

ACNR

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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

In this issue

Gérard Said – Vasculitic Neuropathy

Famous Neurologists

J van Gijn – Joseph Babinski 1857-1932

Hugh Rickards – How Helpful is it to Global Outcome to Treat Abnormal Movements in Tourette's Syndrome?

Personal Perspectives

Parkinson's Disease: personal experience

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

in patients treated concomitantly with antidepressants/SNRIs and rasagiline. Avoid concomitant use with fluoxetine or fluvoxamine. Leave at least five weeks between discontinuation of fluoxetine and initiation of treatment with rasagiline. Leave at least 14 days between discontinuation of rasagiline and initiation of treatment with fluoxetine or fluvoxamine. Administer potent CYP1A2 inhibitors with caution. Co-administration with dextromethorphan or sympathomimetics not recommended. Avoid use in patients with moderate hepatic impairment. Use caution in patients with mild hepatic impairment. Use with caution in pregnancy or lactation. There is an increased risk of skin cancer in Parkinson's disease, not associated with any particular drug. Suspicious skin lesions require specialist evaluation. Cases of elevated blood pressure have been reported in the post-marketing period, including one report of hypertensive crisis associated with the ingestion of unknown amounts of tyramine. **Undesirable effects in clinical trials:** **Monotherapy:** >1%: headache, influenza, skin carcinoma, leucopenia, allergy, depression, hallucinations, conjunctivitis, vertigo, angina pectoris, rhinitis, flatulence, dermatitis, musculoskeletal pain, neck pain, arthritis, urinary urgency, fever, malaise. <1%: decreased appetite, cerebrovascular accident, myocardial infarction, vesiculobullous rash. **Adjunct therapy:** >1%: dyskinesia, decreased appetite, hallucinations, abnormal dreams, dystonia, carpal tunnel syndrome, balance disorder, orthostatic hypotension, abdominal pain, constipation, nausea and vomiting, dry mouth, rash, arthralgia, neck pain, decreased weight, fall. <1%: skin melanoma, confusion, cerebrovascular accident, angina pectoris. **Please refer to the SmPC for the rates of adverse events.** **Basic NHS Price:** Azilect® (tablets) 1mg x 28 £70.72 **Legal category:**

POM Marketing Authorisation Number: 1mg tablets (28 pack size) EU/1/04/304/003 **Marketing Authorisation Holder:** Teva Pharma GmbH, Kandelstr 10, D-79199 Kirchzarten Germany **Date last revised:** December 2009. **Further information available from:** Lundbeck Limited, Lundbeck House, Caldecotte Lake Business Park, Caldecotte, Milton Keynes, MK7 8LG

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

References:

1. Olanow CW et al. N Engl J Med 2009;361:1268-78.
2. Parkinson Study Group. Arch Neurol 2002;59:1937-1943.
3. Horstink M et al. Eur J Neurol 2006;13:1170-1185.



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Editorial board and contributors



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

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

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

ABN Case Report Winner

Congratulations to Dr Charles Marshall who has received £100 from ACNR, for winning the ABN case report competition. Dr Marshall studied Medicine at Oxford and UCL, and is currently a Neurology Registrar in London.



Queen's Birthday Honours

Congratulations to Professor Linda Luxon, who has been awarded a CBE in the Queen's Birthday Honours for services to medicine.

Professor Luxon is a Consultant in Neuro-otology at the National Hospital for Neurology and Neurosurgery and Professor of Audiovestibular Medicine at the UCL Ear Institute.

She is the Director of the UCL MSc programme in Audiovestibular Medicine and supervisor to a number of PhD, MD and post-doctoral students across a range of topics including genetic, autoimmune and noise induced hearing loss, paediatric vestibular disorders, novel vestibular rehabilitation, auditory electrophysiology, efferent auditory dysfunction and auditory processing.



New Awards for Innovation in Acquired Brain Injury

The United Kingdom Acquired Brain Injury Forum has announced an award scheme for innovation in the field of acquired brain injury. The aim of the awards is to acknowledge the good work which is being done in the sector and reward those who excel in their practice. Due to the variety of professions in the sector the awards have been divided into a number of categories:

- Innovation by a law firm in the field of ABI
- Innovation by a clinician in the field of ABI
- Innovation by a care provider in the field of ABI
- Innovation by a social care worker in the field of ABI
- Innovation by a voluntary sector provider or registered charity in the field of ABI



'We know that there are many people who go the extra mile or come up with a clever idea which goes unrecognised. We are not necessarily looking for big projects – these might be very small things which help to make life easier for those people suffering from an acquired brain injury,' said Professor Mike Barnes, Chair of UKABIF.

Nominations may be made by those involved in or benefiting from a project or piece of work. There is an application which must be completed with each nomination and the deadline for submission is 15th October 2010. The awards will be presented at the UKABIF Annual Conference which takes place on 11th November 2010 at The Russell Hotel in London.

Full details about the awards and the conference are available on the UKABIF website. www.ukabif.org.uk

MND Association Awards Grant

The Motor Neurone Disease (MND) Association has awarded Oxford BioMedica one of the leading gene therapy biopharmaceutical companies, a grant for up to £255,000 to continue work to develop a potential treatment for MND.

The MND Association is funding a collaborative three-year project between Oxford BioMedica and the Vesalius Research Centre at the University of Leuven, Belgium. Led by Dr Scott Ralph at Oxford Biomedica and Prof Peter Carmeliet at the University of Leuven, the project aims to use gene therapy to deliver a neurotrophic (nerve nourishing) factor called VEGF-B to affected motor neurones and muscles in a model of MND.

Dr Brian Dickie, director of research development at the MND Association, says: "One of the major hurdles to treating MND is ensuring that therapeutic agents are delivered to their site of action in the brain and spinal cord. "We are delighted to support a research initiative which combines innovative approaches to drug delivery with the development of a promising therapeutic compound."

