

ACNR

www.acnr.co.uk

ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

In this issue

Julia Granerod and Nicholas Davies

– Encephalitis: recent advances and challenges ahead

Katie Gilkes and Gareth Evans

– Neurosurgery Article – Neurofibromatosis Type 2

Gautam Ambegaonkar

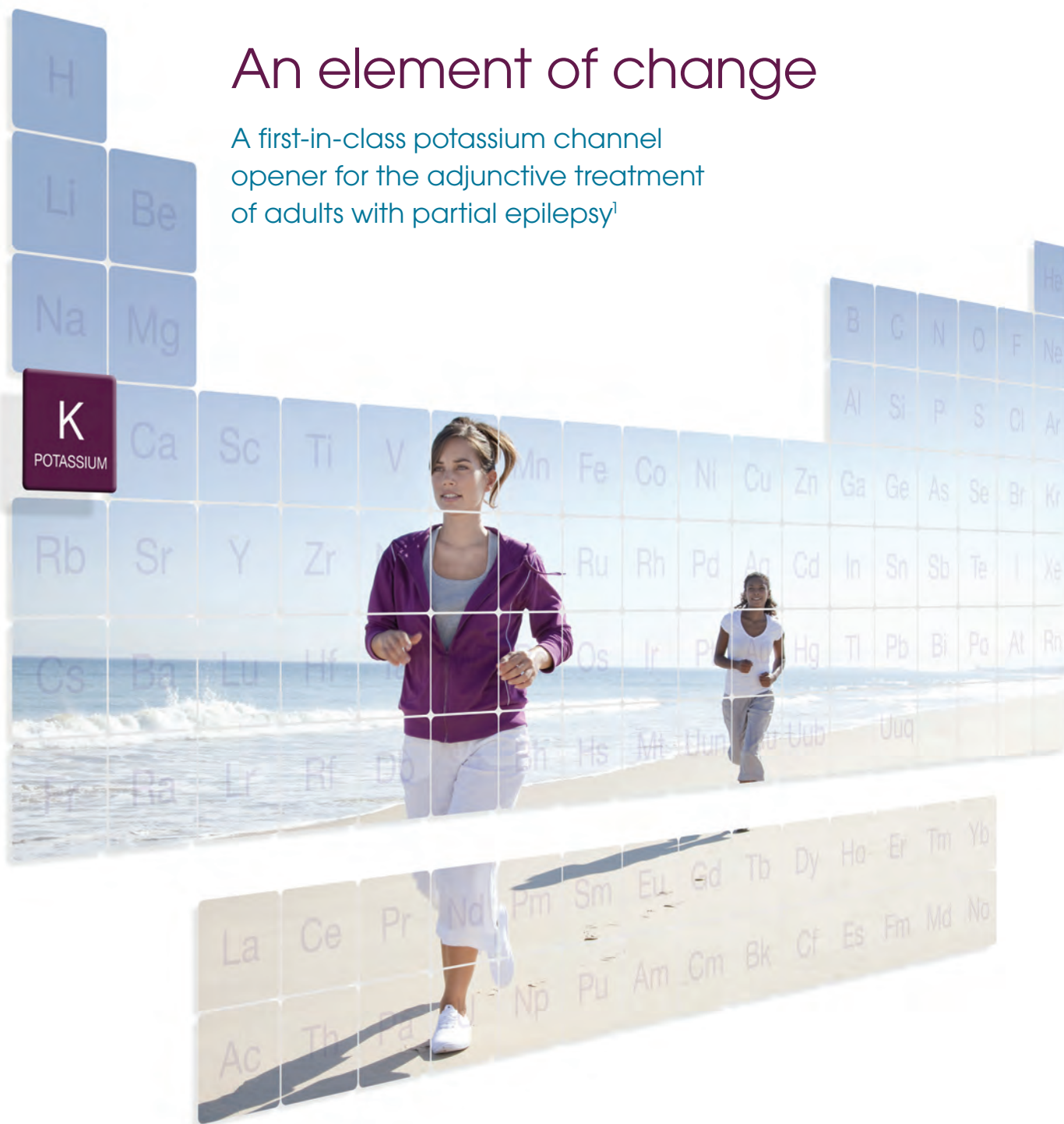
– Paediatric Article – Continuous Spike Wave Discharges in Slow-Wave Sleep
– don't let it catch you napping!

Rhys Thomas

– Association of British Neurologists Trainees – Australasian Fellowships

An element of change

A first-in-class potassium channel opener for the adjunctive treatment of adults with partial epilepsy¹



www.trobalt.co.uk



Trobalt®
retigabine tablets

Professor Masud Husain

Masud Husain (pictured right), previously Professor of Clinical Neurology at UCL Institute of Neurology, has been appointed Professor of Neurology & Cognitive Neuroscience at Oxford University. He was recently awarded a Wellcome Trust Principal Fellowship to study inattention, impulsivity and apathy in neurological disorders.



Investing £1.2 million in research for sick babies and children

Action Medical Research – the leading UK children's charity – has announced grants worth more than £1.2 million for top researchers across the country.

The charity is celebrating its anniversary in 2012 by marking 60 years of funding which has led to some key scientific breakthroughs. The new grants have been awarded to research institutes at universities and hospitals investigating conditions affecting babies and children.

Researchers at Newcastle University and The Newcastle upon Tyne NHS Hospitals Foundation Trust have been given a grant of £109,372 for research into upper limb rehabilitation for children with hemiplegic cerebral palsy.

The John Radcliffe Hospital, Oxford has also been awarded a three year grant of £173,364 for further research into understanding the genetic basis of childhood ataxias.

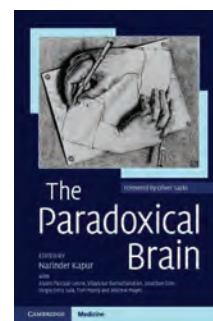


For further information see: action.org.uk

The Paradoxical Brain awarded runners up prize by the American Medical Writers Association

The Paradoxical Brain, edited by Professor Narinder Kapur, has won the runners-up prize in the annual book awards of the American Medical Writers Association. The book focuses on a range of phenomena in clinical and cognitive neuroscience that are counterintuitive and go against the grain of established thinking.

Available from www.cambridge.org



Dr Doug Brown

The Alzheimer's Society has appointed Dr Doug Brown (pictured right) as the new Director of Research and Development. His previous post was Head of Biomedical Research at the Multiple Sclerosis Society.



Dr Doug Brown is determined to make life better for people with the condition.

Increasing investment is a key goal of the society which last year spent more than £3.5 million on research – a rise of 33 percent. By 2017, Alzheimer's Society aims to invest £10 million a year in dementia research.

More information is available at: alzheimers.org.uk

Trobal® ▼ (Retigabine) Prescribing Information

(Please refer to the full Summary of Product Characteristics before prescribing).

Presentation Trobal tablets: each containing retigabine equivalent to either: purple film coated round tablets containing 50 mg retigabine; green film coated round tablets containing 100 mg retigabine; yellow film coated oblong tablets containing 200 mg retigabine; green film coated oblong tablets containing 300 mg retigabine; purple film coated oblong tablets containing 400 mg retigabine. **Indications** Adjunctive treatment for partial onset seizures with or without secondary generalisation in adults aged 18 years and above. **Dosage and Administration** Trobal must be taken orally in three divided doses each day. The maximum total daily starting dose is 300 mg (100 mg three times daily). Thereafter, the total daily dose is increased by a maximum of 150 mg every week according to individual patient response and tolerability. An effective maintenance dose is expected between 600 mg/day and 1,200 mg/day. **Renal impairment:** No dose adjustment is required in patients with mild renal impairment. A 50% reduction in the initial and maintenance dose of Trobal is recommended in patients with moderate or severe renal impairment (creatinine clearance <50 ml/min). The total daily starting dose is 150 mg, and it is recommended that during the titration period the total daily dose is increased by 50 mg every week to a maximum total dose of 600 mg/day. **Hepatic impairment:** No dose adjustment is required in patients with mild hepatic impairment. A 50% reduction in the initial and maintenance dose of Trobal is recommended in patients with moderate or severe hepatic impairment (Child-Pugh score ≥7). The total daily starting dose is 150 mg and it is recommended that during the titration period the total daily dose is increased by 50 mg every week to a maximum total dose of 600 mg/day. **Elderly** (65 years of age and above): A reduction in the initial and maintenance dose of Trobal is recommended in elderly patients. The total daily starting dose is 150 mg/day and during the titration period the total daily dose should be increased by a maximum of 150 mg every week according to the individual patient response and tolerability. Doses greater than 900 mg/day are not recommended. **Contra-indications** Hypersensitivity to retigabine or any of its excipients. **Special warnings and precautions** Urinary retention, dysuria and urinary hesitation were reported in controlled clinical studies with retigabine generally within the first 8 weeks of treatment. Trobal must be used with caution in patients at risk of urinary retention and it is recommended that patients are advised about the risk of these possible effects. Caution should be taken when Trobal is prescribed with medicinal products known to increase QT interval and in patients with known prolonged QT interval, congestive cardiac failure, ventricular hypertrophy, hypokalaemia or hypomagnesaemia and in patients initiating treatment who are 65 years of age and above. In these patients it is recommended that an electrocardiogram (ECG) is recorded before initiation of treatment with Trobal and in those with a corrected QT interval >440 ms at baseline, an ECG should be recorded on reaching the maintenance dose. Psychiatric disorders: Confusional state, psychotic disorders and hallucinations were reported in controlled clinical studies; it is recommended that patients are advised about the risk of these possible effects. Suicide risk: Suicidal ideation and behaviour have been reported in patients treated with anti epileptic agents in several indications. Patients (and caregivers of patients) should be advised to seek medical advice if signs of suicidal ideation or behaviour emerge. Elderly (65 years of age and above): Elderly patients may be at increased risk of central nervous system events, urinary

retention and atrial fibrillation. Retigabine must be used with caution in this population with a reduced initial and maintenance dose recommended. As there is individual variation in response to all antiepileptic drug therapy, it is recommended that prescribers discuss with patients the specific issues of epilepsy and driving. **Overdose** In the event of overdose it is recommended that the patient is given appropriate supportive therapy as clinically indicated, including ECG monitoring. Further management should be as recommended by the national poisons centre, where available. **Fertility, pregnancy and lactation** Trobal is not recommended during pregnancy and in women of childbearing age not using contraception. It is unknown whether retigabine is excreted in human breast milk. The effect of retigabine on human fertility has not been established. **Drug interactions** *In vitro* data indicated a low potential for interaction with other antiepileptic drugs. Pooled analysis from clinical studies showed no clinically significant effect of the inducers (phenytoin, carbamazepine and phenobarbital) on retigabine clearance. Steady-state data from a limited number of patients in smaller studies indicate that phenytoin and carbamazepine could reduce retigabine systemic exposure by 35% and 33% respectively. Trobal interaction with digoxin at therapeutic doses may increase digoxin serum concentrations. Retigabine may increase the duration of some anaesthetics. **Adverse reactions** A dose relationship seems to exist between dizziness, somnolence, confusional state, aphasia, coordination abnormal, tremor, balance disorder, memory impairment, gait disturbance, blurred vision and constipation. **Metabolism and nutrition disorders:** common: weight increase, increased appetite. **Psychiatric disorders:** common: confusional state, psychotic disorders, hallucinations, disorientation, anxiety. **Nervous system disorders:** very common: dizziness, somnolence, common: amnesia, aphasia, coordination abnormal, vertigo, paraesthesia, tremor, balance disorders, memory impairment, dysphasia, dysarthria, disturbance in attention, gait disturbance, myoclonus, uncommon: hypokinesia. **Eye disorders:** common: diplopia, blurred vision. **Gastrointestinal disorders:** common: nausea, constipation, dyspepsia, dry mouth, uncommon: dysphagia. **Hepatobiliary disorders:** common: increased liver function tests. **Skin and subcutaneous disorders:** uncommon: skin rash, hyperhidrosis. **Renal and urinary disorders:** common: dysuria, urinary hesitation, haematuria, chromaturia, uncommon: urinary retention, nephrolithiasis. **General disorders and administrative site conditions:** very common: fatigue, common: asthenia, malaise, peripheral oedema. **Basic NHS costs** Initiation packs of 21 x 50 mg tablets and 42 x 100 mg tablets (EU/1/11/681/013) is £24.33. Maintenance packs of 21 and 84 x 50 mg tablets are (EU/1/11/681/001) £4.87 and (EU/1/11/681/002) £19.46 respectively. Maintenance packs of 21 and 84 x 100 mg tablets are (EU/1/11/681/004) £9.73 and (EU/1/11/681/005) £38.93 respectively. Maintenance packs of 84 x 200 mg tablets are (EU/1/11/681/007) £77.86. Maintenance packs of 84 x 300 mg tablets are (EU/1/11/681/009) £116.78. Maintenance packs of 84 x 400 mg tablets are (EU/1/11/681/011) £127.68. **Legal category:** POM. **Marketing authorisation holder** Glaxo Group Limited, Berkeley Avenue, Greenford, Middlesex, UB6 0NN, United Kingdom. **Further information is available from:** Customer contact centre, GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex UB11 1BT. Email: customercontactuk@gsk.com Customer Services Freephone 0800 221441. **Trobal®** is a registered trademark of the GlaxoSmithKline group of companies. All rights reserved. **Prescribing information last revised** September 2011 UK/RTG/0151/11

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to GlaxoSmithKline on 0800 221 441

Reference: 1. Trobal Summary of Product Characteristics. GlaxoSmithKline; 2011.

Julia Granerod and Nicholas Davies describe in their beautifully clear, short review where we are in 2012 with encephalitis, in terms of what causes it and how we can best pursue a diagnosis. This includes a discussion on the realisation that many cases of encephalitis now have an auto-immune basis along with the discovery of new aetiological infective agents that may spread to new geographical areas with global warming.

Christopher Roy explains when and how you would undertake phenol blocks for upper limb spasticity. He describes why this should be considered in place of botulinum toxin injections and what benefit you might expect the patients to see over what time. This is an extremely helpful and practical guide to a procedure that many know very little about.

NF2 is a rare condition which is well known to cause bilateral acoustic neuromas. In the article in the Neurosurgical series Katie Gilkes and Gareth Evans discuss all aspects of this condition starting with making the diagnosis as the genetic defect may only be found in the tumour which may not be a vestibular schwannoma. They go on to discuss that 50% of cases are familial and the rest sporadic and that patients are best managed

by regular follow up in a number of specialised clinics. The article also discusses the use of auditory brainstem implants as well as new drug trials designed to slow down tumour growth in these patients.

Gauten Ambegaonkar in his contribution to the Paediatric Neurology series reminds us about the condition Continuous Slow Wave discharges in slow wave sleep (CSWS). This condition can easily be missed and whilst having several causes often responds to therapy albeit with long term sequelae to the patient. This is a useful practical update on this disorder.

Ever fancied some time in Australia or New Zealand? Rhys Thomas tells you how this may be possible in his short article in the ABNT section. This article includes the experiences of others who have spent time out there honing their neurological skills which can then be used (and recognised!) for good effect once back in the UK.

We have our usual collection of book, conference and journal reviews including two sponsored articles on the use of different types of dopaminergic therapy for Parkinson's Disease (PD). ♦



Roger Barker, Co-Editor.

Roger Barker, Co-Editor,

Clinical CMS Training Fellow Post

Applications are invited for this clinical research fellow post working within the Nationally Commissioned Congenital Myasthenia Service based in Oxford. This is an exciting opportunity to gain clinical experience in neuromuscular disorders and to participate in research with the aim of acquiring a higher degree (MSc or DPhil). In addition the post also entails 2 monthly specialist clinics at Great Ormond Street Hospital.

The post holder will have access to research and training facilities within Oxford University and the Oxford University Hospital NHS Trust. There is opportunity to undertake work within the Neurosciences Group laboratory led by Professor David Beeson at the Weatherall Institute of Molecular Medicine based on the same site. The post holder will also gain skills in presentations and preparation of papers.

The applicant is required to have full GMC registration and have obtained MRCP (UK) or MRCPCH (UK) or equivalent. The post is suited to someone at STR level or who already has a CCT and who is interested in pursuing a career in adult or paediatric neurology or clinical neurophysiology.

For the job description and to apply please contact **julia.goodgame@ouh.nhs.uk**

For further specific details of the job email **jacqueline.palace@ndcn.ox.ac.uk**

The closing date for applications is **Friday 23rd November 2012.**

Interviews will be held on **Tuesday 4th December 2012.**

Approximate start date will be **the end of March 2013.**

Oxford University Hospitals NHS
NHS Trust

CONTENTS

NOVEMBER/DECEMBER 2012

03 Awards and Appointments

04 From the Editor

Review Article

08 Encephalitis: recent advances and challenges ahead

Julia Granerod and Nicholas Davies

Neurosurgery Article

12 Neurofibromatosis Type 2

Katie Gilkes and Gareth Evans

Association of British Neurologists Trainees

18 Australasian Fellowships

Rhys Thomas

Paediatric Neurology

20 Continuous Spike Wave Discharges in Slow-Wave Sleep
– don't let it catch you napping!

Gautam Ambegaonkar

Sponsored Feature

23 Continuous dopaminergic stimulation therapy in advanced
Parkinson's disease: would earlier use be beneficial?

Sponsored Feature

25 2nd Parkinson's Review Meeting

Rehabilitation Article

34 Phenol Block for Upper Limb Spasticity

Christopher W Roy

Regulars

16 Book Reviews

22 Events Diary

26 Conference News

37 Journal Reviews

39 News Review



Cover picture: Nikon Small World Competition 2012, Image of Distinction. Dr Timothy James Mosca, Stanford University, Department of Biology, Stanford, California, USA. The *Drosophila* larval musculature and its innervating neurons and synaptic connections (10x).

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.



The Q-Sense from Medoc

for Quantitative Thermal Sensory Testing (QTST)

Product Features

Comparison to Normative Reference Data
Easy to Interpret Clinical Test Report
Versatile Patient Database & Export Utility
Pre-programmed Test Algorithms
Sensitive and Reproducible

Specifications

Temperature Range: 20 - 50°C
Heating Rate Max 2 °C/sec
Cooling Rate Max 1 °C/Sec
Test Mode: Interval Operated
Thermodes: 30x30
Modalities: CS, WS, HP
Methods: Limits, Levels, TSL

Medoc
advanced medical systems

Competitively priced at £9,995.00.

Available at £7,500.00
for a limited time only.

For further information on the Q Sense please
contact sales@brainvision.co.uk
Tel. 020 8543 0022.

Brain Vision UK Limited, Zeal House,
8 Deer Park Road, London SW19 3GY
www.brainvision.co.uk

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 Neuroimmunology at Cambridge University. He works on experimental immunological therapies in multiple sclerosis.



Mike Zandi is co-editor of ACNR and Specialist Registrar in Neurology at Addenbrooke's Hospital, Cambridge. He trained in Cambridge, Norwich and London. He is interested in clinical and experimental neuroimmunology.



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.



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 microdissection. 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.

Episenta® (sodium valproate) Prescribers should consult the Summary of Product Characteristics before prescribing Episenta®

Sodium valproate available as Episenta® 150 or 300mg Prolonged-release Capsules, Episenta® Sachets containing 500mg or 1000mg Prolonged-release Granules and Episenta® 100mg/ml Solution for Injection. **Indication:** Epilepsy. **Solution for injection:** For use in patients normally maintained on oral sodium valproate but temporarily not possible. **Oral:** For treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to valproate for acute mania. **Dose and Administration:** **Epilepsy:** **Oral:** **Monotherapy:** **Adults:** 600mg daily increasing by 150-300mg at 3-day intervals until controlled; usual dose range 1000mg to 2000mg/day. Max dose 2500mg/day. **Children >20kg:** 300mg/day increasing until controlled; usual dose range 20-30mg/kg/day. Max dose 35mg/kg/day. **Children <20kg:** 20mg/kg per day; in severe cases up to 40mg/kg/day. Daily dosage should be given in 1-2 single doses. Contents of the capsule/sachet may be sprinkled or stirred into soft food or drinks (cold or room temperature) and swallowed immediately without chewing or crushing the granules. Changing from sodium valproate enteric coated tablets to Episenta®, keep the same daily dose. **Elderly:** Care when adjusting dosage. Dosage should be determined by seizure control. **Renal insufficiency:** May be necessary to decrease dosage. **Hepatic insufficiency:** see Contraindications, Warnings and Precautions and Undesirable effects. Salicylates should not be used concomitantly. **Combined Therapy:** Start Episenta® in patients already on anticonvulsants gradually. Target dose reached after about 2 weeks. In combination with barbiturates, barbiturate dose should be reduced, particularly if sedation observed. **Solution for injection:** **Adults:** 400-800mg daily increasing by 150-300mg at 3-day intervals until controlled; usual dose range 1000mg to 2000mg/day. Max dose 2500mg/day. **Children:** 300mg/day increasing until controlled; usual dose range 20-30mg/kg/day. Max dose 40mg/kg/day, only in patients in whom plasma levels can be monitored. Above 40mg/kg/day clinical chemistry and haematology should be monitored. Patients already satisfactorily treated with oral continue at current dosage. The total daily dose divided into 3-4 single slow intravenous injections or given by continuous or repeated infusion. Should not be administered via same line with other drugs. Should be replaced with oral therapy as soon as practicable. Close monitoring of plasma levels required during therapy and when changing to/from parenteral therapy. **Manic episodes:** **Adults:** initial daily dose 750mg or 20mg/kg body weight, rapid dose increase if possible, mean daily dose btw. 1000 and 2000mg. Patients receiving daily doses higher than 45mg/kg/day body weight should be carefully monitored. **Contraindications:** Active liver disease; History of severe hepatic dysfunction, especially drug related; Porphyria; Hypersensitivity to valproate or excipients. **Warnings and Precautions:** Monitor for signs of suicidal ideation/behaviour. Discontinue gradually. Patients should be closely monitored for early signs of liver damage. Use with carbapenem not recommended. Risk of severe liver damage, including fatal hepatic failure; children <3 years most at risk especially with multiple anticonvulsants, severe seizure disorders, organic brain disease, diseases associated with mental retardation. Avoid concomitant salicylates in children <3 years. Salicylates should not be used in children <16 years. Measure liver function before treatment and during the first 6 months. Risk of severe or fatal pancreatitis, particularly young children; risk decreases with increasing age. Blood cell count, platelet count, bleeding time and coagulation tests recommended prior starting therapy before surgery, or if spontaneous bruising/bleeding. Caution in patients with systemic lupus erythematosus. Risk of hyperammonaemia in patients with urea cycle enzymatic deficiency. Risk of weight gain. Caution in women of childbearing potential. **Interactions:** Episenta® on other drugs: may potentiate psychotropics, e.g. antipsychotics, monoamine oxidase inhibitors, antidepressants, benzodiazepines. Increases phenobarbital concentrations which may cause sedation particularly in children. Increases primidone levels exacerbating side effects. Phenytoin total levels decreased, the free form is increased leading to possible overdose symptoms. Toxic effects of carbamazepine may be potentiated. May reduce lamotrigine metabolism and increase its mean half-life. May raise zidovudine concentrations leading to increased toxicity. Anticoagulant effect of warfarin and other coumarin anticoagulants may be increased. **Effects of other drugs on Episenta®:** Antiepileptics with enzyme inducing effects e.g. phenytoin, phenobarbital, carbamazepine, decrease levels. Combination with felbamate may increase levels. Mefloquine and chloroquine increases metabolism. Levels may be increased with highly protein bound agents e.g. acetylsalicylic acid. Levels may be increased with cimetidine/erythromycin. Decreased levels with carbapenem. Colestyramine may decrease absorption. Rifampicin may decrease levels. **Other interactions:** No enzyme-inducing effect. Does not reduce efficacy of oestrogenic agents including oral contraceptive pill. Caution in combination with newer antiepileptics. Coadministration with topiramate has been associated with encephalopathy/hyperammonaemia. **Pregnancy and Lactation:** **Women of childbearing potential should not be started on Episenta® without specialist neurological advice.** Women who are taking Episenta® who may become pregnant should receive specialist neurological advice and the benefits should be weighed against risks. Increased incidence of minor and major malformations in children born to mothers treated with valproate. When Episenta® treatment is deemed necessary, precautions to minimize the potential teratogenic risks should be followed. Very rare cases of haemorrhagic syndrome have been reported in neonates. Lactation: Small quantities of valproic acid pass into breast milk (1-10% of the maternal serum level). The safety profile of Episenta® and particularly possible haematological risks must be taken into account. **Manic episode additionally:** Valproate should not be used in pregnant women or women of childbearing age unless clearly necessary. **Effects on ability to drive and use machines:** Reaction time may be altered at start of treatment, at higher doses or with combination of other centrally acting drugs. Risk of transient drowsiness especially when taken during anticonvulsant polytherapy, with benzodiazepines or with alcohol. **Undesirable effects:** Frequently reported side effects include: nausea; gastralgia; diarrhoea; increased liver enzymes; hyperammonaemia without change in liver function; thrombocytopenia; transient hair loss; weight gain (risk factor for the development of a polycystic ovary syndrome, therefore requires careful monitoring). When using Episenta® intravenously, transient nausea or dizziness may occur. The following side effects have also been reported: hepatic dysfunction; severe liver damage including hepatic failure; pancreatitis; sedation; lethargy; stupor with/without hallucinations/convulsions; encephalopathy; coma; reversible extrapyramidal symptoms; reversible dementia with reversible cerebral atrophy; ataxia; fine postural tremor; aggression; hyperactivity; behavioural deterioration; hyponatraemia; hyperammonaemia with clinical presentation of vomiting, ataxia and increase in clouding of consciousness; anaemia; leucopenia; pancytopenia; bone marrow failure, including red cell aplasia; agranulocytosis; reduction in blood fibrinogen and/or increase in prothrombin time; spontaneous bruising/bleeding; rash; toxic epidermal necrolysis; Stevens-Johnson syndrome; erythema multiforme; hirsutism; acne; decrease in bone mineral density, osteopenia, osteoporosis and fractures in long-term therapy; amenorrhoea; irregular periods; gynaecomastia; vasculitis; reversible or irreversible hearing loss; reversible Fanconi's syndrome; enuresis; angioedema; Drug Rash with Eosinophilia, Systemic Symptoms (DRESS syndrome); allergic reactions (rash to hypersensitivity reaction); non-severe peripheral oedema. **Pack sizes and NHS price:** Packs of 100, 150mg capsules £7.00 [PL14040/0024]; Packs of 100, 300mg capsules £13.00 [PL14040/0025]; Packs of 100, 500mg sachets £21.00 [PL14040/0026]; Packs of 100, 1000mg sachets £41.00 [PL14040/0027]. Packs of 5, 3ml ampoules 100mg/ml solution for injection £35.00 [PL14040/0028]. **Legal category:** POM. **Marketing Authorisation Holder:** Desitin Arzneimittel GmbH Weg beim Jäger 214 D-22335 Hamburg Germany. **Prepared in:** July 2012. For further information on Episenta® please contact Medical Information on MedInfo@desitin.co.uk

References:

1. Episenta® Summary of Product Characteristics 2012.
2. Retzow A et al. *Arzneim-Forsch/Drug Res* 1997;47(II):1347-1350.
3. MIMS, July 2012.





Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Desitin Pharma Limited on MedInfo@desitin.co.uk



UK/EP/12/0011 Date of preparation: August 2012.

At the centre of managing epilepsy – is a treatment your patient should take



-  **Unique mini-tablet formulation: An innovative way of delivering sodium valproate**
-  **Extended release provides once daily evening dosage option**
-  **Easy to swallow – can be taken with food or drinks^{1,2}**
-  **Lower cost than extended release oral forms of leading sodium valproate³**

Prescribing information can be found opposite.

O.D. or B.D.
Episenta®
Prolonged release
sodium valproate 

Tried, tested and cost-effective control

A decision to use Episenta® in women of childbearing potential should not be taken without specialist neurological advice, and only if the benefits outweigh the potential risks to the unborn child. See Summary of Product Characteristics for more information.

Encephalitis: recent advances and challenges ahead



Julia Granerod

is an Epidemiologist at the Health Protection Agency. Julia obtained her first degree in Medical Microbiology (Hons) at the University of Edinburgh and subsequently went on to complete a Masters in Clinical Tropical Microbiology at University College London. She has spent time in both Thailand and Tanzania working on infectious disease epidemiology. For the last seven years Julia's work has focused on encephalitis. She completed a PhD on the incidence and causes of encephalitis in England at the London School of Hygiene and Tropical Medicine. She was the lead scientist and national coordinator of a multicentre prospective study of encephalitis in England and has received a further grant to continue with various encephalitis projects. She has published numerous peer reviewed papers and is a Member of the Professional Advisory Panel for the Encephalitis Society.



Nicholas Davies

Nicholas Davies is a Consultant Neurologist at Chelsea & Westminster and Charing Cross Hospitals in London, UK. He trained in neurology in London and HIV neurology in Sydney, Australia. His subspecialty interest is neurological infection.

Correspondence to:

Dr Julia Granerod, PhD,
Health Protection Agency,
Microbiology Services Division:
Colindale,
Virus Reference Department,
61 Colindale Avenue,
London NW9 5EQ, UK.
Tel: 0208 327 7060,
Email: Julia.granerod@HPA.org.uk

Introduction

Coma accompanying fever, which now would be termed encephalitis, was described by Sydenham as early as the 17th century, although associations between fever and brain dysfunction were recognised even earlier.¹ Since then, much progress has been made in understanding the causes, biological mechanisms, epidemiology and treatment of encephalitis; however, numerous gaps still exist in our knowledge: there is still a long way to go.

One reason for the increased interest in encephalitis is the recognition that it is a sentinel condition for new and emerging infections (Table 1). Consequently numerous national studies have been implemented in different continents to investigate its aetiology and epidemiology.^{2,5} The recent discovery of antibody-associated forms of encephalitis has given added impetus to this effort. Other reviews have described what is already known about encephalitis.^{6,7} This paper will focus on the challenges faced in studying encephalitis and recent advances of direct clinical relevance that have occurred in the field.

Importance

Although considered a rare syndrome in resource-rich settings, the incidence of encephalitis is likely to be higher than previously estimated. It was estimated that only 700 cases of encephalitis occur per year in England;⁸ however, new data suggest that this is an underestimate and that the occurrence of encephalitis is substantially higher (Granerod et al., submitted). Outcomes remain poor: over one-third of encephalitis patients recruited to a multicentre prospective study of encephalitis in England either died or were left with severe disabilities.² The median age of patients in this study was only 30 years; 34% of cases occurred in children <18 years of age. Other studies have shown similarly poor outcomes. In a contemporary French study 10% of patients died in the acute phase of the illness.³ After three years follow-up of 167 surviving patients, a further nine patients had died of encephalitis-related causes and 15% were severely impaired or in a vegetative state.⁹ It is estimated that ~70,000 cases of Japanese encephalitis (JE), considered the most important of the viral encephalitides in Asia, occur annually in the 24 JE-endemic countries.¹⁰ This is predominantly a disease of children; approximately 20–30% of cases are fatal and 30–50% of survivors have significant neurological sequelae.¹⁰ Survivors who make a seemingly good recovery are often left with milder impairments that impact upon quality of life. Encephalitis has significant implications

not only for patients directly but also wider economic and public health implications.

Current problems

Encephalitis is challenging to diagnose, manage and study. It is a syndrome of multiple aetiologies and pathogeneses. Pathogenetic mechanisms for the parenchymal inflammation of encephalitis range from direct infectious to immune-mediated; however, specific mechanisms within each of these groups are diverse and often incompletely understood. For example, *Mycoplasma pneumoniae* is increasingly implicated in encephalitis; however, its exact role (i.e. whether through direct infection or as a trigger for immune-mediated disease) remains controversial due to incomplete understanding of the biology of the organism and host immune response to it, and inherent limitations of its specific microbiological diagnostic test in the context of central nervous system (CNS) disease.^{11–13}

Despite greater than 100 known causes, in most cases of encephalitis neither a pathogenetic mechanism nor aetiology is identified. Accurate and complete case ascertainment of encephalitis cases is made difficult by the complexity of the syndrome, difficulties in distinguishing it from non-encephalitis mimics, and the lack of standard clinical case definitions. There is no standard laboratory diagnostic algorithm for encephalitis in the United Kingdom (UK); although most laboratories test for herpes simplex virus (HSV), varicella zoster virus (VZV) and enteroviruses nucleic acid sequences in the cerebrospinal fluid (CSF) of immunocompetent patients. This practice is supported in the recently published National Guidelines for the Management of Suspected Viral Encephalitis in the UK.¹⁴ Testing beyond this varies greatly between centres. To complicate matters further, the test specificity following detection of some viruses, such as lymphotropic herpes viruses (EBV; CMV; HHV-6), in CSF is much lower than for the neurotropic herpesviruses (HSV; VZV). For certain viruses, such as EBV, calculation of the CSF EBV viral load can be helpful: higher values are more likely indicative of aetiological significance.¹⁵ However, one pitfall for the diagnostician and researcher is HHV-6. A minority of patients have chromosomal integration of HHV-6 DNA; such patients have consistently high levels of HHV-6 DNA in CSF, blood and plasma.^{16,17} For other agents, such as West Nile Virus (WNV), detection of an acute serological response in CSF or serum provides strong evidence for causality. Although written primarily for epidemiological studies proposed diagnostic criteria for infectious aetiologies of

Table 1 – Emerging viral encephalitides

Infectious agent	First emerged/endemic	Subsequent spread
Japanese encephalitis	Endemic in Asia	Northern Australia and parts of the Western Pacific: 1995 – Torres Strait 1998 – Badu & mainland Australia (Cape York)
Nipah virus	1999 - Malaysia	2001 & 2003 - Bangladesh
Hendra virus	1994 – Brisbane, Australia	Queensland & New South Wales
Avian influenza A virus	2004 – Vietnam	
Australian bat lyssavirus	1996 - Australia	
European bat lyssavirus	2002 - Scotland	
Tick-borne encephalitis virus	Czech Republic, Estonia, Latvia, Lithuania, Russia and Slovenia, Germany, Poland, Switzerland, Sweden, Finland, Slovakia and Hungary	Denmark, France, Greece, Italy, Norway and Turkey
Murray Valley encephalitis virus	Early 20th century - Australia's east coast	1951 & 1974 - re-emerged as epidemics in the Murray-Darling River basin Now considered enzootic in the Kimberley and possibly the adjacent areas of the Northern Territory. Reappearance in central Australia and western NSW in 2000–2001.
West Nile virus	1999 - Western hemisphere	Across North America and as far south as Argentina
WNV (Kunjin clade)	1960 - Northern Queensland, Australia	Across tropical northern Queensland, the Northern Territory and Western Australia

encephalitis may aid the clinician in interpreting these laboratory results.¹⁸

Emerging infections

There is growing evidence that an increasing number of viruses can cause encephalitis in human hosts (Table 1). Many recently emerged zoonotic viruses, including Hendra virus and Australian bat lyssavirus, have presented with an encephalitic syndrome in humans.¹⁹ European bat lyssavirus resulted in the death of a man from rabies in Scotland in 2002.²⁰ Two outbreaks that occurred in Bangladesh in 2001 and 2003 marked the re-emergence of Nipah virus encephalitis.²¹ A Vietnamese child, whose death in 2004 was reported to be from encephalitis of unknown cause, was later found to be infected with avian influenza H5N1, suggesting a wider clinical spectrum than previously recognised for this microbe.²² The 1999 outbreak in New York marked the detection of WNV in the Western hemisphere for the first time; it has since spread across America and as far south as Argentina.²³ Although some aetiological agents are at present geographically restricted, global warming, ecological change, and an increase in international travel may help infectious agents to cross boundaries. The experience of WNV in North America illustrates the potential for diseases to be introduced to new areas if the vectors are present and the environment supportive.²⁴ Hypothetically, new infectious causes could be found amongst the many encephalitis cases of unknown aetiology. Clinicians are encouraged to notify cases of acute encephalitis, as the prime purpose of the statutory notification system is to allow for rapid detection of potential outbreaks and epidemics.

Aetiological developments

Determining aetiology is a key first step to improve patient outcome. Several recent advances in the field of encephalitis are perti-

nent to the large proportion of cases of unknown cause.

A recent study by the Health Protection Agency (HPA) showed that systematic and extensive testing in a prospective cohort significantly reduced the proportion of cases of unknown aetiology from 60% previously described to 37%.²⁸ It highlighted the importance of rigorous investigation for known causes of encephalitis – achieved in this study by involvement of a wide multidisciplinary team with expertise ranging from the clinical to laboratory.

The HPA study represents the largest prospective cohort of encephalitis patients to date in the British Isles. HSV was confirmed as the most common known aetiological agent, consistent with the findings of other international studies.³ It reinforces maintaining a low threshold for initiating acyclovir treatment in patients with suspected encephalitis. Interestingly of 38 HSV cases, three were diagnosed through detection of intrathecal production of HSV-specific antibody; these samples were PCR negative and would have been missed using only the latter diagnostic technique.²⁵ Sampling CSF early (<3 days after the onset of neurological symptoms) or late (>14 days) in the disease course reduces the probability of a positive viral PCR.²⁶ Thus, if CSF HSV PCR is not performed acutely, a later CSF and serum, taken 10–14 days after symptom onset, should be tested for intrathecal production of HSV antibodies to confirm the diagnosis.¹⁴

Arguably the most important recent aetiological development in the field of encephalitis is the recognition of antibody-associated forms of encephalitis, in particular N-methyl-D-aspartate receptor (NMDAR)-antibodies and voltage-gated potassium channel (VGKC)-complex antibodies. In the HPA study almost 10% of all encephalitis cases were associated with these antibodies. This was the first study to highlight their significance

within a cohort of encephalitis patients, suggesting that they are more common than initially thought and emphasising the importance of considering this diagnosis, especially in patients with prominent seizures, normal cranial imaging, absence of fever, and only mild CSF pleocytosis. These syndromes are amenable to treatment if it is initiated promptly. Almost 60% of patients with antibody-associated encephalitis in the HPA study either died or were left severely disabled; their antibody status was only recognised retrospectively at the end of the study.²

The California Encephalitis Project (CEP), initiated in 1998 to study the epidemiology and aetiology of encephalitis in California, has reported similar findings.⁴ Since 2007, when NMDAR-antibodies were first reported, cases of encephalitis of uncertain aetiology in individuals ≤30 years of age referred to CEP have been tested for these antibodies. The frequency of NMDAR-antibody encephalitis was found to surpass that of individual viral aetiologies, including HSV.²⁷

Antibody-associated encephalitis

There has been enormous interest over the last few years from researchers worldwide with regard to encephalitis associated with antibodies that target synaptic proteins. As mentioned above, the most common type is NMDAR-antibody encephalitis, followed by encephalitis associated with leucine-rich glioma inactivated 1 (LG11) antibodies.²⁸ Encephalitis has also been associated with antibodies to another VGKC-complex protein, namely contactin-associated protein-like 2 (CASPR-2). Still further antibodies have been described in limbic encephalitis, including those to alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and gamma-aminobutyric acid-B (GABA_B) receptors. More recently, antibodies to metabotropic glutamate receptor 5 (mGluR5) have been described in limbic encephalitis, as have anti-

bodies to white matter glial or myelin antigens in acute disseminated encephalomyelitis.²⁹ The field of antibody-mediated CNS disease is only in gestation; more antibody-associated syndromes may yet be identified amongst the many encephalitis cases of unknown cause. Rapidity of testing for antibody-associated encephalitis will be considerably assisted with the development of commercial assays. It is hoped that these will soon be available.²⁹

Other developments

The recent HPA study led to the development of published clinical and aetiological case definitions, which informed how cases were classified.¹⁸ These present the UK perspective on aetiological case definitions for acute encephalitis; they include immune-mediated causes. Wide usage of these definitions is encouraged to facilitate better comparison between studies. They are the basis for an International Working Group that aims to determine by consensus an optimal set of criteria/case definitions to recommend for use in clinical practice, public health, and research internationally.

Within the UK a major practice development is the recent publication of National Guidelines for the Management of Suspected Viral Encephalitis in Adults and Children, briefly referred to above.^{14,30} The guidance covers initial investigation of all patients with suspected acute encephalitis; it includes specific management advice for the viral encephalitides, particularly HSV, VZV and enteroviral encephalitis; as well as advice for assessment of encephalitis in the immunosuppressed and returning traveller. A management algorithm is included modelled on the successful guidance for management of suspected bacterial meningitis. It can be downloaded from: <http://www.braininfectionsuk.org/resources/documents/YJINF2823.pdf>.

Whilst high dose intravenous acyclovir is well established as treatment for HSV encephalitis the role of other treatments, such as steroids, are not.^{31,32} There is circumstantial and animal model evidence to suggest that corticosteroids with acyclovir might improve clinical outcome in HSV encephalitis.³³ The German trial of Acyclovir and Corticosteroids in Herpes-simplex-virus-Encephalitis (GACHE) is a multicentre, multinational, randomised, double-blind, placebo-controlled trial that aims to assess the efficacy of acyclovir and corticosteroids in the treatment of HSV encephalitis; it is recruiting at present.³⁴

Challenges ahead

Despite numerous advances in the field of encephalitis, many challenges remain. Cases of unknown aetiology still form the largest subgroup. Virus discovery methods, which sought to amplify nucleic acid sequences of novel pathogens, did not prove fruitful in the HPA study. However, almost a quarter of unknown cases were shown to have intrathecal synthesis of IgG, for which antigenic specificity was not found following screening against a battery of microbial antigens.²⁵ The presence of intrathecal IgG gives weight to an inflammatory or infective

pathogenesis in these cases – they are less likely to be non-inflammatory syndromic mimics. Studying the antigenic specificity of intrathecal IgG could provide clues to the cause in these cases.³⁵ Future studies could use peptide libraries to seek putative antigenic targets for CSF antibodies: such a technique might reveal novel infectious or autoimmune aetiologies.

For sporadic and epidemic causes of infectious encephalitis it is not understood why only a minority of individuals exposed to an infection develop encephalitis – the majority of encephalitic patients are not immunosuppressed. Host and pathogen-related factors are likely to be important. It has been shown in horses that a naturally occurring variation in a single amino acid position of the viral DNA polymerase enzyme results in differing pathogenic potential of a herpesvirus.^{36,37} Whether distinct strains of human HSV differ in their pathogenic capacity has yet clearly to be established in cases of HSV encephalitis. Host factors are increasingly implicated in encephalitis. Alleles in the innate immune effectors TLR3 and UNC93B have been identified that mediate susceptibility to herpes encephalitis in children.^{38,39} Further studies to address both pathogen neurovirulence and host susceptibility could increase our understanding of the pathogenesis of encephalitis, perhaps even providing potential targets for novel treatment strategies.

The HPA study showed that rigorous and systematic laboratory testing in a prospective study reduced the proportion of cases of unknown aetiology. Now a standard diagnostic algorithm for laboratory investigation is needed incorporating testing for infectious and antibody-associated causes. Such a development should be combined with improved access to specialist diagnostic tests performed in centres participating in rigorous quality control programmes.

Research and development programmes are currently underway in the UK addressing some of these issues. A major new NIHR programme grant on "Understanding and improving the outcome of encephalitis" is being co-ordinated by the Brain Infections Group in Liverpool. Further research co-ordinated by the HPA is underway to better define associations between neuroimaging results and specific encephalitis aetiologies, and to assess specific post-encephalitic morbidities in the UK. Furthermore, multicentre prospective studies in other parts of the world, including Australia, are underway to study aetiology seeking emerging infections.


Conclusions

Encephalitis has only recently become a priority for researchers, funders and policy makers. Recent research, particularly the emerging field of antibody-mediated CNS disease, has decreased the proportion of cases of unknown aetiology. But the proportion of encephalitic patients for whom no aetiology is found remains unacceptably high. Both novel infectious aetiologies and new antigenic targets for immune-mediated encephalitis could underlie these cases. Recent advances are encouraging but there is still a way to go. ♦

REFERENCES

1. Sydenham T. *Of the continued fever of the years 1673, 1674, 1675*. Wallis G, ed. The work of Thomas Sydenham MD on acute and chronic disease with annotations by George Wallis. London: Robinson, Otridge, Hayes & Newbery; 1788. 299.
2. Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D et al. *Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study*. *Lancet Infect Dis* 2010;10(12):835-44.
3. Mailles A, Stahl JP. *Infectious encephalitis in France in 2007: a national prospective study*. *Clin Infect Dis* 2009;49(12):1838-47.
4. Glaser CA, Honarmand S, Anderson LJ, Schnurr DP, Forghani B, Cossen CK et al. *Beyond viruses: clinical profiles and etiologies associated with encephalitis*. *Clin Infect Dis* 2006;43(12):1565-77.
5. Huppatz C, Durrheim DN, Levi C, Dalton C, Williams D, Clements MS et al. *Etiology of encephalitis in Australia, 1990-2007*. *Emerg Infect Dis* 2009;15(9):1359-65.
6. Granerod J, Crowcroft NS. *The epidemiology of acute encephalitis*. *Neuropsychol Rehabil* 2007;17(4-5):406-28.
7. Granerod J, Tam CC, Crowcroft NS, Davies NWS, Borchert M, Thomas SL. *Challenge of the unknown: a systematic review of acute encephalitis in non-outbreak situations*. *Neurology* 2010;75:924-32.
8. Davison KL, Crowcroft NS, Ramsay ME, Brown DW, Andrews NJ. *Viral encephalitis in England, 1989-1998: what did we miss?* *Emerg Infect Dis* 2003;9(2):234-40.
9. Mailles A, De Broucker T, Costanzo P, Martinez-Almoyra L, Vaillant V, Stahl JP. *Long-term outcome of patients presenting with acute infectious encephalitis of various causes in France*. *Clin Infect Dis* 2012;54(10):1455-64.
10. Campbell GL, Hills SL, Fischer M, Jacobson JA, Hoke CH, Hombach JM et al. *Estimated global incidence of Japanese encephalitis: a systematic review*. *Bull World Health Organ* 2011;89(10):766-74.
11. Lewis P, Glaser CA. *Encephalitis*. *Pediatr Rev* 2005;26(10):353-63.
12. Kolksi H, Ford-Jones EL, Richardson S, Petric M, Nelson S, Jamieson F et al. *Etiology of acute childhood encephalitis at The Hospital for Sick Children, Toronto, 1994-1995*. *Clin Infect Dis* 1998;26(2):398-409.
13. Bitnun A, Richardson SE. *Mycoplasma pneumoniae: Innocent Bystander or a True Cause of Central Nervous System Disease?* *Curr Infect Dis Rep* 2010;12(4):282-90.
14. Solomon T, Michael BD, Smith PE, Sanderson F, Davies NW, Hart IJ et al. *Management of suspected viral encephalitis in adults—Association of British Neurologists and British Infection Association National Guidelines*. *J Infect* 2012;64(4):347-73.
15. Majid A, Galetta SL, Sweeney CJ, Robinson C, Mahalingham R, Smith J et al. *Epstein-Barr virus myeloradiculitis and encephalomyeloradiculitis*. *Brain* 2002;125(1):159-65.
16. Ward KN, Leong HN, Nacheva EP, Howard J, Atkinson CE, Davies NW et al. *Human herpesvirus 6 chromosomal integration in immunocompetent patients results in high levels of viral DNA in blood, sera, and hair follicles*. *J Clin Microbiol* 2006;44:1571-4.

17. Isaacson E, Glaser CA, Forghani B, Amad Z, Wallace M, Armstrong RW et al. *Evidence of human herpesvirus 6 infection in 4 immunocompetent patients with encephalitis*. Clin Infect Dis 2005;40(6):890-3.
18. Granerod J, Cunningham R, Zuckerman M, Mutton K, Davies NW, Walsh AL et al. *Causality in acute encephalitis: defining aetiologies*. Epidemiol Infect 2010;138(6):783-800.
19. Paterson BJ, Mackenzie JS, Durrheim DN, Smith D. *A review of the epidemiology and surveillance of viral zoonotic encephalitis and the impact on human health in Australia*. NSW Public Health Bull 2011;22(5-6):99-104.
20. Warrell MJ, Warrell DA. *Rabies and other lyssavirus diseases*. Lancet 2004;363(9413):959-69.
21. Hsu VP, Hossain MJ, Parashar UD, Ali MM, Ksiazek TG, Kuzmin I et al. *Nipah virus encephalitis reemergence, Bangladesh*. Emerg Infect Dis 2004;10(12):2082-7.
22. de Jong MD, Bach VC, Phan TQ, Vo MH, Tran TT, Nguyen BH et al. *Fatal avian influenza A (H5N1) in a child presenting with diarrhea followed by coma*. N Engl J Med 2005;352(7):686-91.
23. Petersen LR, Hayes EB. *West Nile virus in the Americas*. Med Clin North Am 2008;92:1307-22.
24. Campbell GL, Marfin AA, Lanciotti RS, Gubler DJ. *West Nile virus*. Lancet Infect Dis 2002;2(9):519-29.
25. Ambrose HE, Granerod J, Clewley JP, Davies NW, Keir G, Cunningham R et al. *Diagnostic strategy used to establish etiologies of encephalitis in a prospective cohort of patients in England*. J Clin Microbiol 2011;49(10):3576-83.
26. Davies NWS, Brown LJ, Gonde J, Irish D, Robinson RO, Swan AV et al. *Factors influencing PCR detection of viruses in cerebrospinal fluid of patients with suspected CNS infections*. J Neurol Neurosurg Psychiatry 2005;76:82-7.
27. Gable MS, Sheriff H, Dalmau J, Tilley DH, Glaser CA. *The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project*. Clin Infect Dis 2012;54(7):899-904.
28. Graus F, Dalmau J. *CNS autoimmunity: new findings and pending issues*. Lancet Neurol 2012;11(1):17-19.
29. Zuliani L, Graus F, Giometto B, Bien C, Vincent A. *Central nervous system neuronal surface antibody associated syndromes: review and guidelines for recognition*. J Neurol Neurosurg Psychiatry 2012;83:638-45.
30. Kneen R, Michael BD, Menson E, Mehta B, Easton A, Hemingway C et al. *Management of suspected viral encephalitis in children - Association of British Neurologists and British Paediatric Allergy, Immunology and Infection Group national guidelines*. J Infect 2012;64(5):449-77.
31. Skolden B, Forsgren M, Alestig K, Bergstrom T, Burman L, Dahlqvist E et al. *Acyclovir versus vidarabine in herpes simplex encephalitis. Randomised multicentre study in consecutive Swedish patients*. Lancet 1984;2(8405):707-11.
32. Whitley RJ, Alford CA, Hirsch MS, Schooley RT, Luby JP, Aoki FY et al. *Vidarabine versus acyclovir therapy in herpes simplex encephalitis*. N Engl J Med 1986;314(3):144-9.
33. Meyding-Lamade UK, Oberlinner C, Rau PR, Seyfer S, Heiland S, Sellner J et al. *Experimental herpes simplex virus encephalitis: a combination therapy of acyclovir and glucocorticoids reduces long-term magnetic resonance imaging abnormalities*. J Neurovirol 2003;9(1):118-25.
34. Martinez-Torres F, Menon S, Pritsch M, Victor N, Jenetzky E, Jensen K et al. *Protocol for German trial of Acyclovir and corticosteroids in Herpes-simplex-virus-encephalitis (GACHE): a multicenter, multinational, randomized, double-blind, placebo-controlled German, Austrian and Dutch trial [ISRCTN45122933]*. BMC Neurol 2008;8:40.
35. Burgoon MP, Owens GP, Carlson S, Maybach AL, Gilden DH. *Antigen discovery in chronic human inflammatory central nervous system disease: panning phage-displayed antigen libraries identifies the targets of central nervous system-derived IgG in subacute sclerosing panencephalitis*. J Immunol 2001;167(10):6009-14.
36. Goodman LB, Leregian A, Perkins GA, Nugent J, Buckles EL, Mercorelli B et al. *A point mutation in a herpesvirus polymerase determines neuropathogenicity*. PLoS Pathog 2007;3(11):e160.
37. Nugent J, Birch-Machin I, Smith KC, Mumford JA, Swann Z, Newton JR et al. *Analysis of equid herpesvirus 1 strain variation reveals a point mutation of the DNA polymerase strongly associated with neuropathogenic versus nonneuropathogenic disease outbreaks*. J Virol 2006;80(8):4047-60.
38. Luring AS, Cheng HH, Eiden MV, Overbaugh J. *Genetic and biochemical analyses of Pti1 determinants for FeLV-T suggest a novel mechanism for entry*. J Virol 2002;76:8069-78.
39. Webster DR, Hekele AG, Luring AS, Fischer KF, Li H, Andino R et al. *An enhanced single base extension technique for the analysis of complex viral populations*. PLoS One 2009;4:e7453.



The Encephalitis Society
Support, Awareness & Research for Inflammation of the Brain

The Encephalitis Society Professional Seminar

VIP Launch of New Diagnostic Algorithm and Management Guidelines for Encephalitis

Keynote Topics:

- Diagnosis and Management of Encephalitis in Adults and Children
- Co-existent Infection and Antibodies in Encephalitis
- Patient Outcome and Experiences of Encephalitis
- Patient and Public Involvement

Monday 3rd December 2012
13.30 – 18.00 (to include a cheese & wine reception)

CPD Approval - 4 credits
By the Royal Colleges of Physicians

For more information please contact
admin@encephalitis.info or call 01653 692583

Brain Ageing and Dementia in Developing Countries

4-7 December 2012
Safari Park Hotel, Nairobi, Kenya



An International Symposium on 'Brain Ageing and Dementia in Developing Countries' will be held in Nairobi, Kenya. This second symposium to be hosted by the WFN Research Group on Dementia is particularly aimed at attracting participants interested in dementing illness in the developing world.

