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ACNR

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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

In this issue

positivesteps IN PARKINSONS DISEASE

Friday 9th - Saturday 10th March 2012
Hilton Birmingham Metropole hotel

Dear Colleague,

This year we will be celebrating five years of Positive steps in Parkinson's disease. We have seen and heard from some of the top Parkinson's disease (PD) experts in the country, shared revolutionary research and practices and have had many debates. Our 5th anniversary meeting is set not to disappoint!

This meeting would not be such a success without the many healthcare professionals that come and share their thoughts and practices with us. So please, come and join us to hear what's new in PD and take part in our interactive sessions.

Yours sincerely,

Professor David Burn
Institute for Ageing and Health
Newcastle University

Dr Doug MacMahon
University Hospitals Coventry and Warwickshire

For more information and to register please visit the meeting website:

www.**positive**stepsinpd.com

Friday 9th March 2012

10:30 Registration

11:00 Chairman's welcome
Professor David Burn, Newcastle University

11:15 The Parkinson's Challenge
Professor David Burn, Newcastle University

11:40 Managing newly diagnosed patients
Professor Werner Poewe, Innsbruck Medical University, Austria

12:10 False positive PD diagnoses: top tips for detection
Dr Donald Grosset, Southern General Hospital, Glasgow

12:40 Recent progress in non-motor aspects of PD
Professor Ray Chaudhuri, King's College London

13:10 Lunch

14:10 Beyond initial management... medical options
Dr Romi Saha, Brighton and Sussex University Hospitals NHS Trust

14:40 Beyond initial management... surgical options
Dr Alan Whone, Frenchay Hospital Bristol

15:10 Common complications with PD medications
Dr Iracema Leroi, Lancashire Care NHS Foundation Trust

15:40 Tea and coffee

16:10 Challenging case studies
Dr Michele Hu, University of Oxford and Milton Keynes Hospital NHS Foundation Trust

16:50 Question Time session
Facilitated by Professor David Burn, Newcastle University

17:50 Chairman's close

19:30 Dinner speaker: What PD has taught me
Tom Isaacs, The Cure Parkinson's Trust

Saturday 10th March 2012

08:30 Chairman's welcome
Professor David Burn, Newcastle University

08.35 PD Med update
Professor Carl Clarke, City Hospital, Birmingham

09.10 Clinical update in PD
Professor Olivier Rascol, Toulouse University Hospital, France

09.45 Olfaction and weight in PD
Professor Jagdish Sharma, United Lincolnshire Hospitals

10.20 Tea and coffee

10.50 Current and future roles of transplantation
Dr Roger Barker, Cambridge Centre for Brain Repair

11:25 Pharmacology of current and future PD treatments
Professor Peter Jenner, King's College London

12:00 Debate: Commissioning in the NHS
Dr Chris Gordon, Winchester and Eastleigh Healthcare NHS Trust
Sue Thomas, Neurological Commissioning Support

13:00 Meeting close and lunch

THIS MEETING IS INITIATED AND FUNDED BY

TEVA Teva Pharmaceuticals Ltd

Lundbeck

CPD accreditation has been applied for (9 points).

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ABN Winners Announced

Congratulations to Dr Kathryn Peall, Dr Nils Muhlert and Dr Sean Slaght for winning awards at the ABN conference in Newcastle.

Dr Kathryn Peall was awarded the Charles Symonds prize for best platform presentation. Dr Peall has been investigating Myoclonus Dystonia Syndrome in Cardiff, for the past two years. With the enormous support of both adult and paediatric collaborators she travelled throughout the UK and Ireland visiting patients. Her principal interests have been determining the prevalence of SGCE mutations and assessing the presence of any psychiatric co-morbidity within this group. This work has now established a sizeable cohort of patients with a variety of SGCE mutations, along with supporting the notion that psychiatric symptomatology does indeed form part of the disorder's phenotype, in particular obsessive-compulsive disorder (OCD).


Dr Nils Muhlert

Dr Nils Muhlert is a research associate in the NMR Research Unit at the Institute of Neurology, UCL. He received the Charles Symonds prize for best poster presentation for his work involving the quantification of glutamate in the cortex, hippocampus, and thalamus and its relationship to cognitive performance in MS.

In this work with Dr Olga Ciccarelli and colleagues he quantified levels of glutamate in brain grey matter of people with MS and healthy controls. Using single voxel spectroscopy on MRI, they found reduced glutamate neurotransmission in MS, which correlated with cognitive impairment. In particular, memory problems were associated with reduced glutamate in the hippocampus. These findings were surprising as previous work reports increased glutamate in the white matter of people with MS compared to controls. However, the results fitted with post-mortem work, which shows fewer glutamate receptors and excitatory amino acid transporters in demyelinated MS hippocampi. In future work, they hope to clarify the relationship between glutamate in the grey matter and demyelinating lesions, and to assess whether glutamate levels could provide an early marker of cognitive impairment in MS.

Dr Sean Slaght won the ACNR Case Report Prize – his winning case report will be published on our website and in the next issue of ACNR.

New Years Honours


Prof Clare Fowler

Professor Clare Fowler, UCL Professor of Uro-Neurology at the Institute of Neurology and Honorary Consultant Uro-Neurologist at the NHNN, UCLH Trust, has been awarded a CBE in the New Year Honours List 'for services to Uro-Neurology'.

Professor Fowler established a specialist unit in 1987 for patients with urological problems and sexual dysfunction as a consequence of neurological disease.

In 1985, a syndrome was named after her – Fowler's Syndrome – after she discovered why people suffer from urinary retention.

She said: "I will be accepting the award on behalf of all the nurses and doctors who have helped me care for patients and build up the department of uro-neurology."

Professor Ray Dolan elected Fellow of the APS


Prof Ray Dolan

Congratulations to Professor Ray Dolan who has been elected a Fellow of the Association for Psychological Science (APS) for 'sustained outstanding contributions to the science of psychology'.

Roger Barker, Co-Editor.

Progressive Supranuclear Palsy (PSP) is a devastating disease without available disease modifying therapy. As a relatively pure tauopathy, study of the disease holds great promise in leading to progress in other neurodegenerative diseases. Tim Rittmann and James Rowe take us through the advances in the neuropathology and nosology of PSP,and discuss new therapeutic approaches to the pathological tau protein in this disorder. They provide a useful clinical and radiological summary, and highlight the work of the PSP Association in improving standards of care for patients and their carers.

The finer points of the anatomy and organisation of the descending components of the motor system are surprisingly poorly understood and are key to developing future treatments in neurorehabilitation. Karen Fisher, Demetris Soteropoulos and Claire Witham in the latest article in the series of motor control edited by Martyn Bracewell, present a clear and interesting account of the origins, anatomy and function of the corticospinal tracts, and its relationship to the other descending motor pathways that originate from the brainstem.

Alastair Compston and Alasdair Coles present the first of their three articles on the Top Ten Papers in Multiple Sclerosis, and note that the application of the best available technology at the time has been key to many developments.The papers in this issue are JD Dawson's pathological account of nine cases from 1916, Lowenthal and colleagues' application of agar electrophoresis to identify cerebrospinal fluid oligoclonal bands specific to MS in 1960, and a well designed placebo controlled multi-center trial of ACTH in the treatment of an acute relapse by Rose and colleagues from 1970. It also highlights that dropping out of medical school can ultimately lead to a Nobel prize winning discovery.

In the second in the neuro-ophthalmology series, Rebecca McLean and Irene Gottlob provide a useful framework for the categorisation and symptomatic treatment of infantile nystagmus and acquired nystagmus. In this short review they discuss the advances that have been made in better modelling these disorders of eye movement which in turn should lead proper trials of novel therapies.

If you are right handed and right footed, are you right eared? Kenneth Hugdahl in the series of articles on leading Norwegian discoveries gives an introduction to auditory laterality. He summarises his research group's work in using a delayed forced auditory task to study perception, attention, and executive function and introduces a new paradigm which may have use in quantifying perceptual difficulties in a range of neuropsychiatric and neurological conditions.

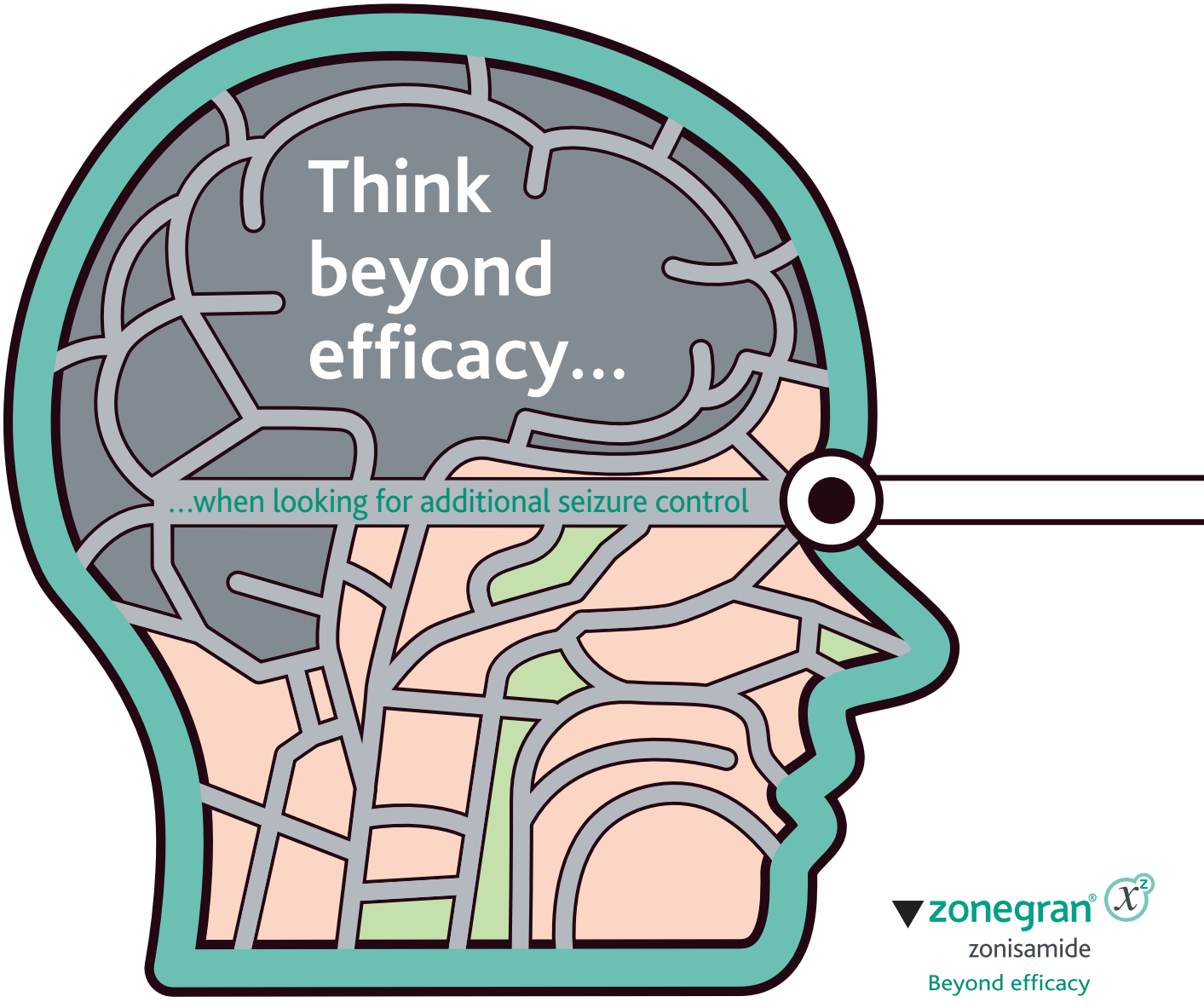
The neurosurgical article by Shawn Agius et al takes us through the unique problems of managing paediatric cervical spinal injuries.These unique issues relate to the type of injury such children are likely to suffer coupled to their head to neck size and the developmental status of their skeleton. This review distils the critical issues and is clearly written and provides a clear practical approach that comes from those who have great experience with such patients.

Elizabeth Neal provides a brief account of the ketogenic diet and its variants in the management of refractory epilepsy, and presents some surprising findings on the efficacy of this dietary treatment!.

Brian Payne in a short letter responds to the recent article on physician assisted dying and encourages others to offer their thoughts on this ethical dilemma.

In our book reviews section, Clive Bezzina reviews a book on exercise physiology in special populations, and Andrew Larner reviews a handbook to internet addiction, which warns us that the internet may have psychoactive properties. This paragraph is as good a place as any to remind you to follow us on twitter: #acnrjournal. We have a large selection of informative conference and journal reviews. Finally, we are also delighted to have our 2011 MS supplement with this issue, which presents and discusses the major papers in this field over the last 12 months. We are very grateful to Dr Alasdair Coles and colleagues for doing such a great job in distilling down the 2011 publications in this condition, which is the subject of so much great research. We hope you enjoy it. ◆

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



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Women of childbearing potential must use contraception during treatment and for one month after discontinuation. ***Lactation:*** Excreted into breast milk. Either discontinue Zonegran or stop breast-feeding. ***Warnings and precautions:*** Serious rashes occur, including cases of Stevens-Johnson syndrome. Contains a sulphonamide group which is associated with serious immune-based adverse reactions. Closely supervise and consider discontinuation in patients with unexplained rash. Cases of agranulocytosis, thrombocytopenia, leukopenia, aplastic anaemia, pancytopenia and leucocytosis have been reported. Monitor for signs of suicidal ideation and behaviours and consider appropriate treatment. Use with caution in patients with risk factors for nephrolithiasis, including prior stone formation, family history of nephrolithiasis and hypercalcuria. Evaluate and monitor serum bicarbonate levels in patients who are at risk of metabolic acidosis. If metabolic acidosis develops and persists, consider reducing Zonegran dose, discontinuing Zonegran treatment or adding alkali treatment with Zonegran as osteopenia may develop. Use with caution in patients treated with carbonic anhydrase inhibitors, e.g. topiramate. Decreased sweating, elevated body temperature and heat stroke have been reported. Patients should maintain hydration and avoid excessive temperatures. Monitor pancreatic lipase and amylase levels in patients taking Zonegran who develop clinical signs and symptoms of pancreatitis, consider discontinuation. In cases of severe muscle pain/weakness with or without fever, assess markers of muscle damage and consider discontinuation. Zonegran 100 mg capsules contain E110. Caution in patients less than 40 kg. In patients with weight loss consider dietary supplement, increased food intake or discontinuation. ***Drug interactions:*** No clinically relevant pharmacokinetic effects on carbamazepine, lamotrigine, phenytoin, sodium valproate, oral contraceptives (ethinylestradiol or norethisterone). Insufficient data with carbonic anhydrase inhibitors, e.g. topiramate. Zonegran was not affected by lamotrigine or CYP3A4 inhibitors. Caution with drugs which are P-gp substrates. Avoid concomitant administration with drugs causing urolithiasis. Zonisamide is metabolised partly by CYP3A4, N-acetyl-transferases and conjugation with glucuronic acid; therefore caution with substances that can induce or inhibit these enzymes. ***Side effects:*** Most common adverse reactions in controlled adjunctive therapy studies were somnolence, dizziness and anorexia. Refer to SPC for all side effects. 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Post-marketing data suggests patients aged ≥65 years report a higher frequency of Stevens-Johnson syndrome and Drug Induced Hypersensitivity syndrome. ***Legal Category:*** POM. ***Basic UK NHS cost:*** Zonegran 25 mg: packs of 14 £8.82, Zonegran 50 mg: packs of 56 £47.04, Zonegran 100 mg: packs of 56 £62.72. ***Irish price to wholesaler:*** Zonegran 25 mg: packs of 14 €9.20, Zonegran 50 mg: packs of 56 €48.78, Zonegran 100 mg: packs of 56 €65.18. ***Marketing authorisation numbers:*** Zonegran 25 mg 14 capsules: EU/1/04/307/001, Zonegran 50 mg 56 capsules: EU/1/04/307/003, Zonegran 100 mg 56 capsules: EU/1/04/307/004. ***Marketing authorisation holder:*** Eisai Ltd. ***Further information from/marketed by:*** Eisai Ltd, European Knowledge Centre, Mosquito Way, Hatfield, Hertfordshire, AL10 9SN. ***Date of preparation:*** July 2011.

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Limited published data suggest that the safety profile in adolescents aged 12–16 years receiving Rebif 22 TIW is similar to that in adults. Do not use in patients under 12 years of age. Prior to injection and for 24 h afterwards, an antipyretic analgesic is advised to decrease flu-like symptoms. Evaluate patients at least every second year of the treatment period. **Contraindications** History of hypersensitivity to natural or recombinant interferon beta, or to any of the excipients; treatment initiation in pregnancy; current severe depression and/or suicidal ideation. **Precautions** Inform patients of most common adverse reactions. Use with caution in patients with previous or current depressive disorders and those with antecedents of suicidal ideation. Advise patients to report immediately any symptoms of depression and/or suicidal ideation. Closely monitor patients exhibiting depression and treat appropriately. Consider cessation of therapy.Administer with caution in patients with a history of seizures and those receiving anti-epileptics, particularly if epilepsy is not adequately controlled. Closely monitor patients with cardiac disease for worsening of their condition during initiation of therapy. Patients should use an aseptic injection technique and rotate injection sites to minimise risk of injection site necrosis. If breaks in skin occur, patients should consult their doctor before continuing injections. If multiple lesions occur, discontinue Rebif until healed. Use with caution in patients with history of significant liver disease, active liver disease, alcohol abuse or increased serum ALT. Monitor serum ALT prior to the start of therapy, at months 1, 3 and 6 and periodically thereafter. Stop treatment if icterus or symptoms of liver dysfunction appear. Treatment has potential to cause severe liver injury including acute hepatic failure. Full haematological monitoring is recommended at months 1, 3 and 6 and periodically thereafter. All monitoring should be more frequent when initiating Rebif 44. New or worsening thyroid abnormalities may occur. Thyroid function testing is recommended at baseline and if abnormal every 6–12 months. Use with caution in, and closely monitor patients with, severe renal and hepatic failure or severe myelosuppression.Serum neutralising antibodies may develop and are associated with reduced efficacy. If a patient responds poorly and has neutralising antibodies, reassess treatment. Use with caution in patients receiving medicines with a narrow therapeutic index cleared by cytochrome P450. Women of childbearing potential should use effective contraception. Limited data suggest a possible increased risk of spontaneous abortion. During lactation, either discontinue Rebif or nursing. If overdose occurs, hospitalise patient and give supportive treatment. **Side effects** In the case of severe or persistent undesirable effects, consider temporarily lowering or interrupting dose. *Very common:* flu-like symptoms, injection site inflammation/reaction, headache, asymptomatic transaminase increase, neutropenia, lymphopenia, leucopenia, thrombocytopenia, anaemia. *Common:* injection site pain, myalgia, arthralgia, fatigue, rigors, fever, pruritus, rash, erythematous/maculo-papular rash, diarrhoea, vomiting, nausea, depression, insomnia, severe elevations of transaminase. *Serious side effects include:* injection site necrosis, hepatic failure, hepatitis with or without icterus, severe liver injury, anaphylactic reactions, angioedema, erythema multiforme, erythema multiforme-like skin reactions, seizures, thromboembolic events, thrombotic thrombocytopenic purpura/haemolytic uremic syndrome, suicide attempt, Stevens-Johnson syndrome, dyspnoea, retinal vascular disorders. Consult the Summary of Product Characteristics for more information relating to side effects. **Legal category** POM **Price** Rebif 8.8 µg and 22 µg: 6 (0.2 ml) + 6 (0.5 ml) syringes - £552.19 Rebif 22 µg: 12 syringes (0.5 ml) - £613.52 Rebif 44 µg: 12 syringes (0.5 ml) - £813.21 Rebif 8.8 µg and 22 µg: 6 (0.2 ml) + 6 (0.5 ml) pens - £552.19 Rebif 22 µg: 12 pens (0.5 ml) - £613.52 Rebif 44 µg: 12 pens (0.5 ml) - £813.21 Rebif 8.8 µg/0.1 ml and 22 µg/0.25 ml: 2 cartridges - £406.61 Rebif 22 µg/0.5 ml: 4 cartridges - £613.52 Rebif 44 µg/0.5 ml: 4 cartridges - £813.21 For prices in Ireland, consult distributors Allphar Services Ltd. **Marketing Authorisation Holder and Numbers:** Merck Serono Europe Ltd, 56 Marsh Wall, London, E14 9TP; EU/1/98/063/007; 003 ; 006 ; 017; 013 ; 016 ; 010 ; 008 ; 009. **For further information contact: UK:** Merck Serono Ltd, Bedfont Cross, Stanwell Road, Feltham, Middlesex, TW14 8NX. 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What's New in Progressive Supranuclear Palsy?

Timothy Rittman
is a Clinical Research Fellow in Cambridge and holds an MRC Clinical Research Training Fellowship. He trained in Nottingham and has worked in Lincoln, Norwich and London before arriving in Cambridge. He is interested in linking clinical features with pathological changes in neurodegenerative disorders, reflected in his current work developing functional connectivity disease biomarkers in tauopathies, with a focus on Progressive Supranuclear Palsy and Corticobasal Degeneration.

James Rowe
is a Wellcome Trust Senior Research Fellow in Clinical Science and Reader in Cognitive Neurology at the University of Cambridge. He is a consultant neurologist at Addenbrooke's Hospital with specialist clinics for Progressive Supranuclear Palsy, Corticobasal Degeneration and Frontotemporal Dementia. His research interests include understanding and restoring cognitive function in neurodegenerative disease, using brain imaging with network modelling and psychopharmacology.

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In this article we review recent developments in understanding and treating Progressive Supranuclear Palsy (PSP). Although relatively uncommon, it is an important disease both in terms of severity and progression for patients, and its characteristic tau-pathology which has much to teach us about other diseases associated with tau pathology, including Pick's disease and Alzheimer's disease.

Phenotype and prevalence

Clinically, PSP often presents with akinetic-rigidity, falls and a supranuclear vertical gaze palsy. However, cognitive impairment including apathy and executive dysfunction are common even in the early stages and were recognised in the earliest reports of PSP. Early dementia is unusual. Recognising cognitive impairment and retained cognitive abilities (despite speech and writing problems) is essential for good holistic management of patients and their carers. For example, it facilitates patients' role in decisions about their own care, and may help carers adjust to changing behaviour. Typically, PSP causes mild to moderate problems with verbal fluency, flexibility of thought and impulse control, but without marked memory impairment. Recent evidence also points to impaired recognition of emotions, an important aspect of cognition and highly relevant to dependent patients with poor communication.[1] Although the term 'subcortical dementia' has been used for PSP, it is misleading as cortical pathology and cortical atrophy contribute to cognitive deficits.

