several minor improvements can be made, the book is largely successful in achieving its aim of being a practical manual. ♦



Reviewed by:
S Sathasivam, Walton Centre NHS Foundation Trust, Liverpool, UK.

This book is a useful addition to the vast array of neurological books already in the market, not for its size, but for its conciseness

Authors: Talbot K, Turner MR, Marsden R, Botell R. Published by: Oxford University Press, 2011. ISBN: ISBN 9780199547364. Price: £22.95



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Low-grade Gliomas

Low grade glioma is an uncommon diagnosis. Patients are younger than those with high grade glioma and most commonly present with seizures. The diagnostic modality of choice is MRI. There is a significant risk of dedifferentiation of residual LGG to higher grade secondary to accumulation of genetic alterations. Whilst many patients in low risk prognostic groups remain stable for years, the median survival is in the region of ten years. Clinical, radiological and pathological prognostic factors have been identified. Management is carried out under the auspices of an MDT. Surgery currently remains the mainstay of treatment with a trend to aim for gross total resection in suitable patients. Surveillance alone or biopsy and subsequent surveillance have a role to play in some cases. Various adjuncts are available, but radiotherapy may be best reserved for high risk patients or until there is evidence of tumour progression. Future advances may eventually be able to justify the "benign" nature implied by the term "low-grade" glioma.

Introduction

The first reported glioma resection was performed in London, by Sir Rickham Godlee, in 1884, after a physician colleague, Dr Alexander Hughes Bennett, correctly surmised that a 25-year-old man with seizures and progressive left hemiparesis must have a right-sided cortical tumour.^{1,2,3}

Although primary central nervous system neoplasms represent 2% of all cancers, intrinsic low grade gliomas (LGG) are uncommon, representing 15% of this total. The incidence is about 1 in 100,000 per year and they present at a younger age than high grade gliomas, most commonly at age 30-40.^{1,4,5} Like the higher grade gliomas (HGG), there is a slightly increased incidence in males.

Presentation

80% of LGG typically present with seizures.^{1,5,6} Frequently these can be resistant to drug therapy.^{1,5} Increased availability of imaging has resulted in more "incidental" findings. Although patients appear neurologically intact, neuropsychology assessments reveal abnormalities in 91% of patients.⁷ These neurocognitive deficits affect quality of life. Large lesions may present with symptoms of raised intracranial pressure (ICP) or focal neurological deficit, though new presentation of these symptoms in a previously known lesion may be a harbinger of progression and/or transformation.

Investigation

Conventionally these lesions have been diagnosed and investigated using computed tomography (CT) and magnetic resonance imaging (MRI). CT demonstrates an area of hypodensity, but tumours may be difficult to detect or substantially larger than visualised, often being near iso-dense. Calcification may be seen in 20% of diffuse astrocytomas and 40% of oligodendrogliomas. On MRI, low-grade gliomas usually appear as low signal on T1 weighted imaging and a well-defined area of high signal on T2, often with a more extensive abnormality than seen on CT. See Figure 1. FLAIR sequences attenuate the signal from CSF and can better define peri-ventricular lesions. Typically, in contrast to high grade gliomas, there is little mass effect and little surrounding vasogenic oedema. The specificity and sensitivity of contrast enhancement, as an indication of high tumour grade, is poor: 20-60% of grade I-II oligodendrogliomas enhance. Conversely, anaplastic astrocytomas (WHO grade III lesions) fail to enhance in 31-54% of cases,⁸ as do even 4% of glioblastomas (WHO grade IV).¹ Thus, conventional imaging has substantial limitations.

Histology

Low grade gliomas arise from supporting glial cells in the brain. The predominant cell type determines the pathological classification.

LGG	Low grade glioma
FDG	Fluorine-18 fluorodeoxy-D-glucose
HGG	High grade glioma
PET	Positron emission tomography
ICP	Intracranial pressure
EORTC	European Organisation for Research and Treatment of Cancer
CT	Computed tomography
UCSF	University of California, San Francisco
MRI	Magnetic resonance imaging
KPS	Karnofsky Performance Status
WHO	World Health Organisation
MDT	Multi-Disciplinary Team
GFAP	Glial fibrillary acidic protein
RCT	Randomised controlled trials
IDHI	Isocitrate dehydrogenase 1
RTOG	Radiation Therapy Oncology Group
MIB-1	Monoclonal mouse anti-human Ki-67 antibody
PCV	Procarbazine, Lomustine (CCNU), Vincristine chemotherapy
ADC	Apparent diffusion coefficient
EFNS	European Federation of Neurological Societies
rCBV	Regional cerebral blood volume
EANO	European Association of Neuro-oncology
GBM	Glioblastoma multiforme
5-ALA	5-Aminolevulinic acid
NAA	N-acetyl aspartate
QD-EGF	Quantum dot epidermal growth factor

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of nodularity and induration. **Side Effects:** Local induration and nodules (usually asymptomatic) often develop at subcutaneous site of injection leading to areas of erythema, tenderness, induration and panniculitis. Irritation, itching, bruising and pain may also occur. Rarely injection site necrosis and ulceration have been reported. Pruritus may occur at the site of injection. Drug-induced dyskinesias during "on" periods can be severe, and in a few patients may result in cessation of therapy. Postural hypotension is seen infrequently and is usually intransient. Transient sedation following each dose of apomorphine may occur at the start of therapy, but this usually resolves after a few weeks of treatment. Dizziness and lightheadness have also been reported. Nausea and vomiting may occur, particularly when APO-go treatment is initiated, usually as a result of the omission of domperidone. Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine therapy and neuropsychiatric disturbances may be exacerbated by apomorphine. Positive Coombs' tests and haemolytic anaemia and thrombocytopenia have been reported in patients receiving apomorphine and levodopa. Local and generalised rashes have been reported. Eosinophilia has occurred in only a few patients during treatment with apomorphine HCl. Patients treated with dopamine agonists, including apomorphine, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality (especially at high doses). Apomorphine is associated with somnolence. Yawning and breathing difficulties have been reported as has peripheral oedema. *Prescribers should consult the Summary of Product Characteristics in relation to other side effects.* **Presentation and Basic NHS Cost:** APO-go ampoules contain apomorphine hydrochloride 10mg/ml, as follows: 20mg in 2ml – basic NHS cost £37.96 per carton of 5 ampoules. 50mg in 5ml – basic NHS cost £73.11 per carton of 5 ampoules. APO-go pens (disposable multiple dosage injector system) contain apomorphine hydrochloride 10mg/ml, as follows: 30mg in 3ml – basic NHS cost £123.91 per carton of 5 pens. APO-go Pre-filled syringes contain apomorphine hydrochloride 5mg/ml, as follows: 50mg in 10ml – basic NHS cost £73.11 per carton of 5 syringes. **Marketing Authorisation Numbers:** APO-go Ampoules: PL 06831/0245, APO-go Pens: PL 06831/0246, APO-go Pre filled syringes: PL 06831/0247. **Legal Category:** POM. **Date of last revision:** February 2010. For further information please contact: Genus Pharmaceuticals, Park View House, 65 London Road, Newbury, Berkshire, RG14 1JN, UK.

Reference: 1. Lees A and Turner K, Practical Neurology 2002;2:280-287.

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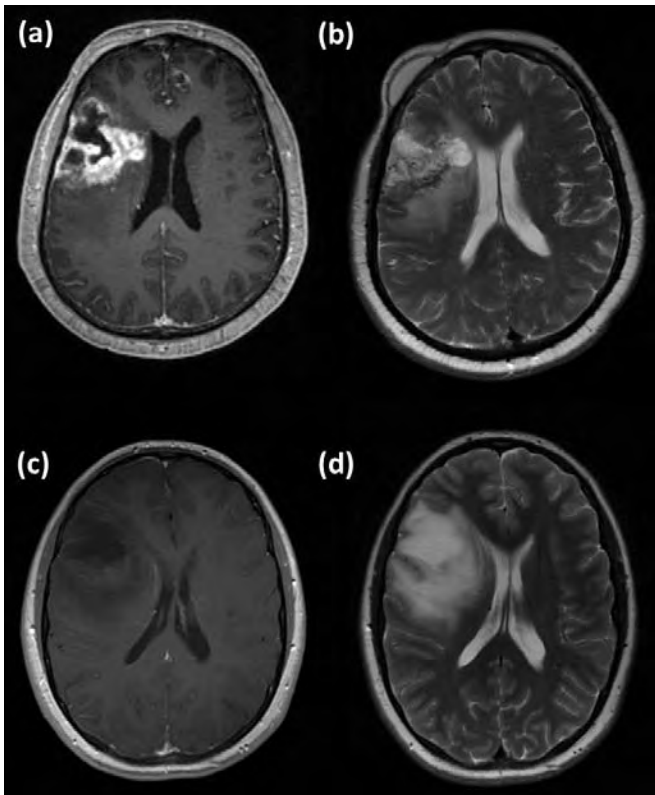
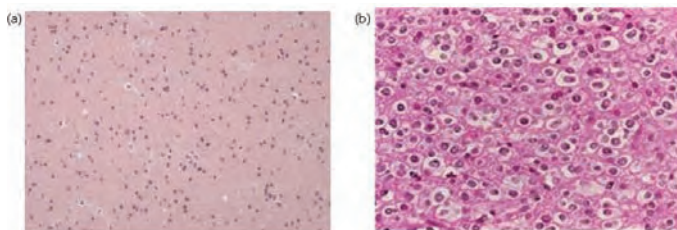


Figure 1: Conventional MR imaging of high and low grade gliomas. The upper panels show a glioblastoma (HGG) (a) contrast enhanced T1-weighted image and (b) T2-weighted image. There is clear evidence of mass effect with marked enhancement. The lower panels show a WHO Grade II oligodendroglioma (LGG) (c) contrast enhanced T1-weighted image and (d) T2-weighted image. Here there is little mass effect and no enhancement. Note the presence of an incidental scalp lesion in figure 1(b).



Fibrillary astrocytoma

Oligodendroglioma

Figure 2: Histology of low grade gliomas. (a) The fibrillary astrocytoma shows increased cellularity of astrocytic cells which demonstrate some atypia but no microvascular proliferation and no evidence of mitotic activity. (b) The oligodendroglioma shows the classic 'fried egg' appearance of a central rounded nucleus surrounded by clear cytoplasm. This appearance is an artefact caused by cellular degeneration during processing causing cell swelling. Mitotic activity is either low or absent.

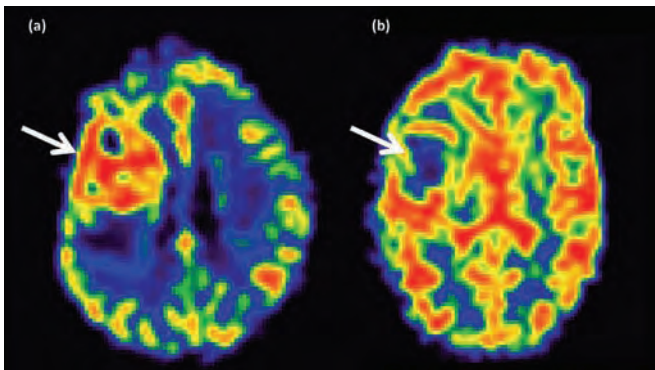


Figure 3: Perfusion MRI showing the relative cerebral blood volume (rCBV) of (a) high grade tumour and (b) WHO Grade II oligodendroglioma. The high grade tumour shows increased rCBV indicating the increase in tumour vascularity whereas the low grade tumour shows decreased rCBV compared to the surrounding normal cortex.

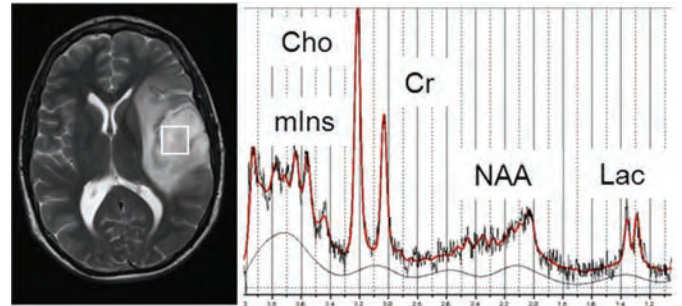


Figure 4: A single voxel MR Spectroscopy scan of a low grade astrocytoma. It shows an increase in the choline peak (Cho – a marker of membrane turnover) and a reduction in the N-acetyl aspartate (NAA – a marker of neuronal integrity). There is also a small peak at about 1.3ppm that is likely due to mobile lipids or lactate. These are unusual in low grade gliomas. Interestingly this patient transformed within two years of diagnosis.

Tumours are graded according to the World Health Organisation (WHO) grading system (grades I to IV; grades III and IV are considered malignant).⁴ LGG are a heterogeneous group of WHO grade I and II tumours. The most common histological subtypes are pilocytic astrocytomas (WHO gd I), ependymomas and the diffuse gliomas: astrocytomas (gd II), oligoastrocytomas (gd II) and oligodendrogliomas (gd II). Here we discuss low grade diffuse gliomas. See Figure 2. The tumours have low cellularity and normal brain tissue is mixed in with the tumour.⁵ Anaplasia and mitoses are absent (though a single mitosis is allowed), vascularity is lower than in high grade tumours. Necrosis is absent.⁴ Histological stains mark for cell type and proliferation. GFAP (glial fibrillary acidic protein) and S-100 protein are both found in the central nervous system and can be markers that the tumour is of glial origin: S-100 is less specific and is also found in Schwann cells, chondrocytes and melanomas. Conversely cytokeratin is found in epithelial cells and therefore stains metastatic carcinoma, but not primary glioma. Staining for IDH1 mutation is positive in 70-80% LGG, but rare in HGG. MIB-1 (monoclonal mouse anti-human Ki-67 antibody) stains cells leaving the G0/G1 phase of the cell cycle i.e. performing DNA synthesis. A high MIB-1 index indicates high mitotic activity and correlates with malignancy.⁹ Genetic studies have demonstrated patterns of mutation: p53 and 17p mutations are associated with diffuse astrocytoma, whereas loss of the short arm of chromosome 1 is found in oligodendroglioma.^{10,11}

Modern imaging

Modern imaging techniques can take advantage of the histological features to differentiate low-grade gliomas from high grade tumours. Because of their low cellularity, LGG have a higher apparent diffusion coefficient (ADC) on diffusion weighted MRI than HGG. HGG have a higher regional blood flow (rCBV) than LGG. See Figure 3. Perfusion studies can reliably differentiate grade II diffuse astrocytoma from glioblastoma multiforme (GBM), but discriminating between grade II versus III and III versus IV is more difficult because of marked overlap in appearances between individual tumours. Perfusion imaging may also distinguish radiation-necrosis (low rCBV) from tumour recurrence (high rCBV).⁸

Metabolism and proliferation are elevated in HGG, but normal or lower than normal brain in LGG. MR spectroscopy non-invasively assesses the metabolism of a small region (single voxel) of brain. In all gliomas, the choline peak (a marker of membrane turnover) is increased and N-acetyl aspartate (NAA, a neuronal marker) is reduced. Lipid, marking necrosis, and lactate, marking hypoxia, are increased in HGG, but not in LGG. See Figure 4. MR spectroscopy may also be useful in differentiating cortical dysplasia and other benign conditions from LGG. Fluorine-18 fluorodeoxy-D-glucose (FDG) labelled positron emission tomography (PET) imaging quantifies glucose utilisation, which is increased in HGG but the same as, or lower than, normal brain in LGG. Again, it can also be useful to differentiate tumour recurrence (hyper-