Contacts:
Email: advvascular@ncl.ac.uk
Website: <http://advvascular.ncl.ac.uk>



Neurofibromatosis Type 2



Katie Gilkes

is a Consultant Neurosurgeon, specialising in skull base and pituitary surgery at the Walton Centre for Neurosciences, Liverpool. She completed her neurosurgical training in Bristol and Plymouth; followed by fellowships in pituitary surgery at the National Hospital for Neurology and Neurosurgery and in Manchester with the skull base and NF2 services.



Prof Gareth Evans

has established a national and international reputation in clinical and research aspects of cancer genetics, particularly in neurofibromatosis and breast cancer. He has published 477 peer reviewed research publications; 180 as first or senior author, with over 100 on neurofibromatosis. He has lead a successful bid for a Nationally funded NF2 service (£7.5 million pa) that started in 2010 and is involved in the national complex NFI service.

Correspondence to:

Miss Katie Gilkes,
Department of Neurosurgery,
Walton Centre for Neurology and
Neurosurgery,
Lower Lane,
Liverpool L9 7LJ, UK.

Neurofibromatosis is the umbrella term for three distinct genetic disorders (NF1, NF2 and Schwannomatosis) that share the hall mark of tumour growth on the tissues surrounding nerves. It is a misnomer in Neurofibromatosis type 2 (NF2), as the predominant tumours are schwannomas and meningiomas.

Epidemiology

The birth incidence of NF2 is 1 in 33,000 and prevalence, 1 in 60,000.¹ There is no predilection for sex, race or ethnic origin. Approximately half of the cases are familial and half are sporadic,² due to a spontaneous mutation in the NF2 gene.

Diagnostic criteria

The first case report of neurofibromatosis appeared in the early 19th century. It gradually became clear that there were two clinically distinct entities, 'peripheral neurofibromatosis', or von Recklinghausen's disease and 'central neurofibromatosis'. It wasn't until 1987 that these were described as NF1 and NF2 respectively and diagnostic criteria were established.³ These have subsequently been reviewed and updated in 1990,⁴ 1997 (Box 1)⁵ and most recently in 2011 (Box 2).⁶

The diagnosis of NF2 remains clinical, although in most cases can be confirmed with molecular testing. All of the tissues may not be affected and all the potential genetic mutations have not been identified for a reliable genetic test. The diagnosis can therefore take years as many of the features are age dependant. The hall mark is bilateral vestibular schwannomas. The numerous changes to the diagnostic criteria reflect the difficulty in establishing a confident diagnosis as early as possible in those who do not (yet) have bilateral vestibular schwannomas, or a positive family history. The most recent (Baser) criteria are listed in Box 2. They incorporate mutation testing for those with 'probable' NF2 and have a diagnostic sensitivity of 79% and a specificity of 100%.⁶

Genetics

The NF2 gene is a tumour suppressor gene located on the long arm of Chromosome 22 (22q12.2). It was discovered independently by two teams who named the encoded protein merlin⁷ and schwannomin⁸ respectively. This is expressed in many different cells including neurons, schwann cells, fibroblasts and some

Box 1 – The National Neurofibromatosis Foundation Diagnostic criteria for NF2, 1997 (5)

Confirmed or definite NF2:

- A Bilateral VS
- Or
- B First degree family relative with NF2 and: Unilateral VS at <30y
- Or any 2 of: neurofibroma, glioma, schwannoma or cataract.

Presumptive or probable NF2:

- C Unilateral VS <30y and: Meningioma, glioma, schwannoma or juvenile lens opacity (posterior subcapsular cataract or cortical cataract)
- D Multiple meningiomas (two or more) and: Unilateral VS <30y or at least one of glioma, schwannoma, juvenile lens opacity (posterior subcapsular cataract or cortical cataract).

Box 2 – The Baser criteria for the diagnosis of NF2 (6)

Feature	Present at or before 30y	Present after 30y
First-degree relative with NF2 by these criteria	2	2
Unilateral vestibular schwannoma (VS)	2	1 ^a
Second vestibular schwannoma	4	3 ^a
One meningioma	2	1
Second meningioma (no additional points for more than 2 meningiomas)	2	1
Cutaneous schwannoma(s)	2	1
Cranial nerve tumour(s) excluding VS	2	1
Mononeuropathy	2	1
Cataract(s)	2	0

- A Diagnosis of definite NF2 is established if the total number of points is 6 or more
- NF2 mutation testing is indicated if the total number of points is 4 or 5.
- A diagnosis of definite NF2 is established if a constitutional pathogenic NF2 mutation is found on mutation testing.
- A diagnosis of mosaic NF2 is established if mosaicism for a pathogenic NF2 mutation is found in the blood or no detectable pathogenic NF2 mutation is found in the blood but the same pathogenic NF2 mutation is found in two separate NF2 associated tumours.
- A temporary diagnosis of possible NF2 is made, pending further clarification. Clarification may occur if patient is diagnosed with a different condition eg schwannomatosis or if the disease evolves to permit diagnosis of NF2 by these criteria.

^a Points are not given for unilateral or second vestibular schwannoma if the age at diagnosis is more than 70y.

meningiomas. There are two isoforms of the protein depending on the location.^{2,9} Only one of them can acquire the conformation to allow tumour suppressor activity.¹⁰ The name merlin (moesin, ezrin and radixin-like protein) reflects the close similarity to a group of proteins including moesin, ezrin, radixin, talin and erythrocyte protein 4.1 which regulate interactions with the cell cytoskeleton, determining cell shape and influencing cell division and interactions with other cells and the extracellular matrix. Many mutations have been located throughout the NF2 gene. Most (90%) have the effect of truncating the transcribed protein.⁹ Both copies of the NF2 gene are mutated within tissue of NF2 related vestibular schwannomas and meningiomas and 30-70% of sporadic meningiomas i.e. tumour formation is initiated when there is a 'second hit' to the gene, supporting the theory that merlin is a tumour suppressor.

Familial NF2 is inherited in an autosomal dominant manner with almost 100% penetrance. It accounts for 50% of NF2.² Sporadic cases may be prezygotic, ie the mutation is present in one of the gametes and therefore uniformly distributed through all of the cell lines, or post zygotic. The stage at which post zygotic mutations occur in development and cell differentiation, determines the distribution of the mutation and thus the distribution and severity of the clinical manifestations. 25-33% of those with sporadic NF2 have somatic mosaicism^{2,11,12} where the genetic defect is restricted to a group or population of cells. NF2 can therefore be difficult to diagnose in such individuals as genetic testing may be normal in unaffected tissues and they may not have the pathognomonic clinical feature of NF2, bilateral VS.² When mosaicism levels are greater than 10% the mutation will be present in lymphocyte DNA² and therefore detectable on blood tests. Tumour material is required to detect the mutation when the mosaicism is less.

Genetic testing can be used to confirm a diagnosis of NF2 and/or to identify the mutation which is invaluable for screening relatives and offspring. The tests available are not 100% sensitive as the gene is large and there are so many potential mutations. Gene sequence analysis or mutation analysis, combined with deletion / duplication analysis can achieve a detection rate of more than 90% of pathogenic inherited NF2 mutations on blood testing.² The detection rate is reduced to 64% in *de novo* cases as around one third of these cases have low levels of mosaicism that are not detectable in lymphocyte DNA^{6,11,12} and overall the mutations are less easy to detect as they include a smaller percentage of large deletions.²

Where a causal mutation has been identified within a family, other members can confidently be tested to confirm or exclude the mutation. The risk of transmission is very low in those with somatic mosaicism, when the mutation is only detectable in the tumour.¹¹

The Gene Tests laboratory directory (www.genetests.org) lists the testing available from genetics laboratories world wide. The

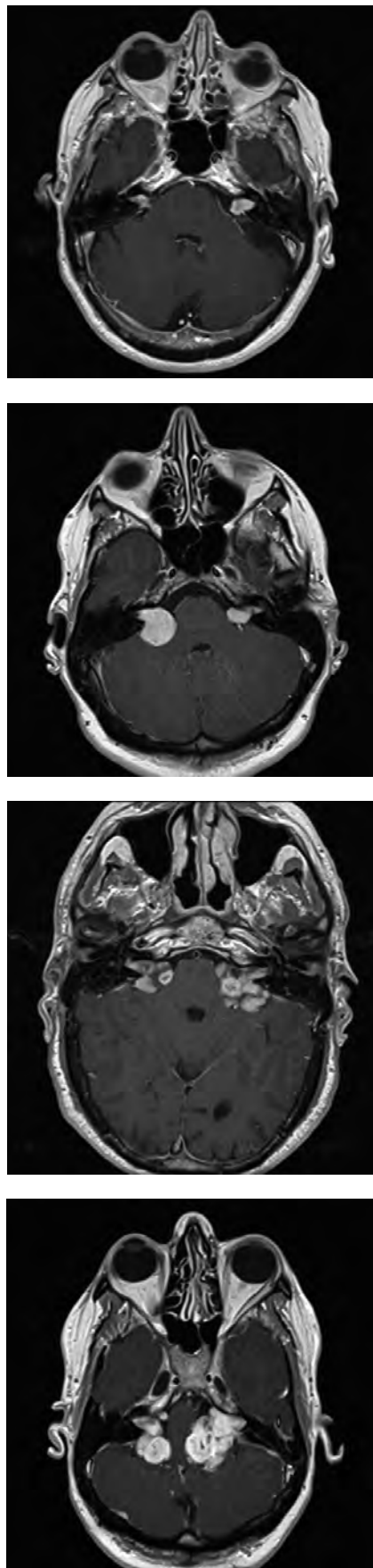


Figure 1: A series of T1 weighted axial MRI scans with gadolinium from 4 NF2 patients with bilateral vestibular schwannomas of varying size and nature. Ranging from almost completely intracanalicular (1a Top) to large multi-lobulated schwannomas with significant brainstem compression (1d bottom).

genetics laboratory in Manchester (<http://www.mangen.co.uk/>) is the only one in the UK to offer NF2 testing. Any tumour samples should be sent fresh or frozen to allow DNA sampling and accompanied by a lymphocyte DNA sample.

Clinical presentation / Natural history

The clinical manifestations and the severity of NF2 vary enormously. There is a strong genotype-phenotype correlation. In inherited NF2 the severity of the condition and its progression is similar within successive generations of the same family⁹ and the type of mutation appears to be an important determinant. Nonsense, frameshifting and truncating mutations are associated with more severe disease.² Those with mutations that cannot be identified tend to have milder disease.¹¹ With sporadic NF2 it is more difficult to predict the course of the condition; however those with mosaicism tend to have a milder form. Two forms of NF2 have been described, to denote the aggressiveness of the disease. The Wishart type is more aggressive, the Gardner type is less aggressive, presenting in older patients. Overall the average age of onset is 18-24 years.²

Whatever the form of NF2 it is impossible to predict the location and types of tumours that will develop. Manifestations of NF2 include schwannomas, meningiomas, ependymomas, rarely, low grade astrocytomas and eye conditions including retinal hamartoma.

Schwannomas

Almost all adults with NF2 will develop bilateral vestibular schwannomas (VS) (Figure 1), which present in a similar fashion to sporadic VS (see Ramnarine D, Whitfield P. *Management of patients with vestibular schwannomas*. ACNR 2005;(4):24-5). However NF2 related VS tend to be more aggressive in terms of rate of growth, recurrence and involvement of the facial nerve. Most affected individuals have developed bilateral VS by 30 years of age.² Also, given the propensity of NF2 patients to develop schwannomas and meningiomas, one must consider whether what on first impression appears to be a VS may be a schwannoma arising from another cranial nerve such as the cochlear, facial or trigeminal, or a CP angle meningioma. All of the other cranial nerves are potential sites for schwannomas, though the trigeminal is the most common. Trigeminal schwannomas can extend above and below the tentorium and involve the cavernous sinus.

Spinal schwannomas (Figure 2)

The most common type of spinal tumour in NF2. They are often multiple, dotted throughout the cauda equina and those in the cervicothoracic region are often indistinguishable from the neurofibromas of NF1. They originate on the dorsal root and adopt a dumb bell shape as they extend through the lateral and medial intervertebral foramen. NF2 patients can also develop schwannomas of the peripheral nerves and dermis.

Table 1: NF2 Hearing score

1	>70 % SDS* in better ear	No need for aids
2	50-70% SDS in better ear	Good benefit from aids
3	<50% SDS in better ear, >50% sentence score	Some added benefit from aids
4	<50% SDS in better ear, <50% sentence score	Poor benefit from aids, more detailed assessment of hearing function.
5	Deaf ears	No hearing

* Speech discrimination score (SDS)

Table 2 Management of NF2

Tumour management	Restoration of function
Observation	Auditory Brainstem Implant
Surgery	Cochlear Implant
Stereotactic Radiosurgery (SRS)	Internal Auditory canal decompression
Medical Treatment	Facial rehabilitation, Vestibular rehabilitation

Meningiomas

Approximately 50-75% of NF2 patients develop meningiomas, most commonly in supratentorial locations.⁹ These present in a similar way to sporadic meningiomas. They are usually of the fibroblastic type.²

Ependymomas and low grade

Astrocytomas

These intrinsic tumours tend to occur in the spinal cord and brain respectively. They are rarely the predominant symptomatic lesion in NF2.

Eye conditions

These are common and tend to develop early in the course of NF2. One third of individuals develop reduced visual acuity. Problems include early cataracts, an important diagnostic feature, retinal hamartomas, epiretinal membrane,¹⁰ strabismus and amblyopia, orbital meningiomas and corneal damage following loss of facial and trigeminal nerve function.

Neuropathy

NF2 is associated with a mononeuropathy of childhood and a polyneuropathy of adulthood. Children may present with a facial palsy, unrelated to a tumour mass that partially recovers, a third nerve palsy, a hand or foot drop² or a polio like illness with wasting of the lower limb muscles.¹³ Approximately 40% of adults will have evidence of polyneuropathy on nerve conduction studies and 3-10% will be symptomatic.¹³

Skin

Seventy percent of NF2 patients develop skin lesions which include skin plaques, subcutaneous tumours and intradermal tumours. The cutaneous features of NF2 are far more discreet than those of NF1. Intracutaneous tumours/skin plaques tend to be raised, slightly pigmented plaques which may have associated hair.¹⁰

Congenital Dysplasias

Increasing numbers of children are being screened and diagnosed with NF2. With the improvement in the resolution of MR Imaging,

we are increasingly recognising congenital glial and vascular abnormalities in children and young adults with NF2.

Assessment and Investigations

NF2 patients may harbour many or all of these pathologies at various locations. It is therefore very important to perform a thorough history and neurological and radiological assessment to establish which are symptomatic and whether there has been any deterioration. Patients with an established diagnosis, or a strong suspicion of NF2 are now managed in specialist multidisciplinary clinics where they are seen by neurologists, geneticists, an ophthalmologist and skull base surgeons with the support of neuroradiologists, audiologists and specialist nurses. However, it is not unheard of for a patient with a VS or meningioma, under follow up in a general neurosurgical clinic, to develop further symptoms or lesions on surveillance scanning, suggestive of NF2.

During the history pay particular attention to hearing; can they use the telephone? Do they use any aids? Do they have any balance disturbance, which many quality of life studies report to be more disabling than hearing loss. The NF2 service in the UK uses the NF2 hearing score (Table 1). A very functional categorisation of hearing, using the speech discrimination score. Also ask about symptoms suggestive of other cranial nerve neuropathies eg diplopia, dysphagia, visual disturbances, peripheral numbness or weakness that might be secondary to peripheral neuropathy or spinal disease, seizures and a detailed family history if they are a new patient.

Management

NF2 is a condition of multiple slow growing tumours which rarely turn malignant. The main ethos of management is therefore preservation of function, rather than cure. Management options can be classified into those directed at tumour treatment and those directed at restoration of function (Table 2).

This generally involves a strategy of watchful waiting where tumours are treated when they



Figure 2: Sagittal T2 weighted MRI of the thoracolumbar spine with multiple spinal schwannomas associated with the cauda equina.

become symptomatic or are clearly growing radiologically. There is still debate. Some advocate an early, anticipatory approach to stop tumours becoming symptomatic eg the treatment of small VS with stereotactic radiosurgery (SRS) or hearing preservation surgery.¹⁴

The first priority is to evaluate the disease load and symptoms with full brain and spinal MRI, neurological examination, ophthalmological examination, full hearing assessment including brainstem auditory evoked responses (BAERs), cutaneous examination and genetics consultation. Unless symptoms progress, patients should undergo regular annual neurological, ophthalmology and audiology assessment as well as brain MRI. Spinal MRIs are generally performed every four to five years unless patients develop worrying symptoms or lesions.

Vestibular schwannomas

NF2 related VS are more difficult to treat than their sporadic counterparts. This is because they are often large by the time they are treated and they tend to be more aggressive in nature. Therefore, whatever the treatment modality, the risk of recurrence, facial nerve injury and other complications is higher.

SRS: It is widely accepted that Stereotactic Radiosurgery is less effective in NF2 related VS. Relative growth ratios with contralateral controls indicate that SRS does have a beneficial effect in slowing tumour growth.¹⁵ Approximately 50% are controlled at eight years.¹⁵ Tumour volume is the main determinant of outcome and that coupled with their propensity to grow, restricts the size of tumour suitable for treatment. The Sheffield group suggest a volume limit of 10cm³.¹⁶ There is a 5% risk of facial palsy and whilst there is great individual variation in the rate of hearing loss, overall SRS does not appear to slow the rate of deterioration.¹⁵ Many have concerns about the risk of malignancy, delivering radiation to a tumour prone condition.¹⁷ In contrast, others advocate fractionated stereotactic radiotherapy in an attempt to preserve hearing and facial nerve function.

Surgery: Surgery remains the primary treatment for NF2 related vestibular schwannomas. Most are large, in which case, hearing preservation surgery is not possible. The timing of surgery is a balance between hearing, facial nerve function and brainstem compression. When there is no functional hearing, the threshold for surgery is lower, by which time the tumour may have reached a considerable size, increasing the risk of facial nerve injury and other surgical complications.

Some advocate an early surgical approach to small intracanalicular VS by a middle fossa approach with hearing preservation rates of up to 50%.¹⁴

Hearing Preservation and Augmentation

All NF2 patients should be referred to an audiologist for regular hearing assessments and training in anticipation of losing their hearing. Hearing and communication may be optimised by hearing aids initially. Lip reading, sign language and cochlear or auditory brainstem implants are options for those who have completely lost their hearing.

Of the surgical implants, cochlear implants provide a better quality of auditory input however they require an intact cochlear nerve. The scenario where this might occur in NF2 related VS is following attempted hearing preservation surgery or where there is a stable vestibular schwannoma with no hearing loss. Where there is early hearing loss secondary to a small intracanalicular VS, one option is to decompress the internal auditory canal, via a middle fossa approach.¹⁸

Auditory Brain Stem Implants (ABI): ABIs are used to treat total deafness when there has been permanent damage to the cochlear nerves and hearing can therefore not be improved by other (more effective) means such as hearing aids or cochlear implant. Electrodes are placed on the cochlear nucleus at the auditory prominence, through the Foramen of Luschka in the lateral recess of the 4th ventricle, guided by electrophysiology recordings of the brainstem auditory evoked responses. This is connected to an external receiver and sound processor which convert sounds into electrical signals. The auditory sensations that are gained are a perception of environmental sound which can be a great aid to lip reading. Excellent speech perception is possible. ABIs are often placed immediately following removal of vestibular schwannomas in the same surgical sitting. In patients with NF2 and bilateral vestibular schwannomas, 'sleepers' ABIs are increasingly being placed with the removal of the first VS in anticipation of complete hearing loss as the opposite VS grows or is treated. There is some growing evidence that patients can derive greater benefit from their ABI if they have the opportunity to practise using it particularly whilst they have some residual normal hearing (personal communication). Overall, the outcomes with ABIs are extremely variable ranging from non users to excellent hearing function. There are no clear predictors of

outcome.¹⁹ The external receiver contains a magnet that risks getting dislodged during MRI scanning. This is not an absolute contraindication to MRI imaging but special precautions need to be taken. Our local protocol includes head wrapping a protective guard over the device.

Medical treatment

There is an ongoing search for an effective medical treatment for NF2 related tumours. Phase 2 trials are under way for Lapatinib, a tyrosine kinase inhibitor at EGFR receptors, Everolimus an immunosuppressant and Bevacizumab/Avastin. The latter is a monoclonal antibody that inhibits vascular endothelial growth factor and therefore tumour angiogenesis. It is currently approved for off label use in England under strict criteria including active schwannoma growth of at least 4mm or 60% volume in 12 months, in the context of severe multi tumour disease. It is suggested in situations where the tumour load is so high that targeted surgery would not be possible or beneficial or where there is loss of hearing secondary to growth in the only hearing ear, in an effort to re establish and preserve hearing for as long as possible. The initial observations are that Avastin is very effective at halting tumour growth and is therefore being increasingly used with rapidly growing tumours. The main disadvantages of Avastin therapy are that it poses a contraindication to surgery which is delayed until three months after stopping treatment and the benefits tend to last as long as the treatment, such that there is a risk of rebound on stopping. It also does not have any real efficacy against meningiomas.

Facial reanimation

NF2 patients may develop facial paresis secondary to mononeuropathy, tumour growth or following surgery. Several options are available to reduce this disfiguring palsy and to protect the cornea, including, botulinum injections, gold eyelid weights and surgery. Restoration of the continuity of the facial nerve by cable graft following the removal of a large VS is not possible as the proximal stump will be very short and unidentifiable with post operative changes in the internal auditory canal. In such circumstances cross over techniques such as end to end or end to side hypoglossal facial anastomosis can be employed. The strategy for facial reanimation depends on the grade of facial weakness, the duration of the facial palsy, the status of the underlying tumour and other NF2 related tumours.

Children with a family history of NF2

If the mutation has been identified within the family then the diagnosis / mutation can easily be confirmed or excluded with direct DNA testing. Screening with MRI usually begins at 10-12 years in those known to carry a disease causing mutation or those at risk of inheriting NF2 where the mutation is unknown. However the timing is guided by family history and should be earlier if the family history is of early

onset NF2. If the diagnosis cannot be excluded annual MRIs are continued until at least the fourth decade of life.²

In the UK, NF2 is one of the rare conditions whose services are commissioned at a National level. The rationale is that concentrating the management of this complex condition in a few (4) centres will increase the experience, quality and 'uniformity' of the overall service. ♦

REFERENCES

- Evans DG, Howard E, et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. *Am. J. Med. Genet. A.* 2010 Feb;152A(2):327-32.
- Evans DG, Pagon RA TDB. Neurofibromatosis 2 [Internet]. GeneReviews Editors: Pagon RA, Bird TD, Dolan CR, Stephens K. 1998 [cited 2011 Sep 14]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK1201/?report=printable>
- Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference. *Arch. Neurol.* 1988 May;45(5):575-8.
- Mulvihill JJ, Parry DM, et al. NIH conference. Neurofibromatosis 1 (Recklinghausen disease) and neurofibromatosis 2 (bilateral acoustic neurofibromatosis). An update. *Ann. Intern. Med.* 1990 Jul 1;113(1):39-52.
- Gutmann DH, Aylsworth A, et al. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. *JAMA.* 1997 Jul 2;278(1):51-7.
- Baser ME, Friedman JM, et al. Empirical development of improved diagnostic criteria for neurofibromatosis 2. *Genet. Med.* 2011 Jun;13(6):576-81.
- Trofatter JA, MacCollin MM, et al. A novel moesin-, ezrin-, radixin-like gene is a candidate for the neurofibromatosis 2 tumor suppressor. *Cell.* 1993 Nov 19;75(4):826.
- Rouleau GA, Merel P, et al. Alteration in a new gene encoding a putative membrane-organizing protein causes neuro-fibromatosis type 2. *Nature.* 1993 Jun 10;363(6429):515-21.
- Korf BR, Rubenstein AE. Neurofibromatosis: A Handbook for Patients, Families and Health Care Professionals. 2nd ed. Thieme Medical Publishers; 2005.
- Asthagiri AR, Parry DM, et al. Neurofibromatosis type 2. *Lancet.* 2009 Jun 6;373(9679):1974-86.
- Moyhuudin A, Baser ME, et al. Somatic mosaicism in neurofibromatosis 2: prevalence and risk of disease transmission to offspring. *J. Med. Genet.* 2003 Jun;40(6):459-63.
- Kluwe L, Mautner V, et al. Molecular study of frequency of mosaicism in neurofibromatosis 2 patients with bilateral vestibular schwannomas. *J. Med. Genet.* 2003 Feb;40(2):109-14.
- Evans GR, Lloyd SKW, Ramsden RT. Neurofibromatosis type 2. *Adv. Otorhinolaryngol.* 2011;70:91-8.
- Slattery WH 3rd, Fisher LM, et al. Hearing preservation surgery for neurofibromatosis Type 2-related vestibular schwannoma in pediatric patients. *J. Neurosurg.* 2007 Apr;106(4 Suppl):255-60.
- Rowe J, Radatz M, et al. Clinical experience with gamma knife stereotactic radiosurgery in the management of vestibular schwannomas secondary to type 2 neurofibromatosis. *J. Neurol Neurosurg Psychiatry.* 2003 Sep;74(9):1288-93.
- Rowe JG, Radatz M, et al. Stereotactic radiosurgery for type 2 neurofibromatosis acoustic neuromas: patient selection and tumour size. *Stereotact Funct Neurosurg.* 2002;79(2):107-16.
- Carlson ML, Babovic-Vuksanovic D, et al. Radiation-induced rhabdomyosarcoma of the brainstem in a patient with neurofibromatosis type 2. *J. Neurosurg.* 2010 Jan;112(1):81-7.
- Slattery WH, Hoa M, et al. Middle Fossa Decompression for Hearing Preservation. *Otology & Neurotology.* 2011 Aug;32(6):1017-24.
- Sanna M, Di Lella F, et al. Auditory brainstem implants in NF2 patients: results and review of the literature. *Otol. Neurotol.* 2012 Feb;33(2):154-64.

Epilepsy and Memory

Hearing complaints of memory problems is a familiar experience for most if not all clinicians having any dealings with epilepsy patients. It is well recognised that such memory difficulties are heterogeneous, ranging from subjective to objective, and multifactorial in origin – related to underlying brain lesions causing the epilepsy, frequency of seizures, antiepileptic drug therapy, concurrent mood disorder, or any combination thereof. This fascinating volume seeks to review what is known about the interrelationships of memory and epilepsy, summarising both clinical and laboratory studies.

That research on patients with epilepsy has contributed to knowledge of the neural basis of memory and temporolimbic models of memory function cannot be denied. The critical importance of epileptic patient HM (Henry Gustav Molaison, 1926-2008) and the studies of Brenda Milner (summarised in Chapter 2) cannot be overstated.