The prevalence of PSP has been estimated at 5-7 per 100,000 in epidemiological studies.[2] However, the pathology of PSP may be more common than the clinical syndrome. For example, in 277 adults with longitudinal motor and neuropsychological assessment, five cases of PSP pathology were found with no relevant symptoms or objective motor and cognitive phenotype in life.[3] Confirmation in population representative cohorts with prospective clinical data will be important to determine the true clinical and pathological prevalence of PSP. Approaching the problem from the opposite direction, by examining retrospectively records of cases with pathological proven PSP, Williams et al found approximately half of those with PSP pathology had a clinical syndrome of PSP, the other half had the syndrome of Parkinson's disease.[4] The authors distinguished PSP-Richardson's Syndrome (PSP-RS: with a classical PSP phenotype) from PSP-Parkinson (PSP-P: with a phenotype resembling Parkinson's disease). This greatly increases the likely prevalence of PSP pathology, and work is now under way to distinguish PSP-P from Parkinson's disease in lifetime.

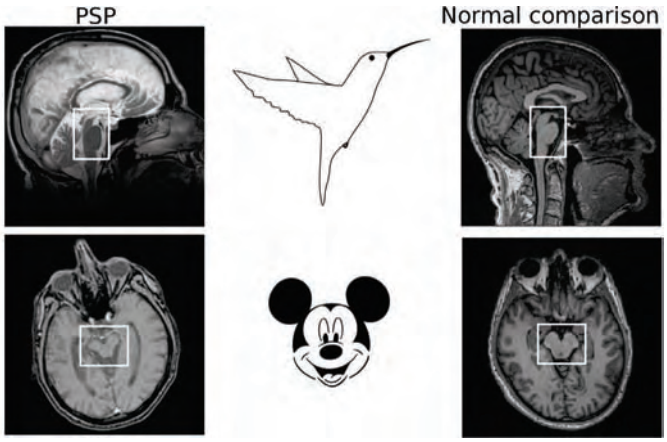
Pathology

The pathology of PSP is characterised by aggregations of the microtubule associated protein tau (MAPT or 'tau'). Typical findings on histology are tufted astrocytes, neurofibrillary tangles and argyrophilic tau-positive inclusions with a predominantly subcortical distribution and associated severe midbrain atrophy. A lifetime diagnosis of PSP is associated with its characteristic tau pathology in over 90% of cases.[5] The aetiological role for tau aggregation, rather than a bystander effect, is supported by genetics (below) and the correlation between severity of disease and density of pathological tau in the substantia nigra, caudates and dentate nucleus.[6] Interestingly, PSP is not associated with accumulation of aggregates of other key proteins linked to neurodegenerative disease, such as beta-amyloid, alpha-synuclein, ubiquitin and TDP-43. In terms of protein aggregation PSP represents a consistent and relatively pure tauopathy, in contrast with Alzheimer's disease and Pick's disease. A role for inflammation in the pathogenesis of PSP remains possible, in line with other major neurodegenerative diseases.

The nosology of PSP and related disorders is complex, reflected in an ongoing debate between 'lumpers' and 'splitters'. There is a close relationship between PSP and other syndromes associated with tau pathology, including CBD and Progressive Non-Fluent Aphasia (PNFA) within the spectrum of frontotemporal degeneration. Indeed, some patients may change clinical phenotype and diagnosis during the course of their illness. The cross-over of symptoms and similarities in pathology is sometimes reflected in a generic term 'tauopathy'. The pathology of PSP can be particularly difficult to distinguish from CBD, leading some to group these disorders within a single clinicopathological spectrum.[7] Conversely, it has been proposed PSP-PNFA represents a separate subdivision of PSP alongside Richardson's syndrome, PSP-parkinsonism, PSP-Primary Akinesia with Gait Freezing (PAGF), and a PSP-Cortcobasal Syndrome (CBS).[4] Both sides of this debate have valid points, and it is important not to let these issues stand in the way of a patient's need for a clear diagnosis and management plan.

Genetics

An association of the H1 MAPT-haplotype with PSP has been known for many years and rare families with MAPT mutations causing PSP-like syndromes have been identified. While a role for tau in the aetiology of cognitive impairment in Parkinson's disease exists,[8] a link to cognitive decline is not established for PSP. A recent major advance has been the genome-wide association study of 2065 people with PSP (and 3816 control



Imaging findings in PSP: Characteristic findings of PSP on structural imaging are the 'Mickey mouse' sign (axial slices) and the 'humming bird' sign (on sagittal slices). Imaging may also exclude hydrocephalus, extensive vascular disease, signs of normal pressure hydrocephalus and mass lesions.

subjects). In addition to two independent variants of the tau gene on chromosome 17, three new susceptibility loci were identified.[9] The new genes implicate proteins involved in vesicle-membrane fusion, the Golgi-endosomal interface and a myelin structural component. These results do not support clinical diagnostic testing for PSP, but open up the possibility of identifying critical causal pathways for PSP and novel therapeutic targets.

Treatments

The strong association of tau pathology with PSP has supported the development of novel therapies aimed at altering hyperphosphorylation and aggregation of tau. One approach is to inhibit tau phosphorylation via GSK-3b kinase. This has led to potential new uses for old drugs (e.g. lithium, valproate) as well as new compounds. A phase II trial of lithium as a GSK-3b inhibitor was stopped early due to poor tolerability (Clinical trials identifier NCT00703677). Other GSK-3 inhibitors currently in phase II trials are NP031112 (Tideglusib, Noscira, NCT01049399) and sodium valproate (Depakine, NCT00385710). Alternatively, one might stabilise microtubule function by the synthetic octapeptide intranasal NAP and a phase II trial has recently finished recruitment with ongoing follow-up (Davunetide, Allon Therapeutics, NCT01110720). Other compounds such as Paclitaxel have been found to stabilise microtubules in a cellular model of PSP, but without preventing neuronal loss.[10] It has not yet been taken forward to clinical trials.

Many other approaches to arrest neurodegeneration have been proposed. Riluzole has neuroprotective properties and prolongs disease survival in motor neurone disease. However, a phase III trial of Riluzole (NNIPPS study) showed no effect of treatment in PSP or Multiple System Atrophy (MSA).[5] Growth-colony stimulating factor has been suggested to counteract neuronal degeneration, enhance plasticity and promote migration of stem cells to damaged areas in PSP and similar diseases, although no benefit was seen in a small phase II trial of subjects with PSP, MSA and CBD.[11] Supporting mitochondrial function is thought to help slow down neurodegenerative processes; a phase II trial of coenzyme Q10 showed encouraging results[12] and a second trial is now underway (NCT00382824). A combination of creatine, pyruvate and niacinamide has also been proposed to support mitochondrial function in a forthcoming phase II trial (NCT00605930). A phase III trial examining the effect of the monoamine oxidase inhibitor Rasagaline on disease progression is recruiting participants (NCT01187888), and this might have symptomatic as well as disease-modifying effects. Finally, a small non-pharmacological study using Transcranial Magnetic Stimulation (TMS) to modulate cortical excitability is underway (NCT01174771).

The range of new disease-modifying treatments under investigation means that the next few years may see a transformation in the treatment options and prognosis of people with PSP. If these new agents are effective at slowing progression, it will place even greater emphasis on the need for better early diagnosis and symptomatic treatment.

Table 1: clinical phenotypes and extended nomenclature of syndromes related to PSP.

Acronym	Clinical Features
PSP	Typical presentation with symmetrical onset of truncal rigidity, bradykinesia, early falls and supranuclear gaze palsy. Cognitive impairment (apathy, dysexecutive) common.
PSP-RS (Richardson's Syndrome)	In post mortem series, some cases had presented with the classical features of PSP as described by Steele, Richardson and Oslewski (above). This subtype was called PSP-RS.
PSP-P (Parkinsonism)	Many post mortem cases of PSP had presented with a clinical picture that resembled idiopathic Parkinson's disease. This subtype has been named PSP-P. It remains to be shown whether these cases can be prospectively identified (in life) as being distinct from Parkinson's disease.
PAGF (Pure Akinesia with Gait Freezing)	These patients present with akinesia and gait freezing in the absence of other features. Resistant to dopamine medication, and may progress with or without the emergence of other features of PD or PSP.
PIGD (Postural instability and gait disorder)	Postural instability, falling, freezing and difficulty walking may represent a prodrome of PSP or a subtype of Parkinson's disease. Often associated with cognitive impairment and resistant to dopaminergic therapy.
PSP-CBS (Corticobasal Syndrome)	Occasionally patients with PSP develop features of corticobasal degeneration (and vice versa). Clinical features may include asymmetric dystonia, alien limb, apraxia or cortical sensory loss in addition to typical features of PSP. Note that these are exclusion criteria under the NINDS-SPSP clinical diagnostic criteria for PSP (Litvan et al, 1996).
PSP-PNFA (Progressive Non-Fluent Aphasia)	Uncommon presentation with non-fluent speech, with other PSP features developing later in the disease process.
Pick's disease complex	PSP, corticobasal degeneration, non-fluent aphasia and frontotemporal lobar degeneration have many overlapping clinical features. A patient's phenotype may evolve within this group of diseases over time, leading some to propose the generic term of Pick's disease complex.

Imaging

Midbrain atrophy in PSP causes characteristic 'hummingbird' and 'Mickey mouse' signs on magnetic resonance imaging in many patients. However, clinical imaging is mainly motivated by exclusion of other pathologies (eg. vascular disease, hydrocephalus). In the research setting, imaging has confirmed patterns of cortical and subcortical atrophy.[13] MRI based functional connectivity has suggested abnormal thalamic connections within the brainstem may be responsible for the imbalance and falls in PSP.[14] In addition, positron emission tomography (using the ligand [11C] N-methylpiperidin-4-yl acetate) indicates decreased thalamic cholinergic function in PSP.[15]

Care pathway

Despite progress towards disease modification, the mainstay of PSP management remains supportive. The UK PSP Association (www.pspeur.org) is currently consulting on a model for improved standards of care, to ensure that the needs of people affected by PSP are adequately addressed. This is anticipated early in 2012. Ideally, early and correct diagnosis by a specialist would lead to comprehensive support from an integrated multidisciplinary team (including physiotherapists, speech and language therapists, occupational therapists, dieticians and specialist nurses) in liaison with social services, community based nurses and lay organisations. One feature that has often been overlooked is the need for specialist palliative care, including placing patients on palliative care registers such as the Gold Standards Framework (www.goldstandardsframework.org.uk). This is likely to improve in the next few years. The PSP association is a useful resource for patients, carers and professionals alike, through online publications, specialist nurses and training, and a network of local meetings.

Summary

In summary, PSP is a fascinating and important neurodegenerative disease whose prevalence may have been underestimated. There is rapid progress in clinical, genetic and therapeutic research that will not only benefit people affected by PSP, but also the broad range of neurodegenerative diseases in which tau pathologies are implicated. ◆

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Dear Editor...

I have just read the current issue of ACNR and am responding to your invitation to comment on assisted dying.

To declare my own interests at once:

1. I am a member of Dignity in Dying and strongly support the idea of physician assisted dying (PAD), within the close legal framework and safeguards of the Bills that Lord Joffe has introduced in the recent past in the House of Lords.
2. I am a retired geriatrician, of 28 years NHS consultant service, and have therefore seen at close hand many dying patients, and many who died badly within our acute hospital service (in which a majority of us now end our lives).
3. I have a metastatic malignancy, the nature of which provides many possible modes of actual dying, quite a few of which I would find intolerable or demeaning.

Dr Sathasivam's paper is well written and dispassionately argued. Dr Coles' commentary, in contrast, is weak, not least in his resort to his 'gut' as an irrational guide to good medical practice.

I would suggest that a narrative approach to the dying process is more helpful than competing abstract philosophical arguments: in the best, often community-based palliative care, there can arise a point at which the option of PAD becomes acceptable and desirable to the competent autonomous patient. As Dr Sathasivam correctly points out, there is good evidence that where PAD is legal, as in Belgium, good palliative care exists alongside it and the two are genuinely complementary. It cannot be a truly ethical position for a physician to condemn his patient to a painful, prolonged, undignified, inevitable end where an agreed alternative exists. Here, one finds an example of where what may be illegal may well in fact be better ethical/clinical practice. The law as it stands is in a curious position: the Director of Public Prosecutions had made it clear, both in theory and now in recent practice, that a relative or close friend will not be charged with having assisted a suicide if acting compassionately, whilst this motivation is denied to an attending doctor. Who better as a friend at the end than a compassionate physician, acting in the best, requested, interests of his dying patient?

Public opinion polls have consistently shown steady and unwavering support, at the 80+% level, for assisted dying for terminally ill, mentally competent adults (BSA surveys 2007, 2010). The nursing profession, ahead of their medical colleagues, are shifting their previous position of opposition to one of neutrality (RCN member consultation, 2009).

Perhaps a final word may be said on the doctor-patient relationship. Far from this being undermined by PAD, in a Europe-wide survey patients in the Netherlands had the highest regard and trust in their doctors, with as many as 97% confident in their GP (J-J Georges et al. J. Med. Ethics 2008;34:150-5). I look forward to your publishing details of your respondents' views,

Yours sincerely,
Brian Payne, FRCP,
Norwich.

The Motor Cortex and Descending Control of Movement

In the latest in our series on Motor Control, Fisher, Soteropoulos and Witham bring us up-to-date on the descending control of somatic movement. In particular, they present recent work that expands our view of the corticospinal tract, which is much more than the connection from the primary motor cortex to the ventral horn of the spinal cord. In this age of functional imaging and gene sequencing, this review is a reminder of the importance of careful anatomical and neurophysiological studies in animals.

Martyn Bracewell, Series editor.

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Over the course of evolution the motor areas of cerebral cortex and the corticospinal tract (CST) have become increasingly important for the control of movement. In particular, there has been a relative expansion in the size of the CST and the development of direct synaptic connections between corticospinal neurons and upper limb motoneurons (corticomotoneuronal synapses) which is correlated with increased hand and finger dexterity.[1] From new world monkeys such as marmosets to old world monkeys such as macaques and then to apes, including humans, there has been a large increase in the number of direct connections to motoneurons. Other mammals such as cats have few if any direct connections (one exception is the racoon, which has both significant direct connections and good manual dexterity).

Primary motor cortex (M1) and the CST are known to be essential for voluntary control of the contralateral skeletal musculature. This is particularly evident in patients with unilateral motor cortical damage (e.g. following stroke). The result, depending on the extent and location of the lesion, is usually paresis of the contralateral limbs. Further functional consequences of CST damage have been described following bilateral surgical lesions to the CST in macaques.[2,3] It was demonstrated that after an initial period of paralysis, animals actually recovered most gross motor function very quickly and permanent deficits in movement were restricted largely to fractionated finger movements. By contrast, lesioning other descending pathways (rubrospinal & reticulospinal tracts) resulted in permanent loss of grasping and impaired gross movements of the axial and proximal musculature with preserved fine finger movements.

A detailed overview of corticospinal neurons and their role in voluntary movement has been published by Porter and Lemon.[4] In the past two decades there has been a number of advances in the basic anatomy and physiology of the corticospinal and other descending tracts in primates including improvements in tracing techniques and recording from deep structures such as the brainstem. These advances may explain some features of recovery seen after stroke and suggest future targets for rehabilitation.

Multiple origins of corticospinal tract

Across species the largest proportion of the CST originates in M1.[5] However significant populations of corticospinal neurons are found in other frontal and parietal areas such as the supplementary motor area (SMA) and primary somatosensory cortex (S1). Improvements in tracing techniques have led to a better understanding of the origin and termination of different corticospinal populations. For example S1 corticospinal neurons project to the dorsal horn of the spinal cord whereas SMA corticospinal neurons project to the intermediate zone and ventral horn (similar to M1 corticospinal neurons).[6] Some of the main areas contributing to the CST and their spinal termination are shown in Figures 1A and B.

The CST has multiple functions including control of voluntary movement, gating sensory inputs during movement, control of spinal reflex loops and preparing the spinal cord for movement. The projection patterns of different areas suggest that each serves a different function, however evidence linking discrete areas to different functions is lacking. Groups have recorded from identified corticospinal neurons in different areas in an attempt to understand function. Early studies showed that M1 corticospinal neurons are active approximately 200ms before movement onset and S1 corticospinal neurons are active after M1 neurons (but still in advance of movement).[7] A recent study has shown that corticospinal neurons in premotor cortex exhibit 'mirror neuron' behaviour, being active both when the monkey performs a precision grip and when the monkey observes the experimenter perform the same action.[8] Another study has shown that interneurons in the spinal cord are active during movement preparation as well as during movement.[9]

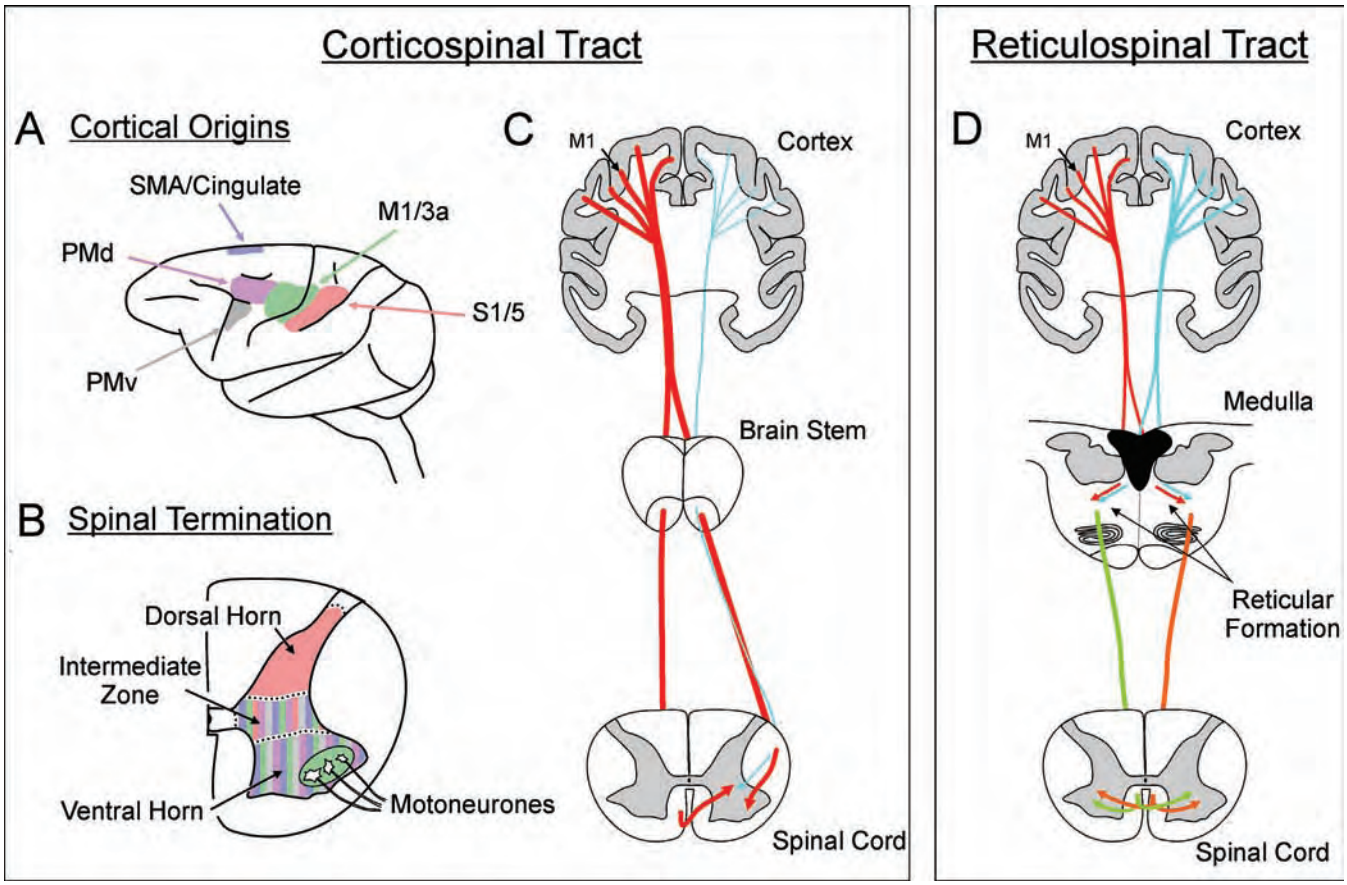

Figure 1. Corticospinal and reticulospinal tracts. A, main cortical origins of the CST. B, simplified spinal terminations of areas in A. C, contralateral (red) and ipsilateral (cyan) projections of the CST. D, bilateral cortical projections to PMRF (red and cyan) and bilateral projection from PMRF to the spinal cord (orange and green).

Anatomical experiments by Rathelot and Strick[10] have shown that corticospinal neurons with direct connections to motoneurones (important in the control of independent finger movement) in monkeys originate in two areas. The main population is in the caudal bank of M1 (85%). A second population originates in somatosensory area 3a; these particular corticospinal neurons are also active before M1[7] suggesting that the function of the area 3a corticospinal projection is different to the rest of S1.

It is increasingly clear that multiple areas of the cerebral cortex project to different targets in the spinal cord and that these play different roles in motor control.

Ipsilateral corticospinal tract

The extent to which the motor cortex contributes to the control of movements of the ipsilateral limb is poorly understood. It is well supported that neural activity in M1 is modulated with movements of the ipsilateral forelimb – this has been demonstrated with invasive recordings of M1 neurons in monkeys[11] as well as with non-invasive (MRI) imaging in humans.[12] Some patients with unilateral motor stroke display deficits in control of the ipsilateral arm, in addition to the more severely affected contralateral arm.[13] These studies suggest the M1 is more than just a passive bystander during ipsilateral movements.

Anatomically, a small fraction (up to 10%) of the CST projects to the ipsilateral spinal cord; this projection is hypothesised to give M1 access to ipsilateral muscles (Fig. 1B). However recent work[14] has found little evidence that these ipsilateral axons contact ipsilateral spinal circuits. Instead they cross to the contralateral side at the level of the spinal cord. A second study using a more widespread M1 tracer injection has found more extensive crossing of the CST at the level of the spinal cord such that individual corticospinal axons may project contralaterally, ipsilaterally or bilaterally[15]. It is unclear at this stage how much of the ipsilateral projection is related to proximal and axial muscles rather than distal forearm and hand muscles.

Beyond the anatomical connectivity, the functional role of these ipsilateral projections is unknown. Activation of M1 in monkeys (via intra-cortical microstimulation) or humans (via transcranial magnetic stimulation – TMS) does not typically evoke ipsilateral muscle responses. Although TMS at maximal intensity can sometimes elicit longer latency ipsilateral muscle responses, these are likely to be mediated by the brainstem descending pathways.[16] A recent study used multiple electrophysiological techniques to identify direct inputs to ipsilateral forearm and distal motoneurons, but failed to find any evidence for such inputs.[17] The lack of ipsilateral corticomotoneuronal connections suggests that the functional role of the ipsilateral projection differs from that of the contralateral one. Questions still remain regarding how the M1 activity during ipsilateral movements is related to the ipsilateral CST projection, and to other brain regions involved in movement control, and how (if at all) this activity is related to control of ipsilateral movements.