Table 1: Prognostic factors and observed survival

EORTC ¹⁴	Prognostic factors studied	No. factors present	Median survival (years)	
Factors	Age >40 Diffuse astroglioma Max. diameter >6cm Crosses midline Neuro deficit	0-2 3-5	7.7 3.2	
UCSF ³	Prognostic factors studied	No. factors present	5 year Overall Survival (%)	5 year Progression Free Survival (%)
Factors	Age >50 Max. diameter >4cm Eloquent location KPS ≤80	0-1 2 3-4	97 87 56	76 49 18

metabolic) from radio-necrosis (hypo-metabolic). FDG PET is, however, limited by the uptake of FDG in all metabolically active areas of the brain. Methionine PET provides a measure of increased protein synthesis due to incorporation of this into proteins. It appears to be a more reliable marker of proliferating tissue than FDG PET and can distinguish between neoplastic and inflammatory processes. FLT (a thymidine analogue) marks DNA synthesis and correlates with MIB-1 index on histological staining. However, FLT can give false positives in LGG after radiotherapy due to disruption of the blood brain barrier.⁸

Modern imaging techniques thus offer additional information to that provided by conventional imaging. Whilst not yet approaching the gold-standard of tissue histology, they may optimise target selection for diagnostic biopsy.⁸

Prognosis

The ultimate behaviour of these tumours is not benign. The natural history is of serial accumulation of genetic abnormalities resulting in malignant transformation and, ultimately, death.¹ The behaviour of LGG is highly variable and whilst some may remain stable for a long period, others dedifferentiate sooner.¹² In studies pre-1990, a 5-year survival rate of 40-50% was reported.¹ More recently, data show a median-survival approaching 10 years. Whether this advantage is entirely due to improved treatment, or whether this is in part due to 'starting the clock earlier' with earlier diagnosis from better imaging modalities, is unclear.¹

Many studies have undertaken a multi-variate analysis to evaluate potential prognostic factors. A number of patient-related, tumour-related and treatment-related prognostic factors have been elucidated.¹² Young age, good performance status and presentation with seizures confer a survival advantage. Symptoms of raised ICP or focal neurological deficit are associated with a worse prognosis. Small tumours and oligodendroglioma subtype are positive prognostic factors. Larger tumours (greater than four-six centimetres),^{12,13,14} poorly circumscribed tumours or

multifocal lesions have a worse prognosis. Pilocytic astrocytoma is WHO grade I and may be cured by gross total resection. Gemistocytic subtype tumours have a high risk of anaplastic transformation. The 1p19q chromosome deletion correlates with oligodendroglioma subtype and is a marker of good prognosis.^{1,4,13,15} The p53 gene mutation (more common in astrocytomas)¹³ and a high MIB-1 proliferation index (>8%) on histological staining⁵ carry a poorer prognosis. More recent studies have shown that the IDH1 mutation is a common, early mutation in both astrocytic and oligodendroglial tumours that predicts prolonged survival.¹⁶ Growth rate predicts prognosis.^{17,18} Evidence from imaging studies shows that these tumours grow with a mean increase in diameter of 4mm/year. Tumours growing faster than 8.1mm/year in diameter have a median survival of just five years versus over 15 years for those growing more slowly.¹⁷ Recent imaging studies have shown that rCBV is also an important marker of prognosis. Patients with regions of increased rCBV have a much lower overall survival.^{19,20} The increase in rCBV can be seen up to six months before these tumours clinically transform.²⁰ Further studies are required to see if this could predict when to initiate further treatment.

Prognostic scores have been developed based on these factors. See Table 1. These high- versus low-risk groups may be useful to guide management strategies.

Management

The management of LGGs should be conducted through a multi-disciplinary team (MDT) approach:²¹ options include conservative and operative approaches.

Conservative management

Conservative management may be initiated at a number of stages. A "watch and wait" policy may be followed from the outset with radiological surveillance, without histological diagnosis. These patients would have imaging demonstrating lesions without any features associated with malignancy and would be stratified in a low-risk group.^{5,15} They may have a long, stable history of well-controlled

seizures or have a deep lesion not amenable to biopsy. Informed patient-preference must play a role. However, in the absence of a pathognomonic radiological appearance¹³ of "low-gradeness", and the fact that up to 20% of tumours thought to be grade II radiologically are actually grade III histologically,⁵ a conservative approach requires careful consideration. Conservative management may also be followed after diagnostic stereotactic biopsy.²²

Surgery

Surgery ranges from diagnostic biopsy, to debulking, to gross total resection. Stereotactic biopsy is minimally invasive, well-tolerated and suitable for deep lesions. Larger lesions may be biopsied using frameless image guidance. Biopsy has the limitations of small sample size which can fall foul of the heterogenous nature of LGG resulting in under-grading of a more aggressive tumour or producing a sampling error in mixed oligo-astrocytoma (which would be more suitable for early adjunctive chemotherapy than pure astrocytoma).^{5,13}

Intuitively, cytoreductive surgery, i.e. debulking, has the benefit of reducing the tumour load, perhaps reducing the risk of future disease progression. In the absence of level one studies (randomised controlled trials), many authors claim that the weight of evidence is in favour of attempted resection in suitable cases with reduced rates of recurrence and transformation and improved survival.^{13,23,26} One of the major difficulties in interpreting the studies looking at the extent of resection is that they rarely report objective measurements achieved by comparing pre- and post-operative imaging. In addition, other authors note that the groups undergoing gross total resection, debulking and biopsy of unresectable lesions are not directly comparable. Those most suitable for gross total resection may already have a better prognosis.¹⁵

The development of a range of surgical adjuncts (pre-operative PET, functional MRI and Wada test; operative tools such as the ultrasonic aspirator, operating microscope, stereotactic methods, intraoperative ultrasound, intraoperative stimulation and awake

The ultimate behaviour of these tumours is not benign. The natural history is of serial accumulation of genetic abnormalities resulting in malignant transformation

craniotomy) has been associated with an improvement in the morbidity and mortality profile of surgery. Intra-operative MRI is a modern tool to maximise resection but is not yet widely available.²⁷ Functional mapping may increase extent of resection and improve overall survival.²⁶ The rate of significant morbidity in debulking is now around 2%.²⁸ Whilst pre-existing neurological deficits may be temporarily exacerbated, most patients return to baseline or better within three months.¹³ Debulking can provide immediate benefit in relief of mass effect and raised intracranial pressure. It can improve deficits which are due to the mass effect of the tumour (rather than those due to direct invasion).^{5,28} It allows reduction in steroid use if post-operative radiotherapy is required. It may also give better diagnostic information from the larger histological sample. In LGG with medically intractable seizures, resection improves seizure control.¹

Radiotherapy

The role of radiotherapy after biopsy or debulking is debated. An EORTC randomised controlled trial (RCT) reported longer (radiological) progression free survival (5.3 years versus 4 years) and better seizure control for the group of LGG patients treated with early radiotherapy than those given delayed treatment at the time of progression, but found no difference in overall survival. However, over one third of patients in the conservative group did not require radiotherapy during the follow up period.²⁹ Two prospective RCTs found no difference in outcome between a high-dose radiotherapy group and a lower-dose, but the high-dose group had a poorer quality of life.^{15,30} Dose-related radiological abnormalities included white matter changes and radionecrosis. Such radiation leukoencephalopathy can result in gait disturbance, urinary incontinence, deterioration in personality and cognitive dysfunction.¹³ Patients treated with high dose radiotherapy reported poorer quality of life, especially fatigue, insomnia and emotional symptoms.¹⁵ Medium-term follow up (six years) of one cohort had suggested that radiotherapy only caused cognitive side effects at higher doses. However, more recent data show that long term survivors (12-year follow-up) who have had even lower-dose radiotherapy develop progressive decline in attention, executive functioning and information processing,

Those who did not have radiotherapy had stable cognitive status, with 27% having a cognitive deficit (which was attributed to their tumour and possibly influenced by antiepileptic use) compared to 53% of those who had undergone radiotherapy.³¹ Thus, given a prognosis in excess of 10 years in low risk groups, the decision whether or not to give early radiotherapy must be informed by the potential benefits in symptom control, including better seizure regulation, and the risk of long-term side effects. Keeping radiotherapy in reserve for use at the time of disease progression may be the optimal strategy.

Chemotherapy

Chemotherapy is not in routine use for astrocytic LGG but is known to be effective for oligodendroglioma subtypes (grade II and III) and for HGG. Early data from the Radiation Therapy Oncology Group (RTOG) did not show any advantage to adding PCV chemotherapy to radiotherapy for grade II tumour patients deemed at high risk.¹⁵ Phase II trials demonstrate that temozolamide is active against both untreated and previously irradiated enlarging LGGs. In addition, there are reports of cases where neoadjuvant chemotherapy given to surgically irresectable tumours has allowed subsequent gross total resection.^{13,15} The role of chemotherapy is to be investigated in the BR13 (EORTC 22033-26033) trial (www.eortc.be/protoc/details.asp?protocol=22033).

The future

A century and a bit on, modern neuro-oncology would be unrecognisable to Sir Rickham Godlee. MRI has improved pre-operative specificity of diagnosis: additional technologies such as PET are used to target treatment in difficult cases. Image-guided stereotactic techniques have become established in the last two decades, enabling mini-craniotomies to be placed directly over brain tumours, whilst maximising resections with reduced morbidity. The safety and accuracy of deep brain tumour biopsies has been optimised. The morbidity and mortality of surgery has been reduced from 50-100% – “...many ‘successful’ operations resulted in dead patients”² – to 2%.²²

Progress continues. Recent evidence-based guidelines published by the European Federation of Neurological Societies (EFNS)

and the European Association of Neuro-oncology (EANO)³² should help to develop services for patients with low grade gliomas. Non-invasive investigations are likely to better inform the diagnostic process. A number of molecular markers (from biopsy tissue and from blood) are under investigation for utility in diagnosis and prognostication.^{13,33} Newer imaging techniques continue to improve and in the future may have the potential to avoid biopsy altogether.⁸ Operative techniques such as pre-operative functional mapping, intra-operative MRI and other imaging modalities are likely to become more widely used. Fluorescent markers such as 5-aminolevulinic acid (5-ALA) are proving useful in improving extent of resection in high grade glioma,³⁴ but cannot detect LGG.³⁵ In vitro studies of new markers, such as quantum dot epidermal growth factor (QD-EGF), demonstrate potential for the development of similar tools for LGG.³⁶

Whilst radiotherapy is often reserved for progressive disease, newer highly conformal techniques may improve outcomes. Modern radiotherapy techniques can significantly reduce the radiation dose to normal brain, but are limited by the difficulty in identifying the tumour margin and by tumour volume.^{15,30} Further imaging developments are needed to better delineate these tumours.

The role of concurrent chemotherapy in astrocytic LGG remains unclear. The European Organisation for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG) are conducting clinical studies that aim to assess the value of radiation plus concurrent chemotherapy in high risk LGG patients.^{13,33} ♦

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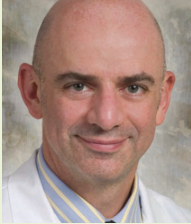
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Rehabilitation of Hemianopic Visual Field Defects



**Jose G Romano,
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Disclosures:

Dr Romano has no current conflicts of interest to disclose. In the past, he served as a scientific advisor to NovaVision, a private company that developed a visual rehabilitation intervention.

Visual function is distributed over large areas of the cerebral cortex. Consequently, visual field defects (VFD), and in particular homonymous defects, are very common after cerebral insults such as stroke and traumatic brain injury (TBI). Population based studies have shown a prevalence of VFD of 0.8%.¹ In chronic stroke, the proportion of homonymous VFD has been reported to vary between 8.3% and 16%^{1,2} while in the acute and subacute period, VFD occur in 25% of stroke³ and 39% of TBI⁴ patients. Visual field defects tend to improve in the first few months after insult as a result of resolution of oedema and diaschisis, with improvement of neurotransmission near and remote to the lesion. However, by three to six months after insult, VFD are unlikely to continue improving and only about 5% resolve completely.^{5,6}

The disability that attends VFD is significant. Fluent reading requires preserved function in the central 5° of vision; as most VFD extend to the vertical meridian, affected individuals have problems identifying half of a word and finding the next line of text, resulting in hemianopic alexia.⁷ Standards for driving vary by country and, in the US, also by state, but most require at least 120° of vision, and in some cases as much as 140°; therefore, many of those with a VFD are unfit to drive. Collisions with obstacles and people in crowded areas, difficulty seeing television and finding icons on a computer screen are commonly reported and result from both visual loss, as well as disordered visual search. VFD also worsen the prognosis of other neurologic deficits, with a ten-fold decrease in independent walking and a 20% decrease in reaching functional independence when a VFD is present in unilateral hemispheric stroke.⁸ The impact of VFD can be quantified with vision-related and health-related quality of life measures; these show worse quality of life compared to both healthy subjects and stroke patients without a VFD.⁹

In spite of their frequency and the disability imposed by their presence, in the past little attention was paid to rehabilitating homonymous VFD. However, developments in the last two decades have advanced the field, with three main lines of research: substitutive methods with the use of prisms, compensatory strategies with saccadic therapy, and restorative approaches.¹⁰

Substitutive methods use optical devices, namely prisms, to enlarge and shift the visual

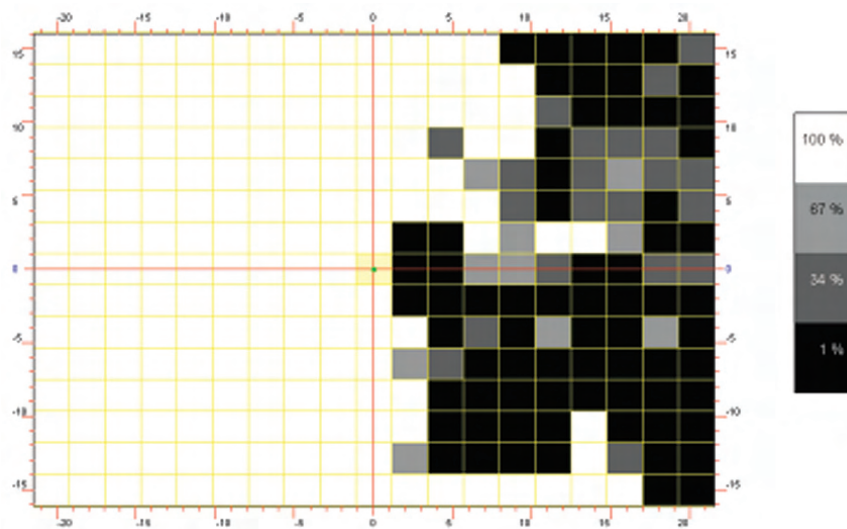
field. Although there are encouraging reports about their tolerability and efficacy,¹¹ others have reported lack of translation of visual field function into activities of daily living.¹² New prism designs attempt to avoid the diplopia reported by prior studies,¹³ but their tolerability remains an important issue. In a prospective report, only 47% were still using prisms at one year; the main reasons for discontinuing their use included image confusion and distress over sudden appearance of objects in the visual field.¹⁴ Although reasonable as a rehabilitative approach, substitutive therapy requires training in the use of the devices, and poor adherence due to visual distortion remains an issue.

