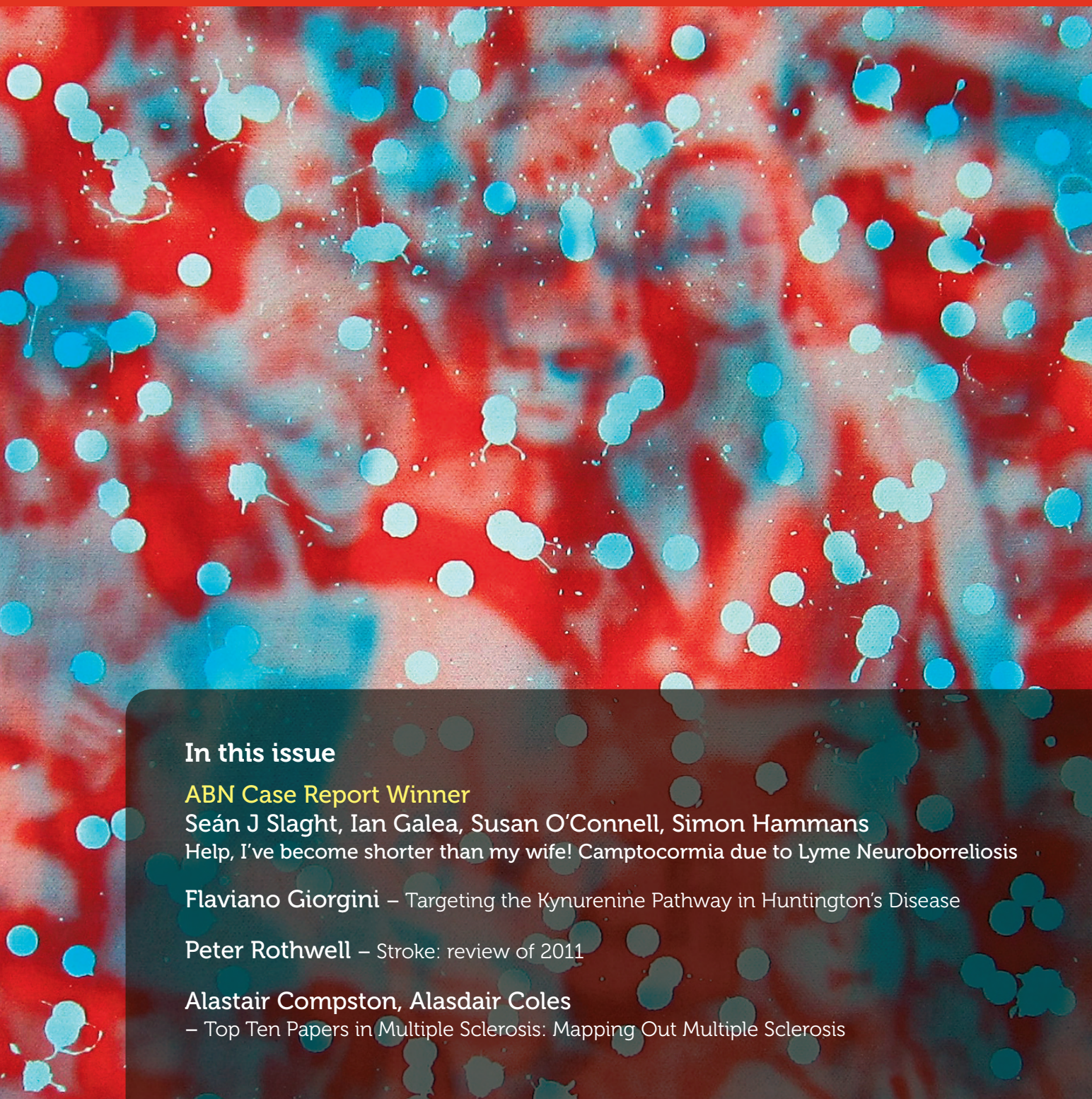
ISSN 1473-9348 VOLUME 12 ISSUE 1 MARCH/APRIL 2012

ACNR

www.acnr.co.uk

ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION



In this issue

ABN Case Report Winner
Seán J Slaght, Ian Galea, Susan O'Connell, Simon Hammans
Help, I've become shorter than my wife! Camptocormia due to Lyme Neuroborreliosis

Flaviano Giorgini – Targeting the Kynurenine Pathway in Huntington's Disease

Peter Rothwell – Stroke: review of 2011

Alastair Compston, Alasdair Coles
– Top Ten Papers in Multiple Sclerosis: Mapping Out Multiple Sclerosis

*Individual needs may vary.

That's why there's Rebif® – with tailored treatment, device and support options, and more than **900,000 patient–years' experience** of use worldwide[1]

Rebif® (interferon beta-1a) sc injection

Different patients. Different needs.

Reference: 1. UKDOFREB110003 Merck Serono Data on File 2011.

PRESCRIBING INFORMATION – UK AND ROI

REBIF® 8.8 MICROGRAMS AND 22 MICROGRAMS SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE
REBIF® 22 MICROGRAMS SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE
REBIF® 44 MICROGRAMS SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE
REBIF® 8.8 MICROGRAMS AND 22 MICROGRAMS SOLUTION FOR INJECTION IN PRE-FILLED PEN
REBIF® 22 MICROGRAMS SOLUTION FOR INJECTION IN PRE-FILLED PEN
REBIF® 44 MICROGRAMS SOLUTION FOR INJECTION IN PRE-FILLED PEN
REBIF® 8.8 MICROGRAMS/0.1ML AND REBIF® 22 MICROGRAMS/0.25ML SOLUTION FOR INJECTION IN CARTRIDGE
REBIF® 22 MICROGRAMS/0.5ML SOLUTION FOR INJECTION IN CARTRIDGE
REBIF® 44 MICROGRAMS/0.5ML SOLUTION FOR INJECTION IN CARTRIDGE

Interferon beta-1a

Presentation Rebif 8.8 µg and 22 µg: Pre-filled glass syringe containing 8.8 µg or 22 µg of Interferon beta-1a in respectively 0.2 or 0.5 ml. Rebif 22 µg or 44 µg: Pre-filled glass syringe containing 22 µg or 44 µg Interferon beta-1a in 0.5ml. Rebif 8.8 µg and 22 µg: Disposable pre-filled pen injector (RebiDose) containing 8.8 µg or 22 µg of Interferon beta-1a in respectively 0.2 or 0.5 ml. Rebif 22 µg or 44 µg: Disposable pre-filled pen injector (RebiDose) containing 22 µg or 44 µg Interferon beta-1a in 0.5ml. Rebif 8.8 µg/0.1ml and Rebif 22 µg/0.25ml: Pre-filled glass cartridge containing 132 µg of Interferon beta-1a in 1.5 ml. Rebif 22 µg/0.5 ml or Rebif 44 µg/0.5 ml: Pre-filled glass cartridge containing 66 µg or 132 µg of Interferon beta-1a in 1.5 ml. **Indications** Rebif is indicated for the treatment of

- patients with a single demyelinating event with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis N.B. The individual Rebif 22 µg presentations are not indicated in the treatment of single clinical events suggestive of multiple sclerosis
- patients with relapsing multiple sclerosis. In clinical trials, this was characterised by two or more acute exacerbations in the previous two years.

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: 8.8 µg three times per week (TIW); weeks 3 and 4: 22 µg TIW: week 5 onwards: 44 µg TIW (22 µg TIW can be used if patients cannot tolerate higher dose, but only in treatment of relapsing multiple sclerosis). 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 22 TIW is similar to that in adults. Do not use in patients under 12 years of age. Prior to injection and for 24 h 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 44. 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. If overdose occurs, hospitalise patient and give supportive treatment. **Side effects** In the case of severe or persistent undesirable effects, consider temporarily lowering or interrupting dose. Very common: flu-like symptoms, injection site inflammation/reaction, headache, asymptomatic transaminase increase, neutropenia, lymphopenia, leucopenia, thrombocytopenia, anaemia. Common: injection site pain, myalgia, arthralgia, fatigue, rigors, fever, pruritus, rash, erythematous/maculo-papular rash, diarrhoea, vomiting, nausea, depression, insomnia, severe elevations of transaminase. Serious side effects include: injection site necrosis, hepatic failure, hepatitis with or without icterus, severe liver injury, anaphylactic reactions, angioedema, erythema multiforme, erythema multiforme-like skin reactions, seizures, thromboembolic events, thrombotic thrombocytopenic purpura/haemolytic uremic syndrome, suicide attempt, Stevens-Johnson syndrome, dyspnoea, retinal vascular disorders. Consult the Summary of Product Characteristics for more information relating to side effects. **Legal category** POM Price Rebif 8.8 µg and 22 µg: 6 (0.2 ml) + 6 (0.5 ml) syringes - £552.19 Rebif 22 µg: 12 syringes (0.5 ml) - £613.52 Rebif 44 µg: 12 syringes (0.5 ml) - £813.21 Rebif 8.8 µg and 22 µg: 6 (0.2 ml) + 6 (0.5 ml) pens - £552.19 Rebif 22 µg: 12 pens (0.5 ml) - £613.52 Rebif 44 µg: 12 pens (0.5 ml) - £813.21 Rebif 8.8 µg/0.1 ml and 22 µg/0.25 ml: 2 cartridges – £406.61 Rebif 22 µg/0.5 ml: 4 cartridges – £613.52 Rebif 44 µg/0.5 ml: 4 cartridges – £813.21 For prices in Ireland, consult distributors Allphar Services Ltd. **Marketing Authorisation Holder and Numbers:** Merck Serono Europe Ltd, 56 Marsh Wall, London, E14 9TP; EU/1/98/063/007; 003 ; 006 ; 017; 013 ; 016 ; 010 ; 008 ; 009 **For further information contact: UK:** Merck Serono Ltd, Bedfont Cross, Stanwell Road, Feltham, Middlesex, TW14 8NX. Tel: 020 8818 7373. **Republic of Ireland:** Merck Serono, 4045 Kingswood Road, Citywest Business Campus, Dublin 24. Tel: 01 4687590
Date of Preparation: December 2011.

Date of Preparation: January 2012

REB12-0002

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. In the Republic of Ireland information can be found at www.imb.ie. Adverse events should also be reported to Merck Serono Limited - Tel: +44(0)20 8818 7373 or email: medinfo.uk@merckserono.net.

Merck Serono

Merck Serono is a division of Merck

MERCK

One of the impressive features of clinical research in stroke is the capacity to undertake studies in thousands of patients. Peter Rothwell in his excellent review of the major trials in stroke in 2011 shows how such studies can help inform clinical decisions in a truly evidence based way. Over the last 12 months this has led to a number of significant recommendations as well as highlighting that in patients requiring long term anti-coagulation, there are now serious competitors to warfarin!

The role of the kynurenine pathway in Huntington's Disease (HD) has received much attention and Flaviano Giorgini explains why in his excellent review. He highlights how peripheral manipulation of this system can have CNS benefits and by so doing novel treatments that target this pathway but that do not cross the BBB, may still be able to help slow down the disease process in HD.

Did you want to know about the Achilles tendon H-reflex in Danish ballet dancers? Well, in their fascinating account on spinal cord motor organisation Simon Giszter et al discuss this, as they explain the amazing complexity of circuits that can be found within the spinal cord which control and execute movements. They then go on to discuss how this knowledge can be used to develop better rehabilitation therapies in patients with a range of spinal cord pathologies.

Acute, isolated optic neuritis has always attracted a lot of attention in terms of the extent to which it is a harbinger of MS as well as how it should be optimally managed. Mithu Storoni in her excellent review in our series on Neuro-Ophthalmology discusses this condition in the context of NMO spectrum disorders and the associated aquaporin 4 autoantibody, and once more highlights that the management of patients presenting with optic neuritis is not necessarily that straightforward.

The diagnosis of convulsive psychogenic non-epileptic seizures can be difficult to make, and even harder to manage especially when it has been going on for some time. Roderick Duncan, in his contribution to the series on Clinical Dilemmas in Neuro-psychiatry, discuses how this condition can best be recognised in Casualty and then managed. This is a clearly written account steeped in experience and common sense, and is a wonderful guide to those who have to see those patients as they come into hospital acutely.

Rashmi Adiga reviews Non-convulsive Status epilepticus in children, highlighting that the diagnosis can be easily missed. She discusses the differential diagnosis for this condition as well as providing helpful practical information on how to investigate and treat children affected by this disorder.

In the second in their series on the 10 best papers in MS, Alastair Compston and Alasdair Coles take us through the major original studies on MS genetics and epidemiology as well as the seminal studies on CNS demyelination and remyelination undertaken by the group of the late Ian McDonald. As one would expect from these authors, the review contains a delightful combination of personal detail along with scientific explanation whilst also clearly highlighting why the chosen studies have been so important to our understanding of MS.

Don't miss the unique Case Report, which also has an accompanying video at www.acnr.co.uk/case report.htm. Entitled "Help, I've become shorter than my wife!", this is the first ever case described of a case of camptocornia due to Lyme neuroborreliosis. It won the ACNR sponsored prize for Best Case at the ABN meeting in Newcastle last year.

We also have in this issue the first report from the UK MSA research group that had their meeting in London last November. The report summarises this rapidly moving field with great clarity and ends on a note of optimism about the power of networks of researchers to change the therapeutic landscape in relatively rare neurological disorders.

So that's almost it for this issue, apart from our usual collection of journal, book and conference reviews. You'll also find some extra information on our website from Christine Burness and Biba Stanton of the ABNT, listing the courses available for neurological trainees and consultants. This should ensure that you can plan your study leave and CPD without the usual degree of last minute urgency! See http://www.acnr.co.uk/conferences.htm for more details. ◆

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

Roger Barker, Co-Editor.

Erratum: In the MS Supplement published with the last issue of ACNR, the article 'Mesenchymal stem cells, a note of caution' on page 9 is co-authored by Jonathan Witherick, MRCP, University of Bristol Institute of Clinical Neurosciences. The editors apologise for the omission of his name.

CONTENTS

MARCH/APRIL 2012

03 From the Editor

Review Article

07 Targeting the Kynurenine Pathway in Huntington's Disease
Flaviano Giorgini

Review Article

09 Stroke: review of 2011
Peter Rothwell

10 Awards & Appointments

Top Ten Papers in Multiple Sclerosis

11 Mapping Out Multiple Sclerosis
Alastair Compston, Alasdair Coles

Paediatric Neurology

14 Non Convulsive Status Epilepticus In Children
Rashmi Adiga

Neuro-Ophthalmology Series

16 Current Concepts in Optic Neuritis
Mithu Storoni

Clinical Dilemmas in Neuropsychiatry

18 How do you identify and manage convulsive psychogenic nonepileptic seizures presenting acutely to casualty?
Roderick Duncan

Case Report

20 Help, I've become shorter than my wife! Camptocormia due to Lyme Neuroborreliosis
Seán J Slaght, Ian Galea, Susan O'Connell, Simon Hammans

Motor Control Series

25 The Role of Spinal Cord in Motor Control: reflexes, patterning and final motor production
Simon Giszter, Corey Hart, Ubong Ime Udoekwere

Regulars

22 Journal Reviews

24 Book Reviews

30 Events Diary

32 Conference Reports

43 News Review

Download the ABNT's comprehensive list of courses Available at www.acnr.co.uk

Cover picture: **Out of control 1** by Mariano Molina. Picture taken from 'The art of visual perception,' an exhibition at the University of Leicester in January 2012. For more information see page 43.

ACNR

Published by Whitehouse Publishing,
1 The Lynch, Mere, Wiltshire, BA12 6DQ.
Publisher. Rachael Hansford
E. rachael@acnr.co.uk

ADVERTISING
Rachael Hansford
T. 01747 860168 M. 07989 470278
E. rachael@acnr.co.uk

COURSE ADVERTISING
Rachael Hansford E. rachael@acnr.co.uk

EDITORIAL
John Gustar E. editorial@acnr.co.uk

PRINTED BY
Buxton Press T. 01298 21 2000

Copyright: All rights reserved; no part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise without either the prior written permission of the publisher or a license permitting restricted photocopying issued in the UK by the Copyright Licensing Authority.
Disclaimer: The publisher, the authors and editors accept no responsibility for loss incurred by any person acting or refraining from action as a result of material in or omitted from this magazine. Any new methods and techniques described involving drug usage should be followed only in conjunction with drug manufacturers' own published literature. This is an independent publication - none of those contributing are in any way supported or remunerated by any of the companies advertising in it, unless otherwise clearly stated. Comments expressed in editorial are those of the author(s) and are not necessarily endorsed by the editor, editorial board or publisher. The editor's decision is final and no correspondence will be entered into.

ACNR
Advances in Clinical Neuroscience & Rehabilitation
REPRINTS AVAILABLE
• Peer reviewed • ABPI compliant
• Translations available • Multiple country coordination
For more information & quotes, contact: reprints@whitehousepublishing.co.uk

AVONEX (interferon beta-1a) PEN Built Around Patients' Needs

ONCE-A-WEEK AVONEX (interferon beta-1a)

Efficacy that fits lives

Prescribing information can be found overleaf

Code: AV-PAN-0352b
Date of preparation: June 2011

Prescribing Information: AVONEX® (interferon beta-1a) Please refer to the Summary of Product Characteristics for further information. **Indication:** For the treatment of patients with relapsing multiple sclerosis or patients who have experienced a single demyelinating event with an active inflammatory process who are determined to be at high risk of developing clinically definite multiple sclerosis. **Dosage and Administration:** 30 μg injected IM once a week. **Contraindications:** Initiation of treatment in pregnancy. Patients with a history of hypersensitivity to any of the constituents. Patients with severe depression and/or suicidal ideation. **Warnings & Precautions:** Use with caution in patients with previous or current depressive disorders – depression and suicidal ideation are known to occur in increased frequency in the multiple sclerosis population in association with interferon use. Administer with caution to patients with a history of seizures, or receiving treatment with anti-epileptics, particularly if their epilepsy is not adequately controlled with anti-epileptics. Use with caution and monitor closely in patients with cardiac disease, severe renal or hepatic failure or severe myelosuppression. Routine periodic blood chemistry and haematology tests are recommended during treatment. Development of neutralizing antibodies to AVONEX may decrease efficacy. **Pregnancy & Lactation:** Initiation of treatment is contraindicated during pregnancy. Women of child bearing potential should take appropriate contraceptive measures. If the patient becomes pregnant or plans to become pregnant, or breast feeding while taking AVONEX, discontinuation of therapy should be considered. **Drug Interactions:** No formal interaction studies have been conducted with AVONEX in humans. Corticosteroids or ACTH can be given during relapses. Caution should be exercised in combining AVONEX with products with a narrow therapeutic index and dependent on cytochrome P450 for clearance. **Side Effects:** The most commonly reported symptoms are of the flu-like symptoms: myalgia, fever, chills, asthenia, headache and nausea. Other common events include: decreased lymphocyte, white blood cell, and neutrophil counts; decreased haematocrit and increased blood potassium and blood urea nitrogen. Nervous system disorders: muscle spasticity, hypoesthesia. Respiratory, thoracic and mediastinal disorders: rhinorrhoea. Gastrointestinal disorders: vomiting, diarrhoea, nausea. Skin and subcutaneous tissue disorders: rash, increased sweating, contusion. Musculoskeletal and connective tissue disorders: muscle cramp, neck pain, myalgia, arthralgia, pain in extremity, back pain, muscle stiffness, musculoskeletal stiffness. Metabolism and nutrition disorders: anorexia. Vascular disorders: flushing. General disorders and administration site conditions: flu-like symptoms, pyrexia, chills, sweating, injection site pain, injection site erythema, injection site bruising, asthenia, pain, fatigue, malaise, night sweats. Psychiatric disorders: depression, insomnia. **Legal Classification:** POM. **Pack Size and UK NHS Price:** Box containing four injections £654, box containing twelve injections £1962. Reimbursed through High Tech Scheme in Ireland. **Package Quantities:** AVONEX 30 micrograms powder and solvent for solution for injection: 1 box containing four trays. Each tray contains a 3 ml glass vial with BIO-SET device containing a 30 μg dose of interferon beta-1a per vial, a 1 ml pre-filled glass syringe of solvent and one needle. AVONEX 30 micrograms/0.5 ml solution for injection: 1 box containing four or twelve trays. Each tray contains a 1 ml pre-filled syringe made of glass containing 0.5 ml of solution (30 μg dose of interferon beta-1a) and one needle. AVONEX 30 micrograms/0.5 ml solution for injection, in pre-filled pen: 1 box containing 4 cartons. Each carton contains a single-use AVONEX PEN with one injection needle and a pen cover. **Product Licence Numbers**: EU/1/97/033/002-005. **Product Licence Holder**: Biogen Idec Ltd., Innovation House, 70 Norden Road, Maidenhead, Berkshire SL6 4AY, United Kingdom. **Date of last revision of Prescribing Information**: June 2011.

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk or www.imb.ie. Adverse events should also be reported to Biogen Idec on 0800 008 7401 (UK) or 1800 812 719 (Ireland).

biogen idec™

Date of preparation: June 2011.
Code: AV-PAN-0352b

Editorial board and contributors

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

Alasdair Coles is co-editor of ACNR. He is a University Lecturer in Neuroimmuniology at Cambridge University. He works on experimental immunological therapies in multiple sclerosis.

Mike Zandi is co-editor of ACNR. He is an Honorary Specialist Registrar in Neurology at Addenbrooke's Hospital, Cambridge and a Research Fellow at Cambridge University. His research interests are in neuroimmunology, biomarkers and therapeutics in particular.

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

Boyd Ghosh is the Editor of our Conference News section. He is currently a Specialist Registrar in Southampton having completed a PhD in Cambridge in cognitive neuroscience. His special interests are cognition and movement disorders, with a particular interest in progressive supranuclear palsy. He is currently secretary for the ABN trainees committee.

Rhys Davies is the editor of our Book Review Section. He is a consultant neurologist at the Walton Centre for Neurology and Neurosurgery in Liverpool and at Ysbyty Gwynedd in Bangor, North Wales. He has a clinical and research interest in cognitive neurology.

Alastair Wilkins is our Case Report Co-ordinator. He is Senior Lecturer in Neurology and Consultant Neurologist, University of Bristol. He trained in Neurology in Cambridge, Norwich and London. His research interests are the basic science of axon degeneration and developing treatments for progressive multiple sclerosis.

Peter Whitfield is ACNR's Neurosurgery Editor. He is a Consultant Neurosurgeon at the South West Neurosurgery Centre, Plymouth. His clinical interests are wide including neurovascular conditions, head injury, stereotactic radiosurgery, image guided tumour surgery and lumbar microdiscectomy. He is an examiner for the MRCS and is a member of the SAC in neurosurgery.

Heather Angus-Leppan is ACNR's ABN representative on the Editorial Board. She is Head of the Neurology Department at Barnet Hospital and Consultant Neurologist, Honorary Senior Lecturer and Epilepsy Lead at the Royal Free Hospital, London, UK. She is the Honorary Assistant Secretary of the Association of British Neurologists, Honorary Secretary of the Neurosciences Section of the Royal Society of Medicine and current Chair of the Map of Medicine Epilepsy Group, UK.

International editorial liaison committee

Professor Riccardo Soffietti, Italy: Chairman of the Neuro-Oncology Service, Dept of Neuroscience and Oncology, University and S. Giovanni Battista Hospital.

Professor Klaus Berek, Austria: Head of the Neurological Department of the KH Kufstein.

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.

Targeting the Kynurenine Pathway in Huntington's Disease

Flaviano Giorgini
is the Reader in Mammalian Genetics in the Department of Genetics, University of Leicester. His group is interested in the role of genetic modifiers in neurodegenerative diseases such as Huntington's disease and Parkinson's disease.

Correspondence to:
Flaviano Giorgini,
Department of Genetics,
University of Leicester, UK.
Email: fg36@le.ac.uk

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by expansion of a polyglutamine tract in the huntingtin (htt) protein.[1] This fatal disorder most severely affects the neostriatum of the brain, with symptomatic manifestations including chorea, cognitive deficits and psychiatric disturbances. Recent studies have found that perturbation of kynurenine pathway (KP) metabolism represents a signature for HD pathology, and that alteration of brain KP metabolite levels plays a causative role in this disease and may thus be targeted therapeutically. The KP is responsible for >95% of tryptophan degradation in mammals, ultimately yielding NAD+.[1] As three KP metabolites are neuroactive, this pathway is of particular interest for the neuroscience community. The enzyme kynurenine 3-monoxygenase (KMO) lies at a critical branching point in the pathway between the formation of the neurotoxic metabolites 3-hydroxykynurenine (3-HK) and quinolinic acid (QUIN), and the neuroprotective metabolite kynurenic acid (KYNA) – such that inhibition of KMO leads to neuroprotection via increased levels of KYNA relative to 3-HK/QUIN. In addition to HD, the metabolites in this pathway have been implicated in several brain diseases and are discussed at length below.

Neuroactive kynurenine pathway metabolites

QUIN, described as a central intermediate of the KP in 1964, was the first metabolite in the pathway to receive attention by neuroscientists when it was discovered that it was a potent excitotoxin in vivo via specific agonism of NMDA-sensitive glutamate receptors.[2] Subsequent studies spearheaded by Robert Schwarcz found that intrastriatal injection of QUIN in rodents produced several phenotypes reminiscent of HD.[3] Furthermore, intrastriatal injections of QUIN spare a subclass of aspiny striatal neurons[4] which are also retained in HD patient brains.[5,6] In addition, QUIN generates free radicals and antioxidant treatments reduce QUIN-dependent toxicity in rats,[7] suggesting a combinatorial action of QUIN. The KP metabolite 3-HK is also toxic in neuronal cell lines and primary neurons by production of free radicals such as H^2O^2 via autoxidation.[1] 3-HK can potentiate QUIN phenotypes in striatal co-injection experiments – increasing lesion volume and further impairing behavioural phenotypes.[8]

KYNA, the third neuroactive KP metabolite, is a broad-spectrum antagonist of ionotropic excitatory amino acid receptors at supraphysiological concentrations.[9] At endogenous concentrations KYNA competitively inhibits the glycine co-agonist site of NMDA receptors[10] and is a strong non-competitive inhibitor of the α7 nicotinic acetylcholine receptor.[11] KYNA is neuroprotective against QUIN-induced excitotoxicity and seizures in rats[12] and results in behavioural changes in rodents, mimicking properties of NMDA receptor antagonists.[13] Mice with a targeted deletion of the gene encoding KATII, a kynurenine aminotransferase which synthesizes KYNA, exhibit a reduction in cerebral levels of KYNA and increased neuronal vulnerability to QUIN[14] – underscoring the neuroprotective properties of KYNA.

The kynurenine pathway and Huntington's disease

Perturbations in levels of KP metabolites have been documented in several brain diseases, including HD, Alzheimer's disease (AD), stroke, cerebral malaria, and HIV dementia.[1] Levels of QUIN and 3-HK in the neostriatum and neocortex of early stage HD patients (Grade 0/1) are elevated several-fold, but no significant changes in levels of these metabolites are observed in the cerebellum.[15] Exacerbating this increase in neurotoxic KP metabolites, levels of the neuroprotective metabolite KYNA are decreased in the cortex of HD patient brains.[16] In total, these data suggest that in HD the KP is shifted away from the neuroprotective branch of the pathway. Interrogation of several HD mouse models has confirmed the brain region-specific increases of 3-HK and QUIN observed in HD patients.[1] Interestingly, the timing of the increases in 3-HK/QUIN levels mirrors the differences in onset of pathology observed in these models – suggesting a causative role for KP metabolites in disease progression.

KMO inhibition as a therapeutic strategy in Huntington's Disease

Interest in the therapeutic potential of the KP was further stimulated by a study we published in 2005 using the baker's yeast Saccharomyces cerevisiae.[17] In a genome-wide screen, we found that deletion of the gene encoding the yeast orthologue of KMO reduced cellular toxicity caused by mutant htt. We proceeded to show that flux through the central KP is increased in HD yeast – mirroring the observations in HD patients and HD mice. Importantly, we found that 3-HK and QUIN were undetectable in the KMO deletion strain, and that levels of ROS returned to control levels, suggesting a role for ROS in KP dependent toxicity in yeast. Furthermore, manipulation of the KP via deletion of other KP genes showed a strong correlation between levels of 3-HK/QUIN and mutant htt toxicity.

Recently, in collaboration with Charalambos

Kyriacou, we performed a detailed mechanistic study of KMO and the KP in a fruit fly model of HD.[18] Here we found that genetic inhibition of KMO was robustly neuroprotective. Furthermore, we discovered that several compounds which inhibit KMO activity also reduce neurodegeneration in HD flies. Complementing this, both genetic and pharmacological inhibition of KMO led to a reduction of 3-HK relative to KYNA. By feeding KP metabolites to HD flies, we showed for the first time that KP metabolites are causative in mutant htt dependent neuron loss. We observed that HD flies fed 3-HK no longer displayed the neuroprotective benefits of KMO gene deletion, and that HD flies fed KYNA exhibited decreased neurodegeneration. Genetic inhibition of tryptophan 2,3-dioxygenase (TDO), which catalyses the first step in the KP, was similarly neuroprotective. As this step is catalysed in the mammalian brain by both TDO and indoleamine 2,3-dioxygenase (IDO) – and inhibitors are available for both enzymes – this work suggests that additional points in the KP could be targeted therapeutically in HD, and perhaps other neurodegenerative disorders.