Other descending systems

As well as directly influencing the spinal cord via the CST, the cerebral cortex also has connections to descending motor control pathways which originate in other brain regions. Such alternate pathways are conventionally considered to be less important in humans than in lower species but recent studies in primates have demonstrated that they may form the basis of parallel control systems which are likely to contribute significantly to recovery following damage to the CST. One projection of interest is the reticulospinal tract (RST) which originates in the pontomedullary reticular formation (PMRF) of the brainstem (see review: ref 18). This area receives direct bilateral cortico-reticular input from fibres which originate mainly in motor and premotor cortical areas as well as collateral input from CST neurons projecting to the spinal cord.

The reticulospinal tract itself is a bilateral projection system (Figure 1D). It is highly collateralised, much more so than the CST, and axons

terminate within multiple segments of the spinal cord. These features collectively show that outputs from the PMRF have the potential to influence multiple motoneuron pools and subsequently numerous different muscles. The traditional view is that the RST is largely concerned with control of proximal and postural muscles, however recent work has demonstrated that there are also direct monosynaptic RST projections to the distal musculature;[19] these were found to be weaker than equivalent CST projections but nevertheless were present in primates. Evidence also suggests that there is convergence of CST and RST axons onto the same spinal interneurons.[20] The presence of these connections doesn't necessarily mean they have a significant functional role in hand control, but the modulation of reticulospinal activity during reaching movements has been demonstrated in both cats[21] and primates[22] and we can evoke responses which are likely to be of reticular origin in humans (acoustic startle, ipsilateral motor evoked potentials). This evidence together suggests that the RST forms a parallel system of descending control alongside the CST which could act as a potential target for rehabilitation interventions.

Another notable descending motor pathway is the rubrospinal tract which has substantial input from M1 and shares many remarkably similar features with the CST. Both have direct monosynaptic projections to the spinal cord, terminate onto similar interneurons and can influence both proximal and distal muscles. Interestingly there seems to be an inverse relationship between the two tracts so that as the CST expands through evolution the rubrospinal tract diminishes in size.

The rubrospinal tract originates in the red nucleus of the midbrain. In primates this structure is divided into magnocellular (mRN; giant cells) and parvocellular regions (medium and small cells). The mRN gives rise to the rubrospinal tract and has been shown to be far more developed in the foetal brain than in adult humans,[23] losing prominence alongside the maturation of the CST. However, what remains of the rubrospinal tract following development is a projection system which has preferred access to the distal musculature and a strong extensor bias.

The overlap between rubrospinal and corticospinal systems provides potential compensation following damage to CST. This has been shown in one monkey; whereby a lesion of the pyramidal tract led to remarkable reprogramming of rubrospinal outputs.[24] Not only did the muscle targets of the mRN change after the lesion, they changed to a pattern that looked more like the corticospinal system than the rubrospinal. This type of plastic reorganisation suggests that the rubrospinal tract could, like the RST, be a useful target for rehabilitation therapy.

A large body of work has also focussed on other descending tracts although we do not describe these here in detail. Other systems under cortical influence include the vestibulospinal and the tectospinal tracts which predominantly control postural movements and neck muscles respectively.

Although each of the descending motor pathways is specialised it is important to note that there is substantial crossover between many of them. This makes human motor control an extremely complex process and consequently there are many properties and features which remain elusive. However, this complicated matrix of interconnected motor control pathways does explain the recovery of function observed following precise lesions in animals and gives us an opportunity to provide useful interventional therapy which can promote plastic changes and enhance recovery in patients.

Conclusions and questions for the future

We have highlighted some important recent findings regarding the CST and descending motor control. Firstly, the CST is not equivalent to M1, as more than half of CST fibres come from outside this area. Secondly, the functional connectivity of the CST with ipsilateral motoneurons is not as direct as often assumed. Finally, while M1 and CST are vital for voluntary hand function, other descending systems such as the RST are also able to influence distal forelimb muscles.

Whilst our anatomical understanding of descending pathways has improved recently, the functional role of these connections in voluntary movement is poorly understood. For example, the role of CST neurones originating outside M1 is unknown as well as how these compare with projections which arise within M1. Also unknown is the role of ipsilateral corticospinal terminations given that they are unlikely to be able to directly activate motoneurones. Finally, the relative contribution of the brainstem in the control of voluntary hand movements remains to be elucidated as well as how this is influenced by descending signals from the cortex.

Further work is needed to clarify the functional contribution of the CST at a finer level, taking into account its varied anatomical origins and terminations. This is essential not just for understanding the role of the motor system in normal function but more importantly for the potential avenues it could offer for rehabilitation following cortical damage. ◆

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Top Ten Papers in Multiple Sclerosis

The first understandings of the disease

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Having been recognised only since the late nineteenth century, there has been just over a hundred years of research on multiple sclerosis. Over this time, a picture has emerged of this disease as an inflammatory disorder of the central nervous system, caused by a complex interplay of multiple genetic susceptibility alleles and unknown environmental triggers. We have tried to illustrate this in our choice of landmark papers, at the same time being aware that strong cases could be pressed for other studies to be included. It is clear that many lines of scientific attack on the disease have benefited from increasingly potent weapons, and in many cases our papers reflect the application of the very latest technology of the day. Finally we note that three of our 'top ten' were authored by Ian McDonald (1933-2006), testimony to his extraordinary contribution to understanding multiple sclerosis.[1] Here are our first three landmark papers, which chart the beginnings of understanding of pathology, immunology and treatment of multiple sclerosis.

1916: The pathological anatomy of the lesion in multiple sclerosis

Dawson JD. The Histology of Disseminated Sclerosis. Transactions of the Royal Society of Edinburgh 1916;50: 517-740.

James Dawson (1870–1927) left the greatest pathological account of multiple sclerosis in the English language (Dawson 1916). First he summarises the literature. The issue (then as now for some contemporary logicians) is whether the the disease is 'inflammatory' or 'developmental' (degenerative). The primary vascular, inflammatory, doctrine was espoused by Dejerine,[2] Williamson[3,4] and Marie,[5] who suggested that infections initiate the changes in blood vessels. Bielschowsky[6] considered that the vascular process is directed primarily at nerve fibres. Strumpell[7] considered that exogenous insults act upon an 'intrinsically weakened' system; and Bramwell[8] also saw multiple sclerosis as primarily a developmental disturbance. Müller,[9] the most articulate teacher from the developmental school, proposed that any participation of the blood vessels within the lesion is secondary and his concept of 'multiple gliosis' as the essential process rehearses the final position taken by Charcot[10] and most of his school. Redlich[11] and Huber[12] also saw the insult as a toxin- or microorganism-induced primary degeneration of the myelin sheath with secondary inflammation and blood vessel changes. But, as often is the case, the best account was the first: Rindfleisch[13] assigned priority to the blood vessels, proposing a sequence in which a chronic irritative condition of the vessel wall alters the nutrition of nerve elements, leading to atrophy with metamorphosis of the connective tissue producing monster glia (Deiters or Rindfleisch cells).

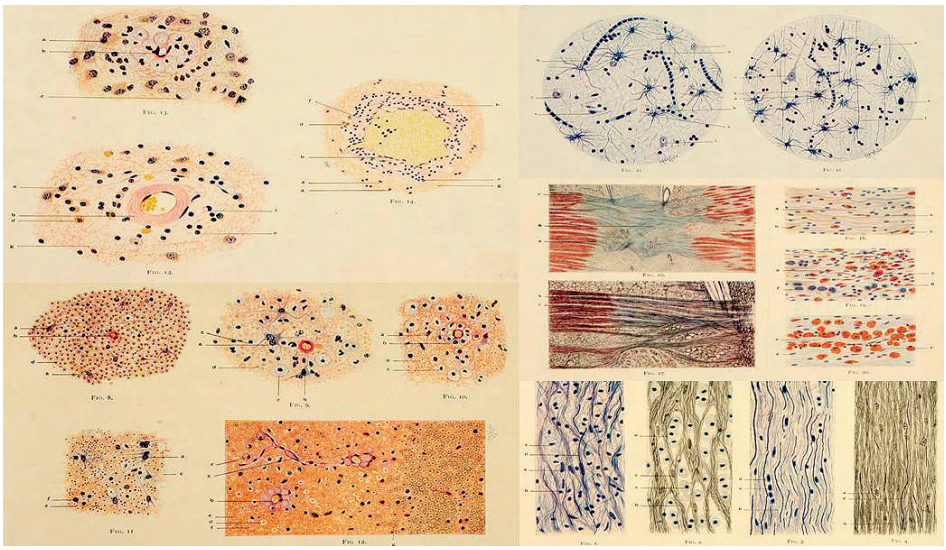

Figure 1 from 25. (A) [Figures 1-4] Successive stages in the evolution of a sclerotic area in the posterior columns of the cervical spinal cord. Sections cut in longitudinal direction of the nerve fibres show increasing glia fibril formation. a: Glia nuclei; b: glia fibrils; c: fat granule cells; d: persistent axis cylinders. [Figures 1 and 3] Ford-Robertson's methyl violet stain. [Figures 2 and 4] palladium methyl violet. (B) [Figures 16-17] Persistence of axis cylinders across a demyelinated area in the pons. [Figures 18-20] Stages in the demyelination of an area and in the evolution of the fat granule cell. a: Small glial nuclei; b: transition forms between a and b; c: fat granule cell; d: nerve fibre; e: blood vessel; f: proliferated glia nuclei. (C) [Figures 8-12] Successive stages in the evolution of a sclerotic area in the posterior columns of the cervical cord. a: Glia nuclei; b: blood vessel; c: fat granule cell; d: myelinated nerve fibre; e: finely granular glia tissue; f: naked axis cylinder; g: transition to normal tissue. [Figure 8] Alterations in the glia cell and myelin. [Figure 9] Gitter cells. [Figure 10] Fat granule cells accumulated in blood vessels. [Figure 11] Glial fibrils increasing and axons intact. [Figure 12] Gliosis with few cells and preserved axons.

Reviewing the histology of nine personal cases (LW, a kitchen maid, aged 28; CS, aged 22; Mrs G, aged 30; JW; SS, a nurse aged 44; CG, a baker's shop-woman, aged 24; J McN, a cabinet maker, aged 42; MR, a typist, aged 33; and LH, aged 30), Dawson devotes the majority of his text to LW. She was admitted to hospital in Edinburgh under the care of Dr Alexander Bruce on 4th April, 1910 with a two year history of weakness and tremor in all four limbs, dysarthria and sphincter disturbance. In hospital (from May 29th) she has an episode of brainstem demyelination (deafness and tinnitus, right facial palsy, numb left arm, right lateral rectus weakness, tongue deviation to the left and dysphagia). In August, she loses vision in both eyes, develops increasing bulbar failure and dies from septicaemia on 5 September, 1910.

Dawson describes the features of early and established lesions in the spinal cord and cerebrum (Figure 1), offering an analysis of their evolution through stages of fat granule cell myelitis (in the cord) to glial hyperplasia. He devotes text to the unusual lesions, including Markschattenherde (shadow plaques), and those appearing in grey matter and around the ventricles, optic nerve, peripheral nerves and roots which he considers to be evolving lesions, and he mentions three hyperacute cases with an accelerated clinical pattern of relapses, rapid accumulation of deficits and characteristic histological features. Curiously, he neglects Marburg's (1906) important monograph identifying shadow plaques which we now know to be indicative of remyelination not partial demyelination.

Next, Dawson turns to an analysis of the changes to be observed in each cellular element of the nervous system – nerve cells and their axons, neuroglia, blood vessels and lymphatics. Form, symmetry and the distribution of lesions are all addressed. After listing the tragic accumulation of lesions throughout the brain and spinal cord of the unfortunate LW, Dawson attempts a clinico-pathophysiological correlation. Weakness in the legs is consistent with the extensive spinal cord gliosis; intention tremor with lesions in the superior cerebellar peduncles and red nuclei; disordered eye movements with the periaqueductal plaques; and the several cranial nerve palsies with involvement of the pons and medulla. Dawson shows that old (sclerotic lesions) are characterised by complete absence of myelin (Weigert stain), dense fibrillary tissue (glial stain), persistence of axis cylinders (silver stain), numerous blood vessels (diffuse stains), no active myelin degeneration (Marchi stain) and an abrupt transition to normal tissue. In acute lesions, the differences are infiltrated blood vessels, active demyelination with fat granule cells, and transitional zones shading into normal tissue. He illustrates the text with 22 colour and 434 black-and-white figures in 78 plates.

Dawson summarises his ideas on plaque formation around brain inflammation to include a sequence of events that, although not disease-specific, produces recognisable clinical characteristics when directed at glia, leading to degeneration of the myelin sheath with fat granule cell formation, and a reactive change in glia involving cell proliferation with fibril formation culminating in sclerosis. The whole process is triggered and modified by exogenous factors whose influences fluctuate, causing the characteristic relapses. Remissions depend more on rerouting of synaptic connections – for us, plasticity – than remyelination. Maybe he falls into the trap of believing that the pathologist can see the cause, effects and evolution of disease merely by observing snap-shots of its end-state.

1960: Evidence for an immune response within the central nervous system in multiple sclerosis

Lowenthal A, Vansande M, Karcher D. The differential diagnosis of neurological diseases by fractionating electrophoretically the CSF proteins. J. Neurochem. 1960;6:51-60.

The most consistent laboratory abnormality in multiple sclerosis is the finding of a restricted number of 'oligoclonal' immunoglobulins within the cerebrospinal fluid. These are produced by B cells in the parenchyma of the central nervous system and drift into the cerebrospinal fluid like oil in the sump. However, their role in the pathogenesis of multiple sclerosis, if any, remains completely unknown. But their everyday importance is their value as a biomarker that supports the diagnosis of multiple sclerosis, being found in 90-95% of people with the disease; but also in conditions having an inflammatory basis and, rarely, apparently by chance. The history of their discovery is intimately tied to technological advances.

In 1948, the Nobel Prize for chemistry was awarded to the Swede, Arne Tiselius, for his application of physical techniques to biological molecules, mainly electrophoresis of proteins. This work was soon taken up by medical researchers. For instance, Elvin Kabat and Harold Landow studied protein electrophoresis of cerebrospinal fluid from patients with a variety of conditions, including multiple sclerosis, at the Neurological Institute of the College of Physicians and Surgeons at Columbia University in New York. In their 1942 paper, submitted a few days after Landow's death, Kabat and Landlow showed that the ratio of gamma-globulin to albumin in cerebrospinal fluid is normally identical to serum, except in patients with neurosyphillis.[14] Rather poetically, they conclude that 'the data would suggest that some formation of gamma globulin could take place within the tissues of the central nervous system and be poured into cerebrospinal fluid'. This was a new concept; up until then, there was little evidence in humans for an immune response confined to the central nervous system. The researchers commented in passing within the results section that, of five cases of multiple sclerosis, one had some evidence for intrathecal gamma-globulin synthesis. But they made no more of this.

The Tiselius technique is based on fluid boundaries, requires expensive bulky equipment, and is difficult to perform. From the 1940s onwards, 'zone' electrophoresis was developed, with filter paper used as a substrate. Then, in 1955, an English medical-school drop-out called Oliver Smithies developed gel-based electrophoresis.[15] In 2007, he received the Nobel Prize with Mario Capecchi and Martin Evans 'for their discoveries of principles for introducing specific gene modifications in mice by the use of embryonic stem cells'.

The paper we have chosen comes from Lowenthal and colleagues, at the Neurochemical Research Laboratory of the Neurological Department, Antwerp, translated from the French by Charles Poser, author of another of our top ten papers. This group pioneered the application of agar electrophoresis to cerebrospinal fluid proteins. They saw, for the first time, multiple sharp gamma-globulin bands (γ1, γ2 and γ3) in the cerebrospinal fluid of patients with multiple sclerosis, which were not present in normal individuals. And they distinguished these from the increased γ4 and γ5 bands seen in subacute sclerosis panencephalitis (Figure 2). They made a point of saying that such bands were rarely seen in cases of African trypanosomiasis (although they confessed that the electrophoresis of these specimens had been delayed by one week because the lumbar punctures were performed in the Belgian Congo!). Now, cerebrospinal fluid electrophoresis was being promoted as a diagnostic aid for multiple sclerosis in clinical practice.

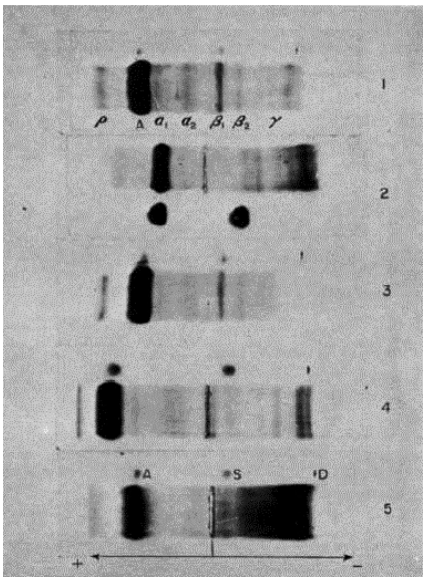

Figure 2 from 26. Lowenthal's agar gel micro-electrophoresis pattern of CSF from: 1 Multiple sclerosis. 2 Subacute sclerosing leucoencephalitis (SSLE). 3 Normal. 4 Neurosyphilis. 5 African trypanosomiasis.

The next technological innovation was isoelectric focusing of agarose-gel electrophoresis, which improved sensitivity yet further. Hans Link and colleagues were early in exploiting this showing, as well as improved definition of the 'oligoclonal bands' (a term he coined), that these were largely due to the presence of IgG antibodies.[16,17]

The scientific dividend from the discovery of cerebrospinal fluid oligoclonal bands has been frustratingly small. It seems that there is no consistent antigenic target for the antibodies and they are unaffected by most effective therapies. But the recent discovery of meningeal B cell lymphoid follicles and the moderate efficacy of B-cell depleting antibodies, has reawakened interest in the role of B cells and antibodies in multiple sclerosis.[18]

In clinical practice, the advent of magnetic resonance imaging has reduced the frequency with which it is necessary to test the cerebrospinal fluid in the diagnosis of multiple sclerosis. But in the tricky diagnostic case, the finding of cerebrospinal fluid oligoclonal bands can be an indispensable ally, for it remains the only direct clinical test of the pivotal disease process – active inflammation within the central nervous system.

1970: An exemplary trial of steroid treatment of the acute relapse

Rose AS, Kuzma JW, Kurtzke JF et al. Cooperative study in the evaluation of therapy in multiple sclerosis: ACTH vs placebo: Final report. Neurology 1970;20:1-19.

"In 1960, at a symposium concerned with the evaluation of drug therapy in neurologic and sensory diseases, the many particular difficulties involved in the clinical trials of therapy in multiple sclerosis were recognized, including those pertaining to the conduct of cooperative studies."

So opens this massive, 59-page, report on a trial of ACTH as a treatment of multiple sclerosis relapse. The symposium mentioned led to an ad hoc committee which reported in 1965 on the ideal trial for a multiple sclerosis therapy.[19] And, five years later, the first application of its principles were published. It represents a landmark in trial rigour and quality, despite a rather unsatisfactory conclusion.

By 1965, there was agreement that ACTH did not influence multiple sclerosis in the long-term, but conflicting small-scale reports on its short-term effect on relapses. Rose and colleagues suspected that ACTH might have an effect, but of small magnitude, which would require careful trial design to reveal. So, they insisted on a placebo control, and on the use of 10 neurology centres, to maximise recruitment of the required number of patients (in the end 197). They described as a particular strength of the trial: "a statistical centre office and staff, backed by computer facilities, ensured randomisation, diminished bias in data review, and provided opportunity for the multiple analyses that were required for the extensive clinical observations."

Each patient was in hospital for two weeks, receiving twice daily injections of diminishing doses of ACTH or placebo. They were assessed each week for four weeks on several scales:

- A rather arbitrary "Estimate of Overall Condition"
- Kurtzke's Disability Status Scale & Functional Systems Score
- The Standard Neurological Examination
- Seven Day Symptom Score, which attempted to capture what would now be called an "area under the curve" disability metric
- Quantitative examination of neurological function

Fifty-two pages of charts, tables and text describe the results of these analyses. Each outcome assessment is compared to another, and across centres, to see which was the most consistent, and which scales correlated with each other. The conclusion, which has been tested many times ever since and has yet to be upset, was "the Disability Status Scale, together with the Functional Systems, comprises an adequate system of evaluating change in a therapeutic trial of MS and, of all the measures used in this study, apparently is the most consistent indicator of change". In contrast to the detail on outcome measures, there is none on the trials' selection criteria, just a reference to the protocol, published in a previous issue of *Neurology*. And there is no discussion at all of statistical technique and power.

The primary outcome measure was comparison of patients' disability at baseline with that at four weeks after starting treatment. There was a significant difference in favour of ACTH, but the authors were not impressed. Firstly, they noted that the size of benefit fell between week three and four, suggesting that it might disappear altogether on extended follow-up. Secondly, they questioned whether the statistically significant difference was clinically significant: "the treatment results of the study as revealed by extensive analysis of a large mass of data may be considered noteworthy for, although the degree of improvement of the patients treated by ACTH attained statistical significance by each of the several methods of evaluation, at no time was the improvement particularly obvious or outstanding. Indeed, 69% of the patients who were treated by placebo attained improvement, a factor that will not be overlooked by thoughtful investigators. It is evident that the "placebo effect" of a well ordered, seriously applied therapeutic effort, although complex and difficult to define, provides a powerful influence which may qualify treatment results. These observations should serve to temper the enthusiasm of those who would advocate a specific therapy for MS unless the therapeutic trial is adequately and appropriately controlled."

Soon, clinicians moved to using synthetic corticosteroids, rather than using ACTH to promote release of endogenous steroids. The lack of extended follow-up in the Rose study was corrected by a study in Wales of 50 people with multiple sclerosis treated with placebo or intravenous methylprednisolone.[20] And more still was learnt from the effect of steroids on optic neuritis.[21-24] The conclusion of all of these studies is that steroids reduce the duration of a relapse of multiple sclerosis, but have no impact on the extent of residual disability nor of the subsequent disease course. ◆

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An Update on Nystagmus

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Nystagmus is an involuntary to and fro movement of the eyes. Pathological nystagmus can be classified into infantile nystagmus (IN), which emerges in the first six months of life, and acquired nystagmus (AN), which develops later.[1] AN can be due to peripheral and central vestibular disorders or caused by neurological disease. IN can be of an idiopathic nature or associated with other visual disorders such as albinism, retinal disease, low vision and neurological childhood diseases. Nystagmus causes decreased visual acuity due to movement of images away from the foveal area of the retina. The prevalence of nystagmus is reported to be 24/10,000[2] and the impact of nystagmus is significant, with nystagmus scoring worse than in other visual disease, such as age related macular degeneration, on visual function questionnaires. In general, mechanisms underlying AN are better understood than those behind IN. We give a summary of the recent literature in the field of nystagmus.