For more information contact: louise.coxon@mindassociation.org





Image: Peter Fraser

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

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

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



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

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We are extremely fortunate to have Gérard Said write on a subject that he has contributed enormously to over the years, namely vasculitic neuropathy. In this short review he highlights some of the major features of different types of vasculitic neuropathy at the clinical and histopathological level and the whole account is steeped in the wisdom that comes from someone who has spent much time working and thinking about this subject.

What do you do with the patient with Tourettes who has moderately bad motor and vocal tics? Do you treat the patient or the family? Hugh Rickards takes us through this scenario in the second in our series on Neuropsychiatry, and highlights how the patient must always be at the centre of our decision making.

Some of you may have heard of cases of "Parkinson's Disease" (PD) with "scans without evidence for dopaminergic deficits" (SWEDDs). These cases came to prominence with the dopamine agonist trials in de novo PD patients some 10 or more years ago. Whilst some argued that these were atypical cases of PD, others were more sceptical and assumed that they were cases of misdiagnosis. Nin Bajaj, in his excellent synopsis, tells us how these cases should now be viewed and how we can best spot them in our clinics.

Not many of us have diagnosed patients as displaying lycanthropy but Andrew Lerner, in a short article, educates us as to what this means and what causes it to happen. It is not solely "the transformation of a human into a wolf" but in fact any animal as Andrew explains.

In the personal perspective section, a retired orthopaedic surgeon (who wished to remain anonymous) tells us about his journey with PD. In particular he talks about the time before he was diagnosed – the pre-PD phase of his illness – along with the decisions that subsequently needed to be made about careers and optimal therapy. In this latter he explores the debate and value of deep brain stimulation over drug therapies in advancing disease.

In the latest in our long running series on Neurosurgery, Neil Malhotra, Peter Whitfield and colleagues discuss the rare problem of intramedullary spinal cord tumours (IMSCTs). These present with an evolving spinal cord syndrome that can be easily misdiagnosed but which are now much more amenable to treatment as this article discusses. The success of this treatment relates primarily to the pathology as one might expect, but the once gloomy prognosis of such tumours can now be tempered in the knowledge that some patients can do very well with early diagnosis and neurosurgery.

Topun Austin and Robert Cooper discuss a new approach to monitoring neonatal seizures that combines EEG with diffuse optical imaging as a means of trying to get at cortical, as well as subcortical structures, to identify whether seizures are occurring in this age of patient, and if so where they originate. This very clear account shows the value of combining technologies to develop better tools by which to probe for common problems that are sometimes difficult to diagnose clinically.

Jan van Gijn in his historical article describes how Joseph Babinski sought to champion the physical examination of patients and through this, observed the extensor plantar response in upper motorneuron lesions. Jan explains that this desire to define the patient through a detailed clinical examination was driven by a wish to do things differently to his contemporary Charcot who sought to capture what was wrong with patients more by their history than examination.

In our paediatric neurology series Deepa Krishnakumar takes through the process by which to diagnose adolescents with myoclonus, helping to distinguish benign causes from those which herald the onset of some more progressive neurological condition. This is done with the aid of many useful tables and figures.

We have our usual summary of conferences, book and journal reviews, and again we hope you enjoy this latest issue of our journal. ♦



Roger Barker, Co-Editor.

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

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

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



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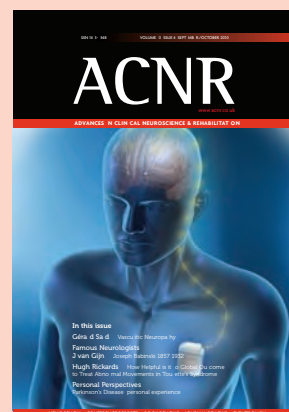
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- **APO-go website www.apo-go.co.uk**

For further information, please call your local APO-go business manager or contact the APO-go Helpline.

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APO-go® APOMORPHINE HYDROCHLORIDE. ABBREVIATED PRESCRIBING INFORMATION. Consult Summary of Product Characteristics before prescribing. **Uses:** The treatment of disabling motor fluctuations ("on-off" phenomena) in patients with Parkinson's disease which persist despite individually titrated treatment with levodopa (with a peripheral decarboxylase inhibitor) and/or other dopamine agonists. **Dosage and Administration:** Apomorphine hydrochloride is administered subcutaneously either as an intermittent bolus injection or by continuous subcutaneous infusion. Its rapid onset (5-10 mins) and duration of action (about 1 hour) may prevent an "off" episode which is refractory to other treatments. Hospital admission under appropriate specialist supervision is necessary during patient selection and when establishing a patient's therapeutic regime. Please refer to the Summary of Product Characteristics for full details before initiating therapy. Treatment with domperidone (typical dosage 20mg three times a day) before and during apomorphine HCl therapy is essential. The optimal dosage of apomorphine HCl has to be determined on an individual patient basis; individual bolus injections should not exceed 10mg and the total daily dose should not exceed 100mg. **Contraindications:** Children and adolescents (up to 18 years of age). Known sensitivity to apomorphine or any other ingredients of the product. Respiratory depression, dementia, psychotic disease or hepatic insufficiency. Intermittent apomorphine HCl treatment is not suitable for patients who have an "on" response to levodopa which is marred by severe dyskinesia or dystonia. **Pregnancy and lactation:** Apomorphine should not be used in pregnancy unless clearly necessary. Breast feeding should be avoided during apomorphine HCl therapy. **Interactions:** Patients should be monitored for potential interactions during initial stages of apomorphine therapy. Particular caution should be given when apomorphine is used with other medications that have a narrow therapeutic window. It should be noted that there is potential for interaction with neuroleptic and antihypertensive agents. It is recommended to avoid the administration of apomorphine with other drugs known to prolong the QT interval. **Precautions:** Use with caution in patients with renal, pulmonary or cardiovascular disease, or who are prone to nausea or vomiting. Extra caution is recommended during initiation of therapy in elderly