The therapeutic potential of KMO inhibitors was further underscored by a complementary collaborative study directed by Paul Muchowski and Robert Schwarcz.[19] In this work, a novel orally bioavailable prodrug (JM6) of the KMO inhibitor Ro 61-8048 was developed and tested in both HD and AD model mice. In both models, treatment with JM6 led to decreased synaptic loss. Furthermore, JM6 treatment increased the lifespan of HD model mice and rescued behavioural deficits in AD mice. Quite provocatively, it was found that neither JM6 nor Ro 61-8048 crosses the blood-brain barrier in rodents, indicating that the protective effects conferred upon these mouse models of neurodegeneration are due to inhibition of KMO in the periphery. Further analyses in this study suggest that the observed neuroprotection is due to increased blood levels of kynurenine, transport of this metabolite into the brain, and preferential conversion into KYNA. The peripheral action of JM6 may prove particularly useful in increasing clinical benefits and reducing possible toxic side-effects of combinatorial therapies with other neuroprotective brain-penetrant compounds.[20]

In summary, these studies highlight the therapeutic potential of targeting the KP with small molecular inhibitors in HD and other neurodegenerative disorders. In all cases it appears that reduction of 3-HK/QUIN relative to KYNA is central to the neuroprotective effects observed. While KMO inhibition is thus far the most robustly validated of the KP targeting approaches, other pathway enzymes such as IDO and TDO may also prove to be important therapeutic targets for these disorders, and are worthy of further exploration. ◆

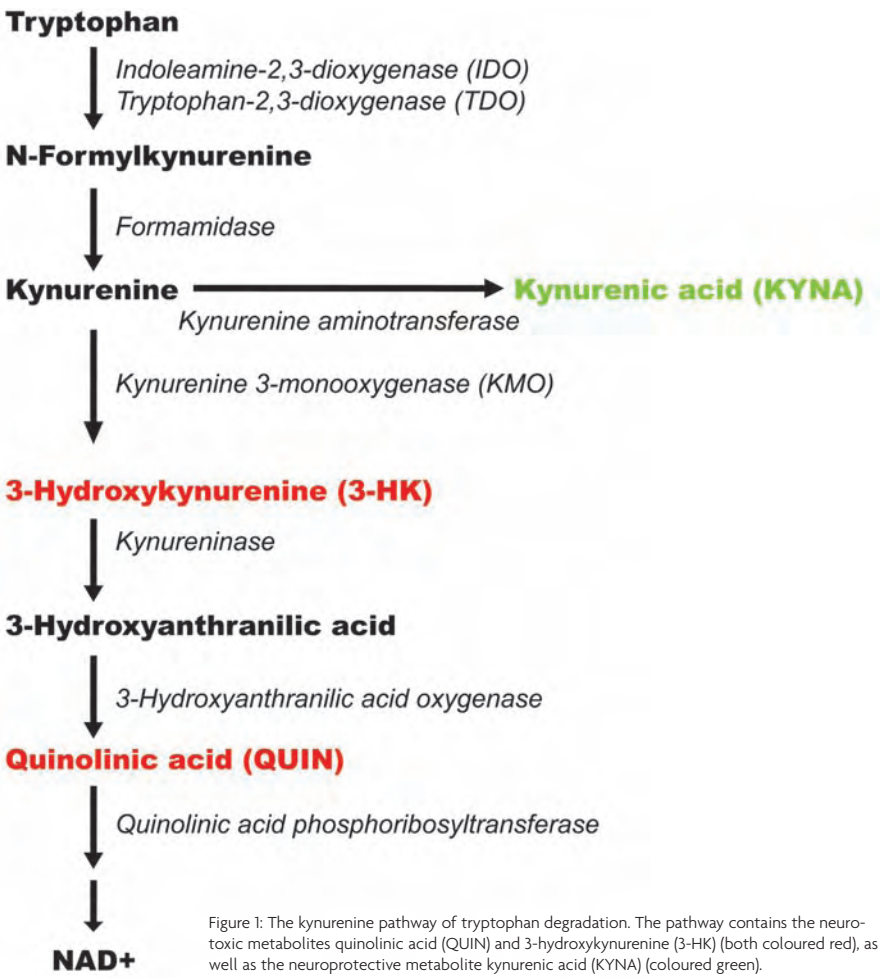


Figure 1: The kynurenine pathway of tryptophan degradation. The pathway contains the neurotoxic metabolites quinolinic acid (QUIN) and 3-hydroxykynurenine (3-HK) (both coloured red), as well as the neuroprotective metabolite kynurenic acid (KYNA) (coloured green).

REFERENCES

1. Thevandavakkam MA, Schwarcz R, Muchowski PJ, Giorgini F. *Targeting kynurenine 3-monooxygenase (KMO): implications for therapy in Huntington's disease.* CNS Neurol Disord Drug Targets 2010;9:791-800.
2. Stone TW, Perkins MN. *Quinolinic acid: a potent endogenous excitant at amino acid receptors in CNS.* Eur J Pharmacol 1981;72:411-2.
3. Schwarcz R, Whetsell WO, Jr., Mangano RM. *Quinolinic acid: an endogenous metabolite that produces axon-sparing lesions in rat brain.* Science 1983;219:316-8.
4. Beal MF, Kowall NW, Ellison DW, Mazurek MF, Swartz KJ, Martin JB. *Replication of the neurochemical characteristics of Huntington's disease by quinolinic acid.* Nature 1986;321:168-71.
5. Beal MF, Martin JB. *Effects of lesions on somatostatin-like immunoreactivity in the rat striatum.* Brain Res 1983;266:67-73.
6. Beal MF, Marshall PE, Burd GD, Landis DM, Martin JB. *Excitotoxin lesions do not mimic the alteration of somatostatin in Huntington's disease.* Brain Res 1985;361:135-45.
7. Santamaria A, Flores-Escartin A, Martinez JC, et al. *Copper blocks quinolinic acid neurotoxicity in rats: contribution of antioxidant systems.* Free Radic Biol Med 2003;35:418-27.
8. Guidetti P, Schwarcz R. *3-Hydroxykynurenine potentiates quinolinate but not NMDA toxicity in the rat striatum.* Eur J Neurosci 1999;11:3857-63.
9. Perkins MN, Stone TW. *An iontophoretic investigation of the actions of convulsant kynurenines and their interaction with the endogenous excitant quinolinic acid.* Brain Res 1982;247:184-7.
10. Kessler M, Terramani T, Lynch G, Baudry M. *A glycine site associated with N-methyl-D-aspartic acid receptors: characterization and identification of a new class of antagonists.* J Neurochem 1989;52:1319-28.
11. Hilmas C, Pereira EF, Alkondon M, Rassoulpour A, Schwarcz R, Albuquerque EX. *The brain metabolite kynurenic acid inhibits alpha7 nicotinic receptor activity and increases non-alpha7 nicotinic receptor expression: physiopathological implications.* J Neurosci 2001;21:7463-73.
12. Foster AC, Vezzani A, French ED, Schwarcz R. *Kynurenic acid blocks neurotoxicity and seizures induced in rats by the related brain metabolite quinolinic acid.* Neurosci Lett 1984;48:273-8.
13. Vecsei L, Beal MF. *Intracerebroventricular injection of kynurenic acid, but not kynurenine, induces ataxia and stereotyped behavior in rats.* Brain Res Bull 1990;25:623-7.
14. Sapko MT, Guidetti P, Yu P, Tagle DA, Pellicciari R, Schwarcz R. *Endogenous kynurenate controls the vulnerability of striatal neurons to quinolinate: Implications for Huntington's disease.* Exp Neurol 2006;197:31-40.
15. Guidetti P, Luthi-Carter RE, Augood SJ, Schwarcz R. *Neostriatal and cortical quinolinate levels are increased in early grade Huntington's disease.* Neurobiol Dis 2004;17:455-61.
16. Beal MF, Matson WR, Storey E, et al. *Kynurenic acid concentrations are reduced in Huntington's disease cerebral cortex.* J Neurol Sci 1992;108:80-7.
17. Giorgini F, Guidetti P, Nguyen Q, Bennett SC, Muchowski PJ. *A genomic screen in yeast implicates kynurenine 3-monooxygenase as a therapeutic target for Huntington disease.* Nat Genet 2005;37:526-31.
18. Campesan S, Green EW, Breda C, et al. *The kynurenine pathway modulates neurodegeneration in a Drosophila model of Huntington's disease.* Curr Biol 2011;21:961-6.
19. Zwilling D, Huang SY, Sathyasaikumar KV, et al. *Kynurenine 3-monooxygenase inhibition in blood ameliorates neurodegeneration.* Cell 2011;145:863-74.
20. Reinhart PH, Kelly JW. *Treating the periphery to ameliorate neurodegenerative diseases.* Cell 2011;145:813-4.

Stroke: review of 2011

Peter Rothwell
is Professor of Clinical Neurology at the University of Oxford. As an MRC Senior Clinical Fellow he set up the Stroke Prevention Research Unit in 2000, which now employs over 30 staff. He was elected a fellow of the Academy of Medical Sciences in 2008 and a Wellcome Trust Senior Investigator in 2011. He has published over 250 scientific papers and several books.

Correspondence to:
PM Rothwell,
Professor of Clinical Neurology,
Nuffield Department of Clinical Neurosciences,
Level 6, West Wing,
John Radcliffe Hospital,
Headington,
Oxford OX3 9DU, UK.
Fax: +44 (0)1865 234639
Email: peter.rothwell@clneuro.ox.ac.uk

Competing interests:
The author was on the Executive Committee of the PERFORM Trial and on the Data Monitoring Committee of the ROCKET-AF Trial.

Stroke causes nearly 10% of all deaths worldwide and is the leading cause of neurological disability. It accounts for more than 4% of direct health-care expenditure, with an absolute cost of about £9 billion in the UK and over US$40 billion in the USA, and also has substantial indirect costs related to complications, such as post-stroke dementia, depression, falls, fractures, and epilepsy. However, significant progress is being made in the prevention and treatment of stroke. Two reports in 2011 showed that stroke mortality has fallen significantly in the US and Europe over the last decade,[1,2] probably due mainly to more effective prevention.[3]

Indeed, improvements in medical therapy probably also explain the diminishing benefits of revascularisation procedures for patients with extracranial or intracranial atherosclerotic stenoocclusive disease that has been found repeatedly in 2011.[4-6] Perhaps most surprising were the findings of the SAMMPRIS trial in patients with symptomatic atherosclerotic intracranial arterial stenosis,[5] which is increasingly diagnosed in patients with TIA and stroke due to the more widespread availability of MR and CT angiography. Although this group was generally considered to be at very high risk of stroke, it has been uncertain whether percutaneous transluminal angioplasty and stenting was more effective in preventing recurrent stroke than medical treatment alone. The SAMMPRIS trial therefore randomised patients who had a recent TIA or stroke attributed to 70-99% stenosis of a major intracranial artery to aggressive medical management alone or aggressive medical management plus angioplasty or stenting. Enrolment was stopped early after 451 patients were recruited, because the 30-day rate of stroke or death was 14.7% in the intervention group and only 5.8% in the medical-management only group (p=0.002).[5] Beyond 30 days, stroke in the same territory occurred in 13 patients in each group. Follow-up is ongoing, but the likelihood that the cumulative risk of stroke in the medical treatment only group will offset the difference in 30-day risk seems low.

Aspirin maintained its position as a first line antiplatelet drug in secondary prevention of stroke in patients without atrial fibrillation in 2011 following publication of the results of the PERFORM trial,[7] which compared it with a selective thromboxane-prostaglandin receptor antagonist, terutroban. 9562 patients with an ischaemic stroke in the previous three months or a TIA in the previous eight days were randomised to terutroban and 9558 to aspirin. After mean follow-up of 28 months the trial was stopped on the basis of futility, the primary endpoint having occurred in 1091 (11%) patients receiving terutroban and 1062 (11%) receiving aspirin (HR=1.02, 95%CI 0.94-1.12), without any difference in risk of major bleeding. The annual risk of recurrent stroke was again surprisingly low.

Atrial fibrillation remains the least well treated of the major risk factors for stroke, due mainly to the perceived risk of bleeding with vitamin K antagonists, the requirement for monitoring, and the potential for drug and lifestyle interactions. About 20% of TIAs and ischaemic strokes occur in patients with atrial fibrillation (AF). Prevalence of AF increases sharply with age and is therefore increasing in line with life expectancy. Aspirin is relatively ineffective in prevention of stroke in patients with AF, either alone or in combination with clopidogrel, and warfarin has been the mainstay of treatment in both primary and secondary prevention for more than two decades. Progress was made on two fronts in 2011. First, in terms of risk-stratification, the CHA2DS2-VASc score was shown to have somewhat better predictive power for risk of stroke and systemic embolisation than previous risk scores, particularly in identifying patients at low and intermediate risk.[8,9]

Second, in terms of alternative anticoagulants to warfarin, several new agents have emerged. Previously, the factor Xa inhibitor, ximelagatran, had been shown to be as effective as warfarin in prevention of stroke in patients with AF and to cause fewer major bleeding complications, but it was hepatotoxic and was subsequently withdrawn.[10] In 2009, the direct thrombin inhibitor, dabigatran, was reported to have advantages over warfarin in the PROBE-design RE-LY trial in over 12000 patients, 20% of whom had a prior TIA or stroke.[11] With a dose of 110mg twice-daily the risk of ischaemic events did not differ from that with warfarin, but there were fewer major haemorrhages. With a dose of 150mg twice-daily there were fewer ischaemic events and a similar number of major bleeds compared with warfarin. There was net clinical benefit (vascular events, bleeding and death) for the 110mg dose (RR=0.92, 0.84-1.02) and for the 150mg dose (0.91; 0.82-1.00). In 2011, trials were published on the safety and effectiveness of two new factor Xa inhibitors in patients with non-valvular AF.[12-14]

In the first trial to report in 2011, ROCKET-AF,[12] 14,264 patients with nonvalvular AF who were at increased risk for stroke were randomised, double-blind, to rivaroxaban 20mg daily vs dose-adjusted warfarin. In the intention-to-treat analysis, rivaroxaban reduced the risk of stroke or systemic embolism (2.1%/yr vs 2.4%/yr; HR=0.88; 0.74-1.03; p<0.001 for noninferiority; p=0.12 for superiority) with a lower risk of intracranial hemorrhage (0.5% vs. 0.7%, p=0.02) and fatal bleeding (0.2% vs. 0.5%, p=0.003).

In the comparable ARISTOTLE trial, 18,201 patients with AF and at least one additional risk factor for stroke were randomised, double-blind, to apixaban 5mg twice-daily vs warfarin.[13] After a median duration of follow-up of 1.8 years, the risk of stroke or systemic embolism was lower in the apixaban group (1.27% vs 1.60%; HR=0.79, 0.66-0.95; p<0.001 for noninferiority; p=0.01 for superiority), with a lower rate of major bleeding (2.13% vs 3.09%; HR=0.69, 0.60-0.80; P<0.001) and haemorrhagic stroke (0.24% vs 0.47%; 0.51, 0.35-0.75; P<0.001). Apixaban 5mg bd was also compared

to aspirin (81-324mg daily) in 5599 patients with AF who were at increased risk for stroke but unsuitable for warfarin in the double-blind AVERROES trial.[14] After a mean follow-up of 1.1 years, the trial stopped early because of benefit in favor of apixaban (stroke or systemic embolism – 1.6%/yr vs 3.7%/yr; HR=0.45; 0.32-0.62; p<0.001), without any excess of major bleeding (1.4% vs 1.2%, HR=1.13; 0.74-1.75) or intracranial bleeding (n=11 vs n=13).

Thus, there are now three potential alternative anticoagulants to warfarin and guidelines will need to be updated to take these recent trial results into account, along with further analyses of cost-effectiveness and subsequent reports on long-term safety.

In treatment of acute stroke, progress was made in understanding the risks and benefits of blood pressure lowering. Blood pressure is often elevated after a TIA or stroke but tends to fall spontaneously during the first few days. Ischaemic and infarcted brain cannot autoregulate blood flow and so increases in cerebral perfusion pressure can cause hyperaemia, cerebral oedema, and haemorrhagic infarction, whereas a fall in pressure may exacerbate ischaemia. The Scandinavian Candesartan Acute Stroke Trial (SCAST) trial therefore randomised patients with acute ischaemic (85%) or haemorrhagic (14%) stroke and SBP≥140mmHg within 30 hours of symptom onset (average 18 hours) to candesartan (n=1017) or placebo (n=1012) for seven days, with doses increasing from 4mg on day one to 16mg on day three to seven.[15] Mean blood pressure was 171/90mmHg on admission, but SBP was 5mmHg (95% CI 3-7; p<0.0001) lower and DBP was 2mmHg (1-3; p=0.001) lower in patients allocated to candesartan than in those on placebo on day seven. The composite endpoint of stroke, myocardial infarction, or vascular death occurred in 120 patients in the candesartan group and in 111 patients in the placebo group (adjusted hazard ratio 1.09, 0.84-1.41; p=0.52). Analyses of functional outcome showed a trend towards worse outcome in the candesartan group (modified Rankin scale: adjusted odds ratio 1.17, 1.00-1.38, p=0.048). The SCAST investigators added their results to a meta-analysis of nine smaller RCTs of BP-lowering drugs within the first week of acute stroke and found no evidence of a beneficial effect on functional outcome.

Progress in research to improve prevention and management of stroke was therefore significant in 2011, due mainly to the findings of large pragmatic randomised controlled trials. ◆

REFERENCES

1. Minin o AM, Xu J, Kochanek KD. *Deaths: preliminary data for 2008.* National Vital Statistics Reports 2010;59:1-52.
2. Kunst AE, Amiri M, Janssen F. *The decline in stroke mortality: exploration of future trends in 7 Western European countries.* Stroke 2011;42:2126-30.
3. Towfighi A, Saver JL. *Stroke declines from third to fourth leading cause of death in the United States: historical perspective and challenges ahead.* Stroke 2011;42:2351-5.
4. Naylor AR. *What is the current status of invasive treatment of extracranial carotid artery disease?* Stroke 2011;42:2080-5.
5. Chimowitz MI, Lynn MJ, Derdeyn CP, et al. *SAMMPRIS Trial Investigators. Stenting versus aggressive medical therapy for intracranial arterial stenosis.* N Engl J Med 2011;365:993-1003.
6. Powers WJ, Clarke WR, Grubb RL, Videen TO, Adams HP, Derdeyn CP. *Extracranial-intracranial bypass surgery for stroke prevention in hemodynamic cerebral ischemia.* JAMA 2011;306:1983-92.
7. Bousser MG, Amarenco P, Chamorro A, Fisher M, Ford I, Fox KM, Hennerici MG, Mattle HP, Rothwell PM, de Cordoe A, Fratacci MD; PERFORM Study Investigators. *Terutroban versus aspirin in patients with cerebral ischaemic events (PERFORM): a randomised, double-blind, parallel-group trial.* Lancet 2011;377:2013-22.
8. Lip GY. *Implications of the CHA(2)DS(2)-VASc and HAS-BLED Scores for thromboprophylaxis in atrial fibrillation.* American Journal of Medicine 2011;124:111-4.
9. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. *Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation.* Chest 2010;137:263-72.
10. Executive Steering Committee on behalf of the SPORTIF III Investigators. *Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial.* Lancet 2003;362:1691-8.
11. Connolly SJ, Ezekowitz MD, Yusuf S et al. *Dabigatran versus warfarin in patients with atrial fibrillation.* N Engl J Med 2009;361:1139-51.
12. Patel MR, Mahaffey KW, Garg J, et al. *ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation.* N Engl J Med 2011;365:883-91.
13. Granger CB, Alexander JH, McMurray JJ, et al. *ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation.* N Engl J Med 2011;365:981-92.
14. Connolly SJ, Eikelboom J, Joyner C, et al. *AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation.* N Engl J Med 2011;364:806-17.
15. Sandset EC, Bath PM, Boysen G, et al; SCAST Study Group. *The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial.* Lancet 2011;377:741-50.

Wellcome Trust Centre for Neuroimaging researcher scoops Lloyd's 2011 Science of Risk Prize

UCL's Wellcome Trust Centre for Neuroimaging Research Fellow, Klaus Wunderlich, has won the Lloyd's "Science of Risk" Prize in the category of Behavioural Risk. His paper was also voted "Best Overall Paper".

Wunderlich and his team at WTCN took the top prize for their research which, using Functional Magnetic Imaging (fMRI) looked at the brains of study participants as they played a simple resource management game. The researchers continually changed the parameters of the game, varying risk and reward outcomes, and thus forcing participants to revise their predictions as they played. They found that generally participants learned as they played, changing their behaviour in light of the new information, and that they were more successful when they did this, than simply by trial and error.

Upon receiving the prize Wunderlich commented: "Our paper gives insight into how the brain is capable of learning structures in our environment, and how this helps us to reduce the risk in our choices. Apparently behavioural risk is a very important topic for insurance and I am delighted that our work got recognised by that industry."

Awards made by the Encephalitis Society

Exceptional Service Awards presented at the AGM

Six Exceptional Service Awards were presented in recognition of exceptional service in health, education and social care at the Encephalitis Society's AGM. The awardees were nominated by members of the Encephalitis Society. Among those awarded was Dr Rachel Kneen, a Paediatric Neurologist at Alder Hey Hospital who was nominated by Tracy Jennings and Irwin McMillan.

More information about the winners of the awards is available at: www.encephalitis.info/images/iPdf/Newsletter/newsletter52.pdf

Rachel Kneen receiving her Award from Dr Nick Davies.

Sophie Binks announced as winner of essay prize

The Encephalitis Society has announced Sophie Binks as the winner of their essay prize. The Encephalitis Society launched an essay prize as part of their work in engaging with up and coming medical students. The winning essay was entitled: *The Story of a Patient with Childhood Encephalomyelitis, the Effect on the Patient, Family and Society, and the Role of Healthcare Professionals.*

The runner up prize in the competition was awarded to David Bargiela for his essay entitled *Exploring the Iceberg: Caring for the Child with Herpes Simplex Encephalitis.*

Both Sophie and David's essays can be read in full at http://www.encephalitis.info/TheSociety/AboutUs/2011essayprize.html

Pictured are Sophie Binks with Dr Nick Davies and Professor Tom Solomon.

Top Ten Papers in Multiple Sclerosis

Mapping Out Multiple Sclerosis

In the second of our articles on the Top Ten papers in multiple sclerosis, we look at seminal works in the 1970s which began to sketch out the epidemiology and genetics of multiple sclerosis, and to explore demyelination and remyelination.

Alastair Compston
is Professor of Neurology and Head of the Department of Clinical Neurosciences in Cambridge; President of the Association of British Neurologists (2009-2010); and Editor of Brain (from 2004). He is a foundation Fellow of the Academy of Medical Sciences, and Foreign Member of the National Academy of Sciences of Germany. His research on the clinical science of human demyelinating disease has been recognised by the award of the Sobek Foundation International Research Prize (2002), the Charcot Award of Multiple Sclerosis International Federation (2007), and the Zülch Prize of the Max-Planck Society (2010).

Alasdair Coles
is co-editor of ACNR. He is a University Lecturer in Neuroimmuniology at Cambridge University. He works on experimental immunological therapies in multiple sclerosis.

Correspondence to:

Alastair Compston
Email: alastair.compston@medschl.cam.ac.uk

Alasdair Coles
Email: ajc1020@medschl.cam.ac.uk

1972: the first clinical demonstration of demyelination

Halliday AM, McDonald WI, Mushin J 1972. Delayed visual evoked response in optic neuritis. Lancet i: 982–985.

Ian McDonald and Martin Halliday showed that visual evoked potentials can detect past episodes of optic neuritis, not least by introducing a non-invasive test to assist in the diagnosis of suspected multiple sclerosis.

Recording of electrical activity of the brain over the scalp had been pioneered by Hans Berger in the 1920s. The motivation behind his experiments, it seems, was to identify the mechanism underlying telepathic communication with his sister during an accident whilst Berger was serving with the cavalry. In 1924, he recorded the first human electroencephalogram.[1] Lord Adrian, who received the 1932 Nobel Prize in Physiology or Medicine with Sir Charles Sherrington, promoted Berger's work and showed the value of EEG in neurological practice.[2] It was a small step from there to measure scalp potentials over the parietal or occipital lobes following a sensory stimulus or flash of light: somatosensory and visual 'evoked potentials' respectively. George Dawson methodically solved the technical challenges, not the least by introducing a technique to reduce noise in small evoked potentials.[3]

Martin Halliday (Figure 1) set to applying these new methods to people with multiple sclerosis, showing in 1963 that delayed somatosensory evoked potentials are associated with the disease,[4] but the changes were not robust and he soon turned his attention to visual evoked potentials. In the meantime, Tom Sears and Ian McDonald had demonstrated the electrical consequences of central nervous system demyelination.[5,6] They showed that direct micro-injection of diphtheria toxin into the spinal cord of the cat produces a highly circumscribed demyelinating lesion which leads to conduction block, or prolongation of the refractory period for transmission, and an impaired ability to transmit high frequency trains of impulses.

Patients were trawled from Ian McDonald's clinic at the Moorfields Eye Hospital. Nineteen patients with unilateral optic neuritis,[17] in the acute phase, were studied with flash visual evoked potentials and a new technique, 'pattern' visual evoked potentials (an alternating black and white checkerboard"). In optic neuritis, the mean latency of visual evoked potentials in the affected eye was 155 msec, an increase of 30% over that from healthy people or the unaffected eye; and the peak amplitude was halved at 3.68 microV. In the five patients seen acutely with visual acuities of 6/60 or less, there was no evoked response at all; but, as their vision recovered over weeks, so their visual evoked potential reappeared, although much delayed. Evoked potentials remained delayed even when visual acuities had recovered to normal, for up to five years. Pattern-evoked responses elicited more reproducible and sensitive responses than a flash response. The authors concluded: 'since a persistently increased latency may be present with normal optic discs, fields, and fundi, the technique described here provides a useful objective test for previous damage to the optic nerve. Its potential usefulness in the diagnosis of multiple sclerosis when patients present with clinical evidence of only a single lesion not involving the visual system is obvious.'

They went on to test the 'obvious' in a group of unselected multiple sclerosis patients.[7] In 24 individuals with a previous history of optic neuritis, nine had normal discs and all had abnormal visual evoked potentials; so abnormal visual evoked potentials are especially reliable indicators of past optic neuritis. Perhaps more usefully, in 27 patients with no history of optic neuritis, 25 had abnormal visual evoked potentials, of whom discs appeared normal in 12. So, it seems as though abnormal visual evoked potentials provide a sensitive means of identifying previous subclinical optic neuritis.

The authors went on to propose diagnostic criteria for multiple sclerosis which incorporated visual evoked potentials.[8] To date, it remains true that the only clinical diagnostic test that can demonstrate that a central neurological lesion is demyelinating is the cortical evoked potential, of which the pattern-evoked visual potential is by far the most sensitive and robust.

1972: identifying the primary genetic association for multiple sclerosis

Naito S, Namerow N, Mickey MR, Terasaki PI. 1972. Multiple sclerosis: association with HL-A3. Tissue Antigens. 2:1-4

Discoveries in the genetic basis for susceptibility to multiple sclerosis have followed each increment of technological and statistical innovation in genetics. But the most important association of the disease, with alleles of the human leukocyte antigen system, began to be uncovered in the early 1970s.

Human leukocyte antigens were first identified as serum factors in transplant recipients that

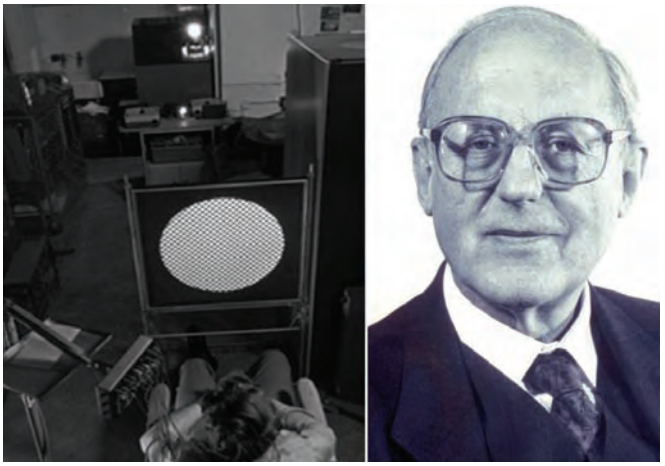


Figure 1 (left): Martin Halliday and his equipment for measuring visual evoked potentials.
Figure 2 (above): John Kurtzke's map of multiple sclerosis prevalence.

reacted against a third party 'tissue', and which were associated with transplant rejection. A key figure was Paul Terasaki at UCLA who (having clawed his way into medicine from the low point of being interned as a schoolboy during the war because of his Japanese origins) developed the microcytotoxicity test, a tissue-typing test for organ transplant donors and recipients that required only 1 microliter each of antisera.[9] (He founded a company to exploit the technology, One Lambda, which grew to generate sufficient income to enable him to make a $50 million donation to UCLA in 2010).

In 1970, Terasaki organised the Fourth Histocompatibility Workshop in Los Angeles in 1970 which brought together fifteen different laboratories testing 116 highly selected antisera. The conclusion was that there were 11 official HL-A specificities (HL-A1, 2, 3, 5, 7, 8, 9, 10, 11, 12 and 13), and perhaps eight other specificities. Shortly after this workshop, Terasaki turned his attention to multiple sclerosis. His group concluded, from 94 patients and 871 controls, that HL-A3 was overrepresented.[10] Furthermore, they demonstrated that the geographical variation in prevalence of multiple sclerosis paralleled the prevalence of HL-A3. For instance, both are high in Scandinavian countries, middle range in America and low in 'oriental'. They summarised some of the epidemiology suggesting an environmental cause for multiple sclerosis and concluded that "the evidence to date on MS, however, is still consistent with the idea that a genetic difference in susceptibility underlies some environmental influence."