Considering brain lesions, the loss of hippocampal functional integrity in medial temporal lobe epilepsy may account for the retention deficits found in this condition (Chapter 4) but findings of lateralized material-specificity (verbal-dominant, nonverbal-nondominant) have proven inconsistent, perhaps in part because 'nonverbal tests' may not be entirely nonverbal (Chapter 10).

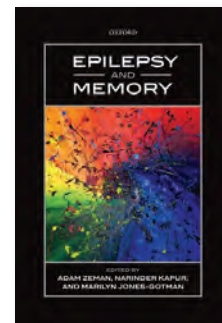
The role of seizures per se is addressed by the study of transient epileptic amnesia (Chapter 8) which, despite

its rarity (vis-a-vis transient global amnesia) has afforded some insights, including the phenomenon of accelerated long-term forgetting (surely, intuited by anybody who has ever crammed for an exam). Whether epileptiform EEG changes are also detrimental to memory function ('transient cognitive impairments') remains uncertain, in part because of the difficulty of distinguishing such events from subtle nonconvulsive seizures (Chapter 9).

Antiepileptic drugs (AEDs) are often blamed for memory problems, with justification in the case of older, sedating, medications. The newer AEDs largely escape culpability, with the exception of topiramate and possibly zonisamide, although not all new drugs have been submitted to rigorous study (Chapter 23).

Psychiatric factors, particularly co-morbid psychosis or depression may play a role in epilepsy-related memory problems and impact on performance in neuropsychological test performance (Chapter 15).

The editors have achieved their aims with this book (as perhaps might be expected considering a gestation period of some six years): it is well-produced, and handsomely illustrated with paintings and drawings by artists who have epilepsy. My only criticism is the absence of any extended analysis of epileptic seizures in Alzheimer's disease, a subject of current interest and possible relevance in understanding mechanisms of concurrent memory impairment and epilepsy. ♦



Editors: Zeman A, Kapur N, Jones-Gotman M
Published by: Oxford University Press, 2012
Price: £65.00
ISBN: 9780199580286

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

The Paradoxical Brain

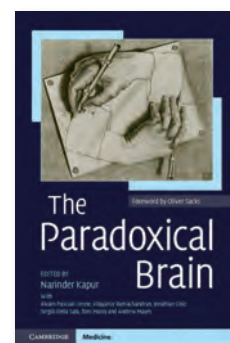
Thomas Browne, physician and author, coined the term paradoxology, the use of paradoxes, in his *Pseudodoxia Epidemica* or, *Enquiries into Very many Received Tenets, and commonly Presumed Truths*. Now Narinder Kapur has assembled a crack team of eminent scientists and clinicians to use paradoxology to illuminate various facets of how we understand (but very often don't understand) the brain today. In this extremely interesting and ambitious book, with a foreword from Oliver Sacks (surely the foremost exponent of popular neuropsychology), the experts candidly discuss counterintuitive phenomena observed while studying the brain. Most relate to patient groups and treatment effects, but there are also chapters on topics such as comparative cognition between different species (it is humbling to know that my visuospatial performance on certain tasks is likely to be worse than a well-trained chimp's) and the nature of human expertise.

The book is refreshingly targeted at people who are interested in the brain regardless of particular career path or level of seniority, and I very much doubt that there is anyone who is well-versed with all of the paradoxes, from the creativity of those with psychiatric conditions to the relationship between allergies and gliomas, described here. Moreover, many of the chapter authors, who are leaders in their fields, seem to relish being able to be discursive without the need to be as forcefully directed as is sometimes necessary for a journal article or specialist review. In addition, most of them cite across the breadth of

the topic, rather than concentrating on their own contributions. Personally, I found the chapters on paradoxes in Parkinson's Disease (Ashwani Jha and Peter Brown) and Learning and Memory (Henry L Roediger, III and Andrew C Butler) especially interesting. A number of the authors begin with historical introductions to each subject and I particularly enjoyed the backgrounds in the chapters on ECT (Angela Merkl and Malek Bajbouj) and psychosurgery (Perminder Sachdev) showing us just how far we haven't come.

One drawback to the book is the occasional feeling that it is trying too hard to contrive a paradox, where the underlying issue is one of biological complexity ('non-linear' effects etc) rather than apparent contradiction.

In the final chapter, ten 'principles of brain function' are proposed in order successfully and sensibly to disentangle the paradoxes of brain research. Whether or not the ten principles catch on remains to be seen but Professor Kapur and colleagues have succeeded in producing a book that will stimulate thought on phenomena encountered during the course of our neuroscientific work and in our daily lives, which is a great achievement. I would recommend it to anyone (presumably all the people reading this) genuinely interested in the workings of the brain and how we go about trying to understand them. Thomas Browne, whose own brain has been commemorated in stone in his hometown of Norwich, would have approved. ♦



Editors: Narinder Kapur, with Alvaro Pascual-Leone, Vilayanur Ramachandran, Jonathan Cole, Sergio Della Sala, Tom Manly and Andrew Mayes
Published by: Cambridge University Press, 2011
Price: £65.00
ISBN: 9780521115575

Reviewed by:
 Parash Malhotra
 Senior Lecturer in Neurology
 Imperial College London, UK.

Clinical Pocket Reference Neurosciences

Authors: Juliet Bostwick and Deborah Slade, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford.

ISBN: 978 0 9543065 7 1

Selected pages from Clinical Pocket Reference Neurosciences - *second instalment*.

Reviewer's comments:

From a nurse's perspective, I recommend this booklet as a handy reference guide to neurological aspects of nursing care.... The format is clear, logical and easy to read.

...It will be most useful as a reference for general nurses and nurses new to Neuroscience. However, the referencing and bibliographies mean that it would also be a useful acquisition for more experienced nurses and other practitioners.

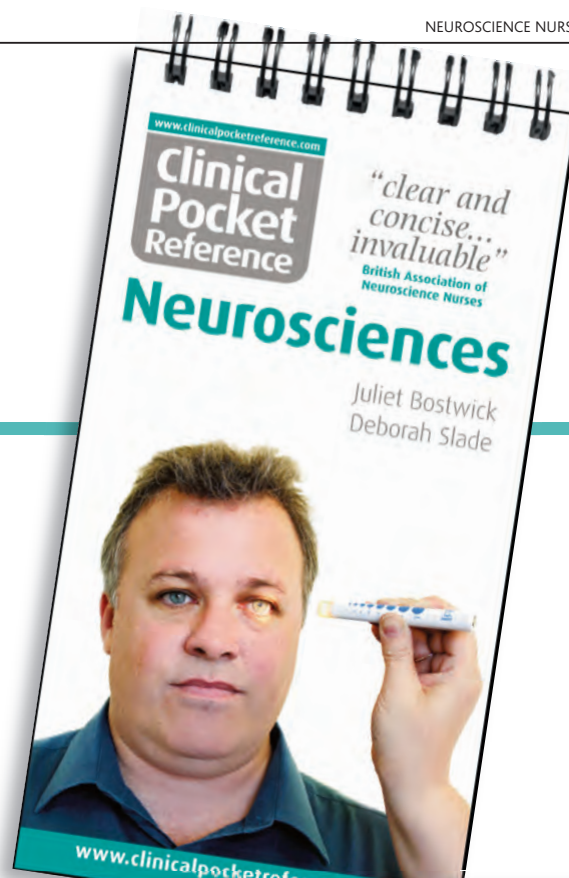
ACNR

This book will be an invaluable resource for nurses and allied healthcare professionals of all backgrounds and levels of experience...

It is clear and concise, pitched at the right level, with good use of images.

British Association of Neuroscience Nurses

ACNR are publishing selected content from **Clinical Pocket Reference: Neurosciences** over current issues... neuroscience nurses will find this a useful aide memoire. Ideal for keeping on the ward or in the pocket as a teaching and reference tool.



Name	Effect	Nerve	Action
Acetylcholine (ACh) - released by many neurones in the PNS and some in the CNS	Excitatory Inhibitory	Neuromuscular junction Parasympathetic neurones of vagus nerve	Muscle innervation Slows heart rate
Dopamine	Inhibitory	Substantia nigra Basal ganglia	Coordinates skeletal muscle activity
Gamma aminobutyric acid (GABA)	Inhibitory	Affects a third of all brain synapses in spinal cord, cerebellum, basal ganglia and cerebral cortex	Regulates the activity of glutamate Main inhibitory neurotransmitter in CNS
Glutamate	Excitatory	Nearly all neurones in CNS	Sensory pathways
Noradrenaline	Excitatory but may also be inhibitory	to brain stem and hypothalamus	Main transmitter of the sympathetic nervous system Controls activity and mood
Serotonin	Inhibitory	Nuclei in brain stem, projecting to dorsal horns of spinal cord and hypothalamus	Controls body heat, hunger, mood and sleep

ABCDE - immediate assessment, monitoring and treatment approach

A systematic approach to assessment of the acutely ill or deteriorating patient should minimise mistakes and ensure timely and accurate management. Reassessment is essential to check the effect of interventions and to recognise further deterioration regardless of, or because of, treatment.

A - Airway

- Check for patency (e.g. can the patient speak?)
- If the airway is compromised, use airway manoeuvres (e.g. head tilt, chin lift or jaw thrust), recovery position or airway adjuncts (e.g. oral or nasopharyngeal airways)
- Initiate oxygen therapy via a non-rebreather mask with reservoir bag or a bag-valve-mask system

B - Breathing

- Look, listen and feel for breathing - rate and depth
- Check for central cyanosis - lips and oral mucosa
- Listen for airway noise - any retained secretions or partial obstruction?
- Auscultate the chest to identify nature of breath sounds

C - Circulation

- Look for signs of circulatory compromise - cool, pale peripheries, peripheral cyanosis
- Listen for a blood pressure (BP) - may be maintained due to compensation mechanisms (tachycardia)
- Feel for peripheral and central pulses
- If necessary, instigate fluid resuscitation, if indicated, control haemorrhage

D - Disability

- Rapid assessment of conscious level should use the 'AVPU' system (below)
- Check pupils for size and reaction to light, and check blood glucose to exclude hypoglycaemia as a cause of altered mental state

E - Exposure

To complete the assessment, expose the patient's body appropriately to assess suspected causes of deterioration (e.g. check abdomen for signs of internal bleeding)

AVPU system

- A** Alert
- V** Responds to Voice
- P** Responds to Pain
- U** Unresponsive

- The AVPU system is for 'urgent' assessment of conscious level
- A, B and C must be stabilised
- Reassessment of conscious level should use the Glasgow Coma Scale

Sources/bibliography: Smith G (2003) ALERT™ - Acute Life-threatening Events - Recognition and Treatment. Plymouth: Learning Media Development, University of Plymouth



To order the complete book with special offer for readers of ACNR, go to www.clinicalpocketreference.com and at check-out enter Offer Code ACNR1213

Save 15%: retail £9.99 ACNR readers' price £8.50 P&P free

www.clinicalpocketreference.com

**Clinical
Pocket
Reference**



Rhys Thomas

is a Clinical Lecturer at Swansea and Cardiff Universities and is completing his PhD focusing on the genetic basis of the juvenile myoclonic epilepsies and the phenotype of hyperekplexia. He is currently the ABNT Treasurer.

Correspondence to:

Email: Rhys.Thomas@swansea.ac.uk



A medical degree is also a ticket to see the world. In recognition of this, undergraduates spend longer on their medical elective than they do learning clinical neurology. Many training schemes have formal or informal opportunities to learn skills outside of the region – but international attachments may bring with them a prohibitive volume of red tape. There is a personal odyssey where each prospective fellow networks to learn about visas, the health system and potential vacancies abroad. This is particularly unfortunate as modern era ‘ST’ trainees will be more likely to spend their four or five years within their geographical location rather than flit between departments and regions as their supervisors may have done. Many enthusiastic trainees stymied by the bureaucracy have previously worked in accredited training posts abroad – without being able to have it count towards their UK training.

In recognition of this the ABN in conjunction with the SAC has recently developed a series of Australasian Fellowships. In the first year of its inception the posts will start in February 2013; one in Sydney, one in Melbourne and a third in Auckland. Not only are these posts in sites recognised for their exceptional training opportunities but they come with the necessary accreditation – allowing the fellows to count the year abroad towards their UK CCT. The scheme (in keeping with most out of programme applications) is not aimed at those within the last months of their UK training – but is open to all on a competitive basis. If a year in the Southern hemisphere sounds tempting – you are not alone: here Matt Armstrong, Lucie Aldous, Charlotte Lawthom and I report our experiences.

Dr Charlotte Lawthom is Consultant Neurologist at the Royal Gwent Hospital in Newport. During her training in Wales she worked in Adelaide to further her epilepsy experience.

“As I sit here after one of the worst UK Summers on record, I remember fondly my time in Adelaide. I even had a pool in my private garden and I lived a ten-minute walk from the beach. Of course, I could move to the coast in South Wales and benefit, no doubt, from the sea air. Australian leisure time though, is largely predicated on outside living and (sunscreen requirements notwithstanding) is all the richer for it.

Australia is similar enough to the UK to cushion the shock of living and working in a different culture. At work, UK examination systems are grudgingly respected and UK trained doctors are generally welcomed. Working in a two-tier medical system can prove somewhat uncomfortable and paying to see your own GP (should you need to) feels bizarre. The relative wealth of the main hospitals though, is a major bonus. The instant access to investigations such as EEG and MRI spoiled me for my return to Neurology SpR training in the UK. Indeed, the availability of ictal SPECT with a 4-bed

The availability of ictal SPECT with a 4 bed epilepsy telemetry unit in my neurology SpR placement hospital was largely responsible for my subsequent epilepsy specialty

epilepsy telemetry unit in my neurology SpR placement hospital was largely responsible for my subsequent epilepsy specialty.

The location was serendipity. I applied to a service by emailing them my CV. I expected to get a Registrar in General Medicine position but was warned that Neurology can be competitive. Plus ça change! I was blessed with both, medicine first. The obtaining of a visa and related applications were quick though visiting London twice was obligatory. Leasing a car, renting a house and setting up bank accounts were painless. I started work eight days after arriving and had moved into my new house and driven my new car. I also fitted in a four-day trip to the region's vineyard and an overnight stay in Kangaroo Island!

I had been to Australia twice before my application to work there. I confess this was motivated more by the search for life skills than a desire to practice my clinical skills in a different setting. The pace of work was everything we are used to here, and weekend ward rounds are mandatory – though I got a Thursday afternoon off in return. I rolled up my sleeves and got stuck in. I returned greatly enriched; bolstered in confidence and loaded with new knowledge. Go with an open and inquisitive nature, take the POM (prisoner of the motherland) jokes with good humour. Avoid competitive rows over sport – no good will come of it! Embrace Australian Rules Football instead. Oh, and take your own supply of marmite. Vegemite is simply not the same."

Matt Armstrong is a technical writer originally from Southport who has been living in Melbourne for four years – here he describes the process of going to live abroad and how to mitigate against missing the best of Blighty.

"So you've decided to come to Australia? Well the first thing you should know is that this place is big. Properly big. If you're heading for one of the Eastern states (that's the bit where all the people are) then even after your flight crosses into Australian airspace you'll probably still be closer to the place you took off from than to your destination. In a country this size, daily life for the inhabitants of, let's say, far North Queensland or remote Western Australia probably bears little relation to that of the latte-sipping hipsters that stalk inner city Melbourne. But there are a few cultural reference points that unite this vast land.

It is a fervently religious place. Worship is held in stadia across the country every weekend, and if you want to fit in you'd do well to acquaint yourself with the local denomination as quickly as possible. In NSW and QLD that means both codes of Rugby, while in Victoria you'll need to select an Aussie Rules team to 'barrack' for (it doesn't matter who you pick, as long as it's not Collingwood).

The locals will happily talk sport with you for hours (although it's probably best not to mention the cricket or the Olympics right now) so once you've selected a team you will

have something to discuss at your next barbie, of which there will be many. This sacred Aussie ritual brings its own unspoken rules and customs: you will typically be expected to supply your own meat or salad (this is largely gender dependent) and definitely your own beer, which should be brought in your Esky (cool box) and is under no circumstances to be consumed at anything other than sub-arctic temperatures.

The beer itself is not as bad as you might think, as long as you steer clear of the mass produced fizzy lagers and seek out something from one of a growing number of small craft brewers dotted around the country (Melbourne's Mountain Goat and Byron Bay's Stone and Wood are particularly worth a try). Australian wine of course is just like the stuff you know and love from the British supermarket shelves, only better.

Aussie music is better than you might expect too, and all the major capital cities have vibrant live music scenes. Tune your radio to the ABC's Triple J to hear the latest up and coming local bands. Their annual Hottest 100 countdown, held on Australia Day every January is an institution that you are likely to find yourself listening to at a barbie (see above). You may also find yourself in a pub at some point during your stay singing along to something by either AC/DC, Cold Chisel, or John Farnham, but it's best not to admit to this in the cold light of day."

The ANZAN Fellowships (a reciprocal direction of travel) have been in place for twenty years. Dr Lucie Aldous describes the benefits of a fellowship abroad.

"I did not have any real preconceived ideas about working in the UK prior to arriving. I was obviously aware that they had a system of health care called the NHS however did not really understand the structure of the system or the way it impacts on practicing medicine, which is something in retrospect I would have liked to have known about. There are significant differences both in the training programmes and the structure of healthcare and the way that it influences practice compared to Australia. Gaining an understanding of this was the biggest challenge for me when working in the UK, whereas the patient demographic and the spectrum of disease is not significantly different to Australia."

My plan is to spend a year in Melbourne from February 2013 to complement my training in Wales; I (Rhys Thomas) feel that I have had ample opportunities to sample clinic based epilepsy services – but the limited epilepsy surgery programme within the Principality has prevented me from having sufficient exposure to the multimodal elements that constitute a thriving surgical programme. I want to return with a greater aptitude in a new skill – this is a common reason for a foreign fellowship: for me it is EEG. British epileptologists (unlike their

colleagues in Europe, North America or elsewhere) often do not have the skills to report their own EEGs. I may not attain fluency but it would be reward to return with a greater EEG proficiency. In addition – the population of Melbourne alone exceeds that of Wales and I hope that general neurology in the big city may bring a juxtaposition with my experiences in Gorseinon for example (population 19,000).

Melbourne is the base for Professors Sam Berkovic and Ingrid Scheffer's epilepsy genetics group and this is why Melbourne ahead of any other Commonwealth city was my first choice of location. I aim to split my time equally between telemetry and their research group. It just happens that there is world class tennis, formula one, an Ashes series and the British and Irish Lions tour during my time there...

Practicalities

You will of course need a visa to work here. The options are too numerous to detail here, so see www.immi.gov.au for just about everything you need to know, and most importantly get things moving early. It can take several months to complete your application (which as well as form filling is likely to involve police checks, medicals, and potentially an interview, all of which take time to organise).

Once you are here, you will need a Tax File Number when you start work (apply online at www.ato.gov.au) and a bank account (simply wander in to a branch of any of the high street banks with your passport).

Unless you are migrating permanently, you won't be eligible for full access to Medicare (Australia's public health system), but you may be entitled to emergency/essential medical treatment under Australia's reciprocal health care agreements. Check www.humanservices.gov.au/customer/enablers/medicare/reciprocal-health-care-agreements/health-care-for-visitors-to-australia to see how the rules apply to your situation. You might want to consider taking out private health insurance during your stay, or at the very least Ambulance Cover, just in case.

If an opportunity to revel in a new culture whilst sharpening your clinical skills thousands of miles from home appeals – then it is likely that the Fellowships for 2014/15 will be announced this winter with Sydney and Melbourne likely to be included as host cities.

Continuous Spike Wave Discharges in Slow-Wave Sleep – don't let it catch you napping!



Dr Gautam Ambegaonkar, MBBS, DCH, MRCPCH

is a Paediatric Neurologist based at Addenbrookes hospital in Cambridge. He qualified in Medicine from the University of Mumbai and acquired his Diploma in Child Health from The B.J. Wadia Children's hospital in Mumbai. He came to the UK to specialise in Paediatric Neurology and completed his CCT in Paediatric Neurology from Great Ormond Street hospital in London. He is the lead for Paediatric Neuromuscular services at Addenbrookes and supports the paediatric epilepsy service.

Correspondence to:
Email: gautam.ambegaonkar@nhs.net

Continuous Spike Wave discharges in slow wave Sleep (CSWS) is a clinical encephalopathy characterised by neurocognitive regression, motor impairment and an EEG pattern of Electrical Status Epilepticus in Sleep (ESES). It is a rare disorder comprising 0.2-0.5% of all childhood epilepsies¹ and usually reported in children with epilepsy secondary to pre-existing brain pathology such as cortical malformations or acquired brain injury.^{2,3} Children with CSWS usually present with non-specific motor and behavioural symptoms.⁴ The diagnosis can easily be missed unless a sleep EEG is obtained which typically shows a high spike-wave index in slow wave sleep. Treatment options include specific antiepileptic drugs (often in combination), oral steroids, IV Immunoglobulin, Ketogenic diet and Epilepsy surgery. A longer duration of CSWS correlates with poor neuropsychological outcome^{5,6} therefore a high degree of clinical suspicion is essential and may significantly alter prognosis.

History

CSWS was first described by Patry et al in 1971 in six children with epilepsy who had 'subclinical electrical status epilepticus' induced by sleep.⁷ Over the past 40 years, there has been much progress in our understanding about it and CSWS is now recognised as a separate entity by the ILAE.^{8,10} There exists, however, confusion over terminology and specifically the terms ESES (Electrical Status Epilepticus in Sleep) and CSWS are often incorrectly used interchangeably. ESES merely represents an electrophysiological pattern of 'near-continuous' spike-wave discharges observed in sleep; the accompanying clinical signs and symptoms may differ with different syndromes for example, ESES is seen in both Landau Kleffner syndrome and CSWS – which are two different entities.¹⁰ Table 1 represents the different clinical syndromes which can be associated with ESES.

Aetiology

The exact aetiology of CSWS is unknown but there is an apparent relationship between CSWS and underlying structural brain abnormalities, both inherited and acquired.¹ Up to 1/3rd of children who develop CSWS have had a preceding neurological insult such as meningitis or neonatal encephalopathy.¹¹ Radiological abnormalities such as cortical atrophy and neuronal migrational abnormalities are often found in children with CSWS.^{12,13} The pathophysiology of CSWS has been attributed to disruption of physiologic thalamocortical rhythms by some authors⁶ and activation of reticulo-thalamic-cortical system with secondary bilateral synchronisation by others.⁹

Clinical presentation

Children who develop CSWS present to medical services with increasing seizure frequency¹⁴ accompanied by a history of slowly progressive motor impairment such as ataxia, dyspraxia and increased 'clumsiness'. There is often a history of loss of language and temporo-spatial skills, hyperactivity, short-term memory deficits and behavioural problems. The child may be perceived to have recently 'become challenging' or to be 'misbehaving' which often results in difficulties at school leading to short and long-term exclusions. Parents complain of increased aggressiveness towards family members and that the child is 'not himself'. The clinical changes during the evolution of CSWS have been well described in the literature along with detailed description of the accompanying electrophysiological features¹⁵ and it is important to recognise that CSWS develops over a period of time.

Diagnosis and differential diagnoses

When presented with a child with symptomatic epilepsy who has recently had an increase in seizure frequency, it is necessary to ask for a history of regression of skills, language and behavioural difficulties. A report from school is essential. This should be complemented by a careful clinical examination to exclude possible differential diagnoses (Table 2). Early discussion about the patient with the regional paediatric neurologist is often useful. An urgent sleep/sleep-deprived EEG must be requested to look for ESES in slow-wave sleep. The diagnosis is confirmed if the spike wave index is > 85%. (Spike wave Index = total number of minutes of all spike and slow wave abnormalities X 100 divided by total number of NREM sleep minutes).

Treatment of CSWS

There are no controlled trials for the treatment of CSWS, only large cohort studies. The goal of treatment is not only to control seizures but also improve neurocognitive function which requires a significant improvement or amelioration of the electrophysiological abnormalities. An aggressive approach is indicated, supported by neuropsychological treatment wherever possible.

Antiepileptic drugs:

Specific anti-epileptic drugs (AEDs) have been reported to be efficacious in treating CSWS including traditional AEDs such as Sodium Valproate (VPA) and Ethosuximide (ETX); in the past decade newer AEDs such as Levetiracetam (Keppra) and Sulthiame (STM) have also been shown to be effective.¹⁶ Benzodiazepines (BZDs) play a key role in treating CSWS. Clobazam remains the first choice owing to its safer side effect profile

Table 1: Epileptic syndromes in which ESES may occur in sleep

Syndrome	Features	Epileptic focus on EEG
CSWS	Global cognitive decline, motor impairment, increased seizure frequency, behavioural difficulties	Fronto-central Fronto-temporal
Landau Kleffner	Receptive/ Mixed aphasia, verbal agnosia, infrequent seizures	Posterior temporal
Atypical BECTS	Nocturnal (partial) seizures with cognitive/ behavioural difficulties	Posterior Occipital
Opercular syndrome	Inability to speak, swallowing difficulties, hemiplegia	Centro-temporal

Table 2: Differential diagnoses

Disorder/ Syndrome	Salient clinical differences
Non convulsive status epilepticus	Both daytime and nocturnal confusional state
Progressive leucoencephalopathy	New-onset or progressive spasticity and/ or upper motor neurone signs on clinical examination
Meningoencephalitis	Acute, reversible state of altered sensorium often accompanied by systemic signs (fever, meningism)
Mitochondrial/ Metabolic disorder	Episode of altered sensorium encephalopathy often triggered by illness or fasting, MRI changes
Psychogenic seizures	Inconsistent clinical features such as 'migrating' onset of seizures, identification of secondary gain

and tolerability but other BZDs such as short courses of oral diazepam¹⁷ and IV flunitrazepam¹⁸ have also been used. In line with good practice for treatment, AEDs should be used at the maximum doses possible without side effects for four to six weeks before being considered ineffective.

Steroid treatment:

Oral Prednisolone (2-5mg/kg/day), IV Methylprednisolone (30mg/kg/day for three days), ACTH (80 IU/day) and Hydrocortisone (5mg/kg/day) have been shown to be extremely effective and safe in the treatment of CSWS¹⁹ with a positive outcome in over two thirds of patients. A combination of AEDs and steroids is often necessary for four to six weeks following the diagnosis following which a repeat EEG is recommended to look for resolution of ESES (personal practice).

Alternative treatments:

IV immunoglobulins (IVIGs 2gm/kg/day for two days) and the ketogenic diet have both been used with limited success.^{20,21} Epilepsy surgery should be considered early if the patient has a structural brain malformation.

tion.^{22,23} Figure 1 is a Therapeutic approach to treatment of CSWS (Veggiotti et al; Epileptic Disorders 2012).

Outcome

Children who develop CSWS have a poor long-term neuropsychological outcome despite resolution of seizures and electrophysiological abnormalities.^{5,24,25} Treatment for co morbidities such as attention deficit hyperactive disorder and behavioural difficulties is also essential. Pharmacological treatment such as Methylphenidate and behavioural/family therapy may often be necessary.