and/or debilitated patients. Since apomorphine may produce hypotension, care should be exercised in patients with cardiac disease or who are taking vasoactive drugs, particularly when pre-existing postural hypotension is present. Neuropsychiatric disturbances are common in Parkinsonian patients. APO-go should be used with special caution in these patients. Apomorphine has been associated with somnolence and other dopamine agonists can be associated with sudden sleep onset episodes, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution whilst driving or operating machines during treatment with apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa with given concomitantly with apomorphine. Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists, including apomorphine. Since apomorphine, especially at high dose, may have the potential for QT prolongation, caution should be exercised when treating patients at risk for torsades de pointes arrhythmia. Apomorphine has been associated with local subcutaneous effects that can be reduced by rotation of injection sites or use of ultrasound on areas of nodularity and induration. **Side Effects:** Local induration and nodules (usually asymptomatic) often develop at subcutaneous site of injection leading to areas of erythema, tenderness, induration and panniculitis. Irritation, itching, bruising and pain may also occur. Rarely injection site necrosis and ulceration have been reported. Pruritus may occur at the site of injection. Drug-induced dyskinesias during "on" periods can be severe, and in a few patients may result in cessation of therapy. Postural hypotension is seen infrequently and is usually intransient. Transient sedation following each dose of apomorphine may occur at the start of therapy, but this usually resolves after a few weeks of treatment. Dizziness and lightheadedness have also been reported. Nausea and vomiting may occur, particularly when APO-go treatment is initiated, usually as a result of the omission of domperidone. Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine therapy and neuropsychiatric disturbances may be exacerbated by apomorphine. Positive Combs' tests and haemolytic anaemia and thrombocytopenia have

been reported in patients receiving apomorphine and levodopa. Local and generalised rashes have been reported. Eosinophilia has occurred in only a few patients during treatment with apomorphine HCl. Patients treated with dopamine agonists, including apomorphine, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality (especially at high doses). Apomorphine is associated with somnolence. Yawning and breathing difficulties have been reported as has peripheral oedema. *Prescribers should consult the Summary of Product Characteristics in relation to other side effects.* **Presentation and Basic NHS Cost:** Apo-go ampoules contain apomorphine hydrochloride 10mg/ml, as follows: 20mg in 2ml – basic NHS cost £37.96 per carton of 5 ampoules. 50mg in 5ml – basic NHS cost £73.11 per carton of 5 ampoules. APO-go pens (disposable multiple dosage injector system) contain apomorphine hydrochloride 10mg/ml, as follows: 30mg in 3ml – basic NHS cost £123.91 per carton of 5 pens. APO-go Pre-filled syringes contain apomorphine hydrochloride 5mg/ml, as follows: 50mg in 10ml – basic NHS cost £73.11 per carton of 5 syringes. **Marketing Authorisation Numbers:** APO-go Ampoules: PL 06831/0245. APO-go Pens: PL 06831/0246. APO-go Pre-filled syringes: PL 06831/0247. **Legal Category:** POM. **Date of last revision:** February 2010. For further information please contact: Genus Pharmaceuticals, Park View House, 65 London Road, Newbury, Berkshire, RG14 1JN, UK.

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Vasculitic Neuropathy



Gérard Said, MD, FRCP

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Vasculitis, primary or secondary, is the cause of many acquired neuropathies. Peripheral nerves are at high risk of ischaemic lesions in primary vasculitis, which predominantly affect small arteries of the size of the vasa nervorum present in the epineurium of nerve trunks. Thus primary necrotizing vasculitis is the key manifestation of connective tissue disorders and related conditions that include polyarteritis nodosa (PAN) and the Churg Strauss syndrome variant, rheumatoid arthritis, systemic lupus and Wegener's granulomatosis. In these conditions ischaemic focal and multifocal neuropathy results from destruction of the arterial wall and occlusion of the lumen of small epineurial arteries. Vasculitis also occurs as a secondary phenomenon in other conditions including infection with HIV and hepatitis B and C as well as in diabetes mellitus and sarcoidosis. In all these settings the neuropathy is often curable after treatment of the vasculitis with corticosteroids, often with the adjunct of immunosuppressive drugs.

Different patterns of vasculitis

Primary vasculitis and connective tissue disorders (CTD)

Primary vasculitides are often classified according to the size of vessels predominantly affected but overlaps are common. In the medium-sized vessel vasculitis, neuropathy occurs in patients with PAN. Small vessel vasculitis includes Wegener's granulomatosis (WG), the Churg-Strauss syndrome (CSS), and microscopic polyangiitis with involvement of capillaries often overlaps with PAN.

Necrotising arteritis (NA) of the type observed in PAN is related to the formation of soluble, circulating immune complexes, which is a consequence of the large-scale synthesis of antibodies by plasma cells. Wegener granulomatosis (WG) is an antibody-mediated autoimmune, granulomatous vasculitis, in which antibodies against proteinase 3 and myeloperoxidase are demonstrable in the serum of patients. Serologic demonstration of these ANCAs is a sensitive and specific means by which to confirm WG and monitor patients with WG.

Secondary vasculitis

In vasculitis secondary to inflammatory disorders, the role of cellular factors is often prominent. In such conditions macrophages and cytotoxic T lymphocytes seem to play a major role in vessel wall damage.

The Peripheral Neuropathy of Primary vasculitis

The consequences of vascular inflammation and occlusion depend on the size and number of blood vessels affected. Clinical neuropathy occurs in more than 75% of the patients with systemic vasculitis of the PAN group.