Soon after this paper, Casper Jersild and colleagues from Copenhagen wrote a brief letter to the Lancet, to make some generic points around HLA genetics[11]. They described correction for multiple testing, the need for replication datasets and the usefulness of meta-analyses. Illustrating their argument, they announced the results of HLA serotyping in 36 Danish patients with multiple sclerosis followed by a replication set in 71 other patients. From these analyses, HL-A7 as the one most associated with multiple sclerosis. However, when the Danes merged their data with that from the Terasaki study, and corrected for multiple testing, only HL-A3 retained significance. This set the tone for the years to follow of underpowered studies leading to false positive results and real associations revealed by combining datasets.

Paul Terasaki returned to multiple sclerosis with the discovery of the B-lymphocyte alloantigen serotypes. In 1976 both his group and one of the authors of this chapter discovered the association with what would come to be called the class II allele HLA-DR15 [12,13]. (This explains, at least in part, Naito et al's finding of an association of multiple sclerosis with HL-A3 serotype; in Western Eurasia, A3 is part of the longest known multigene haplotype, A3-B7-DR15-DQ6). HLA-DR15 remains the best characterised candidate susceptibility gene for multiple sclerosis. After 1976, several decades of increasingly large, expensive and sophisticated molecular genetic studies followed; all confirmed the association with DR15, but very little else. Only in the last few years has there been sufficient power in the techniques and cohorts, forged through large collaborations, to uncover the much smaller individual genetic contributions of a host of other alleles, especially studies from the International MS Genetics Consortium.[14]

The finding that multiple sclerosis is associated with the HLA system implicates the immune system in its pathogenesis; explains some of the geographical variation of the disease; provides a molecular substrate for the interaction of genetics and environment; and suggests treatment directed at the T-lymphocyte, the T cell receptor and the class II molecule.

1973: remyelination is possible in the central nervous system

Gledhill RF, Harrison BM, McDonald WI. 1973. Pattern of remyelination in the CNS. Nature 244(5416):443-4.

A principal hope of people affected by multiple sclerosis is not only control of their disease but reversal of any damage already accrued: repair, possibly facilitated by therapy. Although not yet an everyday probability, trials of potential remyelinating therapies are being conducted. Key steps that made such therapies possible were the demonstrations that remyelination was possible in the central nervous system; that this was mediated by the oligodendrocyte precursor; and that it was accompanied by functional improvement. We could have chosen one of several studies which contribute to this narrative. We have chosen the paper which definitively demonstrated remyelination in the adult mammalian central nervous system, and – perhaps most importantly- showed how to identity demyelinated fibres.

Critical work had already been done by Dick and Mary Bunge[15] who studied myelin repair in cats following demyelination induced by cerebrospinal fluid barbotage. They showed that the remyelinating cell differed from the mature oligodendrocyte and, proposed incorrectly as it turned out, that mature oligodendrocytes de-differentiated into a cell capable of remyelination. Perier and Gregoire[16] showed, from electron microscopic multiple sclerosis plaques, that axons were surrounded by thin myelin lamellae, which they considered to be evidence for remyelination.

The next paper we have chosen comes from Richard Gledhill, Barry Harrison and Ian McDonald.[17] They compressed the spinal cord of three adult cats, which causes early demyelination with retained axons, and remyelination which starts three weeks later. Their main discovery, under the electron microscope, was that the remyelinated sheath is abnormally thin and has an intermodal distance reduced by 50% compared to control fibres of the same diameter. Under the light microscope, they found no evidence for the presence of Schwann cells, so concluded that oligodendrocytes had been responsible for the remyelination. These ultrastructural characteristics – reduced internode distance and inappropriately thin myelin – have become the defining features used to recognise remyelinated axons (as opposed to the partially demyelinated

axons) in experimental and human pathological studies.

The next important step was the demonstration that such remyelinated axons could restore function. This work was also supervised by Ian McDonald working with the electrophysiologist Ken Smith.[18,19]

1977: Plotting the epidemiology of multiple sclerosis

Kurtzke JF.1977. Geography in multiple sclerosis. J Neurology 215(1):1-26.

Epidemiology is less dependent upon technological advances than other disciplines represented in this review, and more reliant on the steady accumulation of disparate data. So, it is less easy to identify one paper which has made a seminal impression on the field. We could have chosen something from the oeuvre of Geoffrey Dean, who published on multiple sclerosis from 1949 to 2002, focusing especially on the effect of migration on the risk of multiple sclerosis, initially on migration to South Africa, then from Asia, the Caribbean, and Africa to the United Kingdom.[20-22] We choose instead one of John Kurtzke's key papers. John Kurtzke saw action in World War Two as a pharmacist's mate (2nd class). On discharge, he went to medical school and spent most of his professional life as a neurologist in the Veteran's Administration service, remaining in the Naval Reserve and achieving the rank of Rear Admiral. He wrote his first paper on multiple sclerosis in 1953[23] and is still publishing.[24] He is responsible for producing the industry-standard 'Kurtzke Scale' of disability in multiple sclerosis.[25-27] And he organised the first placebo-controlled clinical trial (of isoniazid) in multiple sclerosis.[28] But, his principal contribution has been the careful documentation and analysis of the varying prevalence of multiple sclerosis around the world and especially within the cohorts of US military personnel. Characteristic of his papers are a distrust of complex statistics and meticulously presented hand-drawn charts.

In this paper, which is part review and partly based on original data, Kurtzke lays out the big picture of multiple sclerosis epidemiology (Figure 2). He points out that the assertion of the day, that latitude determined multiple sclerosis prevalence, is incorrect. In Asia and the Pacific, latitude seemed not a factor at all and 'at 40° north, for example, MS is high in America, medium in Europe, and low in Asia'. In Europe and North America, there are zones of high frequency of multiple sclerosis between 65° and 45° north latitude. Neighbouring these (in Europe to the north, east, and south; in America for southern US; and the remainder of Australia) are zones of medium frequency; everywhere else is of low frequency.

Measured serially in the same small region, Kurtzke asserts that the prevalence of multiple sclerosis appears stable over time although our experience in East Anglia, UK, for example, is different.[29] One area stands out as having a high prevalence of multiple sclerosis; this Fennoscandian focus... 'from the waist and southeastern mountain plains of Norway eastward across the inland lake area of southern Sweden, then across the Bay of Bothnia to southwestern Finland, and then back to Sweden in the region of Ume...This clustering, as well as the broader geographic distributions already considered, mean to me that the occurrence of MS is intrinsically related to geography, and therefore that MS is an acquired, exogenous, environmental disease.' To determine when this disease might be acquired, Kurtzke turned to the migration studies, both his own and those of others. By comparing the age at which migration alters the risk of acquiring multiple sclerosis, he concluded that the key exposure occurs between the ages of 10 and 15 years, and that there is an 'incubation' period of some 20 years before the disease manifests. He then presents new data on the risk of multiple sclerosis in veterans by race and gender, showing that it is greatest in white women. Thus, he concludes 'MS is the white man's burden spread from western Europe'. Kurtzke argues that if multiple sclerosis is due to an infectious agent, rather than a toxin, transmissibility should be evident. This is why he is so keen to discuss possible 'epidemics' of multiple sclerosis. In 1977, he had just returned from a second visit to the Faroe Islands, where there seemed to be a cluster of new cases of multiple sclerosis following the stationing of British troops. He was to visit the Faroes many more times, and has just recently advanced the idea that gastrointestinal infections mediated the transmission between British troops and Faroese.[30]

Kurtzke's interpretation of the Faroese epidemic of multiple sclerosis has been the most controversial aspect of his work, with other commentators suggesting more prosaic explanations, for instance increased diagnostic vigilance resulting from improved medical services.[31,32] But that should not detract from the enormous service John Kutzke has made in marshalling the huge and complex multiple sclerosis epidemiological dataset into digestible synopses, of which this paper is a prime example. ◆

REFERENCES

1. Berger H. *Über das Elektroenkephalogramm des Menschen.* Archiv für Psychiatrie und Nervenkrankheiten, 1929;87:527-70.
2. Adrian EDM, *BHC; The Berger rhythm: potential changes from the occipital lobes in man.* Brain, 1934;57:355-85.
3. Dawson GD. *A summation technique for the detection of small evoked potentials.* Electroencephalogr Clin Neurophysiol, 1954;6(1):65-84.
4. Halliday AM and Wakefield GS. *Cerebral evoked potentials in patients with dissociated sensory loss.* J Neurol Neurosurg Psychiatry, 1963;26:211-9.
5. McDonald WI and Sears TA. *Focal experimental demyelination in the central nervous system.* Brain, 1970;93(3):575-82.
6. McDonald WI and Sears TA, *The effects of experimental demyelination on conduction in the central nervous system.* Brain, 1970;93(3):583-98.
7. Halliday AM, McDonald WI, and Mushin J. *Visual evoked response in diagnosis of multiple sclerosis.* Br Med J, 1973;4(5893):661-4.
8. McDonald WI and Halliday AM. *Diagnosis and classification of multiple sclerosis.* Br Med Bull, 1977;33(1):4-9.
9. Terasaki PI and McClelland JD. *Microdroplet Assay of Human Serum Cytotoxins.* Nature, 1964;204:998-1000.
10. Naito S, et al. *Multiple sclerosis: association with HL-A3.* Tissue Antigens, 1972;2(1):1-4.
11. Jersild C, Svejgaard A, and Fog T. *HL-A antigens and multiple sclerosis.* Lancet, 1972;1(7762):1240-1.
12. Terasaki PI, et al. *Multiple sclerosis and high incidence of a B lymphocyte antigen.* Science, 1976;193(4259):1245-7.
13. Compston DA, Batchelor JR, and McDonald WI. *B-lymphocyte alloantigens associated with multiple sclerosis.* Lancet, 1976;2(7998):1261-5.
14. De Jager PL, et al. *Meta-analysis of genome scans and replication identify CD6, IRF8 and TNFRSF1A as new multiple sclerosis susceptibility loci.* Nat Genet, 2009;41(7):776-82.
15. Bunge MB, Bunge RP, and Ris H. *Ultrastructural study of remyelination in an experimental lesion in adult cat spinal cord.* J Biophys Biochem Cytol, 1961;10:67-94.
16. Perier O. and Gregoire A. *Electron microscopic features of multiple sclerosis lesions.* Brain, 1965;88(5):937-52.
17. Gledhill RF, Harrison BM, and McDonald WI. *Pattern of remyelination in the CNS.* Nature, 1973;244(5416):443-4.
18. Smith EJ, Blakemore WF, and McDonald WI. *Central remyelination restores secure conduction.* Nature, 1979;280(5721):395-6.
19. Smith KJ and McDonald WI. *Spontaneous and mechanically evoked activity due to central demyelinating lesion.* Nature, 1980;286(5769):154-5.
20. Dean G. and Elian M. *Age at immigration to England of Asian and Caribbean immigrants and the risk of developing multiple sclerosis.* J Neurol Neurosurg Psychiatry, 1997;63(5):565-8.
21. Dean G. and Kurtzke JF. *On the risk of multiple sclerosis according to age at immigration to South Africa.* Br Med J, 1971;3(5777):725-9.
22. Elian M, Nightingale S, and Dean G. *Multiple sclerosis among United Kingdom-born children of immigrants from the Indian subcontinent, Africa and the West Indies.* J Neurol Neurosurg Psychiatry, 1990;53(10):906-11.
23. Berlin L, Kurtzke JF, and Guthrie TC. *Acute respiratory failure in multiple sclerosis and its management.* J Nerv Ment Dis, 1953;117(2):160-1.
24. McLeod JG, Hammond SR, and Kurtzke JF. *Migration and multiple sclerosis in immigrants to Australia from United Kingdom and Ireland: a reassessment.* I. Risk of MS by age at immigration. J Neurol, 2011.
25. Kurtzke JF. *A new scale for evaluating disability in multiple sclerosis.* Neurology, 1955;5(8):580-3.
26. Kurtzke JF. *On the evaluation of disability in multiple sclerosis.* Neurology, 1961;11:686-94.
27. Kurtzke JF. *Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS).* Neurology, 1983;33(11):1444-52.
28. Berlin L, and Kurtzke JF. *Isoniazid in treatment of multiple sclerosis.* J Am Med Assoc, 1957;163(3):172-4.
29. Robertson N, et al. *Multiple sclerosis in south Cambridgeshire: incidence and prevalence based on a district register.* J Epidemiol Community Health, 1996;50(3):274-9.
30. Wallin MT, Heltberg A, and Kurtzke JF. *Multiple sclerosis in the Faroe Islands. 8. Notifiable diseases.* Acta Neurol Scand, 2010;122(2):102-9.
31. Poser CM and Hibberd PL. *Analysis of the 'epidemic' of multiple sclerosis in the Faroe Islands. II. Biostatistical aspects.* Neuroepidemiology, 1988;7(4):181-9.
32. Poser CM, et al. *Analysis of the 'epidemic' of multiple sclerosis in the Faroe Islands. I. Clinical and epidemiological aspects.* Neuroepidemiology, 1988;7(4):168-80.

Non Convulsive Status Epilepticus In Children

Dr Rashmi Adiga
is a consultant paediatrician at Kings Lynn. After qualifying from Bangalore Medical College she trained at the Institute of Child Health, Madras and obtained a CCT in paediatrics following training in the Eastern Deanery. She currently leads the service for paediatric neurology and epilepsy at Queen Elizabeth Hospital, Kings Lynn.

Correspondence to:
Dr Rashmi Adiga,
Consultant Paediatrics,
Queen Elizabeth Hospital,
Foundation Trust.
Gayton Road
Kings Lynn PE30 4ET
Tel: +44 (0)1553 613882
Fax: +44 (0)1553 613909
Email: rashmi.adiga@qehkl.nhs.uk

Acknowledgements:
Thanks to Dr Anna Maw for help with the editing.

Status epilepticus (SE) is a major clinical problem, often occurring in childhood, with a high potential for morbidity. The condition is subdivided into convulsive and nonconvulsive forms (CSE and NCSE, respectively). Non convulsive status epilepticus denotes electrographic seizures without convulsive activity and often manifests as altered mental status or coma. It may be difficult to diagnose in paediatric patients in whom changes of behaviour and consciousness may not be as easily recognised as in adults.

History

One of the first detailed accounts of nonconvulsive status epilepticus (or 'automatisme ambulatoire'), was by Charcot in 1888, who described a patient who got into trouble with the law because he had boarded a train without a valid ticket (Charcot,1888).[1] Lennox in 1949 described S, a boy aged 11 years who had occasional days of being confused, when he was able to eat but not to converse, i.e. periods of what he then termed 'petit mal' status which were successfully treated with Tridione.[2]

Clinical presentation

Children with non convulsive status epilepticus usually present with altered levels of consciousness, without convulsive activity. It is often a difficult diagnosis to make as there are many other conditions which can cause altered mental status in childhood. It is important to rule out other causes of altered consciousness in children, some of which are life threatening, before considering NCSE.

Differential diagnosis of NCSE.

1. Head injury: Often a clear history and other signs of head injury.
2. Meningitis and encephalitis: There is often a history of high temperatures, irritability and headaches. The child is systemically unwell.
3. Raised intra-cranial pressure: There is often a history of fluctuating level of consciousness, headache, vomiting and focal neurological deficits.
4. Toxic causes: It is important to ask if there is a history of drug abuse or access to medication. Accidental overdose is more common in young children or toddlers. Pupil size can give an indication of aetiology.
5. Metabolic causes: Inborn errors of metabolism may present with altered consciousness. For example, MCADD (medium chain acyl CoA dehydrogenase deficiency) can cause acute episodes of altered consciousness. These are triggered by prolonged fasting and hypoglycaemia is usually present.
6. Altered consciousness following syncope.
7. Prolonged post ictal confusion.
8. Specific epilepsy syndromes: for example, Panayiotopoulos syndrome.

A thorough history and examination is mandatory

History of NCSE

1. Preceding symptoms: Most children with NCSE will have had preceding seizures in the acute setting, most of which are isolated brief convulsions rather than convulsive status epilepticus.[3] Autonomic symptoms prior to the episode, particularly vomiting would suggest Panayiotopoulos syndrome.
2. Classify epilepsy: In a child who has previously been diagnosed with epilepsy, it is important to take a full history and classify the epilepsy according to the ILAE classification.
3. Current anti-epileptic medication history: Erroneous classification of idiopathic generalised epilepsy and inappropriate treatment with narrow spectrum anti-epileptic drugs like carbamazepine can precipitate NCSE.[4] It is also important to note whether the epilepsy was well controlled on medication and also verify compliance with medication.
4. Observation by carers: In a review of children presenting with NCSE, 32 out of 50 children presented with 'change in behaviour'.[6] This consisted essentially of a reduction in activity, slowness, and impairment of consciousness to a varying degree constituting a confusional state. Poor balance or incoordination usually associated with intermittent bilateral jerks of the limbs was reported as an additional prominent feature in eight of the group. Table 1 lists some descriptions by parents, teachers, or hospital staff of children during NCSE and on remission.

Table 1: Non-convulsive status epilepticus: examples of Psychological features as described by observers[6]

During NCSE	On remission
'forgetful'	'brighter'
'difficult to motivate'	'more alert'
'excessively sleepy'	'more talkative'
'lost and disorientated'	'happier'
'unresponsive'	'like a fog was lifted from her mind'
'switches off'	
'zombie-like'	
'apparently deaf and blind'	
'drugged state'	
'poor balance'	
'frequent falls'	
'poor control of movements'	

Clinical examination specific to NCSE

The counting test: In a child with 'absence status epilepticus', it is worth asking the child to count from 1 to 100. If the child has absences during the counting process, you are able to see it, as the child will suddenly stop counting, stare or have automatisms and start counting again.[5]

Investigation

1. EEG is diagnostic in non convulsive status epilepticus.
2. Consider intracranial imaging if you are concerned about an underlying serious cause like head injury or raised intracranial pressure.
3. Blood tests which may be useful to diagnose metabolic disorders include liver function tests, urea and electrolytes, ammonia and lactate and don't forget glucose.

Classification

NCSE may be classified as generalised non convulsive status epilepticus and focal non convulsive status epilepticus.

Generalised non convulsive status epilepticus.

Absence status epilepticus:

a. Typical absence status epilepticus[7]: The main clinical feature of typical absence status epilepticus is altered state of consciousness, but changes in behaviour have also been reported. Children with typical absence status epilepticus may be able to eat and drink, withdraw from pain, walk about and respond to simple commands. The counting test (see above) may be useful. The duration may last minutes to days or weeks. An EEG during typical absence status epilepticus shows generalised spike wave discharges that occur at a frequency of 3Hz.

   Only 3 out of 50 children in the series described by Stores et al.[6] had typical absence status epilepticus. Typical absence status epilepticus occurs in children with idiopathic generalised epilepsies, particularly in children with absence epilepsy and juvenile myoclonic epilepsy. It may be triggered by inappropriate antiepileptic drugs like carbamazepine, fever, excitement or fatigue.

b. Atypical absence status epilepticus:[7] On clinical grounds alone the distinction between typical and atypical absence status epilepticus may be difficult.

   In the series by Stores et al., 31 out of 50 children were classified as having atypical absence status epilepticus, EEG revealed 4-7Hz spike wave activity with a variable proportion of spikes to waves from one child to another. 18 out of 31 were classified as having Lennox-Gestaut syndrome and 13 out of 31 were classified as having myoclonic astatic seizures.

Focal non convulsive status epilepticus.

Focal non convulsive status epilepticus may be classified on the basis of which lobe the seizures arise from though this may be difficult.

Epilepsia partialis continua is a distinctive syndrome which should not be considered as NCSE as it has clonic focal motor symptoms.

Focal non convulsive status epilepticus arising from the temporal lobe may present with confusion, strange behaviour, oral or manual automatisms. EEG may be variable with focal spike waves or spike wave or sharp wave discharges with inconsistent localisation.

Management

Treatment of NCSE will be guided by the precise syndromic diagnosis and the underlying cause. As most clinical forms of NCSE are not associated with systemic and chronic neurological complications, a less aggressive pharmacological management is suggested.[7] However Stores et al reported convincing levels of intellectual or educational deterioration in 27 out of 50 children over the course of the seizure disorder of which NCSE had been a part.[6] Detailed prospective study with neuropsychological follow up is required to clarify these issues. However in the meantime, it is important to recognise episodes of NCSE at an early stage and instigate prompt treatment.

Treatment approaches.

1. Focal and generalised non convulsive status epilepticus may be treated with administration of buccal midazolam, based on the child's weight and age. If seizures continue for more than 10 minutes the dose may be repeated or intravenous lorazepam may be given.[8]
2. Another approach to treatment may be to give a short course of oral benzodiazepines. This may be considered in children who present with recurrent NCSE, whose parents are able to recognise the signs and symptoms of NCSE and initiate management at home.[8]
3. Typical absence status epilepticus precipitated by inappropriate anti epileptic drugs will require discontinuation of the medication.
4. Adjustments to the child's continuous medication may be undertaken. One example of this may be to increase the dosage according to the child's weight, as children may have had a growth spurt.[8] Compliance issues with the medication should also be discussed.[8]
5. Atypical absence status epilepticus may not respond to benzodiazepines. In these circumstances further emergency medication like phenobarbitone may be required.[7,8]

Summary

Non convulsive status epilepticus is difficult to diagnose in children as it can present with altered mental status and change in behaviour. It is important to rule out other serious differential diagnoses. EEG can be helpful in establishing a diagnosis. Management approaches are generally less aggressive than with convulsive status epilepticus. ◆

REFERENCES

1. Reuber M and Mackay RD. *Epileptic automatisms in the criminal courts: 13 cases tried in England and Wales between 1975 and 2001.*
2. Lennox W. *The petit mal epilepsies: their treatment with tridione.* JAMA 1945;129:1069–73. [Abstract/FREE Full text]
3. Stacey KH. *Tay, Non convulsive status epilepticus in children: Clinical and EEG characteristics.* Epilepsia, 2006;47(9):1504-9.
4. Thomas P. *Absence and myoclonic status epilepticus precipitated by anti-epileptic drugs in idiopathic generalised epilepsy.* Brain 2006;129:1281-2.
5. Dr Abbie Reeve – Consultant Paediatrics Kings Lynn, Personal correspondence.
6. Stores G. *Non Convulsive Status Epilepticus.* Archives of diseases in childhood 1995;73:106-11.
7. Meierkord H. *Non convulsive status epilepticus in adults: clinical forms and treatment.* Lancet Neurology 2007;6:329-39.
8. Personal practice.

Non convulsive status epilepticus is difficult to diagnose in children as it can present with altered mental status and change in behaviour. It is important to rule out other serious differential diagnoses

Current Concepts in Optic Neuritis

Mithu Storoni, MA, MRCOphth
did her medical training at Cambridge University. She is currently a Fight for Sight sponsored Clinical Research Fellow based at The National Hospital for Neurology and Neurosurgery, Queen Square and Moorfields Eye Hospital in London, completing a PhD on Optic Neuritis. In her research, she is comparing Multiple Sclerosis related optic neuritis with Neuromyelitis Optica related optic neuritis, in an effort to identify the underlying diagnosis of isolated optic neuritis at first presentation.

Correspondence to:
Dr Mithu Storoni,
The National Hospital for Neurology and Neurosurgery,
London, UK.

The Optic Neuritis Treatment Trial (ONTT) has been the largest study on optic neuritis, to date. It revealed the presentation, course and prognosis of optic neuritis and has heavily influenced the treatment protocol for acute isolated optic neuritis around the Western world.[1] The results of the final follow-up from this study have recently been published[2] and reiterate the prognostic role of magnetic resonance imaging in optic neuritis.

The ONTT trial was conducted, however, in an era preceding the discovery of the aquaporin 4 autoantibody, which has been recognised as a biomarker for neuromyelitis optica (NMO).

Aquaporin 4 autoantibody

The discovery of the Aquaporin 4 autoantibody was reported in 2004.[3] Immediately prior to its discovery, NMO was starting to be recognised as both a monophasic and a relapsing and remitting illness (Figure).[4] However, at the time of the conduction of the ONTT, NMO was not included within the differential diagnosis of cases of 'typically presenting' acute isolated optic neuritis. Although approximately 3% of patients enrolled in the ONTT had a visual acuity of 6/60 or worse, five years following an episode of optic neuritis, none of these patients were considered to be suffering from an NMO-related disorder at the time.[5]

Shortly after the aquaporin 4 autoantibody was discovered, various reports describing neurological presentations outside of the hallmark syndrome of optic neuritis and transverse myelitis were increasingly described, in conjunction with the presence of the aquaporin 4 autoantibody. This led to the birth of a new concept of 'NMO spectrum' disorder.[6]

The advent of the concept of an NMO spectrum disorder has challenged existing protocols in the treatment of acute isolated optic neuritis. The occurrence of an isolated acute optic neuritis in the absence of any other underlying sign of disease on clinical examination, serological testing and imaging can no longer be classified as a 'clinically isolated syndrome' (CIS) without first testing for the aquaporin 4 autoantibody. In the presence of antibody positivity, acute isolated optic neuritis becomes an NMO spectrum disorder and as such the ONTT derived protocol (involving either a short course of intravenous corticosteroid therapy or conservative management) for its management becomes less appropriate.[7] Although there has been no randomised controlled study on the acute treatment of NMO-related optic neuritis, a recent study reports that the administration of intravenous corticosteroid therapy within 48 hours of the onset of optic neuritis may prevent irreversible retinal nerve fibre layer loss.[8]

The presence of aquaporin 4 autoantibodies also influences the long-term management of a patient following optic neuritis. Prolonged immunosuppression has been shown to reduce the relapse rate in NMO and may be initiated after its first presenting symptom.[9]

Following the identification of the NMO spectrum disorder, there is now a wider clinical appreciation of the possibility of a patient presenting with acute isolated optic neuritis having NMO. The incidence of aquaporin 4 autoantibody positivity in Western Europe has been recently shown to be higher than previously believed.[10] As a result, there is renewed interest in the identification of NMO spectrum disorder, even before seroanalysis for the aquaporin 4 autoantibody has been undertaken.

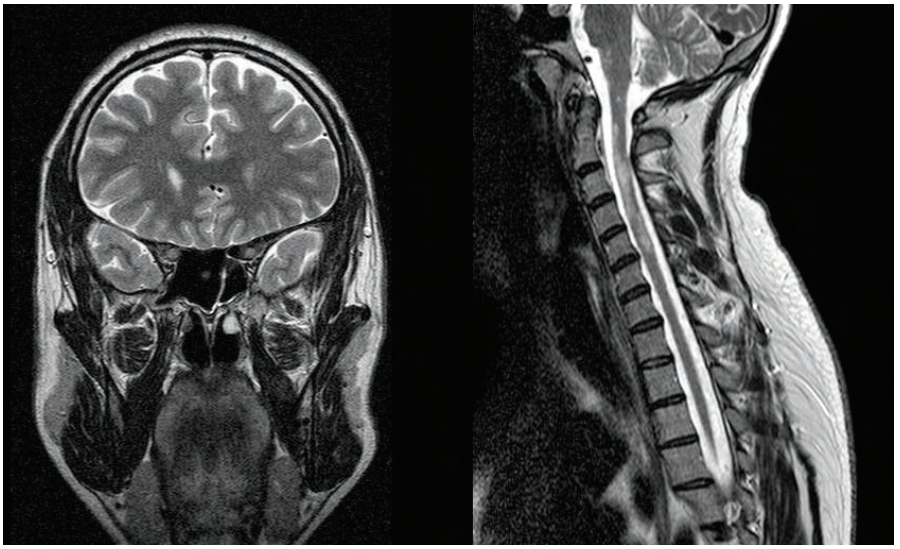
Other biomarkers and optic neuritis

Attempts to identify NMO spectrum disorder as the underlying aetiology of optic neuritis through serological analysis for biomarkers have met with some success. Recent reports suggest that serum levels of glial fibrillary acidic protein (GFAP), a marker of astrocytic damage, as well as N-acetyl aspartate may be elevated in NMO spectrum disease, compared with MS, and may help to distinguish between the two.[11,12] Serum GFAP levels have also been shown to be elevated despite the absence of extra-optic nerve disease. Such tests may be incorporated into the standard workup for optic neuritis in the future.

Ethnicity and optic neuritis

Approximately 13% of patients enrolled in the ONTT were of African-American ethnic origin (59 out of 448 patients), although a separate analysis with respect to ethnic background was

The ONTT must now be revisited in the aquaporin 4 autoantibody era in light of recent findings



Coronal brain (left) and sagittal cervical spine (right) T2-weighted magnetic resonance images demonstrating bilateral high signal optic nerve lesions and a longitudinally extensive spinal cord lesion in a patient with neuromyelitis optica.

not carried out for the majority of the trial. Traditionally, the ethnic background of a patient has not been separately considered when managing a case of acute isolated optic neuritis. A recent study, however, has suggested there may be a differing genetic susceptibility to NMO and MS.[13] More recently, a report from the United Kingdom on the incidence of optic neuritis within an ethnically diverse patient population has suggested there may be an ethnicity bias within an NMO patient cohort.[14] Despite only 14% of all patients presenting with acute isolated optic neuritis with no previously known underlying cause (who did not develop a collagen-vascular/ granulomatous/ infectious/ autoimmune/ neoplastic illness to account for the optic neuritis over the course of 16 months) being of African or African-Caribbean descent, 63% of all patients presenting with NMO-related optic neuritis over three years were of African or African-Caribbean descent. These findings suggest that a patient's genotype and phenotype should be taken into consideration when forming a management plan in the acute setting of optic neuritis.

The future

An episode of acute isolated optic neuritis is viewed differently today from how it was viewed twenty years ago, when the ONTT was first conducted. Traditional markers of visual function showed an optimistic picture of visual prognosis following optic neuritis and contributed to ONTT based management protocols in which intravenous corticosteroid therapy and conservative management were deemed to be of equal efficacy. The concept of an NMO spectrum disorder was unknown and NMO did not score highly on the differential diagnosis of optic neuritis. Little consideration was given to genetic factors and to the patient's ethnic background.