Conclusion

CSWS is an often under-recognised entity in children with symptomatic epilepsy and diagnosis is often delayed unless a sleep EEG is requested. Duration of ESES appears to be a particularly important predictive factor for poor outcome.²⁶ A high index of suspicion and early aggressive treatment with AEDs and/or steroids supported by neuropsychiatric management is needed to offer this vulnerable group of patients the best chance of a good recovery. ♦

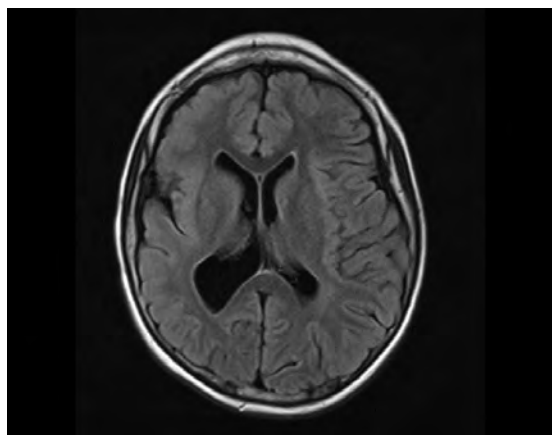
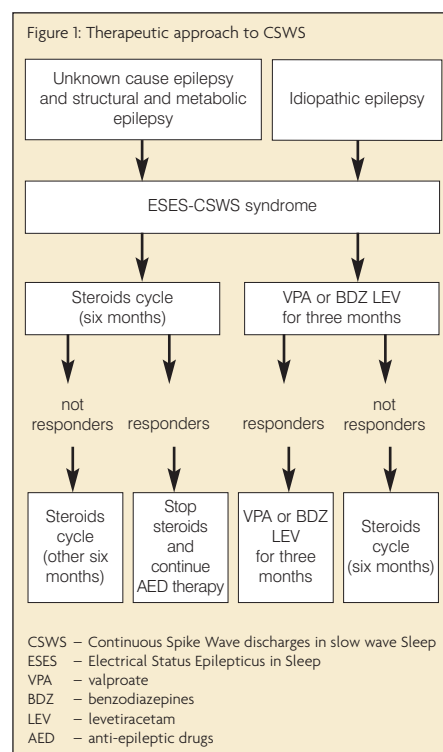


Figure 2: MRI Brain showing right side cortical malformation (polymicrogyria) in a child with left hemiparesis, epilepsy and learning difficulties who developed CSWS 3.2 years after onset of epilepsy.

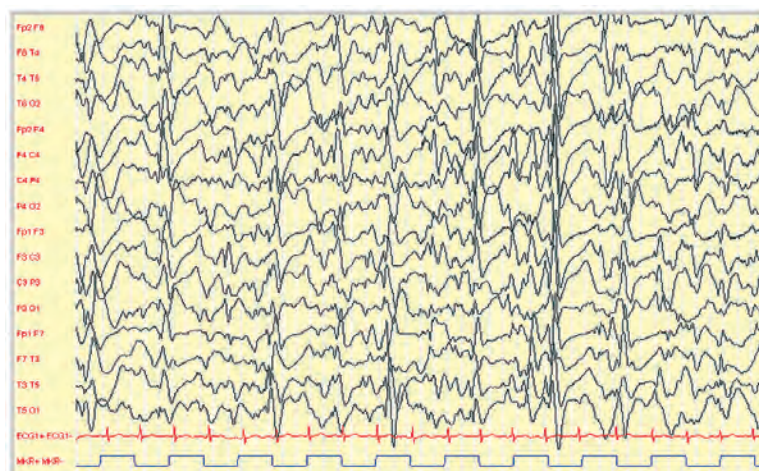


Figure 3: CSWS on sleep EEG in child shown left.

REFERENCES

- Nickels K, Wirrell E. *Electrical status epilepticus in sleep*. *Semin Pediatr Neurol* 2008;15(2):50-60.
- Guzzetta F, Battaglia D, Veredice C, Donvito V, Pane M, Lettori D, et al. *Early thalamic injury associated with epilepsy and continuous spike-wave during slow sleep*. *Epilepsia* 2005;46(6):889-900.
- Wang L, Deng YC, Liu YH, Huang YG. *Characteristics of continuous spike-and-wave during slow wave sleep syndrome in children*. *Zhongguo Dang Dai Er Ke Za Zhi* 12(2):93-5.
- Herguner MO, Inceci F, Altunbasak S, Kiris N. *Clinical characteristics of 10 patients with continuous spikes and waves during slow sleep syndrome*. *Pediatr Neurol* 2008;38(6):411-4.
- Scholtes FB, Hendriks MP, Renier WO. *Cognitive deterioration and electrical status epilepticus during slow sleep*. *Epilepsy Behav* 2005;6(2):167-73.
- Seegmuller C, Deonna T, Dubois CM, Valenti-Hirsch MP, Hirsch E, Metz-Lutz MN, et al. *Long-term outcome after cognitive and behavioral regression in nonlesional epilepsy with continuous spike-waves during slow-wave sleep*. *Epilepsia* 53(6):1067-76.
- Patry G, Lyagoubi S, Tassinari CA. *Subclinical "electrical status epilepticus" induced by sleep in children. A clinical and electroencephalographic study of six cases*. *Arch Neurol* 1971;24(3):242-52.
- Brazzo D, Pera MC, Fasce M, Papalia G, Balottin U, Veggiotti P. *Epileptic Encephalopathies with Status Epilepticus during Sleep: New Techniques for Understanding Pathophysiology and Therapeutic Options*. *Epilepsy Res Treat* 2012:642725.
- De Negri M. *Electrical status epilepticus during sleep (ESES). Different clinical syndromes: towards a unifying view?* *Brain Dev* 1997;19(7):447-51.
- Veggiotti P, Beccaria F, Guerini R, Capovilla G, Lanzi G. *Continuous spike-and-wave activity during slow-wave sleep: syndrome or EEG pattern?* *Epilepsia* 1999;40(11):1593-601.
- Jayakar PB, Seshia SS. *Electrical status epilepticus during slow-wave sleep: a review*. *J Clin Neurophysiol* 1991;8(3):299-311.
- Galanopoulou AS, Bojko A, Lado F, Moshe SL. *The spectrum of neuropsychiatric abnormalities associated with electrical status epilepticus in sleep*. *Brain Dev* 2000;22(5):279-95.
- Tassinari CA, Rubboli G, Volpi L, Meletti S, d'Orsi G, Franca M, et al. *Encephalopathy with electrical status epilepticus during slow sleep or ESES syndrome including the acquired aphasia*. *Clin Neurophysiol* 2000;111 Suppl 2:S94-S102.
- Nieuwenhuis L, Nicolai J. *The pathophysiological mechanisms of cognitive and behavioral disturbances in children with Landau-Kleffner syndrome or epilepsy with continuous spike-and-waves during slow-wave sleep*. *Seizure* 2006;15(4):249-58.
- Fernandez IS, Peters JM, Hadjiiozou S, Prabhu SP, Zarowski M, Stannard KM, et al. *Clinical staging and electroencephalographic evolution of continuous spikes and waves during sleep*. *Epilepsia* 53(7):1185-95.
- Aeby A, Poznanski N, Verheulpen D, Wetzburger C, Van Bogaert P. *Levetiracetam efficacy in epileptic syndromes with continuous spikes and waves during slow sleep: experience in 12 cases*. *Epilepsia* 2005;46(12):1937-42.
- Inutsuka M, Kobayashi K, Oka M, Hattori J, Ohtsuka Y. *Treatment of epilepsy with electrical status epilepticus during slow sleep and its related disorders*. *Brain Dev* 2006;28(5):281-6.
- Kawakami Y, Matsumoto Y, Hashimoto K, Kuwabara K, Hirata K, Fujita T, et al. *Treatment with flunitrazepam of continuous spikes and waves during slow wave sleep (CSWS) in children*. *Seizure* 2007;16(2):190-2.
- Buzatu M, Bulteau C, Altuzarra C, Dulac O, Van Bogaert P. *Corticosteroids as treatment of epileptic syndromes with continuous spike-waves during slow-wave sleep*. *Epilepsia* 2009;50 Suppl 7:68-72.
- Kramer U, Sagi L, Goldberg-Stern H, Zelnik N, Nissenkorn A, Ben-Zeev B. *Clinical spectrum and medical treatment of children with electrical status epilepticus in sleep (ESES)*. *Epilepsia* 2009;50(6):1517-24.
- Nikanorova M, Miranda MJ, Atkins M, Sahlholdt L. *Ketogenic diet in the treatment of refractory continuous spikes and waves during slow sleep*. *Epilepsia* 2009;50(5):1127-31.
- Battaglia D, Veggiotti P, Lettori D, Tamburrini G, Tartaglione T, Graziano A, et al. *Functional hemispherectomy in children with epilepsy and CSWS due to unilateral early brain injury including thalamus: sudden recovery of CSWS*. *Epilepsy Res* 2009;87(2-3):290-8.
- Loddenkemper T, Cosmo G, Kotagal P, Haut J, Klaas P, Gupta A, et al. *Epilepsy surgery in children with electrical status epilepticus in sleep*. *Neurosurgery* 2009;64(2):328-37; discussion 337.
- Rossi PG, Parmeggiani A, Posar A, Scaduto MC, Chiodo S, Vatti G. *Landau-Kleffner syndrome (LKS): long-term follow-up and links with electrical status epilepticus during sleep (ESES)*. *Brain Dev* 1999;21(2):90-8.
- Praline J, Hommet C, Barthez MA, Brault F, Perrier D, Passage GD, et al. *Outcome at adulthood of the continuous spike-waves during slow sleep and Landau-Kleffner syndromes*. *Epilepsia* 2003;44(11):1434-40.
- Robinson RO, Baird G, Robinson G, Simonoff E. *Landau-Kleffner syndrome: course and correlates with outcome*. *Dev Med Child Neurol* 2001;43(4):243-7.

To list your event in this diary, email brief details to Rachael Hansford at Rachael@acnr.co.uk by 6th December, 2012

2012

November

Managing Cognitive Impairment

7 November 2012;
Bedford Lodge Hotel, Newmarket
E: info@communitytherapy.org.uk
www.communitytherapy.org.uk

Assessment and Treatment of the Thorax in Neurology

14 November 2012; Derby, UK
T: 01332 254679
E: ncore@derbyhospitals.nhs.uk
www.ncore.org.uk

8th Essential Neuro MRI Study Day
One day course in how to interpret MRI Brain & Spine

17 November, 2012; Liverpool, UK
Limited places. Kath Tyler,
T: 07799 723 925,
E: essentialneuromri@hotmail.co.uk

Navigation and Spatial Memory
in Terrestrial Species
UCL CDCN Workshop:

27 November, 2012; London, UK
E: cdcn@ucl.ac.uk
www.ucl.ac.uk/cdcn/events/forthcomingworkshops

RaATE 2012: Recent Advances in Assistive Technology & Engineering

26 November, 2012; Warwick, UK
T: 024 7615 8000,
E: hdti.info@coventry.ac.uk

University Classes in Multiple Sclerosis IX, focused on Clinical Forms of Multiple Sclerosis

28 November, 2012; Marbella, Spain.
E: ellen.duijn@charcot-ms.eu
www.charcot-ms.eu

Delivering Community Rehabilitation

— Learning from Experience
28 November 2012;
Hippodrome, Birmingham, UK
E: info@communitytherapy.org.uk
www.communitytherapy.org.uk

MS Trust Specialist Health Professionals Master Class:

Sexuality in MS
29 November, 2012; London, UK.
E: education@mstrust.org.uk
www.mstrust.org.uk/professionals/

December

The Encephalitis Professional Seminar

3 December, 2012; London, UK
E: admin@encephalitis.info,
T: 01653 692583

BNPA Neurology and Psychiatry SpRs Teaching Weekend

7-9 December 2012; Oxford, UK
T: 020 8878 0573/0560 1141307,
E: admin@bnpa.org.uk or
jashmenall@yahoo.com

2013

January

RCP/BAD Medical Dermatology Meeting

— Neurology
10 January, 2013; London, UK
E: Dawn.Moore@theabn.org

Biomarkers for Brain Disorders:
Challenges and Opportunities

3-5 February, 2013; Cambridge, UK
https://registration.hinxton.wellcome.ac.uk/display_info.asp?id=303
E: Lucy.Criddle@hinxton.wellcome.ac.uk

February

BNPA 26th Annual General Meeting

7-8 February, 2013; London, UK
T: 020 8878 0573,
E: admin@bnpa.org.uk or
jashmenall@yahoo.com

Dementias 2013

7-8 February, 2013; London, UK
www.mahealthcareevents.co.uk/dementias2013
or T: 020 7501 6762.

Basic Applied Neurophysiology

13th Feb. 2013; Derby, UK
T: 01332 254679
E: ncore@derbyhospitals.nhs.uk
www.ncore.org.uk

Understanding and Management of Fatigue and Sleep Disorders following Acquired Brain Injury

22 February 2013; The Oliver Zangwill Centre, Ely, Cambridgeshire, UK
T: 01353 652173,
E: rachel.everett@ozc.nhs.uk

April

5th Advanced Masterclass

Complex Parkinson's – neuropsychiatry and complex management issues
4 April, 2013; Marriott Hotel, Leeds City Centre, UK
Early bird booking by 17th December £40 per attendee. Programme and booking www.redpublish.co.uk

Research for Clinicians – Integrating Research into Day to Day Practice

19 April, 2013; The Oliver Zangwill Centre, Ely, Cambridgeshire, UK
T: 01353 652173,
E: Rachel.everett@ozc.nhs.uk

Matthew's Friends European Dietitian/Nurses Meeting

Ketogenic Dietary Therapies
25-26 April, 2013; Lingfield, Surrey UK
T: +44 (0)1342 836571,
E: enq@matthewsfriends.org
www.matthewsfriends.org

May

The 11th International Conference on Alzheimer's and Parkinson's Diseases (AD/PD*)

6-10 May, 2013; Florence, Italy
T: +41 22 906 0488
E: reg_adpd2013@kenes.com

June

Consultant & final year SpR Parkinson's Masterclass

Module 1 - Bristol City Centre, 3-5 June, 2013
Further details and booking www.redpublish.co.uk

New Avenues for Brain Repair: Programming and Reprogramming the Central Nervous System

10-11 June, 2013; Cambridge, US
E: events@abcam.com

The Advanced Balance Course

19-21 June, 2013; Chilworth Manor, Southampton, UK
Fiona Barker,
T: 0790 779 1619,
E: fiona.barker@windsor-ent.co.uk

November

Consultant & final year SpR Parkinson's Masterclass

Module 2 - London, 28 November (1 day)
Further details and booking www.redpublish.co.uk

Continuous dopaminergic stimulation therapy in advanced Parkinson's disease: would earlier use be beneficial?



Despite developments in oral and transdermal therapy for Parkinson's disease (PD) over the last few decades, many patients continue to suffer motor complications and dyskinesias. The standard initial treatment for this progressive neurodegenerative condition is oral levodopa. While this effectively alleviates motor symptoms, long-term treatment with oral levodopa induces motor fluctuations. Evidence shows that treatment with continuous dopaminergic stimulation (CDS) can reduce the motor complications that occur in patients receiving oral treatment and also improve non-motor symptoms (NMS).¹

At an interactive symposium held at the recent 16th Congress of the European Federation of Neurological Societies in Stockholm, speakers discussed the rationale for earlier use of CDS therapy in patients with advancing PD. Dr Tove Henriksen (Denmark) outlined that three CDS therapies are available: deep brain stimulation (DBS), levodopa-carbidopa intestinal gel (LCIG) and continuous subcutaneous apomorphine infusion.

Recent studies have demonstrated reduced health-related quality of life (HRQoL) in PD patients compared with the general population,² suggesting that better control of motor symptoms may improve patients' QoL and that earlier introduction of CDS therapy may therefore help maintain patient QoL. As to the long-term efficacy of CDS therapy in patients with advanced PD, studies have shown that treatment with continuous subcutaneous apomorphine infusion reduces daily 'off' time in patients with advanced PD.³ In addition, improvements in motor complications have been demonstrated in long-term studies of LCIG,^{4,5} and DBS has been shown to reduce duration and severity of dyskinesias.³ However before offering these treatments, Dr Henriksen believes it is important to take into account the cost of CDS, as well as its potential side effects and complications.

Debating whether earlier intervention with CDS

is justified, Professor Angelo Antonini (Italy) stressed that the issue with CDS treatment is not just that "We should do it sooner but we should also do it better to improve HRQoL for PD patients." Earlier CDS therapy would provide more effective control of motor fluctuations earlier in the disease and alleviate NMS.

The challenge, in Professor Antonini's view, is to find the optimum moment to start the treatment between early and advanced disease and to smooth out the delivery of the drug in order to provide more constant stimulation that mimics physiological dopamine concentrations at the synaptic cleft, thereby preventing the motor complications which the majority of PD patients develop with oral medication. Professor Antonini believes that switching from pulsatile to continuous delivery as early as possible to reproduce normal physiology would lead to fewer complications and less dyskinesia, a decline in 'off' time and extended 'on' time, thus improving QoL.

However, while patients do indeed improve dramatically with CDS, Professor Eduardo Tolosa (Spain) questioned the justification for treating the patient who has only mild fluctuations with these complex and sometimes risky therapies without long-term safety and efficacy data and without comparative studies between the various CDS strategies. While improvements in QoL in advanced PD are seen in most patients receiving CDS, not all patients experience these beneficial effects and we have no information on how many patients in the early stages of the disease will actually improve with CDS. For Professor Tolosa the key issue is therefore that these CDS-based therapies are given to the right patients.

In addition, the side effects of complex CDS therapies are numerous – including leg oedema, psychiatric problems, and postural hypotension. These are accepted by patients with advanced disease because the treatment improves their

disability dramatically. But to apply treatments with these side effects to patients in the early (mild) stages of PD is a decision that should not be taken lightly, in Professor Tolosa's view.

Another consideration is that very little is known about the natural history of the motor complications of PD. Their impact on QoL is hard to predict so for any individual patient it is difficult to forecast their level of disability in ten years' time. The question is how to identify those patients with progressive disability who have the phenotype that will benefit from earlier intervention. Professor Tolosa noted that it appears that younger patients, and those with low bodyweight and low BMI, are more likely to suffer motor complications.

In the view of symposium chairman Professor Ray Chaudhuri (UK), many are persuaded of the potential benefits of early intervention with CDS in PD. Others, however, need more evidence before they are convinced. It is clear that CDS is accepted as a valuable treatment in advanced PD. Whether or not it should be started at an earlier stage of the disease requires further study.

References

1. Antonini A, et al. The progression of non-motor symptoms in Parkinson's disease and their contribution to motor disability and quality of life. *J Neurol* 2012; Jun 19.
2. Winter Y, et al. Quality of life in Parkinson's disease in Europe: a multi-centre study of the EuroPa Study Group. MDS Abstract of the 16th International Congress of Parkinson's Disease and Movement Disorders, Ireland, 2012. Abstract 945.
3. Antonini A, et al. A 5-year prospective assessment of advanced Parkinson disease patients treated with subcutaneous apomorphine infusion or deep brain stimulation. *J Neurol* 2011;258:579-85.
4. Zibetti M, et al. Long-term duodenal levodopa infusion in Parkinson's disease: a 3-year motor and cognitive follow-up study. *J Neurol* 2012; Jul 8.
5. Nyholm D, Kiangemo K, Johansson A. Levodopa/carbidopa intestinal gel infusion long-term therapy in advanced Parkinson's disease. *Eur J Neurol* 2012;19:1079-85.

A grant was provided by Britannia Pharmaceuticals Ltd as a contribution towards the production and design costs of this article, which was written by Helen Lawn & Associates. Britannia Pharmaceuticals co-sponsored the satellite symposium held on 9th September during the recent 16th EFNS Congress held in Stockholm.

Britannia
Pharmaceuticals Limited



Needle delivery too difficult for who ?

*i still play saxophone
all over the world*

Barbara Thompson, APO-go patient
and world class saxophonist

APO-go® Apomorphine hydrochloride PRESCRIBING INFORMATION

Consult Summary of Product Characteristics before prescribing.

Uses Treatment of motor fluctuations ("on-off" phenomena) in patients with Parkinson's disease which are not sufficiently controlled by oral anti-Parkinson medication. **Dosage and Administration** Apomorphine hydrochloride is administered subcutaneously either as an intermittent bolus injection or by continuous subcutaneous infusion. Its rapid onset (5-10 mins) and duration of action (about 1 hour) may prevent an "off" episode which is refractory to other treatments. Hospital admission under appropriate specialist supervision is necessary during patient selection and when establishing a patient's therapeutic regime. Please refer to the Summary of Product Characteristics for full details before initiating therapy. Treatment with domperidone (typical dosage 20mg three times a day) before and during apomorphine HCl therapy is essential. The optimal dosage of apomorphine HCl has to be determined on an individual patient basis; individual bolus injections should not exceed 10mg and the total daily dose should not exceed 100mg. Do not use if the solution has turned green. The solution should be inspected visually prior to use. Only clear, colourless and particle free solution should be used. **Contraindications** Children and adolescents (up to 18 years of age). Known sensitivity to apomorphine or any other ingredients of the product. Respiratory depression, dementia, psychotic disease or hepatic insufficiency. Intermittent apomorphine HCl treatment is not suitable for patients who have an "on" response to levodopa which is marred by severe dyskinesia or dystonia.

Pregnancy and lactation Apomorphine should not be used in pregnancy unless clearly necessary. Breast-feeding should be avoided during apomorphine HCl therapy. **Interactions** Patients should be monitored for potential interactions during initial stages of apomorphine therapy. Particular caution should be given when apomorphine is used with other medications that have a narrow therapeutic window. It should be noted that there is potential for interaction with neuroleptic and antihypertensive agents. It is recommended to avoid the administration of apomorphine with other drugs known to prolong the QT interval. Apomorphine can increase the antihypertensive effects of domperidone. **Precautions** Use with caution in patients with renal, pulmonary or cardiovascular disease, or who are prone to nausea or vomiting. Extra caution is recommended during initiation of therapy in elderly because of the risk of postural hypotension. and/or debilitated patients. Since apomorphine may produce hypotension, care should be exercised in patients with cardiac disease or who are taking vasoactive drugs, particularly when pre-existing postural hypotension is present. Neuropsychiatric disturbances are common in Parkinsonian patients. APO-go should be used with special caution in these patients. Apomorphine has been associated with somnolence and other dopamine agonists can be associated with sudden sleep onset episodes, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution whilst driving or operating machines during treatment with apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa with given concomitantly with apomorphine. Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists, including apomorphine. Since apomorphine, especially at high dose, may have the potential for QT prolongation, caution should be exercised when treating patients at risk for torsades de pointes arrhythmia. Apomorphine has been associated with local subcutaneous effects that can be reduced by rotation of injection sites or use of ultrasound on areas of nodularity and induration. Contains sodium metabisulphite which rarely causes severe allergic reactions and bronchospasm. **Side Effects** Local induration and nodules (usually asymptomatic) often develop at subcutaneous site of injection leading to areas of erythema, tenderness, induration and panniculitis. Irritation, itching, bruising and pain may also occur. Rarely Injection site necrosis and ulceration have been reported. Pruritus may occur at the site of injection. Drug-induced dyskinesias during "on" periods can be severe, and in

a few patients may result in cessation of therapy. Postural hypotension is seen infrequently and is usually intransient. Transient sedation following each dose of apomorphine may occur at the start of therapy, but this usually resolves after a few weeks of treatment. Dizziness and lightheadedness have also been reported. Nausea and vomiting may occur, particularly when APO-go treatment is initiated, usually as a result of the omission of domperidone. Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine therapy and neuropsychiatric disturbances may be exacerbated by apomorphine. Positive Coombs' tests and haemolytic anaemia and thrombocytopenia have been reported in patients receiving apomorphine and levodopa. Local and generalised rashes have been reported. Eosinophilia has occurred in only a few patients during treatment with apomorphine HCl. Patients treated with dopamine agonists, including apomorphine, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality (especially at high doses). Apomorphine is associated with somnolence. Yawning and breathing difficulties have been reported as has peripheral oedema. *Prescribers should consult the Summary of Product Characteristics in relation to other side effects* **Presentation and Basic NHS Cost** APO-go ampoules contain apomorphine hydrochloride 10mg/ml, as follows: 20mg in 2ml – basic NHS cost £37.96 per carton of 5 ampoules. 50mg in 5ml – basic NHS cost £73.11 per carton of 5 ampoules. APO-go pens (disposable multiple dosage injector system) contain apomorphine hydrochloride 10mg/ml, as follows: 30mg in 3ml – basic NHS cost £123.91 per carton of 5 pens. APO-go Pre-filled syringes contain apomorphine hydrochloride 5mg/ml, as follows: 50mg in 10ml – basic NHS cost £73.11 per carton of 5 syringes. **Marketing Authorisation Numbers:** APO-go Ampoules: PL 06831/0245 APO-go Pens: PL 06831/0246 APO-go Pre filled syringes: PL 06831/0247 **Legal Category POM Date of last revision:** July 2012

For further information please contact: Genus Pharmaceuticals, Park View House, 65 London Road, Newbury, Berkshire, RG14 1JN, UK

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.mhra.gov.uk. Adverse events should also be reported to Medical Information on 0870 851 0207 or dso@genuspharma.com

Version Number: APG.APL.V15
Date of preparation: July 2012
APO-0712-1445



APO-go®
apomorphine hydrochloride

Their life, your choice

2nd Parkinson's Review Meeting

Conference details: Friday 21st September 2012, Eden Building, Hope University, Liverpool.

Chairs: Prof Andrew Lees & Dr Malcolm Steiger **Reviewed by:** Sarah Woolley, Genus Pharmaceuticals.



On Friday 21st September, the second annual Parkinson's Review Meeting (PRM) was held at Liverpool's Hope University. The meeting was supported by an unrestricted grant from Genus Pharmaceuticals Ltd and attracted 6 CPD points with its keynote speakers and comprehensive review of apomorphine, management options in Complex Parkinson's and the effect of the changing NHS on Neurological services.

The day was chaired by Professor Andrew Lees, Clinical Director of Queen Square Brain Bank for Neurological Disorders, London, and Dr Malcolm Steiger, Consultant Neurologist and Director of Research and Development at The Walton Centre, Liverpool. Over 140 delegates registered for the event and included Parkinson's disease Nurse Specialists, Consultant Neurologists and Elderly Care, SpRs, GPs and Pharmacists.