Typically the clinical picture is that of an acute or subacute mononeuritis multiplex, with successive or simultaneous involvement of multiple nerve trunk territories over days, weeks or months.^{6,9,10} Distal sym-

metrical sensory or sensorimotor neuropathy also occurs. The peroneal nerve, which is the most commonly affected nerve, is involved unilaterally in 27%; bilaterally in 30% of the patients. In the upper extremities the ulnar is the most commonly affected (one side; 16%; both sides in 9%). In typical cases, the onset of the neuropathy is abrupt and the deficit severe, but in many cases only partial deficit in a nerve territory is observed. A slowly progressive course is observed in some cases, especially in the elderly. The CSF is usually normal. Recovery from a motor deficit due to an ischaemic neuropathy takes months, because of the axonal pattern of nerve lesions. Residual pains are common and may be difficult to differentiate from relapses of the neuropathy.

Polyarteritis nodosa

In PAN the ischaemic neuropathy induced by NA can be observed as an isolated manifestation, or in the context of a multisystemic disorder. In classic PAN, which was the most common disorder encountered in our series, cutaneous vasculitis was the most common non-neurological manifestation with livedo, cutaneous necrosis and nodules. Non specific focal oedema, usually affecting one limb extremity, often preceded the onset of neuropathy. Arthritis, renal involvement and asthma were present in 10% of the patients on average. Biological markers of inflammation including CRP and ESR, increased platelet and white blood cell count with eosinophilia are often seen. However, they remain normal in nearly 30% of the patients seen in neurology.

Churg and Strauss variant of polyarteritis nodosa

In 1951, Churg and Strauss reported a study of 14 cases of a form of disseminated necrotising vasculitis occurring frequently among asthmatic patients, with fever, eosinophilia, and a fulminant multisystem disease with pathology of NA, eosinophilic infiltration and extravascular granulomas.² The vascular and nerve lesions observed in nerve biopsies from patients with this syndrome are responsive to treatment and are similar to those observed in PAN, with on occasions elevated ANCA.⁵

Necrotizing arteritis and neuropathy in patients with rheumatoid arthritis

The occurrence of NA in the context of rheumatoid arthritis is associated with a poor outcome. In our series patients with rheumatoid arthritis and neuropathy due to histologically proven necrotising vasculitis in muscle and/or in nerve biopsy specimens, 15 had a sensory and motor neuropathy; the others a purely sensory neuropathy. Low CH50, C3 and C4 complement levels were associated with a poorer outcome.⁸

Wegener's granulomatosis

Wegener's granulomatosis (WG) is characterised by granulomatous vasculitis of the upper and lower respiratory tract with or without glomerulonephritis. Peripheral neuropathy has been observed in

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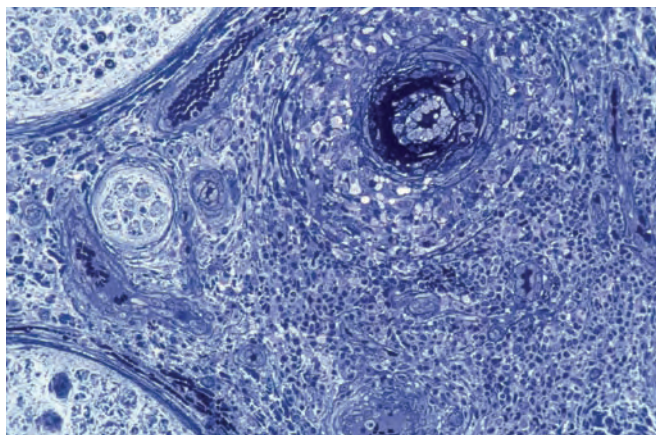
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One-micron thick section of an epon embedded nerve biopsy specimen of the superficial peroneal nerve from a patient with mononeuritis multiplex, to show necrotising vasculitis of an epineurial artery. Note the degeneration of most nerve fibres in neighbouring fascicles. Thionin blue staining. Bar: 50 μ m.

25% of the patients with WG but peripheral neuropathy is seldom the first manifestation of the disease.⁷

Necrotising arteritis and isolated neuropathy

In many instances peripheral neuropathy is the presenting and only manifestation of necrotising arteritis,^{9,10,14,3} but silent involvement of other organs is common in such patients, as shown by the frequent finding of specific arterial lesions in muscle biopsy specimens.⁹

General signs or symptoms, usually minor, including fever and loss of weight are present in half of them. From a neurological standpoint, approximately a quarter of the patients present with a distal symmetrical sensory or sensorimotor neuropathy, and the diagnosis of NA is seldom considered before the results of the nerve and muscle biopsies.

One third of patients with the so-called non systemic vasculitis subsequently develop systemic manifestations within an average of six years, but the overall outcome remains better than in classic PAN.

Vasculitic neuropathy in the elderly

Neuropathy is an important factor in the disability of the elderly. In a series of 100 patients over 65 years of age referred for a disabling neuropathy, we found that 23% had a vasculitic neuropathy.¹

Morphological aspects

Demonstration of NA in nerve and muscle biopsy specimens

The diagnosis of NA needs histological confirmation, which can sometimes be achieved by biopsying a specific skin lesion. If not, nerve and/or muscle biopsies are advised in the search of the characteristic lesions of muscular or epineurial arteries.¹⁰

The specific lesion can be found in the muscle, in the nerve, or both in the nerve and the muscle specimens, which must often be studied on serial sections because NA is segmental.

The diagnostic criteria include transmural infiltration of small arteries with polymorphonuclear cells, leukocytoclasia; fibrinoid necrosis and usually sparing of adjacent venules. These lesions result in arterial occlusion that are followed after days or weeks by spontaneous recanalation of the artery.