The discovery of the aquaporin 4 autoantibody has profoundly improved diagnostic and prognostic accuracy. It has encouraged a strong deviation away from ONTT based protocols in some cases of optic neuritis where NMO spectrum disease may be the underlying aetiology. Additional factors are now recognised which need to be considered before deciding on the management of an acute episode of optic neuritis. The ONTT must now be revisited in the aquaporin 4 autoantibody era in light of recent findings. A further large scale study is also indicated to consider how serological markers such as GFAP and N-acetyl aspartate and genetic influences can influence the management and outcome of acute isolated optic neuritis. ◆

REFERENCES

1. Ghosh A, Kelly SP, Mathews J, Cooper PN, Macdermott N. *Evaluation of the management of optic neuritis: audit on the neurological and ophthalmological practice in the north west of England.* J Neurol Neurosurg Psychiatry. 2002;72(1):119-21.
2. Optic Neuritis Study Group. *Multiple sclerosis risk after optic neuritis: final optic neuritis treatment trial follow-up.* Arch Neurol. 2008;65(6):727-32.
3. Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, Nakashima I, Weinshenker BG. *A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis.* Lancet. 2004;364(9451):2106-12.
4. Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. *The clinical course of neuromyelitis optica (Devic's syndrome).* Neurology. 1999;22;53(5):1107-14.
5. Gotkine M. *Neuromyelitis optica and the Optic Neuritis Treatment Trial.* Arch Neurol. 2008;65(11):1545-6; author reply 1546.
6. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. *The spectrum of neuromyelitis optica.* Lancet Neurol. 2007;6(9):805-15.
7. Beck RW, Gal RL. Treatment of acute optic neuritis: a summary of findings from the optic neuritis treatment trial. Arch Ophthalmol. 2008 Jul;126(7):994-5.
8. Nakamura M, Nakazawa T, Doi H, Hariya T, Omodaka K, Misu T, Takahashi T, Fujihara K, Nishida K. *Early high-dose intravenous methylprednisolone is effective in preserving retinal nerve fiber layer thickness in patients with neuromyelitis optica.* Graefes Arch Clin Exp Ophthalmol. 2010;248(12):1777-85.
9. Collongues N, de Seze J. *Current and future treatment approaches for neuromyelitis optica.* Ther Adv Neurol Disord. 2011;4(2):111-21.
10. Asgari N, et al. *A population-based study of neuromyelitis optica in Caucasians.* Neurology. 2011;76(18):1589-95.
11. Storoni M, Petzold A, Plant GT. *The use of serum glial fibrillary acidic protein measurements in the diagnosis of neuromyelitis optica spectrum optic neuritis.* PLoS One. 2011;6(8):e23489.
12. Tortorella C, Ruggieri M, Di Monte E, Ceci E, Iaffaldano P, Direnzo V, Mastrapasqua M, Frigeri A, Amato MP, Hakiki B, Ghezzi A, Lugaresi A, De Luca G, Patti F, D'amico E, Sola P, Simone AM, Svelto M, Livrea P, Trojano M. *Serum and CSF N-acetyl aspartate levels differ in multiple sclerosis and neuromyelitis optica.* J Neurol Neurosurg Psychiatry. 2011 May 27.
13. Deschamps R, Paturel L, Jeannin S, Chausson N, Olindo S, Béra O, Bellance R, Smadja D, Césaire D, Cabre P. *Different HLA class II (DRB1 and DQB1) alleles determine either susceptibility or resistance to NMO and multiple sclerosis among the French Afro-Caribbean population.* Mult Scler. 2011;17(1):24-31.
14. Storoni M, Pittock SJ, Weinshenker BG, Plant GT. *Optic neuritis in an ethnically diverse population: higher risk of atypical cases in patients of African or African-Caribbean heritage.* J Neurol Sci. 2012 Jan 15;312(1-2):21-5.

Series Editor

Alan Carson

Series editor Alan Carson is a Consultant Neuropsychiatrist and Part-time Senior Lecturer. He works between the Neurorehabiltation Units of the Astley Ainslie Hospital and the Department of Clinical Neurosciences at the Western General Hospital in Edinburgh. He has a widespread interests in neuropsychiatry including brain injury, HIV and stroke. He has long-standing research and teaching collaboration with Jon Stone on functional symptoms in neurology.

Series Editor

Jon Stone

Series editor Jon Stone is a Consultant Neurologist and Honorary Senior Lecturer in the Department of Clinical Neurosciences in Edinburgh. Since 1999 he has developed a research and clinical interest in functional symptoms within neurology, especially the symptom of weakness. He writes regularly on this topic in scientific papers and for textbooks of neurology and psychiatry.

Correspondence to: Email: Jon.Stone@ed.ac.uk

Welcome to the tenth 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 specialties 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.

How do you identify and manage convulsive psychogenic nonepileptic seizures presenting acutely to casualty?

Roderick Duncan

trained in neurology in Aberdeen, Glasgow and Rennes. Appointed Consultant Neurologist and Epilepsy Specialist in Glasgow in 1994. Research and clinical interests are presurgical localisation of focal epilepsy and psychogenic non-epileptic seizures. He leads a large multidisciplinary service for PNES and is chairman of the Scottish Managed Surgical Network for Epilepsy Surgery.

Correspondence to:
Email: roderick.duncan@clinmed.gla.ac.uk

Case

A 35-year-old man presented to casualty, having had a prolonged seizure. He had a diagnosis of epilepsy and was taking carbamazepine. He had further seizures in casualty, each with several minutes of generalised movements, followed by a similar period of unresponsiveness. On the last occasion the motor manifestations of the seizure went on for 12 minutes, and intravenous diazepam was given, following which the movements settled, and he appeared to sleep. During all this, his oxygen saturation remained at near 100%. Staff who witnessed the attacks expressed the view that they might have been psychogenic rather than epileptic, as they felt there was a degree of responsiveness during them. What clinical clues help you identify psychogenic seizures? How do you manage the situation acutely? What do you say to patients and relatives? Where do you refer, and in what terms?

Psychogenic non-epileptic seizures (PNES, pseudoseizures) have an incidence of 4-6/100,000/year,[1,2] up to one eighth that of epilepsy. There are a number of reasons why convulsive PNES might be more likely to present to casualty than epileptic seizures. They last longer, they are often serial, and the movements are often more impressive,[3] all producing a picture that can be quite alarming to carers and relatives. Attending paramedics are likely to have protocols requiring them to treat long or recurring seizures with benzodiazepines. These drugs disinhibit, and may may make progression to prolonged serial PNES or pseudostatus more likely.

It has been practice in the past to disregard the diagnostic problem and treat all such cases as epilepsy, on the grounds of safety. This is in many ways understandable: the clinical risk of treating pseudostatus as epilepsy is rightly perceived as being less than that of making the opposite error. However, neither choice is risk-free: treating pseudostatus as status epilepticus carries a significant risk of iatrogenic death.[4] Treatment with intravenous benzodiazepines can depress respiration sufficiently to require respiratory support, and patients occasionally end up in ITU for this reason. These risks can be kept to a minimum if the focus is kept firmly on the patient's life support systems. Is the patient breathing? Are his pulse and blood pressure consistent with good perfusion to vital organs? Are blood gases or oxygen saturation consistent with adequate ventilation or hyperventilation? If the answer to these questions is yes, then the emergency doctor should think very carefully indeed before giving treatments that carry risk.

This patient had a diagnosis of epilepsy. In the past, it was thought that most patients with PNES also had epilepsy. Recent consensus is that only 10-15% have a dual diagnosis,[5] with the exception that the rate is probably 30% in the learning disabled.[6] In the the emergency situation, it is difficult to meaningfully evaluate a past diagnosis of epilepsy, and it is probably better to concentrate on the identity of the attacks that are happening there and then.

Clinically, the great majority of PNES fall into two clinical patterns.[5] The majority are convulsive, with unresponsiveness accompanied by generalised movements, eyes usually closed. The movements have been described in a number of ways, but are essentially tremors, either high frequency and low amplitude, or

The longer the duration of convulsive movements before measurement of a normal O2 saturation, the more likely the diagnosis is to be PNES

low frequency and high amplitude. The latter may look quite dramatic, and in a few patients develop into actual 'thrashing' movements. A large minority of patients have fall-down-lie-still attacks (sometimes called 'swoon' attacks) during which the eyes are usually closed and the patient is unresponsive. For obvious reasons, these do not fall into the differential diagnosis of tonic clonic convulsion (rather with vasovagal syncope, cardiac syncope, or death), and present less commonly to casualty.

There is an extensive literature on the clinical diagnosis of PNES,[7] comparing the clinical features of epileptic seizures with PNES. Much of this is difficult to apply usefully in the emergency situation, partly because many studies lump convulsive and non convulsive PNES together, and partly because some studies do not distinguish reported features of seizures from observed features (they are often not the same). Nonetheless, some simple diagnostic clues are helpful, focusing initially on life support. Patients do not breathe during the tonic and clonic phases of a tonic clonic convulsion, whereas hyperventilation is usual during a PNES. Therefore, if a patient has been in what appears to be a convulsive seizure for several minutes with normal oxygen levels (or saturations), particularly if accompanied by low CO_2, then it becomes difficult to sustain the diagnosis of tonic clonic convulsion. The longer the duration of convulsive movements before measurement of a normal O_2 saturation, the more likely the diagnosis is to be PNES. Oxygen saturations should not drop below normal levels during PNES. In tandem with this, a 'grey' colour, or cyanosis indicates an epileptic seizure (though patently it does not occur in all cases, especially if the seizure is short). Impressive rubefaction usually means hyperventilation and PNES. Clear observation of breathing may not be all that easy, but should be attempted. Rhythmic grunts or guttural noises with no normal breathing pattern suggests tonic clonic seizure. Rapid but otherwise nortmal respiration suggests PNES.

This particular patient had a sinus tachycardia of 140, with a blood pressure of 180/100. Both sinus tachycardia and mildly raised blood pressure are usual during PNES of convulsive type. Oxygen saturations were over 97% throughout his attacks, even when the convulsive movements had been going on for more than 10 minutes. This would be difficult to reconcile with a diagnosis of tonic clonic seizure.

Other clinical features of PNES can be of some help, though all have an error rate.[7] PNES are generally much longer than epileptic seizures. Side-to-side head movement is fairly common in PNES, not usually seen during tonic clonic convulsions. PNES do not usually have a tonic phase, and similarly tonic posturing of limbs is uncommon. Signs of emotional distress are common after PNES, uncommon after epileptic seizures. Resistance to forced eye-opening is highly suggestive of PNES. However, tolerance of painful stimuli may be surprisingly great, so this test is of limited use. Similarly, plantar responses may be difficult to interpret or misleading.

The best acute management of a prolonged PNES is to reduce the general bustle around the patient and monitor discreetly in a quiet location. Attempts to reassure verbally should be low-key at most, as over-reassurance may reinforce the attacks. The presence of a relative manifesting anxiety may also be counterproductive, and (as in most normal clinical situations), relatives should be asked to wait outside until the attacks settle. Medication is neither required nor helpful. In this case, the attacks did settle, the patient was kept overnight, and was referred as an outpatient to the regional epilepsy service.

On discharge from the medical ward, this patient was simply told that he would be referred to the regional epilepsy service. It is important that such a referral is made. It is estimated that up to 20% of patients with a diagnosis of intractable epilepsy have PNES.[6] Confirmation of the diagnosis of PNES usually requires video EEG monitoring,[3,7] and it may be difficult to manage the situation long term if such confirmation is not obtained. This is not just to confirm the diagnosis for the neurologist, but to allow a positive and convincing approach to giving the diagnosis to patients and relatives (which has a positive therapeutic effect in up to half of all patients[2]), to ensure that the other doctors involved in the patient's care are convinced, and to provide a sound platform for psychological intervention.

Was the rather sparing approach to patient information correct? In principle you keep the patient fully informed at all stages, but the reality is that it is difficult and probably inadvisable to discuss the diagnosis at this stage. As emergency doctors or physicians, you may not be confident that the episode has been PNES. Further, you may well be in some difficulty defending your diagnosis if it is challenged by the patient or relatives, as it will fairly often be, particularly if the patient and relatives do not perceive you as being the appropriate 'expert'. In many cases, the 'possible' or 'probable' diagnosis will not be accepted, and may indeed be received negatively, sometimes prejudicing later medical consultations.

What should be written in the referral letter? Firstly, you should say clearly that there is doubt that the attack has been epileptic, so that the epilepsy or neurology service is signalled to examine (or re-examine) the diagnosis. Secondly, the referral should contain a clinical description of the witnessed attacks, plus an account of any eyewitness descriptions of previous attacks obtained by relatives. This not only allows a diagnostic evaluation, but allows evaluation of whether the attacks are like those previously documented. The use of labels for the attacks (e.g. 'This patient presented today with a tonic-clonic seizure...') is much less helpful. Clearly, relevant measurements, such as oxygen saturations, should also be included.

In this case, the patient eventually underwent video-EEG monitoring, which confirmed the diagnosis of PNES. There was no evidence of epilepsy (only one attack type clinically, no history suggestive of tonic clonic seizures, no interictal epileptiform EEG abnormality over two days of video EEG monitoring[9]). The diagnosis of PNES was explained to him, carbamazepine was withdrawn without incident, and he was referred for psychological intervention. ◆

REFERENCES

1. Szaflarski, JP, Ficker DM, Cahill WT, Privatera MD. *Four year incidence of psychogenic seizures in adults in Hamilton County, H.O.* Neurology 2000;55:1561–3.
2. Duncan R, Razvi S, Mulhearn S. *Newly presenting psychogenic nonepileptic attacks:incidence, population characteristics and early outcome from a prospective audit of a First Seizure Clinic.* Epilepsy & Behaviour 2011:20:308-11.
3. Reuber M, Elger CE. *Psychogenic nonepileptic seizures: review and update.* Epilepsy Behav 2003;4:205–16.
4. Reuber M, Baker GA, Gill R, Smith DF, Chadwick DW. *Failure to recognise psychogenic nonepileptic seizures may cause death.* Neurology 2004;62:834-5.
5. Benbadis SR, Agrawal V, Tatum WO. *How many patients with psychogenic non-epileptic seizures also have epilepsy?* Neurology 2001;57:915–7.
6. Duncan R, Oto M. *Psychogenic nonepileptic attacks in patients with learning disability:comparison with patients with no learning disability.* Epilepsy & behaviour 2008;12:183-6
7. Duncan R. *Psychogenic non epileptic seizures: diagnosis and initial management.* Expert Review of Neurotherapeutics 2010;10:1803-9
8. Benbadis SR, Hauser WA. *An estimate of the prevalence of psychogenic non-epileptic seizures.* Seizure 2000;9:280–1
9. Duncan R. *The withdrawal of antiepileptic drugs in patients with nonepileptic seizures: safety considerations.* Expert Opinion on Drug Safety 2006;5:609–13.

Help, I've become shorter than my wife! Camptocormia due to Lyme Neuroborreliosis

***Seán J Slaght** (pictured)[1], **Ian Galea**[1], **Susan O'Connell**[2], **Simon Hammans**[1]*

1: Wessex Neurological Centre, Southampton General Hospital, Tremona Road, Southampton, SO16 6YD.

2: Health Protection Agency Lyme Borreliosis Unit, Southampton General Hospital, Tremona Road, Southampton, SO16 6YD.

Correspondence to:
sean.slaght@uhs.nhs.uk

This case report won the ACNR sponsored prize for Best Case Report at the ABN meeting in Newcastle, October 2011.

Camptocormia (or bent spine syndrome) is the abnormal flexion of the thoracolumbar spine, which increases with standing or walking and resolves on lying down. Camptocormia is particularly associated with advanced Parkinson's disease, but is also described in a number of other (predominantly neurodegenerative) central nervous system disorders, as well as disorders of the peripheral nerve, muscle and psychiatric conditions. For a recent review of camptocormia see Finstere and Strobl.[1]

The only infection previously reported to have camptocormia as part of its clinical course is Viliuisk encephalomyelitis.[2] This is a rare and devastating disorder of the central nervous system, seen only in the Yakut population of Eastern Siberia, which invariable leads to death. Viliuisk encephalomyelitis is transmitted horizontally, but the causative organism has not yet been identified.[3]

Lyme neuroborreliosis (LNB) is the major complication of Lyme borreliosis (LB), which is due to infection with the spirochaete *Borrelia burgdorferi*.[4] Prospective, population based studies show that around 3% of patients with LB develop LNB.[4] The most common presentations are with facial palsy (unilateral or bilateral), meningoencephalitis or polyradiculopathy.[5] Neuroborreliosis can be successfully treated with either oral doxycycline or intravenous ceftriaxone.[6]

We believe this is the first case of camptocormia due to Lyme neuroborreliosis to be reported in the medical literature.

The case

In October 2009, the patient sought medical help as he had become shorter than his wife. He was a 57-year-old ex-smoker with well-controlled hypertension and type-2 diabetes mellitus. He was otherwise fit and well and a keen amateur ornithologist and wildlife photographer (Figure 1a).

About four to six weeks prior to presentation he had noticed a slightly itchy rash behind his left knee. Shortly after this, he developed pain in his left knee, which gradually progressed up his left leg to his hip. His left leg became weak and over the next four to six weeks posture started to stoop. This continued to the point that he became shorter than his wife.

Examination revealed a stooped posture consistent with camptocormia (video at www.acnr.co.uk/case report.htm and Figure 1b). Muscle tone was normal. He had mild weakness of the neck flexors, truncal and abdominal muscles, as well as in the left arm and leg. He was areflexic. There was a suspended sensory level from T8-T10 on the left hand side.

Routine blood screen was unremarkable, as was MRI of his spine. Lumbar puncture showed clear cerebrospinal fluid with an opening pressure of 15 cmH_2O. There were no red cells, but 100 white blood cells: 66% neutrophils and 32% lymphocytes. The protein was 1884 mg/L and the glucose 5.9 (matched serum 10.9). Unmatched cerebrospinal fluid oligoclonal bands were seen. Western blot for antibodies against *Borrelia burgdorferi* were positive in blood and cerebrospinal fluid (Figure 2).

He was treated with a two-week course of IV ceftriaxone, with rapid resolution of his leg pain. The strength in his leg and his posture recovered back to normal over the next few months (video). In March 2010, he was able to take part in a sponsored 10 km walk (Figure 1c).

Discussion

We believe this is the first reported case of camptocormia caused by an identified infectious agent: *Borrelia burgdorferi*. As with most cases of Lyme neuroborreliosis, our patient made a full recovery after treatment with antibiotics. The camptocormia appeared to be caused by paraspinal muscle weakness secondary to a polyradiculopathy. This assumption is backed by a recent case of camptocormia caused by chronic inflammatory demyelinating polyradiculopathy, which responded to treatment with intravenous immunoglobulins.[7]

Lyme disease classically presents with erythema migrans; an expanding area of erythema associated with the point of entry of

the spirochaetes.[4] Eighty-nine per cent of patients with LB in a large prospective population based study in Germany had erythema migrans.[8] Although, in a laboratory based study in Devon only 36% of patients with LBN had a preceding erythema migrans and 27% had no memory of a bite, rash, headache, fever or arthralgia/myalgia.[5] Our patient did have an itchy rash prior to developing his camptocormia, but this only came to light following direct questioning. The patient is a keen wildlife photographer and had spent time in Lyme infested areas prior to his illness, although he did not have any memory of a tick bite, in common with 45% of patients with Lyme neuroborreliosis.[5]

Most cases of camptocormia are due to degenerative disorders such as Parkinson's disease and develop several years after the diagnosis has been made.[1] The rapid onset of camptocormia in our patient would be unusual for a degenerative cause and in such cases a search for reversible causes should be sought.

Lyme neuroborreliosis should be considered in the differential diagnosis of camptocormia. ◆

Figure 1: Photographs of the patient prior to his illness (A), at presentation (B) and following his recovery (C).

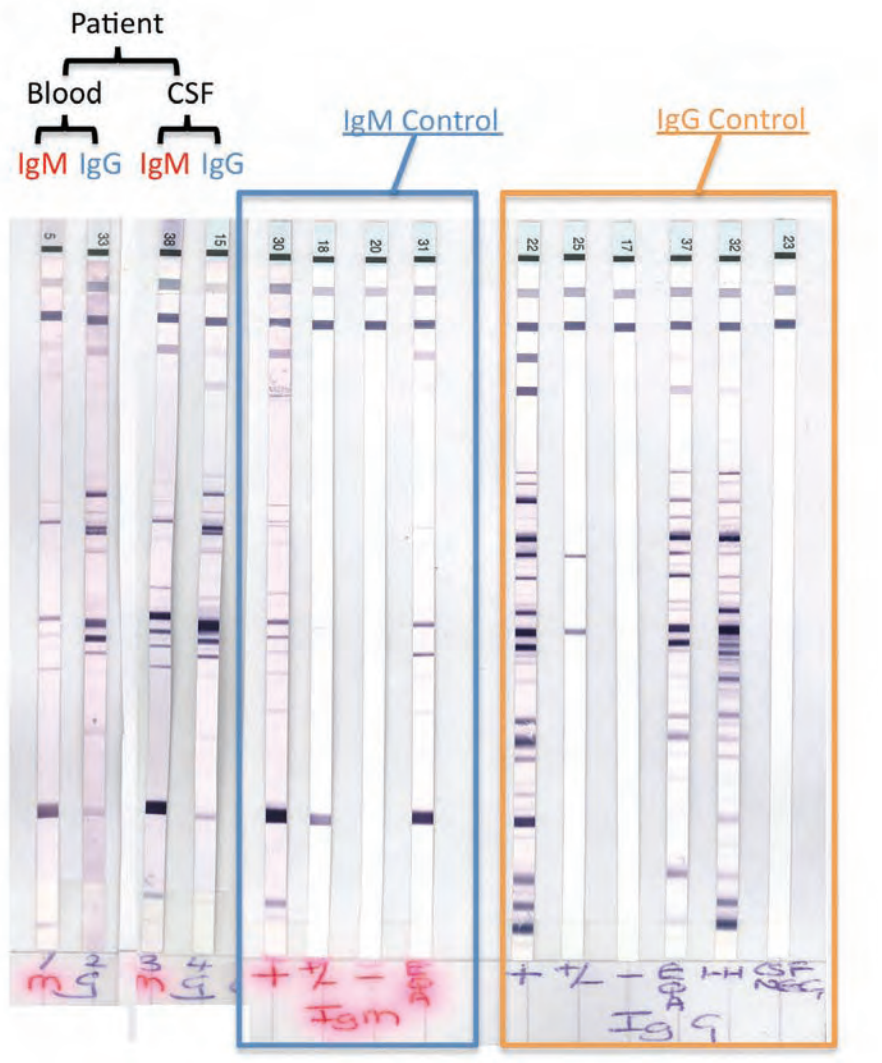


Figure 2: Western blots from the patient (first 4 lanes) from blood and CSF for both IgM and IgG as well as positive and negative controls for IgM (within blue square) and IgG (within orange square). The positive bands to IgG and IgM in the patient's CSF and blood confirm the diagnosis of Lyme neuroborreliosis.

REFERENCES

1. Finstere J and Strobl W. *Presentation, Etiology, Diagnosis, and Management of Camptocormia.* Eur Neurol 2010;64:1–8.
2. Goldfarb LG and Gajdusek DC. *Viliuisk Encephalomyelitis In The Iakut People Of Siberia.* Brain 1982;115:961-78.
3. Goldfarb LG, Vladimirtsev VA, Platonov FA, Lee H-S, McLean CA and Masters CL4. *Viliuisk encephalomyelitis in Eastern Siberia – analysis of 390 cases.* Folio Neuropathologica, 2009;47:171-81.
4. Stanek G, Wormser GP, Gray J, Strle F. Lancet 2011. *Lyme borreliosis.* Published online September 7, 2011 DOI:10.1016/S0140-6736(11)60103-7
5. Lovett JK, Evans PH, O'Connell S and Gutowski NJ, *Neuroborreliosis in the South West of England.* Epidemiol. Infect. 2008;136:1707–11.
6. Ljøstand U, Skogvoll E, Eikeland R, Midgard R, Skarpaas T, Berg A, and Mygland A. *Oral doxycycline versus intravenous ceftriaxone for European Lyme neuroborreliosis: a multicentre, non-inferiority, double-blind, randomised trial.* Lancet Neurology 2008;7:690-5.
7. Terashima M, Kataoka H, Sugie K, Horikawa H and Ueno S. *Coexistence of chronic inflammatory demyelinating polyneuropathy and camptocormia.* J Neurol Neurosurg Psychiatry 2009;80:1296-7.
8. Huppertz HI, Böhme M, Standaert SM, Karch H, Plotkin SA. *Incidence of Lyme borreliosis in the Würzburg region of Germany.* Eur J Clin Microbiol Infect Dis. 1999;18:697-703.

C9ORF72: hammering home the clinical, genetic and pathological overlap between ALS and FTLD

Around 10% of ALS is familial (fALS), while ~40% of FTLD is familial. Mutations in over a dozen genes cause ALS, while mutations in MAPT and progranulin are major causes of fFTLD. Relatively little clinical overlap occurs in the syndromes associated with these ALS and FTLD-associated gene mutations. However, it had long been known that patients can develop both ALS and FTLD. This overlap has been of great interest, particularly since the discovery in 2006 of TDP-43 as the common pathological denominator of both conditions. Furthermore, 2006 also saw the publication of the first papers linking autosomal dominant ALS-FTLD to chromosome 9p. The race to identify the causative gene has lasted five years, finishing in 2011. This delay was a frustrating consequence of the nature of the mutation: a hugely expanded intronic hexanucleotide repeat in the C9ORF72 gene (chromosome 9 open reading frame 72). The size and 'G-C rich' nature of the expansion made it impossible to detect using conventional and next-generation sequencing technology. Good old-fashioned microsatellites and Southern blotting were needed. C9ORF72 seems to localise to synapses but has no known function. It does, however, have a mouse homologue, which bodes well for animal studies.

Recently, several groups have published clinicopathological studies of C9ORF72 cases (all with European ancestry). Hsiung et al (2012) describe 30 cases from 16 different families harbouring C9ORF72 mutations. 15 had FTLD, 8 ALS and 7 ALS-FTLD. Of the latter, 5 began with FTLD, 1 with ALS, and 1 with synchronous onset. Mean age of onset was 54y (range 34-74), age of death 61y (41-84) and disease duration 5y (1-16). Patients with ALS had markedly shorter survival (2.8y versus 8.4y without ALS). Interestingly, anticipation also appeared to occur, with a trend to earlier onset by 5-10y in younger generations.

Of their 22 cases with FTLD, the commonest dementia subtype was behavioural variant (15 cases). The others had progressive non-fluent aphasia (PNFA) with or without bvFTLD. No one had semantic dementia. In keeping with frontal predominant dementia, memory problems were only mild, and visuospatial problems and apraxia were uncommon. In patients with ALS, nearly half had prominent bulbar features, and even the FTLD patients had bulbar findings. An extrapyramidal syndrome (akinetic rigidity) was seen in 12 patients in all. Four had overt Parkinsonism with tremor. A variety of other clinical features were seen in small numbers, including ataxia, supranuclear gaze palsy and urinary incontinence, suggesting more widespread pathology. Marked clinical heterogeneity was seen between and within families and only three families demonstrated a consistent clinical phenotype (bvFTLD).

Hsiung et al also performed structural and functional imaging studies, which further confirmed predominantly frontal lobe failure (asymmetric in only one out of 21 cases imaged, with left predominant atrophy). Pathological studies of 21 cases again showed frontal atrophy (with relative sparing of the temporal lobes) and corticospinal tract degeneration. Degenerative changes were also seen in the basal ganglia in over half the cases studied. TDP-43 staining was prominent and widespread in all layers of the cortex, subcortical areas, hippocampus, white matter, brainstem motor nuclei and anterior horn of the spinal cord. These were ubiquitin positive, and thus characteristic of pure FTLD-TDP and ALS. C9ORF72 itself did not seem to colocalise with these inclusions.

It is interesting to note a couple of features that might mark C9ORF72 mutation cases out from other causes of TDP-43 proteinopathy. Firstly, ubiquitinated inclusions negative for TDP-43 are observed, most consistently in the cerebellar granule cell layer. This appears to be a characteristic signature for C9ORF72 mutation disease, originally described by Al-Sarraj et al (2011). Secondly, Snowden et al (2012) found a significant association between a psychotic presentation of FTLD and presence of C9ORF72 mutation. Prominent features included complex repetitive behaviours and delusions. More studies are needed to corroborate these findings.

In summary, C9ORF72 mutations are clearly a major cause of FTLD. Furthermore, they may be the single most common genetic cause of fALS (accounting for 25% of familial cases). Hsiung et al found that C9ORF72 mutations accounted for 100% of their fALS-FTLD cases. However, the story is not that clear cut, as Snowden et al (2012) found that they only accounted for 8 out of their 30 fALS-FTLD cases. Thus, while C9ORF72 mutations further strengthen our understanding of ALS and FTLD as being two TDP-43 diseases on a clinical and pathological spectrum, it is clear that other ALS-FTLD genes are waiting to be discovered.

– Jemeen Sreedharan, National Hospital for Neurology and Neurosurgery, Queen Square.

Clinical and pathological features of familial frontotemporal dementia caused by C9ORF72 mutation on chromosome 9p. Hsiung GY, Dejesus-Hernandez M, Feldman HH, Sengdy P, Bouchard-Kerr P, Dwosh E, Butler R, Leung B, Fok A, Rutherford NJ, Baker M, Rademakers R, Mackenzie IR. BRAIN 2012 Feb 17.