The day started with Prof Lees' overview of the history of apomorphine, which was licensed in the UK as APO-go 20 years ago this year. Following the recognition that this therapy can improve Parkinson's symptoms,^{1,2} it is now believed that continuous subcutaneous infusion of apomorphine may reset the dyskinesia threshold.³

Prof Lees spoke about the two presentations of apomorphine available in the UK: the intermittent injection and continuous infusion. He noted that the intermittent injection tended to be used earlier for 'milder' cases: in patients with active lives, with one or two predictable 'off' periods a day. With the Infusion, he recommended getting the patients off as much of their concomitant oral medication as possible, with apomorphine offering a cleaner therapeutic option. The use of apomorphine has been shown to have a sustained effect, allowing for many years of therapy, as was demonstrated in the following session.

Dr Steiger presented his long-term experience of using apomorphine, declaring that the therapy is underused and questioning why this might be when you consider the results seen. "If you think the drug is expensive, consider the cost of the condition to the economy, to the patient and their family" he stated.

Misunderstandings around apomorphine include (1) the inaccurate belief that it is morphine – yet apomorphine has no narcotic properties and is NOT morphine; and (2) clinicians think it is a cumbersome therapy – it isn't, stated Dr Steiger: patients will use what works. The delivery mechanism means the drug avoids the gut, removing issues around absorption and gastric emptying. So, although there is an initial investment of time by HCPs, use in appropriate patients offers a reliable, quick and effective treatment. Dr Steiger recommended that the dialogue about what therapeutic options are available as the condition progresses should be held early on to remove fear of the unknown.



The next session from Prof David Burn, IAH Director & Professor of Movement Disorder Neurology at the University of Newcastle, covered cognition in Parkinson's: There is a known link between the D3 receptor and behavioural issues in Parkinson's, which is not surprising considering the D3 receptors are found in the limbic areas of the brain – those areas implicated in psychosis, noted Prof Burn.

Newer dopamine agonists tend to have high D3 affinity. Concern that apomorphine, with weak D3 affinity, may cause adverse neuropsychiatric effects is not founded in evidence, explained Prof Burn. Published studies tended to be small or have methodological flaws but the balance of evidence does not suggest neuropsychiatric issues are a major issue with apomorphine. Apomorphine has powerful antioxidant effects and has been shown to inhibit fibril formation, which may have implications across other disease areas.

Dr Biju Mohamed, Consultant Physician and Geriatrician, Rockwood Hospital, Cardiff subsequently discussed dopamine dysregulation syndrome (DDS) and impulse control disorders (ICDs), and the link with D3 receptor activity.

Healthcare professionals need to be vigilant for potential ICD issues, commented Dr Mohamed, by listening to the patient and their family member or carer who may accompany them to clinic. There are questionnaires available to aid in identifying at-risk individuals, and one audience member highlighted a tool available from Parkinson's UK: <http://www.parkinsons.org.uk/pdf/CompulsiveBehaviourInformationTool.pdf>

The role of long-acting non-ergot dopamine agonists in complex Parkinson's was covered by Dr Sandip Raha, Associate Specialist in Integrated Medicine, Movement Disorder Clinic, Princess of Wales Hospital, Bridgend. Continuous dopaminergic stimulation with a long-acting dopamine agonist is a more physiological option for the treatment of complex Parkinson's than using short-acting formulations. Dr Raha covered data on various long-acting dopamine agonists – oral formulations, the patch, and continuous infusions of apomorphine.

Next, Sue Thomas, Chief Executive, Neurological Commissioning Support (NCS), covered the topic of how the changes now underway in the NHS mean that clinicians will be increasingly involved in commissioning services. NCS was created to help clinicians

influence service development. HCPs must become familiar with the efficiency indicators that are used to measure the performance of their services, e.g. admission ratios and length of stay, and identify potential savings, such as through avoiding unplanned admissions or reducing in-patient stays.

The final session of the day covered the role of PDNS⁴, with Brian Magennis from Mater Misericordiae University Hospital, Dublin and Anne Martin from the National Parkinson Foundation International Centre of Excellence, Kings College Hospital, London.

Mr Magennis covered his apomorphine audit data, which showed a substantially reduced tablet burden and polypharmacy dose reduction in patients successfully initiated onto apomorphine infusion, as well as significant UPDRS and Webster motor score improvements and reduction in ICDs.

Ms Martin then described her experience at the tertiary centre, managing an array of Complex Parkinson's patients, with a restriction on in-patient beds. She highlighted the importance of patient selection, not leaving it too late to consider non-oral treatment options, and covered her protocol for managing the polypharmacy reduction when initiating apomorphine patients, including the crucial point of planning existing dopamine agonist withdrawal and levodopa dose reduction.

Thereafter followed a debate on planned admission versus day-case initiation of apomorphine therapy, taking into consideration the pressure on NHS resources, the needs of the patient and those around them. In-patient initiation can mean respite for the family or carer of a Parkinson's patient, with the opportunity to review the patient more fully. Day case initiation is carried out increasingly frequently, removing the anxiety associated with having to stay in hospital, and also saving hospital resources surrounding the need for a planned admission.

Ultimately, the needs of the patients need to be taken into consideration on an individual basis, but there shouldn't be any fear associated with day-case initiations on apomorphine.

The day included frequent audience interaction and informative question and answer sessions, as well as panel discussions. The feedback from the delegates has been extremely positive and a similar one day meeting is planned for 2013.

For further information on the day's talks and outcomes, please contact Genus on Tel. 01635 568400, Email. info@genuspharma.com

References

1. Hagell P, Odin P 2001. Apomorphine in the treatment of Parkinson's disease. *Journal of Neuroscience Nursing*, 9(33):No.1.
2. Katzenschlager R, Hughes A, Evans A et al 2005. Continuous Subcutaneous Apomorphine Therapy Improves Dyskinesia in Parkinson's Disease: A Prospective Study Using Single-Dose Challenges. *Movement Disorders*, 20(2):151-7.

4th Biannual Symposium of the NeuroUnit Biomarkers for Inflammation and Neurodegeneration (NUBIN)

Conference details: 14-15 June, 2012, VU Medical Center, Amsterdam. *Reviewed by:* Marta del Campo Milan on behalf of NUBIN.

The fourth NUBIN symposium was held in the Vrije Universiteit Medical Center (VUmc) of Amsterdam. This biannual symposium has been organised by Dr Charlotte Teunissen and others since 2004. In previous editions the symposium was mainly focused on Alzheimer's disease (AD) and Multiple Sclerosis (MS). However, we have now extended our interest to other neurological diseases, such as Parkinson's disease (PD), trauma and amyotrophic lateral sclerosis (ALS). This symposium gathered together more than 70 participants from all over the world combining both neurologists and researchers, all with wide experience in the discovery and development of biomarkers in different neurodegenerative disorders. The two days were divided into seven plenary lectures of 30 minutes each. Additionally, eight submitted abstracts were selected for oral presentations in which novel results were presented. Moreover, a poster session also took place, allowing young scientists to present their new data.

Dr Leslie Shaw opened the symposium with a talk explaining the Alzheimer's Disease Neuroimaging Initiative (ADNI). This initiative is focused on the standardisation of neurochemical, biochemical and genetic biomarkers. Afterwards, Dr Davide Chiasserini presented an overview of the performance of several biomarker combinations for PD diagnosis including total and oligomeric α -synuclein, tau proteins and CSF lysosomal enzymes activities. Both talks were highly appreciated by the audience. After the lunch break in which all the participants had the opportunity to meet each other, the symposium continued with the talk by Dr Philip Scheltens who explained the String of Pearls Initiative focussed on connecting Biobanks of the main University Medical Centres within the European Union to improve the research of different disorders including the neurodegenerative diseases. Dr Jochen Schwenk gave a more technical talk explaining the single-binder beads assay to discover novel candidate biomarkers in body fluids. This technique identifies and suggests the best antibodies that can be used for biomarkers analysis after further technical and biological validation. Dr Ales Bartos explained on behalf of the Bio-MS-eu Network how critical the choice is of appropriate control groups in cerebrospinal fluid (CSF) biomarker research. The Bio-MS-eu network proposes consensus definitions and nomenclature for different control groups, which will lead to a better comparability of



biomarker studies, optimal use of available resources and improved quality for CSF biomarker studies. Afterwards, Dr Piotr Lewczuk gave a deep and clear overview about how the preanalytical sample handling and storage conditions can strongly influence the quality of the neurochemical dementia diagnosis biomarkers. Dr Nathalie LeBastard closed the first day of the symposium with a plenary lecture in which the diagnostic value of AD CSF biomarkers was evaluated in pathologically confirmed AD patients.

On the second day, Dr Leonard van der Berg gave a great overview of the current state of biomarkers for ALS. Successful results measuring neurofilament chains, TDP-43 or MCP-1 have been obtained so far although there is a lack of reproducibility; highlighting the need to optimise, standardise and harmonise methods for sample collection and data analysis. A newly established EU consortium including 15 ALS centres within Europe (SOPHIA) will try to achieve those aims. Afterwards, Dr Michael Khalil switched the topic to MS. He showed how the levels of neurofilament in CSF are already changed in the earliest stage of MS and are related to the level of physical disability. Additionally, he showed a relationship between neurofilaments and disease progression in MS. Karin van Dijk showed her results for the CSF levels of α -synuclein in PD using a robust, reproducible and sensitive time resolved Förster resonance energy transfer (TR-FRET).

After the lunch break the plenary lectures continued again with the talk by Dr Saskia

Vosslamber who showed how the expression levels of type I IFN-response genes in peripheral blood of Relapsing Remitting Multiple Sclerosis (RRMS) patients prior to treatment as well as genetic variation in IRF5, have roles as biomarkers in predicting the clinical response to IFN β . Then Dr Michiel Petgel gave one of the most valued talks about the use of microvesicles (MVs) as minimally invasive disease biomarkers. He clearly explained how new evidence suggests that disease cells are able to secrete MVs into multiple body fluids. These MVs may contain different molecules that may be useful as biomarkers. His group is currently investigating the genomic content of MVs from different biofluids in order to find genetic markers (as microRNA) that can be used to distinguish healthy MVs from MVs secreted in different patients. Afterwards, Argonde van Harten showed that it is possible to measure microRNAs in CSF, suggesting a potential use of those molecules as biomarker tools. The symposium finished with the talk of Dr Connie Jimenez who gave an overview of the result obtained in the CNEUPRO (clinical NEUROPROteomics) project in which novel candidate CSF biomarkers for early diagnosis of AD were identified using an hypothesis free proteomics approach.

Oral presentations of selected abstracts were performed during both days which were also much appreciated by the audience. The presenters showed results of biomarker analyses for different neurological disorders. Additionally, the poster session contained presentations of scientific results related to multiple diseases including AD, MS and ALS. More technical posters related to antibody development were also presented.

The combination of the three types of presentation (plenary lectures, oral and poster presentations) together with the coffee, lunch breaks and evening program, promoted a stimulating environment in which all the participants were able to meet and discuss their work in an informal atmosphere. It has been an excellent opportunity to start collaborations with other biomarker colleagues. In conclusion, in this meeting we have observed not only which stage we are at in the biomarker field, but also how new approaches for biomarker discovery have been developed; and we are all looking forward to the next biannual meeting in which we hope to find validation of novel biomarkers in the different neurodegenerative disorders. ♦



Childhood Epilepsy Masterclass: The Drugs Aren't Working – What Next?

Conference details: 5 July 2012, Young Epilepsy headquarters, Lingfield, Surrey. **Reviewed by:** Angela Mensah, Young Epilepsy Research Co-ordinator.

This summer's Childhood Epilepsy Masterclass was held in the Neville Childhood Epilepsy Centre at Young Epilepsy headquarters in Lingfield, Surrey. Young Epilepsy, as the only UK charity working exclusively to improve the lives of the 112,000 children and young people with epilepsy, brings together medical, therapy and research expertise to diagnose and treat children and young people with epilepsy from across the UK.

The one-day Masterclass was hosted by Professor Helen Cross, The Prince of Wales's Chair of Childhood Epilepsy. The event, which was sponsored by Special Products Limited and Cyberonics, brought together a wide array of specialists with varied experience; Staff Nurses, Registrars, Consultant Paediatric Neurologists, Neuropsychologists, Consultant Neurodisability Paediatricians and Community Paediatricians.

With such a wide field, the programme was designed with a series of presentations and interactive workshop sessions to appeal to the trainees, while being detailed enough to engage the experts. The day opened with a welcome from Professor Cross. This was followed by the first talk from Dr Colin Ferrie titled 'What makes epilepsy 'difficult'?'. Dr Ferrie is a Consultant Paediatric Neurologist at Leeds General Infirmary where he is the Clinical Lead for Paediatric Neurosciences. His major interest, both clinically and from the research point of view is epilepsy and this was evident in the very practical approach to the talk which included clinical scenarios. Dr Ferrie discussed the impact of seizures (the frequency, semiology and duration), epilepsy co-morbidities and the reaction of the child, family and school to epilepsy.

The second talk titled 'The role of the ketogenic diet in epilepsy management' was delivered by Dr Christin Eltze who is a Consultant Paediatric Neurologist with a special interest in epilepsy at Great Ormond Street Hospital for Children. Dr Eltze works in the Complex Epilepsy Unit, where her responsibilities include being the lead for the ketogenic diet service. Her very informative presentation covered the first application of the dietary treatment in childhood epilepsy reported almost 100 years ago and the number of different types of the diet available now such as the classical ketogenic diet, medium-chain triglyceride type diet and modified ketogenic diet – previously termed modified Atkins diet. Results from a number of open studies in humans were discussed as was the long-term follow up data.

These talks were followed by three interactive workshop sessions on surgery, vagus nerve stimulation and behaviour. The sessions ran for an hour at a time over a 3 hour period and dele-



Above – Prof Helen Cross
Below – Venue



gates were divided into three groups. This gave each delegate the opportunity to attend all the workshop sessions over the course of the day.

The workshop on surgery was led by Dr Krishna Das who is a Consultant Paediatric Neurologist at Great Ormond Street Hospital and at the Neville Childhood Epilepsy Centre at Young Epilepsy in Lingfield. His main areas of interest are management of complex epilepsy, neurophysiology and presurgical evaluation. The surgery workshop gave delegates excellent factual insights into presurgical evaluation and Dr Das' use of MRI and EEG images made for very engaging case discussions.

The session on vagus nerve stimulation (VNS) provided an introduction to VNS therapy, and presented delegates with an opportunity to see the devices and the programming equipment. This session was led by Dr Sophia Varadkar, a Consultant Paediatric Neurologist and Clinical Lead of the Epilepsy Unit at Great Ormond Street Hospital. Her workshop included discussions on appropriate case-selection, the benefits and adverse-effects of VNS therapy.

The session on behaviour was led by Dr Teresa Lax-Pericall, a Consultant in Child and Adolescent Psychiatry at South London and Maudsley NHS Paediatric Liaison Department and Acquired Brain Injury Service and a visiting Consultant at Young Epilepsy. Her case study discussions were engaging and practical and offered the delegates a general overview of psychiatric problems in epilepsy.

A highlight of the Masterclass was a debate with the controversial motion titled 'New drugs don't offer anything more than older generation'. Dr Colin Ferrie and Professor Helen Cross were for and against the motion respectively. They each delivered a very impressive 15-minute presentation in support of their case before the moderator, Dr Sophia Varadkar, opened the floor for questions and clarifications. The debate highlighted the lack of data in the drug treatment of children with epilepsy and led to much discussion as to the wording of the motion itself. However it led to a very informative and entertaining 45 minutes.

The day continued with a talk on 'Cognition and Academic Achievement' by Colin Reilly who is an Educational Psychologist at Young Epilepsy. He is currently working on a research project which aims to determine the prevalence of learning and behaviour difficulties in school-age children with epilepsy and gave a good overview of the educational problems they face. The talk highlighted the significant association between epilepsy and learning (intellectual) disability and made good reference to research data and case studies.

The final talk of the day on 'Epilepsy services and guidelines' was delivered by Dr Colin Dunkley, a General Paediatric Consultant with 'expertise in epilepsies' at King's Mill Hospital, Mansfield. Dr Dunkley is lead for the Epilepsy12 National Audit; a three-year audit to help improve patient outcomes in the quality of care and service provided. Despite being the last talk of the day this was very engaging with discussion of practices experienced by delegates. ♦

This Masterclass was one of an ongoing programme at Young Epilepsy where Masterclasses are held twice a year. The next one is scheduled for 22 November 2012. Visit <http://youngepilepsy.org.uk/news-and-events/news/1110-young-epilepsy-to-host-a-masterclass-by-professor-helen-cross> to book your place on the next Masterclass.

The FENS Forum Comes of Age

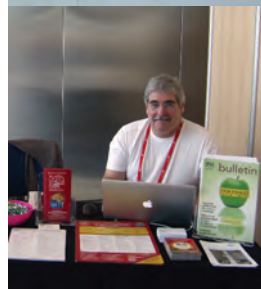


Conference details: 14-18 July, 2012, Barcelona, Spain. **Reviewed by:** Dr Duncan Banks, The Open University, Milton Keynes.

The Federation of European Neuroscience Societies (FENS) was founded in 1998 and aims to advance research and education in neuroscience, representing neuroscience research in the European Commission and other granting bodies. It represents 36 national and European neuroscience (mono-discipline) societies and has around 18,000 members.

The 8th FENS Forum was held in Barcelona 14-18 July, 2012. This biennial event provided a unique opportunity to meet and discuss the most recent advances in basic neuroscience and clinical research. Without doubt, FENS 2012 was a great success with 6,985 participants from 75 countries ranging from Argentina, Armenia and Australia to Uruguay, USA and Uzbekistan. The top five countries participating included Spain (1091), Germany (986), France (590) and the UK (542) with 451 attendees from the USA. Whilst not on the scale of the 2011 Society for Neuroscience meeting in Washington with 31,000 attendees, FENS nevertheless has developed into one of the largest scientific meetings in Europe where representatives from all 32 member societies indulged in neuroscience in all its forms. The attraction for the world-wide audience was a combination of the programme, the location and for the UK contingent the weather, guaranteed sunshine. The programme included plenary and special lectures, a variety of symposia and technical workshops. A large part of the event was devoted to poster presentations (4,338 of the 4,459 abstracts submitted) but perhaps the major departure from previous fora was that all scientific information, except for the programme synopsis, was paperless. Assuming that you were savvy enough to have brought your wireless-enabled laptop, smartphone or tablet, the abstracts and the detailed programme were accessible through a variety of electronic tools including the extensive use of QR codes and 'apps'. The programme alone, all 684 pages of it, would have been far too cumbersome to have carried around each day of the meeting.

The Host Society Committee, chaired by Maria del Mar Dierssen Sotos, had prepared an eclectic and inspirational programme of scientific and social events. Barcelona provided a truly magnificent venue with major attractions throughout the city. If you had time away from the science or had the good sense to add a few days to your visit you could have seen the UNESCO World heritage works of Antonio Gaudí dotted across Barcelona. Possibly Gaudí's greatest achievement is the Sagrada Família or Gaudí's cathedral, the still unfinished monument to a mixture of gothic and art nouveau styles. The FENS meeting in Barcelona provided the perfect opportunity to meet colleagues from across the World to discuss research, more



Accessing the scientific programme using a QR code and an app of your choice.

The author indulging in some rest during a busy schedule.

often in a 'social setting' for example the typically Catalan neighbourhood of Gràcia where public squares are surrounded by bars and a plethora of restaurants.

As with any large scientific meeting any attendee needs to plan ahead to be certain not to miss the most relevant talks or posters. There were, however, several distractions from my intended schedule, particularly on the emerging field of optogenetics. On Sunday I discovered how a worm no more than one millimetre long could help clarify the nature-nurture debate (Rockefeller University, USA) and how slow brain waves during sleep promote learning (Instituto de Investigaciones Biomédicas, Barcelona, Spain). On Monday I found out how to block traumatic memories by electrically stimulating the brain (Universidad Pablo de Olavide, Spain) and how neuroscientists are using optogenetics to map and study how the brain changes during addiction, and how these changes link to altered behaviour (University of Geneva, Switzerland). Dr Marta Navarette's group in Spain described how astrocytes are necessary for memory and their involvement in drug addiction whilst Dr Karl Deisseroth from Stanford University elegantly

demonstrated how optogenetics was taking the neuroscience world by storm by using a combination of genetics, optics, virology, microbial proteins and light to control neurons. Other interesting distractions included 'inattention blindness' and how for the first time, new technology allows geneticists to study all of a person's genes, rapidly and accurately revealing the cause of learning disabilities, such as autism and schizophrenia. As a father to a teenage son I was not completely convinced that action video game players unwittingly train themselves in a wide range of attentional, cognitive, sensory, and spatial skills. However, Dr Daphne Bavelier's research (University of Geneva, Switzerland) indicated that action video game playing does enhance a number of brain functions.

The FENS-IBRO Alumni Symposium on the role of body image and peri-personal space and pain suggested that pain perception goes beyond conscious detection of pain and that many people sense a disconnection from the painful region of their body arising from a complex interplay between the body and the brain's internal map. As someone who was involved in the early development of deep brain stimulation I was also intrigued to know whether deep brain stimulation could be used to treat people with psychiatric disorders to alter their personality, how happiness could be induced and how psychiatrists face difficult dilemmas over where the line is drawn between therapy and enhancement. Dr Peter Uhlhaas (Max Planck Institute of Brain Research, Germany) gave an excellent explanation of why it's not easy being a teenager. The physical and emotional development and the moods that mark the transition from adolescence to adulthood are revealed by new brain connections that occur, which may also be relevant to psychiatric disorders.

Undoubtedly for me the highlight of the meeting was the FENS-EJN Awards Lecture given by Barry Everitt (Cambridge) describing how "Dynamically shifting neural circuitries underlie addictive behaviour". In it he showed how drug addiction is characterised by the compulsive seeking and taking of drugs. Using rats he demonstrated that in order to take on the characteristics of a stimulus-response habit and ultimately emerge as compulsive, depends upon shifting striatal circuitries.

Finally I would like to thank Sociedad Española de Neurociencia for hosting such a memorable event. ♦

If you are interested further details of the meeting can be obtained from <http://forum.fens.org/2012>.

A Disease Attacked on Many Fronts: The 8th International Conference on Frontotemporal Dementias

Conference details: 5-7 September, 2012, Manchester Central, Manchester, UK. **Reviewed by:** Dr Timothy Rittman, Clinical Research Fellow, Department of Clinical Neurosciences, University of Cambridge, UK.

Advances in the field of frontotemporal dementia over the past 15 years have been breath-taking in genetic, molecular and clinical arenas. A corresponding expansion of the International Conference on Frontotemporal Dementia from a handful to 550 participants now provides a forum where clinicians and researchers from vastly different backgrounds come together and discuss their work. So I set off for Manchester with an open mind and came away with a degree of optimism about the future.

Clinical considerations

Carers were a particular focus of the conference. The burden that carers undergo was highlighted in two presentations, including psychological techniques to help carers cope better with the stresses of inappropriate behaviour and apathy. A parallel meeting for carers was well attended. Selina Wray (Alzheimer's Research Trust Research Fellow at the Department of Molecular Neuroscience, University College, London) received an award in recognition of her engagement with carers, and told me "It was great to see such a large turnout of around 100 carers, many of whom had travelled long distances to be at the meeting (including one couple from Switzerland). I was impressed by their enthusiasm to find out more about FTD research and it was a privilege to talk to them about our own ongoing work and to hear their stories and experiences in return."

Although FTD was in the conference title, related tau-associated diseases and motor neurone disease were mentioned often. The murky world of clinicopathological correlation was a theme for a number of clinical talks. In addition to known associations such as semantic dementia and TDP-43 accumulation, Keith Josephs and Jennifer Whitwell presented evidence from the Mayo clinic that the recently described syndrome of progressive apraxia of speech reliably predicts tau aggregation.¹ However, the link to pathology is still uncertain in most syndromes, in particular behavioural variant FTD.

Neuropsychology presentations added some depth to the debates around clinical features, but did not have a large impact on discussions of diagnosis or prediction of pathology.

Imaging has emerged as a useful intermediate phenotype between the molecular and clinical. DTI scans in pathologically confirmed cases, presented by Corey McMillan from the University of Pennsylvania, were able to differentiate tau pathology from TDP-43. He used a data-driven factor analysis that took advantage of the white matter degeneration characterising tau-related neurodegeneration.²



The stunning Manchester Central Convention Complex, previously Manchester Central train station.

Disease modification

Understanding mechanisms of disease and identifying targets for drugs is a key part of many biochemical and cellular research programmes. Karen Duff's (Taub Institute for Alzheimer's Disease Research, Columbia University) talk on how tau protein may propagate between cells and be taken up by mass endocytosis stood out as a carefully considered look at the emerging concept of direct protein spread contributing to pathological changes.³ However, questions remain around why some neurons are more susceptible to pathology, the role of glial cells and whether this mechanism is sufficient in itself to cause disease.

Disease modifying treatments were often mentioned, usually as a long-distant aim, but with two notable exceptions. The much anticipated results of a phase 2/3 trial of Davunetide (Allon Therapeutics) in Progressive Supranuclear Palsy are due in early 2013, a microtubule stabiliser showing encouraging functional improvements in mouse models and administered via a nasal spray. Seglin, a compound at a much earlier stage of development was discovered by Summit PLC to inhibit O-GlcNAcase (OGA) and prevent the conversion of tau oligomers to aggregates.

A cautious message from Jada Lewis (McKnight Brain Institute, University of Florida) highlighted that despite encouraging efforts in animal models, the recently discovered genetic defects have a long way to go before they are realistically replicated in mice or other animals.

Genetics

Genetics permeated virtually every session of the meeting, particularly the recently discovered C9ORF72 found in an astounding one third of familial FTD and around 5% of sporadic disease.⁴ The enthusiasm of finding this mutation has clearly not worn off yet, particularly on Bryan Traynor who introduced the FTD and Motor Neurone Disease session. He animatedly talked about his own 'Eureka moment' on finding the mutation, but highlighted that international

collaborations have been vital and will continue to be vital in making advances in what remains a relatively rare disease.

A lively debate discussed whether to spend more money on genetics in FTD, with two heavy-weights in the field taking a light-hearted but passionate approach. Chris Shaw argued there is still much genetic variability in disease to discover, and John Hardy proposed we channel existing knowledge towards mechanistic understanding and drug discovery.

Conclusions

The standard of science was high, although research and clinical work in diverse disciplines did feel like floating islands still gradually drifting towards each other. Bridges are beginning to form, but there is some way to go in achieving a 'grand theory' of how genetic changes influence molecular and cellular processes to result in diverse pathologies and explain the clinical syndromes of FTD and its related disorders. In the meantime people with FTD and their carers benefit from what we learn about the clinical syndromes.