Lesions of nerve fibres - The ischaemic neuropathy

Nerve ischaemia due to a vasculitic neuropathy induces acute axonal degeneration, often with asymmetry of lesions between, and within, fascicles, which may predominate in the centrofascicular area. Large myelinated fibers are affected. The nerve lesions appear to result from the summation of lesions of different ages involving the nerve blood vessels.⁴

Secondary vasculitic neuropathy

Vasculitis can complicate the course of different conditions including an inflammatory immune reaction triggered by an infective agent, a delayed

type hypersensitivity reaction, diabetes mellitus or malignancy.

Necrotising vasculitis and viral infection

Symptomatic viral infection, including HIV infection, cytomegalovirus (CMV infection at a late stage of HIV infection); hepatitis B and C and HTLV-1 infection can be associated with neuropathy and necrotising vasculitis. In HIV patients, necrotising arteritis is usually associated with marked inflammatory infiltrates affecting the endoneurium and capillaries.

Sarcoidosis

Angiitis has been recognized at autopsy in the CNS and occasionally in patients with sarcoid neuropathy.¹²

Vasculitis in focal and multifocal diabetic neuropathy

A small proportion of diabetic patients over the age of 50, may present with proximal neuropathy of the lower limbs characterised by a variable degree of pain and sensory loss associated with uni- or bilateral proximal muscle weakness and atrophy. Others develop a subacute multifocal nerve trunk involvement, with pains and weakness.^{11,13}

Treatment

Prednisone is usually started at 1mg/Kg/day. Simultaneous treatment with cyclophosphamide, 2mg/Kg/day, or azathioprine may help reduce the doses of corticosteroids. We usually give a full dose of steroids for approximately 6-8 weeks and then taper prednisone over 6-10 months, or more. It is necessary to control the ESR and other markers of disease activity, including CRP and eosinophilic polymorphonuclear cell levels, which may vary from one patient to another, and to adjust the doses of prednisone accordingly. In our experience, up to half of the patients relapse during tapering of the prednisone or after treatment has been stopped. In some patients treatment with low dose prednisone must be pursued indefinitely.

In the evaluation of the efficacy of treatments of vasculitic neuropathies, it must be remembered that there is a wide range of modalities of evolution in NA, and that spontaneous remissions after several years duration can occur. Sensorimotor deficit resulting from nerve ischaemia will take months to recover, because of the underlying axonal lesions. Motor recovery will be helped by physiotherapy, but residual pains are common. ♦

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

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

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How Helpful is it to Global Outcome to Treat Abnormal Movements in Tourette's Syndrome?

Tourette's Syndrome (TS) is the quintessential neuropsychiatric condition in the sense that it is a brain disorder displaying motor, cognitive, behavioural and affective symptoms.

Case

A 17-year-old man with Tourette's syndrome is referred to clinic with a history of motor and vocal tics, of moderate severity. His family are very concerned and embarrassed by them and say "something must be done". The patient is not personally troubled by the actual movements but is socially conscious of others' response. He has no substantive psychiatric co-morbidity but does acknowledge his disorder "gets me down" on occasions. How should this situation be managed? In particular, what are the advantages and disadvantages in using pharmacological treatments for his movement disorder? What else might be done?

This clinical dilemma is best solved with reference to seven key points, which will be discussed in order. The first point is that people with TS often have symptoms that cover a variety of domains (not just tics) which can include depression, obsessive compulsive disorder (OCD), anxiety, attention deficit and impulsive behaviours. Some of these symptoms are intrinsic to the syndrome itself and some represent co-morbid diagnoses. Second, quality of life in TS may not be primarily related to the motor disorder, so treatment of the motor disorder may not help the patient significantly. Third, prognosis in TS is largely good so it may be better simply to "weather the storm" rather than risk the adverse effects of treatment. Fourth, pharmacological treatments are often effective against tic symptoms but commonly have unacceptable adverse effects. Fifth, non-pharmacological treatments can often be effective against tics, although are not always available. Sixth, if the disability caused by tics is in relation to ignorance, discrimina-

tion or social exclusion, then social, legal or political steps may be more appropriate than medical ones. Finally, most people with TS have intact capacity to decide about treatment, so their subjective experience of their illness may be the key factor in any choices about management.

People with TS often have symptoms in a variety of domains, not just tics

Studies of clinic populations with TS have shown that OCD and obsessive compulsive behaviours are very common (the rule rather than the exception) and may be part of the TS phenotype.¹ Community epidemiological evidence also points to the co-morbid existence of TS with attention deficit hyperactivity disorder (ADHD)² although the two conditions do not share the same genetic vulnerability.³ Both depression and anxiety disorders are common in TS and their causation is likely to be multi-factorial including a response to disability and social exclusion. Non-obscene socially inappropriate behaviours

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and bronchospasm. Haemolytic anaemia has been reported in patients treated with levodopa and apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa, when given concomitantly with apomorphine. Neuropsychiatric disturbances may be exacerbated by apomorphine. Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including apomorphine. **Side Effects: Very common:** Local induration, nodules and pruritis at subcutaneous injection/infusion sites. At high doses of apomorphine these may persist and produce areas of erythema, tenderness and induration. Panniculitis has been reported where a skin biopsy has been undertaken. **Common:** Nausea and vomiting, transient sedation at initiation of therapy and somnolence. **Uncommon:** Postural hypotension, dyskinesias during 'on' periods. Local and generalised rashes. Haemolytic anaemia and positive Coombs' test. Breathing difficulties. **Rare:** Eosinophilia. **Presentation and Basic NHS Cost:** Apomorphine ampoules contain apomorphine hydrochloride 10mg/ml, as follows: 20mg in 2ml – basic NHS cost £34.16 per carton of 5 ampoules. 50mg in 5ml – basic NHS cost £59.95 per carton of 5 ampoules. **Marketing Authorisation Number:** Apomorphine 10mg/ml solution for injection: PL12406/0024. **Legal Category:** POM. **Date of last revision:** April 2009. For further information please contact: Archimedes Pharma UK Ltd, 250 South Oak Way, Green Park, Reading, Berkshire, RG2 6UG, UK. AP0054. Date of Preparation: January 2010.

are also common in TS and can cause significant impairment.⁴ Around a third of clinic attendees with TS have self-injurious behaviours. Recent studies of social cognition in TS indicate deficits in the understanding of non-literal language which may impair function and quality of life.⁵

In this setting, the important clinical skill is to identify the symptoms which are most likely to be causing disability and to treat them. In a child, this can be more difficult and in this case, the aim is to establish which symptoms are leading to impaired development.