Distinct clinical and pathological characteristics of frontotemporal dementia associated with C9ORF72 mutations. Snowden JS, Rollinson S, Thompson JC, Harris JM, Stopford CL, Richardson AM, Jones M, Gerhard A, Davidson YS, Robinson A, Gibbons L, Hu Q, Duplessis D, Neary D, Mann DM, Pickering-Brown SM. BRAIN 2012 Feb 2.

p62 positive, TDP-43 negative, neuronal cytoplasmic and intranuclear inclusions in the cerebellum and hippocampus define the pathology of C9orf72-linked FTLD and MND/ALS. Al-Sarraj S, King A, Troakes C, Smith B, Maekawa S, Bodi I, Rogelj B, Al-Chalabi A, Hortobágyi T, Shaw CE. ACTA NEUROPATHOL 2011;122(6):691-702.

(The March edition of Brain (Vol 135 issue 3) has 8 papers on C9orf72 with an editorial by John Hodges, among related papers including a CHMP2B mouse and non-human primate model of TDP-43 ALS – Ed.)

The link between iron and tau

Several lines of evidence are presented by this group into the link between loss of soluble tau in the neuronal cytoplasm in Alzheimer's disease, Parkinson's disease and tauopathies, a loss of functional iron cellular export, and iron accumulation associated with disease severity. A key finding in this paper is of prevention of onset of disease phenotype in a tau knockout mouse with iron chelation (clioquinol, fed orally for 5 months), which adds to the evidence presented in the 2003 paper by Kaur and colleagues in a mouse MPTP model of Parkinson's Disease. The paper also provides insights into disease mechanisms, with in vitro evidence of reduced soluble tau leading to decreased amyloid precursor protein (APP) cell surface trafficking and then reduced iron export.

– Mike Zandi, National Hospital for Neurology and Neurosurgery, Queen Square, London.

Lei et al. Tau deficiency induces parkinsonism with dementia by impairing APP-mediated iron export. NATURE MEDICINE 18, 291–295 (2012)

Kaur et al. Genetic or Pharmacological Iron Chelation Prevents MPTP-Induced Neurotoxicity In Vivo: A Novel Therapy for Parkinson's Disease. NEURON 37(6), 899–909,(2003)

A blast from the past

In the UK, the driving regulations for an ordinary (type 1) licence are based on a calculation of a risk of seizures of 20% in a year. Less than this and you are allowed behind the wheel, more and then the keys go back on the hook. Consequently the epidemiological data informing these decisions is crucial and a central pin has been the MRC drug withdrawal study which has celebrated its 21st birthday. With its coming of age is a further analysis of the data within the study and an analysis of related studies. The broad brush figures which we have known for a long time are that after two years of seizure freedom, the risk of seizures is 22% in the next two years if a patient continues on treatment and 41% if they do not (30% in the first year). The current analysis looked at patients over 16 (potential drivers) and asked the question: "what is the risk of seizures in the next 12 months at various points" in their course. They found that if a patient was seizure free for three months after completion of a six month drug withdrawal, then their risk of seizures in the subsequent 12 months was 15% (CI 10-19%) and at six months, the risk was 9% (CI 5-13%). 127 patients had a seizure following drug withdrawal and reinstated treatment. The risk of a further seizure from 3-15 months after reinstatement was 26% and the risk from 6-18 months, if seizure free for the first 6 months was 18%. Five other studies looking at recurrence risk in the 12 months following drug withdrawal found 12-30% but methods and cohorts differ. These data suggest that the DVLA guidelines recommending six months off driving

after withdrawal are not too far off the mark, although may be a little conservative with the annualised risk falling below 20% at three months. Equally ensuring seizure freedom for six months after reinstatement of treatment may be long enough off driving, although the numbers from the MRC study are too small to be sure.

– Mark Manford, Addenbrooke's Hospital, Cambridge and Bedford Hospital NHS Trust, Bedford.

Seizure recurrent after anti-epileptic drug withdrawal and the implications for driving: further results from the MRC antiepileptic drug withdrawal study and a systematic review. Bonnett LJ, Shukralla A, Tudor-Smith C, Williamson PR, Marson AG. JNNP 2011;82:1328-33.

Deep brain stimulation for amnesia?

Suthana and colleagues from the University of California, Los Angeles and Tel Aviv University, implanted intracranial depth electrodes in seven subjects with pharmacological treatment refractory epilepsy to plan for epilepsy surgery, and noted improvement in a virtual spatial navigation memory task with entorhinal cortex stimulation at a low level, compared to no stimulation. This stimulation was associated with resetting of the phase of the theta rhythm of the hippocampal EEG. Direct hippocampal stimulation was ineffective. A repeated measures block design was used for statistical analysis and the p values are quite modest (0.03). Clearly the studies require replication and then a relevant trial in disorders with amnesia in which the risks of DBS may be allowable, for instance herpes simplex encephalitis or Alzheimer's disease. Even small gains in memory encoding ability may be clinically meaningful and aid to quality of life. This study adds to the potential roles of DBS in neuropsychiatric diseases including the so far studied obsessive compulsive disorder and major depression in which perhaps the acceptable risks are smaller.

– Mike Zandi, National Hospital for Neurology and Neurosurgery, Queen Square, London.

Memory Enhancement and Deep-Brain Stimulation of the Entorhinal Area. Suthana et al. NEJM 2012;366:502-10.

So much for history

This is quite a small study of just 35 patients with 120 seizures from a telemetry unit. Twelve patients had 36 non-epileptic seizures and eighty six seizures were recorded from the remaining patients, mostly partial seizures. The videos were compared against witnesses' histories of the seizures. At least half of witnesses reported more than 30% of signs incorrectly. The six signs which were found on video-telemetry to discriminate most clearly between epilepsy and non-epileptic seizures were reported incorrectly by 37-62% of witnesses. The signs, on video telemetry, which most clearly predicted non-epileptic attacks were preserved awareness, eyelid fluttering, evidence of seizure activity changing in response to observers. Those most clearly predicting epileptic attacks were eye opening/widening, abrupt onset and post-ictal confusion or sleep. This study re-emphasises the problems inherent in epilepsy diagnosis from the history. This diagnostic minefield has high error rates for all of us. Marcus Reuber has shown us that it is not just what you say but also how you say it and this can be used to augment diagnostic accuracy but in the end, diagnostic proof requires video telemetry. Yet only a fraction of patients who might benefit from telemetry can avail themselves of it. How many other serious conditions have such poor access to diagnostic tests?

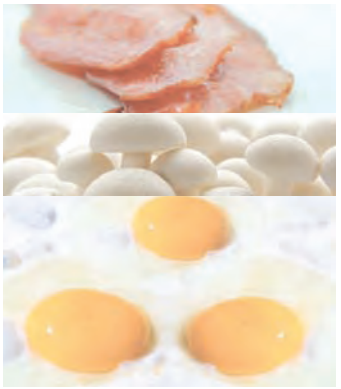
– Mark Manford, Addenbrooke's Hospital, Cambridge and Bedford Hospital NHS Trust, Bedford.

Can semiology predict psychogenic non-epileptic seizures? A prospective study. Syed TU, LaFrance WC, Kahriman ES et al. ANN NEUROL 2011;69:997-1004.

Matthew's Friends Clinics aim to complement existing NHS provision, by offering a comprehensive Ketogenic dietary therapy service; a tertiary service delivered by a team of experienced neurologists, dietitians and keto assistants, to which those children and adults who are unable to access local NHS provision, can be referred. Privately funded referrals are also accepted.

MATTHEW'S FRIENDSCLINICS
KETOGENIC DIETARY THERAPIES

Ketogenic Diets for Epilepsy & Other Neurological / Metabolic Disorders

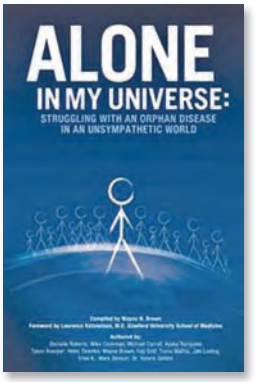


- ✔ Classical Ketogenic Diet
- ✔ MCT Ketogenic Diet
- ✔ Modified Ketogenic Diet
- ✔ Low Glycemic Index Treatment
- Health & Well-Being For Epilepsy
- Ketogenic Training & Resources

SUPPORTED BY

FOR MORE INFORMATION:
+44(0) 1342 836571 www.mfclinics.com

Alone In My Universe: struggling with an orphan disease in an unsympathetic world



Alone In My Universe provides a unique insight into the perceptions of patients with acromegaly, a condition with numerous neurological sequelae as well as relevance for ACNR's Skull-base Neurosurgery readership. The book is aimed not just at healthcare professionals but also at people with acromegaly, both recently diagnosed and with longstanding disease.

For healthcare professionals the book stimulates reflection particularly around how better communication may have a positive impact on patient's perspective of disease, as well as providing greater insight into the isolation incurred by being diagnosed with a rare condition. For patients the book provides a very accurate and useful resource about acromegaly, written in understandable language and may also be useful in providing a form of peer support to patients who may never have met another person with the condition.

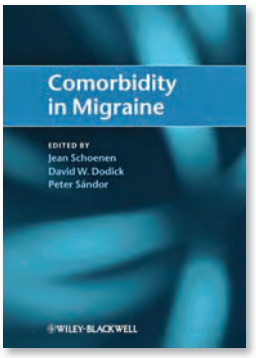
The somewhat daunting (some would argue negative) title should not deter the reader as many positive experiences are described within the text. The chapters are written by people with acromegaly and each describes a different part of the disease process and its management in succession including experiences prediagnosis, at diagnosis, treatments undertaken and effects on work and relationships with friends and family.

In summary, the book gives a very balanced view of acromegaly from a patient's perspective and is an important and unique source of information for healthcare professionals involved in the management of patients with acromegaly and people affected by the condition. ◆

Authors: Roberts D, Cookman M, Carroll M, Nangumo A, Koerper T, Zelenka H, Brown W, Graf R, Mathis T, Loebig J, Ellen K, Stinson M, Golden V.
Editor: Wayne Brown. **Publisher:** iUniverse. **Price:** US$ 23.95. **ISBN:** 978-1450295925.

Reviewed by: Dr Helen White, Consultant Endocrinologist, University Hospital Aintree and Liverpool Neuroendocrine Clinic

Comorbidity In Migraine



Authors: J Schoenen
David W Dodick
Peter S Sándor
Published by: Wiley-Blackwell
Price: £49.99
ISBN: 978- 1405185554

Reviewed by:
Rhys Davies.

Neurologists must learn to love migraine, or at least learn to live with it. Neurology trainees quickly realise that they need an approach for dealing with headaches occurring in the absence of structural disease, and for dealing with the myriad transitory neurological disturbances that also occur within the migraine spectrum. Furthermore, better understanding of how such phenomena may relate to more substantial disease in the nervous system must be a secret desire of most neurologists.

So, it was with a sense of having found the 'key to all mythologies' that I picked up Comorbidity in Migraine by Schoenen and colleagues.

Of course, no single volume could ever hope to meet such high expectations, still less a slim one hundred or so A5 pages. Nonetheless, the book does deliver insights relevant in clinical practice that would be hard to acquire from ordinary textbooks or from searching the primary literature.

The book is divided into 10 chapters, contributed by the editors and other Headache luminaries. Early chapters concentrate on the relationship between migraine and vascular diseases, including patent foramen ovale. There are then discussions about epilepsy and migraine, migraine and pain disorders more generally as well as about migraine in children.

Though the chapter on epilepsy provides a good overview, I was disappointed that the relationship between seizures, migraine auras and behavioural (non epileptic) attacks was not explored more fully; instead, there is a brief section on 'migraine variants commonly confused with epilepsy'. Similarly, I would have liked to see more about how migraine may affect 'illness behaviour' in the chapter on psychiatric disorders. In these chapters, as elsewhere, the authors understandably concentrate on summarising what is known and less on exploring some of the important questions whose answers we would wish to know.

Conversely, the chapters summarising the evidence concerning migraine and vascular disease are strong. Strangely, as an adult neurologist, my favourite chapter was that on migraine in paediatric practice, discussing migraine associations that range from asthma to Gilles de la Tourette syndrome.

The final chapter propounds the view that the selection of antimigraine drugs in an individual patient should take account of co-morbid diagnoses. Of course, I understand that those writing about migraine abhor conjecture, precisely because understanding of the condition remains so vague, but I must say that I found this conclusion rather prosaic. Who among us would give Amitriptyline in preference to an anticonvulsant migraine prophylactic to a migraineur with epilepsy, or Topiramate to an anorexic migraineur?

Certainly, I was glad of Schoenen's book as a concise package of the existing evidence on the relationship between migraine and other disorders. I think, however, its appeal to general neurologists would have been enhanced by an additional chapter outlining current research questions and describing important clinical questions yet to be formulated in a way that research can penetrate. ◆

The Role of Spinal Cord in Motor Control: reflexes, patterning and final motor production

Simon Giszter

is Professor of Neurobiology and Anatomy at Drexel University College of Medicine, Philadelphia, PA, USA. He has a BA from Cambridge University in Zoology, and a PhD from the Institute of Neuroscience and Department of Biology at the University of Oregon, in the United States. His postdoctoral training was with Emilio Bizzi, in Brain and Cognitive Sciences, at MIT, where he became a Research Scientist before moving to the College of Medicine. He is a member of the Spinal Cord Injury Research Centre at Drexel and College of Medicine Co-Director for the Neuroengineering Initiative. His work focuses on modularity in the motor system and spinal cord injury and rehabilitation approaches using animal models.

Corey Hart

is an Instructor at Drexel University College of Medicine. He has a BS in Physics from Villanova University, and a PhD in Neuroscience from Pennsylvania State University College of Medicine, Hershey, USA. His subsequent training and career has been at Drexel University College of Medicine, where he is now research faculty. His work focuses on fundamental spinal mechanisms and signal analysis methods in the motor system.

Ubong Ime Udoekwere

is a Postdoctoral fellow at Drexel University College of Medicine. He has a BS in Electrical Engineering from the University of North Carolina, Charlotte, NC, USA, and a PhD in Biomedical Engineering from Drexel University. His work focuses on robot rehabilitation and epidural stimulation after spinal cord injury and their effects on spinal reflex mechanisms in animal models of spinal cord injury. His interests are in human applications and translation of basic research.

Correspondence to:
Simon Giszter,
Neurobiology and Anatomy,
Drexel University College of Medicine,
2900 Queen Lane,
Philadelphia, PA 19129, USA.
Email: sgiszter@gmail.com

The spinal cord has an unambiguous position in motor control, containing the final common pathway to the musculoskeletal system. It is also among the evolutionarily most ancient structures, with homologues of vertebrate spinal cord in lower chordates such as amphioxi or lancelets. The precise role and operations of spinal cord circuitry continue to be areas of dispute and occasional controversy. Some of the very earliest experimental physiologists (e.g., Whytt, Legalois, and Marshall Hall[18]) had already shown that the spinal cord, isolated from the rest of the CNS, could organise semi-purposive goal-directed behaviours. As a result of these fundamental observations, three areas of discussion and controversy have dominated the investigation of spinal motor control almost from the outset:[1] What are the relative roles and relationships between the brain proper and this potentially semi-autonomous spinal cord circuitry?[2] What are the relative roles of peripheral inputs and central spinal circuitry in organising the spinal generated behaviours?[3] How modular and generalisable is the organisation underlying spinal generated behaviours and is this organisation used in executing skilled voluntary behaviours? Following Hall and others, Sherrington and colleagues used decerebrate mammalian preparations, adopted the neuron doctrine, promulgated the idea of the synapse and established the motor unit description, while Brown worked on central generation of pattern.[29] Together they set the stage for the exquisite neurophysiology, and other developments and idea swings that have followed over the past century.[17,18]

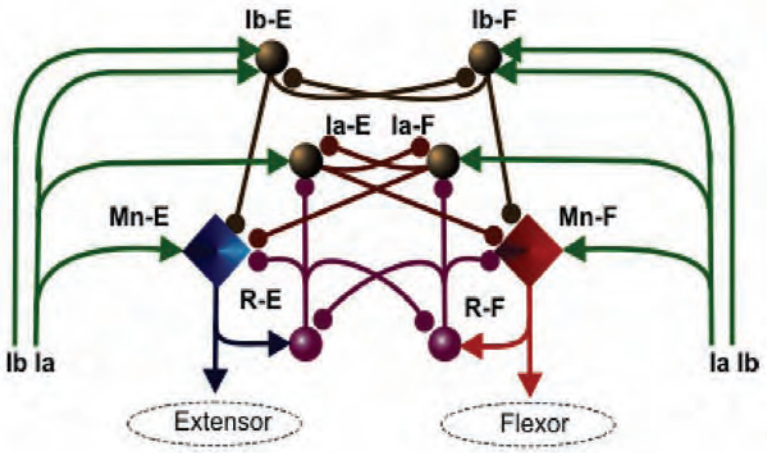
What do the spinal segmental reflexes contribute to movement?

The spinal cord circuitry is the 'fastest responder' for motor corrections and adjustments besides the corrections managed by the muscle properties themselves. It is involved in regulating these limb biomechanical, muscle and reflex properties. Spinal cord organisation is intimately matched to the body. At the most fundamental level the motor pools mirror musculature, and through development proprioceptive projection patterns are also precisely topographically organised, prior to any active use of these circuits. The precision and repeatability of the projections has allowed identification of various sensorimotor interneuron circuits in detail, first physiologically, and more recently with cellular and molecular genetics methods.[12] The understanding of spinal connectivity, interactions and descending targets together can also suggest novel therapeutic strategies.[1,13] The monosynaptic reflex arc, and motoneuron control circuits comprising Ia, Ib interneurons and Renshaw cells are now the stuff of basic physiology and medical texts (see Figure 1). Less well appreciated is the subtlety and precise wiring structures actually needed. What is presented in textbooks as a uni-articular single-joint feedback system for position control as in Figure 1A, in the working spinal controls must regulate properties of a complex limb with multi-articular muscles of diverse actions. Though the basic story is correct, the devil is in the details.[24]

Motoneuron pool control of the muscle

Fundamental to limb control is the process of regulating muscle contraction. For vertebrates, high safety factor end-plate synapses guarantee 1 for 1 following of motoneuron drive by motor unit muscle fibres. Well graded contractions can only arise from a progressive recruitment of the motor pool population. This process is quite well understood in broad terms: the Henneman size principle operates throughout the motor pool. The size principle is extremely robust and has withheld severe scrutiny.[4] Small motoneurons that are attached to slow, small twitch non-fatiguing fibres have high input resistance (based on both their size and their cellular membrane properties). As a result, these are thus brought to threshold first by common synaptic drive. Larger fatigue-resistant, and still larger fast-fatigable fibres are innervated by proportionately larger and lower input resistance motoneurons, and thus are recruited later by the distributed common drive. Fibre types of muscles are dynamically determined properties. They depend on motor-

A. Simplified Reciprocal Reflex Circuit Organisation
(Sherrington, Lundberg, Jankowska and others).



B. Basic Half-Centre Circuit Organisation (Brown, Lundberg).

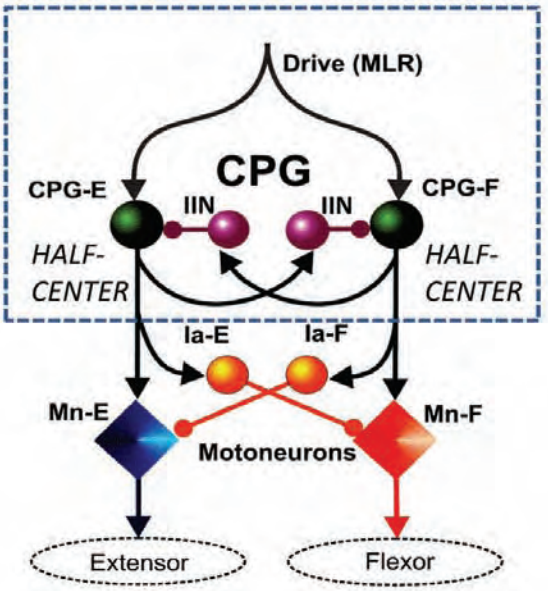


Figure 1:
Reflex circuitry and the half-centre concepts. A. The basic reflex circuitry now identified comprises the Ia afferents (muscle spindle, length and velocity sensing, Ia), the Ia interneurons Ia-E and Ia-F, the Ib afferents (Golgi tendon organ, muscle force sensing, Ib), the Ib interneurons Ib-E and Ib-F and the Renshaw cells (recurrent inhibition of motor pools, R-E and R-F). These are arranged to manage agonist and antagonist muscles and their interactions and are generally drawn in the kind of simplified schematic shown. The schematic shows two things: Firstly, length and force feedback are in competition, for example in control of an extensor on the left. Secondly, synergist and antagonist circuits interact and inhibit one another. Together these two sets of interactions regulate the spring-like properties of muscles and joints, and manage their spinal control. If regulation goes awry spasticity and clonus can result. However, in real limbs the anatomical and mechanical organisation does not permit the level of simplicity of this textbook scheme, and it is not correct to infer that individual joints are managed in this way in isolation from one another. More likely, these pathways are structured to regulate multi-joint and whole limb properties and are organised and integrated into multi-joint controls and modules. B. The basic half-centre central pattern generator (CPG) concept of Brown. Extensor (CPG-E) and Flexor (CPG-F) Half-centres and their associated inhibitory interneurons (IIN) act to inhibit one another. When activated by neuromodulation, and/or directly driven from the mesencephalic locomotor region (MLR) the two half centres interact to create an alternating dynamics and oscillation. These half-centres then drive the appropriate motor pools and muscles (Mn-E, Mn-F) and modulate interneurons in the reflex pathways (Ia-E and Ia-F).

unit firing patterns received, and hence in part on the size principle. Motoneurons act as linear summing junctions for their inputs to a first approximation. However, they also possess persistent inward current (PIC) mechanisms that alter their recruitment drive responses, primarily after initial recruitment, allowing persistent firing with reduced synaptic drive. Exactly how these active mechanisms operate in normal motor control is still murky, though they likely contribute to spastic post-injury spinal behaviour.[14] Renshaw cells, through recurrent inhibition act to focus drive, vary recruitment gain and likely act to desynchronise motoneuron action potentials, perhaps particularly important in PIC conditions. Despite the importance of muscle fatigue processes in both performance and pathology, the spinal cord mechanisms that manage fatigue at spinal and voluntary control levels remain only poorly understood.[8] Motor unit rotation is believed to perhaps contribute.

Feedback regulation of muscles and mechanics

The classic monosynaptic stretch reflexes and interneuron systems in Figure 1A have considerable delays. Such delays would be intolerable to a design engineer. Modeling how the spinal feedback pathways might operate has spawned a range of motor control theories, including the Merton follow-up servo, and alpha and lambda variants of equilibrium control.[27,18] What now seems most clear is that the spinal feedback circuitry is set up to regulate and coordinate the mechanical properties of muscle and joints: like the shocks in a car, the springy stiffness and damping properties (the mechanical 'impedance') of muscles and joints must be set appropriately for context. For example, a mogul skier, a soccer player and a driver will all need different mechanical springiness at the knee. Due to seminal contributions of Rack and Westbury, and Nichols and Houk, it is now understood that the Ia and Ib feedback pathways, from spindles and Golgi tendon organs (GTO) respectively, partly linearise muscle responses and disturbance rejection.[24] Spindle and GTO pathways act in opposition. It is not physically possible to arbitrarily control both force and position simultaneously, and the two opposing controls of force and position/velocity act in concert to vary the impedance responses of muscle and joint so as to adapt them to task context.

Because most muscles are not uniarticular, the segmental spinal feedback regulations act to regulate multi-joint or whole limb impedance. Biarticular muscles are likely contributors to within-limb energy exchanges that are mechanically efficient in locomotion, and regulating multi-joint impedance in locomotion is likely a key spinal function. Further, segmental feedback patterns spanning multiple joints must be precisely balanced to avoid instabilities in the limb as a whole which could be both pathological and physically damaging. All of these pathways and interneuron systems are targets of corticospinal and other regulations, both directly and through presynaptic 'primary afferent depolarisation' (PAD) mechanisms. In this fashion, classically, the spinal cord has been thought to form a general purpose motor control substrate, available for the execution of a rich variety of behaviours under direct and full control by descending pathways.

The semi-autonomous spinal system – Generation of behaviours and patterns locally in the spinal cord

Both Sherrington and Brown recognised that headless newts, frogs and decerebrate cats could generate purposive behaviour closely resembling natural movement. They differed primarily in how they considered it to be generated. Sherrington more strongly favoured a reflex chaining like framework in which limb state and sensory inputs determined the control action and unfolding of reflex behaviour. Brown favoured a centrally driven pattern and popularised the half-centre model of central rhythm generation (see Figure 1B). Today a synthesis of these perspectives is thought to be closer to the truth. The spinal circuits are now believed to partly anticipate future states, so as to cope with the neural delays, to be able to generate pattern, both in feedforward and in more flexible fashions, and to respond to the

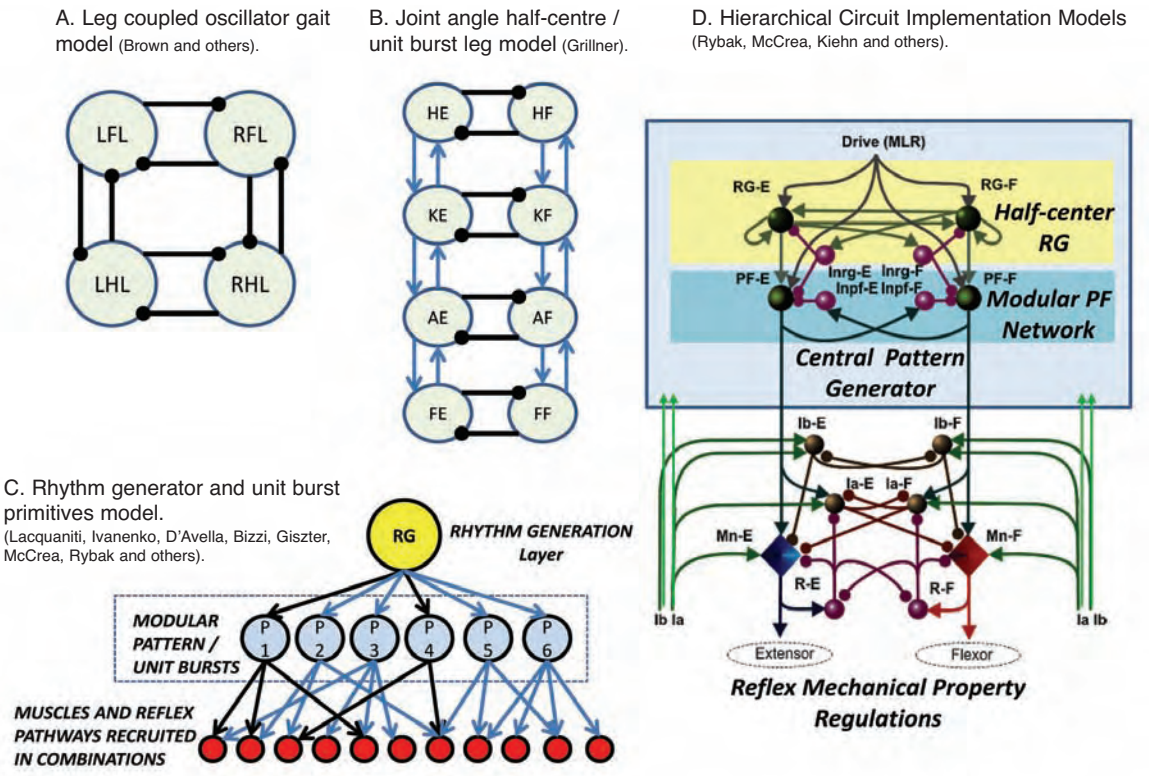


Figure 2:
Spinal circuits can manage basic patterns of gait and limb control in isolation. From the basic understanding of pathways and pattern generation current research is elaborating an understanding of how spinal circuits support movement. A. The half-centre oscillator formulation of Brown can be applied to the four legs of a quadruped – the four oscillators can synthesise a range of gaits, and form a well-regarded model of quadrupedal locomotion. (LFL – left forelimb/upper-limb, RFL– right forelimb/upper-limb, LHL – left hindlimb/lower limb, RHL – right hindlimb/lower limb), B. The half-centre oscillator framework was extended conceptually to reciprocating unit bursts acting around joints by Grillner and colleagues in order to manage leg degrees of freedom and more complex rhythmic motions in a decentralised dynamic network (HE/HF Hip extensor/flexor half-centres or unit burst generators; KE/KF Knee extensor/flexor half-centres; AE/AF Ankle extensor/flexor half-centres; FE/FF Foot extensor/flexor haf-centres). The unit burst notion is also adopted in the synergy/primitive framework, but not tied to specific joints. C. Current data support a hierarchy of a rhythm generator system which presumably involves half-centres (see D), recruiting a collection of discrete modular synergies or primitives in a pattern formation layer (P1-P6). The primitives each individually control different groups of muscles and low-level reflexes, lumped together as biomechanical units or building blocks for movement. These hierarchical spinal functional units are likely to be the ideal targets of physical therapies and interventions such as epidural stimulation to activate intrinsic spinal rhythmic capacities, and may represent evolved structures common across individuals. D. As more detailed circuit structures are garnered from physiology and developmental molecular genetics a synthetic effort is underway to develop and understand the detailed wiring diagrams of spinal cord circuitry that support the functional modularity and units in A-C. PF-E and PF-F represent pattern formation modules in this scheme. This type of detailed modeling and physiology of spinal movement construction systems may enable better understanding of rehabilitation and new therapies after spinal cord or segmental spinal circuit damage.

mechanics through feedback mechanisms to adjust sequences and the associated phase and frequency of rhythmic motions.