Compensatory strategies use the intact residual function of eye movements and can be broadly categorised into reading training and exploratory training. A controlled trial of patients with right homonymous hemianopia-hemianopsia and hemianopic alexia found that a home-based intervention that induced optokinetic nystagmus delivered through right-to-left moving text increased reading speed by 18% (≈17 words per minute).¹⁵ These results are smaller than those reported in non-controlled studies, in which reading training was delivered by therapists.^{16,17} Hemianopic patients employ multiple saccades and fixations due to disorganised and inefficient visual search. Exploratory training aims to address this issue by specifically teaching individuals to make saccades into the blind field while scanning the environment. A number of reports have noted a decrease in reaction time, improved detection and better performance in activities of daily living scales and tasks.^{18,21} A randomised study of exploratory saccade training found improvement towards the blind side in response time and reduced fixations in search tasks, particularly in a digit search paradigm, with no change in visual field size and without translation into reading speed.²² A controlled study comparing saccadic training with attentional training (without the exploratory saccadic component) also found improvement in the digit search task for exploratory training, but other visual search tasks and reading improved similarly in both treatment arms, suggesting that attention plays a vital role in saccadic visual rehabilitation.²³

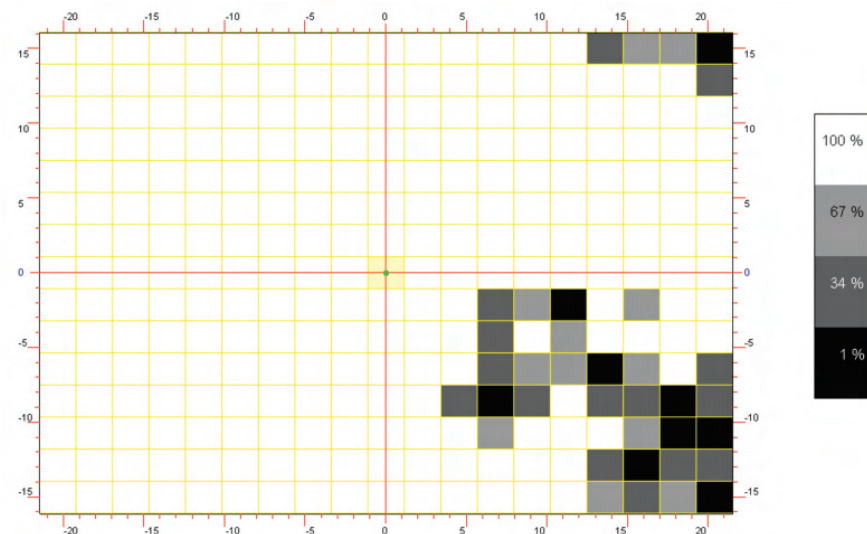
Restorative approaches are based on the premise that the visual system is plastic and that neural reorganisation can be achieved through targeted and repetitive photostimulation. The most studied approach is denominated vision

Figure: A 55 year old man, 9 months after a left occipital infarct, is left with an incomplete right homonymous hemianopsia. Panel A is a superimposition of 3 consecutive visual field tests performed with suprathreshold stimuli at baseline, and panel B shows the visual field after 6 months of visual rehabilitation with VRT. Panel C is a subtraction map between the pre and post VRT visual fields, showing in blue the areas of improvement and in red the areas of worsening.

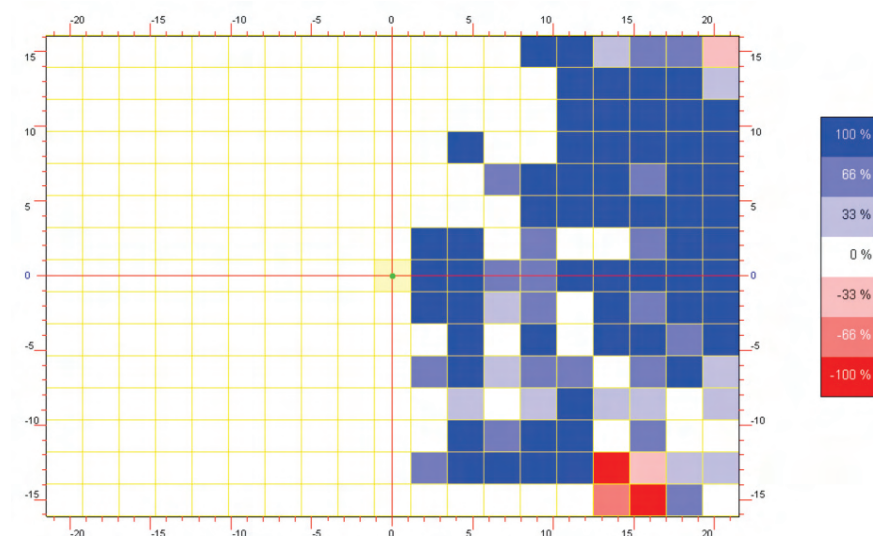
Panel A. Baseline
Stimuli detection: 69.3 %; Fixation detection: 100 %; False positive responses: 1.2 %; Avg. response time: 425 ms.



Panel B. Post VRT
Stimuli detection: 91.9 %; Fixation detection: 100 %; False positive responses: 1.9 %; Avg. response time: 354 ms.



Panel C. Areas of change



restoration therapy (VRT), where therapy is directed to the border between the seeing and the blind field with thousands of stimuli over weeks and months. This tactic has resulted in expansion of the visual field by about 5°. In a randomised controlled study of 19 patients with retrochiasmatic lesions, those treated with VRT showed a 4.9° improvement in central visual field compared to controls.²⁴ Large retrospective studies employing VRT in the US²⁵ and Europe^{26,27} also confirmed an expansion of 5° of the central visual field, representing a 10-13% increase in the number of detected stimuli. The figure exemplifies a case treated with VRT. Between two thirds and three quarters of patients treated show visual field improvement, but predicting who will respond has proven difficult; age, time from lesion and type of visual field defect were not shown to be good predictors of response.²⁵ In addition to expansion of visual fields, functional improvements have also been documented after VRT by structured questionnaires²⁷, validated visual functional scales²⁸ and in reading and attention testing.^{29,30} Other modalities of repetitive stimulation close to the border of the hemianopic field have documented visual improvement.³¹ Huxlin and colleagues studied individuals with primary visual cortex V1 injury before and after direction discrimination training with dynamic stimuli while carefully monitoring eye movements, and confirmed improvement in both direction discrimination as well as other visual functions.³² Others have repeatedly stimulated deep in the blind field in order to enhance “blind sight” and noted significant changes in both perimetric studies as well as in contrast sensitivity.³³

Nonetheless, controversy has arisen regarding VRT's efficacy after a report of 16 patients where the visual field expansion found with perimetric methods using near-threshold and supra-threshold stimuli could not be confirmed by scanning laser ophthalmoscopy.³⁴ This raised the possibility that the effects of VRT are not due to a true expansion of visual fields but result from more effective eye movements.³⁵ However, others argued that the scanning laser ophthalmoscopy strategy employed in that report was too complex for those with a VFD.³⁶ Studies that controlled for eye movements with other controls argue against eye movements as the sole explanation of the visual field expansion seen with VRT. In a study of 15 patients whose visual fields were monitored with an eye tracker, patients treated with VRT spent 88.3% of the time within 1° and 98.9% of the time within 2° of fixation, which was actually improved from baseline; furthermore, less than 5% of all saccades were larger than 2°. In a small series of patients with direct retinal microperimetry, which controls for eye movements, all patients had visual field improvement after VRT.³⁸

The mechanisms by which restorative approaches exert their effects are incompletely understood. As eye movements alone do not explain the effects noted, cortical reorganisation has been invoked. In motor recovery, neuro-imaging suggests that perilesional reorganisation is the main neurobiological substrate associated with functional improvement.³⁹ Indeed, both positron emission tomography⁴⁰ and functional magnetic resonance imaging (fMRI)^{41,42} have noted changes in visual areas after restorative approaches. Whether this represents expansion of receptive fields in the primary visual cortex is unclear.^{43,44} However, other mechanisms may also play a role. Studies where the blind field was stimulated suggest that it is the activation of extrastriate pathways, which bypass the damaged V1 cortex, that correlate with improved function.^{32,33} Finally, the role of top-down focused attention on information processing is recognised,⁴⁵ and combining attentional cues with VRT has resulted in greater visual field changes;⁴⁶ fMRI studies after VRT have also documented increased BOLD activity in attentional areas.⁴¹ These mechanisms may well interact. One may hypothesise that activation of extrastriate pathways through repetitive stimulation, and expansion of receptor field size in areas close to the border of the blind field may result in greater detection; this would then shift focused attention which in turn lowers detection threshold in a particular area.^{23,47,48}

Although the field of visual rehabilitation for hemianopic defects has recently expanded, further research is needed to: i) determine the precise mechanisms of action of the available techniques in order to enhance therapeutic approaches; ii) develop sensitive and significant measures of successful therapy; and iii) identify predictors of outcome to apply treatment to those most likely to benefit from these interventions. The modest outcomes reported to date may also be enhanced. For example, augmenting the effects of restorative therapies by brain electrical stimulation to improve effects and shorten the course of therapy is being explored, with initial encouraging results.⁴⁹ The benefits of consecutive restorative followed by compensatory strategies should also be studied. Nevertheless, there are currently a variety of options are now clinically available for hemianopes, and clinicians should strongly consider these rehabilitative interventions in eligible patients. ♦

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NHS 'Reforms': Right Care or Destruction?



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The NHS faces radical change. Depending on your perspective, this change is either the greatest threat it has ever faced; or a move to efficiency, less waste, and open information for patients and purchasers.

Threats and opportunities

For neurology on the outpatient front, proposed changes to tariff arrangements have a huge potential impact. Suggested figures are £217 for a new consultation, and £120 for a follow up, to include all investigation costs. Initial back-of-the-envelope calculations make it difficult to see how NHS trusts can make ends meet with neurology consultations. Are we expected to send patients back with a list of tests for the GP to do (inconvenient for patients, messy, makes GPs feel like house officers, creates a bureaucratic nightmare of chasing results), simply ignore the problem and hope dermatology will subsidise our neurological musings, or stop doing tests (potentially dangerous and we won't be thanked if it goes pear-shaped)? High quality neurology consultations involve a lot of time thinking, appear slow and somewhat passive compared to the cut and thrust of some specialties. Thinking is expensive and, in the current climate, clearly less valued than other attributes.

There is sound evidence that patients benefit when neurologists are involved in acute emergency work, including stroke. This is essential for our patients, even from a purely financial point of view (a point of view which has certainly featured in recent debates on UK healthcare). The Association of British Neurologists (ABN), in partnership with the Royal College of Physicians, has drafted a report on local neurological services, which stresses our involvement and discussion with commissioners. Any sound neurological service must surely involve both individual and regional variation in the way we do things and the balance of acute and outpatient work we do. The ABN will examine these variations through a stroke working group and we need to hear about the variety of services throughout the UK.

PCT power?

Specialists may find the current changes tumultuous, but the situation certainly doesn't seem easier for GPs. Like us, they face the tasks of looking after their patients, and proving they are doing a good job

(patient satisfaction surveys which bundle everything from the music in the waiting room, to how well we introduce ourselves, and how well we explain things). GPs are now expected to analyse, prioritise and commission all services.

GPs face mountains of documentation to assist them, and they are sometimes very contradictory. Worrying examples of such contradictions are apparent. Last week, I was encouraged to hear of attempts to formulate improved guidelines for acute subarachnoid haemorrhage, encouraging more careful assessment of patients with thunderclap headache presenting to emergency departments. Two days later, I joined colleagues to dissuade commissioners from recommendations that all patients with acute headache should be sent home from the emergency department for management by GPs (unsurprisingly, none of us were keen on the logical extension of this recommendation – outpatient treatment of subarachnoid haemorrhage).

There are similar contradictions in epilepsy treatment. NICE, SIGN and other epilepsy guidelines all stress that people with epilepsy must have access to surgical assessment for refractory epilepsy. Surgical treatment for temporal lobe epilepsy is a beacon of evidence based medicine. Patient support groups and epilepsy specialists are therefore concerned and puzzled by the "Right Care Commissioning for Value" project's problematic analysis of epilepsy surgery. In a document entitled "Empowering patients to make the right choices and empowering commissioners to improve value" surgery for epilepsy is described as an intervention of lower clinical value. How can PCTs make sensible judgements when the documents that are supposed to guide them are diametrically opposed to guidelines already in place? Potentially, epilepsy surgery in the UK may become a rare intervention in those with refractory epilepsy, except for those with private funding.

Free healthcare for all?

When I came to the UK as a visiting Fellow, the NHS was one of the most impressive aspects of life in the UK—a real attempt at a just healthcare system. Seventeen years later, it is being remodelled, and in that process, the philosophy of free healthcare for all at the point of service is being seriously challenged. ♦

Neurology Trainees Thrombolysis Survey



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Following the introduction of the Department of Health's National Stroke Strategy in 2007,¹ national clinical guidelines² and NICE guidelines³ for the treatment of acute stroke have been introduced. Since August 2010, these guidelines have been implemented with the aim of admitting all patients with acute stroke to an acute stroke unit with assessment for thrombolysis where appropriate.¹ Thrombolysis for acute stroke is beneficial up to 4.5 hours after onset.⁴ However, UK provision of thrombolysis for acute stroke shows wide variability.⁵

Various models have been developed to provide a thrombolysis service.^{6,8} Frequently, SpRs in neurology, acute medicine or emergency departments are the 'front line' medic assessing the patient.⁸ Trainees in the UK now have to work within a 48 hour week as stipulated in the European Time Working Directive, creating extra demands when designing service provision for thrombolysis rotas. We wished to assess the involvement of Neurology SpRs in thrombolysis provision in the UK and collect trainees opinions on the part that thrombolysis should play in general neurology training.

Methods: A survey of 10 questions was emailed to all trainee members of the ABNT.

Results: 30 trainees responded to the questionnaire with representatives from all regions of the UK.

Total training in thrombolysis varied from four months on a stroke unit to five years on an on call rota. Only one centre has no exposure to thrombolysis during training. In 32 % of cases the rota consisted of non resident on call overnight with normal working hours the next day. Two centres have reduced 9.5 hours to compensate for the intensity of the on call period and in one centre trainees are only on call till 22:00, to meet EWTD.

The move to Hyperacute Stroke Units has meant full shift rotas (with consecutive nights on call) being operated in London with plans for other major centres to adopt a full shift system. Most centres did not have the assistance of a specific stroke nurse out of hours.

The majority (86%) of trainees who responded felt thrombolysis was an important part of general neurology training; however several respondents felt the time spent on a rota should be limited so as not to affect general neurology training.

The intensity of antisocial hours was strongly correlated with perception of a negative effect of thrombolysis on training and of stroke as a specialty.

Discussion

The survey results represent a minority of trainee respondents. However, despite this small number, we have information from all UK centres.

The involvement in acute stroke care in the UK by neurology trainees varies widely.

Acute stroke provision is changing rapidly in the UK and we are often required to provide the necessary manpower to meet stroke targets

The ABNT feel that thrombolysis training is an important part of neurology training. Acute stroke is part of the 2010 neurology curriculum for neurology trainees, but perhaps a minimum time of 6 or 12 months for involvement in acute stroke care should be stipulated. Care should be taken to ensure that this does not detract from general neurology training. This may mean that a maximum period of participation in an acute stroke on call rota should also be defined. ♦

SUMMARY

- The implementation of national acute stroke care guidelines has dramatically increased the need for 'stroke specialists' in the UK.
- These specialists are often geriatricians or neurologists
- Exposure to thrombolysis varies from none to 5 years in UK neurology training centres
- Clear guidelines are needed to ensure optimal exposure to acute stroke care for all neurology trainees whilst protecting general neurology experience both within and out of hours.

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Welcome to the fifth in a series of articles in *ACNR* exploring clinical dilemmas in neuropsychiatry. In this series of articles we have asked neurologists and psychiatrists working at the interface of those two specialities to write short

pieces in response to everyday case-based clinical dilemmas. We have asked the authors to use evidence but were also interested in their own personal views on topics. We would welcome feedback on these articles, particularly from readers with an alternative viewpoint.