Acquired nystagmus

The more common forms of acquired nystagmus are downbeat nystagmus (DBN), upbeat nystagmus (UBN), acquired pendular nystagmus (APN), periodic alternating nystagmus (PAN) and gaze evoked nystagmus (usually causes very few problems in primary position).[1] Animal experiments have provided evidence as to the underlying mechanisms for AN and these experiments have also helped to identify useful therapeutic interventions. Each form of AN has distinguishing characteristics that can be influenced by the aetiology.

PAN consists of a horizontal jerk nystagmus that periodically switches direction and is probably the best understood form of nystagmus. Results from animal studies have suggested that PAN may arise from the disinhibition of the optokinetic vestibular system.[3] The treatment reported to reduce PAN is baclofen. However these results are based upon case reports and it is important to note that to date no large randomised controlled trials that assess the efficacy of baclofen use in PAN have yet been performed.

Animal studies have suggested that DBN (a vertical nystagmus with a slow drift upward and fast downward phase) is related to vertical gaze-velocity cerebellar Purkinje cells in the flocculus and paraflocculus. This has been more recently confirmed with functional magnetic resonance imaging in humans with DBN, who showed reduced activity of both floccular lobes during downward pursuit.[4] Furthermore, computational model simulation of the effect of extensive loss of floccular Purkinje cells resulted in ocular motor features that are typically associated with DBN. The most effective pharmacological treatments for DBN have been reported in studies administering the potassium channel blockers 3,4-diaminopyridine (3,4-DAP) and, more recently, 4-aminopyridine (4-AP). As cerebellar Purkinje cells are potassium channel-rich it has been thought that enhancing Purkinje cell activity would restore the inhibitory influence of the cerebellum upon vertical eye movements to a normal level. A recent randomised controlled trial has compared the use of 10mg doses of 3,4-DAP and 4-AP and concluded that although both 3,4-DAP and 4-AP significantly reduced DBN, 10mg doses of 4-AP led to a more pronounced decrease in the slow phase velocity of DBN than equivalent doses of 3,4-DAP[5] (Figure 1). An alternative hypothesis for the mechanism behind 4-AP is that it restores the diminished precision of the Purkinje cells pacemaking ability by prolonging the action potential. 4-AP may also be useful for upbeat nystagmus (UBN) by increasing the excitability of the cerebellar Purkinje cells.

APN is a sinusoidal movement that can occur in the horizontal or vertical plane but often has both horizontal and vertical components and most commonly occurs in disorders of central myelin (often multiple sclerosis [MS]) and vascular disease (syndrome of oculopalatal myoclonus). These two conditions result in APN that differs in clinical features. In a direct comparison of the clinical features of APN associated with MS and APN associated with syndrome of oculopalatal myoclonus the oculopalatal group showed a nystagmus of a significantly higher mean amplitude and mean peak velocity with a lower mean frequency than that of the MS group.[6] The oculopalatal group also presented with more disconjugacy and irregularity of APN. These distinct features have led to separate models for their pathogenesis. For APN in demyelinating disease it is suggested that the oscillations arise in the eye movement neural integrator which ensures steady gaze.[1] For APN related to oculopalatal tremor the main pathologic finding is hypertrophic olivary degeneration. It is hypothesised that deafferentation of the inferior olive gives rise to modification of connexion junctions between adjacent neurons leading to abnormal oscillatory neural activity. Successful pharmaceutical therapy for APN has been reported with gabapentin and memantine. Two randomised crossover trials, administering memantine (40-60mg) and gabapentin (1200mg) for APN due to multiple sclerosis and oculopalatal tremor, have recently been reported.[7,8] These trials similarly recommend the use of both gabapentin and memantine as safe and effective methods of improving APN, oscillopsia and visual acuity. Furthermore it is

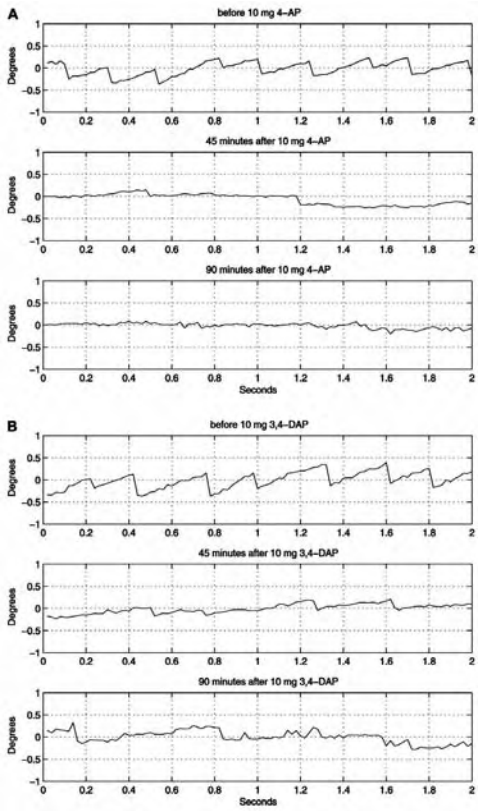

Figure 1: Eye movement recordings in one patient with downbeat nystagmus prior to administration and 45 minutes and 90 minutes following administration of 4-Aminopyridine and 3,4-Diaminopyridine (B). Reproduced from: Comparison of 10-mg Doses of 4-Aminopyridine and 3,4-Diaminopyridine for the Treatment of Downbeat Nystagmus. Journal of neuro-ophthalmology: the official journal of the North American Neuro-Ophthalmology Society 2011.

possible to analyse the effects drugs have to test models of nystagmus; analysis of the effects gabapentin and memantine have on APN is reported to support the hypothesis' for APN pathogenesis models.[9]

Infantile nystagmus

Infantile nystagmus (IN) can be idiopathic or associated with other visual disease such as albinism, retinal disease and low vision, for example congenital cataracts. IN develops within the first few months after birth and individuals can be singly affected or have a strong family history. A gene (FRMD7) has recently been discovered to be the cause of most X-linked idiopathic familial nystagmus.[10] Further studies have shown that FRMD7 is expressed in the ventricular layer of the forebrain, midbrain, cerebellum primordium, spinal cord, and also the developing neural retina. Although the function of the gene is not yet known FRMD7 has been shown to be involved in neurite outgrowth and development.[11]

IN is usually of either a pendular waveform or a jerk waveform with an accelerating slow phase occurring in the horizontal plane that is bilateral and conjugate.[12] Many models have been produced that are able to generate waveforms that are associated with IN; several of which include unstable circuitry of the slow eye movement and gaze holding systems. Contrary to this it has also been suggested that IN may be attributed to early visual deprivation, perhaps due to delayed visual maturation. Currently there is no consensus as to which of these theories are correct. Recently a classification for eye movement abnormalities and strabismus (CEMAS) has collectively termed all IN as 'infantile nystagmus syndrome' (INS), suggesting that IN has one underlying primary cause. However, in terms of classifying IN, eye movement recordings have shown subtle but significant difference between IN subtypes such as albinism and retinal disease[13]. In addition to eye movement recordings, the use of optical coherence tomography is able to document the progression of retinal diseases with age and also predict visual acuity based upon the foveal development in albinism. These findings suggest that the classification of all IN into one form (INS) is inappropriate at this time until further evidence is available.

The pharmacological treatment of IN has been largely based upon the success of medication for AN. Following on from reports that gabapentin and memantine were successful in the treatment of APN, these drugs were trialled for use in IN.[14] The first randomised controlled trial for IN included participants who had both idiopathic IN and IN associated with other visual disease and concluded that both gabapentin and memantine reduced eye movement and improved vision in idiopathic IN. Although vision did not significantly improve for the group that had other visual deficits, eye movement was significantly less for this group.

Surgical options that have been reported for IN include large recessions of the horizontal rectus muscles, Kestenbaum procedures for the correction of head postures, artificial divergence surgery and, most recently the tenotomy procedure.[15] The tenotomy procedure is the removal and replacement of the horizontal eye muscles into the original position. The suggested mechanism by which tenotomy reduces nystagmus is by an interruption of the afferent proprioceptive loop which in turn produces a dampened peripheral ocular motor response to the nystagmus signal. Tenotomy procedures can be combined with strabismus surgery and Kestenbaum operations. Other treatment options include refractive correction, prisms, botulinum toxin injections and biofeedback.

Future considerations

The lack of understanding of the underlying mechanisms behind nystagmus has led to a delay in ascertaining effective treatment for nystagmus, although, of late, more treatment options have emerged. A limited amount of these reports are randomised controlled trials. Further high quality evidence is required in order to validate potential pharmacological treatments for all forms of nystagmus. Most recently pharmacological therapies are being reported as a method for testing models for APN and in the future this technique may be applied to test hypotheses for other eye movement disorders.

The characterisation and classification of nystagmus types has been helped with recent developments in genetic and imaging methods. The genetic sources for forms of IN are being recognised, including the discovery of the FRMD7 gene for idiopathic IN.[10] This, coupled to advances in imaging, such as OCT, allows for greater discrimination of sensory deficits in IN.[13] As these techniques advance further this may lead to a greater understanding and a more informed classification, of nystagmus. ◆

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How to deal with paternal mitochondria. By the Oocyte

Inherited mitochondrial disorders are passed mainly from the maternal side. Of course, this broad statement ignores the increasing awareness of the role of autosomal encoded genes and proteins in many conditions attributed to mitochondrial dysfunction that we neurologists encounter in our clinics. This aside, we know and accept that mitochondria and their DNA are almost exclusively maternal. But why and how is this so?

Until recently, maternal inheritance of mitochondria was believed to be simply a consequence of the dilution of the spermatozoan mitochondria within the larger fertilised oocyte. However, recent work, both published in the same edition of *Science*, suggest that the process of paternal exclusion is far more active. Al Rawi et al. and Sato and Sato describe their work using the nematode Caenorhabditis elegans to study the events surrounding oocyte fertilisation. Independently, they both show that shortly after fertilisation, both the paternal mitochondria and associated mitochondrial DNA from the sperm disappear. This process was found to be due to the activation of autophagy in the oocyte, a process by which a double-membraned structure engulfs cytoplasmic contents for transportation to the lysosome for degradation. By disrupting autophagy, paternal mitochondria and DNA persist, leading to a situation known as heteroplasmy where two different mitochondrial genomes exist. Interestingly, 95% of worms missing a key component of the autophagy machinery die before the larval stage, although it is not clear whether this is due to the persistence of paternal structures per se or a general consequence of disturbed protein clearance. While these findings are interesting with respect to worm development, importantly, Al Rawi et al. also show that autophagy appears to be activated in mouse zygotes suggesting a conserved mechanism in higher organisms, probably extending to humans.

Why does the oocyte actively discard paternal factors? One suggestion is that a basic mechanism identifying the sperm mitochondria and associated DNA as foreign intruders is activated, similarly to invading bacteria, and cleared using a conserved mechanism of degradation. However, this does not address why maternal mitochondria and DNA are preferentially inherited, sometimes with deleterious consequences when harbouring mutations leading to disease. Another possible explanation proposed is that after such a long journey to meet the oocyte, the paternal mitochondria are exhausted and susceptible to reactive oxygen species damage posing a risk to the developing organism if not cleared. Whatever the reason, identifying these mechanisms may allow specific manipulation of the underlying processes and provide possible therapeutic targets as we improve our understanding of mitochondrial diseases.

– Rhys Roberts, Cambridge Institute for Medical Research and Addenbrooke's Hospital, Cambridge.

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Myasthenia Gravis with antibodies to MuSK – potential pathogenic mechanism

Antibodies against Muscle Specific Tyrosine Kinase (MuSK) are present in 40-60% of myasthenic patients that test negative for acetylcholine receptor (AChR) antibodies. These patients often have a distinct phenotype with selective involvement of bulbar and facial muscles and typically respond well to immunosuppressive agents and plasma exchange (Guptill et al Muscle Nerve 2011).

It has been ten years since the first description of myasthenia caused by MuSK antibodies but the pathophysiology of MuSK MG remains poorly understood (Hoch et al 2001). MuSK is a transmembrane end plate protein. It is essential for the formation and maintenance of the neuromuscular junction (NMJ) via a complex intracellular signalling pathway involving nerve secreted agrin and other post synaptic proteins including Lrp4, Dok7 and rapsyn. A second function of MuSK is to anchor acetylcholinesterase (AChE) to the basal lamina. At the NMJ AChE is linked to a collagenic subunit-ColQ- the C terminal of which binds to MuSK (Cartuad et al J Cell Biol 2004).

In this current paper, Kawakami et al suggest via three sets of experiments that MuSK IgG may exert a pathological effect by disrupting the interaction between MuSK and ColQ. The investigators firstly showed that MuSK antibodies disrupt the binding of ColQ tailed AchE to the neuromuscular junction by way of an *in vitro* overlay assay on ColQ-/- muscle preparations. Secondly, an *in vitro* plate binding assay demonstrated that MusK IgG decreases the binding of ColQ tailed AchE to MuSK in a dose dependent fashion whereas binding of Lrp4 to MuSK was unaffected. Finally, passive transfer experiments were performed to show that MuSK IgG significantly reduced the expression of ColQ and AChE at the neuromuscular junction whereas AChR and MuSK expression were only moderately affected.

This study is significant as it compellingly suggests a novel mechanism of action of MuSK IgG. However, there are discrepancies between human and animal data that leave important questions unanswered. The findings of this study suggest that patients with MuSK MG should have end plate AChE deficiency. However, there has been no evidence of this from patients' intercostal muscle biopsies. Moreover, there are discrepancies between this study and previously described passive transfer experiments. Kawakami et al showed that AChR expression was only moderately reduced by MuSK IgG whereas previous investigators have shown evidence of significant AChR loss in passive transfer models (Cole et al J Physiol 2010, Punga et al Exp Neurol 2011).

One possible explanation for these disparities is that individual muscles have different levels of expression of MuSK and ColQ tailed AchE as well as different twitch properties. These differences seem to render some muscles more vulnerable than others to the effects of MuSK IgG. In light of the recent finding that ColQ participates in controlling AChR clustering via its interaction with MuSK, the authors also suggest that even a partial disruption of the ColQ/MuSK interaction may be sufficient to cause post synaptic destabilisation (Sigoillot et al J Neuroscience 2010). Further research is required to fully outline the reasons for these discordant results. Nevertheless, the current study is an exciting development in that it sheds new light on the pathogenesis of this complex autoimmune disease.

– Jennifer Spillane, Clinical Research Associate, Institute of Neurology, Queen Square.

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Immunogenic VGKC-complex antibodies: in mice and men

A recent fascinating paper has elegantly correlated a set of human clinical and serological observations with an experimental animal model. The clinical observation was the development of a monophasic, sensory-predominant, inflammatory polyradiculopathy in swine abattoir workers (Lachance DH, et al). Those working near to the point of the brain extraction/aerosol emission were preferentially

affected. In all patients, the authors observed a pattern of patient serum-IgG binding to mouse brain sections ('signature-IgG'). Now, they build on these clinical findings with refinements of the patient IgG-specificities, and report some remarkable clinical and serological correlations in mice exposed intranasally to liquefied brain tissue (Meeusen JW, et al.)

Seventy-nine percent of affected abattoir workers had VGKC-complex antibodies whose concentrations correlated well with the concentrations of signature-IgG. However, the frequent presence of antibodies against VGCCs and myelin basic protein (MBP), and the absence of VGKC-complex antibodies in 21%, show that polyclonal specificities were also generated by immunisation. This was also the case in mice that were intranasally challenged with brain tissue: all developed signature-IgG and specific antibodies against the VGKC-complex, VGCC and MBP. Neither patients nor mice had antibodies against the NMDA-receptor, aquaporin-4 or amphiphysin. In both the mice and patients, MRI showed swollen nerve roots and neural histology was often demyelinating. In mice, anaesthesia induction produced marked hyperactivity which is characteristic of VGKC-dysfunction. Subsequent removal of the murine intranasal antigenic stimulus, was followed by a fall in the VGKC-complex IgG levels.

The most striking aspect of this study is the generation of VGKC-complex antibodies in mice and patients who were intranasally exposed to brain antigens. While polyclonal antibody specificities were also present, this strongly suggests there is something innately immunogenic about the VGKC complex proteins – but which protein in particular? It is now established that the VGKC-complex proteins (LGI1, CASPR2 and Contactin-2), not the VGKC itself, are the major targets of the patient antibodies (Irani SR, et al.). Only around 10% of the VGKC-complex antibodies in mice and abattoir workers were directed against CASPR2, and none targeted LGI1. In humans, CASPR2-antibodies are often associated with neuromyotonia, but many patients with neuromyotonia have VGKC-complex antibodies without LGI1, CASPR2 or Contactin-2 antibodies. Therefore, it is possible that an immunogenic component of the VGKC-complex involved in peripheral nerve function is yet to be established in mice and men.

– Sarosh R Irani, Nuffield Dept of Clinical Neurosciences, University of Oxford.

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From alpha to omega: a paradox is unraveling in hypokalaemic periodic paralysis

Attacks of weakness in periodic paralysis occur when a proportion of muscle fibres flip to an abnormally depolarised resting potential that inactivates sodium channels and renders the cells inexcitable. Strangely, the trigger in hypokalaemic periodic paralysis (HypoPP) is a fall in external potassium. These cells appear to be making a rather basic physiological gaff; the textbook says that increasing the potassium gradient by reducing external potassium enhances potassium efflux and leads to hyperpolarisation. Curiously, paradoxical depolarisation in low external potassium occurs in normal muscle too, but only in extreme hypokalaemia (<1 mmolar external potassium). In HypoPP an abnormal inward current predisposes to depolarisation in the context of mild hypokalaemia. The origin of this current was mysterious for a long time. Francis and colleagues provide important support for a fascinating idea that has come to dominate thinking about the pathomechanism of HypoPP – the 'gating pore hypothesis'.

Nav1.4, the skeletal muscle sodium channel, is associated with a spectrum of phenotypes from pure myotonia, through paramyotonia and hyperkalaemic periodic paralysis to HypoPP. But unlike the other phenotypes, HypoPP mutations almost invariably neutralise a positive charge in one of the four voltage sensing S4 helices of the channel alpha subunit. The same is true for HypoPP mutations in Cav1.1, which has a homologous structure. This loss of positive charge creates an accessory pathway through the alpha subunit past the mutant S4 helix, completely independent of the main pore. The inward leak of cations through the accessory pathway, known as ω-current or gating pore current, could well be the critical abnormality in HypoPP.

While virtually all HypoPP is associated with neutralisation of a positive S4 arginine residue, not all such mutations cause HypoPP; one of them (R1448C in Nav1.4) leads to Paramyotonia Congenita. The gating pore hypothesis holds that the fundamental difference between HypoPP and other sodium channelopathy phenotypes is the presence of an ω-current in former and not in the latter. So the R1448C paramyotonia mutation is a fly in the hypothetical ointment. Francis and colleagues tested both R1448C and a previously untested HypoPP mutation of the sodium channel, R1132Q. Only the HypoPP mutation supported an ω-current. The ointment is clean. All 6 of the HypoPP mutations tested so far support the ω-current.

The gating pore hypothesis is the first mechanistic theory that satisfactorily links the clustering of HypoPP mutations on voltage sensing channel segments with the muscle phenotype. But it has not explained everything (yet). Several HypoPP mutations are substitutions of an arginine to a histidine, but the accessory pathway created is predicted to be permeable only to protons – in muscle this proton leak is somehow converted into a leak of sodium and other ions. Furthermore HypoPP muscle displays a number of ion channel abnormalities that, while they may be secondary, are nevertheless potentially important for the development of the phenotype. Lastly, the origin of the extreme and dangerous hypokalaemia that frequently accompanies attacks of HypoPP remains unclear. The story is not over yet.

– James Burge, Clinical Fellow to Prof. MG Hanna, UCL MRC Centre for Neuromuscular Diseases, Queen Square, London.

Francis DG, Rybalchenko V, Struyk A, Cannon SC. Leaky sodium channels from voltage sensor mutations in periodic paralysis, but not paramyotonia. NEUROLOGY 2011;76(19):1635-41.

Another shocking revelation for the distal hereditary motor neuropathies

Distal hereditary motor neuropathies (dHMN) are rare diseases that attract attention due to the insights they provide into other motor neuron disorders such as ALS. To date, 11 causative genes have been discovered accounting for only 20% of all cases. The recent discovery by Blumen et al. that homozygous mutations in the heat shock protein (HSP), Homo-Sapiens J-domain protein 1 (HSJ1) are a cause of dHMN is therefore welcome (Blumen, et al., In press). They report a family of Moroccan Jewish ancestry with an aggressive form of autosomal recessive dHMN.

HSPs are a family of molecular chaperones that prevent protein aggregation and target misfolded proteins to the proteasome. Mutations in the small HSPs, HSPB1, HSPB8 and HSPB3 are known to cause autosomal dominant dHMN by a presumed toxic gain of function. HSJ1, on the other hand, is a member of the J domain class of HSPs and is the first to be identified as a cause of a motor neuropathy. In the paper by Blumen et al, the reported mutation affects a donor splice site leading to the translation of a truncated protein implying that loss of HSJ1 function leads to motor neuron death. This is intriguing as pharmacological up-regulation of HSPs has been shown to be an effective treatment in the SOD1 mouse model of ALS (Kieran, et al., 2004). Exactly which HSPs are responsible for this therapeutic effect is unknown. HSJ1 now appears to be a promising candidate for targeted pharmacological up-regulation in motor neuron diseases generally.

– Alexander M Rossor, Clinical Research Fellow, MRC Centre for Neuromuscular Diseases, The National Hospital for Neurology and Neurosurgery and Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, UK.

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Visualising the problem in Parkinson's Disease

Parkinson's disease patients experience an array of visual symptoms throughout the course of their disease but their neural basis and prognostic significance is not well understood. Archibald et al studied these symptoms in patients with PD (n=64) and PD dementia (n=26) using a variety of methods (questionnaires, semi-structured interview, ophthalmological assessment), comparing the findings to an elderly control group (n=32). Complex visual hallucinations (i.e. specific and well-defined images, often involving animals or people) and minor hallucinatory experiences (including illusions, feelings of presence and feelings of passage) were more common in PD patients, especially when responses were confined to the month prior to questioning. With the exception of passage hallucinations, each was even more common in patients with PD dementia. Complex visual hallucinations – present in 38% of the total PD and PD dementia cohort – were also associated with depression and impaired visual acuity, suggesting a multifactorial aetiology. Excessive daytime sleepiness and REM sleep-behaviour disorder contributed to models predictive of illusions and presence, hinting at a more brainstem origin. Reduced visual acuity and loss of contrast sensitivity were more common in PD patients (with or without dementia) compared to controls, and disease-related risk factors included age and higher UPDRS III score rather than cognitive status. Diplopia was reported by 38% of the total PD and PD dementia cohort and logistic regression pointed towards longer PD duration, excessive daytime sleepiness, abnormal ocular alignment and hypometric saccades as causative factors. There was no difference in the frequency of floaters, simple visual hallucinations (e.g. brief flashes of light) or migrainous visual aura between PD patients and controls.