Pattern generation – sensory versus central control of behaviours

It has been established that the basic patterns of locomotion can be generated in the isolated mammalian spinal cord, devoid of both patterned descending and sensory feedback. Spinal locomotion thus fulfils the classic operational definitions of 'central pattern generation[20]' (CPG). Spinal central pattern generation is established in animals ranging from the jawless fishes such as lamprey to the mammals.[12,20] Half centre mechanisms (Figure 1B), network mechanisms, and intrinsic neuronal properties together support the rhythmic pattern formation. Descending neuromodulation strengthens and varies pattern generator dynamics and overall state. Pattern generators arise in mammals in utero, and are progressively elaborated. By birth a rat can crawl effectively, and a few hours after birth a wildebeest can walk with its parents and herd. Some rats with complete mid-thoracic spinal transection at birth succeed in developing effective quadrupedal weight bearing coordination strategies despite the transection.[10] There is evidence of similar CPG mechanisms in human infants.[6] However, a major controversy has been the extent to which these mechanisms are players in subsequent voluntary bipedal locomotor tasks, and the degree of persistence of a CPG into human adulthood. Recent data from various laboratories support a role and persistence of pattern generator circuitry in human development, normal function and post injury processes and therapy.[6,7,8]

Spinal structure – Modularity in pattern formation and reflex organisation

Beside the basic observation of rhythmic pattern generating and purposive reflex behaviours such as scratching and defensive motions, data have also accumulated supporting a modular composition of spinal generated and rhythmic behaviours. In able-bodied human locomotion, animal locomotion and other behaviours, the compact modular descriptions of the muscle activity patterns and adjustments prove useful (see Figure 2 for examples). Classic pattern generator views have emphasised coupled oscillators and perhaps joint level oscillators as a compositional basis of pattern (Figure 2A and B). However, a range of studies of intact and fictive (paralysed) decerebrate animals, and spinalised animals, now support a spinal hierarchical structure for pattern generation and other spinal behaviours (Figure 2C). McCrea and Rybak have demonstrated the need for separated rhythm generation and pattern formation layers using classical neurophysiology and computational models.[21] The pattern generators schedule both reflex gain changes, and unitary muscle bursts to accomplish locomotion. Elements of pattern (unit bursts) in this framework can be likened to building blocks. Building blocks, unit burst synergies or primitives, support both reflex and other behaviours in spinal cord, and can be identified independent of rhythmic pattern, in flexible reflexes and other adjustments.[11] Together with McCrea and Rybak's analysis, work has established single unit bursts of fixed muscle composition as the fundamental elements of movement composition by spinal cord,

rather than more complex sequenced time-varying patterns. These act rather like notes in a musical score to construct behaviours. It is suggested that by sequencing (the 'score') and combining (the 'chords') these unitary elements, much of the basic structure of motor patterns can be accounted for. Interneurons that specifically act to drive muscles in these synergies or primitives have been found in the frog spinal cord,[15] and might form some of the spinal 'piano keys' for descending pathways. Skilled acts likely augment this basic 'instrument' (see below). The primitive burst structures in the frog are likely to be conserved across species, and similar modular patterns exist in mammals[6] (see Figure 2C and D). It continues to be controversial how these synergies or primitives identified in other species relate to human movement but a role seems clear.[6] In stroke recovery and post stroke motor patterns some authors[2,3] have published data supporting a common modular basis for the intact and injured pattern, and they have represented recovery as an elaboration and differentiation of control of the synergies. Post stroke, some lower limb stepping synergies may collapse and two synergies be active together, for example. If this can be precisely understood, then rehabilitation could then be better tailored to the patient, and therapy targeted to aid control of specific synergies that are deficient. This could lead to a more 'natural' set of motor compensations, that are more easily integrated into an individual's existing motor repertoire and other activities of daily living. This perspective of synergy and primitive contributions in voluntary skills remains controversial. However, early spinal mediated infant behaviours such as grasp reflex, Babinski and so on emerge post-injury in adults. The structural circuit support for these patterns is not 'dissolved' through development of adult behaviours, and their synergies appear to be conserved throughout life.

Descending control of the spinal cord and its local behaviours – working through or working round?

The most primitive mammalian spinal cords have corticospinal projections focused on the dorsal horns. One interpretation is that early corticospinal control simply modulated feedback pathways and thereby adjusted or co-opted how spinal motor circuitry responded. The corticospinal projections have moved to deeper laminae and added corticomotoneuronal synapses throughout mammalian evolution, and the likelihood is that descending controls can thus exert control over reflexes, spinal modules, rhythm generation, and muscle feedback regulation, or could bypass these altogether. Which of these control strategies are optimal or normal in humans, and in different skills and individuals? This will likely determine how these mechanisms act post-injury, and whether spinal circuits act as aids or detriments to recovery of function. How much are the spinal cord mechanisms 'bypassed' in skilled voluntary motor acts and supplanted by direct controls and long-loop reflexes? Much of our current understanding is for the upper limb. Work of Scott and colleagues[26] and Wolpert, Franklin and colleagues[5,31] shows that implementations of fast task-dependent optimal feedback controls may occur primarily at the level of long-loop transcortical reflex effects (latency ~50-60ms in upper limb), rather than by using direct alterations of the fastest responses of segmental levels (latency ~25-35 ms in upper limb). The notion of 'downloading' all task details into spinal cord and allowing the cord to reconfigure the fastest reflexes (i.e., the segmental reflex) on a momentary basis seems to be wrong. The fast segmental reflex systems appear to operate with a preset pattern in voluntary tasks, one of which is largely unaltered by the detailed unfolding of events occurring in individual trials, and unresponsive to specific changes in the task that happen 'on-line'. Segmental responses are thus most likely to be anticipated by the 'internal models' that are used to organise the more flexible long-loop responses, and more flexible on-line corrections of movement. Adjustments of the fastest and purely segmental components of reflexes to better match them to repeated voluntary tasks and skills appear to only be accomplished on much longer time scales using long term plasticity mechanisms outlined in the next section.

Spinal plasticity and its local and descending modulation

It is now well established that in addition to the strongly conserved structures in the spinal cord of mammals, there is also considerable plasticity. This plasticity arises locally in the spinal cord and is also imposed through descending controls, even in mature individuals. These controls alter spinal mechanisms to better match persistent task demands and have the potential to radically alter the way the feedback systems of the spinal cord function after sufficient training. Seminal work on the H-reflex from Wolpaw and colleagues shows that the gains of the (electrical stimulation elicited) H-reflex can be voluntarily conditioned and altered up and down on long time scales.[30] These types of changes are likely to contribute to adjusting the segmental motor reflex gains optimally for frequently used skills 'on average'. They involve a complex of descending controls and intrinsic spinal plastic adjustments in response to these inputs.[30] As a concrete example, Hultborn and colleagues showed that professional dancers in the Royal Danish Ballet had a significantly diminished Achilles H-reflex compared to other well-trained athletes and control subjects.[25] Thus, although momentary flexible adjustment of rapid low-level segmental reflexes to task context may not be routinely possible, long-term adjustments of rapid low-level segmental reflexes in response to repeated practice of skilled activities are likely to happen under control of descending systems.

The spinal cord itself also shows plasticity in isolation, and this is seen for both protective reflexes and pattern generation. Nociceptive reflex thresholds and protective reflex execution speeds can be altered in the isolated spinal cord with repeat practice in both lower tetrapods and mammals. Perhaps more interestingly, the pattern generators for locomotion, though surgically isolated from the brain in cats and rats, can gradually improve weight bearing, and recover quite detailed and normal appearing kinematics following repetitive (mass) training.[7,27] These data suggest the spinal cord itself may have specifically embedded objectives for its intrinsic plasticity [and see reference 10]. These could potentially be exploited in post-injury therapies. Recent efforts along these lines are very promising. Use of combined training and epidural stimulation after SCI can lead to significant improvements.[7,8,14] Further, coordinated plastic changes in both cortex and spinal cord can be promoted using therapies with appropriate stimulation regimes.[21,22] However, independent spinal plastic changes operating out of the context of descending controls might also sometimes conflict with functional needs and contribute to pathology. It will be essential to manage spinal plasticity carefully, in order to successfully coordinate it with descending plasticity, so as to promote appropriate functional changes through a rehabilitative scheme.[1,8,22,30]

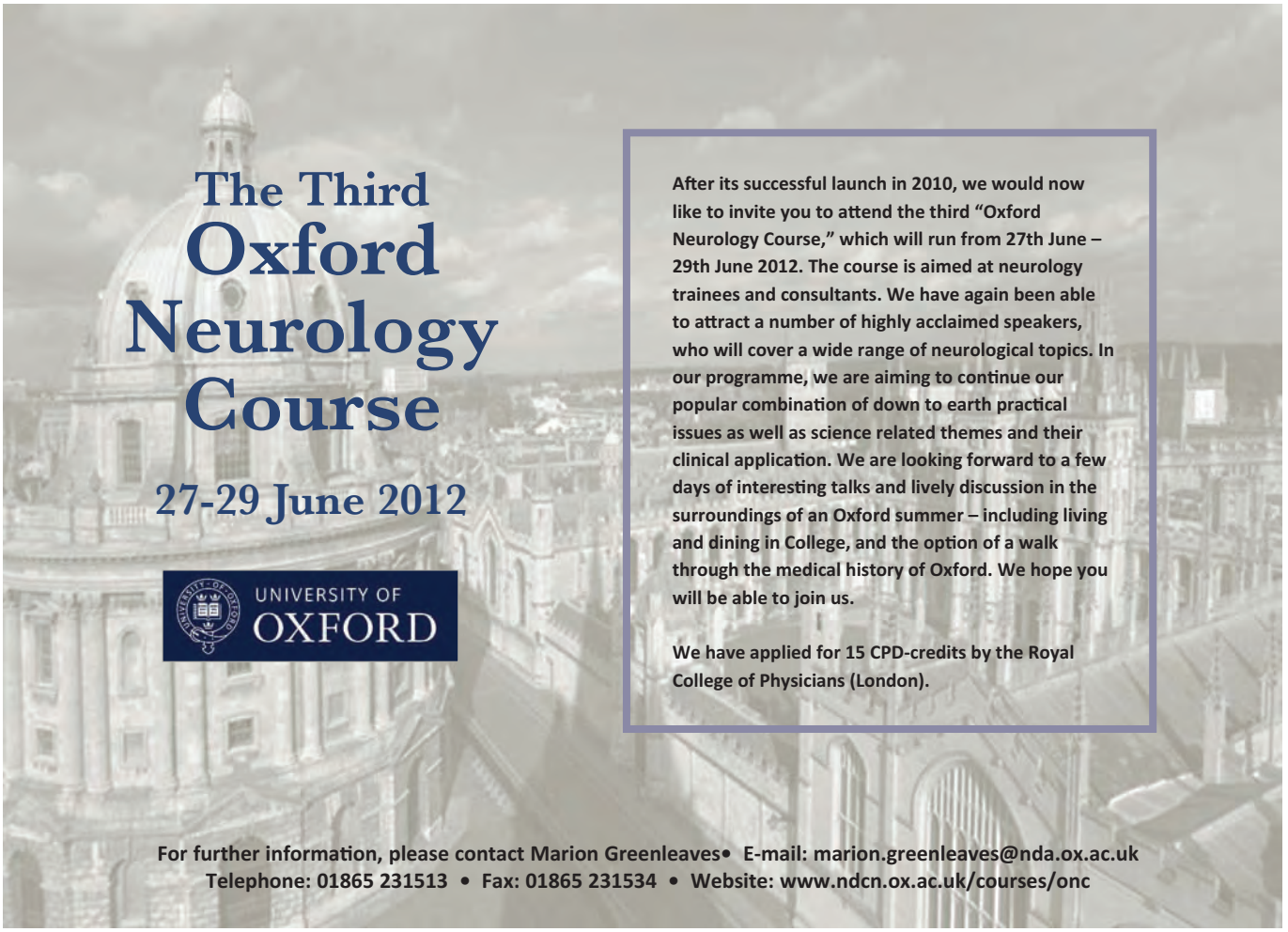
Conclusions

Spinal mechanisms form the fundamental foundations for motor development and skill formation. The spinal circuitry and intrinsic behaviours cannot be ignored by the brain in developing motor skills or managing a developing pathology. Structure in the spinal cord supports a range of protective and movement generating mechanisms, with potential building blocks for movement and control. These are seen in newborn human movements as well as pathologies. However, despite considerable advances in understanding the spinal cord since the time of Sherrington, the relationships of such intrinsic spinal segmental mechanisms to adult skill development and recovery of function after injury remain controversial. It is likely that the newborn's motor infrastructure may bootstrap subsequent skill development and be subsumed into these skills through ontogeny. However, to the extent such infrastructure is simply suppressed or bypassed in adult behaviour, it also has the potential to emerge and run covert or overt interference in motor control when this occurs in the context of pathology or injury. ◆

Acknowledgments
Supported by NIH NS54895, NS072651 and NSF IIS0827684. Dr. Ilya Rybak and colleagues generously shared some of their spinal circuit figures with us for modification.

REFERENCES

1. Campos L, Ambron RT, Martin JH. *Bridge over troubled waters.* Neuroreport. 2004;15(18):2691-4.
2. Cheung VC, Piron L, Agostini M, Silvoni S, Turolla A, Bizzi E. *Stability of muscle synergies for voluntary actions after cortical stroke in humans.* Proc Natl Acad Sci U S A. 2009;106(46):19563-8.
3. Clark DJ, Ting LH, Zajac FE, Neptune RR, Kautz SA. *Merging of healthy motor modules predicts reduced locomotor performance and muscle coordination complexity post-stroke.* J Neurophysiol. 2010;103(2):844-57.
4. Cope TC, Pinter MJ. *The size principle: still working after all these years.* Physiology 1995;10:280–6.
5. Dimitriou M, Franklin DW, Wolpert DM. *Task-dependent Coordination of Rapid Bimanual Motor Responses.* J Neurophysiol. 2011 Nov 9. [Epub ahead of print]
6. Dominici N, Ivanenko YP, Cappellini G, d'Avella A, Mondì V, Cicchese M, Fabiano A, Silei T, Di Paolo A, Giannini C, Poppele RE, *Lacquaniti F. Locomotor primitives in newborn babies and their development.* Science. 2011;334(6058):997-9.
7. Edgerton VR, Courtine G, Gerasimenko YP, Lavrov I, Ichiyama RM, Fong AJ, Cai LL, Otoshi CK, Tillakaratne NJ, Burdick JW, Roy RR. *Training locomotor networks.* Brain Res Rev. 2008;57(1):241-54.
8. Edgerton VR and Harkema S. *Epidural stimulation of the spinal cord in spinal cord injury: current status and future challenges.* Expert Rev. Neurother. 2011;11(10):1351-3.
9. Enoka RM, Baudry S, Rudroff T, Farina D, Klass M, Duchateau J. *Unraveling the neurophysiology of muscle fatigue.* J Electromyogr Kinesiol. 2011;21(2):208-19.
10. Giszter SF, Hockensmith G, Ramakrishnan A, Udoekwere UI. *How spinalized rats can walk: biomechanics, cortex, and hindlimb muscle scaling--implications for rehabilitation.* Ann N Y Acad Sci. 2010;1198:279-93.
11. Giszter S, Patil V, Hart C. *Primitives, premotor drives, and pattern generation: a combined computational and neuroethological perspective.* Prog Brain Res. 2007;165:323-46.
12. Grillner S, Jessell TM. *Measured motion: searching for simplicity in spinal locomotor networks.* Curr Opin Neurobiol. 2009;19(6):572-86.
13. Haque RM, Malone HR, Bauknight MW, Kellner MA, Ogden AT, Martin JH, Tanji K, Winfree CJ. *Spinal cord bypass surgery with intercostal and spinal accessory nerves: an anatomical feasibility study in human cadavers.* J Neurosurg Spine. 2011 Dec 2. [Epub ahead of print]
14. Harkema S, et al. *Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study.* Lancet. 377(9781):1938-47.
15. Hart CB, Giszter SF. *A neural basis for motor primitives in the spinal cord.* J Neurosci. 2010;30(4):1322-36.
16. Heckmann CJ, Gorassini MA, Bennett DJ. *Persistent inward currents in motoneuron dendrites: implications for motor output.* Muscle Nerve. 2005;31(2):135-56.
17. Jankowska E, Hammar I. *Spinal interneurones; how can studies in animals contribute to the understanding of spinal interneuronal systems in man?* Brain Res Brain Res Rev. 2002;40(1-3):19-28.
18. Jeannerod, M. (1985). *The Brain Machine: The Development of Neurophysiological Thought.* Harvard University Press.
19. Jessell TM, Sürmeli G, Kelly JS. *Motor neurons and the sense of place.* Neuron. 2011;72(3):419-24.
20. Marder E, Bucher D. *Central pattern generators and the control of rhythmic movements.* Curr Biol. 2001;11(23):R986-96.
21. Martin JH. *Chapter 3 Development of the corticospinal system and spinal motor circuits.* Handb Clin Neurol. 2007;82:39-56.
22. Martin JH, Chakrabarty S, Friel KM. *Harnessing activity-dependent plasticity to repair the damaged corticospinal tract in an animal model of cerebral palsy.* Dev Med Child Neurol. 2011 53 Suppl 4:9-13.
23. McCrea DA, Rybak IA. *Organization of mammalian locomotor rhythm and pattern generation.* Brain Res Rev. 2008;57(1):134-46.
24. Nichols TR. *Musculoskeletal mechanics: a foundation of motor physiology.* Adv Exp Med Biol. 2002;508:473-9.
25. Nielsen J, Crone C, Hultborn H. *H-reflexes are smaller in dancers from The Royal Danish Ballet than in well-trained athletes.* Eur J Appl Physiol Occup Physiol. 1993;66(2):116-21.
26. Pruszynski JA, Kurtzer I, Scott SH. *The long-latency reflex is composed of at least two functionally independent processes.* J Neurophysiol. 2011;106(1):449-59.
27. Rossignol S, Frigon A. *Recovery of locomotion after spinal cord injury: some facts and mechanisms.* Annu Rev Neurosci. 2011;34:413-40.
28. Shadmehr R and Wise SP. *The Computational Neurobiology of Reaching and Pointing: A Foundation for Motor Learning.* 2004, MIT Press, Cambridge, MA
29. Stuart DG, Hultborn H. *Thomas Graham Brown (1882--1965), Anders Lundberg (1920-), and the neural control of stepping.* Brain Res Rev. 2008;59(1):74-95.
30. Wolpaw JR. *What can the spinal cord teach us about learning and memory?* Neuroscientist. 2010;16(5):532-49.
31. Wolpert DM, Diedrichsen J, Flanagan JR. *Principles of sensorimotor learning.* Nat Rev Neurosci. 2011;12(12):739-51. doi: 10.1038/nrn3112.



To list your event in this diary, email brief details to Anna Phelps at anna@acnr.co.uk by 6th April, 2012

2012

March

Neurology and Pain Management
13-27 March, 2012; Sydney, Australia
E. 031312Neuro@continuingeducation.net

10th Austrian Society of Neurology (ÖGN) Annual Congress
14-17 March, 2012; Graz, Austria
T. +43 1 512 80 91-19
E. weinhart@oegn.at
www.oegn.at/kongress2012

Latest advances in stroke patient care and research
16 March, 2012; London, UK
T. +357 25 87 88 44
www.medineo.org

7th Annual Brain Injury Rehabilitation Conference
16-17 March, 2012; California, USA
www.scripps.org/events/category/events

18th Mediterranean Meeting of Child Neurology
18-22 March, 2012; Ein Bokek, Israel
E. childneuro2012@targetconf.com

Goal Setting for ABI
19 March, 2012; London, UK
T. 07501 483989
E. info@biswg.co.uk
www.biswg.co.uk

International Society of Minimally Invasive Neurosurgery 1st International Congress 2012 (ISMINS 2012)
20-23 March, 2012; Florence, Italy
T. +39 055 50351
E. icmins2012@oic.it

Genomic Disorders 2012
21-24 March, 2012; Cambridge, UK
www.treat-nmd.eu/events/305/

9th World Congress on Brain Injury
21-25 March, 2012; Edinburgh, Scotland, UK
T. 01512 80 9119
E. mjroberts@internationalbrain.org
www.internationalbrain.org

UK Neuromuscular Translational Research Conference 2012
22-23 March, 2012; Newcastle, UK
www.treat-nmd.eu/events/296/

9th Asian & Oceanian Epilepsy Congress
22-25 March, 2012; Manila, Philippines
E. manila@epilepsycongress.org

9th International Brain Injury Association World Congress
22-25 March, 2012; Edinburgh, Scotland
T. + 703 960 0027
www.internationalbrain.org

9th Asian & Oceanian Epilepsy Congress International Congress on Neurology and Epidemiology
22-25 March, 2012; Seville, Spain
T. +33 4 78 176 176
www.neuro-conference.com/2012/

Quantitative proteomics and data analysis
26-27 March, 2012; Chester, UK
E. niamh.mangan@biochemistry.org
www.biochemistry.org/MeetingNo/WS008/view/Conference/

Intrinsically disordered proteins
26-27 March, 2012; York, UK
Tel: +44 (0)20 7685 2450
E. niamh.mangan@biochemistry.org
www.biochemistry.org/conferences

2nd International Congress on Epilepsy, Brain and Mind
28-31 March, 2012; Prague, Czech Republic
www.epilepsy-brain-mind2012.eu

April

Optic neuritis
5 April, 2012; London, UK
T. 020 7290 2906
E. events@rsm.ac.uk

AANS 2012
14-18 April, 2012; Miami Beach, USA
E. las@aans.org

Parkinson's Awareness Week 2012
16-22 April, 2012; UK
T. 020 7963 9351
E. sweston@parkinsons.org.uk

8th International Conference on Psychiatry Comorbidity within Psychiatric disorders and Medical Illnesses
17-19 April, 2012; Jeddah, Saudi Arabia
T. 0096626829000
http://jed.sghgroup.com.sa/

The Society Of British Neurological Surgeons Spring Meeting
18-20 April, 2012; Aberdeen, UK
www.sbns.org.uk

American Academy of Neurology 2012 Annual Meeting
21-28 April, 2012; New Orleans, USA
T. (800) 879-1960
E. memberservices@aan.com

ASNR 2012
21-26 April, 2012; New York, USA
T. (630) 574 0020
www.asnr.org/

BISWG Spring Conference
26th April, 2012; Bristol, UK
T. 07501 483989
E. info@biswg.co.uk
www.biswg.co.uk/

May

23rd ESPN conference
1-5 May, 2012; Amsterdam, The Netherlands
T. +30 210 7414700
E. info@espncongress2012.com
www.erasmus.gr

7th Symposium on Neuroprotection and Neurorepair
2-5 May, 2012; Potsdam, Germany
E. johannes.boltze@izi.fraunhofer.de
www.neurorepair-2012.de

Peripheral nerve
3 May, 2012; London, UK
T. 020 7290 2906
E. events@rsm.ac.uk

Diagnosis and Treatment of Psychopathy
3 May, 2012; London, UK
T. +357 25 87 88 44
www.medineo.org

8th International Congress On Mental Dysfunction & Other Non-Motor Features In Parkinson's Disease and Related Disorders
3-6 May, 2012; Berlin, Germany
T. + 41 22 9080488 ext. 524
E. Dnuriel@kenes.com
www.kenes.com+4

Update in Neuromuscular Disorders Course 2012
8-11 May, 2012; London, UK
E. j.molyneaux@ucl.ac.uk

BALCONE 2012
9-12 May, 2012; Tartu, Estonia
T. +372 740 4095
info@lapub.ee

12th International Symposium on Advances in Alzheimer Therapy
9-12 May, 2012; Stockholm, Sweden
T. (217)545-7711
E. ahamilton@siumed.edu

Portuguese Societies of Neurology and Neurosurgery 2012 (SPNC 2012)
10-12 May, 2012; Porto, Portugal
E. secretariado@spnc.pt

EFNS Academy 2012 - Spring School for Young Neurologists
10-13 May, 2012; Staré Splavy, Czech Republic
T. +420 721 725 816
E. pragueoffice@efns.org
www.efns.org/EFNS-Academy-2012.255.0.html

The International Conference and Exhibition on Neurology and Therapeutics
14-16 May, 2012; Las Vegas, USA
T. +1- 650-268-9744
E. neuro2012@omicsonline.org
www.omicsonline.org

The International Conference and Exhibition on Neurology and Therapeutics 2012
16-19 May, 2012; Melbourne, Australia
T. +612 9954 4400
W: www.dcconferences.com.au/wcnr2012

7th World Congress Of NeuroRehabilitation
16-19 May, 2012; Melbourne, Australia
www.dcconferences.com.au/wcnr2012

17th Meeting of the ESNCH
17-20 May, 2012; Venice, Italy
E. meet@meetandwork.com
www.neurosonology2012.it

3rd Annual Conference of NeuroTalk
18-20 May, 2012; Beijing, China
T. 0086 411 84799609
www.bitlifesciences.com/neurotalk2012

2nd Essential Stroke Imaging Course- 6 Cat 1 CPD
19 May, 2012; Liverpool, UK
T. 07799 723 925
E. essentialcourses@hotmail.com

The Society Of Neurological Surgeons Annual Meeting
19-22 May, 2012; Atlanta, USA
E. bradleys@ohsu.edu

12th International Conference on Myasthenia Gravis and Related Disorders
21 May, 2012; New York, USA
T. + 212 298 8600
E. customerservice@nyas.org

ESC 2012 – European Stroke Conference
22-25 May, 2012; Lisbon, Portugal
E. esc@congrex.com

EFNS Regional Teaching Course Novosibirsk 2012
24-26 May, 2012; Novosibirsk, Russia
E. pilipen@rambler.ru

International Child Neurology Congress 2012
27 May – 2 June, 2012; Brisbane, Australia
T. +61 7 3844 1138
E. icnc2012@icms.com.au

18th European Congress of Physical and Rehabilitation Medicine
28 May – 1 June, 2012, Thessaloniki, Greece
T. +30 210 3274570
E. info@esprm2012.eu

ABN Annual Meeting
29-31 May, 2012; Brighton, UK
T. 020 7405 4060
abnexhibition@affinityevents.co.uk

EFNS Regional Teaching Course Lasi 2012
30 May – 2 June, 2012; Lasi, Romania
E. cdpopescu@ssnn.ro

June

4th International congress on ADHD
6 June, 2012; Milan, Italy
E. adhd@cpo-hanser.de
www.adhd-congress.org

The Clinical Neurosciences Summer symposium
8 June, 2012; London, UK
T. 020 7290 2906
E. events@rsm.ac.uk

ENS 2012 – 22nd Meeting of the European Neurological Society
9-12 June, 2012; Prague, Czech Republic
E. info@ensinfo.org
www.congrex.ch/ens2012/

4th Biannual NUBIN Symposium on Biomarkers in Neurodegenerative Disease
14-15 June, 2012, Amsterdam, Netherlands
E. c.teunissen@vumc.nl

Download the ABNT's comprehensive list of courses for neurology trainees

Chrissie Burness and Biba Stanton from the ABNT have collated this indispensable guide to courses for neurology trainees.

Courses for Neurology Trainees

The neurology curriculum covers a wide variety of sub-specialties.It is certainly beneficial to attend some national courses but can be difficult to choose which ones. This article aims to provide details of some of the most relevant and useful courses. Which ones you chose depends on individual interests and local strengths and weaknesses in clinical training.

Due to increasingly complex working patterns and rotas, and the fact that several of these courses only run once every two years with limited places, it is sensible to plan attendance in advance. This article will help you to do just that.

Download the article from www.acnr.co.uk

UCL INSTITUTE OF CHILD HEALTH

Great Ormond Street Hospital for Children NHS Trust

Baby Brains Around the World: An International On-line Conference

The 3rd UK Paediatric Neuropsychology Symposium: Early Brain-Behaviour Relationships and Prognostic Indicators will take place at the UCL Institute of Child Health, London on **23-27 April 2012**, with speakers from major centres throughout the world.

Register now to attend or for ON-LINE ONLY access to the conference. Lectures will be filmed and broadcast on the conference website, remaining accessible until 4th June 2012. On-line delegates will also have access to posters, lecture hand-outs and interactive discussion forums.