Quality of life (QoL) in TS may not be related to motor disorder

A number of recent studies have addressed the issue of quality of life in TS. There are six studies in total and the outcomes are mixed. However, OCD and ADHD appear to contribute just as much to impairment in QoL when compared to motor disorder (tics). Recent development of disease-specific QoL measures (TS-QoL) in both adults and children will lead to a better understanding of which TS-related symptoms lead to greatest impairment of QoL.

Prognosis in TS is largely good, so it may be easier to “weather the storm”

The mean age for maximum severity of tics in TS is 11 years.⁶ Although tics wax and wane in severity, they tend to gradually improve into late adolescence and early adulthood. This patient is 17 years old, so he should expect to continue improving gradually over the next decade. The absence of psychiatric co-morbidity is likely to be a good prognostic factor in his case. However, the absence of good quality longitudinal data in TS makes it difficult to assess which factors confer a good or bad prognosis. A counter argument could be that, as the condition is likely to improve, any pharmacological treatment would be likely to be short-term. However, adverse effects are extremely common with conventional TS treatments which would count against treatment, even in the short term.

Pharmacological treatments are good for motor symptoms but may cause unwanted effects

Although numbers are relatively small, randomised, controlled trial data suggests that a number of pharmacological treatments can substantially reduce tics in people with TS.⁷ Treatments such as risperidone have clearly been shown to be effective in reducing tics. However, the mainstays of treatment (atypical antipsychotic drugs) are not well tolerated. Weight gain is a very common adverse effect of these drugs. This is commonly unacceptable to young people and often results in them stopping the drug. There is also a risk of impaired glucose tolerance and Type II diabetes although this is difficult to quantify in a TS population. Drug-induced dysphoria is very common and can lead in some cases to school refusal, impaired concentration and a general reduction in function. The incidence of drug-induced

Diagnostic criteria for Tourette syndrome. (DSM-IV)

- 1) Presence of both motor and phonic tics, not necessarily at the same time.
- 2) Tics occur many times per day (usually in bouts), nearly every day or off and on for more than a year, with no tic-free period of longer than three months.
- 3) Onset of symptoms occurs before 18 years of age.
- 4) The symptoms are not caused by the direct effects of other substances or medications or due to another general medical condition.

motor disorders appears to have declined with the move from typical antipsychotics (such as haloperidol) to the atypical. However, all the major motor complications have still been described with the atypical neuroleptics (parkinsonism, acute dystonia, akathisia, tardive dyskinesia). It is more common for people with TS to cease treatment than to carry on with it in the first year of treatment.

Non-pharmacological treatments are often effective but are not easy to access

Psychological treatments for tics are enjoying a deserved renaissance. Habit reversal therapy (HRT) and exposure with response prevention (ERP) have now been proven to be effective treatments for tics.⁸ Clinical experience suggests that these therapies are most successful if they are combined with a broader psychological approach, addressing conflicts in the individual's life and problems within the family. Behavioural therapies can be difficult to apply to those people who have problems with attention and concentration deficits or who have multiple tics and complex disability. Unfortunately, behavioural therapies are often difficult to access in the UK. Botulinum toxin has been used successfully as a treatment for phonic tics by injecting one or both vocal chords under EMG guidance.⁹ This appears to reduce the severity of phonic tics as well as the premonitory urge to tic. Other non-pharmacological treatments include neurosurgery, which has been applied relatively successfully to around 60 cases world wide in nine different targets.¹⁰ Currently, neurosurgery has a number of serious but uncommon risks and is not recommended outside of clinical trials and then, only in extremis.

If the disability is related to ignorance or discrimination, then social, legal or political steps may be most appropriate

Commonly, tics are still labelled as willed acts of defiance and lead to social exclusion and discrimination. This is not to minimise the disturbing effects that vocal tics in particular can have on the classroom or workplace. It may be that some phonic tics are fragments of behaviour whose original function was to create a state of vigilance in others of the same species.

Ignorance about the nature of TS can lead to children and adults being punished for their