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The Purposes of Neuropsychological Assessment and How to Achieve Them

Case

Excerpt from a neuropsychological report.

"... A 68-year-old, right-handed, retired man suffered from a recent stroke. The patient presented with Wernicke's aphasia, alexia, and agraphia, coupled with limb apraxia, right hemianopia, verbal short-term memory problems and constructional apraxia. This neuropsychological profile is compatible with a left temporo-parietal lesion". The site of the lesion had been confirmed by CT scan as a left temporo-parietal infarct at the time of admission, so what was the point of this assessment? What is the use of this technical description of the symptoms?

The remit of clinical neuropsychology

Clinical neuropsychologists are called to investigate the impairments of higher mental functions following brain damage in individual patients. They use methods derived from experimental psychology, i.e., standardised tests requiring behavioural responses. In the dawn years clinical neuropsychologists had three main aims: to identify the cognitive deficit, to locate the associated brain lesion, and to devise suitable rehabilitation trainings.¹ The more knowledge accrued on the complex relationship between brain structures and cognition, the less justifiable the localisation aims of the neuropsychological assessment appeared. It became clear that the alleged relationship between the performance on individual tests and the functioning of circumscribed brain areas was based on ingenuous assumptions. Moreover, the prepotent advent of modern neuroimaging techniques made this enterprise outmoded, as they were able to address this same question directly, avoiding the fallacies intrinsic in the probabilistic approach which characterises neuropsychological localisation. A neuropsychological report that professes to predict the site of the brain lesion given a particular cognitive profile is unwarranted and necessarily prone to mistakes.

In parallel, the remaining two aims, which constitute the focus of modern neuropsychology, flourished, capitalising on the upsurge of cognitive modelling, which allows clinicians and researchers to account for the observed patterns of spared and impaired abilities "in terms of damage to one or more components of a theory or model of normal cognition" (p.4).² In turn, this refined diagnosis consents to take an informed decision on whether or not to initiate a cognitive treatment and, if so, to make precise the targets and the working hypotheses of rehabilitation programmes. Aside from any therapeutic choice, which could be

dictated by pragmatic reasons, a detailed diagnosis allows the neuropsychologist to better inform patients and carers. For example, a meticulous neuropsychological evaluation would permit to differentiate various forms of limb apraxia according to the type of gestures impaired. Different types of limb apraxia differently affect everyday activities; problems with intransitive gestures affect gestural communication, difficulties in carrying out transitive gestures affect object manipulation, whereas deficits of unfamiliar gestures affect rehabilitation exercises requiring imitation.^{3,4}

Furthermore, a sound neuropsychological diagnosis will allow the consultants in charge of the patients to advise them and their carers on daily activities, such as renewing the driving licence or suitability to specific jobs.

The role of clinical neuropsychologists

To achieve the above aims, neuropsychologists use relatively simple tasks, such as reading aloud, drawing, recognising objects, or memorising lists of words, and are equipped with off-the-shelf tests or pre-packed test batteries. The apparent simplicity of the neuropsychologist's trade-mark instruments is deceptive. The core competence of a neuropsychologist is not solely to administer the tests (which could be presented by different professionals), but to plan the individual assessment, to refine the testing programme, to decode the findings, and to unravel the observed pattern of performance. Central to their remit is the interpretation of the outcome from such tests, based on both accuracy scores and the qualitative analysis of errors. Like a radiologist who could carry out a scan, but whose main chore is to interpret it, the neuropsychologist is asked to derive hypotheses on the patient's cognitive functioning. Hence, the diagnostic process should not be merely applying gross clinical labels (i.e. Broca's aphasia, dysexecutive syndrome, unilateral neglect,

episodic amnesia), but to identify the damaged component(s) of the cognitive processes in individual patients.

The neuropsychological interpretation

A single error is per se opaque. Take a patient who reads the word "deer" as "beer"; this error could be classed as letter substitution, but it could be interpreted by means of five different accounts. The error could be (i) perceptual (d → b), revealing a problem in coding the spatial orientation of the letter shape, which will involve also non-orthographic stimuli; (ii) orthographic (<D> →), due to a deficit in processing the letter identity, specific to reading tasks; (iii) lexical-semantic (deer → beer), because of the selection of another lexical unit which could be semantically related (like in deer-beer root beer or in Beer Deer - or Beef - Roast); (iv) phonological (/d/ → /b/), reflecting the substitution of one distinctive feature, in this case the point of articulation, which would be apparent also in spontaneous speech; (v) attentional (deer → -eer), due to a defective coding of the beginning letter, as in neglect dyslexia. The ambiguity of single errors needs to be disentangled considering the overall pattern of spared and impaired abilities and their matching onto the relevant cognitive model.

It is paramount to distinguish between error classification and their interpretation. The labelling of an error, like "letter substitution", derives from agreed mutually exclusive categories, that is, a given response could be listed under one, and one only, error category. Classing an error does not imply its interpretation, which instead ought to be vetted against the full assessment and nested within verified cognitive models. A naming error, e.g. tiger → lion, classed as semantic paraphasia, does not necessarily imply the impairment of semantic knowledge, rather it could be traced to a pre-semantic deficit, as in associative agnosia, or it could result from a post-semantic deficit, as in anomic aphasia.⁵

Psychometrics is not all

Good tests are furnished with norms, which allow the identification of performances that deviate from psychometric values like the median, or the lower 5th centile, relative to validated cut-off scores derived from a reference sample. These arbitrary criteria can give rise to false positives or false negatives, which could be avoided by acknowledging that a poor performance does not necessarily equate to a pathological one.

To assess a given cognitive function one single test cannot suffice, as the test-function correspondence is weak. The Token Test⁶ is recognised as a good test to assess language comprehension, yet it includes only a limited number of lexical units (names of shapes and colours) and does not assess linguistic processes like inferential knowledge ("I heard a dog" conveys the information that the dog is barking) and the assignment of thematic roles (the role of agent is assigned to nouns occupying pre-verbal and post-verbal positions in active and passive sentences, respectively).

Moreover, there are several different ways to fail a test. A patient may fail the Token Test, not because of aphasia, but because of colour agnosia or a working memory problem in binding shapes to colours, or in keeping track of the word sequence.

Moreover, the validity of a test should not be taken for granted. A test might not assess exactly what it was devised for, because of faulty selection of the stimuli. The Judgement of Line Orientation Test,⁷ widely assumed to detect selective visuo-spatial deficits in right hemisphere damaged patients, is biased by an uneven distribution of the stimulus lines, which are easier to discriminate in the left space.⁸

Structure of the neuropsychological assessment

A sound neuropsychological assessment should entail four separate but intertwined steps. The clinical neuropsychologist begins with an interview aimed at gathering a targeted personal and clinical history, in order to isolate and contextualise the problem(s). The context within which the complaint arises is relevant as it allows the clinician to ascertain whether other, non-neuropsychological, factors (e.g., familiar, socio-economical, professional) may play a causal role. This should be followed by a screening phase, whereby a comprehensive battery of brief tests is given.^{9,10} The purpose of this step is twofold. On one hand it confirms the existence of the stated problem, on the other it informs further, deeper, investigations by revealing expected errors as well as flagging unexpected hints. Limiting the examination to this level would only attain the scope of corroborating the problem as lamented by the patient and their carers, perhaps by labelling it more eloquently, like a doctor diagnosing a knee pain as gonalgia. The third step encompasses a full-blown neuropsychological examination based upon the information gleaned with the preliminary steps. Here the neuropsychologist's tools are tests or batteries geared at investigating the presence and the severity of specific disorders,^{11,12} by means of which one could reach a clinical labelling. The diagnostic process should not stop at this stage, as clinical labels cover a wide range of cognitive disturbances lumped together under a syndromic umbrella. For example, three different forms of developmental surface dyslexia have been described¹³ or multifarious phenomena of neglect have been reported.¹⁴ To identify the precise locus of cognitive impairment is the objective of the latter step, in which the neuropsychologist should use experimental tests, culled from the literature, or even devised ad hoc.

Conclusions

The use of the neuropsychological evaluation as a tool to localise the cerebral lesion has become largely redundant owing to the development of modern neuroimaging techniques. The use of standardised batteries is still helpful to classify patients according to widely accepted clinical taxonomies. However, to move forward the clinical management of an individual patient, a more detailed evaluation is needed.

The neuropsychological evaluation can come to an end when the full picture of spared and impaired cognitive mechanisms of the individual patient is specified. Even if the instruments used by the neuropsychologists are deceptively simple, as any other diagnostic procedure, the interpretation of their outcome requires considerable expertise which only a psychologist trained in clinical neuropsychology is able to offer. The assessment of the consequences resulting from brain damage is incomplete without a thorough neuropsychological examination, as this will better serve the needs of the patients.

In the case above, a detailed neuropsychological assessment allows going beyond any clinical label or meaningless list of symptoms and provides useful information to plan a rehabilitation program tailored upon the specific deficits shown by the patient. Instead of naming the deficit (for instance, by using the word "alexia" which means "inability to read") and adopting a fixed set of exercises to be applied to all patients belonging to the same vague category, the treatment approach requires detailed hypotheses concerning the impaired linguistic and cognitive mechanisms in order to plan an effective strategy. Indeed, only the correct identification of the underlying cause(s) of the functional deficit allows choosing the most achievable goal of the treatment, either the restoration of the damaged mechanisms or the enhancement of the spared processes or the everyday managing of the impaired behaviour. ♦

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To list your event in this diary, email brief details to Anna Phelps at anna@acnr.co.uk by 6th April, 2011

2011

March

Education

9 March, 2011; Sheffield, UK
E. louisewilkinson@cbituk.org
www.cbituk.org

International Conference on Alzheimer's & Parkinson's Diseases (ADPD 2011)

9–13 March, 2011; Barcelona, Spain
E. adpd@kenes.com
www.kenes.com/adpd

Neuroscience Symposium

10 March, 2011; Dublin, Ireland
www.iicn.ie/meetings/neuroscience_symposium

Brain Injury

10 March, 2011; Derby, UK
T. 01332 254679
www.ncore.org.uk

British Neurosurgical Research Group Meeting

10–11 March, 2011; Dundee, Scotland
www.ncl.ac.uk/bnrg

Clinical Update in Epilepsy

11 March, 2011; Dublin, Ireland
T. 020 7290 2980
E. nevena.marjanovic@rsm.ac.uk
www.rsm.ac.uk/diary

Analysing and moderating the function of regulatory T cells in Autoimmunity

11 March, 2011; Welwyn Garden City, UK
E. enquiries@euroscicon.com
www.regonline.co.uk/autoimmune11

Understanding Brain Injury

11 March 2011; Cambridge, UK
T. 01353 652173
E. Rachel.everett@ozc.nhs.uk

Epilepsy 2011 (RSM 2011)

11 March, 2011; Dublin, Ireland
www.rsm.ac.uk

Third Annual Knock Out Stroke Symposium

12 March, 2011; Coral Gables, USA
E. juliez@baptisthealth.net
www.baptisthealth.net/cme

SIGAM 11th Advanced Prosthetic & Amputee Rehabilitation Course

14–16 March, 2011; Stanmore, UK
T. 01992 638865
E. admin@bsrm.co.uk

Cognitive Rehabilitation Workshop

14–15 March, 2011; Auckland, New Zealand
E. workshops@iphltd.co.nz
www.braintreetraining.co.uk

9th Austrian Society of Neurology (ÖGN) Annual Congress

March 16–19, 2011; Vienna, Austria
E. weinhart@oegn.at
www.oegn.at/kongress2011

12th Annual Queen's Square Symposium

18 March, 2011; London, UK
T. 020 7837 3611
www.ion.ucl.ac.uk

Insight Workshop

21–22 March, 2011; Auckland, New Zealand
E. workshops@iphltd.co.nz
www.braintreetraining.co.uk

No Limits - Exploring adolescent behaviour following childhood acquired brain injury

23 March, 2011; Birmingham, UK
T. 01869 341075
E. Lisaturan@cbituk.org

STARS Cardiac Update Course

24 March, 2011; Liverpool, UK
www.stars.org.uk/news-events/events

Essential Stroke Imaging Course

26 March, 2011; Liverpool, UK
T. 07799 723 925
E. essentialcourses@hotmail.com

Amputee Rehabilitation: an Intro to basic concepts for AHP's

29 March, 2011; Derby, UK
T. 01332 254679
www.ncore.org.uk

No Mind Left Behind: International Conference on Autism, ADHD and other early onset neurodevelopmental disorders

29–30 March, 2011; Glasgow, UK
E. nomindleftbehind@congreg.com
www.mindroom.org/nomindleftbehind

10th International Eating Disorders Conference

29–31 March, 2011; London, UK
E. anne.haylock@markallengroup.com

Basic Applied Neurophysiology for qualified therapists working in neurology

30 March, 2011; Derby, UK
T. 01332 254679
www.ncore.org.uk

Society of British Neurological Surgeons Spring Meeting 2011 (SBNS 2011)

30 March – 1 April 2011; Bristol, UK
www.sbns.org.uk/

Education

31 March, 2011; Belfast, UK
E. louisewilkinson@cbituk.org
www.cbituk.org

Chronic Pain Advanced Study day

31 March, 2011; Derby, UK
T. 01332 254679
www.ncore.org.uk

April

Transverse Myelitis Conference

2–3 April, 2011; Wyboston, UK
E. lewgray@blueyonder.co.uk
www.tmsconference.org.uk

ABN Joint Annual Meeting with the Neurology Section of the Cuban Society of Neurology and Neurosurgery

4–6 April, 2011; Cuba, Havana
www.theabn.org

Education

5 April, 2011; Stoke on Trent, UK
E. louisewilkinson@cbituk.org
www.cbituk.org

Medicine and Me: Brain Tumours

6 April, 2011; London, UK
T. 020 7290 2983
E. sections@rsm.ac.uk

Education

7 April, 2011; New Malden, UK
E. louisewilkinson@cbituk.org
www.cbituk.org

Distinguishing frontotemporal dementia from other dementias: An update

7 April, 2011; London, UK
T. 020 7290 2983
E. sections@rsm.ac.uk

STARS Cardiac Update Course

7 April, 2011; Birmingham, UK
www.stars.org.uk/news-events/events

Annual Meeting of the Infantile Seizure Society

9–10 April, 2011; Tokyo, Japan
E. isns2011@juntendo-nerima.jp
www.iss-jpn.info

AAN Annual Meeting

9–16 April, 2011; Honolulu, Hawaii
T. (800) 879-1960;
www.aan.com/am.