At the welcoming reception Ian Jacobs (Dean of the Faculty of Medical/Human Sciences at Manchester University) pointed out the camaraderie he saw among conference delegates. Established scientists and clinicians rubbed shoulders and talked to younger researchers in a relaxed atmosphere. Those relationships will be vital if the multiple calls for collaboration and data pooling are to succeed. It seems the field of FTD is in good shape to take on the many challenges still to face. ♦

References

1. Josephs KA, Duffy JR, Strand EA, Machulda MM, Senjem ML, Master AV, et al. Characterizing a neurodegenerative syndrome: primary progressive apraxia of speech. *Brain*. 2012 135(Pt 5):1522-36. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3338923&tool=pmcentrez&rendertype=abstract>
2. McMillan C, Brun C, Siddiqui S, Churgin M. White matter imaging contributes to the multimodal diagnosis of frontotemporal lobar degeneration. *Neurology*. 2012 78:1761-8. Available from: <http://www.neurology.org/content/78/22/1761.short>
3. Liu L, Drouot V, Wu J, Witter M, Small S, Clelland C, et al. Trans-Synaptic Spread of Tau Pathology In Vivo. *PloS one*. 2012 7(2):1-9. Available from: <http://dx.plos.org/10.1371/journal.pone.0031302>
4. Hodges JR. Familial frontotemporal dementia and amyotrophic lateral sclerosis associated with the C9ORF72 hexanucleotide repeat. *Brain*. 2012 135(3):652-5. Available from: <http://www.brain.oxfordjournals.org/cgi/doi/10.1093/brain/aws033>

The next International Conference will be held in
October 2014 in Vancouver, Canada

5th Special Conference of the International Society for Neurochemistry

'Synapses and Dendritic Spines in Health and Disease'

Conference details: 12-15 September, 2012, Buenos Aires, Argentina. **Reviewed by:** Professor Francisco Barrantes, organiser of the conference, Lab. Molec. Neurobiology, Faculty of Medicine, Catholic University of Argentina and Arg. Sci. & Technol. Research Council (CONICET), Buenos Aires, Argentina.

Buenos Aires, the vibrant capital of Argentina, was host for four days to the 2012 5th Special Conference of the International Society for Neurochemistry (ISN). In 2004 the International Society for Neurochemistry began a series of Special Conferences to serve as a forum for reporting outstanding research and development and novel techniques in the field. The first Special Conference took place in Avignon, France, and focused on "Changes in Neuronal Gene Expression and CNS Drug Responses". The second, on "Neural Glycomics and Lipidomics" was held in Antigua, West Indies, in 2006. The 3rd Special Conference, entitled "Neurodegeneration and Regeneration" was held in Beijing in 2008, and the 4th was held in Erice, Sicily, in May 2010 on "Membrane Domains in CNS Physiology and Pathology".

For this year's conference over 140 neuroscientists from around the world gathered at the convention centre of the Catholic University of Argentina, located in the area of Buenos Aires known as Puerto Madero. Formerly the city's main port and then abandoned for decades, Puerto Madero waterfront is now a complex of boulevards with modern buildings and red-brick warehouses totally refurbished into offices, residences, hotels, banks, and trendy restaurants with the most varied international cuisine and pubs.

The topic of the 2012 5th ISN Special Conference in Buenos Aires was 'Synapses and dendritic spines in health and disease', a rapidly moving subject at the forefront of the Neurosciences. The dendrites of neurons receive and incorporate input from thousands of partner cells. The majority of the incoming informational traffic occurs at highly specialised structures termed synapses, distributed all over the dendritic branching of the input neuron. Improper function and/or abnormal regulation of synaptic transmission are implicated in countless neurological and psychiatric disorders. Disturbances of neurotransmission has been associated with the pathophysiology of diseases ranging from schizophrenia, depression and autism to epilepsy and addiction, and increasing evidence suggests that synapses are among the earliest targets in the pathogenesis of Alzheimer's and other CNS diseases. We now refer to this wide variety of pathologies as "synaptopathies".

Understanding the complexity of synapse structure and function, and in particular, how these two properties are linked to regulate circuit function and behaviour, is a major



Prof Federico Dajas, centre, together with students and staff participating at the ISN Advanced Neurochemistry School in the gardens of the Institute Clemente Estable in Montevideo, Uruguay.

driving force in the field of dendritic spine biology. These structure-function studies are leading to amazing advances in our understanding of CNS diseases.

A group of eminent neuroscientists like Alessandro Prinetti from the University of Milano, Italy; Tomoaki Shirao, from Gunma University, Maebashi, Japan; Peter Penzes, from Northwestern University in Chicago, USA, and Gavin Rumbaugh, from The Scripps Florida Research Institute, in Jupiter, USA, actively collaborated with the local organising committee (Laura Morelli, Ana Belén Elghoyen, Jorge Medina and Javier Baier, all from Buenos Aires) and myself to put together an exciting scientific programme.

During the Special Conference in Buenos Aires several presentations dealt with the application of the latest advanced methodologies to tackle the study of synapses and dendritic spines in animal or human subjects. Light microscopy has undergone a revolution in the field. The centuries-old light microscope has now broken the diffraction-limit, allowing unprecedented resolution in studying cells. In the case of the nervous tissue, this has resulted in the application of new high-resolution, high-speed imaging techniques like STED, SIM or STORM modalities of superresolution microscopy ("nanoscopy") to the study of the synapse and the tiny dendritic spines. These new methods are at the vanguard of research in the field, and are being developed and can already be applied to cultured neurons and even live animals to examine the temporal domain and spatial features of the molecular events at individual, living synapses. However powerful these exquisitely refined analytical techniques may be, they nevertheless fall short of unraveling the integrative aspects of synaptic ensembles and neuronal networks, which were

covered in other presentations at the meeting.

Neuroscientists and students alike engaged in lively discussions on the latest advances in homeostatic plasticity in neurons, neuronal polarity, pre- and postsynaptic long-term potentiation and depression at central nervous system synapses, the organisation of neurotransmitter receptors in normal and diseased synapses, and detailed dissection of molecular components in dendritic spines themselves. A group of 15 young participants from Argentina, Brazil, Chile, Colombia, India, Mexico, Uruguay, and the U.S.A. were "primed" during the Advanced School on Neurochemistry held during the previous fortnight in Buenos Aires and Montevideo, Uruguay, with the more sophisticated subjects dealt with at the Special Conference. In addition to these 15 young participants, around 25 doctoral students/postdocs from around the world received scholarships to participate in the Conference, making the input from the audience a vibrant and dynamic learning process for all attendees alike.

The opening plenary lecture, by Nobel Awardee Erwin Neher ("Biophysics of neurotransmitter release and short-term plasticity"), and the closing lecture, by Morgan Sheng ("Life, Death and Disease of Synapses"), spanned the field from the basic biophysical foundations of neurotransmission to the more integrative facets of current research on the synapse and higher circuits, impinging on behavioural consequences of synaptic alterations.

In summary, by focusing on the synapse and synaptopathies, the 2012 ISN Special Conference brought together leading researchers in the field of synapse biology in an attempt to forge a path toward a better understanding of how synapses and circuits contribute to important neurological and psychiatric disease processes. ♦

10th European Congress on Epileptology

Conference details: 30 September - 4 October 2012, ExCel International Conference Centre, London, UK. **Reviewed by:** Dr Mark Manford, Consultant Neurologist, Addenbrooke's Hospital, Cambridge, UK.

I walked into the Excel Arena, amid thousands of smiling expectant faces, the familiar five rings and a friendly jostling for places – Oh no! Sorry, that was the Olympics. But there was the same warmth of hospitality even for 3500 European Congress of Epilepsy delegates, even if they did not even fill one small corner of this vast building. Simon Shorvon and Phil Smith, the British contingent leading the organising committee did what the Brits do best. They created a conference that was scientifically interesting, educational, well-organised and tinged with quirky eccentricity, starting with a video celebrating London including the brain surgery sketch from Monty Python's Flying Circus. The theme continued through the conference with a quiz loosely based on University Challenge, with the winner's trophy being taken by Ireland.

There were two major general interest lectures. The first, given by mathematician Timothy Gowers, grandson of Gowers of neurological fame, concerned the problems with the distribution of knowledge in modern science. He espoused the view that the age of the subscription journal was passing. He argued that journals act as a distorting filter and a brake on scientific publication and that science should be published online and reviewed online, which would allow a trail of review and arguably improve the peer review process. He argued that the journals had a vested interest in preventing this process which they exercised. Sir Peter Mansfield, to whom every neurologist should genuflect each morning on their way to work, gave a talk on some aspects of the development of MRI. As a physicist, I was impressed with his comprehensive knowledge of anatomy. I should have liked to hear a little more of his personal story, but it was enough to be in the presence of the great man himself.

However hard I tried to escape educating myself about epilepsy, there were inevitable moments when guilt struck and I found myself, for better or for worse, updating my knowledge.

A few years ago I was rather pessimistic about the future of epilepsy treatment, with an endless series of drugs that seemed to me to be a variation on a theme that had not really changed since the introduction of phenytoin in 1937. However, things are moving and with deeper understanding of the mechanisms of epileptogenesis, we are slowly but steadily moving towards treatments which address these mechanisms. Previous experimental models have required most of the treatments to be given either before the insult triggering epilepsy, or very soon afterwards. But most patients present with seizures and we may not necessarily know when the trigger occurred.



View from Royal Dock Bridge. The southern side of Excel centre and the northern bank of Excel Marina.

But now we are starting to see some mechanisms which will act later in the process. Histones which upregulate NSRF will block some of the effects of epileptogenesis, even if given after the insult which triggered seizures and similarly neuropeptide Y seems to have a powerful effect. Professor Dimitri Kullman described how the potassium channel Kv1.1 can be upregulated when introduced focally into the cerebral cortex by modified lentivirus and this will completely suppress seizures even after seizures have started. Of course, making every patient with refractory epilepsy have a minor neurosurgical procedure will cause eyebrows to be raised in the Treasury. However, Stephen Gray described how the adeno-associated virus, a tiny nonpathogenic human virus, enters the brain across the blood brain barrier. Since seizures disrupt the blood brain barrier, there is the potential to concentrate the virus in the region of epilepsy activity. By repeated cycles of intravenous virus injection then purification from the brain, his group has selected a virus that when injected intravenously will appear in high concentrations in the region of seizure activity, with relatively little elsewhere. The potential of combining these techniques to introduce a gene by intravenous injection, which modulates epilepsy activity and is concentrated in the appropriate brain is a very exciting prospect.

We conventionally describe epilepsies as either focal or generalised, but the term generalised is really descriptive of a clinical syndrome rather than the basic mechanism. Indeed some patients with so-called absences of idiopathic generalised epilepsy have much greater alteration of awareness than others and functional neuroimaging in these patients shows that the degree of alteration of awareness correlates with the extent of cortical involvement in the process. We know that in

Idiopathic Generalised Epilepsy, there is an interaction between the cerebral cortex and the thalamus, but which is the chicken and which the egg in the process. The conclusion seems to depend on the investigative technique used and remains a cause of debate.

There are some practical advances in the treatment of status epilepticus which are grounded in new revelations of the underlying science. It has been known for some time that GABA is depleted early during status epilepticus and that this explains the failure of the response to benzodiazepines, which occurs after about an hour of continuous seizure activity. But new research shows that drugs that regulate calcium entry by changing potassium channel properties such as flutripine or retigabine can prevent the habituation to the action of benzodiazepines. As well as being of mechanistic interest, this has potential practical relevance, since retigabine is already available. The new drug perampanel which is the first drug to block glutamate transmission and not be unacceptably toxic, may also have a role in this regard. One thing is clear, that other than for benzodiazepines, clinical studies of drugs in status epilepticus are inadequate. I have previously written about a recent study demonstrating that the ease of use of intramuscular midazolam means that its effect is as rapid as more complex to administer intravenous preparations and it should be thought of as a first-line drug. In the UK, phenytoin remains sacrosanct as first-line treatment after benzodiazepines, despite the fact that it is clearly a nasty drug to give. Valproate, levetiracetam and lacosamide are effective and widely used but we need studies see if they work better, although they are generally cleaner. Other treatments for the desperate include the anaesthetic ketamine, which paradoxically also has some pro-convulsive effects and the ketogenic diet, which is relatively easy to administer in the intensive care setting.

As well as these highlights, there were large numbers of smaller studies discussing surgical treatment, imaging techniques, the inevitable league of new genes, which I shall never remember, and a session on infective and inflammatory causes of epilepsy. There were also sessions on comorbidities of epilepsy and a debate on whether it is more important to treat them than the epilepsy itself. The result predictably is that one should try to do both, without jeopardising the other.

Overall, there is the feeling that epilepsy is starting to emerge from the 20th century into the 21st with new vistas on basic mechanisms and treatment and a broader view of the importance of other aspects of quality of life than simply seizure number. ♦

125th Anniversary Meeting of the Anatomical Society

Conference details: 10-12 July 2012, Royal College of Surgeons, Edinburgh, UK. **Reviewed by:** Dr Simon Parsons.


In 2012 The Anatomical Society celebrated its 125th anniversary by organising a joint international meeting and symposia with our colleagues from the Sociedad Anatómica Española, at the Royal College of Surgeons at Edinburgh, 10-12th July 2012. The major scientific theme of the meeting was Motor Neurones and Diseases of Motor Neurones. The meeting attracted over 165 delegates from around the World and almost 100 abstracts were submitted. The symposium joint organisers, Dr Simon Parson and Professor Tom Gillingwater (both of Edinburgh University's Euan MacDonald Centre for Motor Neurone Disease Research) set out to organise a meeting that brought together basic and applied scientists and clinicians working in the field of motor neurones and the diseases which target them. The opening plenary lecture by Pico Caroni (Basel, Switzerland) filled the auditorium in the King Khalid building and riveted the audience with a wide-ranging discourse on his seminal work on the SOD1 ALS model mouse.

Gareth Miles from St Andrews University followed, informing us about inhibitory circuitry in spinal cord motor pathways, while Maria Lanuza (Reus, Spain) brought a different player to the party, discussing the role of protein kinases at the neuromuscular junction. After lunch, we were very fortunate to have managed to fly in Harvard Professor of Neuroscience, Jeff Lichtman, to bring us up to date about his hugely ambitious project to map the 'connectome' of the brain. This tour-de-force visually stunning presentation left many old hands amazed, especially as it seems he is really going to be able to map every synapse in the brain, possibly within a year! Lucia Tabares (Seville, Spain) followed this with some beautifully detailed work on the organisation of presynaptic proteins at the neuromuscular junction to round off day one in style.

Michael Sendtner (Wurzburg, Germany) opened day two with a talk which brought together his thoughts on both Amyotrophic Lateral Sclerosis and Spinal Muscular Atrophy,

in terms of the involvement of axonal growth and plasticity. Angela Vincent (Oxford) and Hugh Willison (Glasgow) educated us all in the importance of antibody mediated and inflammatory interactions at the neuromuscular junction, followed by a thought provoking dissection of what we really know about ALS, from Kevin Talbot (Oxford). The final talk was by Chris Lorson (Missouri, USA), which nicely brought us back to the development of therapeutic tools to treat Spinal Muscular Atrophy and also his pioneering work developing a large animal model of the disease.

The meeting was very friendly and provided ample opportunities to discuss the content of the talks and many posters. It was rounded off by a gala dinner and ceilidh dancing at the Hub on the Royal Mile and delegates went away happy that they had heard some excellent research talks from leaders in the field. A special symposium issue of the Journal of Anatomy will be produced for publication in 2013 containing articles from the invited speakers mentioned in this review. ♦



3rd WORLD PARKINSON CONGRESS

Palais des congrès
October 1-4, 2013 | Montréal, Canada

Science, Community, Hope | Science, Communauté, Espoir

The 3rd World Parkinson Congress is a unique international event designed to bring together the full spectrum of people who live with Parkinson's disease and those who serve the Parkinson community as researchers and clinicians. We hope this cross-pollination helps in finding a cure as well as identifying the best treatment practices for people living with Parkinson's.

November 5, 2012
Video competition opens

December 3, 2012
Abstracts open

January 2, 2013
Registration opens

April 15, 2013
Abstracts close

Important Dates

www.worldpdcongress.org

The official language of the WPC 2013 is English.



NeuroID 2013: Liverpool Neurological Infectious Diseases Course

Liverpool Medical Institution, UK
Thursday 9th – Friday 10th May

Ever struggled with a patient with meningitis or encephalitis, and not known quite what to do? Then the Liverpool Neurological Infectious Diseases Course is for you!

For Trainees and Consultants in Adult and Paediatric Neurology, Infectious Diseases, Acute Medicine, Emergency Medicine and Medical Microbiology who want to update their knowledge, and improve their skills.

- Presented by Leaders in the Field
- Practical Management Approaches
- Rarities for Reference
- Interactive Case Presentations
- State of the Art Updates
- Pitfalls to Avoid
- Controversies in Neurological Infections
- Join us for Brain Infections Research Update Day on 8th May

Convenors: Prof Tom Solomon, Dr Enitan Carrol, Dr Rachel Kneen, Dr Nick Beeching, Dr Benedict Michael

For more information and to REGISTER NOW VISIT:
www.liv.ac.uk/neuroidcourse

2009-2012 courses sold out at 110 delegates, register now to avoid disappointment!

Fantastic value at £231 for two days!

The European Headache And Migraine Trust International Congress (Ehmtic)

Conference details: 20-23 September 2012, London, UK. **Reviewed by:** Modar Khalil, Fayyaz Ahmed, Department of Neurology, Hull Royal Infirmary.

The European Headache and Migraine Trust International Congress (EHMTIC) is a joint conference of the Migraine Trust and European Headache Federation that is held once every two years alternating with the International Headache Congress organised by the International Headache Society. The two meetings are considered the best headache conferences and provide an opportunity for younger scientists and clinicians to present their research and network with the leading headache experts. The meeting was attended by 800 healthcare professionals from more than 50 countries and various disciplines with an interest and expertise in dealing with headache patients. A central venue at the Hilton Metropole near the Edgware Road tube station was attractive to the delegates for its proximity to some of the most famous Middle Eastern restaurants in the vicinity. Moreover the venue had the facilities to run all activities under one roof avoiding the need to commute in unpredictable British weather.

The conference, held over four days, had teaching sessions on the first day and public awareness sessions on the last day. The teaching courses were aimed at a general audience of general practitioners, specialist nurses and therapists involved in headache care. There were invited lectures delivered by the leading experts, scientific presentations as platforms and posters along with a satellite symposium with academic and promotional contents. The parallel sessions were carefully planned to attract the relevant audience in each session. There were sessions dedicated to headaches in primary care, paediatric headaches and headaches in women.

Dr Tobias Kurth delivered the McDonald Critchley lecture on the epidemiology of migraine genetics and updated the conference on the recent advances on the hunt for a specific gene for migraine. Migraine has a genetic cause but so far the gene has only been identified in the rare familial hemiplegic migraine.

Dr Irene Tracey from Oxford University presented a very interesting lecture on the relevance of pain imaging studies in understanding migraine. She discussed the recent advances in understanding pain processing, cognitive and emotional modulation as well as the consequent pain perception using very advanced neuroimaging modalities such as a seven Tesla MRI scanner, functional MRI and PET scanning. Dr Tracey touched upon the role of various brain structures such as periaqueductal grey matter (PAG) and the rostral ventromedial medulla (RVM) in modulating the way we perceive pain! The imaging studies indicate that patient expectations of treatment can play a major role in the treatment outcome.



Hilton Metropole Hotel.

Dr Clifford Woolf from Harvard University gave a talk on how traditional preclinical research approaches in developing analgesics has its own pitfalls. With the creation of non human pain surrogate models, it is not able to predict how efficacious new analgesics will be in treating human pain, which in turn is responsible for the lack of discovery of new analgesics over the last twenty years. Dr Woolf is advocating a new approach in developing new pharmacological pain treatments which target the disease phenotype, with the patient being the main driver in that approach.

Professor Messlinger delivered the Migraine Trust lecture on research approaches in understanding the biology of migraine. He stressed the importance of a better understanding of pain sensitive structures of the cranium, the trigeminocervical complex along with pain-modulating brainstem structures. He also suggested that the role of neurotransmitters in migrainous pain and their utility in pain models as experimental triggers was key to future research.

Dr Rigmor Jensen gave a nice overview that summarised advances achieved in combating migraine. His starting point was the discovery of the currently used triptans and extended to recent advances in understanding the pathophysiology of migraine, the emerging implementation of Botox and the future utilisation of magnetic stimulation in migraine management.

Dr S Ashina talked about the relationship between depression and risk of transformation to chronic migraine, for which he received the Enrico Greppi award.

There were three invited lectures by new scientists in the headache world. Dr Ashgar reported findings on the use of glyceryl trinitrate and calcitonin-gene-related peptide (CGRP) on Blood-Oxygen-Level-Dependent (BOLD) signal using functional MRI. The study showed that CGRP dilates the middle meningeal artery but not the middle cerebral artery. He concluded that sumatriptan and CGRP exercise their effect outside the blood brain barrier. Dr Andreou presented fascinating new results studying cortical spreading depression and its ability to modulate tertiary neurons central sensitisation in the thalamus even after trigeminal ablation. These findings have great potential for the

development of innovative approaches in treating migraine.

Dr Magis presented results of functional imaging in a large series of their patients with chronic cluster headache treated with occipital nerve stimulation. Patients were followed up for five years and their results showed that although patients with cluster headache show normalisation of hyperactivation at the pain centre, the autonomic centre remains active. This accounts for the persistence of such symptoms even during pain freedom. She received the Giuseppe Nappi award.

There were interesting posters related to all aspects of headache. The headache group in San Francisco lead by Peter Goadsby reported that changes in the functional MRI of patients commence long before the actual migraine attack in the prodrome phase.

As in every conference there were satellite symposia sponsored by the manufacturers of drugs and devices. The symposium by eNeura that manufactures the spring Transcranial Magnetic Stimulation (TMS) device reviewed the past, present and future of neurostimulation and how the research is heading towards non-invasive and non-pharmaceutical ways of treating migraines. Although the evidence stemmed from its use in patients with aura, the real life experience has seen benefit in all forms of migraine as an abortive treatment. The symposium sponsored by Allergan had speakers talking on the post-licensing experience of using Botox in Chronic Migraine and studies looking into the cost-effectiveness of this treatment. Allergan also arranged a breakfast workshop where attendees had a chance to learn the injection technique for Botox in Chronic Migraine. The technique was demonstrated on an MIA head. A symposium by Linde discussed cluster headache in Europe, its economic cost, and a recent trial on which was the best oxygen mask to use and another trial on utilising a demand valve in oxygen delivery for cluster headache attack. The symposium by Menarini focused on issues of migraine in women. Dr Anne MacGregor described menstrual related migraines as more disabling than other forms and how this could be treated with long acting triptans.

All in all, the conference was an excellent opportunity for anyone with an interest in headache to learn about the diagnosis and management of common headache disorders. There were many opportunities for them to familiarise themselves with the ongoing research in the disorder and the development of new treatments. This also provided an opportunity to meet some of the famous names in headache research and be able to ask them questions face to face! ♦

Phenol Block for Upper Limb Spasticity



Christopher W Roy

recently retired as Consultant in Rehabilitation Medicine at the Southern General Hospital, Glasgow, where he had been appointed in 1993. He had previously (since 1988) worked as Senior Lecturer in Rehabilitation Medicine at Wellington School of Medicine, New Zealand. Clinical interests include spasticity, and the locomotor consequences of neurological disease. Research interests include shoulder pain in paralysed people, and measuring the effectiveness of rehabilitation.

Correspondence to:

Email: chrisroy.work@yahoo.co.uk

This article follows that of Moheb Gaid, which appeared in a recent edition of *ACNR*,¹ where phenol nerve block of lower limb spasticity was discussed. Here, attention is given to upper limb procedures. Before any focal technique is performed, intercurrent disease as a cause of increased spasticity must be excluded, and intervention at a local rather than systemic level deemed appropriate. This process is similar to preparation for botulinum toxin injection, which has been well described elsewhere.² This article assumes that these preparatory considerations have been completed.

Although a treatment that has been used since the 1960s,³ the widespread use of botulinum toxin for focal spasticity has reduced the frequency of phenol procedures, particularly in the upper limb; many situations call for the injection of smaller muscles, which are eminently susceptible to botulinum toxin techniques. In a series conducted in the late 1990's, Ahmed and colleagues⁴ found that of 254 consecutive Phenol procedures for spasticity 35% applied to the upper limb (10% biceps, and 25% wrist and/or finger flexor procedures). Greater availability of botulinum toxin has altered this picture; in a recent period of approximately 18 months in our own department, 283 procedures for treating spasticity were performed using botulinum toxin. Of this, 65% were for upper limb indications, and the remainder lower limb; whereas in the same period, of 196 peripheral phenol procedures, the vast majority applied to the lower limb, with a few procedures only employed in the upper limb, or trunk. Nevertheless, there remain a number of situations where phenol remains a useful option, in view of the (generally) longer

duration of effect of phenol, the large dose range that can be used, and the relatively low cost of the medication: typically, sufficient phenol to treat elbow flexors might cost 5% of the botulinum dose required. These reasons are summarised in Table I.

Phenol blockade may be performed either to a nerve trunk, or to motor points of target muscles. The technique of nerve block is generally similar to that of those lower limb procedures described in Gaid's paper,¹ but this paper will explain the technique of motor point blockade, used in many upper limb procedures. This technique also has applicability in some lower limb procedures, and thus will add to Gaid's discussion of that. These techniques are generally low risk, and have been performed both in hospital and community settings. Although phenol concentrations of 4-8% have been used for neurolysis, and stimulation frequencies of 0.5-4Hz, for simplicity we report here doses needed for 6% aqueous phenol, and 2Hz stimulation, as our usual practice.

In principle motor point blockade can be applied to virtually any superficial muscle, but the more common sites of intervention in the upper limb are listed in Table 2, together with those areas where nerve block is preferred. Upper limb procedures employing nerve blocks as part of an open surgical procedure have been described,⁵ but this is less commonly used now, and will not be further discussed here. Figure 1 shows a typical patient where upper limb phenol blockade was found helpful.

Actions of Phenol, and adverse reactions

A comprehensive description of these is detailed in a helpful review by Gracies et al.⁶ In brief, phenol has transient local anaesthetic actions, but later neurolytic, and in some cases myolytic activity. Gracies cites laboratory work identifying microvascular changes also, but the clinical significance of this is uncertain. As a phenolic, there must be a theoretical risk of mutagenic changes, but the author is not aware of clinical reports of this.

The principal adverse effects that should be communicated to the patient before a procedure are bruising and pain. Bruising is of course a possi-

Table 1: Indications for phenol injections

Sensitivity, or previous reaction, to Botulinum toxin
Unsuccessful treatment with Botulinum Toxin
Long duration of effect sought
To supplement Botulinum treatment where total dose required would be excessive
Cost reduction

Table 2: More common sites of phenol injection for upper limb spasticity

Problem	Nerve block	Motor point block
Shoulder internal rotation		Pectoralis major, subscapularis
Arm adduction		Latissimus dorsi
Elbow flexion	Musculo-cutaneous	Biceps, brachioradialis
Wrist flexion		Flexor carpi ulnaris, flexor carpi radialis
Finger flexion		Flexor digitorum superficialis
Thumb-in-palm	Recurrent motor branch of median	

bility in any procedure at or near muscle, but may be more common in spasticity procedures as the muscle may contract due to stimulation or spasm whilst the needle is in situ. On occasion, appreciable haematoma formation can occur, and in one case in the author's experience, this organised, resulting in contracture. Caution is needed therefore in anticoagulated patients. In our department, we generally employ an empirical limit of an INR of 2.0, especially in areas, such as the forearm flexor compartment, where space is constrained. Similar considerations apply to those with bleeding diatheses.