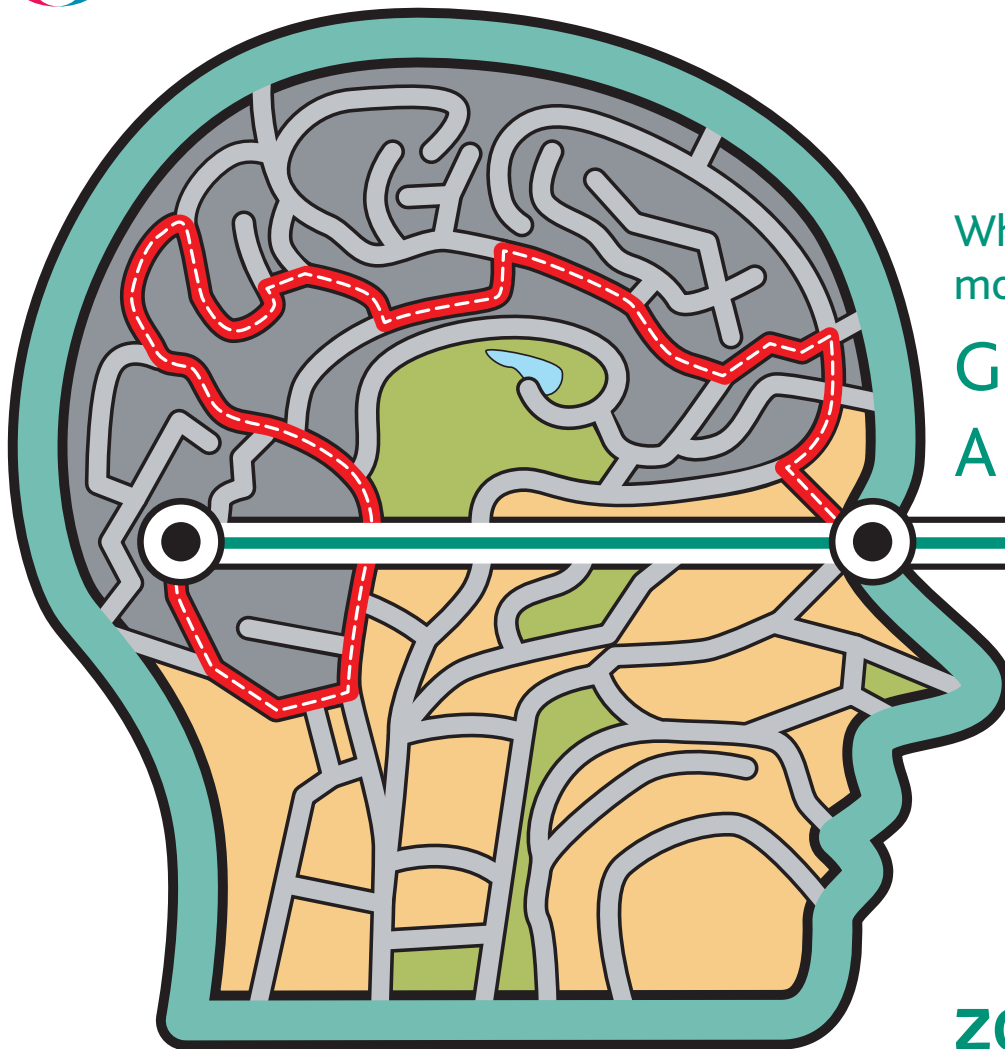
symptoms and, in some cases, to exorcism. Education of parents, families, teachers and others can help to reduce the stigma attached to this disorder. Adjustment of the environment (for instance, granting “time out” from the classroom or workplace, or allowing students to take written exams in a separate area) can be of great help to people with TS. The Disability Discrimination Act has been particularly helpful in placing the onus on employers or schools to make appropriate adjustments to the working environment.

Most people with TS have capacity to make informed decisions about treatment

There is nothing about a diagnosis of TS that would necessarily limit a person's capacity to make decisions about treatment. Cognition is grossly intact and receptive and expressive functions are not substantially impaired. Therefore, people with TS should be at the centre of any decision-making with regards to treatment. The symptoms of TS are mainly problematic in relation to social disability. This means that the patient has a vital role in establishing the balance between taking treatment to minimise symptoms (and risking adverse effects) and tolerating or tackling the social disability resulting from tics. People with TS take a variety of positions about this. Some feel that TS is not a disorder at all and that the problem is purely related to the intolerance of other people. People with TS and their families can also disagree about the necessity to treat tics and this needs sensitive handling, especially with children. In the end, people with TS should take centre stage in any decisions about treatment. ♦

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diplopia, decreased bicarbonate. Common effects ($\geq 1/100$, $< 1/10$): ecchymosis, hypersensitivity, affect lability, anxiety, insomnia, psychotic disorder, bradyphrenia, disturbance in attention, nystagmus, paraesthesia, speech disorder, tremor, abdominal pain, constipation, diarrhoea, dyspepsia, nausea, rash, nephrolithiasis, fatigue, influenza-like illness, pyrexia, weight decreased. Uncommon ($\geq 1/1000$, $< 1/100$): pneumonia, urinary tract infection, hypokalemia, anger, aggression, suicidal ideation, suicidal attempt, convulsion, vomiting, cholecystitis, cholelithiasis, calculus urinary. For very rare side effects see SmPC. Isolated cases of Sudden Unexplained Death in Epilepsy Patients (SUDEP). Post-marketing data suggests patients aged ≥ 65 years report a higher frequency of Stevens-Johnson syndrome and Drug Induced Hypersensitivity syndrome. **Legal Category:** POM. **Basic UK NHS cost:** Zonegran 25 mg: packs of 14 £8.82, Zonegran 50 mg: packs of 56 £47.04, Zonegran 100 mg: packs of 56 £62.72. **Irish price to wholesaler:** Zonegran 25 mg: packs of 14 €10.95, Zonegran 50 mg: packs of 56 €58.07, Zonegran 100 mg: packs of 56 €77.59. **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 2009.

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J van Gijn

(1942) studied medicine in Leiden and trained as a neurologist in Rotterdam and London (Queen Square). His MD thesis (1977) was on the plantar reflex. From 1983-2007 he was professor and chairman of the University Department of Neurology in Utrecht. His main research interest used to be stroke, but after retirement it is shifting towards somatisation and the history of neurology.