Youth Offending

12 April, 2011; Newbury, UK
E. louisewilkinson@cbituk.org
www.cbituk.org

Schizophrenia, 5th National Conference

14–15 April, 2011; London, UK
E. anne.haylock@markallengroup.com

Behaviour Change in Neuro-Rehabilitation

15 April, 2011; Cambridge, UK
T. 01353 652173
E. Rachel.everett@ozc.nhs.uk

8th Improving Immunohistochemistry Meeting

15 April, 2011; London, UK
E. enquiries@euroscicon.com
www.regonline.co.uk/workihc2010

2nd International Symposium on Disorders of Consciousness

26–28 April, 2011; Santiago de Cuba, Cuba
www.engraciacal.com

STARS Cardiac Update Course

28 April, 2011; Stoke, UK
www.stars.org.uk/news-events/events

May

EANS Annual Meeting - 4th World ICH Conference

2–5 May, 2011; Newcastle, UK
E. jpatchick@kenes.com
eans@kenes.com

Brain plasticity and diversity

3–5 May, 2011; Valencia, Spain
T. (0034) 96 197 46 70
E. catedrag@cac.es

Gene targeting into the 21st century: Modeling of human disease from cancer to neuropsychiatric disorders

3–5 May, 2011; Valencia, Spain
T. (0034) 96 197 46 70
E. catedrag@cac.es

Tel Aviv Conference on Headache and Pain (CoPain)

4–5 May, 2011; Tel Aviv, Israel
E. copain@comtechmed.com
www.comtechmed.com/cury

9th Quadrennial Congress of the European Association of Neuroscience Nurses

4–7 May, 2011; Blakenberge, Belgium
www.eann2011.com

Diseases of the sellar and suprasellar regions

5 May, 2011; London, UK
T. 020 7290 2983
E. sections@rsm.ac.uk

Education

10 May, 2011; London, UK
E. louisewilkinson@cbituk.org
www.cbituk.org

Ninth European Paediatric Neurology Society

11–14 May, 2011; Cavtat (Dubrovnik), Croatia
E. epns2011@gmail.com
www.epns2011.com

STARS Cardiac Update Course

12 May, 2011; Leicester, UK
www.stars.org.uk/news-events/events

Irish Neurological Association Meeting 2011

12–13 May, 2011; Sligo, Ireland
admin@iicn.ie

EFNS Academy 2011

12–15 May, 2011; Stare Splyav, Czech Republic
E. pragueoffice@efns.org
www.efns.org

25th Annual PSG Symposium on Etiology, Pathogenesis, and Treatment of Parkinson's Disease and Other Movement

13 May, 2011; Irving, USA
www.parkinson-study-group.org

Education

17 May, 2011; Birmingham, UK
E. louisewilkinson@cbituk.org
www.cbituk.org

EFNS Regional Teaching Course – Yekatarinburg

May 18–20, 2011; Yekatarinburg, Russia
www.efns.org

SCE Examination for Neurology

18 May, 2011; London, UK
T. 020 3075 1321
F. 020 7486 8401
E. lisa.walsh@mrcpuk.org
www.mrcpuk.org

Education

19 May, 2011; Glasgow, UK
E. louisewilkinson@cbituk.org
www.cbituk.org

STARS Cardiac Update Course

19 May, 2011; Newcastle, UK
www.stars.org.uk/news-events/events

STARS Cardiac Update Course

20 May, 2011; Oxford, UK
www.stars.org.uk/news-events/events

Executive Function

20 May 2011; Cambridge, UK
T. 01353 652173
E. Rachel.everett@ozc.nhs.uk

6th Invest in ME International ME/CFS Conference 2011

20 May, 2011; London, UK
www.investinme.org

BITs 2nd Annual World Conference of NeuroTalk 2011

22–25 May, 2011; Dalian, China
Rose@bit-neurotalk.com
www.bitlifesciences.com/neurotalk2011/

XX European Stroke Conference

24–27 May, 2011; Hamburg Germany
www.eurostroke.eu

25th International Symposium on Cerebral Blood Flow, Metabolism and Function & 10th International Conference on Qualification of Brain Function with PET

25–28 May, 2011; Barcelona, Spain
www.kenes.com/brain

International Conference on Cognitive and Neural Systems Engineering

25–27 May, 2011; Tokyo, Japan
E. alerts@waset.org
www.waset.org/conferences/2011/tokyo/iccnse/

A 21st century review of complex Parkinson's therapy

27 May, 2011; Cambridge, UK
E. register@apo-go.co.uk

Magstim/University of Oxford TMS Summer School

28–29 May, 2011; Oxford, UK
E. tmschool@fmrib.ox.ac.uk

Cognitive Rehabilitation Workshop

28–29 May, 2011; Madrid, Spain
E. isabelvq@hotmail.com
www.braintreetraining.co.uk

21st Meeting of the European Neurological Society (ENS 2011)

28–31 May, 2011; Lisbon, Portugal
E. info@ensinfo.org
http://www.ensinfo.org/

June

7th Joint Annual Meeting of Austrian, German and Swiss League against Epilepsy

1–4 June, 2011; Graz, Austria
E. epilepsie2011@comeinsbruck.at
www.epilepsie-graz2011.at

CENTRE FOR BRAIN REPAIR
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 SCHOOL 2011**

**Restructuring the
 Deconstructing Brain:
 Neurodegeneration and its Repair**

*An advanced course for PhD students,
 Post Docs and Group Leaders*

Wednesday 30 March – Friday 1 April 2011
 Cripps Court, Magdalene College, Cambridge, CB4 3AD, UK

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[https://sales.admin.cam.ac.uk/
 events/eventdetails.asp?eventid=130](https://sales.admin.cam.ac.uk/events/eventdetails.asp?eventid=130)

For further information contact:
 BRC Reception, 01223 331160,
 skt37@cam.ac.uk



A 21st century review of complex Parkinson's

**FRIDAY 27TH MAY 2011,
 DOWNING COLLEGE, CAMBRIDGE, UK**

Introduction

Options for the management of the complex Parkinsonian patient

N Bajaj

Therapy related side effects in complex Parkinson's T Henriksen

History of apomorphine – an “old” drug? P Odin

Managing Complex Parkinson's – The Essentials

The role of Continuous Dopaminergic Stimulation R Katzenschlager
 CDS practicalities A nursing perspective on real life use

A Martin, J Mills, N Bryndum

Case Studies; Nodule management; Role of multidisciplinary teams
 (including Industry)

New dimensions in Parkinson's therapy

Non motor symptoms in Parkinson's – new data P Martinez Martin

Surgery vs Best Medical Therapy Is there a best strategy? R Hilker

EUROPAR – a new initiative for established therapies

K R Chaudhuri, P Reddy

Video case studies & discussion K R Chaudhuri, P Odin, T Henriksen

6 CPD points have been awarded

*This meeting has been funded by Genus Pharmaceuticals Ltd, who will
 also provide lunch, coffee & refreshments,
 and arranged in conjunction with EUROPAR.*

*The views expressed at this meeting are those of the speakers and may
 not necessarily reflect those of the meeting sponsors.*

For more information E. register@apo-go.co.uk

The Second Oxford Neurology Course

29 June – 1 July 2011



After a highly successful launch in 2010, we will be running the second Oxford Neurology Course from 29th June – 1st July 2011. The course is aimed at neurology trainees and consultants, and we will be covering a wide range of neurological topics. Talks will cover down to earth practical issues as well as science related themes and their clinical application. Once again, we have been able to attract highly acclaimed speakers from a range of sub speciality disciplines, and are looking forward to a few days of interesting talks and lively discussion. In addition, you will be able to soak up the atmosphere of Oxford in summer – living and dining in College, some cultural extras and perhaps a round of punting? Places are limited to 70 and will be allocated on a first come, first serve basis. We hope you will be able to join us.

The Course has been approved for 15 CPD credits by the Royal College of Physicians (London).

For further information, please contact Sally Beauchamp • Email: sally.beauchamp@clneuro.ox.ac.uk
 Telephone: 01865 231912 • Fax: 01865 231914 • Website: www.clneuro.ox.ac.uk

PREVIEW: Magstim's 5th Annual TMS Summer School

The Magstim Company is running its fifth annual TMS Summer School this year on Saturday 28th & Sunday 29th May, once again in collaboration with the FMRIB Centre of the University of Oxford. This year's event has two themes, with the first day focusing on 'Mapping causal brain-behaviour relationships' while the second will discuss 'Bench-to bedside translation in neurology and psychiatry'. In addition, there is a celebratory three course dinner in Wadham College Dining Hall on the Saturday.

As with previous events, a Young Investigator Award (YIA) will be announced at the meeting. Nominations, including self-nominations are encouraged. To enter, please send a CV and two recent papers (published or unpublished) to tmsschool@fmrib.ox.ac.uk by Monday 2 May, 2011. YIA applications will be adjudicated by an international panel of invited experts. The winner will be invited to give a brief talk on their work, will be an invited guest at the celebratory dinner on Saturday night, and will also

receive a \$750 prize, sponsored by Magstim.

In addition to the above, the event strongly encourages poster submissions from students, post-doctoral and established researchers working on any aspect of human brain stimulation. Based on attendee feedback from last year, this year's event will have longer poster sessions in a larger physical space to encourage quality scientific interaction. An abstract review committee will grade submissions and assess the poster sessions. A small number of the highest rated abstracts/poster presentations will be awarded prizes. Poster abstract submissions should include title, authors and affiliations, introduction, methods, results, conclusions and references (if required). Figures and tables may be included, but their size should be compressed sufficiently to ensure that they are deliverable by email. The word limit is a maximum of 500 words (excluding authors, affiliations, figure legends and references), and the maximum size is A0 in landscape orientation only.

Poster abstracts should be sent by the deadline of Monday 2nd May 2011, with an indication whether you would like to be considered for a prize oral platform presentation to: tmsschool@fmrib.ox.ac.uk. ♦

Full details about invited speakers, the programme and registration can be found at

<http://www.magstim.com/support/summerschool2011.html>.

Last year's event was heavily oversubscribed, so people are encouraged to book early to avoid disappointment.

The conference registration fee is £72, with an additional charge of £30 for those who wish to attend the dinner.

All payments are to be made in UK sterling and can be done online via Ticketsource at:

<http://magstim.ticketsource.co.uk>

PREVIEW: MS Frontiers 2011: Bringing Research Together to Beat MS

MS research spans many disciplines and involves a wide range of dedicated health professionals. MS Frontiers brings together experts from across the world to speak on MS research. This is your chance to participate in our exciting programme of events.

This year, MS Frontiers will be held on June 23rd and 24th at the Sofitel Hotel in London, Heathrow.

Plenary sessions will include internationally recognised speakers working in the field of MS who will appeal to anybody with an interest in MS research.

Professor Alastair Compston of the University of Cambridge will be recognised for his achievements in the field of MS research and will deliver the Ian McDonald Memorial Lecture.

Professor Mark Freedman of the Ottawa Hospital Research Institute will speak about stem cell transplantation approaches in the treatment of MS.

Professor Robin Franklin of the University of Cambridge will highlight his latest work

towards a regenerative medicine for MS, with a particular emphasis on myelin repair.

Dr Jeremy Chataway of the National Hospital for Neurology and Neurosurgery will speak about developing the MS Clinical Trials Network, a novel initiative that brings together experts across disciplines with the aim of running a groundbreaking clinical trial for people with progressive MS.

Professor Rona Moss Morris of the University of Southampton, Professor Peter Thomas and Dr Sarah Thomas of the Poole Hospital NHS Foundation Trust will cover new cognitive behavioural therapy approaches in helping people adjust to MS and in the management of fatigue, respectively.

In addition, the programme includes a number of parallel sessions to choose from;

- Immunology and therapies of MS
- Advances in imaging and biomarkers
- Measuring success: Health economics and patient reported outcome measures
- Innovations and symptom management care

- Genes and environment
- Protecting and repairing the nervous system

For the first time in the history of MS Frontiers there will also be a debate on the causes of MS, chaired by Professor Sir Andy Haines. Participants include; Professor George Ebers of the University of Oxford, Professor Gavin Giavanonni of Barts and the London School of Dentistry, Professor Alastair Compston of the University of Cambridge and Dr Paul Bull, a person affected by MS.

There will be the opportunity to present your work in the form of a poster. Students will have the chance to win a free place and travel bursary courtesy of the 'Rosemary Anne Price Award'. ♦

For more information visit www.msociety.org.uk/msfrontiers or ring 020 8438 0941 for a booking form. Early bird booking deadline is April 21st 2011.

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.

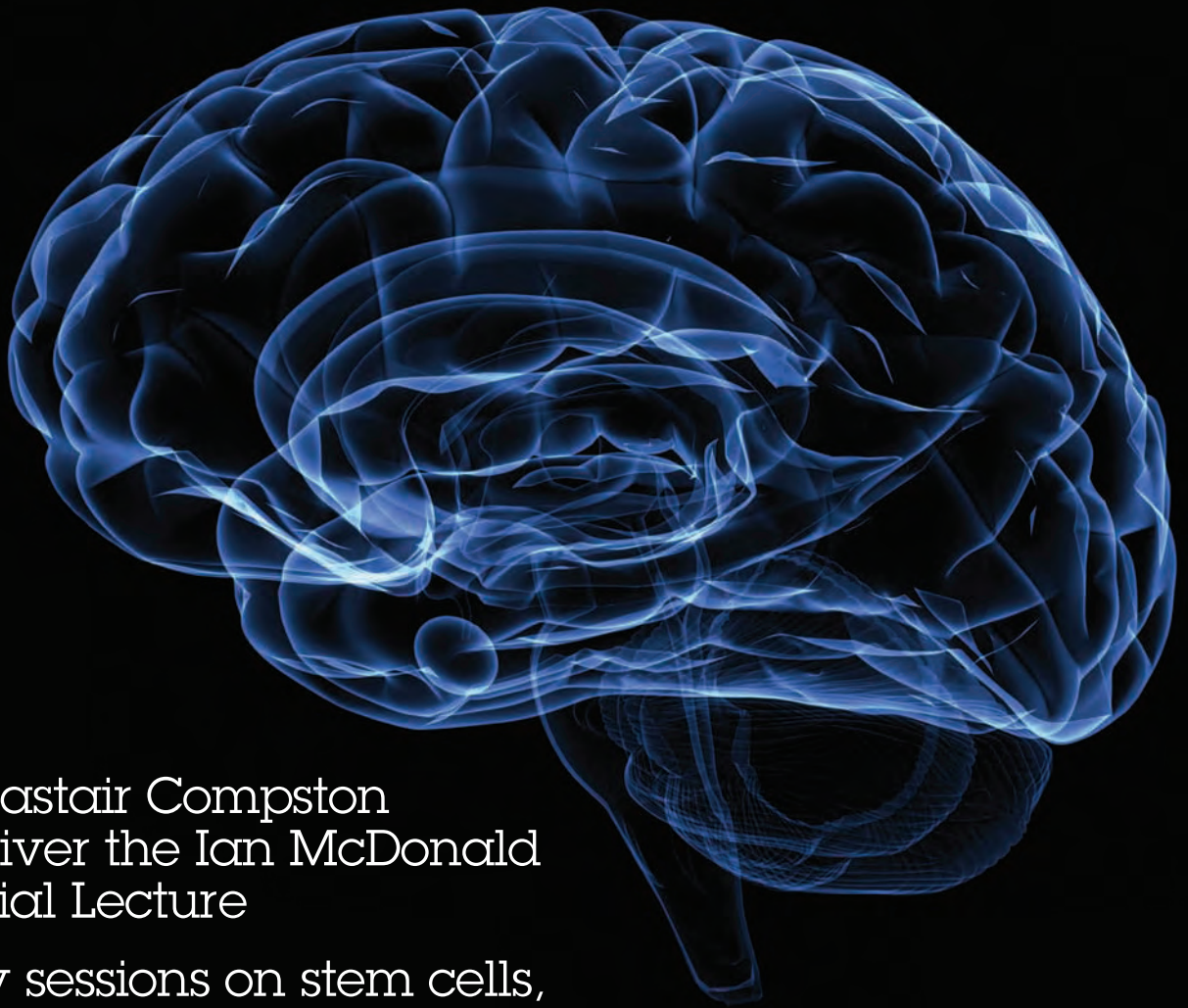


Multiple Sclerosis Society

MS Frontiers 2011

Sofitel London, Heathrow

23-24 June



- Prof. Alastair Compston will deliver the Ian McDonald Memorial Lecture
- Plenary sessions on stem cells, myelin repair, the UK clinical trials network and cognitive behavioural therapy
- Debate session on the causes of MS

Book Online www.mssociety.org.uk/msfrontiers



XXth WORLD CONGRESS OF NEUROLOGY With Africa • for Africa

Marrakesh, Morocco, November 12-18, 2011

With Africa, for Africa, **WCN 2011** provides Neurologists in Africa with a unique opportunity to join colleagues from around the world for the largest scientific event in Neurology. **Discover** scientific achievements and interact with delegates of diverse backgrounds and perspectives to find real solutions to improve the long-term outcomes for patients with neurological disorders.

www.wcn-neurology.org



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Saturday 28th & Sunday 29th May 2011
The Examination Schools, University of Oxford, UK

A scientific program organised as a single stream of lectures by distinguished international faculty. Invited talks have an educational goal in addition to presenting the results of cutting edge research.