Peripheral procedures using Phenol have been reported as commonly producing severe pain during injection, and the chance of late deafferentation pain. In our experience (which extends to over 2000 cases), such side effects are rare. In Ahmed's series,⁴ the overall late complication rate (combining haematoma and neuralgic pain) was 2%, and this is in accord with our longer experience. This rate, lower than some quote, may be because of our preference for avoiding injection of large mixed nerves where possible, preferring injection of more-or-less purely motor nerves, or motor-point procedures. Immediate pain lasts only whilst phenol is being injected. In our series of 196 cases mentioned above, pain during injection was recorded in four cases; but there may have been some under-recording, as in general we estimate a 5% chance of immediate pain. Deafferentation (neuralgic) pain is more troublesome when it does occur. Generally it appears one to two weeks after the injection, and lasts for some weeks. In most cases, it is self-limiting, but some require management with agents such as Gabapentin. We have not seen cases of post-phenol neuralgias lasting more than four to five months, but patients are warned that permanent cases have been reported.

Systemic side effects are unlikely at the doses commonly employed in spasticity procedures. The lethal dose of phenol has been reported as at least 8.5 G,⁶ which is over 140 mls of 6% phenol. Arrhythmias were encountered in a case where 40mls of 6% phenol was injected to the coeliac plexus. A 'house rule' in our department was established as a maximum 50% of that, ie 20mls of 6% in any one day. However, other body areas could be injected a day or two later.

The effect of Phenol may be felt immediately, presumably due to its local anaesthetic action, but the full effect may take two to three weeks to develop. The duration of action is very variable, from a few weeks only to some years. In practice, patients are advised to hope for six to nine months benefit. We rarely re-inject a site less than three months after a first injection. Benefit is not universal in our experience, but we counsel that useful benefit may be expected in 60-80% of patients. Following injection, appropriate exercise and orthotic intervention, as outlined by Gaid, forms an integral part of the treatment.



Figure 1. Severe multifocal upper limb spasticity.



Figure 2. Motor point block of Pectoralis Major. Note that three injection points can be seen, two of which have already been injected.

Motor point blockade

Motor points lie on the surface of the muscle. Each muscle may have a number of motor points. The locations vary greatly from individual to individual, and their location must therefore be identified as the first stage of blockade procedures. It is said that they tend to cluster around the midpoint of a muscle's length; in the author's experience this is largely, but by no means wholly, correct. The advantages of injecting motor points rather than nerve trunks are that individual muscles can be targeted, and that the absence of sensory fibres reduces the chance of dysaesthesia following injection; the disadvantages are the difficulty in injecting deep muscles, and the larger number of injections required. The technique is as follows:

- 1) Using a nerve stimulator, an exploring electrode is systematically swept over the skin overlying the target muscle, and muscle response identified by palpation and/or vision. Initially, a low stimulus amplitude is used, to aid patient tolerance. Maximum response for minimum amplitude is sought, aiming to locate the point to within 1cm. At 2Hz stimulation, it follows that the maximum sweep speed to achieve this is 2cm/second.
- 2) If no suitable point is found, the stimulus amplitude is increased according to toler-

ance until a motor point is identified. The point is marked with a suitable skin pen, and further points sought. Typically in a larger muscle such as biceps, three or four points may be identified; frequently a smaller muscle yields only one point.

- 3) After suitable skin antisepsis, an insulated needle is introduced through the skin at a marked point, and advanced more deeply to reach the surface of the muscle. A resistance is usually felt as the needle penetrates the fascia; the next resistance beyond that is taken to indicate the muscle surface. It is preferable not to enter the muscle, to limit bruising, and as the blockade is accomplished more easily at the muscle surface.
- 4) Using the muscle stimulator, the point of the needle is moved to identify the strongest response. Whilst stimulation continues, 1ml of phenol is injected. If all stimulated contraction is not abolished, further smaller aliquots of phenol are given, titrated to response. It is rare for more than 2mls to be required at one point; that requirement suggests imprecise localisation, and prompt repositioning of the needle.
- 5) The procedure is repeated for each point found at Stage 1 above.

Specific areas of intervention

Internal rotation and adduction of the arm

Pectoralis major is in most cases readily amenable to motor point block, which is illustrated in Figure 2. Typically three to four points are found, most commonly just medial to the axilla.

Subscapularis⁷ motor point injection has also been described, via a medial approach at the level of the spine of the scapula. The patient should be positioned sitting forward, and the operator grasps the medial border of the scapula and pulls it posteriorly, to widen the access. Some patients' bodily habitus will make this procedure difficult or undesirable. Here, skin stimulation is clearly valueless, but the motor point may be expected by advancing the needle close to the anterior surface of the scapula about 7-10cm. The patient should be warned of the possibility of pneumothorax.

Latissimus dorsi is approached by identifying motor points just medial to the posterior axillary fold, near the musculo-tendinous junction. This site is chosen as well away from the so-called 'bare' area of pleura near the inferior border of the muscle.

Elbow flexion

The three muscles to be considered are biceps, brachialis, and brachioradialis. **Musculo-cutaneous nerve block** will impact on biceps and brachialis, but not brachioradialis. The technique is described by

Keenan,⁵ with medial insertion of the needle to pass between the short head of biceps and the brachialis. Some additionally use the brachial artery to aid localisation.

As an injection of a mixed nerve, there may be concern over a greater risk of post-injection neuralgia, and so we have preferred **motor point injection of biceps⁶ and/or brachioradialis**. Biceps is generally less important as an elbow flexor than the other muscles, but it is important when the forearm is pronated, which is commonly the situation in spasticity. In **brachioradialis**, it is rare to identify more than one point. Typically, this is found about 1-2cm distal to the elbow crease, on the lateral side of the supinated forearm.

Wrist and finger flexion

Motor points of the superficial flexors (**flexor carpi radialis, ulnaris, and flexor digitorum superficialis**) are found by scanning the volar surface of the forearm with a surface electrode from approximately 4cm distal to the elbow crease to the musculo-tendinous junction. The motor points of these muscles are often found very close to each other, approximately halfway between the elbow and the wrist (or a little more proximally). Since wrist and finger spasticity often co-exist, it is not usually essential to differentiate which points are selected, but if needed individual muscles (and sometimes individual digits)

can be selected by careful observation of muscle stimulation. **Flexor digitorum profundus** is more difficult to treat by this method, but can sometimes be identified.

Since this compartment has limited space, the total volume of injection is kept low – preferably less than 5mls – achieved by very careful localisation of the motor points.

Thumb-in – palm

Thenar eminence muscles may often respond to a single injection to the recurrent motor branch of the median nerve, as described by Keenan⁹. This is injected where the nerve enters the thenar eminence, at the junction of a line drawn proximally from the radial border of the long finger, and a line formed by projecting the medial edge of the thumb parallel to the first palmar crease. The innervation of the thenar muscles is variable, but in the majority of subjects, this nerve supplies them. 2-3mls of 6% phenol are injected, titrated to ablation of stimulation. Flexor Pollicis Longus may also need injection.

Conclusion

Despite the ready availability of alternative procedure, the long duration of action and relative economy of phenol blockade mean that these procedures remain a useful part of spasticity management. ♦

REFERENCES

1. Gaid M. Phenol Nerve Block for the Management of Lower Limb Spasticity. ACNR, 2012;12(3):23-5.
2. Royal College of Physicians, British Society of Rehabilitation Medicine, Chartered Society of Physiotherapy, Association of Chartered Physiotherapists Interested in Neurology. Spasticity in adults: management using Botulinum toxin. National guidelines. London: RCP, 2009
3. Khalili AA, Harmel MH, Forster S, Benton JG. Management of spasticity by selective peripheral nerve block with dilute phenol solutions in clinical rehabilitation. Arch Phys Med Rehabil 1964;45:513-19.
4. Ahmed S, Hagen P, Forrest S, Roy C. Unpublished data (personal communication), 1995
5. Keenan MAE. Management of the spastic upper extremity in the neurologically impaired adult. Clinical Orthopaedics and Related Research, 1988;233:116-25.
6. Gracies J-M, Elovic E, McGuire JR, Simpson DM. Traditional Pharmacologic treatments for spasticity. Part I: Local treatments. In: Spasticity: Etiology, evaluation, management and the role of botulinum toxin. We Move; 2002:65-93.
7. Chironna RL, Hecht JS. Subscapularis motor point block for the painful hemiplegic shoulder. Arch Phys Med Rehabil 1990;71(6):428-9.
8. Batchelor R, Roy CW. The use of motor point blocks to relieve spasticity in biceps muscle. NZ J Physiother, 1991;19(3):6-7.
9. Keenan MAE, Botte MJ. Technique of percutaneous phenol block of the recurrent motor branch of the median nerve. J Hand Surg 1987;12A:806.

Organised by
**HOSPITAL
MEDICINE**

Gold Sponsors
Lundbeck   **NOVARTIS**

15th national conference

Dementias 2013

The Institute of Engineering & Technology (IET), Savoy Place, London 7th & 8th February 2013

Highlights will include:

Keynote Address: Social care for people with dementia: responding to the Prime Minister's challenge
Sarah Pickup

Safeguarding people with dementia
Jonathan Waite,

Practical use of imaging in dementia
John O'Brien

The place of psychotherapy in regards to dementia
Jane Garner

Individual cognitive stimulation for dementia – the iCST Trial
Vasiliki Orgeta

Dementia care pathways: The West Midlands Model
Karim Saad

What's new in cognitive impairment and dementia in Parkinson's disease
Iracema Leroi

Debate: Dementia should largely be diagnosed in primary care
In favour: Ian Greaves
Against: Roy Jones

Prevalence and quality of antipsychotic drug prescribing in UK mental health services
Thomas R. E. Barnes

The less common dementias
Anoop Varma



For further information and/or to book your place please visit
www.mahealthcareevents.co.uk/dementias13
Alternatively call our booking hotline on 020 7501 6762



Epha4 inhibition suggests axonal therapies may be useful for ALS

ALS is a clinically heterogeneous disease, and genetic factors probably explain much of its variation, including the variable age of onset and disease duration (even within families with heritable ALS). Identifying these factors may tell us how we may be able to manipulate the disease, allowing us to delay onset or slow progression, and thus lead to effective therapies. Van Hoecke et al have recently made a significant step forward in this respect. Their work is an excellent example of the kind of scientifically holistic, collaborative approach needed if we are ever to crack the tough nut that is neurodegeneration.

Van Hoecke and colleagues started with zebrafish expressing ALS-associated mutant SOD1G93A. The embryonic fish have short, aberrantly branching motor axons. They then used a hypothesis-free approach: a genetic screen. With no a priori assumptions they left open the possibility of identifying entirely new molecular pathways relevant to disease. This is the beauty and power of the 'forward screen' approach.

They performed their screen by randomly knocking down zebrafish genes using morpholinos (synthetic oligonucleotides, which possess conventional bases, but whose backbones are made of morpholine rings rather than deoxyribose rings). From a library of just 303 genes, knockdown of 13 genes was found to result in improvements in axon degeneration. Knock down of Rtk2 in particular completely reversed axonal abnormalities. As we now know that ALS is a TDP-43 proteinopathy, another important experiment Van Hoecke et al conducted was to use transgenic zebrafish expressing ALS-linked mutant TDP-43. Indeed, the axons of these fish were also rescued by knockdown of Rtk2 expression.

Van Hoecke et al make no comment on the gross motor phenotype or survival of these fish, but this is not the point of their study (they were not trying to cure fish). Instead, their next key step was to move up to mammals to examine the Rtk2 homologue, Epha4. Mutant SOD1 transgenic mice were crossed with mice expressing only half the normal amount of Epha4. Reducing the expression of Epha4 significantly increased the motor performance and survival of SOD1G93A mice, and increased the number of motor neurones seen in the spinal cord. Furthermore, SOD1G93A rats treated with an Epha4 inhibiting peptide had delayed disease onset.

The team went further, turning their atten-

tion to patients with ALS. While no genetic association was found with SNPs surrounding the Epha4 locus and ALS susceptibility or phenotype, an association was found when measuring blood Epha4 mRNA levels. Lower expression of Epha4 was correlated with later disease onset and prolonged disease duration. Furthermore, two Epha4 gene mutations (both disrupting Epha4 function) were found in one sporadic and one familial ALS patient. Intriguingly, both patients had very long disease durations (the fALS patient is still alive after 12y).

Epha4 is a receptor for ephrins, a family of proteins involved in axon repulsion during development. In the context of neurodegeneration, ephrins may also have a role in adults, playing a role in synapse formation, plasticity and memory. In this respect, it is interesting to note that Van Hoecke found that mice with half the normal expression of Epha4 had an increased ability to reinnervate muscle following experimental injury of the sciatic nerve. This observation adds further weight to the hypothesis of 'dying back' as a critical process in ALS pathogenesis, with degeneration starting peripherally in the axon and nerve terminal and working retrogradely to the cell body. The challenge now is to break down the molecular mechanisms by which Epha4 is involved in motor axon degeneration and determine if any of these pathways can be targeted for therapy.

– **Jemeen Sreedharan, Dept of Neurobiology/Neurology, University of Massachusetts Medical School, 364 Plantation St, Worcester, MA 01605, US.**

Van Hoecke A, et al.

EPHA4 is a disease modifier of amyotrophic lateral sclerosis in animal models and in humans.

NATURE MEDICINE. 2012 Aug 26.

doi: 10.1038/nm.2901.

Brain injury and homelessness, the chicken and the egg

Who are the homeless? Is being homeless a state through which one passes, temporarily? Is homelessness an outcome measure? Following hard on the heels of recent work that has demonstrated an increased prevalence of traumatic brain injury (TBI) amongst the prison population, this survey attempts to shine a similar light upon the homeless. Obviously the homeless, like the prison population are a relatively easily defined group if viewed at a particular point in time and place. The circumstances that would lead one to be without a house or residing at Her Majesty's pleasure are however rather more complex than, perhaps, these surveys would hope to suggest. The

implication here is that if the homeless were screened for cognitive problems arising from traumatic brain injury then the provision of "appropriate and useful support" may be possible. A sample of homeless individuals attending hostels in Leeds were asked a series of questions around their recollection of having sustained a brain injury (along with its severity) and their answers compared with a sample of people "on the streets of Leeds" (who presumably had homes to go to). Unfortunately, the information regarding prior acquisition of a TBI was based on individual recall, although differentiation of severity depending on loss of consciousness was considered. Lifetime prevalence of TBI amongst the homeless was 48% compared with 21% for the non-homeless. A large proportion (90%) of those who were homeless and had sustained a TBI had done so prior to being homeless.

In an ideal world then, perhaps we could prevent homelessness by screening everyone sustaining a brain injury and then giving them the support and guidance that they need. Unfortunately this is almost certainly going to be much more complicated. Alcohol, illicit drug use, parental support, the availability of social housing, mental illness, education and employment are all potential factors in the precipitation and the perpetuation of homelessness. By definition "homelessness" is heavily dependent upon particular environmental factors that are not biologically modifiable. But, as surrogate a measure as this is, the state of being homeless is perhaps more meaningful than a dry score on an abstract cognitive assessment. Are homeless people more likely to sustain TBIs than they would, otherwise? Is this relevant? Perhaps the precipitation and perpetuation of homelessness are not easily delineated and we need to think beyond a simple causal relationship.

– **Lloyd Bradley, Consultant in Rehabilitation Medicine, Western Sussex Hospitals Trust.**

Oddy M, Moir J F, Fortescue D, Chadwick S.

The Prevalence of traumatic brain injury in the homeless community in a UK city.

BRAIN INJURY 2012;26(9):1058-64.

What are you laughing at?

What constitutes "humour" differs greatly between different individuals and groups. Disability-related humour presents a challenge. There is the risk of going beyond being flat or unamusing to becoming offensive. One would like to imagine that comedy has progressed in its level of sophistication such that disability-related humour is more about mining seams of absurdity and laughing at prejudice rather than enforcing it.

This paper reiterates that the attitude of the public, particularly employers, towards people with disabilities is potentially more handicapping than the disabilities themselves. One of the only consistent factors that has been identified in fostering positive attitudes towards people with disabilities is previous contact in work, educational and social settings. Specific training to promote awareness and positively influence employers' attitudes has been rolled out, but any of us unfortunate enough to be corralled into a yearly "diversity awareness training workshop" will appreciate that these are not always as useful as they might be.

So why not try to use humour as a means of promoting attitude change? The central question is whether the use of disability-related humour would be more effective than provision of information, alone. To this end, a group of undergraduate business students and therefore (by extension) future employers were shown a short film; either *Laughing at our Differences* or *Without Pity: A Film About Abilities*. The former is a stand-up comedy routine by an individual with a lower limb amputation consisting of "humorous stories about his experiences as a person with a disability". The latter a documentary about the lives of 3 different individ-

uals with different impairments and their coping strategies. The students were assigned to watch the humorous film, the serious film or no film and then complete the ATDP (apparently the Attitudes Towards Disabled People) scale. There is a small but significant correlation in positive attitudes and viewing the humorous film. Interestingly, the sample that viewed the serious film had a (non significantly) less positive attitude afterwards. The authors suggest, therefore, that disability humour may be a means of positively influencing attitudes towards persons with disability.

Humour does not lend itself to close scrutiny. The social, temporal and personal factors involved are too inscrutable for even the most factor-controlling quantitative analysis. There is nothing more toe-curling than something supposedly comedic that falls flat and given how culturally specific a lot of American stand-up comedy is, the message is likely to be lost on many audience members. The authors suggest that other research to address the types of disability related humour that evoke the most positive attitudes is required. Perhaps a slapstick vs satire cross-over? Or a deadpan vs one-liners case series?

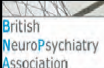

It would be interesting to look at the

effect on attitudes across the population as a whole following the potentially enhanced visibility of persons with disabilities in the context of the Paralympic games, as one senses that the "us" engendered by sporting participation may change more minds than a man telling jokes about the travails of life with one leg.

– **Lloyd Bradley, Consultant in Rehabilitation Medicine, Western Sussex Hospitals Trust.**
Smedema SM, Ebener D, Grist-Gordon V.
The impact of humorous media on attitudes towards persons with disabilities.
DISABILITY AND REHABILITATION
2012;34(17):1431-7.

Panel of reviewers

Dr Jeremy Brown,
 Addenbrooke's Hospital and
 Queen Elizabeth Hospital, King's Lynn.
Roger Barker,
 Cambridge Centre for Brain Repair.
Mark Manford,
 Addenbrooke's and Bedford Hospitals.
Andras Lakatos,
 Cambridge Centre for Brain Repair and
 Addenbrooke's Hospital, Cambridge.
Sarosh Irani,
 Neurosciences Building, University of
 California, San Francisco.

BNPA Neurology and Psychiatry SpRs Teaching Weekend
7th, 8th, 9th December 2012
Venue: St Anne's College, Oxford
www.st-annes.ox.ac.uk

THE ESSENTIALS OF NEUROPSYCHIATRY



This weekend course is aimed at Specialist Registrars in neurology and psychiatry, it is also open to neuropsychologists and will review key areas of neuropsychiatry. Topics will include neurological and psychiatric history taking and examination, investigations (MRI, EEG), psychological presentations of neurological disorder, 'neurological' presentations of psychological disorders and the biological basis of psychiatric symptoms.

The weekend promises to instruct and inspire. Numbers are limited to 50, with 17 speakers and 20 talks.

The weekend registration fee is **£350** which **INCLUDES** attendance at **ALL** the **SESSIONS**, course **HANDBOOK**, 2 nights bed and breakfast ensuite **ACCOMMODATION** at St Anne's College, refreshments, **FRIDAY DINNER** and **SATURDAY LUNCH** and **EXCLUSIVE ACCESS** to BNPA online learning tools.

You can register online NOW
www.bnpa.org.uk

For details of sponsorship opportunities, contact: Jackie Ashmenall
 Phone/Fax: 020 8878 0573/Phone: 0560 1141307
 Email: admin@bnpa.org.uk or jashmenall@yahoo.com

BNPA 26th Annual General Meeting

7 to 8 February 2013

Venue: The Institute of Child Health, Guilford St, London

Topics to include: The neuroscience of stress on brain function • stress and cognition and emotional processes
 • stress and epilepsy • neurophysiology of epilepsy
 • progressive memory loss and epilepsy • depression anxiety and epilepsy • neuroscience of consciousness
 • revelation and psychiatric drugs

Call for research abstracts and registration now open:
www.bnpa.org.uk

For details of exhibition/sponsorship opportunities, contact: Jackie Ashmenall on
 Phone/Fax: 020 8878 0573/Phone: 0560 1141307
 Email: admin@bnpa.org.uk or jashmenall@yahoo.com

Fujifilm promote Huw Shurmer to Programme Manager for the 'All Wales PACS Managed Service Solution contract'

Fujifilm is a pioneer in diagnostic imaging and information systems for healthcare, with a range of constantly evolving, clinically proven, products and technologies designed to assist medical professionals perform efficiently and effectively.

Following Fujifilm being awarded the 'All Wales PACS Managed Service Solution contract', the company have promoted Huw Shurmer (pictured) from Regional Account Manager for Wales to Programme Manager for this key contract.

Huw joined Fujifilm in 2006 following a successful Service Planning career within the NHS. Huw is qualified with an MSc in Computer Science, Post Graduate Diploma in Computer Science and a BA (Hons) in Welsh and Theology.

Commenting on his promotion, Huw said: "I am looking forward to helping integrate imaging solutions throughout Wales which I know in turn will help improve patient care."



For more information see
<http://www.fujifilm.eu/uk/products/medical-systems/>

UK first country in Europe to gain access to new therapy for partial epilepsy

Fycompa® (perampanel), discovered and developed by Eisai in the UK and Japan, launched recently as the first in an entirely new class of treatment for uncontrolled partial epilepsy (the most common form of the condition).

The new therapy has demonstrated efficacy in partial onset seizures, in particular with secondary generalisations. It is indicated as an adjunctive treatment for partial-onset seizures, with or without secondarily generalised seizures, in people with epilepsy aged 12 years and older.

The worldwide supply of this new drug will be manufactured, packaged and distributed from the company's new £100 million facility in Hatfield, Hertfordshire.

Perampanel is the first and only licensed anti-epileptic drug (AED) to selectively target AMPA receptors, a receptor in the brain which plays a critical role in the spread of epileptic seizures. This mechanism of action is different to other, currently available AEDs.

In addition, perampanel has the added benefit of convenient, once-daily dosing at bedtime and is the only third generation partial epilepsy treatment approved to treat adolescents with epilepsy from launch.

Although up to 70 per cent of people with epilepsy have the potential to be seizure-free through accurate diagnosis and optimal treatment, according to the Joint Epilepsy Council, this is achieved in only around half of all patients.

"The successful management of partial-onset seizures remains a significant challenge in many epilepsy patients, and the incidence of uncontrolled seizures remains too high, despite existing treatments," points out Dr Fergus Rugg-Gunn, Consultant Neurologist at the UCLH NHS Foundation Trust. "Perampanel provides doctors and patients with an important new option for the treatment of partial-onset epilepsy and may play a key role in improving seizure management in poorly controlled adults and adolescents."

A New Initiative for the Global Parkinson's Community

A new wiki has been started for all those interested in scientific research into Parkinson's. It is a 'Learning Project' within Wikiversity, a sister project to Wikipedia.

A wiki is a website which allows its users to add and modify its content via a web browser. This new wiki is called The Science Behind Parkinson's Disease and everyone throughout the world, particularly those affected by Parkinson's, is invited to participate as a reader or a contributor.

Go to http://en.wikiversity.org/wiki/Portal:The_Science_Behind_Parkinson%27s to have a look at what has been produced so far.

This Parkinson's Science wiki has been started by a few individuals and now is being opened up globally to interested parties who would like to participate in its development.

Earlier initiation of CDS therapy is beneficial in advanced PD

Almost a third (31%) of the 400 plus delegates attending a symposium held at the 16th Congress of the European Federation of Neurological Societies (EFNS) in Stockholm recently, voted in favour of initiating continuous dopaminergic stimulation (CDS) therapy at the 'early complications stage' of Parkinson's disease (PD), rather than waiting for later-stage disease to develop.

Chairmen Per Odin and K Ray Chaudhuri heard presentations from the expert speaker panel; Tove Henriksen, Angelo Antonini and Eduardo Tolosa.

Tove Henriksen provided an overview of the evidence to support earlier intervention with CDS therapy in advanced PD patients. Factors including the psychosocial impact of PD on patients, better quality of life (QoL) through improved control of motor symptoms in advancing disease and the potential improvement of non-motor symptoms (NMS) were all discussed, with Dr Henriksen concluding that, while the existing evidence shows that CDS therapies improve quality of life and motor function, further studies are required, particularly looking at non-motor symptoms and health economic aspects. Listening to the evidence, 72% of the audience agreed when questioned that specific NMS should be taken into account when considering the optimum time to initiate CDS therapy.

A lively debate between Angelo Antonini and Eduardo Tolosa discussed the motion 'Earlier intervention than present with CDS is warranted'. Professor Antonini noted: "The issue is not just that we should do it sooner but that we should also do it better, to improve patients' quality of life." CDS therapy should be started earlier, prior to the fluctuations and increase in 'off' periods that occur in advanced disease, taking advantage of the 'honeymoon period'. Professor Tolosa agreed that therapies used in CDS-based treatment strategies – continuous subcutaneous apomorphine infusion (CSAI), deep brain stimulation (DBS) and levodopa carbidopa intestinal gel (LCIG) – provide a dramatic improvement in reversing fluctuations and dyskinesias in complicated patients.

While studies have shown that CDS with subcutaneous apomorphine infusion led to significant improvements in non-motor symptoms, Professor Tolosa also believes that further trials are needed to support the use of these advanced therapies in patients with mild disease.

If you would like to feature your news here please contact Rachael Hansford on

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



Copaxone. Helping RRMS patients maintain a working life

As effective as high-dose IFN-beta at reducing relapses, with less flu-like symptoms^{1,2}



COPAXONE® (glatiramer acetate)

PRE-FILLED SYRINGE PRESCRIBING INFORMATION

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

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

Product Licence Number – 10921/0023 **Further Information** – Further medical information available on request from Teva Pharmaceuticals Limited, The Gate House, Gatehouse Way, Aylesbury, Bucks, HP19 8DB. **Date of Preparation** – February 2012.

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

References

1. Mikol DD et al. Lancet Neurology 2008; 7:903-914.
2. O'Connor P et al. Lancet Neurology 2009; 8:889-897.

TEVA

Teva Pharmaceuticals Ltd