By grouping all visual hallucinations together, Gallagher et al from Queen Square also uncovered a multitude of risk factors in their PD cohort (n=94). Several of these survived multivariate analysis – presence of REM sleep-behaviour disorder, autonomic dysfunction (SCOPA autonomic scale), executive cognitive deficits (SCOPA-COG executive domain) and impaired higher visuo-perceptive function (Birmingham Object Recognition Battery). Unlike Archibald et al, they failed to find any ophthalmic factors contributing towards visual hallucinations, prompting them to suggest that it is cortical pathology in visual pathways that drives visual hallucinations in the majority of PD patients. They supported this hypothesis by presenting neuropathological data demonstrating higher Lewy body density – particularly in temporal and frontal cortical areas – in patients with visual hallucinations on retrospective case note examination.

These two studies highlight the range and extent of visual symptoms in PD, and help us to understand the pathophysiology underpinning these symptoms.

– David P Breen, Clinical Research Fellow in Neurology, Cambridge Centre for Brain Repair.

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Sig-1R: haloperidol for ALS?

With the mapping of the human genome, homozygosity mapping rapidly developed as a powerful way of identifying recessive mutations. It relies on the simple fact that offspring of consanguineous parents will possess many regions of homozygosity, including at disease-causing loci. The power of this technique is clear in the recent study of a family with atypical ALS (Al-Saif et al 2011). Using the ubiquitous whole-genome SNP microarray they were able to identify a single, tiny linked locus on chromosome 9p in a Saudi family with a recessive, slowly progressive, juvenile onset, predominantly upper motor neurone disorder (depicted nicely in their figure 1). The DNA of only four affected individuals in a single generation was needed and only 9 genes were in the locus. A missense mutation was subsequently found in SIGMAR1 (encoding sigma non-opioid intracellular receptor 1, Sig-1R). Sig-1R has been shown to suppress apoptosis induced by endoplasmic reticulum stress. Al-Saif et al used NSC34 cells (a hybrid cell line produced by fusion of motor neuron enriched, embryonic mouse spinal cord cells with mouse neuroblastoma) to show that the E102Q Sig-1R mutation appeared to reduce this protective capacity. The E102Q mutation occurs in a predicted transmembrane domain and subcellular fractionation suggested that the mutation caused the protein to shift to lower density membrane fractions where it formed detergent-resistant complexes.

The normal roles of Sig-1R are not entirely clear, though it regulates K+ channels and is involved in Ca2+ signalling through IP3R. It is a receptor for a variety of ligands including steroids, psychostimulants and haloperidol. It also has chaperone activities in the ER, which further implicates the unfolded protein response in motor neurone disease. Interestingly, variants in the 3' untranslated region of SIGMAR1 were recently linked with autosomal dominant ALS-FTLD (Luty et al 2010). One variant appeared to increase Sig-1R expression, while two others decreased expression. Pathological studies demonstrated, uniquely, the presence of both TDP-43 and FUS inclusions in different cells (rather than one or the other). *In vitro*, mutant Sig-1R appeared to force TDP-43 into the cytoplasm, an effect reduced by Sig-1R ligands (Luty et al 2010).

Pathological studies of the Saudi cases would be interesting to identify inclusions, though it seems the extended survival of patients may preclude this for the time being. No animal studies of these mutations have yet been conducted, but a recent study in mice showed that the native Sig-1R protein is located exclusively in motor neurones, and that knockout causes motility problems (Mavlyutov et al 2010). Further pathological studies of these mice are needed, and it is necessary to create transgenic animals carrying the disease-linked dominant and recessive mutations to help delineate the underlying pathogenesis. Perhaps there is a loss of function with the recessive mutation and a dominant negative effect with the 3' UTR mutation? Could haloperidol be used as a treatment for ALS?!

– Jemeen Sreedharan, King's College, London.

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Mavlyutov TA, et al. The sigma-1 receptor is enriched in postsynaptic sites of C-terminals in mouse motoneurons. An anatomical and behavioral study. Neuroscience. 2010 May 5;167(2):247-55. Epub 2010 Feb 16.

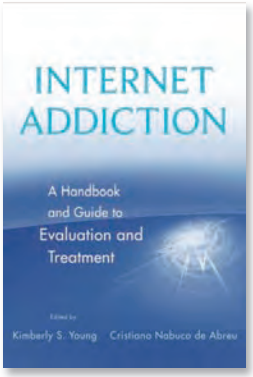
Internet Addiction. A Handbook and Guide to Evaluation and Treatment

Internet addiction is not universally recognised as a clinical disorder as yet, although it will be included in an appendix of DSM-V. The variety of names used for the condition – including problematic internet use, pathological internet use, online addiction, and internet-enabled compulsive behaviour (135) – perhaps reflect its uncertain nosological status. But the problem is real enough, particularly amongst adolescents, such that in countries such as South Korea public health treatment and prevention programmes are already in place (223-243). Screening tests such as the Internet Addiction Test (22-24) are available.

The link to impulse control disorders, and in particular to pathological gambling, is repeatedly made (20, 47, 144, 224), since all the core components of addiction (i.e. salience, mood modification, tolerance, withdrawal symptoms, conflict, relapse) may be encountered. With its "variable ratio reinforcement schedule" the internet has psychoactive properties (144) which may lead to pathological use in predisposed individuals. Some argue, however, that the syndrome arises from behavioural patterns rather than the medium per se (249).

Treatment is problematic for many reasons. Affected individuals seldom see a problem and hence are difficult to motivate to change their behaviour: attendance at outpatient treatment programmes is poor (unless parents are also involved: 245-266). A 45-day inpatient treatment facility in the US (214-220, 271) would not seem to be a feasible approach on the global scale. Abstinence, a favoured strategy for other addictions (alcohol, drugs, sex), is not really an option because of the ubiquity of the internet and its unavoidable use in both domestic and occupational settings. In the absence of controlled trials for any treatment option, prevention (via education) would seem to be the most attractive management approach at present. The importance of assessing for and vigorously treating other, concurrent, psychiatric disorders (depression, bipolar disorder, substance abuse) is repeatedly emphasised.

A number of psychosocial models of internet addiction are discussed in the book, but there is little in the way of neurobiology: the basal ganglia and dopamine are only mentioned in passing (e.g. 10, 136, 248), and pathological gambling in Parkinson's disease patients treated with dopamine agonists not at all. When such links are established, and the neurobiology better understood, it may be that this condition will gravitate away from the psychiatric to the neurological sphere. We may already be seeing cases amongst those patients who have "researched" their condition on the internet. ◆



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Exercise Physiology in Special Populations

Exercise Physiology in Special Populations focuses on health conditions that could potentially be improved by increasing physical activity and fitness. The chapters are written by a range of leading UK researchers and exercise science/rehabilitation practitioners specialising in each of the topic areas. These topics include obesity and diabetes, cardiac disease, lung disease, arthritis and back pain, ageing and older people, bone health, 'the female participant', neurological and neuromuscular disorders, and spinal cord injuries.

As a rehabilitation medicine trainee, and having had the opportunity to be involved in a regular exercise group organised for patients with neurological problems, I have found that the amount of guidance and evidence in the field is limited. The available guidance is usually targeted at the athlete population. As such, this book comes as a welcome breath of fresh air.

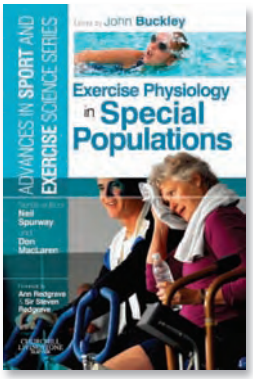
Each chapter is subdivided according to a set pattern, starting with learning objectives and then guiding the reader through aetiology, prevalence, pathophysiology and evidence, finally to 'exercise prescription'. Graphs and algorithms are incorporated to good effect. 'Key points' summarise each chapter. In the exercise guidance section, various forms of exercise such as aerobic endurance, muscular strength and endurance, flexibility, and balance and coordination are discussed. In some cases, this is supplemented by practical hands-on advice in the form of case studies which link theory to real life situations. Comprehensive references and suggestions for further reading are provided at the end of each chapter. The text clearly highlights areas where the evidence is strong, and the gaps in evidence.

The last two chapters were of particular interest as they dealt with exercise physiology in neurological and neuromuscular disorders, specifically stroke, traumatic brain injury, Parkinson's disease, multiple sclerosis, neuropathies and muscular dystrophies, with practical advice about prescribing exercise and some words of precaution.

Two points of mild criticism would be, (1) that the formatting would have benefitted from a clearer differentiation between titles and subtitles, to make the book easier to follow and (2) that case studies and exercise programmes, included very usefully in the arthritis and low back pain chapter, might have been employed more widely.

All in all, I would say this book is a 'must have' for rehabilitation/sports and exercise medicine specialists, both those medically-qualified and allied professionals. Individual chapters will also be of interest to other clinicians according to their speciality.

All too often in seeing patients with long term neurological conditions one can be left frustrated at the lack of therapeutic interventions on offer: an 'exercise prescription pad' should be exactly what the doctor orders for his consulting room! ◆



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Clive Bezzina, Specialist Registrar in Rehabilitation Medicine, Cambridge.

Auditory Laterality: Dichotic Listening and fMRI Studies

Norwegian leading discoveries in neurology and neurolscience are presented in a series of short articles in ACNR, initiated by the journal. All the selected discoveries have links to ongoing research projects in leading groups. They span from clinical to more basic topics. The discoveries are all relevant for clinicians evaluating and treating patients with brain and nervous system disease. Neuroscience with a clinical focus has been a priority for Norwegian research. Further expansion is planned in cooperation between the universities, the university hospitals, the Research Council of Norway, and the Norwegian Brain Council. Although the discoveries in this series are presented as Norwegian, they all appear in an international context. They represent small pieces fitting into the bigger puzzle, but contribute in elucidating mechanisms for brain and neuromuscular function, thus laying foundations for improved treatment of human disease.

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Auditory laterality and hemispheric asymmetry

The differing perceptual and cognitive functions of the two cerebral hemispheres is one of the great discoveries and mysteries of the human brain (see Hugdahl & Westerhausen, 2009 for a recent review of the field). Ever since the groundbreaking work by the Nobel Laureate Roger Sperry (see Sperry 1974), mapping the different functions of the cerebral hemispheres has been a major research area. Most research on hemispheric asymmetry was however focused on the visual system, although the principles governing the workings of the hemispheres should be supra-modal. In 1984 (Hugdahl & Andersson, 1984) our group began research on auditory laterality, using a simple technique called dichotic listening (DL) which had been introduced to neuropsychology in 1961 by Doreen Kimura. We used a variant of the technique with dichotic presentations of simple speech sounds consisting of pairs of consonant-vowel (CV) syllables (see Figure 1) that was first used by Studdert-Kennedy and Shankweiler (1970). The DL technique means that two different auditory stimuli are presented at the same time, one in each ear, and without informing the subject or patient that there are two different sounds. The task of the subject is simply to report which sound she/he perceives on each trial, typically repeating the sequence for a 100 such trials. The result is normally a 'right-ear-advantage' (REA) with better performance for the right ear stimulus, also when controlling for interaural differences in hearing acuity, caused by left temporal lobe processing advantage for speech sounds. This simple technique has several advantages when studying perceptual and cognitive processes particularly in psychiatric and neurological patients, not the least its simple structure which means that patients with severe disorders and diseases can be compared on the same parameters across processes. Over the years our group has used the DL technique to study deficits in hemispheric asymmetry for speech sound processing in numerous psychiatric and neurological disorders, and the CV-syllables variant we developed in the 1980s is today in use in clinics and laboratories worldwide.

Localising the neuronal basis of the REA

In 1999 we published the first brain imaging study, using PET $^{15}0$ with dichotic presentations of CV-syllables stimuli, which showed increased activations in the left superior temporal gyrus (Hugdahl et al., 1999), thus validating the REA performance effects with brain activation measures. The PET results have later been replicated with fMRI (van deen Nort et al., 2008), thus showing the robustness of the neuronal mechanisms generating the REA.

The forced-attention paradigm: How cognition modulates asymmetry of perception

During the 1970s and 1980s there were several studies investigating how cerebral asymmetry may be modulated through influences from higher cognitive processes, e.g. attention (see e.g. Kinsbourne, 1970). In 1986 we reported that the REA could be modulated and even shifted to a left ear advantage in healthy adult individuals when they were instructed to pay attention to the right or left ear stimulus (Hugdahl & Andersson, 1986; see also Bryden et al., 1983), which we labelled "the forced-attention" paradigm. This was a surprising finding since most theories of hemisphere asymmetry at that time considered laterality differences to be the result of the nature of the stimulus. Moreover, there was a general consensus that the 'instruction-effect' was simply the result of differential focusing of attention. This view was however challenged in later studies in our laboratory, particularly in neurological and psychiatric patients with cortical or subcortical damage and/or corresponding cognitive dysfunction (see Wester et al. 2001; Løberg et al., 2006 for examples). We observed that a common denominator across many clinical groups was that the patients could not perform the 'forced-left' condition, when instructed to pay attention to the left ear stimulus of the dichotic pair (see Westerhausen & Hugdahl, 2010 for a recent overview). We realised that the situation with attention focused on the left ear stimulus was a cognitive conflict situation, tapping executive (frontal lobe) functions, while the situation with attention focused on the right ear was a non-conflict situation, tapping attention (parietal lobe) functions. We were later able to verify these assumptions by using fMRI to measure regional changes in neuronal activation in these areas (Thomsen et al., 2004; Westerhausen et al., 2010 using fMRI, see also O'Leary et al., 1996 using PET). See Figure 2 which shows fMRI brain activation data in the prefrontal cortex, particularly in the anterior cingulate. This activation pattern is uniquely associated with instructing the subjects to pay attention to and report the left ear syllable from the dichotic stimulus pair, and not

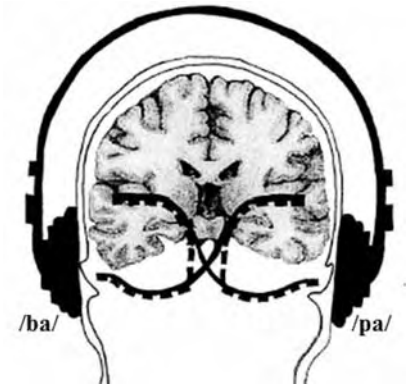

Figure 1: Illustration of outline of the standard consonant-vowel syllables DL paradigm. The right ear advantage is thought to be caused by the more preponderant contralateral auditory pathways and the specialization for processing of speech sounds in the left peri-Sylvian region.

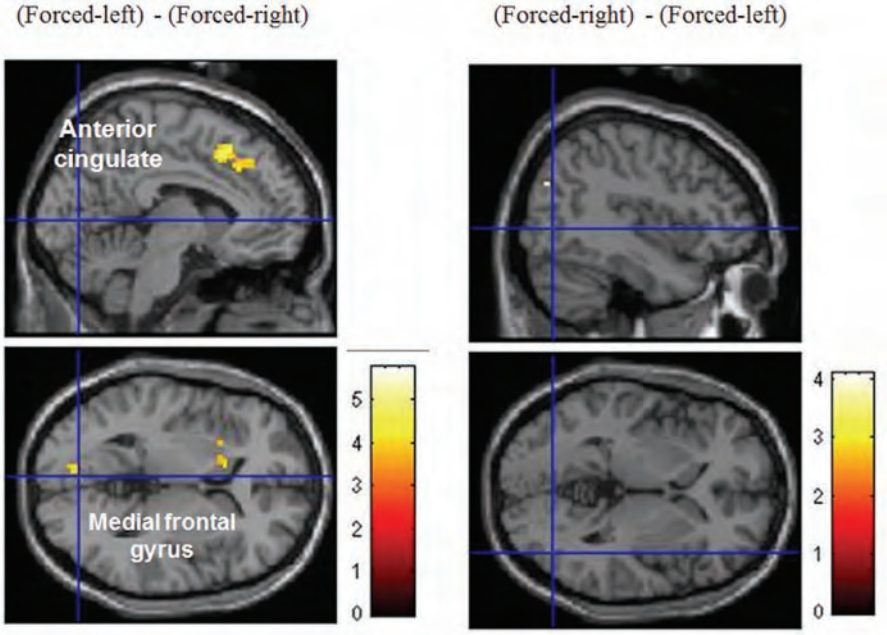

Figure 2: Functional MRI (fMRI) data showing significant activation in prefrontal and anterior cingulate cortex when contrasting images acquired during the "forced-left" condition with images acquired during the "forced-right" condition, not seen in the reversed comparison. (modified after Thomsen et al., 2004)

observed when instructing the subjects to pay attention to and report the right ear syllable. This was a remarkable observation when we first observed it since the only difference between the two conditions is the instruction to move attention to either the right or left ear stimulus, and it should not matter which side in auditory space the subject was attending to.

Based on the early observations in our laboratory, the current view is that the 'forced-attention' DL- paradigm actually taps three different cognitive processes; perceptual, attentive, and executive functions. An important aspect of this discovery is that three complex cognitive phenomena can be studied within the same experimental paradigm, with minimal experimental manipulations between the three conditions, maximising experimental control of extraneous confounding variables. In fact, the only procedural difference between the 'forced-left' and 'forced-right' instructions is a single word in the instruction ('right' versus 'left'), otherwise all parameters stay constant across conditions.

The intensity-modulated paradigm: Quantifying degrees of cognitive dysfunction

In 2008 our group used a simple physical manipulation of the syllable stimuli to increase or decrease the bottom-up load when studying the effects of attention instructions on perceptual asymmetries (see Westerhausen et al., 2010; see also Berlin, 1977). By gradually changing the relative intensity of the right or left ear stimulus in incremental steps of 3dB we were able to show for the first time that subjects tolerated much less of an intensity increase in the right ear when instructed to pay attention to the left ear stimulus, than the other way around, thus showing a parametric way of manipulating cognitive effort needed to exert cognitive control. A more recent fMRI study (Westerhausen et al, 2010) has in addition shown that there is a corresponding parametric modulation of neuronal activation in prefrontal and anterior cingulate areas corresponding to the gradual change in performance. With this development of the technique we foresee a new way of testing various psychiatric and neurological patients for degrees of neuropsychological dysfunctions across diagnostic categories, something that has not been possible before. Parametrically quantifying degrees of cognitive dysfunction in patient groups with different diagnoses could reveal subtle commonalities in cognitive deficits in aetiologically unrelated diagnostic categories, in particular in psychiatric patients, could have consequences for diagnosis and treatment.

Conclusions

In this brief overview of research in our laboratory on auditory laterality and top-down modulation of a bottom-up perceptual asymmetry effect, I have shown how our laboratory over the years has revealed how an assumed pure behavioural effect has distinct neuronal correlates localised to the upper posterior parts of the peri-Sylvian region, using both PET and fMRI measures. I have furthermore shown how influences from higher cognitive processes, such as attention and executive functions, modulate lower level processes, such as perception, and that this also have neuronal correlates in prefrontal and parietal lobe areas. Finally, I have shown how this research has revealed a common profile of cognitive dysfunction (with unique neuronal correlates) across diagnostic categories for psychiatric and neurological dysfunctions. ◆

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Cervical Spine Injuries in Children – a review

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Cervical spine injury (CSI) in children is rare but can result in mortality and significant morbidity. The biomechanics of a child's cervical spine are very different from those of an adult. This has implications in the management of pediatric CSI.[1]

Epidemiology

CSI is present in 1-3% of paediatric trauma patients.[2-4] Approximately 72% of spinal injuries in children <8 years old occur in the cervical spine.[5] The cause of injury is influenced by age. Falls are the commonest cause of CSI in the younger population. This is followed by pedestrian and passenger seat accidents in the slightly older group. Sports related accidents are seen most commonly among adolescents. Overall, 26-61% of CSI result from motor vehicle accidents, 34-48% from falls, and sports injuries represent 3-20%.[6,7] Studies have shown that young males have a higher incidence of CSI, suggesting higher risk behaviour in this group. Patients who have had cervical spine surgery or have a history of CSI are at an increased risk of CSI. Genetic conditions such as osteogenesis imperfecta may result in an increased incidence of spinal fractures. Diseases affecting the ligamentous structures, including Down's syndrome, Marfan's syndrome and Ehlers Danlos syndrome, are associated with an increased susceptibility to CSI.[8]

Biomechanics – anatomical factors

The paediatric cervical spine is intrinsically susceptible to spinal cord injury. A number of anatomical factors account for this (Table 1). In essence, the relatively large child's head, supported by relatively weak neck musculature, upon a developing spinal column with lax ligaments and pliable discs, is vulnerable to injury.[9-11] In young children the fulcrum for movement is located in the upper cervical spine, leading to a relatively high incidence of injury in the upper cervical spine in this age group. In children over eight years the fulcrum migrates caudally to C5/6 – this is mirrored by an increase in the number of injuries in this region of the spine. Figure 1 shows a typical site of paediatric spinal column injury involving C2.

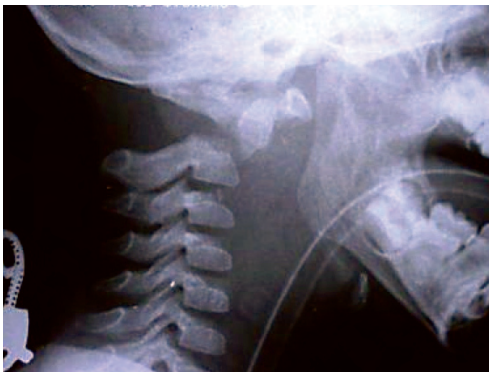


Figure 1: Lateral X-Ray showing a C2 fracture in an intubated child.

Table 1: Anatomical and biomechanical factors contributing to cervical spine injury in children.