Day 1: Mapping causal brain-behaviour relationships

Day 2: Bench-to-bedside translation in neurology and psychiatry

For the current programme and list of invited speakers, please visit:
www.magstim.com/support/summerschool2011.html

Registration

Registration fee: (includes admission to lectures and poster sessions, tea breaks and abstract submission). **£72**

Celebratory candlelit 3-course dinner in Wadham College: **£30**

All payments can be made online via Ticketsource at:

<http://magstim.ticketsource.co.uk/>

Early registration deadline: 30 April 2011

Late registration deadline: 16 May 2011 (conference attendance only).

For all enquiries please contact:
tmsschool@fmrib.ox.ac.uk

www.magstim.com



**Royal College
of Physicians**

Transient loss of consciousness (TLoC) and Epilepsy Wednesday 18 May 2011

National clinical guidelines on TLoC and on Epilepsy (update) are being produced and the Royal College of Physicians has organised this one day conference to facilitate the implementation of these guidelines.

This meeting is aimed at all medical and healthcare professionals who assess and diagnose adults and young people who have experienced transient loss of consciousness and those who diagnose, treat and manage epilepsy. This includes neurologists, cardiologists, acute physicians and trainees, GPs, allied healthcare professionals and pharmacists.

At the Royal College of Physicians, London NW1 4LE
Further information is available at
www.rcplondon.ac.uk/conferences
or Conference Department, Royal College of Physicians
Tel: 020 3075 1436/1300/1252. Email:
conferences@rcplondon.ac.uk



The Parkinson's Consultant Academy

In association with the **Movement Disorders Section British Geriatrics Society & Parkinson's UK**

Target audience: Consultant physicians, staff grade physicians, and final year specialist registrars with an interest in Parkinson's disease wishing to advance their knowledge and skills in this area.

The course will advance understanding of Parkinson's and related movement disorders through taught sessions and mentorship (a mentor will be appointed for each participant). This will be assessed through a range of learner centred methods including formal lectures, interactive workshops, projects, audits, and other assessments.

Residential Modules: Masterclass 20c

Module 1 – 25th-27th May 2011, Cornwall

Module 2 – 23rd-25th November 2011, Birmingham

Additional seminars and learning opportunities will be undertaken more locally with the mentor and through distance learning.

Cost: £650 inc VAT

Advanced Masterclass

This course is designed for all previous graduates from the Parkinson's Disease Classic or SpR masterclasses, mentors & speakers who wish to update their knowledge and further their understanding of PD management. A limited number of places will be available for anyone who hasn't attended the PD Masterclass. The next Parkinson's Academy PD Masterclass in association with the British Geriatrics Society Movement Disorders Section is:

Clinical advances, Commissioning and Parkinson's – A UK perspective

Course Date: 12th July 2011, 9 – 4.30 pm

Location: Hyatt Hotel, Birmingham

Course fee: £120.00 + VAT (Total £144.00)

Total places available 120

Link to site

<http://www.redpublish.co.uk/courses/advanced-masterclass/>

For more information

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Progress Towards Clinical Trials Using Stem Cells for ALS

Conference details: 24-25 January 2011; New York, USA. **Reviewed by:** Dr Brian Dickie, Director of Research Development, Motor Neurone Disease Association, Northampton, UK.

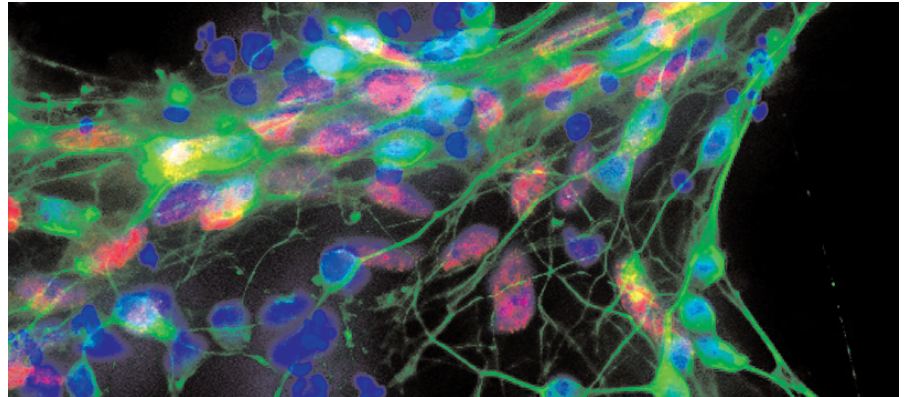
Sixty leading stem cell and amyotrophic lateral sclerosis (ALS) experts braved 18 inches of snowfall in New York, to share expertise and debate future developments in this fast emerging field of research, organised under the banner of the International Consortium of Stem Cell Networks.

The opening session, including presentations by Leonard van den Berg (Utrecht) and Chris Shaw (King's College London) brought everyone up to speed on the clinical and pathological 'spectrum' of the disease. A good amount of presentation time was given over to the role of TDP-43, a recently identified 'pathological hallmark' of dying motor neurons in up to 90% of ALS cases. However, the absence of TDP-43 aggregation in SOD1-mediated familial ALS raises valid questions on the applicability, to sporadic ALS, of much of the knowledge gained from over 15 years of research based on models of SOD1-mediated degeneration. Time will tell...

In his introduction to stem cell derivation and characterisation, Kevin Eggan (Harvard) raised the very pertinent question of whether stem cell derived motor neurons – in particular those derived from induced pluripotent stem (iPS) cells – are truly representative of those in the patient? Prof Eggan has been developing a 'scorecard' which will help predict at an early stage which stem cell lines will be the most efficient in generating the greatest motor neuron yield, saving time, effort and money. But are they really motor neurons? At the moment there is no consensus on what makes a neuron a motor neuron, so he outlined a series of tests that "provide confidence that these have more than a passing resemblance to motor neurons". Additional encouraging results suggest that motor neurons created from iPS cells are phenotypically similar to those obtained from embryonic stem cells. There are some differences however, so comparative work using both types will need to continue for the foreseeable future.

Siddharthan Chandran (Edinburgh) posed a question on the different types of motor neuron found in the spinal cord. There is no such thing as a 'generic' motor neuron, so can stem cell-derived motor neurons reflect this diversity of subtypes?

The answer is preliminary, but encouraging. Both Prof Chandran and Prof Hynek Wichterle (Columbia) presented data showing that iPS and embryonic stem cells can be turned into distinct motor neuron subtypes. Clearly, a model that can faithfully reflect the diversity of types found in the body will greatly assist understanding of vulnerable motor neuron populations in patients with different clinical



Motor neurons derived from human iPS cells. Courtesy of Prof Siddharthan Chandran, Bilada Bilican and Andrea Serio, University of Edinburgh.

patterns of disease.

The possibility of using stem cells for drug screening was covered in more detail by Chris Henderson (Columbia) who outlined some of the challenges being encountered in developing a human stem cell drug screen – one of which is the fact that new motor neurons are being generated in the dish over a prolonged period in culture. Continuous neurogenesis in vitro makes it difficult to establish a stable baseline on which to test the effects of drugs. Prof Henderson explained the strategies his group was adopting to get around the problem.

The remainder of the morning covered preclinical research studies that have laid the foundations for current and forthcoming clinical studies. Clive Svendsen (UW Madison) and Don Cleveland (UC San Diego) gave an introduction to a therapeutic strategy that does not attempt to rewire the nervous system, but instead aims to improve neurotrophic support for the surviving motor neurons through grafting of stem cell-derived astrocytes.

Astrocytes vastly outnumber neurons in the human CNS, dictating the condition of the 'cellular neighbourhood'. If more healthy astrocytes can be implanted into the spinal cord, it could turn an aberrant, toxic environment into a more protective one, with the potential to alter disease progression. The question is whether we can engraft enough cells to radically change the neighbourhood for good?

One human neural stem cell line that has cleared the US Government's regulatory hurdles is that developed by the biotechnology company Neuralstem. Neurosurgeon Nick Boulis (Emory) outlined the system that has been developed to ensure extremely accurate implantation into the spinal cord. He stressed the importance of safety, detailing how the spinal surgery procedure was rigorously tested, evaluated and refined, accompa-

nied by the creation of clear stopping criteria during the surgical procedure itself.

Day two started with an insightful and entertaining presentation from Doug Sipp (Kobe) on unregulated ALS treatments and public education. Dr Sipp provided a series of examples of the plethora of self-styled 'stem cell clinics' and the tactics they employ to attract business. Time was given over for a discussion on the issue of unregulated treatments, moderated by Rick Bedlack (Duke) one of the founders of ALSUntangled (www.alsuntangled.com) a consortium of ALS clinicians that use the Internet and social media to investigate alternative and off-label ALS treatments and providing the sort of objective information that helps patients to separate 'hope from hype'.

Jeff Rothstein (Hopkins) provided an update on the US National ALS Cell Bank, which has to date produced multiple iPS cell lines from patients with various known MND gene mutations. He stressed the need for a large number of well characterised cells to be made available to the research community, as each one will be slightly different, just like the donor patients themselves. The stem cell biotechnology iPerian, established to develop iPS-derived motor neurons for drug screening, is similarly generating multiple cell lines. The company has focused initially on spinal muscular atrophy, screening 78,000 compounds. Dr Ashkan Javaherian (iPerian) pointed out that modelling ALS is more complex, given the multifactorial nature of the disease. The key to developing a useful ALS model will be to find the common target pathways that underlie motor neuron degeneration, no matter what the initial cause of the disease. We are not at that stage yet, but judging from the work presented over the course of the two days of the meeting, we are heading in the right direction. ♦

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EDITOR'S CHOICE

Epilepsy: predicting sudden death

Sudden unexplained death in epilepsy is the unpredictable outcome of a significant minority of patients with epilepsy. Commoner in patients with more frequent seizures, especially tonic clonic seizures, it is assumed to be seizure-related. Necessarily difficult to investigate, the main hypotheses centre around neurogenic autonomic disturbance affecting the heart or breathing. Inspired by a tragic case of a death whilst in the telemetry unit, Jonathan Bird and his team have looked at the EEG characteristics of 30 seizures in 10 patients who later went on to suffer SUDEP and who had been monitored in their unit. They compared them to 90 seizures in 30 controls. In the index case, the EEG flat-lined, which they term postictal generalised EEG suppression (PGES), for nearly eight minutes, before the QRS complexes ceased on ECG, soon to be followed by cessation of P waves. The patient had become apnoeic some time before. They looked at the duration of PGES following tonic clonic seizures (TCS) and found that the mean for those patients who later died was 91.5 seconds (SD 181.3) compared to 15.6 seconds (SD 23.7) for controls. Assessing all seizures, they found that the odds ratio of risk of SUDEP was 1.49 with PGES > 10 seconds, rising in a stepwise fashion to 19.29 if it was over 80 seconds and reaching statistical significance ($P < 0.05$) if over 50

seconds. If they looked at only TCS, then the risk rose to 32.57 over 80 seconds and was significant for any value over 20 seconds. The effect appears only to be significant for TCS and the other seizure types had a diluting effect. The authors have analysed the other published deaths in telemetry units and have found that PGES preceded autonomic disturbance in each.

The numbers in this study are small. If corroborated then it would suggest a different direction as regards the mechanism of SUDEP with a reproducible primary cerebral disturbance underlying SUDEP, rather than a more random autonomic disturbance in response to a seizure. It requires telemetry to identify those at risk, and although those at highest risk (frequent seizures) often receive telemetry, the service is not universal. If they are identified then the next step is to develop appropriate interventions. We already implant a variety of devices into patients with epilepsy. Perhaps we could have one that provides an alarm when a patient has prolonged post-ictal flat-lining or triggers the phrenic nerves and the heart.

– **Dr Mark Manford**

– **An electroclinical case-control study of sudden unexplained death in epilepsy.** Lhatoo S, Faulkner HJ, Dembny K et al. *ANNALS OF NEUROLOGY* 2010;68:787-96.

Meta-analysis of genome-wide association studies (GWAS) in Parkinson's disease (PD)

The precise aetiology of idiopathic PD is, as its name suggests, unknown but, as with many complex diseases, is thought to be due to a mixture of environmental and genetic variables. The investigators involved in the four GWAS published to date for PD collaborated to produce a meta-analysis of these studies, and included a replication cohort for the significantly associated disease loci. Previously, loci associated with the tau and alpha-synuclein genes (MAPT and SNCA, respectively) have shown a consistent association, with BST1, LRRK2, GAK and HLA-DRB5 showing up in some studies. This meta-analysis and replication cohort confirmed these loci reached significance for GWAS, as well as identifying five other novel loci closely associated with the genes ACMSD, STK39, LAMP3, STY11, HIP1R. The genes associated with these loci are biologically plausible candidates for disease risk. For example, the ACMSD is associated with quinolinic acid (an excitotoxin) homeostasis, HIP1R is a huntingtin interacting protein involved in cell death pathways, the locus near STK39 (and of course HLA-DRB5) both support the hypothesis that inflammation is involved in the pathophysiology of PD, and LAMP3 is involved in protein secretion. Of course, it is an assumption that these single nucleotide polymorphisms (SNPs) are associated with causative genes. Furthermore, it is unclear exactly which SNP is the disease-associated SNP within each locus.

The locus associated with STY11 is near the GBA gene, a known risk factor for PD (and accounting for the association between Gaucher's disease and PD), although the signal from this locus was found to be independent of GBA mutations. Similarly, the SNP close to LRRK2 was independent of the common LRRK2 mutation, G2019S, raising the possibility that a splice variant produces a deleterious effect (rather than a gain of toxic function through a mutated protein).

The risk estimate per locus identified was relatively small, and thus the value of this GWAS (as with many other similar studies) lies not so much in their predictive risk and biomarker potential, but more in

predicting pathophysiology, prognosis, disease modelling, and so on. For example, the H1H1 MAPT haplotypes predict an increased likelihood of dementia in PD (Goris et al, 2007).

– **Dr Wendy Phillips, Addenbrooke's Hospital, Cambridge.**

– **International Parkinson's Disease Genomics Consortium. Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies.** *LANCET* 2011;377:641-9.

– **Goris A et al. Tau and synuclein in susceptibility to, and dementia in, Parkinson's disease.** *ANNALS OF NEUROLOGY* 2007;62:145-53.

Novel genetic testing strategies in Charcot-Marie Tooth disease

A year has passed since Lupski et al. reported for the first time the successful use of whole-genome sequencing in making a definitive genetic diagnosis. The inherited condition studied was Charcot-Marie-Tooth disease (CMT). As most readers of this journal will know, CMT is one of the commonest neurological disorders seen in the clinic and is now known to be associated with mutations in over 35 genes. Readers will also know that the facility to request whole-genome sequencing has not yet reached the out-patient clinic (in the UK at least), and with the cost estimated to be still around \$30,000 per patient, there is little prospect that this technology will be in routine use in the very near future. Therefore, how can we balance the need to make a definitive genetic diagnosis whilst ensuring the most efficient use of precious resources?