Programme Directors: Dr Peter Rankin and Dr Michelle de Haan
For further details visit **www.ucl.ac.uk/neuropsych**
or **www.ichevents.com**
Tel: +44 (0)20 7905 2675 / 2699, email info@ichevents.com

UCL

in association with
The National Hospital for Neurology and Neurosurgery
Queen Square, London WC1

Advanced Neurology Short Courses

21st – 25th May 2012

Please see our website for application form and programmes

- Monday 21st May – Rehabilitation after Acquired Brain Injury
- Tuesday 22nd May – Dementia
- Wednesday 23rd May – Movement Disorders
- Thursday 24th May – Sleep
- Friday 25th May – New technologies in the Neuro-Ophthalmology Clinic: including OCT, Automated Perimetry and Saccadic measurements'

Course fee £850 for the week or £250 per day

The following taught courses are also available for entry in 2012

- MSc Advanced Neuroimaging
- MSc Brain and Mind Sciences
- MSc Clinical Neurology
- MSc Neurology for Clinical Trainees
- MSc Clinical Neuroscience
- Graduate Diploma in Clinical Neurology
- UCL Distance Learning Diploma in Clinical Neurology

For further details on all our courses please contact:
Education Unit, UCL Institute of Neurology
National Hospital for Neurology and Neurosurgery
Queen Square, London WC1N 3BG
Tel: 020 3448 4460 • Email: education.unit@ion.ucl.ac.uk
Please see our website www.ion.ucl.ac.uk for further information/ application form and programmes

UCL, Institute of Neurology promotes teaching and research of the highest quality in neurology and the neurosciences

BPS BRITISH PHARMACOLOGICAL SOCIETY
Today's science, tomorrow's medicines

King's College London, UK
7- 9 June 2012

BPS Focused Meeting on Neuropeptides

In association with the European Neuropeptide Club and American Summer Neuropeptide Conference
Local organizers: Professor Susan Brain and Professor Helen Cox

Sessions:
VIP and PACAP
Ghrelin
CGRP receptor and vascular mechanisms
TRP and the regulation of pain and vascular condition
Elucidating roles for neuropeptides in pathophysiology

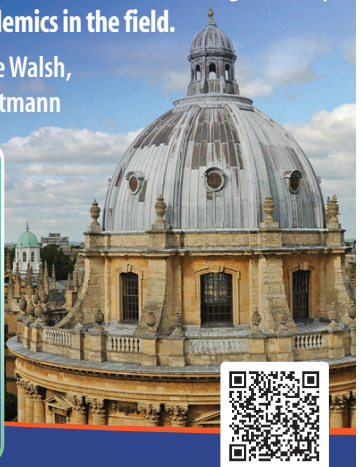
Register today!
e: meetings@bps.ac.uk
w: www.bps.ac.uk
t: 020 7239 0176

THE EXAMINATION SCHOOLS, OXFORD
12TH & 13TH MAY 2012

magstim
NEUROSCIENCE
CONFERENCE
& WORKSHOP 2012

The Magstim Neuroscience Conference & Workshop 2012 is the latest in a series of 'TMS Summer Schools' organised by Magstim and leading academics in the field.

Academic organisers: Vince Walsh, Charlotte Stagg & Sven Bestmann



KEYNOTE SPEAKER
Mark S. George, MD
Distinguished Professor of Psychiatry, Radiology and Neurosciences, Medical University of South Carolina

Daily Prefrontal TMS for Treating Depression:
Are we really modifying cortico-limbic governance and connectivity when we get people undepressed?

For the latest version of the full programme, please visit:
www.magstim.com/magstim-neuroscience-conference

Bringing Multiple System Atrophy (MSA) to the Top of the Research Agenda: The first UK MSA Researchers Meeting

Conference details: Report from the first UK MSA researchers meeting, London UK, 4th November 2011. ***Meeting reviewed by:*** The Multiple System Atrophy Trust. Meeting and report supported by an educational grant from Teva Pharmaceuticals Ltd.
This report contains the use of medicines outside their product licenses, please refer to full prescribing information for further information.

Host and Trustee of the MSA Trust

Professor Clare Fowler, Professor of Uro-neurology, Institute of Neurology, London, UK.

MSA UK research group speakers

Professor Tamas Revesz, Institute of Neurology, London, UK.

Professor Niall Quinn, Institute of Neurology, London, UK.

Dr Janice Holton, Institute of Neurology, London, UK.

Professor John Hardy, Institute of Neurology, London, UK.

Professor Henry Houlden, Institute of Neurology, London, UK.

Professor David Mann, University of Manchester, Manchester, UK.

Dr Penny Foulds, University of Lancaster, Lancaster, UK.

Professor Richard Brown, Institute of Psychiatry, London, UK.

Professor David Burn, University of Newcastle, Newcastle, UK.

Dr Zeshan Ahmed, Institute of Neurology, London, UK.

Ms Yasmine Asi, Institute of Neurology, London, UK.

Dr Anna Sailer, Institute of Neurology, London, UK.

Dr Huw Morris, Cardiff University, Cardiff, UK.

Dr Jalesh Panicker, Institute of Neurology, London, UK.

Professor Chris Mathias, Imperial College London, UK.

Dr David Low, Imperial College London, UK.

Guest speakers

Professor Gregor Wenning, Medical University Innsbruck, Innsbruck Austria.

Professor Francois Tison, University of Bordeaux, Bordeaux, France.

Professor Wassilios Meissner, University of Bordeaux, Bordeaux, France.

Multiple system atrophy (MSA) is a sporadic and rapidly progressive neurodegenerative disorder that presents with autonomic failure in combination with parkinsonism or cerebellar ataxia. Although it is often under-recognised, it is not a rare disease; and it is reported to affect around 4 people per 100 000 of the population (or 1 in 20 people with Parkinson's disease).[1]

Opening the meeting, Professor Tamasz Revesz emphasised the need for UK researchers interested in MSA to share ideas and work together. In just the past few years, there has been significant progress in our understanding of this disabling disease. We now understand much more about the epidemiology, genetics and pathogenesis of the disease, and this knowledge has resulted in revised diagnostic criteria, which enabled the initiation of new clinical trials. These important advances are crucial in the search for an effective treatment for MSA, and were only made possible because of the establishment of networks.

What is our current understanding of MSA?

Professor Niall Quinn began the first of the presentations by reminding the audience of key milestones in MSA research. The term multiple system atrophy was first proposed in 1969 to combine the entities of striatonigral degeneration, olivopontocerebellar ataxia and Shy-Drager syndrome, which were clearly "the expression of neuronal atrophy in a variety of overlapping combinations".[2] It was not until 1989, that abundant argyrophilic filamentous glial cytoplasmic inclusions (GCIs) were described as the pathological hallmark of the disease,[3] and the later finding that misfolded, hyperphosphorylated α-synuclein is a main component of GCIs – led to the classification of MSA as an α-synucleinopathy.[4] Since then, international research groups have successfully developed a MSA specific scale – the unified MSA rating scale (UMSARS)[5] and have defined diagnostic criteria.[6] However, Professor Quinn reminded the group that there is still much to be done, as there is currently no effective treatment for MSA.

Dr Janice Holton continued the presentations by describing the key pathological features of MSA. Whereas the clinical diagnosis of MSA is now described as probable and possible MSA, and is often subdivided into MSA-P (MSA with mainly parkinsonian features) and MSA-C (MSA with mainly cerebellar features),[6] pathologically it is classified into three main subtypes: olivopontocerebellar atrophy (OPCA), striatonigral degeneration (SND) and minimal change MSA. These pathological subtypes have distinctive clinical profiles; whereas patients with OPCA have more frequent cerebellar signs, patients with SND often have the most severe bradykinesia.[7] However, there is still more work to be done in understanding the clinical correlates of 'minimal change' MSA and what is different about those patients who have a long duration of disease. Dr Holton discussed that although it is well established that the frequency of GCIs correlates with neuronal loss and disease duration,[7] we still do not fully understand how GCIs are formed or whether they cause nerve cell death (or are they a protective mechanism?). Recent evidence points to neuroinflammation as being important in the degenerative process and a better understanding of the molecular pathways leading to MSA is essential for the development of disease markers and effective treatments.

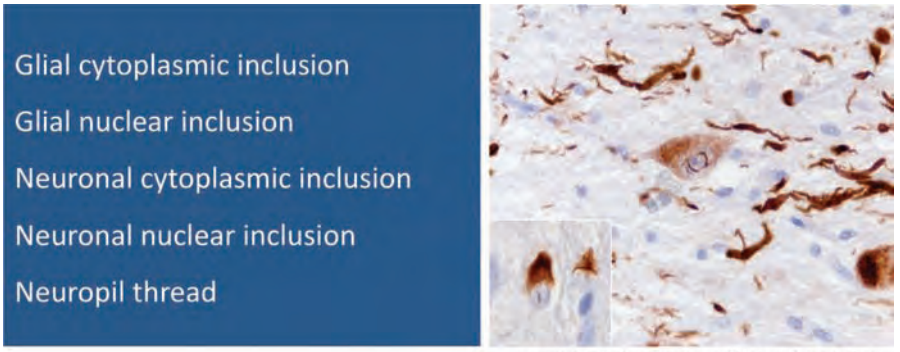
Ongoing research

Animal models of MSA

Much of today's clinical research depends on findings from preclinical studies and Professor Gregor Wenning gave an overview of the several animal models that have been developed in order to reproduce various clinical and pathological features of MSA. Using 'double toxin-double lesion' or 'single toxin-double lesion', neurotoxin-based models were first designed in rats, mice and non-human primates to reproduce the neuropathology of MSA in the nigrostriatal system[8] and partial lesion models have recently been developed that show good stability of the behavioural deficit. A number of transgenic mouse models have also been developed in an attempt to reproduce the accumulation of insoluble alpha-synuclein in oligodendrocytes. Professor Wenning suggested that these are useful as testbeds for potential new treatments as they successfully replicate the pathology of MSA (oligodendrogliopathy with GCI-like inclusions; neuronal and oligodendroglial αSYN toxicity; selective neuronal multisystem degeneration and astro/microglial dysfunction) as well as the autonomic and motor deficits of the disease. Both the lesioning and transgenic approaches have since been merged to create the so-called 'dual-hit' models. Importantly, such animal models have been used to examine the potential utility of a number of drugs including GDNF, rifampicin, and rasagiline; and positive results in these preclinical studies have encouraged the initiation of clinical trials.

Genetics

Professors John Hardy and Henry Houlden issued an urgent call for more genetics research into MSA. MSA has been classically perceived as a non-genetic disorder, but during the last decade, numerous studies



α-synuclein immunohistochemistry

have implicated variants (triplication) in the α-synuclein (SNCA) locus as a risk factor in the pathogenesis of MSA.[9] Although other candidate genes have been implicated, independent replication studies are still necessary to confirm or refute these observations. To date, no protein-changing Mendelian gene mutations have been identified in rare families of MSA.

Professor Hardy discussed that MSA research can learn much from the ongoing work into the genetics of progressive supranuclear palsy (PSP), which has not only looked at rare alleles causing Mendelian disease, but has also used genome wide association studies to find common genetic variants. Such efforts have identified microtubule associated protein tau (MAPT) mutations in familial disease and have confirmed two independent variants in MAPT affecting risk for PSP.[10] Professor Houlden agreed, and together with Dr Anna Sailer, discussed how developing new collaborations can improve ongoing work at the Institute of Neurology, London. Work on MSA exome sequencing is ongoing and, so far, 20 cases have been sequenced. By working with international Brain Banks, the ongoing genome wide association study (GWAS) has been able to show that common variants in SNCA are not associated with MSA. Although the GWAS has found several candidate hits, these need to be verified in a bigger sample size.

A new MSA multidisciplinary clinic

In addition to the many research needs of MSA, Professor Henry Houlden reminded the group of the need to better manage patients with MSA today. He described the basic framework for his new multidisciplinary clinic, which will act as a referral centre for MSA patients across the UK.

Aims of the clinic

1. Short waiting time to see MSA patients from any location
2. Telephone clinic in between appointments
3. Close connections with MSA trust to see patients
4. Work with autonomics, movement disorders, uroneurology and palliative care to manage patients
5. Neurogenetics CNS in clinic
6. Speech and physiotherapy to be in clinic
7. Promote clinical research

Biomarkers

Professor David Mann and Dr Penny Foulds described their collaborative research, which is focused on finding suitable biomarkers for α-synucleinopathies. This is an important area of research, as having a confirmed biomarker would enable an early and accurate diagnosis of MSA, which is particularly important when thinking about neuroprotective interventions. They described their studies that have shown that α-synuclein can be detected within plasma and CSF and thus might serve as a clinical biomarker. When comparing the samples from patients with PD, PSP, dementia with lewy bodies and MSA, they found that CSF levels of oligo-pS-α-synuclein were significantly higher in patients with MSA ($p<0.001$) than those in all other diagnostic groups. However, while these results are encouraging, they stressed that these measures have been made on a small number of post-mortem samples from patients with end stage disease. They suggested that CSF samples taken from living patients, earlier in the course of their illness, might prove more informative. But in order to conduct such research, more patients need to be identified and recruited into studies.

Autonomics research

Autonomic failure is critical for a diagnosis of MSA and includes a variety of features such as orthostatic hypotension (OH), urinary and sexual dysfunction. Some of these disturbances are frequently observed in MSA at the time of diagnosis, and can precede the onset of motor symptoms. Consequently, they are often considered as a marker for differentiation from idiopathic Parkinson's disease. Professor Chris Mathias and Dr David Low described how research conducted at the autonomic research unit at St Mary's hospital aims to improve the treatment of patients with MSA. They described how technological advances now allow 24-hour blood pressure and ambulatory heart rate monitoring to provide important information to both the clinician and researcher. Similarly, developments in software and programming have facilitated the application of complex statistical analyses of data to continuous beat-to-beat heart rate and blood pressure data during various manoeuvres, which can for example complement the traditional assessment of orthostatic hypotension. Such advances have allowed the unit to evaluate the benefits of non-pharmacological interventions such as exercise training, as well as pharmacological interventions with drugs such as droxidopa for the management of OH.

What have we learned from clinical trials?

The Neuroprotection and Natural History in Parkinson's Plus Syndromes (NNIPPS) study

As with other neurodegenerative diseases, it is increasingly recognised that neuropsychiatric symptoms are relatively common in MSA said Professor Richard Brown who gave an overview of neuropsychiatric data from the recent Neuroprotection and Natural History in Parkinson's Plus Syndromes (NNIPPS) study. The NNIPPS study was a prospective study designed to assess the effects of riluzole on the natural history of MSA and PSP.[11] Although it found no significant effect of study drug on survival in MSA (or PSP), the study provided new insights into the natural history of both diseases. Importantly it confirmed that clinically significant cognitive impairment is common in MSA and that impairment tends to increase with disease progression.[12] Such findings have two important implications for MSA research. Firstly, the majority of MSA trials have excluded patients with cognitive dysfunction and applying very strict inclusion criteria may miss a significant number of patients. Secondly, if we can improve the treatment of MSA such that survival increases, it will be increasingly important to consider the management of cognitive impairment.

Another important lesson from the NNIPPS study was the fact that there is often much diagnostic uncertainty, especially in the early days, said Dr Huw Morris. Approximately 7% of patients in the NNIPPS study switched diagnoses during the study,[11] and other studies have found that up to 5% of parkinsonian patients presenting to specialist movement disorder clinics cannot be categorised into a specific parkinsonian syndrome.[13] In the current era of disease modification trials, which require patients in their very earliest stages, this diagnostic uncertainty must be taken into account.

Other clinical trials

The advances that have been made in the past decade have finally enabled researchers to conduct clinical trials in MSA, and although none have so far found an effective treatment – there is much to be learned from this collective experience, said Professor Wassilios Meissner. For example, they have highlighted the importance of using MSA specific scales such as the UMSARS, and studies such as NNIPPS have indicated that patient survival (mortality) may be a robust outcome measure to include in 'neuroprotection' studies. We now also have a better idea of the number of patients required for sufficient powering of a study. Professor Meissner noted that although

the trial growth hormone in MSA did not find a statistically significant treatment effect – there was actually a clear difference between active treatment and placebo at 12 months.[14] However, there is currently no industry interest in growth hormone therapy and it would take a huge collaborative effort to run a larger study. Ongoing studies include the rasagiline MSA trial (results expected early next year), the US rifampicin MSA study, and a study of autologous mesenchymal stem cell therapy.

Building a collaborative network for MSA research

A key aim of the meeting was to encourage networking between the many types of researchers and provide information on where to get practical help for conducting new research. Professor David Burn provided details of how the National Institute for Health Research, Dementias and Neurodegenerative Diseases Research Network (NIHR-DeNDRoN) can provide very practical support to UK researchers interested in MSA.

By supporting the NHS infrastructure and providing a portal for industrial engagement, NIHR-DeNDRoN supports clinical research through seven local research networks. It also offers financial and administrative support to the research community to support the collaborative development as well as writing of new research grant applications. Professor Burn advised that NIHR-DeNDRoN supports RCTs of interventions (including prevention, diagnosis, treatment and care) and other well designed studies for commercial and non-commercial sponsors. However he stressed that DeNDRoN only supports studies that are included on the NIHR Portfolio.

From the European perspective, Professor Gregor Wenning gave an overview of the European MSA Study Group (EMSA-SG), which since its founding in 1999 has successfully run a MSA registry, and used it to conduct a natural history study of MSA.[15] The group represents a consortium of experienced scientific investigators who are committed to clinical trial activity and other research studies aimed at improving the treatment of MSA. Professor Wenning highlighted that EMSA-SG works closely with industry sponsors to develop new clinical trials in MSA. By fostering links with the the North American, Japanese and Chinese study groups, EMSA-SG is able to help its members access the global MSA community.

This first MSA UK researchers meeting met its primary goal, to encourage MSA research and foster new networks. Researchers attending the meeting were enthused by the positive French experience, where funding is provided by the French Ministry of Health within the framework of the rare diseases program. By working together, the French network now consists of two reference centres and 12 competence centres, and the network is well placed to conduct new preclinical research and clinical trials. UK researchers left the meeting having made new research contacts, and the group is now continuing to work to build a UK MSA registry. ◆

References

1. Stefanova N, Bucke P, Duerr S, Wenning GK. *Multiple system atrophy: an update.* Lancet Neurol. 2009;8(12):1172-8.
2. Graham JG, Oppenheimer DR. *Orthostatic hypotension and nicotine sensitivity in a case of multiple system atrophy.* J Neurol Neurosurg Psychiatry. 1969;32(1):28-34.
3. Papp MI, Kahn JE, Lantos PL. *Glial cytoplasmic inclusions in the CNS of patients with multiple system atrophy (striatonigral degeneration, olivopontocerebellar atrophy and Shy-Drager syndrome).* J Neurol Sci. 1989;94(1-3):79-100.
4. Spillantini MG, Crowther RA, Jakes R, Cairns NJ, Lantos PL, Goedert M. *Filamentous alpha-synuclein inclusions link multiple system atrophy with Parkinson's disease and dementia with Lewy bodies.* Neurosci Lett. 1998;251(3):205-8.
5. Wenning GK, Tison F, Seppi K, Sampaio C, Diem A, Yekhlef F, et al. *Development and validation of the Unified Multiple System Atrophy Rating Scale (UMSARS).* Mov Disord. 2004;19(12):1391-402.
6. Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, et al. *Second consensus statement on the diagnosis of multiple system atrophy.* Neurology. 2008;71(9):670-6.
7. Ozawa T, Paviour D, Quinn NP, Josephs KA, Sangha H, Kilford L, et al. *The spectrum of pathological involvement of the striatonigral and olivopontocerebellar systems in multiple system atrophy: clinicopathological correlations.* Brain. 2004;127(Pt 12):2657-71.
8. Stefanova N, Tison F, Reindl M, Poewe W, Wenning GK. *Animal models of multiple system atrophy.* Trends Neurosci. 2005;28(9):501-6.
9. Al-Chalabi A, Durr A, Wood NW, Parkinson MH, Camuzat A, Hulot JS, et al. *Genetic variants of the alpha-synuclein gene SNCA are associated with multiple system atrophy.* PLoS One. 2009;4(9):e7114.
10. Hoglinger GU, Melhem NM, Dickson DW, Sleiman PM, Wang LS, Klei L, et al. *Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy.* Nat Genet. 2011;43(7):699-705.
11. Bensimon G, Ludolph A, Agid Y, Vidailhet M, Payan C, Leigh PN. *Riluzole treatment, survival and diagnostic criteria in Parkinson plus disorders: the NNIPPS study.* Brain. 2009;132(Pt 1):156-71.
12. Brown RG, Lacomblez L, Landwehrmeyer BG, Bak T, Uttner I, Dubois B, et al. *Cognitive impairment in patients with multiple system atrophy and progressive supranuclear palsy.* Brain. 2010;133(Pt 8):2382-93.
13. Katzenschlager R, Cardozo A, Avila Cobo MR, Tolosa E, Lees AJ. *Unclassifiable parkinsonism in two European tertiary referral centres for movement disorders.* Mov Disord. 2003;18(10):1123-31.
14. Holmberg B, Johansson JO, Poewe W, Wenning G, Quinn NP, Mathias C, et al. *Safety and tolerability of growth hormone therapy in multiple system atrophy: a double-blind, placebo-controlled study.* Mov Disord. 2007;22(8):1138-44.
15. Kollensperger M, Geser F, Ndayisaba JP, Boesch S, Seppi K, Ostergaard K, et al. *Presentation, diagnosis, and management of multiple system atrophy in Europe: final analysis of the European multiple system atrophy registry.* Mov Disord. 2010;25(15):2604-12.

PREVIEW: The Third Oxford Neurology Course

Conference details: 27-29th June, 2012.

We would like to announce the Oxford Neurology Course, which will take place from 27 – 29 June 2012. This is the third annual event. It is CPD-accredited and aimed at neurology consultants and trainees. The course has enjoyed consistently excellent feedback and high ratings on the Royal College of Physicians website. Previous delegates liked the practical approach to common clinical dilemmas, as well as the neuroscience, and importantly the lively discussion we encourage. They enjoyed the informal atmosphere, and the opportunity to exchange views with each other and speakers, all of whom are invited by virtue of being opinion leaders in their fields. We will continue this successful formula.

We have again been able to attract highly acclaimed speakers. Beyond providing updates for neurological topics, we consider issues at the interface with other specialties, such as our traditional "Where neurology meets…" session which this year covers rheumatology. One of our special guest lectures will help to decode advances in neuroscience: "How to be optimistically sceptical about stem cell cures, mutant mice and personalised genetics." The popular "Best Of Oxford's Grand Round" keeps its traditional place. Add to that the course dinner in traditional Trinity College, and a historical walking tour through the medical history of Oxford.

The Oxford Neurology Course offers a great opportunity for delegates to update, refresh and discuss their knowledge of clinical neurology and neuroscience, to hear some inspirational speakers, and to enjoy the atmosphere of an Oxford summer. Places are limited but we hope many of you will be able to join us. ◆

For further information, please contact
Mrs Marion Greenleaves.
Email: marion.greenleaves@ndcn.ox.ac.uk
Tel: 01865 231513
Web: www.ndcn.ox.ac.uk
Organising Committee:
Dr Ursula Schulz & Dr Martin Turner
Nuffield Department of Clinical Neurosciences, Oxford University

British Geriatrics Society
Spring Meeting 2012

Wednesday 16th - Friday 18th May 2012
Venue Cymru, Llandudno

Scientific Programme Includes:

Neurodegenerative sessions will include:

- Genetics of late-onset Alzheimer's disease
- Alternatives to neuroleptics in dementia
- Progress in neurotransplantation

Other sessions will include:

- Neuroimaging
- Stroke
- Sleep Apnoea
- Preventing Admissions through Anticipatory Care
- Over 15 Scientific Platforms

For further details about the meeting and exhibition please contact:

Hampton Medical Conferences Ltd
113-119 High Street, Hampton Hill, Middlesex, TW12 1NJ
Tel: +44 (0) 8979 8300 Fax: +44 (0) 8979 6700
Email: bgs@hamptonmedical.com Website: www.bgs.org.uk

ABN Annual Meeting Brighton 2012

29 May 2012 - 31 May 2012
The Brighton Centre, Brighton, UK

Tel: 020 7405 4060
Email: info@theabn.org • www.abn.org.uk
The ABN, Ormond House, 27 Boswell Street, London WC1N 3JZ

Organised by
HOSPITAL MEDICINE

MA Healthcare Conferences
Forthcoming events include:

6th national conference

Treating Schizophrenia
26th – 27th April 2012 London

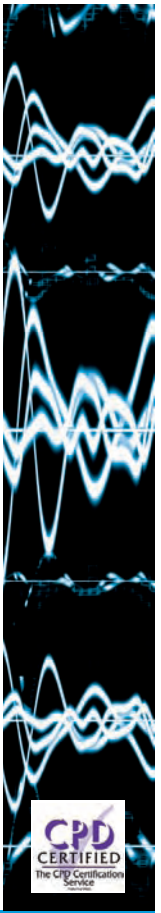
9th national neuroscience conference

Epilepsy in Children
NEUROSCIENCE NURSING
20th June 2012 London

14th national conference

Parkinson's 2012
PARKINSON'S UK CHANGE ATTITUDES. FIND A CURE. JOIN US.
9th July 2012 London

www.mahealthcareevents.co.uk
+44(0)20 7501 6762



CPD CERTIFIED The CPD Certification Service

45 YEARS OF MEDICAL EDUCATION

10th European Congress of Neuropathology

6th – 9th June 2012
Edinburgh, Scotland

The European Confederation of Neuropathological Societies (Euro-CNS) and the British Neuropathological Society (BNS) invite you to attend the 10th Euro-CNS Congress in Edinburgh, one of the world's most historic and enchanting cities.

Registration is now open at www.ecnp2012.org

We hope to welcome you to Edinburgh in 2012!

Early registration deadline – 13th April 2012

ECNP 2012 Congress Secretariat
c/o Meeting Makers, Jordanhill Campus
76 Southbrae Drive, Glasgow G13 1PP
Tel: +44 (0) 141 434 1500
Fax: +44 (0) 141 434 1519
Email: ecnp2012@meetingmakers.co.uk
Website: www.ecnp2012.org

BNS
Euro-CNS

Follow us on
www.facebook.com/ECNP2012
www.twitter.com/ecnp2012

EDINBURGH INSPIRING CAPITAL
Photo © Edinburgh Inspiring Capital
www.edinburgh-inspiringcapital.com

The Oliver Zangwill Centre 15th Anniversary:
The Past, Present and Future of Neuropsychological Rehabilitation

Conference details: 25th January, 2012; The Maltings, Ely, UK. ***Reviewed by:*** Dr Brian O'Neill, Brain Injury Rehabilitation Trust, Glasgow and University of Stirling

Professor Barbara Wilson

Fifteen years of innovation in the assessment and treatment of brain injury brought 150 international delegates to Ely. Dr Andrew Bateman opened the day with a warm welcome.

Neuropsychological rehabilitation's past

Professor Barbara Wilson opened with a three millennia history of neuropsychological rehehabilitation. A tour de force, it encompassed important events from the Edwin Smith papyrus to the founding of the Oliver Zangwill Centre (OZC) in 1996.

Paul Broca's (1865) language localisation work is better known than his rehabilitation of dysphasia or supervision of Zangwill's grandmother's medical training in Paris.

The industrialised warfare of WWI brought cataclysmal death and injury. Antiseptics reduced mortality after penetrating head injury to less than 50% and therapy programmes were first offered by US forces. In Germany, Kurt Goldstein oversaw the development of psychologically guided milieu therapy in Frankfurt. Poppelreuter (1917) published the first textbook on brain injury rehabilitation.

During WWII Alexander Luria pioneered assessments and compensatory treatments for psychological dysfunctions due to neuronal loss and inhibition of intact systems. He emphasised the social context of survivors, exemplified in the 'Man with a Shattered World'.

The WWII Oxford Unit of Ritchie Russell, Freda Newcombe and Oliver Zangwill developed the principles of compensation, substitution and direct retraining of the ability. Further advances followed the Korean and Yom Kippur Wars. Ben Yishay and Diller's (1973) holistic treatment centre in Tel Aviv was an important milestone.

The neurobehavioural rehabilitation of Eames and Wood, Northampton and George Prigatano's work in Oklahoma and Phoenix were inspirational to Prof Wilson's plans to address cognitive, emotional, social and functional problems. With NHS support, the OZC was founded, named for a wartime rehabilitation hero and began to inspire.

The present

Professor Jon Evans, University of Glasgow, surveyed current practice and developments. New models such as the International Classification of Function, Activity and Participation allow improved formulation of the effects of brain pathology on physical, mental and affective functions, impacting, in turn, activity, social function and wellbeing.

Wellbeing models are now prominent. Seligman emphasises positive emotions, engagement, relationships, meaningful activities and accomplishment (PERMA) in recovery. The OZC 'Y-shaped' model suggests that meaningful social group membership can resolve identity discrepancies between 'old me' and 'new me'.

Goal setting improves productivity and outcome(Locke and Latham 2007) and increased participation in goal setting increased goals achieved over rehab as usual.

Evidence for interventions has improved. So too methodology, e.g. Single-n work (Tate 2008). Cicerone has concluded that holistic comprehensive rehab should be offered as a matter of course. Goal planning approaches are advised. Elements of holistic cognitive rehab programmes, such as goal management training, have been independently evidenced. (See www.psychbite.com for evidence by condition, presentation or intervention).

Assistive technology for cognition expands as an area and Neuropage (Neurotext), AIM goal review prompting, GPS routefinding, Sensecam and sequence prompters such as Guide are accruing efficacy evidence.

Prof Evans rightly concluded that neuropsychological rehabilitation is developing well but there is plenty more still to do.

The Future

Professor Sue Gathercole, Director of the Cambridge Cognition and Brain Sciences Unit (CBSU), outlined how understandings from cognitive neuroscience can help prevention, detection and treatment of disorders of cognition. The finding that working memory capacity correlated with academic achievement spurred her interest in translational work.

CBSU research will include work on the processes in emotion recognition and regulation across a variety of conditions such as autism, conduction disorder, anxiety, depression and PTSD. Executive processes form another stream with Tom Manly and John Duncan leading investigations. Other groups study Audition, speech and language, memory and perception.

Transdiagnostic issues include cognitive appraisal of intrusive memories in depression and PTSD. Impairments of attention, working memory, goal monitoring, alertness and executive function will lead to interventions across conditions.

Intensive and regular training (at the edge of ability) of basic cognitive abilities such as attention and working memory bring sustained benefits (e.g. Olesen et al 2003) but this is not yet attributed to strategy or neural plasticity.

Questions will include, whether cognitive control training can reduce intrusions? Can working memory deficits in hypertension be prevented/treated? Can patterns of typical and atypical aging be differentiated?

Prof Gathercole concluded offering support for innovative work with translational potential in terms of partnerships, funding and training.

Current OZC Programme

Dr Jill Winegardner, Lead Clinical Psychologist described how holistic neuropsychological rehabilitation involves team members, clients and families sharing understanding. Integrated goals might require cognitive strategies, communication skills and mood management.

Twenty five adults with non-progressive acquired brain injury complete the 18 week rehabilitation programme each year. Clients are often years since injury and can have considerable social and functional disability.