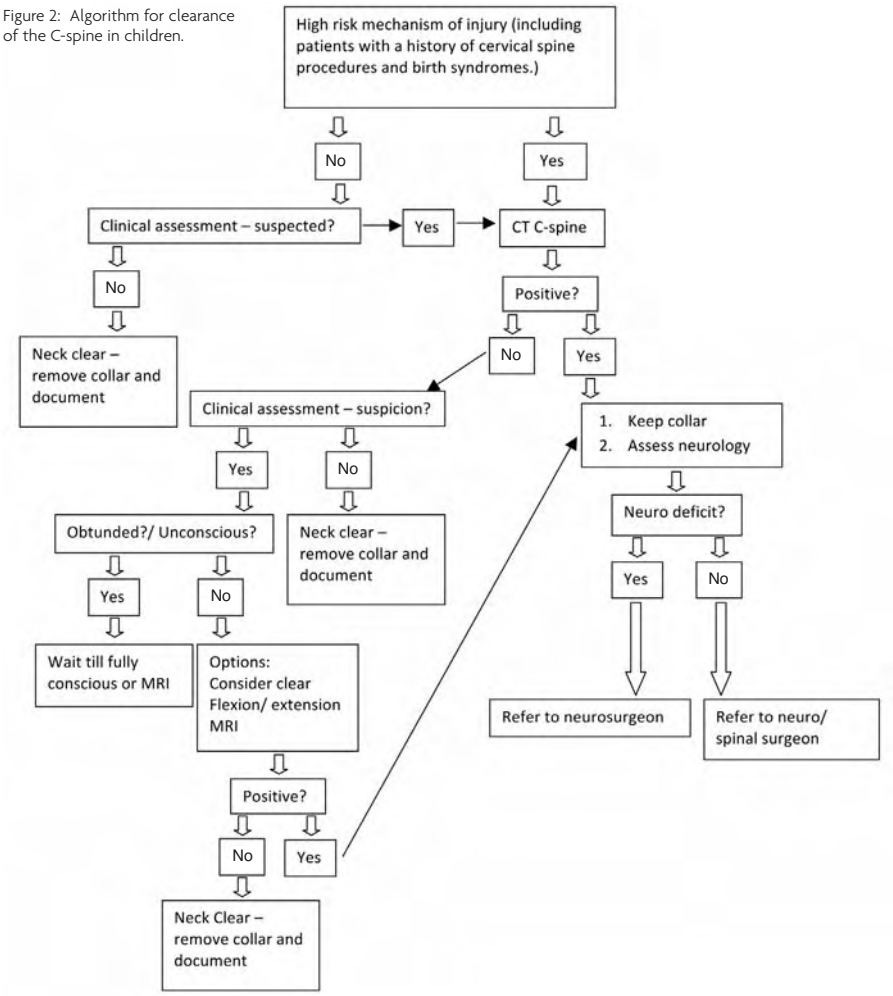
Anteriorly wedge shaped vertebral bodies (poor buttress)
Poorly developed spinous processes (weak tension band)
Poorly developed uncinate processes
Weak neck musculature
Relatively large head
Non-fusion of odontoid synchondrosis
Flattened occipitocervical junction
Pliable intervertebral discs (can cause SCIWORA)
Ligamentous laxity (can cause SCIWORA)

SCIWORA = spinal cord injury without radiological abnormality

Box 1 – High Risk Injuries: Indications for CT Cervical Spine in Children (based on NICE Guidelines)

Age <1 year; GCS <15 at A&E
Age >1 year; GCS <14 at A&E
Age <1 year, bruise, swelling or >5cm scalp laceration
Dangerous mechanism (high speed RTA, fall >3m, high speed projectile injury)
Witnessed loss of consciousness for >5minutes
Seizure with no history of epilepsy
Suspicion of open or depressed fracture
Tense fontanelle
Signs of base of skull fracture
Focal neurological deficit
Loss of consciousness for >5minutes
Abnormal drowsiness
3 or more discrete episodes of vomiting
Clinical suspicion of non-accidental injury
Amnesia (retrograde or anterograde >5minutes)

Figure 2: Algorithm for clearance of the C-spine in children.



Initial management considerations

The management of a child with a cervical spine injury is governed by advanced trauma life support principles. Pertinent issues and differences from adult management will be discussed here.

The relatively large head puts the spine into kyphosis when supine. Thus the body should be raised by 2.5cm, or a spinal board with an appropriate head indentation should be used. The National Institute for Health and Clinical Excellence (NICE) guideline recommends that high risk patients should have a CT scan of the neck before clinical assessment (Box 1). Patients with a significant head injury are considered 'at risk' of a concurrent cervical spine injury as are other high risk patients (eg Down's syndrome).[12-15]

Resuscitation

Paediatric patients in spinal shock are susceptible to hypotension and poor cord perfusion. They require vigilant fluid management, oxygenation and often ventilation. Early introduction of vasopressors for adequate cord perfusion are indicated if blood pressure is suboptimal despite normal volume status. Most fatalities seen in spinal cord injury (SCI) patients result from other injuries including head injuries. A high index of suspicion must be exercised to ensure that concealed causes of haemorrhage are not overlooked. Cases of missed second non-continuous spinal cord injuries among children have also been reported.[16] Lesions above the T6 level may cause autonomic disturbances including impaired temperature regulation, compounded by the high surface area to volume ratio of younger children.

Radiology

Plain cervical radiographs vs CT

Although a plain cervical spine radiograph exposes the immature vertebrae and growing thyroid to less radiation than a CT of the neck, its use as a screening tool for cervical spine injury is suboptimal. In adults, plain cervical spine radiographs have a sensitivity for fracture detection of 46 to 60%.[17-20] Normal variations in children such as pseudosubluxation, absence of lordosis, epiphysial variations, unfused synchondroses, and incomplete ossification render the plain radiograph difficult to interpret. NICE recommends a CT neck in all patients in whom a CT of the head is indicated because of the high association with head injury (Box 1).[21] CT provides the best resolution and detail for bone injury and is a first line investigation. Reconstructions are helpful in diagnosing fractures and misalignments, and in planning management. An algorithm is for radiological clearance of the cervical spine is shown in Figure 2.

The paediatric C-spine radiograph

Although plain radiographs are not as sensitive as CT or MRI in the detection of cervical spine injury an understanding of interpretation is important. A lateral and anteroposterior (AP) view are commonly performed. In younger patients it is difficult to obtain an open-mouth view because of poor compliance.

Vertebral alignment should be studied on the lateral view. The posterior portion vertebral body height is slight taller than the anterior body height, giving the vertebrae a wedge/ rhomboid shape. On the AP view the dens should be equidistant from the lateral masses of C1 and facets of C1/C2 should align. The spinous processes should align and the disc spaces should be symmetrical and similar. In children <8 years the predental space should

Plain cervical radiographs have a sensitivity for fracture detection of 46 to 60%

be less than 5mm (3mm if older), the prevertebral space should be less than 7mm (5mm if older) or less than 1/3 the width of the vertebral body at C3. At C6 it should be less than 14mm (22mm if older). Lack of lordosis is often due to muscle spasm which may be due to a fracture. However, this can be present in some children as a normal variant or as a consequence of positioning on a spinal board. The subdental synchondrosis is the most common normal radiological abnormality mistaken for an odontoid fracture. This shows as a linear lucency at the base of the dens; fusion with the body of C2 occurs between age three and six years. The os terminale is a separate ossification centre that may be present at the tip of the peg i.e. a fragment at the superior-most tip of the odontoid could be a fracture or a normal finding. Pseudosubluxation is found in up to 40% of the paediatric population on lateral C spine x-rays at C2/C3. This shows as 4mm or 40% anterior displacement especially when the child is not placed on a paediatric spinal board. To distinguish from true subluxation (which could imply a Hangman's fracture) the clinical picture must be considered. The position of the anterior aspect of the C2 spinous process should lie within 2mm of Swischuk's line (a line drawn from the anterior aspect of C1 to C3 spinous processes).[22-24]

Clinical assessment

The key steps in the management of a child with a possible spinal column injury are (i) determining if there is a neurological deficit and (ii) whether there is evidence of a radiological abnormality (Box 2). The history should focus on the mechanism and mode of injury. The most common symptom is neck pain and focal midline tenderness is the commonest sign. If the child is orientated, does not have any other painful distracting injury and is not under the influence of drugs, the neck can be assessed before imaging. A child in distress can be examined after analgesia. A neurological examination should be performed followed by checking for focal midline tenderness and then examining the active range of movement of the neck as suggested by the National Emergency X-Radiography Utilisation Study (NEXUS) criteria (Box 3).[25,26]

The Canadian C-spine rule is a checklist evaluated in individuals over 16 years old that identifies low risk patients in which clinical clearance can safely be conducted. Although both the Cervical C-spine rule and the NEXUS guidelines have not been validated for children, they are being applied to fully conscious, compliant children in order to avoid excessive radiation exposure at a young age.[27-29]

MRI

MRI is the most sensitive tool for the detection of spinal cord injury, nerve damage and ligamentous injuries.[30] Transient or persistent neurological symptoms and signs or suspicion of a vascular injury, warrant an MRI. A normal MRI is associated with a good prognosis. Spinal cord injury, including haematomyelia, suggests a poor prognosis. Surgically amenable lesions such as a traumatic prolapsed disc and extradural or subdural haemorrhage are best detected using MRI. In one study 31% of patients with neurological symptoms and signs with normal plain films or CT scans were shown to have abnormal MRI findings.[31]

Box 2 – Clinical Assessment of a child with a suspected cervical spine injury

Pre-assessment:
Involve parent/career
Reassure patient
Awake – not obtunded with GCS 15/15
No distracting injury
Adequate analgesia
Acceptable distress

Assessment:
Neurological examination of upper and lower limbs
Instruct the patient to keep the head still unless asked
Palpate for tenderness, misalignment and spasm
Painless active movement of the neck

Box 3 – NEXUS Criteria – A Clinical Decision Making Tool –
in the presence of a significant injury, if any of the five criteria are not met, cervical spine imaging should be undertaken

- Patient is orientated (GCS 15)
- Patient is not intoxicated
- There are no painful distracting injuries (eg long bone #)
- No focal midline tenderness
- No focal neurological deficit

Management

Role of steroids

To date there are no studies that have evaluated the use of high dose steroids in the management of acute spinal cord injury in a paediatric population. The National Acute Spinal Injury Study excluded paediatric patients.[32] Although the study concluded in favour of early use of methylprednisolone (30mg/kg in the first hour followed by 5.4 mg/kg/h for 23 hours), there have been robust discussions about the clinical significance of the marginal advantages seen. The use of steroids is highly controversial and remains at the discretion of the treating physician.

Thromboembolism

DVT is quite uncommon in this age group. It occurs more commonly in patients with central venous lines and those who suffer from severe sepsis. Studies have not found paralysis or immobilisation alone to be a significant risk factor for thrombosis in children; DVT prophylaxis is therefore not necessarily indicated in every child with a spinal cord injury.[33-35]

Specific cervical spine injuries seen in paediatric patients

Atlanto-occipital dissociation

Atlanto-occipital dissociation is usually a fatal injury seen in children who are involved in high velocity/rapid deceleration motor vehicle accidents. The relatively large head has greater inertial moment than the spine leading to distraction and dissociation. Survivors usually harbour significant neurological deficits. The injury may be difficult to detect with initial imaging; widening of the O-C1 distance (>5mm) is a characteristic sign. MR scanning confirms the presence of injury. Internal fixation and fusion is the mainstay of treatment. Traction can lead to further distraction causing further neurological deficit.

Atlanto-axial rotatory injuries

Rotatory injuries to the atlanto-axial complex are more common in children than in adults. The initiating trauma may be minor and is accompanied by painful torticollis. Imaging investigations may be difficult to interpret in the presence of torticollis. Plain x-rays show anterior displacement of the lateral mass of C1 in relation to the dens, and rotation of the C2 spinous process. CT scans can be helpful, demonstrating the anatomical relationships of C1/2.

Rotation of the neck normally occurs in three phases (Figure 3). Armed with this knowledge Pang and Li have defined three grades of rotatory injury.[36-38] The severity of injury probably represents a continuum from the limits of normality to true subluxation. A grade I injury is at the severe end of the spectrum and represents a 'sticky' association between C1 and C2 in a locked position. A

Figure 3: Rotation of the atlas and axis – a 3 phase process (after Pang and Li, 2004)

0-23 degrees	23-65 degrees	65-90 degrees
C1 rotates C2 is immobile	C1 rotates C2 rotates, but much less than C1	C1 and C2 are "locked" with rotation occurring at subaxial levels

Grade III injury shows mild resistance to rotation. Treatment is usually conservative with minor cases recovering spontaneously. Other cases require manual or halter traction reduction with immobilisation in a hard collar. The duration of collar placement is generally recommended to equal the length of time the torticollis was present before treatment. Fusion is rarely required.[11]

Disruption of the odontoid synchondrosis

The synchondrosis between the dens and the body of C2 is vulnerable to injury before ossification at the age of seven. Such injury is usually treated with prolonged (>10 weeks) external immobilisation, although internal fixation and fusion may be required if a non-operative approach fails to achieve union.

Subaxial spine injuries

In children, subaxial fractures are less common than in adults. Other injuries include unilateral and bilateral facet dislocations. Investigation should actively look for ligamentous instability. An angulation of >11 degrees and/or >3.5mm subluxation should warn of ligamentous injury and instability.[39] Evidence on the management is largely based on retrospective observational studies and case reports. The principles of treatment are similar to those deployed in adults; manual reduction, traction and surgery with internal fixation and fusion.

SCIWORA (spinal cord injury without radiological abnormality) (Figure 4)

SCIWORA is a condition seen in children that is characterised by a traumatic neurological deficit in the absence of fracture or ligamentous injury on plain radiograph, flexion/ extension views or CT.[40,41] Pathology may be evident on MR scanning. About 50-60% of children with traumatic spinal cord injuries do not show any abnormality on X-ray or CT.[16] SCIWORA is more common in children <9 years, but can be caused by sporting injuries in the older child. Signs of myelopathy can develop several days after the injury. SCIWORA can be caused by flexion compression of the cord (which may cause a reversible disc herniation), or hyperextension with inward buckling of the interlaminar ligaments. A distraction injury can also cause cord damage: although the paediatric spinal column can be distracted to up to 5cm, the cord itself is much less extensile.

Patients with congenital spinal canal stenosis, (e.g. trisomy 21) and hyperelasticity conditions (e.g. Ehlers Dahlos syndrome and pseudoxanthoma elasticum) are particularly at risk of SCIWORA. The prognosis of SCIWORA is governed by the MRI findings. Haematomyelia predicts a poor prognosis, whilst an excellent recovery may occur in the absence of a visible parenchymal injury.[42] There have been no reported cases of children with SCIWORA who have later developed spinal instability. Therefore, early immobilisation directed at the avoidance of aggravating the cord injury is appropriate. Although the mainstay of treatment has been prolonged immobilisation others question this view. Once spinal stability has been confirmed with flexion/ extension views, consideration can be given to the early cessation of immobilisation.

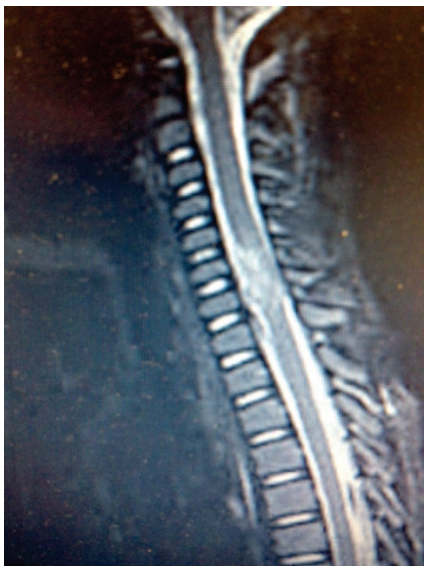


Figure 4: MRI scan in a child who sustained a SCIWORA – note the cord contusion at C6 and C7 and the presence of a subtle disc bulge.

External immobilisation

The unstable cervical spine can be immobilised externally. Options include collar, halo and traction or a Minerva jacket.[43] A collar gives limited protection and can result in pressure sores. A Halo ring is commonly used to enable traction and subsequent external immobilisation in children. Traction is crucial in restoring spinal alignment. For children less than four years of age, one pound per level is used. This can be increased to two pounds per level for older children. Careful serial radiographs are required to check for reduction and to avoid over-distraction. The patient is usually supine in bed, thus exposed to atelectasis, pressure ulcers, and other problems associated with prolonged immobility.[44] In children less than two years of age, multiple pins, up to six or eight, are used to finger tightness. Halo use can be complicated by pin track infections, dural penetration, and supraorbital nerve injuries. In older children fewer pins with greater torque are used. The Minerva jacket has been reported to be superior to a halo in preventing flexion and extension at every vertebral level.[43]

Surgery

Internal fixation and fusion of the cervical spine is normally reserved for the minority of children with occipito-atlanto disruption, unstable subaxial spinal injuries or failed external fixation treatments. The aim of surgery is to stabilise the spine, prevent further neurological deterioration and facilitate early rehabilitation. The challenges seen in paediatric spinal surgery are anatomical and technological. The small vertebral body, epiphysis and endplate may effect abnormal growth and development if insulted. The poorly developed supporting musculature and the limited availability of suitable implants contribute to difficulties. By the age of 10, the cervical spine has almost reached its adult height and the complication rate is lower.

Careful surgical planning is needed to study the anatomical variables. If the patient is placed supine, the head/body position needs to be adjusted by using a head recess or body elevation. In the prone position, careful spinal stabilization is needed. The Mayfield head clamp can be used in older children using a force of 30-40N. Dissection of the C2 muscles must be minimised to avoid instability. Blood loss should also be minimised. In children <10 years of age, posterior instrumentation and plating is avoided because of instrument bulk.[43,44] In children younger than 10 years of age, posterior vertebral arthrodesis can predispose children to the crankshaft phenomenon where the anterior body continues to grow, causing progressive deformity.[45]

Complications of SCI and Treatment

SCI is debilitating and can cause neurological and systemic sequelae. Appropriate spinal care and rehabilitation are mandatory.

- Cardiovascular complications include bradycardia, hypotension and other autonomic disturbances in the early post-traumatic phase.
- Respiratory complications include lung atelactasis, aspiration pneumonia and infection. Tracheostomy may be required in some patients.
- Gastrointestinal complications include reflux oesophagitis, Cushing's ulcer, prolonged ileus and nutritional imbalance, constipation and a risk of laxative overuse. Percutaneous endoscopic gastrostomy (PEG) may be needed in some children.
- Urological complications include a predisposition to calculus formation and urinary tract infection.
- Neurological and musculoskeletal complications include paralysis, disuse atrophy, contractures, joint deformities, heterotopic ossification, sensory loss and neuropathic ulcers, osteopaenia and rarely post-traumatic syringomyelia.
- Psychosocial complications can be a major burden. The child and family can be affected with all aspects of life being subject to significant change.

Conclusion

Childhood SCI is a devastating phenomenon. Fortunately it is rare and has specific injury patterns due to anatomical and biomechanical factors. SCIWORA remains a diagnostic pitfall if not suspected early. MRI is an important tool and provides prognostic information. Management of a child with a SCI requires a multidisciplinary approach to minimise the risk of secondary problems and to rationalise management in the absence of Class I evidence. ◆

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

2012

January

Alpine Brain Imaging Meeting
8- 12 January, 2012; Champéry, Switzerland
E. Marie-Ange.DeLaSen@unige.ch

Cognitive Rehabilitation Workshop
13–14 January, 2012; London, UK
T. 01276 472 369
E. enquiries@braintreetraining.co.uk
www.braintreetraining.co.uk

British Skull Base Society Meeting
18-20 January, 2012; Harrogate, UK
T. 0114 225 9035, E. sarah.bingham@bbraun.com

MYOCON 2012
21-22 January, 2012; Chennai, India
www.treat-nmd.eu/events/286/

5th European Neurological Conference on Clinical Practices
27-29 January, 2012; Warsaw, Poland
www.enccp.net

How to do Cognitive Rehabilitation Therapy
28 January, 2012; London, UK
T. 01276 472 369
E. enquiries@braintreetraining.co.uk
www.braintreetraining.co.uk

International Stroke Conference 2012
31 January-3 February 2012; New Orleans, USA
W: www.strokeconference.org

February

14th National Conference on Dementias 2012
9-10 February, 2012; London, UK
T. 020 7501 6762
www.mahealthcareevents.co.uk/cgi-bin/go.pl/conferences/detail.html?conference_uid=275

British NeuroPsychiatry Association 25th Annual AGM
9-10 February, 2012; London, UK
T. 020 8878 0573, E. admin@bnpa.org.uk

British Neuro Vascular Group Meeting
9-10 February, 2012; Southampton, UK
T. 0114 225 9035, E. sarah.bingham@bbraun.com

7th Annual Biomarkers Congress
21-22 February, 2012; Manchester, UK
T. 01865 304925, E. info@oxfordglobal.co.uk

8th Annual Update Symposium on Clinical Neurology & Neurophysiology
22-23 February, 2012; Tel Aviv, Israel
T. +972-2-6520574, E. meetings@isas.co.il

34th Annual Carrell-Krusen Neuromuscular Symposium
23-24 February, 2012; Texas, USA
www.treat-nmd.eu/events/292/

Modern Thinking in MS Management
25 February, 2012; Birmingham, UK
ModernThinking@apothecom.com

4th International Conference and the 4th Clinical Neurology Course
22-26 February, 2012; Khartoum, Sudan
E. SNS-Conf-2012@hotmail.co.uk

March

1st International Conference on Heart and Brain - ICHB 2012
1-3 March, 2012; Paris, France
E. heart-brain@kenes.com

Insight Workshop
2–3 March, 2012; London, UK
T. 01276 472 369
E. enquiries@braintreetraining.co.uk
www.braintreetraining.co.uk

Neurology, psychiatry, microbiology and pharmacology revision course
3 March, 2012; London, UK
T. 020 7290 2906, E. events@rsm.ac.uk

XIII Pan American Congress of Neurology
4-8 March, 2012; La Paz, Bolivia
T. +56-2-946 2633
www2.kenes.com/pcn2012/pages/home.aspx

Peripheral Nerve Study Day
8th March, 2012; Southampton, UK
E. h.katifi@suht.swest.nhs.uk

British Neurosurgical Research Group Meeting
8-9 March, 2012; Darlington, UK
T. 0114 225 9035, E. sarah.bingham@bbraun.com

The 6th World Congress on Controversies in Neurology (CONy)
8-11 March, 2012; Vienna, Austria
T. 972-3-566-6166, E: noam@comtecmed.com
www.comtecmed.com/

Cell culture technology: recent advances, future prospects
9 March, 2012; Welwyn Garden City, UK
E. enquiries@euroscicon.com
www.regonline.co.uk/workihc2010

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

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

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

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

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

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

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

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

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

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

April

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

ABN National Meeting

Conference details: 4-7th October 2011; The Sage in Gateshead, UK. ***Reviewed by:*** Catherine Pennington and Boyd Ghosh.

Professor Martin Rossor (centre) chairing the debate 'This house believes the ABN should be a college of clinical neuroscience'.

Professor Compston presenting a gift to Professor Eva Feldman after she gave the 17th Gordon Holmes Lecture.

The ABN meeting took place at the impressive Sage Gateshead venue. There was a wide mix of subjects covered, achieving a balance between practical clinical teaching, scientific developments and case presentations.

The meeting opened on the Tuesday with parallel sessions for medical students and registrars. The registrar teaching topics ranged from the familiar territory of Parkinson's disease to a cognitive examination masterclass with Martin Rossor, and ended with the rather neglected arena of oratory and rhetoric. We all speak in public (and indeed to the public) on a regular basis yet often give a less than polished performance. Dr Mumford's talk covered both basic and advanced speechifying with tips on eye contact, correct use of the microphone, and insights into the speech writing tricks of Churchill and Martin Luther King. However the high point of the day had to be the quiz, which tested our ability to identify heavily moustached Victorian neurology heavyweights and MR images of a variety of fruit and veg. These subjects are clearly not adequately covered by the neurology curriculum as the scores were universally low!