Writing in *Annals of Neurology*, Saporta et al. provide useful information upon which to base our investigative approach when confronted by a patient with the clinical features of CMT. The authors describe their experience of evaluating a total of 787 patients with a clinical diagnosis of CMT who have attended their CMT clinic at Wayne State University in Detroit. 527 of these patients were given a genetic diagnosis (67%). Significantly, 91% of these patients with genetically confirmed CMT harboured mutations in one of four genes (PMP22, MPZ, GJB1 and MFN2). This allowed the authors to propose useful clinical algorithms

to make specific genetic diagnoses of CMT using targeted neurophysiological criteria and inheritance patterns. Of course, these algorithms can only be applied to similar populations and therefore they are less likely to be relevant when applied to populations with a higher proportion of autosomal recessive traits. Furthermore, despite the apparent high proportion of patients given a specific genetic diagnosis, a causative genetic diagnosis could only be achieved in around 30% of patients with axonal CMT (CMT2), highlighting again an area that needs further investigation. Nevertheless, Saporta et al.'s work will be particularly relevant in the USA where the use of large genetic panels performed by commercial laboratories is common practice, which is arguably an inefficient use of resources based on their findings. Moreover, the conclusions partly vindicate the practice of careful phenotypic and neurophysiological observation followed by targeted genetic testing.

While Saporta et al. show that the single gene approach will be successful if applied carefully in CMT, improvements in DNA sequencing technology are likely to supersede this approach in order to rapidly identify mutated genes in inherited diseases. One such technique is known as exome sequencing. It is estimated that 85% of all Mendelian diseases are caused by mutations in protein-coding exons. However, protein-coding exons comprise only around 1% of the whole genome. Therefore, in contrast to whole-genome sequencing as described by Lupski et al., exome sequencing has the potential to identify relevant mutations in genetic diseases such as CMT in less time and at a fraction of the cost. Again in *Annals of Neurology*, Montenegro et al. describe the successful application of exome sequencing to pinpoint a mutation in the GJB1 gene in a previously undiagnosed family leading to X-linked CMT (CMT-IX). While the authors are quick to point out that in hindsight there were clinical clues pointing to CMT-IX, the exciting conclusion is that this method is current, and that the cost, estimated to be around \$1250, is likely to continue to fall in conjunction with continued improvements in accuracy and exome coverage. Furthermore, exome sequencing provides information on thousands of genes, including others implicated in CMT, which may help to explain why a single mutation in a causative gene may lead to different degrees of clinical severity.

While these exciting advances offer great diagnostic potential, there remains unfortunately no specific treatment for CMT. Therefore, some will argue that there is little to be gained from obtaining a definitive genetic diagnosis. However, only by identifying mutations in genes associated with CMT and understanding the functions of the resulting proteins will our understanding of peripheral nerve physiology lead to targeted specific therapies in the future. These two studies therefore describe how best to begin to do this at the present time.

– **Dr Rhys Roberts, Norfolk and Norwich University Hospital NHS Trust.**

– **Saporta AS et al. Charcot-marie-tooth disease subtypes and genetic testing strategies. ANNALS OF NEUROLOGY 2011;69(1):22-33.**

– **Montenegro G et al. Exome sequencing allows for rapid gene identification in a Charcot-Marie-Tooth family. ANNALS OF NEUROLOGY 2011 Jan 20 epub.**

A two hit model for motor neuron disease due to FUS mutation

Quite rightly, a lot has been made of the RNA processing genes/proteins that have recently been implicated in motor neurone disease, specifically TDP-43 and FUS. An important next step, to identify how they contribute to neurodegeneration and what exactly they do to RNA, is a challenge, as these molecules have diverse and complex roles, from influencing gene expression to mRNA transport. FUS is normally a mainly nuclear protein, but in rare cases of ALS caused by FUS mutation it ends up in cytoplasmic inclusions (Vance et al; Kwiatkowski et al). Several groups have recently made progress in understanding the nature of these inclusions (Ito et al; Bosco et al; Dormann et al; Gal et al) with results that are reassuringly complementary.

Ito et al. focus on transient transfections in cellular models to show that the C-terminus of FUS contains a nuclear localisation sequence

(NLS). Much of their data simply confirms what was previously demonstrated by Vance et al and Kwiatkowski et al. Bosco et al. go further and describe a particularly severe, early onset ALS caused by a C-terminal truncation of FUS, which causes the greatest degree of cytoplasmic mislocalisation of any FUS mutation so far described. Their hypothesis that increased cytoplasmic localisation correlates inversely with age of onset is nicely supported by quantitative studies of a series of FUS missense mutations conducted by Dormann et al. Further analyses by Ito and Dormann support a mechanism of NLS functioning that utilises Transportin and is dependent on Ran GTPase activity. Nice work, though almost all of these findings had been suggested in studies conducted by Lee et al in 2006! Nevertheless, it is important to have it shown experimentally in the context of disease-linked mutations.

More novel is the finding by these groups that under cellular stress, mutant FUS associates with stress granules (SG). SGs are a type of intracellular aggregate made up of RNA molecules and components of translational machinery. They are formed in times of cellular stress (such as hypoxia, heat shock and oxidative stress) and are thought to arrest unnecessary RNA translation, encouraging cells to focus on recovery and repair (Anderson and Kedersha). Bosco et al. take the analysis further, utilising stable transfections and zebrafish models to show that SG formation is a reversible phenomenon and does not impact on cellular viability. Meanwhile, Dormann et al. demonstrate the presence of SG markers in inclusions in post mortem tissues of mutant FUS ALS cases. They make similar pathological observations in other FUSopathies including atypical FTL-D, basophilic inclusion body disease (BIBD) and neuronal intermediate filament inclusion disease (NIFID). However, even these findings are not entirely novel, as inclusions of BIBD have previously been found to harbour RNA and SG components (Fujita et al.).

These studies agree that C-terminal mutation of FUS shifts the equilibrium towards cytoplasmic expression, and that this mislocalisation encourages SG formation: a 'two hit model'. How this could impact on motor neuronal or glial response to stress remains undetermined, and which (if any) RNA molecules are harboured in these SGs is unknown. Furthermore, not all FUS mutations are C-terminal: the cellular effects of N-terminal mutations remain unidentified.

– **Dr Jemeen Sreedharan, King's College, London.**

– **Vance C et al. Mutations in FUS, an RNA processing protein, cause familial amyotrophic lateral sclerosis type 6. SCIENCE 2009;323:1208-11.**

– **Kwiatkowski TJ Jr et al. Mutations in the FUS/TLS gene on chromosome 16 cause familial amyotrophic lateral sclerosis. SCIENCE 2009;323:1205-8.**

– **Ito D et al. Nuclear transport impairment of amyotrophic lateral sclerosis-linked mutations in FUS/TLS. ANNALS OF NEUROLOGY 2011;69:152-62.**

– **Bosco DA et al. Mutant FUS proteins that cause amyotrophic lateral sclerosis incorporate into stress granules. HUM MOL GENET 2010;19:4160-75.**

– **Gal J et al. Nuclear localization sequence of FUS and induction of stress granules by ALS mutants. NEUROBIOL AGING. 2010 Jul 29. [Epub ahead of print]**

– **Dormann D et al. ALS-associated fused in sarcoma (FUS) mutations disrupt Transportin-mediated nuclear import. EMBO J. 2010 18;29:2841-57.**

– **LEE BJ et al. Rules for nuclear localization sequence recognition by karyopherin beta 2. Cell 2006 11;126:543-58.**

– **Anderson P, Kedersha N. Stress granules: the Tao of RNA triage. TRENDS BIOCHEM SCI. 2008 ;33(3):141-50.**

– **Fujita K et al. Immunohistochemical identification of messenger RNA-related proteins in basophilic inclusions of adult-onset atypical motor neuron disease. ACTA NEUROPATHOL. 2008;116(4):439-45.**

On the origin of NMDAR-antibodies

Most clinicians seeing patients with the now well-recognised syndrome of NMDAR-antibody encephalitis (Dalmau et al *Lancet Neurology* 2008, Irani et al *Brain* 2010) have been able to recollect similar cases during their career: it does not appear to be a de novo clinical phenomenon. Previously, such illnesses were probably attributed to an unknown virus, Hashimoto's encephalopathy or termed encephalitis lethargica (Dale et al. *Ann Neurol* 2009). The study of Pruss et al. confirmed this clinical

suspicion and their cases highlighted many of the emerging clinical and paraclinical observations in this field.

Pruss et al. found that of 505 cases between 18 and 35 years of age admitted to the Berlin ICU over five years (many prior to the description of NMDAR-antibodies), seven met their criteria for an encephalitis of unknown aetiology. Six of these had positive NMDAR-antibodies tested using archived serum/CSF. They concluded that NMDAR-antibody encephalitis is a frequent disorder among young ICU patients with unknown encephalitis, with a higher frequency than estimated from previous similar studies (Davies et al *Crit Care Med* 2010). In particular, their clinical data emphasised a tumour rate of 33% in young females (lower than some previous estimates), a low rate of spontaneous remission (seen in 1 patient) and high relapse rates (50%). Their data agreed with previous calls for early and aggressive immunotherapies in patients with NMDAR-antibody encephalitis (Irani et al *Brain* 2010).

Pruss et al also showed that serum levels of NMDAR-antibodies were many times higher than CSF levels in all but one case. This fits with the concept that the antibody response is generated peripherally and is secondarily perpetuated within the intrathecal compartment. Access to the CNS, and a breach in the blood-brain barrier, may be driven by an infectious process and, interestingly, Pruss et al showed IgM positivity to a variety of microbes in all six patients. The lack of a consistent microbe is against the notion of molecular mimicry in this condition. Finally, they confirmed previous observations that the NMDAR-IgG have the capacity to downregulate surface NMDARs, providing a mechanism of antibody pathogenicity in this disorder.

– Dr Sarosh R Irani, Specialist Registrar in Neurology, John Radcliffe Hospital, Oxford, UK.

– Prüss H et al. Retrospective analysis of NMDA receptor antibodies in encephalitis of unknown origin. *NEUROLOGY* 2010;75:1735-9.

Epigenetic control of regulatory T cells applicable to an animal model of multiple sclerosis

CD4+Foxp3 regulatory T cells (Tregs) are involved in maintaining immune tolerance and are thereby important in protecting against autoimmunity. Tregs are known to be dysfunctional in autoimmune diseases such as multiple sclerosis (MS), but the causes of their abnormal behaviour as well as the precise mechanisms driving Treg differentiation and functions are currently unknown.

Liu et al. (2010) investigated the molecular mechanisms underlying Treg differentiation in mice and found that PIAS1 (protein inhibitor of the activated signal transducer and activator of transcription STAT1) is centrally involved in this process: the PIAS1 protein binds to Foxp3 promoter causing recruitment of DNA methyltransferases and heterochromatin protein 1, which in turn cause epigenetic modifications, i.e. chemical and structural modifications in the DNA. As a result, the promoter region is maintained in a state where the expression of Foxp3 is repressed. While it has been previously shown that Foxp3 is a critical regulator of Treg differentiation and that Foxp3 expression is under epigenetic control, the role of PIAS1 in this process had not been previously demonstrated. Consistent with the role of Tregs in development of autoimmunity, *Pias1*^{-/-} mice were also resistant to the development of experimental autoimmune encephalomyelitis. Although these results provide novel insights into the process of Treg development, it remains to be investigated whether dysfunctions of PIAS1 also contribute to autoimmune disease pathogenesis in humans. At present, there is no evidence suggesting that genetic polymorphisms in PIAS1 would be associated with autoimmune diseases, while the potential role of differential epigenetic control of FOXP3 has not yet been examined. Indeed, epigenetic modifications depend not only on single genes such as PIAS1, but also on exposure to various environmental factors. As platforms are now available for screening epigenetic variations such as

methylation on a whole genome scale, it is likely that epigenetic differences in autoimmune patients will be reported in the near future. These studies will hopefully add to our understanding of molecular mechanisms regulating immune cell functions and autoimmunity.

– Dr Anu Kempinen, Cambridge University.

– Liu et al. The Ligase PIAS1 Restricts Natural Regulatory T Cell Differentiation by Epigenetic Repression. *SCIENCE* 2010;330:521-5.

New ways to improve your memory?

How do we consolidate and retain memories is a question that troubles us all as we struggle to remember this or that, but a new paper in *Nature* by Chen et al. has shown that insulin like growth factor II (IGF-II) may be a rather important molecule in this process. In this paper they studied memory in rodents using an inhibitory avoidance [IA] task and then through a series of different approaches they dissect out the effects, to show that IGF-II is critical in memory consolidation and memory retention.

They show that IA is associated with an increase in (the easy to remember!!) hippocampal transcription factor CCAAT enhancer binding protein β (C/EBP β) and that this then binds to the promoter region of IGF-II exon 1 leading selectively to its increased expression (i.e. not IGF-I). This then underlies the memory consolidation because blocking this pathway prevents the memory being stored, but this is restricted to a time window of up to four days. This having been shown, they then move on to investigate the downstream events following IGF-II activation to show that this then produces a selective effect at hippocampal (not amygdala) synapses. This involves protein synthesis and Arc with changes in GluR1 and GSK3 β expression and enhanced LTP. So there we have it, simple as that!!

This is a true tour de force, as the amount of work that has gone into dissecting this pathway is not to be underestimated, as is the attention to detail showing exactly what changes when and what does not. This study is not only an impressive body of elegant experimental work, but highlights how a single molecule can have profound effects on a rather diffuse process and by so doing it raises the possibility that targeting aspects of this system may have profound effects on memory- assuming one can remember when exactly to give it relative to the memory that needs to be formed!

In contrast to this highly selective approach is the study of Erikson et al. who seek to explore the hippocampus and its mnemonic functions through its capacity to respond to environmental influences through changes in neurogenesis and or neuronal dendritic arborisation, especially in the context of exercise and local BDNF production. Erikson et al. in PNAS report of their study of 120 healthy elderly human adults aged 55-80 years old who completed a 12 month study (~82% recruitment and retention) in which they were subject to either aerobic training or the rather less strenuous stretching exercises. They had MRI scans done at baseline and at 6 and 12 months along with some cognitive tests and serum BDNF levels. They report that patients in the active exercise groups showed selective enlargement of the anterior hippocampus (~2%) compared to a slight loss in volume in the control arm (~1.4%). The changes were only seen in the anterior hippocampus and not the posterior hippocampus or caudate or thalamus and were associated with changes in levels of fitness and serum BDNF levels and possibly to a degree also cognitive function.

This is a very interesting study, although they explain the data by joining the dots up, without proving any causal links. It would be interesting to know whether the volume changes are sustained and how much noise there is in these MRI measurements, and how these changes relate to the common BDNF polymorphism known to alter its secretion. There is no causal link between changes in serum BDNF and volume or cognitive changes, they are simply associated, and it would have been useful to prove this using other strategies that alter serum BDNF levels. So whilst the study clearly shows the effects of exercise are good for the brain, it is not shown how this occurs nor whether it has long term benefits.

– **Roger Barker. A critical role for IGF-II in memory consolidation and enhancement.** Chen DY, Stern SA, Garcia-Osta A et al. *NATURE* 2011;469:491-7.
Exercise training increases the size of hippocampus and improves memory. Erickson KI, Voss MV, Prakash RS et al. *PROC.NATL.ACAD.SCI.* 2011;108:3017-22.

Hepatitis C and neuropathy are we under-estimating the prevalence?