Clinical and family interview, cognitive testing, functional tasks, mood assessment and community observation occur during a two day assessment and ensure a good match between person and service.

There are several rehabilitation programmes. The standard 18 week programme is goal focussed, beginning with six weeks covering rehabilitation, understanding brain injury, attention and memory, executive function, communication and mood.

European Brain Injury Questionnaire symptoms (e.g. headaches, cognitive problems and emotional problems) are significantly improved after the OZC programme (n=78). Goodwin and Bateman (2012) found that dysexecutive problems and carer strain were reduced by the programme. Cost benefit was illustrated by four case studies of post injury severe depression, chronic fatigue, anger dyscontrol and unemployment. All have high social costs if untreated.

Tim Lodge, ex-client, outlined his recovery from a road traffic accident and his impairments of attention, memory, motivation and anger control. His daughter wondered if she would get her daddy back. He lost work, his social world and hope.

Entering OZC allowed experience sharing, understanding and strategy learning. Goal and mood management were crucial skills. His 'tricky brain' was not his fault but he could change.

Mastering challenges again, such as development of an emergency CT scanner for military use, led to a virtuous circle of productivity, improved mood, identity and social functioning. He was thankful for both OZC and family help regaining his life. ◆

PREVIEW: Magstim Neuroscience Conference and Workshop 2012

Conference details: 12th & 13th May 2012, Examination Schools, Oxford, UK. ***Report by:*** Nick Lewis, Communications Manager, Magstim.

Magstim are pleased to open online booking for next year's 'Summer School' – the Magstim Neuroscience Conference & Workshop 2012, which will be held in the Examination Schools in Oxford in the UK on 12th & 13th May 2012. The key note speaker will be Mark S George (Distinguished Professor of Psychiatry, Radiology and Neurosciences, Medical University of South Carolina), who will be talking on the subject "Daily Prefrontal TMS for Treating Depression: Are we really modifying cortico-limbic governance and connectivity when we get people undepressed?"

Based on feedback from previous events, TMS Summer School has been rebranded so as to widen its remit to encompass more than just transcranial magnetic stimulation (TMS) as well as to cater for hands-on workshops with a variety of neuromodulation research equipment that is used in the majority of neuroscience research. The four workshops are titled:

- Motor Threshold & Beyond
- Cognitive Tasks
- TDCS, TACS and Cortical Modulation
- Neuronavigation

Delegates also have the option of booking for the celebratory dinner at Exeter College on the evening of Saturday 12th May. The guest speaker will be Dr Evan Harris.

In addition to the programme and workshops, we strongly encourage poster submissions from students, post-doctoral and established researchers working on any aspect of human brain stimulation. 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. Full abstract guidelines and submission details are available from the website. The Academic Organising Committee consists of Vince Walsh, Charlotte Stagg and Sven Bestmann. ◆

Please visit www.magstim.com/magstim-neuroscience-conference for the full programme, other information, and to book your place today. 'Early Bird' registration will still apply until mid-March. News about the conference can also be found on the Magstim Twitter Feed: www.twitter.com/neuromodulation

UKABIF 3rd Annual Conference Review

Conference details: 10th December, 2011: Birmingham UK. ***Reviewed by:*** Trudie Hanson, Occupational Therapy Student.

With over 1,000,000 people in the UK suffering the effects of Acquired Brain Injury (ABI), and its huge impact on family, friends, employers and carers, the need to raise awareness and improve services in these challenging times remains paramount in the UK Acquired Brain Injury Forum's (UKABIF) upcoming manifesto. The annual conference provides networking opportunities for professionals, clients, service providers, sponsors, planners and policy makers and all delegates and speakers were welcomed by Professor Mike Barnes, consultant in Rehabilitation at Hunters Moor Neuro-rehab and Chair of UKABIF.

Internationally respected speakers at this event covered a broad spectrum of issues relevant to ABI – the opening talk delivered by Professor Leonard Li from Tung Wah Hospital in Hong Kong setting out to raise more questions than answers in the consideration of mental imagery as a tool to improve motor function after brain injury. On-going research suggests that mental imagery may lead to significant improvement for both executive motor function and untrained skill soon after diagnosis, but this benefit is difficult to disassociate from the benefits of physical training alone. Randomised controlled trials show that physical training and mental imagery together have a positive outcome and results can be generalised to a spectrum of patients. The work of Professor Li and colleagues raised a positive response from the delegates.

A quote attributed to Sir Winston Churchill – "Gentlemen, We Have Run Out Of Money; Now We Have to Think" perhaps best summarises the highly informative talk given by Elisabeth Duggins, CBE, recent former chair of NHS West Midlands, emphasising the difficulties experienced by political changes and budgetary restraints. Care pathways, particularly between health and social care, remain in hiatus. However, on-going plans to commission specialist services are addressing the need to deliver quality care at a lower cost and achieve positive outcomes through alternative service provision routes. Advice given to professionals working in the field was to establish strong links with the commissioning bodies. They were also encouraged to show case potential for value in terms of quality of provision and outcomes as well as their role in client advocacy.

A clinical view of aspects and consequences of ABI were the focus of talks by Professor David Bates, Emeritus Professor of clinical Neurology at Newcastle University, Dr Nicholas Davies PhD MRCP, Consultant Neurologist, Chelsea and Westminster Hospital, and Professor Simon Shorvan, Professor of Clinical Neurology at UCL and Consultant Neurologist at the National Hospital of Neurology and Neuroscience.

Professor Bates discussed Coma and the Persistent Vegetative State (PVS) defining the history of this diagnosis and explaining the clinical differentiation between coma, brain stem death, the vegetative state, minimally conscious state, locked-in syndrome, and complete neuro-muscular paralysis. Refinements in the criteria for confirming brain (stem) death have been made over more than 150 years and currently the 1978 Medical Colleges UK guidelines apply which require both inclusion and exclusion criteria to be met and agreed before the diagnosis can be given. There must be a known aetiology for the patient state, and there will be no motor response including pupillary and corneal reflexes, in order to support an irreversible loss of capacity for consciousness. Hypothermia, drugs use, reversible metabolic and endocrine disturbances as potential causes must also be ruled out. The vegetative state (previously known as coma vigile or apallic coma but VS is now regarded as the appropriate terminology by the EU) differs from brain death in that the brain stem remains intact and the patient retains potential for blood pressure control, the ability to open/close eyes, breathing and body temperature control but not to speak or maintain continence. In this case there is a subjective diagnostic element, in that it is considered that the patient has no awareness of themselves or their environment. This particular point stimulated some discussion after the talk, in that relatives and carers MAY have differing perceptions to clinicians in this regard, and discussion continued as to how this could be handled appropriately. Diagnosis of the vegetative state therefore needs a cause as well as clinical criteria and statistical validation, but unlike brain death, in which there is potential for some degree of urgency in terms of consideration of donor potential, there is no advantage to a speedy diagnosis for VS. A degree of urgency is needed however for patients considered to be in a minimally responsive/locked-in state. This condition affects the anterior part of the brain stem and there is considered to be some value in clinical tests such as PET and FMRI scans to assess this more fully. Usually, a largely subjective assessment is made which can require weeks to establish whether patient movements and behaviours are 'purposeful' rather than reflex activity. Withdrawal of support to confirm diagnosis may improve clinical evidence and reasoning but leads to obvious legal considerations. Urgency however is needed in order to address the potential that the patient is experiencing fear, pain and isolation and significant time should be expended at the earliest opportunity in order to facilitate purposeful responses, even if this is a non-verbal communication such as a blink or other small movement.

Professor David Bates, Emeritus Professor of Clinical Neurology discusses Coma and PVS.

Dr Nicholas Davies's talk updated delegates with recent research on encephalitis, which has a high rate of mortality and acquired brain injury, regardless of cause. Encephalitis is a syndrome rather than a disease. It is caused by inflammation in the brain stemming from either infectious or

The team from Hunters Moor Neuro Rehab.

The audience at the conference ranged from allied healthcare professionals and case managers to care providers, personal injury lawyers, brain injury survivors and rehabilitation consultants.

The Executive Committee of UKABIF with keynote speaker Professor Leonard Li and UKABIF Executive Director Chloe Hayward.
L-R bottom row Dr Keith Jenkins, Bill Braithwaite QC, Professor Leonard Li, Paul Brown, Amanda Swain, Mike Hope.
L-R top row Keith Hawley, Chloe Hayward, Lisa Turan, Ava Easton, Prof Mike Barnes.

non-infectious causes. These can manifest acutely (within hours), sub-acutely or as a chronic syndrome with onset taking months to manifest specific symptoms. Dr Davies described problems with misdiagnosis, mimic diseases and the lack of specific data to aid investigation into either prevention or the cause of the syndrome. Since early accurate diagnosis improves outcome, unless more research is continued into the 'unknown causes' of many varieties of the syndrome, then treatment programmes and outcomes will continue to result in extended hospital stay, high levels of fatality and associated poor outcomes.

The lunchtime break for the delegates was preceded by the launch of the Independent Neuro-Rehabilitation Providers Alliance by Professor Nick Alderman. This was followed by the second year of the UKABIF Awards for innovation and Inspiration which incorporate awards for those in the legal, clinical, care and voluntary sectors. This year there was a new award called the Stephen McCabe Award for Inspiration, presented to Julie Cordon of Brainbox by Stephen's parents.

Following the Awards presentations, Professor Simon Shorvon advised delegates about the recent resurgence in research into epilepsy, inspired by an increase in those suffering from the condition, largely resulting from repatriated injured servicemen. Epilepsy is classified into immediate post traumatic epilepsy, caused concurrently with cerebral trauma, early post-traumatic epilepsy which occurs within seven days of trauma and late post traumatic epilepsy which usually occurs within six to eight months of trauma. Early seizures are more common in children, and those suffering from TBI have approximately five times the risk of developing epilepsy within ten years following trauma. Despite Danish studies carried out within the last ten years, little is known about why epilepsy can take so long to develop after injury, and therefore what could potentially be prevented. EEG's do not clearly indicate epilepsy after brain injury, as although spike and spike/wave patterns during seizures are marked, these may not be seen at other times. Common differential diagnoses could include syncope and convulsive syncope, psychogenic seizures or cardiac arrhythmia and diagnosis may be further complicated by factors such as depression, anxiety, PTSD etc. Professor Shorvon showed that treatment with anti-epileptic drug therapy may lower the risk of early seizures, but there is no current evidence that this has any effect on late seizures, which have a reputation for being difficult to treat. Research needs to be continued to investigate the aetiology of epilepsy and methods to improve diagnostic accuracy. Research efforts should also concentrate on treatment, such as the use of protective agents to prevent eleptogenesis, the role and efficaciousness of anti-epileptic drug regimens and the establishment of long term optimal treatment regimes. From a legal perspective, with regard to compensation, there needs to be more study into robust assessments of the prospective risk of developing

epilepsy after trauma and long term prognosis. Questions from the floor explored issues regarding anti-epileptic drugs increasing behavioural issues and the benefit: risk ratio thereof, as well as the regional variations on prophylactic use of anti-epileptic drugs within the first two weeks of severe head injury. These discussions further highlighted Professor Shorvon's position regarding need for evidence-based practice.

Sheona Khan and Catherine Wickens next led delegates through the need for good nutritional support for patients after ABI, by demonstrating the significant weight loss often suffered by hospitalised patients and the rehabilitation difficulties subsequently caused by this, including challenges to mobilisation, positioning and the implications for subsequent increased in-patient stay. The aim of dieticians and the speech and language therapy team was described as being to achieve optimal nutritional status for the patient and to give opportunities for independent eating and drinking as a pleasurable occupation to improve self-esteem and well-being. Difficulties in managing accurate food/fluid charts, behavioural issues, poor motivation, fatigue, pre-existing eating disorders, personal, cultural and family preferences regarding food and dysphagia all have implications for the nutrition of the brain injured patient. Although PEG and Naso-gastric feeding are regulated and manageable methods of ensuring nutritional support, mealtimes are often considered to be about therapy, with opportunities to improve cognition, sequencing, routine and motor skills whilst engaging in the process of eating and drinking. As healthy nutritional levels are achieved, further complications arise including maintaining the BMI of patients with reduced mobility. A particular issue is with wheelchair-bound patients, as it is known that 66% of wheelchair users are overweight or obese. Wheelchair users with a normal BMI, have a body fat percentage which would indicate obesity in ambulant patients, due to the impact that reduced weight-bearing has on body fat percentages. The challenge is therefore an educational one for patients and care staff, especially in view of the effects on rehabilitation for those with weight management issues.

The final session was by Professor Barbara Wilson, author of over 200 books and articles related to her work in rehabilitation of memory. The effects of ABI on memory are usually regarded as being difficulty in recollection after delay or distraction, difficulty processing new information and retrograde amnesia. The purpose of rehabilitating memory is therefore to reduce the impact of memory problems on activities of daily living, to achieve success through compensatory techniques and to enable a patient to return safely to an appropriate environment, rather than to improve scores on specific memory tests. Setting personally meaningful and functionally relevant goals through negotiation with the patient, family and support team will enable a patient to cope better in everyday life after injury. Goals are graded for stages of rehabilitation and levels of memory loss. General principles to assist with memory difficulties were highlighted as: simplifying information; reducing the amount of information provided; checking for understanding; avoidance of trial and error learning; test-rehearse-practice; spaced retrieval of information and avoidance of context-specific learning which decreases transferability.

Professor Wilson demonstrated some of the memory aids available as an equipment trial scheme at the Zangwill Centre in Ely, such as pill-reminders, day clocks etc. but pointed out that often those who most need memory aids are those more likely to forget to use them! A combination of strategies to assist with memory loss might then include compensatory aids and techniques and taught skills such as the use of vanishing cues, errorless learning etc. to maximise memory retrieval. The emotional consequences of memory loss are huge and rehabilitation in this field therefore aims to instil hope and reduce anxiety.

The theme of this conference had largely been the need to continue – or even commence – research into areas that impact on the lives of patients with ABI and their carers and to source the support, resources and effort that this research needs. UKABIF remains committed to this task and this conference has brought with it, not only the continuous professional development welcomed by practitioners in the field, but the opportunity to share ideas, network and aim to improve the lives of the million people affected by brain injury in the UK. ◆

PREVIEW: British Geriatrics Society Spring Conference

Conference details: 16-18th May, 2012.

The British Geriatrics Society (BGS) is a membership association of doctors, nurses, therapists, scientists and others with a particular interest in the care of the frail older person and in promoting better health in old age. It holds two annual conferences, one in Spring and one in Autumn, in order to provide platforms for scientific research to be shared. The BGS Spring Conference is taking place from 16-18 May 2012 in Llandudno in North Wales.

The event starts with a special focus on the latest developments in the field of neurodegenerative disorders with presentations from an internationally renowned panel of speakers including:

- Epidemiology of neurodegenerative disease: a life course perspective, Yoav Ben-Shlomo, Professor of Clinical Epidemiology, University of Bristol
- Genetics of late-onset Alzheimer's disease, Julie Williams, Professor in Neuropsychological Genetics, Cardiff University
- Progress in neurotransplantation, Ann Rosser, Professor of Clinical Neuroscience and Honorary Consultant in Neurology, University hospital of Wales, Cardiff
- Practical and future management of dementia in Parkinson's and Lewy body disease, David Burn, Professor of Movement Disorder Neurology, Newcastle University, and Honorary Consultant Neurologist, Newcastle upon Tyne Hospitals NHS Foundation Trust
- Psychosocial intervention in dementia: effectiveness and applications, Bob Woods, Professor of Clinical Psychology of Older People, Bangor University, Bangor
- Alternatives to neuroleptics in dementia, Clive Ballard, Professor in Age Related Diseases, King's College London

The conference goes on to cover a range of topical issues and scientific research, providing varied and thought provoking educational content. The preliminary programme can be viewed on the BGS website: www.bgs.org.uk

The event is open to non-BGS members and is CPD accredited by the Royal College of Physicians. Registration is now open and there are two registration options, full meeting or one-day registration. There are reductions for BGS members, trainees, retired BGS members and allied health professionals. The BGS offers grants to young doctors, nurses and therapists to help with funding travel and accommodation to attend the event. ◆

For further details visit:
www.bgs.org.uk/Grants/prizes-index.htm
To register for the event visit the website, or contact the Conference Secretariat, Hampton Medical Conferences on 020 8979 8300 or email bgs@hamptonmedical.com
The Venue Cymru is located in Llandudno, an hour's drive from Manchester and Liverpool.
For more information visit:
http://conference.venuecymru.co.uk/

PREVIEW: UCL Institute of Neurology's Short Courses May 2012

UCL's Annual May Short Courses start on 21st May with **Rehabilitation after Acquired Brain Injury,** organised by Dr Richard Greenwood. In the UK, acquired single-incident brain injury (ABI), largely due to stroke and head injury, results annually in about 300,000 admissions to hospital and accounts for over three million bed days. Long term disability is common, and annual direct healthcare and social-care costs, and indirect costs are between £10-15billion. The NHS stroke networks have recently provided the opportunity to put in place organised rehabilitation after stroke, but after head injury the provision of rehabilitation within the NHS trauma networks requires clarification. Nevertheless, it will become increasingly important for all neurologists to understand the principles of rehabilitation after stroke and head injury. This course will invite experts in the field to describe the principles underlying the practice of rehabilitation after ABI, its provision over time and the treatments available, the evidence for its effectiveness at the levels of impairment and function, and likely advances over the next 10 years.

On Tuesday 22nd May, the **Dementia** course, organised by Dr Jonathan Schott, will cover the clinical and scientific aspects of Alzheimer's disease, and non-Alzheimer dementias. The diagnostic approach and features of the various dementias will be illustrated using clinical videos and patient demonstrations. The psychiatric and social aspects of dementia care will be discussed, with an update on current and potential therapeutic strategies. The course is aimed at psychiatrists, geriatricians and other professionals involved in the diagnosis and care of patients with dementia.

Movement Disorders on Wednesday 23rd May will focus on practical aspects of diagnosis and management of abnormal movements. Topics will include hyperkinetic movement disorders and akinetic-rigid syndromes. Video clips will be used extensively and participants are encouraged to bring their video clips in Mpeg 1/WMV/AVI file formats on CD to enable playback of difficult or unusual patients for discussion via a desktop media player. This course is organised by Dr Patricia Limousin; Professor K Bhatia; Professor A Lees; and Dr T Foltynie.

Thursday 24th May – **Sleep**. Sleep disorders are ubiquitous and involve many disciplines including psychiatrists, respiratory physicians, neurologists and anaesthetists. This course will concentrate on pathogenesis, diagnosis and treatment of sleep disorders, and sleep disorders associated with neurological disease. Aimed mainly at neurologists, general practitioners and physicians with an interest in sleep medicine, the topics covered will include differential diagnosis of sleep disorders, periodic limb movements of sleep, restless leg syndrome, nocturnal ventilation in neurological disease, obstructive sleep apnoea, sleep disorders in neurodegenerative disease, insomnia, and narcolepsy. Organised by Dr Sofia Eriksson and Professor M Walker.

The final course on Friday 25th May is **New technologies in the Neuro-ophthalmology Clinic: including OCT, Automated Perimetry and Saccadic measurements**. This is an update with clinical cases on new user-friendly techniques for visual assessment suitable for both neurologists and ophthalmologists. The morning will be devoted to fundus Optical Coherence Tomography (OCT) in the assessment of neurological disorders including multiple sclerosis and optic neuropathies. In the afternoon there will be a session on eye movements illustrating the use of new clinic-based saccadic analysis devices. Organised by Mr James Acheson and Dr Fion Bremner. ◆

COME JOIN US!

IMPORTANT DATES

Early registration deadline
April 20, 2012

Final Pre-registration deadline
May 30, 2012

16th International Congress of Parkinson's Disease and Movement Disorders
June 17 – 21, 2012

The *Movement* Disorder Society

Bloomsday Basic Movement Disorders Course

Recommended Audience

Family physicians, general neurologists, internists, trainees and other clinicians interested in acquiring a basic understanding of and a clinical approach for the evaluation and management of common movement disorders.

Please note that if your residence is outside of the United Kingdom and Ireland, you must register for both the Bloomsday Basic Movement Disorders Course and The 16th International Congress of Parkinson's Disease and Movement Disorders.

For more information please visit:
www.movementdisorders.org/education/

Bloomsday, June 16, 2012
DUBLIN, IRELAND
Proudly Supported by:
Royal College of Physicians of Ireland
No.6, Kildare St.

16th International Congress of Parkinson's Disease and Movement Disorders

DUBLIN, IRELAND JUNE 17–21, 2012

The *Movement* Disorder Society (MDS) is an international, professional society of clinicians, scientists, and other healthcare professionals who are interested in Parkinson's disease, related neurodegenerative and neurodevelopmental disorders, hyperkinetic movement disorders, and abnormalities in muscle tone and motor control. Please visit www.movementdisorders.org.

www.mdscongress2012.org

MDS-0212-351

Twenty-second Meeting of the European Neurological Society

9 – 12 June 2012

Prague, Czech Republic

Neurology: Learning, knowledge, progress and the future

Key symposia:

- Parkinson syndrome: an everlasting challenge
- Neuroimaging and early diagnosis of neurological disease
- Stem cells ready for clinical practice
- MS and acquired demyelinating disorders
- Neurology and sleep-wake disorders

The congress programme includes 22 teaching courses, 11 workshops, practical sessions in clinical neurophysiology, interactive case presentations and selected scientific sessions in the form of oral and poster sessions.

For more details on sessions and courses or direct registration link, please visit: www.congrex.ch/ens2012

For further information please contact:
ENS 2012, c/o Congrex Switzerland Ltd.
Peter Merian-Strasse 80, 4002 Basel / Switzerland
Phone +41 61 686 77 77 Fax +41 61 686 77 88
Email basel@congrex.com

www.ensinfo.org

Specialist website for patients with Parkinson's

Orion Pharma has funded an interactive website for Parkinson's patients, their carers and healthcare professionals. The site www.wearingoff.co.uk offers support and tools on how to recognise wearing-off symptoms as well as information to help patients. It also contains an online symptom diary to track a patient's progress. Levodopa therapies are prescribed eventually to most people with Parkinson's. However, long term use of this medicine may give rise to certain complications where symptom control fades out and the effect of the drug wears off. www.wearingoff.co.uk contains detailed symptom questionnaires which can be

regularly filled in and printed off for patients to prompt discussion with their doctor – allowing treatment to be quickly adjusted to improve symptoms.

University of Oxford gains a European first

The University of Oxford has installed Europe's first 7 Tesla whole body actively-shielded MRI system from Siemens Healthcare. The MAGNETOM® 7T MRI is now in place at the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) within the Nuffield Department of Clinical Neurosciences.

The new 7 Tesla MRI will be primarily used for imaging the structure and function of the brain to advance collaborative work within the University to better understand the healthy human brain and the mechanisms underpinning key diseases of the central nervous system, such as stroke, neurodegeneration, epilepsy, chronic pain and various psychiatric conditions. 7 Tesla MRI provides the potential for microscopic spatial resolution, visualising anatomy at a level of detail previously impossible. It also enables the advanced observation and analysis of tissue metabolism and function. As the system is actively shielded, it can be sited on smaller footprint giving positive implications for the future of this high end technology. If such systems can be installed without the weight and size constraints of passively shielded systems, then 7 Tesla MRI could branch out of research institutions and into the clinical field.

"The increased spatial resolution provided by the MAGNETOM 7T MRI enables us to observe and analyse smaller networks of processing units in the brain than is currently possible. This will assist with our neuroscience research efforts into understanding how the human brain works in healthy and diseased states," said Professor Irene Tracey, Director of the FMRIB Centre.

Playing Against Time: a film about Parkinson's and music

Playing Against Time is a 'medical/musical' exploration of Parkinson's. This documentary focuses on the life and music of Barbara Thompson, one of Europe's finest virtuoso jazz saxophonists and composers who, in 1996, was diagnosed with Parkinson's. As the condition increasingly affected her central nervous system, she fought to continue composing and performing with the constant support of her partner, jazz/rock drummer Jon Hiseman.

By 2001, she had to stop playing in public, but since 2003 different drug treatments have restored intermittent mobility in her fingers, allowing her to play again. The film picks up the story in 2005. Interweaving musical and medical sequences, the camera follows her as she consults Professor Ray Chaudhuri at London's King's College Hospital and Oxford neurosurgeon Tipu Aziz.

Chaudhuri proposes an apomorphine infusion via a pump, and Barbara starts the treatment a year later. This isn't a film simply about the clinical course of the disease, or the potential drugs and surgery on offer. Barbara and Jon's collaboration is central, as they continually come

to terms with the condition and continue with their life's work – making music.

The 75-minute documentary 'Playing Against Time' was transmitted on BBC4 TV on 19 February, and is available on iPlayer for one month from that date.

Art and the eye of the beholder

What goes on in our brain when we look at a work of art? Some answers to this question were in evidence at an exhibition at the University of Leicester in January.

'The art of visual perception' presented the results of a unique collaboration between the art of Argentine artist Mariano Molina and research findings from the University of Leicester neuroscientist and Professor of Bioengineering Rodrigo Quian Quiroga. In the exhibition Molina's work incorporated principles of visual perception identified through neuroscience, and the canvases were accompanied by explanations of how these principles work. Both Mariano Molina and Rodrigo Quian Quiroga are fascinated by visual perception and optical illusions, which offer an insight into how the brain processes information.

Rodrigo Quian Quiroga holds a Research Chair at the University of Leicester and he is the director of the newly created Bioengineering Research Centre. He commented, "Having Mariano in our lab was a unique opportunity to start bridging the gaps between science and arts. It is really a pity that scientists take art as a hobby or pleasure, not as something that can help us in our own research. Those studying visual perception, for example, have a lot to gain from the interaction with visual artists like Mariano.

"The interaction with him has been fascinating, especially when seeing how the discussion of different ideas emerged in each canvas. On the one hand, these art pieces are an excellent way to show principles of visual perception in action and, on the other hand, they have an artistic value and a dose of originality since they use some neuroscience principles that are largely unknown to artists.

European approval to expand use of Rebif in patients with early MS

The European Commission has approved extension of the indication of Rebif® (interferon beta-1a), Merck's treatment for relapsing forms of MS. This EC approval is for the use of Rebif 44 micrograms three times weekly in patients who have experienced a single demyelinating event, an early sign of the disease, and who are at high risk of converting to MS. This approval was based on the results of the REFLEX study, which showed the safety and efficacy of Rebif in this patient population. "We are delighted by the European Commission decision," said Dr Annalisa Jenkins, Head of Global Drug Development and Medical at the Merck Serono division. "Multiple sclerosis has an initial stage when clinical manifestations are not pronounced but irreversible neurological damage is taking place. Throughout the EU, neurologists will now be able to prescribe Rebif for patients with early signs of this devastating disease."

Zebinix-UK2231 Date of preparation: January 2012

PRESCRIBING INFORMATION

Zebinix® (eslicarbazepine acetate)

Please refer to the SPC before prescribing. ***Presentation:*** Tablets containing 800 mg eslicarbazepine acetate. ***Indication:*** Adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation. ***Dose and administration:*** May be taken with or without food. Starting dose is 400 mg once daily, increased to 800 mg once daily after one or two weeks. Dose may be increased to 1200 mg once daily. Withdraw gradually to minimise the potential of increased seizure frequency. ***Elderly patients:*** Caution. ***Children and adolescents <18 years of age:*** Not recommended. ***Patients with renal impairment:*** Adjust dose according to creatinine clearance (CL_{cr}). Not recommended in severe impairment. ***Patients with hepatic impairment:*** No dose adjustment in mild to moderate impairment. Not recommended in severe impairment. ***Contraindications:*** Hypersensitivity to the active substance, other carboxamide derivatives (e.g. carbamazepine, oxcarbazepine) or any excipients. Known second or third degree AV block. ***Pregnancy:*** No data on the use of Zebinix in pregnant women. Carefully re-evaluate treatment if women become pregnant or plan to become pregnant, and use minimum effective doses. Interacts with oral contraceptives. Use an alternative method of contraception during treatment and up to the end of the current menstrual cycle after treatment has been stopped. ***Lactation:*** Excretion in human breast milk is unknown. Breastfeeding should be discontinued during treatment. ***Warnings and precautions:*** May cause some CNS reactions such as dizziness and somnolence. Do not use with oxcarbazepine. Rash has been reported. Discontinue if signs or symptoms of hypersensitivity develop. Screen 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, chest pain, epistaxis, liver disorder, drug toxicity, poisoning. Some rare adverse reactions such as bone marrow depression, anaphylactic reactions, severe cutaneous reactions (e.g. SJS), 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. ***Irish price to wholesaler:*** Zebinix 800 mg: pack of 30 €159.10. ***Marketing authorisation numbers:*** EU/1/09/514/012-020. ***Marketing authorisation holder:*** Bial-Portela & C^{a}., S.A. Â 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:*** November 2011.

Adverse events should be reported. Reporting forms and information can be found at yellowcard.mhra.gov.uk. Adverse events should also be reported to Eisai Ltd on 0208 600 1400/0845 676 1400 or Lmedinfo@eisai.net

1. Zebinix Summary of Product Characteristics, January 2011.
2. Elger C *et al.* Epilepsia 2009;**50**(3):454-463.
3. Ben-Menachem E *et al.* Epilepsy Res 2010;**89**(2-3):278-285.
4. Gil-Nagel A *et al.* Acta Neurol Scand 2009;**120**(5):281-287.
5. Halász P *et al.* Epilepsia 2010;**51**(10):1963-1969.
6. Gabbai AA *et al.* Epilepsia 2008;**49**(suppl. 7):432-433.
7. Lopes-Lima J *et al.* Epilepsia 2008;**49**(suppl. 7):441-442.