There were further clinical talks on the Wednesday, with teaching from the DGH on neurological issues in pregnancy, a cardiologist's outlook on funny turns and a geriatrician's view of falls. The take home messages were to counsel early on and often on reproductive issues in epilepsy, be more worried about cardiac disease in older patients with new collapses with loss of consciousness (and to ditch the 24 hour tape in favour of more prolonged monitoring), and to involve physiotherapy and occupational therapy more in frequent fallers.

We were then taken back to the days of Hughlings Jackson in the history lectures, an era when clinical acumen was king and the West Riding Lunatic Asylum in Wakefield an epicentre of neurological research. The neuropsychiatry session provided an insight into the world of theoretical modelling of brain pathways and how such models may contribute to our understanding of diseases such as Schizophrenia, which according to Professor Bullmore of Cambridge University, may actually result in more robust brain networks in close relatives, possibly providing an evolutionary explanation for the relatively high prevalence of such a debilitating disorder. This was followed by a stimulating debate on the issue 'This house believes that the ABN should be a college of clinical neuroscience'. On the 'for' side was an argument that the current college system fails to adequately serve the needs of neurologists, and that a joint college of neuroscience involving neurology, neurosurgery and neuroradiology would be better placed to meet our professional development needs and to represent neurology in the political world. 'Against' the motion was the practical issue that would arise from removing ourselves further from general medicine, the disparate requirements of neurology, neurosurgery and neuroradiology trainees, and the logistical advantages of being part of a larger body, such as the Royal College of Physicians, when raising issues at a national level. Overall the feeling was that the way forward is for neurologists to be more involved with the existing colleges, both to try raise the standard of service they provide to us and to improve the neurology training provided to non-neurologists. The day closed with the trainee dinner at RASA restaurant for curry and Cobra beer, for which there was an excellent turnout.

The following day the organisation of neurology services in the DGH was considered, stemming from the recent publication of a working party report into the matter. Whilst more neurologists are needed, how to organise services is a matter for debate, particularly in light of the looming NHS re-organisation in England and Wales, and the UK's straitened financial circumstances. Various models of DGH services are in use across the country, reflecting the fact that one DGH may serve a very different population to another, with variation in population size, demographics and distribution. What works for a metropolitan centre will not suit a rural region, let alone areas such as the Western Isles. There is a tendency to try to decentralise neurology services from regional centres out to the DGH, but smaller hospitals are unlikely to be willing or able to sustain a full neurology department with consultants, registrars, nurse specialists, neurophysiology and neuroradiology. Suggested ways to deal with the problem included greater involvement from GPs with a special interest in neurology in the long-term follow up of those with chronic conditions, and the use of telemedicine for outlying regions. Dr Dunn from Leeds gave an account of his experiences of being a liaison neurologist. On the plus side of spending a lot of time in the acute medical unit is the ability to improve the speed and accuracy of the diagnosis of patients as they present, reducing the length of their stay and (potentially) saving the NHS money. There are also opportunities to teach colleagues in medicine along the way. However getting the funding in the first place for such a post is challenging, and only likely to get more difficult in the future.

Dame Barbara Hakin from the Department of Health spoke on the pending reorganisation of the NHS in England and Wales. Details remain thin as to how the new clinical commissioning groups will be organised, and in particular no mention was made of how much involvement from the private sector will be permitted. She acknowledged that a regional commissioning group operating in isolation would not be well placed to organise many neurological services, in particular for

those with rare conditions. She expressed the opinion that the GPs' current role in deciding when to refer patients to specialists and when to delegate care to nurses gives them the expertise to be commissioners. Given the number of inappropriate referrals to neurology clinics this may not be the case. Dame Hakin made it clear that there will be no new Neurologists unless the money is saved elsewhere first.

Later in the day Dr Huw Morris reported breaking news from Wales with the finding of a new mutation on chromosome 9 which may be responsible for a significant proportion of cases of both fronto-temporal dementia and motor neurone disease. Further details are published in *Neuron*. The medallist lecture was given by David Neary on the neurology of dementia, with added reminiscences of his time in Boston in the 1970s living at the YMCA on $3 a day. The evening ended with the Gala dinner at the Discovery museum, with entertainment provided by a barber shop quartet of Neurologists.

On the last morning, one of the parallel sessions was the case presentation competition. Given the early hour, there was a good turn out with plenty of interesting cases, including two with camptocormia (!), transverse myelitis post malaria, rapid cognitive decline due to subacute sclerosing panencephalitis, Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) and micturition induced epilepsy which took twelve years to capture on telemetry! The winner was Dr Sean Slaght from Southampton, describing a reversible camptocormic syndrome due to Lyme disease.

The 17th Gordon Holmes lecture was given by Professor Eva Feldman on ground-breaking human safety trials of the use of stem cells in motor neurone disease, with a fascinating video of the injection of cells into human subjects. In the afternoon, Dr Kevin Talbot toyed with us in the clinic-pathological conference before pulling the correct diagnosis out of the hat. The Neuroradiologists joined us for the last part of the meeting, discussing screening for aneurysms, where the consensus was that we should screen those with two close family members involved; GPs' access to CT scans, where we decided that they shouldn't have direct access; and the use of CT or MRI for acute stroke, where it was decided that CT was adequate currently.

Overall there was a high standard of poster and case presentations, and an excellent attendance of neurologists, trainees and students from across the UK. Dr Kathryn Peall won the Charles Symonds prize for the best platform presentation, Dr Nils Muhlert won the Charles Symonds prize for the best poster and as already mentioned Dr Sean Slaght won the ACNR prize for best case presentation. The feeling amongst trainees we spoke to was that having a single annual UK meeting raised the quality of the material presented, made it easier to attend and created greater opportunity to catch up with colleagues from around the country. We look forward to Brighton 2012! ◆

Fourth Practical Cognition Course

Conference details: 20-21 October 2011; Newcastle upon Tyne, UK. ***Reviewed by:*** Dr Colin Mumford, Consultant Neurologist, Edinburgh, UK.

Most jobbing neurologists have a somewhat restricted concept of the classification of dementia. Many of us would be able to separate typical Alzheimer's disease from fronto-temporal dementia. Others might even be able to make a tentative diagnosis of Pick's disease or, where appropriate, be sensitive to the possibility of Creutzfeldt-Jakob disease in a given patient. However, very few of us have the near encyclopaedic knowledge displayed by the panel of experts who convened in Newcastle during mid October to host, and to contribute to, the annual "Practical Cognition Course".

This excellent course is now in its fourth year. Organised by Professor Tim Griffiths from Newcastle and Dr Chris Butler from Oxford, the course is eminently suitable for trainees in neurology and established consultants alike. Moreover, and perhaps unusually, it is also suitable for clinical psychologists, psychiatrists both at consultant and registrar level, and this year was also attended by at least one specialist in ophthalmology.

The course follows a successful format: first, the different scientific components of the course are closely aligned to presentation and discussion of illustrative cases, the majority of these being admirably exemplified by the use of high quality video recordings. Secondly, the course timetable builds in a great deal of time for discussion, with the mixed professional backgrounds of the delegates making for interesting debate between specialists. Thirdly, the relatively small number of delegates means that nobody is left out, with substantial interaction taking place between individuals in the audience, as well as between delegates and presenters.

This year, much of the early part of the course was practical in its focus. Delegates were introduced to a suggested format for running a cognitive neurological clinic, and then were shown typical cognitive screening instruments, some familiar, and some less so, used in different units around the country. The indispensable role of the clinical neuropsychologist was then very colourfully illustrated by Tom Kelly, one of the local Newcastle experts.

The afternoon of the first day of this two-day programme brought in sections introducing disorders of language and also disorders of consciousness. It was fascinating to see videos of patients with primary progressive aphasia, and also to see – and debate - the rather dubious entity of "foreign accent syndrome". The language disorders component was greatly assisted by a splendid lecture given by Dr Jason Warren from the Institute of Neurology in London. Meanwhile the seemingly complex field of consciousness was tackled sensitively and comprehensively by Professor Adam Zeman from the Peninsula Medical School. His unassailable grasp of this area was manifest in a lecture that moved between the differentiation of the "minimally conscious state" from the "persistent vegetative state", and on into a consideration of the history of our understanding of consciousness, and delved yet further into the very philosophy of consciousness.

The second day began with an analysis of parietal lobe disorders, and continued with a consideration of problems relating to emotion and social cognition. Many of us recall reading about, but never actually seeing, a case of the Gerstmann syndrome, so how nice it was to have a video of a patient exemplifying the key facets of the condition, all elegantly drawn out by the interviewer. A further highlight on the second day was an exceptional lecture on "The Inattentive Brain" by Prof Masud Husain, from the Institute of Cognitive Neuroscience in London.

Professor Griffiths led the final section of the course, presenting a number of case based discussions relating to emotional disturbance and problems with social cognition, including frontotemporal dementia and Huntington's disease. This was then rounded off with a well-crafted lecture addressing the complexity of social cognitive problems given by Dr Roland Zahn, from the University of Manchester.

Courses such as this one are extremely relevant both to established neurologists and also to trainees in neurology who wish to further their knowledge in this area, so often neglected by many other general neurological postgraduate updates. The course is well put-together, efficiently administered, and even offers a first-class course dinner at the "Baltic" arts centre adjacent to the River Tyne. It is a fine way to ensure continuing professional development. The organisers are to be congratulated on an extremely informative teaching course which appears to be going from strength to strength. Let us hope they reproduce this offering for many years to come. ◆

When Stable PD Patients Begin to Fluctuate

Conference details: Report from a satellite symposium at the 2011 Annual Meeting of the Association of British Neurologists (ABN), Newcastle UK, 6th October 2011. Satellite symposium and report supported by an educational grant from Teva Pharmaceuticals Ltd and Lundbeck Ltd.

Chair: Professor David Burn IAH Director & Professor of Movement Disorder Neurology, Newcastle University, Newcastle upon Tyne, UK.

Speakers: Dr Nin Bajaj, University of Nottingham Medical School, Queen's Medical Centre, Nottingham, UK.
Dr Paul Worth, Norfolk and Norwich University Hospital NHS Trust, Norwich, UK.
Dr Malcolm Steiger, The Walton Centre for Neurology and Neurosurgery, Fazakerley, Liverpool, UK.

It is well known that patients with early idiopathic Parkinson's disease (PD) who are initiated on dopaminergic (levodopa or a dopamine agonist) therapy initially respond very well. Indeed, the first few years of pharmacotherapy are often referred to as the 'honeymoon period' because most patients enjoy sustained symptomatic relief with few side-effects. However, it is equally well established that within a few years of starting dopaminergic therapy, the majority of patients will begin to notice a decline in the duration of benefit of each dose. This phenomenon is commonly referred to as 'wearing-off'.

Opening the meeting, Professor David Burn emphasised that the early and effective management of wearing-off is vital for patients with PD, as numerous studies have shown that the emergence of wearing-off has significant impact on patients' daily activities and overall quality of life[1] and it also significantly increases the costs of care.[2] In recent years, there has been a move to recognising and treating wearing-off earlier in the course of PD,[3] and the four presentations in this symposium were designed to review and discuss current thinking in how to best manage this important motor fluctuation.

From stable response to fluctuation response

In order to optimise treatments it is important to understand the mechanisms that underlie the change from a patients' stable response to levodopa to a fluctuating response, said Professor David Burn. The ELLDOPA study provided very important insights into this. It was the first study to clearly demonstrate higher dosages of levodopa are a key factor in both the development of dyskinesia and motor fluctuations. By the end of the 9-month study, almost a third (29.7%) of patients receiving the highest daily dose of levodopa (600 mg/day) experienced 'wearing-off' compared with <20% in the lower dose (150 and 300 mg/day) groups.[4]

Professor Burn reminded the audience that the response to levodopa is comprised of two components. The short-duration response (SDR), which provides an improvement in motor function that lasts a few hours after a levodopa dose, and the long-duration response (LDR), which is a sustained effect derived from chronic levodopa treatment that lasts for several days after stopping levodopa therapy.[5] For many years, most medical students have been taught that the development of wearing-off is due to the progressive loss of nigrostriatal neurons, resulting in a lack of dopamine synthesis and storage and the consequent inability of the brain to 'buffer' short-term changes in the supply of dopamine made from levodopa. Although most would agree that this presynaptic 'storage hypothesis' (reflecting changes in the SDR) does contribute to the development of wearing-off, elegant studies have since shown that changes in the LDR during the course of PD also have a critical role.[6] These studies have shown that while the magnitude of the SDR progressively increases with disease duration, the LDR declines; and that the rate of LDR decline is dependent on disease severity and duration of therapy. Importantly, it has been shown that the decline in the LDR determines the magnitude of the SDR.[6] These observations have significant clinical implications. They suggest that the presence of the LDR in early disease 'masks' changes in the SDR and so patients appear to be stable even though changes to their motor response are already occurring (i.e. the development of wearing-off has already begun).[3]

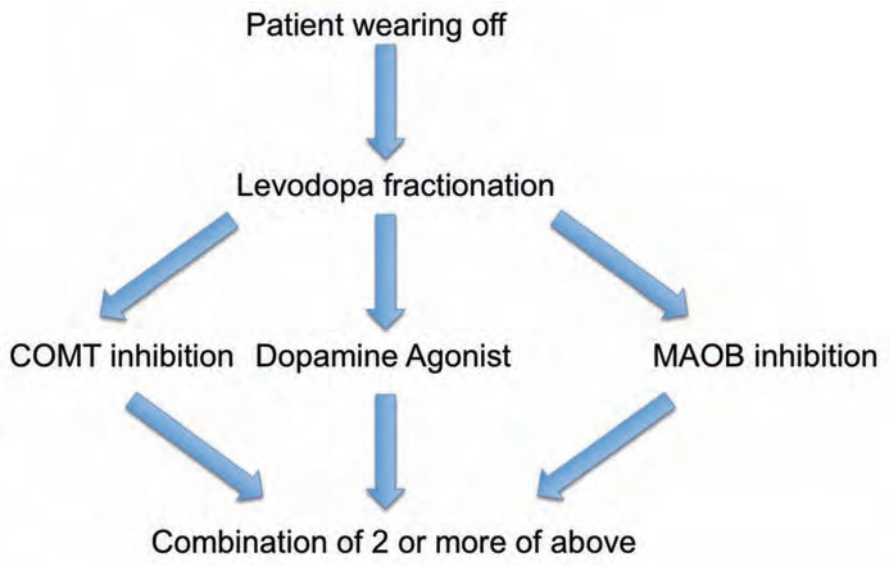
It is also clear that the simple storage hypothesis cannot account for these observations and other mechanisms must also play a part. Indeed, post-synaptic changes are now being investigated and changes in signal transduction, cellular transport, transcription and translation seem to play an important role.[7]

Wearing-off is more than a motor fluctuation

Professor Burn closed his presentation by emphasising that the signs and symptoms of wearing-off can be non-motor as well as motor. Whilst many physicians recognise wearing-off when it is associated with the return of obvious motor symptoms, it is less easy to identify when manifested through non-motor symptoms, such as pain, mood disturbances, fatigue, akathisia, sweating and increased salivation.[8] Indeed, the emergence of non-motor wearing-off has been suggested to precede motor symptoms.[3] Since non-motor symptoms can be very subtle in the beginning, they may often go unrecognised by physicians and, therefore, remain untreated before becoming prominent and disabling. One way to help recognise the full range of symptoms is to use wearing-off questionnaires such as those available on the EPDA website (http://epda.eu.com/medinfo/wearing-off/#).[9,10]

Can wearing-off be prevented?

Dr Paul Worth continued the theme by looking at how best the currently available treatments can be used to manage wearing-off and whether the emergence of wearing-off can be



prevented or at least delayed. As noted earlier, the ELLDOPA study clearly showed that higher doses of levodopa are associated with an increased incidence of wearing-off and dyskinesia.[4] Since this study, most physicians have stopped increasing levodopa doses above a certain level, and now consider introducing other adjunct therapies instead.

Importantly, the ELLDOPA study also showed that some patients can develop the signs of wearing-off within the first year of levodopa therapy – much earlier than originally recognised. The early development of these so-called motor complications was the major impetus for the development of dopamine agonists, and a number of studies have shown a lower incidence of dyskinesia and wearing-off in patients with early PD who were initiated on a dopamine agonist versus those who were initiated to levodopa treatment.[11-13] These observations led to the popular suggestion that providing a continuous stimulation of dopamine receptors through dopamine agonists (vs. the pulsatile stimulation provided by levodopa) may be helpful in avoiding motor complications.[14] This may be the case, but most patients will eventually require levodopa and will therefore develop complications. Moreover, because the risk of developing motor complications is closely associated with disease severity, those patients who have delayed taking levodopa until they are much more severe may develop wearing-off quite rapidly once they start. Attempts to provide continuous stimulation with levodopa have not so far been successful and the recent STRIDE-PD study found that while Stalevo (levodopa/ carbidopa/ entacapone) did reduce the emergence of wearing-off, this was at the expense of a shorter time to the appearance of dyskinesia.[15]

How should wearing-off be treated?

Thus at present, most approaches to the management of wearing-off are currently reactive rather than preventative – many physicians are, however, trying to manage wearing-off in its earliest stages in the hope that it will improve the long-term management of these symptoms. Therapeutic options include modifications to the levodopa regimen and the introduction of adjunct therapies. However, there is little head-to-head evidence comparing all the modalities and NICE guidelines state that "it is not possible to recommend a universal first-choice drug therapy" either for early PD or for adjuvant drug therapy for later PD.[16]

Levodopa-modification strategies, such as increasing the total dose or frequency of levodopa or introducing a night-time dose of controlled release levodopa have classically been the first-line approach taken in the management of wearing-off. The main benefits of these strategies are their low cost and patient familiarity with the drug. Indeed, optimising the levodopa regimen is a good first step in the management of wearing-off. However, since it is now recommended to keep the levodopa dose as low as possible,[16] and patients often find the introduction of extra doses throughout the day difficult to adhere to, other approaches are also often needed.

The use of adjunctive therapies to manage wearing-off is now common practice. There are three main classes of drug to consider; the dopamine agonists, COMT inhibitors and MAO-B inhibitors, and all of these options have good evidence of efficacy in reducing OFF time.[17] The dopamine agonists (pramipexole, ropinirole, rotigotine etc) have also been shown to allow a reduction in the levodopa dose, and recent studies have indicated that there may be some benefits of the newer prolonged-release formulations than with the old immediate-release formulations.[18] However, the benefits of dopamine agonists need to be weighed against their side-effects and costs (higher with prolonged release formulations). In today's clinical practice, most patients who can tolerate a dopamine agonist would already be receiving one before levodopa. Those patients who do not receive early dopamine agonist therapy usually cannot tolerate dopamine agonists due to cognitive and/or neuropsychiatric issues – and the same considerations apply in later disease. Moreover, there is ever increasing awareness of impulse control disorders including excessive gambling and hypersexuality, which may occur even at low dosage but are more prevalent in higher dose ranges.[19]

COMT inhibition with entacapone is a popular option for patients with wearing-off and studies with levodopa plus adjunct entacapone have demonstrated a reduction in OFF time of approximately one hour compared with levodopa plus placebo.[20] Similarly, in a large randomised study for wearing-off (LARGO), adjunct treatment with the MAO-B inhibitor rasagiline was shown to have similar efficacy to entacapone in reducing OFF time.[21] The choice of which adjunct therapies to use necessarily depends on the needs of the individual, however Dr Worth noted that whereas entacapone had a slightly higher adverse event rate, rasagiline had an adverse event rate similar to placebo in this trial,[21] and was generally well tolerated in the elderly.[22] Other options include the COMT inhibitor tolcapone, which due to its potential for hepatotoxicity must only be used when treatment with entacapone fails, and the MAO-B inhibitor selegiline, which (compared to other treatments) has only limited RCT evidence of efficacy as adjunct therapy.

Closing his presentation, Dr Worth noted that many patients are on more than one adjunct therapy and that using combinations of therapies may allow better tailoring of the medication regimen to the needs of the individual.

Current approaches to the treatment of wearing-off are reactive rather than preventative, but by the time a patient's symptoms are fully apparent many maladaptive changes will have already occurred in the basal ganglia. It is therefore of interest to manage wearing-off in its earliest stages in the hope of improving the long-term management of these debilitating symptoms.

What is the future for wearing-off?

Closing the symposium, Dr Steiger looked at products that are in development. Many researchers continue to look at how to optimise levodopa delivery. The best-known of these products is the levodopa intestinal gel – Duodopa. Dr Steiger noted that preliminary evidence from ongoing open-label studies indicate that Duodopa can be very effective, offering 4.6 hours of increased ON time in patients with very severe fluctuations.[23] However, it is an invasive therapy and technical problems are reported to be commonplace.[24] Therefore duodenal levodopa infusion seems to be an effective last-line therapy for motor complications in Parkinson's disease and should be considered as a good alternative to deep brain stimulation (DBS). Like DBS, there are strict criteria that a patient should meet to be suitable for Duodopa. Suitable patients are those with severe "ON-OFF" motor fluctuations who have something to gain from improved motor control (i.e not severely demented, or suffering from other severe chronic disease). Other levodopa therapies in development include a new levodopa 'accordion pill' which has both immediate release and extended release components and which preliminary reports at the Toronto MDS symposium indicate offers significant benefits over classic immediate release levodopa.[25] Finally, Dr Steiger highlighted the numerous non-dopaminergic therapies, which are also in development and include adenosine antagonists,[26] neurotrophic factors and gene therapy.[27] ◆

Case studies

Dr Nin Bajaj used case studies to interact with the audience and gain insights into current practice in general neurology clinics. The case studies were designed to discuss the various ways treatment can be tailored to meet the needs of patients with wearing-off.

Issues discussed included the utility of fractionating levodopa – most of the audience agreed that increasing the dosing frequency from three times to four times a day can often be very helpful and physicians should always try to optimise the levodopa regimen as a first step in the management of wearing-off. While many agreed that Sinemet CR has its place in helping control nocturnal symptoms, Dr Bajaj noted that it can lead to increased end-of-day dyskinesia if used throughout the day. Balancing the need to treat motor fluctuations with the potential to induce dyskinesia was another topic of discussion; many patients say that they prefer to be dyskinetic than suffer OFF periods. Dr Bajaj discussed that the introduction of entacapone (or Stalevo) can induce quite severe dyskinesia in some patients and that a levodopa dose reduction is often needed.