It has been known for some time that Hepatitis C virus can be associated with a peripheral neuropathy. This was mainly thought to be due to an underlying mixed cryoglobulinemia and ensuing vasculitis. However, neuropathic symptoms can be seen in patients without a documented cryoglobulinaemia and are thought to be due to the neurotoxicity of the virus itself or its treatment with alpha interferons. In the recent issue of *Journal of Neurology*, Yoon et al specifically look at the prevalence, clinical and neurophysiological characteristics of sensory neuropathy in patients with HCV infection, but without cryoglobulinaemia. Small fibre neuropathic symptoms like burning pain or paraesthesias cannot usually be evaluated by the standard large-fibre neurophysiological examinations and may require thermal and mechanical quantitative sensory testing or even skin biopsies to assess the intra-epidermal nerve fibre densities.

The authors studied 46 consecutive cryoglobulin negative HCV patients with (24) and without (22) neuropathic symptoms and compared them with 28 age and gender-matched controls. Patients were included if they were between 18 to 55 years of age, with HCV infection and a negative serum cryoglobulin test. Patients with confounding factors like alcohol, diabetes, HIV, entrapment neuropathies or multiple sclerosis were excluded. All patients and controls received standardised questionnaires to assess the neuropathic symptom score (including questions on pain, cramp, numbness, paresthesia and fatigue), using a scale of 0-2, with higher scores for more severe symptoms. Neurological examination was used to assess the neuropathy deficit score, which included assessment of reflexes, perception of pain, vibration sense and theraesthesia. Higher scores were given for absence of reflexes or when the sensory deficit was farthest from the toes. Neurophysiological examination included assessment of sensory nerve conduction velocities (SNCV) of the median, peroneal, tibial and sural nerves. In addition, pain-related evoked potentials (PREP) were elicited to evaluate small fibre neuropathy.

Only 28% of patients had abnormal SNCV of the large nerves, whereas 52% of HCV patients had neuropathic symptoms. However, the use of PREP as a tool for evaluation of small fibre neuropathy showed a prevalence of 43.5% for HCV-related neuropathy in the absence of cryoglobulinaemia. This is interesting since previous reports suggest a prevalence of 5-15% for neuropathy in HCV patients even in the presence of cryoglobulins. However, the current study did not find a correlation of the neuropathy scores with that of viral load or disease duration, possibly due to the small sample size. As with previous observations, patients who have had alpha-interferon therapy were more likely to have an underlying neuropathy (48.5%) as opposed to treatment-naïve (30.8%) patients, confirming the neurotoxicity of these agents.

Treatment in cryoglobulin-negative HCV patients with neuropathy is largely an evidence-free zone until we find an effective test to differentiate the neuropathy due to the virus from neuropathy due to treatment with alpha-interferon. However, in HCV associated with mixed cryoglobulinaemia syndrome (MCS), recent management guidelines (Pietrogrande M. et al.) recommend the following:

1. In mild to moderate HCV-associated MCS, pegylated interferon with ribavirin
 2. Severe HCV with neuropathy, skin-ulcers or vasculitis, rituximab with high-dose pulsed glucocorticosteroids
 3. In severe life-threatening hyperviscosity syndrome, plasma exchange.
- Data for the support of use of cyclophosphamide and colchicine

are limited, but they are still used in certain circumstances. As more and more HCV patients survive longer and are subjected to immune therapies, neurologists should be aware of the rising prevalence of neuropathies in these patients. Evaluations using more sensitive techniques for small-fibre neuropathy might be beneficial in targeting therapy as per the recent guidelines, at least in patients with an underlying cryoglobulinaemia.

– **Saiju Jacob, Consultant Neurologist, Queen Elizabeth Neurosciences Centre, University Hospitals of Birmingham NHS Foundation Trust.**

– **Yoon MS, Obermann M, Dockweiler C, et al. Sensory neuropathy in patients with cryoglobulin negative hepatitis-C infection.** *J NEUROL.* 2011;258(1):80-8.

– **Pietrogrande M, Devita S, Zignego A, et al. Recommendations for the management of mixed cryoglobulinemia syndrome in hepatitis C virus-infected patients.** *AUTOIMMUN REV.* 2011 Feb 14. [Epub ahead of print]

The incredible vanishing control group

It is not always easy to apply the basic tenets of evidence based medicine to the study of brain injury rehabilitation. The vast baseline differences in pre-morbid functioning, the heterogeneity of injury mechanism, the difficulty in standardising the intervention and the challenge of selecting and justifying outcome measures for a particular population mean that applying the gold standard double-blind placebo controlled trial is at best impractical and, at worse unethical.

There are numerous examples of endocrine dysfunction following acquired brain injury; often in the context of a morphologically intact hypothalamo-pituitary axis. While there are obvious implications for physical health as a result of failing to adequately assess and manage hormonal deficiencies following brain injury, there are also the potential effects on cognitive performance to consider. Impairments in emotional consistency, wakefulness and higher functions are well recognised sequelae of specific endocrine disturbances even without the superimposition of focal or generalised brain injury. One would assume that the identification and rectification of endocrine dysfunction following brain injury should result in improvements in cognitive outcome. That specific deficiencies and adequate response to treatment may be identified through biochemical assays mean that correlation of a change in cognitive performance with treatment should be possible.

Of course, in order to prove the benefits to cognitive ability of hormone replacement, it would be necessary to demonstrate changes relative to a control group. So, for example, if a group of individuals with growth hormone (GH) deficiency following a brain injury were identified, their response to treatment could be compared with an untreated group. Clearly this may be an issue for those with untreated GH deficiency, so how about administering GH to those who have had a brain injury but without a demonstrable deficiency? Clearly this may be difficult to justify. A historical sample, looking at individuals with previously undiagnosed GH deficiency and their subsequent response to treatment might be considered? Or, perhaps, assessing GH deficient individuals without brain injury would add more information.

Unfortunately, this paper looking at the effects of GH supplementation on those with GH deficiency following brain injury uses a non-GH deficient brain-injured control group. There are areas of improvement in some sub-scales of cognitive testing in both groups, who also have regular therapist-led “cognitive rehabilitation”. In the end, the effects of this additional rehabilitation, natural recovery and the GH supplementation cannot be untangled and there are more questions than answers. The use of the non GH-deficient control group doesn't really tell us anything about the study group, beyond reinforcing the importance of assessing endocrine function following brain injury.

– **Lloyd Bradley, Western Sussex Hospitals.**

Reimunde P, Quintana A, Castanón B, Casteleiro N, Vilarnovo Z, Otero A, Devesa A, Otero-Cepeda X L, Devesa J. Effects of growth hormone (GH) replacement and cognitive rehabilitation in patients with cognitive disorders after traumatic brain injury. *BRAIN INJURY.* January 2011;25(1):65–73.

Fujifilm introduces their first ultrasound system in the UK

FAZONE CB is a portable, lightweight ultrasound system offering high image quality on its large 12" screen, making it ideal for hospital wards and outpatient departments, as well as examination rooms or vehicles. It is ergonomically designed to provide user-friendly operation, with easy-to-use large buttons, which are grouped according to examination mode. FAZONE CB is equipped with a 'sound speed correction' function for faster, clearer examinations. This is based on ZONE Sonography™ technology, which transmits a broader ultrasound beam to collect extensive echo data immediately by using large zones.

The system has USB, HDMI and network ports, so data can be exported easily in DICOM as well as JPG format. In addition, workflow can be further optimised with the use of Fujifilm's FCR View workstation. The FCR View enables transfer of ultrasound images, and their integration with patient information, to facilitate centralised



management. It also features a one-hour rechargeable battery pack for ultimate ultrasound on the go.

For further information Tel. 01234 326 780, www.fujimed.co.uk

Nikon launches next generation confocal microscope

Nikon Instruments has launched the next generation Confocal Laser Point Scanning Microscope for entry and mid-level confocal imaging. The new modular C2 confocal laser microscope provides increased accuracy and speed. The C2 incorporates the latest version 3.2 release of NIS-Elements C software, providing one, easy-to-use and versatile imaging software platform for complete control with unrivalled imaging options – whether it be confocal or widefield. Offering excellent hardware and software stability, coupled with first class optics, the C2 confocal laser microscope has three dedicated PMTs for multi-channel imaging. The flexible, modular design offers an easy upgrade to the dedicated 32 channel PMT array for spectral detection. The new system can capture and unmix data acquired at any channel resolution across the entire detector bandwidth, while an



increased number of optically ideal pinholes (from four to six) and electronics improvements increase scanning accuracy and speed; up to a maximum 24fps (512x32) and 4 fps (512x512, bidirectional) have been achieved. An optional four laser module is also available.

For more information contact Nikon Instruments Europe, Tel. +44 (0)208 2471718, E. info@nikoninstruments.eu, www.nikoninstruments.eu/C2

GSK drops price of Parkinson's drug ReQuip XL by 60%

GlaxoSmithKline (GSK) UK has reduced the price of ReQuip XL (ropinirole prolonged release) by 60%. ReQuip XL will now cost less than other dopamine agonists, which could deliver a cost-saving to the NHS of up to £15 million in 2011 and allow more people with Parkinson's to access this medicine.

Under the current Pharmaceutical Price Regulation Scheme (PPRS) agreement between the government and the pharmaceutical industry, GSK has committed to reduce the total cost of GSK products to the NHS. In order to deliver on this commitment, GSK has decided to reduce the price of ropinirole prolonged release.

Dr Mark Toms, Medical Director, Neurology, Immunology & Hepatitis, GSK UK Pharmaceuticals commented, "We believe that people with Parkinson's deserve access to once-daily dopamine agonists, but recognise that increasing cost pressures may restrict access to these medicines. We believe that a price reduction will benefit the NHS in delivery of care to patients."

Medical Rehabilitation in 2011 and Beyond

The Royal College of Physicians with support from the British Society of Rehabilitation Medicine have recently published a working party report entitled Medical rehabilitation in 2011 and beyond.

The report examines the current state of rehabilitation medicine, and considers how it is likely to develop over the coming years.

To download the document for FREE, please visit: <http://bookshop.rcplondon.ac.uk/details.aspx?e=320>

Merck committed to Cladribine Tablets

Merck KGaA has received a complete response letter from the US Food and Drug Administration (FDA) on the new drug application for Cladribine Tablets, Merck's proprietary investigational oral formulation of cladribine, as a therapy for relapsing-remitting multiple sclerosis (MS).

A complete response letter is issued by the FDA when their review is complete and the application cannot be approved in its present form. The FDA concluded that substantial evidence of Cladribine Tablets' effectiveness was provided by the CLARITY study. However, they have requested that Merck provide an improved understanding of safety risks and the overall benefit-risk profile either through additional analyses or by additional studies. Merck will identify whether data from completed and ongoing clinical studies can address the Agency's questions.

Merck remains committed to the ongoing clinical trials with Cladribine Tablets. These fully-enrolled trials will provide additional information on the efficacy and safety of Cladribine Tablets in MS.

Cladribine Tablets are approved and available under the trade name Movectro® in Australia and Russia as a treatment of relapsing-remitting MS and are under regulatory review in other countries.

MHRA approve new Bipolar Disorder License for Episenta

Beacon Pharmaceuticals has announced that its once daily Episenta (prolonged release sodium valproate) now has a licence extension for acute mania and continuation of treatment when lithium is not suitable. The simple once daily dose makes Episenta a logical choice when choosing valproate.

For several years NICE have recommended valproate as first line for the treatment and long term management of bipolar disorder. Until now valproate was only licensed for acute treatment - which meant off licence usage for continuation treatment. Now Episenta can offer a fully licensed indication to treat both acute and maintenance treatment in line with NICE recommendations.

NICE also recommend that patient preferences should be taken into account with particular reference to future



prophylactic use. Previous studies in bipolar disorder have found that adherence can be an issue. In one review of 44,637 patients, 46% were either not complying or partially complying with their medication. Results suggested that the effectiveness of bipolar medication treatments is likely to be reduced by high rates of non adherence to treatment, especially when regimens are complicated, resulting in an unnecessary increase in manic or depressive episodes.

Episenta is a once daily treatment that can be taken at bedtime, helping to increase adherence and thus increasing effectiveness and patient satisfaction.



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PRE-FILLED SYRINGE PRESCRIBING INFORMATION

Presentation – Glatiramer acetate 20mg solution for injection in 1ml Pre-filled Syringe. **Indication** – Treatment of patients who have experienced a well-defined first clinical episode and are determined to be at high risk of developing clinically definite multiple sclerosis (MS). Reduction of frequency of relapses in relapsing-remitting MS in ambulatory patients. In clinical trials this was characterised by at least two attacks of neurological dysfunction over the preceding two-year period. **Dosage and administration** – 20mg of glatiramer acetate (one pre-filled syringe) administered sub-cutaneously once daily. **Children (12 – 18 years)** No specific studies. Limited published data suggest the safety profile of 20mg administered sub-cutaneously once daily is similar to that seen in adults. **Children (<12 years)** Not recommended. **Elderly** No specific data. **Impaired renal function** No specific studies. Monitor renal function during treatment and consider possibility of deposition of immune complexes. **Contra-indications** – Known allergy to glatiramer acetate or mannitol (excipient). **Pregnancy. Special warnings and precautions** – Sub-cutaneous use only. Initiation to be supervised by neurologist or experienced physician. Supervise first self-injection and for 30 minutes after. One or more of vasodilatation, chest pain, dyspnoea, palpitations or tachycardia may occur within minutes after injection. These generally resolve spontaneously after a short time. If severe, treat symptomatically. Caution in patients with pre-existing cardiac disorders and review such patients regularly. Rarely convulsions and/or anaphylactic or

allergic reactions. Rarely, hypersensitivity (bronchospasm, anaphylaxis or urticaria). If severe, treat appropriately and discontinue Copaxone. **Interactions** – No formal evaluation. Increased incidence of injection-site reactions with concurrent corticosteroids. Theoretical potential to affect distribution of protein-bound drugs, therefore concomitant use of these should be monitored. **Pregnancy and lactation** – Not to be used in pregnancy. Consider contraceptive cover. No data on excretion in human milk. **Undesirable effects** – Local injection site reactions (erythema, pain, mass, pruritus, oedema, inflammation, hypersensitivity, injection site atrophy). An immediate post-injection reaction (one or more of vasodilation, chest pain, dyspnoea, palpitation, tachycardia) may occur within minutes, reported at least once by 31% of patients receiving Copaxone compared to 13% of patients receiving placebo. Other undesirable effects more than 2% (>2/100) higher incidence in the Copaxone treatment group than in the placebo group: Nausea, anxiety, rash, back pain, chills, face oedema, vomiting, skin disorder, lymphadenopathy, tremor, eye disorder, vaginal candidiasis, weight increased. Rarely: Anaphylactoid reactions. Please refer to the SPC for a full list of adverse effects. **Overdose** – Monitor, treat symptomatically. **Pharmaceutical Precautions** – Store Copaxone in refrigerator (2°C to 8°C). If the pre-filled syringes cannot be stored in a refrigerator, they can be stored at room temperature (15°C to 25°C) once for up to one month. Do not freeze. **Legal Category** – POM. **Package Quantity and Basic NHS Cost** – 28 pre-filled syringes of Copaxone: £513.95. **Product Licence Number** – 10921/0023.

Further Information – Further medical information available on request from Teva Pharmaceuticals Limited, The Gate House, Gatehouse Way, Aylesbury, Bucks, HP19 8DB. Date of Preparation – December 2009.

Adverse events should be reported.
Reporting forms and information can be found at www.yellowcard.gov.uk.
Adverse events should also be reported to
Teva Pharmaceuticals Ltd on
telephone number: 01296 719768.

Date of Preparation: February 2011

C0111/673a



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