Another key topic was the need to help patients first thing in the morning – before they take their first dose of antiparkinsonian medication. The audience discussed that using dispersible levodopa is sometimes useful for a faster ON effect and that long acting dopamine agonists used last thing at night often help manage nocturnal OFF problems. The audience discussed that the new once daily dopamine agonist formulations should help with controlling over night symptoms. Similarly, it has recently been reported that adjunct rasagiline (also given once daily) also improves motor symptoms in the practically defined OFF state.[28]

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The BIRT Conference 2011

Inspiring Learning and Innovation in Brain Injury Rehabilitation

Conference details: 21st-22nd September 2011; Marriott Hotel, Bristol, UK. ***Reviewed by:*** Professor Mike Oddy.

The Brain Injury Rehabilitation Trust (BIRT) Conference 2011 invited national and international delegates to enjoy this two day event. Delegates were presented with engaging discussions on the latest developments in brain injury rehabilitation. The conference also marked BIRT's 20th anniversary year, which included a photographic exhibition 'One Piece at a Time' compiled by BIRT service users for delegates to view. The conference was sponsored by Irwin Mitchell Solicitors and the gala dinner, with after dinner speaker Hardeep Singh Kohli, by Barclays Corporate.

Emotional and social aspects of recovery were the common theme for the five plenary sessions on day one. Professor Rodger Wood, Clinical Neuropsychologist from Swansea University and BIRT's first clinical director, gave a talk that highlighted the neurobehavioural correlates between injuries to the frontal lobe and the alterations of personality that arise as a result. He reviewed recent research suggesting that difficulties in recognising and expressing emotions (alexithymia) are highly prevalent in individuals with acquired brain injury, and discussed the impact that these characteristics have in social functioning.

Professor Jeffery Kreutzer, the Director of Neuropsychology and Rehabilitation Psychology at Virginia Commonwealth University (USA), focused on the clinical and family issues associated with personality changes resulting from acquired brain injury. He argued that one of the key challenges in rehabilitation is dealing with the ambiguous loss experienced by family members of having a loved one physically present but psychologically absent due to the personality changes resulting from brain injury. Close family members of people with brain injury often report feeling they are living with a stranger. This talk gave practical suggestions for addressing this important part of the rehabilitation process. Simple steps to help recognise and learn to deal with this change involve focusing on what is liked about the 'new' individual, encouraging the person to speak in ways that are appreciated, praising and reinforcing social behaviour, and communicating and getting to know the 'new' person better,.

Charles Bombardier, Professor and Head of the Division of Clinical and Neuropsychology at the University of Washington (USA), presented a thorough review of the prevalence, risk factors, diagnostic issues and treatment efficacy of depression following TBI. His research shows that about half of the people who have suffered a TBI will have major depressive disorder. Within the TBI population, depression is associated with poor outcomes. Age, history of psychiatric disorders and excessive alcohol intake are risk factors for depression after brain injury. Screening for depression after TBI is often complicated by trans-diagnostic symptoms, but psychometric tools are available that can effectively guide decisions. There has also been progress in the treatment front, with research suggesting that pharmacotherapy, telephone counselling, Cognitive Behavioural Therapy (CBT) and a combination of approaches can all have positive effects in treating depression in TBI.

Huw Williams, Associate Professor of Clinical Neuropsychology at the University of Exeter, reported a number of case studies illustrating adaptations of CBT to neurorehabilitation of social and emotional dimensions, and the potential of this approach for helping individuals with TBI, and their families.

In the closing session, Professor George Prigatano gave an inspirational and comprehensive discussion of past developments and present day challenges and opportunities in neuropsychological rehabilitation. He argued that whilst there had been few 'advances' in brain injury rehabilitation over the last 20 years there had been important 'refinements'. The refinements he emphasised were closer working with families, more emphasis on psychotherapy and more focus on systematic efforts at cognitive retraining and the correlates of this with changes in chemical and electrical activity in the brain. However, he went on to delineate 10 challenges the field of brain injury rehabilitation continues to face into the current decade. One of these was the absence of a good developmental perspective on neuropsychological rehabilitation which can help us to meet the needs of brain injured children.

Day two offered a number of symposiums and workshops covering a wide range of themes. Following the issues introduced on day one, Prof Kreutzer discussed the importance of the therapeutic alliance in working with brain injury patients and their families, and offered practical approaches for evaluating and developing more effective alliances. Prof Bombardier focused on the issues associated with substance abuse in brain injury. He discussed screening procedures and treatment approaches, including approaches that can be provided to those who refuse treatment.

The influence of emotional and motivational factors on brain injury rehabilitation was, again,

a key topic on the second day. Prof Nick Alderman and Dr Caroline Knight, of the National Brain Injury Centre, St Andrews Hospital and Dr Andrew James, Consultant Neuropsychologist at BIRT Daniel Yorath House, Leeds discussed the assessment and rehabilitation of aggression and sexual disinhibition following brain injury. Dr Camilla Herbert and Dr Siobhan Palmer, of BIRT, described a model considering the interplay of emotional, cognitive factors, and curiosity in working with those who lack awareness of their deficits.

A number of workshops and symposiums addressed the usefulness of new technologies in rehabilitation. Prof Michael Oddy, the Director of Clinical Services at BIRT, Dr Nigel Harris of the Bath Institute of Medical Engineering and Dr Anna Kuppuswamy of the University of Bath, gave an overview of smart technologies available for promoting independence, and described a new easy to use system, based on the International Classification of Functioning, Disability and Health, for assessing and identifying the most suitable technology for specific functional impairments. Dr Brian O'Neill from BIRT Graham Anderson House Glasgow and Dr Alex Gillespie from the London School of Economics, described the rehabilitation principles underlying the use of a new prompting system for guiding individuals with planning and monitoring difficulties through daily activities such as washing clothes. Jon Graham overviewed the latest technologies available for physical rehabilitation.

Jon Graham challenged the notion that rehabilitation is ineffective if delivered long after a brain injury and Liz Parish presented evidence of successful response to rehabilitation more than 10 years post injury. Professor Tom McMillan presented evidence to dispel the myth that disabilities following brain injury stabilise after two years or so and that older adults recover less well than younger adults. The prevalence of traumatic brain injury amongst the homeless and amongst prisoners and the effects of neurological impairment on musical processing were also discussed. ◆

Many people attend conferences simply to satisfy their continued professional development requirements, however the BIRT conference is different. It offers so much more; it's a great networking opportunity, meeting with others in the brain injury neuro-rehabilitation world. You learn a great deal more from respected professionals in a well organised environment such as this

Lee Hart – Clarke Willmott, Bristol.

Dietary Treatments for Epilepsy

Dietary treatments for epilepsy date back ninety years, following reports that a high fat, low carbohydrate, ketone-generating diet brought about similar benefits in seizure control as did the fasting state.[1] This classical ketogenic diet (KD), although still used widely today, has been modified over the years, one version incorporating the higher-ketone yielding medium chain triglycerides (MCT). Other more flexible KD variants are the modified Atkins diet (MAD) and low glycaemic index treatment (LGIT). Efficacy of the KD has been demonstrated in many retrospective and prospective observational studies and a randomised controlled trial[2] which found responder rates similar to those of the newer antiepileptic medications. The MAD has also been shown to be successful in a rapidly growing evidence base. Reported benefits of KD therapy extend beyond seizure control to medication reduction and improvements in behaviour, cognition and quality of life.

KD therapies, although differing in macronutrient proportions and liberality of approach, all employ the similar principle of carbohydrate restriction with fat the main source of dietary energy. The restriction of glucose supply will lead to the ketone bodies acetoacetate and β-hydroxybutyrate becoming the primary brain energy source; high levels in both blood and urine are usually detected, and encouraged, while on a KD therapy. The mechanistic role of ketone bodies in seizure modulation is subject to extensive research; a number of mechanisms are likely to work together related to the changes in metabolism associated with a ketotic state.[3]

Although primarily used to treat childhood epilepsy, KD therapy is gaining popularity for adolescents and adults with refractory seizures. Generally used after failure of two appropriate anticonvulsant medications, it may be first line treatment in syndromes such as GLUT-1 or pyruvate dehydrogenase deficiencies. It should not be used in children who have enzyme deficiencies of organic acid metabolism or disorders requiring high carbohydrate treatment.[4] Emerging evidence suggests KD therapy may also be of benefit in conditions beyond epilepsy, such as neurogenerative disorders and cancer.[5] Full nutritional supplementation is required with any KD therapy, monitoring is essential, and the risk of side effects should be considered before initiation; most commonly constipation, short-term acidosis, raised serum lipids, growth faltering and kidney stones.[6] Management by an experienced multi-disciplinary team is recommended; unfortunately UK availability is both limited and variable. ◆

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Meningitis Research Foundation Conference 2011:

The prevention of meningitis and septicaemia in adults and children.

Conference details: 8-9th November 2011; Royal Society of Medicine, London, UK. ***Reviewed by:*** Claire Wright, Medical Information Officer, MRF.

Over 250 clinicians, researchers, public health professionals and industry leaders gathered to discuss the latest issues in the burden, detection, treatment and prevention of meningitis and septicaemia at Meningitis Research Foundation's (MRF's) 8th biannual conference.

During the conference the burden of disease was highlighted in a series of lectures. Dr Mary Ramsay of the Health Protection Agency (HPA) presented the epidemiology of meningococcal disease in the UK and Europe. Dr Peta Sharples of the University of Bristol discussed the neurological impact of meningitis and explained why some children, who were considered to have made a full recovery at the time of discharge, may go on to experience problems when they reach school age. This concept was further touched upon by Professor Russell Viner who presented results from the MOSAIC study and Dr Liam Dorris who discussed the psychosocial impacts of meningococcal disease.

In a Novartis led satellite session, Mr Fergal Monsell, a consultant paediatric orthopaedic surgeon, emphasised how the skeletal consequences of septicaemia often go unrecognised, and Dr Stuart Clarke examined the public health impact of meningococcal disease. Further discussion on the burden of disease included a moving account from MRF member Scottie Kern, whose son tragically died from pneumococcal meningitis in 2009. A presentation on MRF's 'Counting the Cost of Meningitis' campaign examined the types of disabilities that survivors of severe cases of disease can be left with and the extensive lifelong costs associated with this.

From the burden of disease, the sessions went on to explore cost effectiveness analysis and how decisions are made about the introduction of new meningococcal vaccines to the childhood schedule. Dr Hannah Christensen presented her model of the potential impact of MenB vaccines in England. Discussion on prevention included a talk from Professor Andrew Pollard who suggested the implementation of a teenage booster may soon be required to maintain population protection against meningococcal group C disease. Moving the discussion specifically to MenB prevention, Dr Peter Dull from Novartis spoke about prospects for use of the 4CMenB vaccine and Dr Katherine Jansen from Pfizer discussed the bivalent factor H binding protein vaccine which is in the late stages of development.

Both days included interactive sessions where audience members questioned a panel of experts in the fields of vaccine development, epidemiology, cost-benefit analysis, clinical management, public health, vaccine production and research. These popular sessions covered topics such as purchasing decisions regarding meningococcal vaccines and the issues surrounding the introduction of a MenB vaccine into the UK immunisation schedule.

Q&A with panel of experts.


Dr Nelly Ninis of St Mary's Hospital.

Some of the latest advances from MRF funded research and their implications were presented throughout the two days. Professor Robert Heyderman discussed findings from studies which aim to address the high mortality in adult meningitis in Africa. Professor Michael Levin discussed findings from the Genome Wide study which has identified genetic variation in the Factor H gene and Factor H related genes which control for meningococcal disease susceptibility. Professor Paul Heath presented findings from his study on the burden of bacterial meningitis in infants and discussed how findings from the study may eventually be used to improve current practice with the potential for better outcomes.

The prevention of pneumococcal disease was featured in a talk from Pauline Kaye from the HPA, who discussed the impact of the pneumococcal conjugate vaccines (PCV) and touched upon issues such as serotype replacement and herd immunity. This was followed with a talk from Dr William Hausdorff who discussed the need for and current progress in the development of protein based pneumococcal vaccines. A satellite session from Pfizer vaccines, who manufacture PCV, concluded this group of lectures.

Tackling meningitis in Africa was covered by a series of talks related to the Meningitis Vaccine Project (MVP). Dr Marc Laforce, (Director of MVP) discussed the successful introduction of meningococcal serogroup A vaccine (MenAfriVac) in Burkino Faso and how this success bodes well for the further roll out of the vaccine across other countries in the African meningitis belt. Dr Caroline Trotter then discussed preliminary carriage study results from the MenAfriCar project (a global research effort to study how meningococci are spread in Africa and to document the impact of the meningitis vaccine MenAfriVac on reducing transmission). Professor Richard Adegbola of the Bill and Melinda Gates Foundation concluded the session with a discussion on the evolution and vision of the MVP.

Back in the UK setting, a series of talks on the current issues in recognition and treatment of disease from Dr Nelly Ninis of St Mary's Hospital, Dr Mark Peters of the Institute of Child Health and Professor Mervyn Singer of University College London emphasised the need for getting resuscitation and intensive care management right.

Poster presentations on display throughout the conference covered a range of topics including: host-pathogen interactions; epidemiology and surveillance; diagnosis, treatment and sequelae; public health management; and vaccine discovery and vaccinology and poster presenters were on hand to answer any questions during breaks. The prize for best poster was awarded to Paul Kristiansen's work on the impact of MenAfriVac on carriage of serogroup A Neisseria meningitides.

Comments from those who regularly attend included "the best to date" and "remarkable how much genuinely new and important work gets presented". Whilst one new comer commented: "well organised, informative and enjoyable. I would certainly say that the MRF is punching above its weight!" ◆

Modular Upright Research Microscopes for Bioscience and Medical Research

The Eclipse Ni series offers multi-mode system expandability to meet the imaging needs of bioscience and medical research on one platform. The new Ni range also provides superior optical performance with new CFI Plan Apochromat Lambda series objectives, and the flexibility of assisted observation by motorisation. The range comprises the fully motorised Eclipse Ni-E flagship model with focusing nosepiece or focusing stage options, and the manual Eclipse Ni-U with motorisation upgrade capability.

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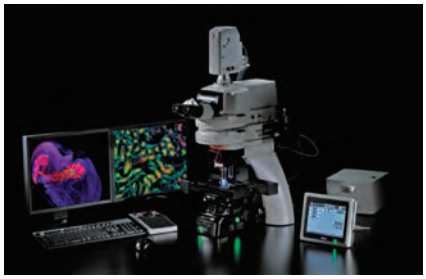

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Winner of Global Design Competition for Multiple Sclerosis Community

Merck Serono has announced that Brian Light of Toronto, Canada is the overall winner of the "Real MS: Your Innovation" campaign, a global design competition that challenged the multiple sclerosis (MS) community to submit unique and innovative ideas to help people overcome the daily challenges of life with MS.

Brian's winning idea, "The Sports Walker," is a six legged, eight wheeled walker and harness system that gives someone with poor balance or weakness in their legs the support to stand and manoeuvre, while keeping their hands free to play sports. The Sports Walker was selected through online voting by the international MS community on the campaign's website.

A volleyball fanatic for more than 30 years, Light's ability to play became difficult as his MS symptoms began to limit his ability to walk and maintain balance. "It was clear I couldn't play volleyball the same way I was accustomed to and I remember a friend coming up to me on the court and suggesting I would probably have to stop playing altogether,'" said Brian. "I wasn't ready to let that happen, so I created the Sports Walker."

Brian will travel to the design studios of IDEO, a global design and innovation firm, where he will work directly with IDEO designers to evolve and refine his idea, which will be shared with the global MS community in 2012.

Data About Early Use and Long-term Benefit of Tysabri Presented at ECTRIMS/ACTRIMS

There were 28 company-supported Tysabri® (natalizumab) presentations at the 5th Joint Triennial Congress of the European and Americas Committees for Treatment and Research in Multiple Sclerosis (ECTRIMS and ACTRIMS).

Key data indicated patients on Tysabri experienced reduced annualised relapse rates (ARR), particularly in those treated with Tysabri early in the course of their disease. Data also indicated a long-term benefit for patients who had achieved freedom from disease activity early in their treatment course. Data from a separate study showed Tysabri-treated patients experienced improved incontinence-related quality of life (QOL). Additional data sets were presented further supporting Biogen Idec's and Elan's efforts to stratify the risk of progressive multifocal leukoencephalopathy (PML) in Tysabri-treated patients.

"Further study of anti-JCV antibody status continues to support its utility for risk stratification, enabling a personalised discussion of benefit/risk for each individual patient," said Ted Yednock, PhD, Executive Vice President, Head of Global Research at Elan. "Our five years in-market experience, along with information resulting from our ongoing study of the efficacy and safety of Tysabri in MS, enables physicians and patients to make decisions on therapeutic approaches for treating this debilitating disease."

For further information about Tysabri please visit www.tysabri.com, www.biogenidec.com

eBrain Launch

eBrain was successfully launched at the Royal College of Surgeons in London at the end of 2011. eBrain is a world first, and represents the largest, most comprehensive web-based training multimedia facility in clinical neurosciences to support both training and Continuous Professional Development. All UK professional societies who are members of the Joint Neurosciences Council www.jointneurosciences.org, are providing free access to this resource for their individual members, as are the European Neurological Society and European Federation of Neurological Societies.

Ebrain currently consists of over 550 eLearning sessions that cover the whole of the clinical neurosciences, including neurorehabilitation. Each session is designed to take 20 minutes to

Simon Thomson, Simon Shorvon and Hannah Cock, Clinical leads eBrain.

complete. Users can self-select which modules to do, or make use of learning pathways being designed to reflect the needs of specific learning groups. Once a session has been completed a certificate can be printed.

eBrain has been developed by over 400 authors, 32 module editors and 4 clinical leads mostly from the UK but with some support from Europe. All these clinicians have given their time free of charge.

eBrain can be found at www.ebrainjnc.com. Members of JNC organisations, ENS or EFNS should have received a login and password via their society, or should contact their member society in the first instance. If you are having problems logging in then use the technical checker on the website first. In particular please make sure that popups are not blocked!

Zebinix-UK2231 Date of preparation: January 2012

PRESCRIBING INFORMATION

Zebinix® (eslicarbazepine acetate)

Please refer to the SPC before prescribing. ***Presentation:*** Tablets containing 800 mg eslicarbazepine acetate. ***Indication:*** Adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation. ***Dose and administration:*** May be taken with or without food. Starting dose is 400 mg once daily, increased to 800 mg once daily after one or two weeks. Dose may be increased to 1200 mg once daily. Withdraw gradually to minimise the potential of increased seizure frequency. ***Elderly patients:*** Caution. ***Children and adolescents <18 years of age:*** Not recommended. ***Patients with renal impairment:*** Adjust dose according to creatinine clearance (CL_{Cr}). Not recommended in severe impairment. ***Patients with hepatic impairment:*** No dose adjustment in mild to moderate impairment. Not recommended in severe impairment. ***Contraindications:*** Hypersensitivity to the active substance, other carboxamide derivatives (e.g. carbamazepine, oxcarbazepine) or any excipients. Known second or third degree AV block. ***Pregnancy:*** No data on the use of Zebinix in pregnant women. Carefully re-evaluate treatment if women become pregnant or plan to become pregnant, and use minimum effective doses. Interacts with oral contraceptives. Use an alternative method of contraception during treatment and up to the end of the current menstrual cycle after treatment has been stopped. ***Lactation:*** Excretion in human breast milk is unknown. Breastfeeding should be discontinued during treatment. ***Warnings and precautions:*** May cause some CNS reactions such as dizziness and somnolence. Do not use with oxcarbazepine. Rash has been reported. Discontinue if signs or symptoms of hypersensitivity develop. Screen for allele HLA-B*1502 in individuals of Han Chinese and Thai origin as this has been shown to be strongly associated with the risk of developing Stevens-Johnson syndrome (SJS) when treated with carbamazepine. Examine serum sodium levels in patients with pre-existing renal disease or who are treated with medicinal products which may lead to hyponatraemia or if clinical signs of hyponatraemia occur. Discontinue if clinically relevant hyponatraemia develops. Do not use in primary generalised seizures. Prolongations in PR interval have been observed. Caution in patients with medical conditions or when taking concomitant medicinal products associated with PR prolongation. Monitor for signs of suicidal ideation and behaviours. ***Drug interactions:*** Has an inducing effect on the metabolism of medicinal products mainly eliminated by CYP3A4 or UDP-glucuronyl transferases, therefore the dose of these products may need to be increased when used concomitantly with Zebinix. May take 2 to 3 weeks to reach the new level of enzyme activity when initiating, discontinuing or changing dose, therefore take time delay into account when using with other medicines that require dose adjustment. Interactions can arise when co-administering high doses with medicinal products that are mainly metabolised by CYP2C19. Carbamazepine: Zebinix dose may need to be increased if used concomitantly with carbamazepine. Concomitant treatment with carbamazepine increased the risk of the diplopia, abnormal coordination and dizziness. An increase in other adverse reactions cannot be excluded. Phenytoin: An increase of Zebinix dose and a decrease of phenytoin dose may be required. Lamotrigine and topiramate: No dose adjustments are required. Valproate and levetiracetam: Concomitant administration appeared not to affect the exposure to eslicarbazepine but has not been verified by conventional interaction studies. Oral contraceptives: Interacts with the oral contraceptive. Simvastatin: An increase of the simvastatin dose may be required when used concomitantly with Zebinix. Warfarin: Can decrease exposure to S-warfarin. No effects on R-warfarin or coagulation. Monitoring of INR should be performed in the first weeks after initiation or ending concomitant treatment. Digoxin: no effect. MAOIs: an interaction between eslicarbazepine acetate and MAOIs is theoretically possible. ***Side effects:*** Adverse reactions were usually mild to moderate in intensity and occurred predominantly during the first weeks of treatment with Zebinix. Refer to SPC for all side effects. Very common effects (≥1/10): dizziness, somnolence. Common effects (≥1/100, <1/10): Headache, abnormal coordination, disturbance in attention, tremor, diplopia, vision blurred, vertigo, nausea, vomiting, diarrhoea, rash, fatigue, gait disturbance. Serious side effects: hypersensitivity, hyponatraemia, dehydration, grand mal convulsion, ocular hyperaemia, palpitations, bradycardia, hypertension, hypotension, chest pain, epistaxis, liver disorder, drug toxicity, poisoning. Some rare adverse reactions such as bone marrow depression, anaphylactic reactions, severe cutaneous reactions (e.g. SJS), systemic lupus erythematosus or serious cardiac arrhythmias did not occur during clinical studies. However, they have been reported with oxcarbazepine and their occurrence during treatment with Zebinix cannot be excluded. ***Legal category:*** POM. ***Basic UK NHS cost:*** Zebinix 800 mg: pack of 30 £154.20. ***Irish price to wholesaler:*** Zebinix 800 mg: pack of 30 €159.10. ***Marketing authorisation numbers:*** EU/1/09/514/012-020. ***Marketing authorisation holder:*** Bial-Portela & C^{a}., S.A. À Av. da Siderurgia Nacional 4745-457 S. Mamede do Coronado – Portugal. ***Further information from:*** Eisai Limited, European Knowledge Centre, Mosquito Way, Hatfield, Herts, AL10 9SN, UK. ***Date of preparation:*** November 2011.

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

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