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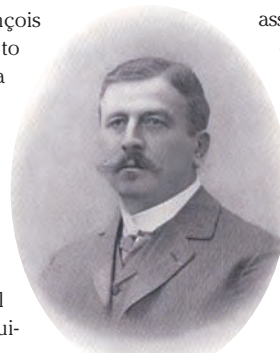
Joseph Babinski 1857-1932

The name of Joseph Félix François Babinski is inseparably linked to the upgoing toe phenomenon, a reliable sign of pyramidal tract damage or dysfunction. His discovery of the sign, in 1896, crowned the development of the neurological examination. In the 19th century physical examination in general was in the ascendancy, reflecting the demise of the time-honoured but theoretical notion of disease as a disturbed equilibrium between liquid components (fluidism). In its place came the new, 'organ-oriented medicine', based on post-mortem observations (solidism). Percussion and auscultation of internal organs, early in the 19th century, were followed by tests to assess the function of the nervous system: ophthalmoscopy (1851), skin sensation and position sense with their different pathways (1855), spasticity (1860), language disorders (1861), individual muscles and their innervation (1860s), tendon reflexes (1875) and skin reflexes (1853-1876).

Babinski's parents were Polish refugees. Revolts were rife around 1848, also in Poland, where nationalists fought against occupation by Russia and Austria. Defeat upon defeat led to a steady stream of refugees to Paris, at that time the hub of political and intellectual freedom. One of them was the engineer Alexandre Babinski. In Paris he married a compatriot, Henriette Weren. They had two children: in 1855 Henri and in 1857 Joseph. Employment was difficult to obtain; from 1862 the father worked as a construction engineer in Peru. In 1870 he came back to enlist in the army of his new country, in the war against Germany. From then on his health deteriorated – he suffered from Parkinson's disease – and it fell upon Henri, a mining engineer, to go abroad and support his parents as well as the medical education of his younger brother Joseph.

During his residencies (1879-1885), Joseph performed morphological and microscopic studies. These resulted in an article about the muscle spindle and a thesis on multiple sclerosis. In 1885 he became Charcot's 'chef de clinique', without ever having served under him as a resident. He had submitted his thesis in a competition of the Paris hospitals, just missing the gold medal, but instead was offered the post as a kind of second prize. In those times Charcot was deeply engaged in the study of hysteria. He regarded it as a localised, albeit functional disorder of the central nervous system. Charcot mainly used the history as the key instrument in making a diagnosis, whereas Babinski came to rely more and more on assiduous physical examination.

Near the end of the 1880's Joseph generated enough income to take his turn in supporting the family, and to move to a more spacious apartment at the Boulevard Hausmann (170bis, 3rd floor). Henri returned from his foreign travels and gradually



The photograph probably dates from 1904, a few years after Babinski discovered the 'toe phenomenon'

assumed the role of housekeeper. After the death of their parents (the mother in 1897 and the father in 1899), the two brothers continued to inhabit the same apartment for 30 more years, in a close and harmonious relationship. Henri would serve as secretary, driver and, above all, cook; under the pseudonym 'Ali Bab' he published a tome on gastronomy that was as authoritative as it was weighty; it went through several editions.

In 1892 Joseph failed in the competition for the academic rank of assistant professor ('professeur agrégé'). The examination was traditionally riddled with nepotism and intrigue, but in that year it even developed into a public scandal. The main culprit was Charles Bouchard (1837-1915), a former pupil of Charcot, now full professor and chairman of the jury. Bouchard, believed to be consumed by ambition and envy, contrived to include all three pupils of his own among the five candidates who passed (from a total of sixteen). Neither a series of incensed articles in the 'Progrès Médical' nor a petition to the responsible minister reversed the outcome. Babinski never tried again. Meanwhile (from 1890) he had left Charcot's 'Salpêtrière' and started to practise in 'La Pitié', where he was nominated chief in 1895 and would remain until his retirement.

As was usual in those times, Babinski spent only mornings at the hospital; in the afternoon he would see private patients. It is said that, when ward rounds at the Pitié encroached upon the time for lunch, a sister might come up to the chief and whisper in his ear that Henri's soufflé was nearing perfection. Joseph's appearance was un-French: of long stature, with steel-blue eyes, thoughtful and deliberate in his words and gestures. The traditional ward round did not suit him – he preferred to have the patients brought in. The room reserved for that purpose was always full with residents and visitors. Patients were already undressed on entering; the history was limited to a few laconic questions, soon followed by the most important part of the encounter – the neurological examination. He was especially looking for objective signs – elicited with pin, patella hammer and electrical stimulator. All this took place in silence, occasionally interrupted by a brief comment. Then, rather abruptly, he would summon the next patient. His scientific work was by no means restricted to semiology: among the subjects he also published on were brain tumours, involuntary movements, bulbar and cerebellar disorders, disorders of spinal cord, peripheral nerves and muscle, and hysteria (a condition he called 'pithiatisme', to dissociate it from female sexuality).

In 1922 Babinski retired, at the age of 65. Meanwhile he had been awarded many distinctions, especially from abroad. His successor, L.H. Vaquez (1860-1936), allowed him to continue a weekly clinical demonstration. Also, Babinski con-



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Presentation Rebif 8.8µg and 22µg: Pre-filled glass syringe containing 8.8µg or 22µg of Interferon beta-1a in respectively 0.2 or 0.5ml. Rebif 22µg or 44µg: Pre-filled glass syringe containing 22µg or 44µg Interferon beta-1a in 0.5ml. Rebif 8.8µg and 22µg: Disposable pre-filled pen injector (RebiDose) containing 8.8µg or 22µg of Interferon beta-1a in respectively 0.2 or 0.5ml. Rebif 22µg or 44µg: Disposable pre-filled pen injector (RebiDose) containing 22µg or 44µg Interferon beta-1a in 0.5ml. Rebif 8.8µg/0.1ml and Rebif 22µg/0.25ml: Pre-filled glass cartridge containing 132µg of Interferon beta-1a in 1.5ml. Rebif 22µg/0.5ml or Rebif 44µg/0.5ml: Pre-filled glass cartridge containing 66µg or 132µg of Interferon beta-1a in 1.5ml. **Indication** Treatment of relapsing multiple sclerosis. Efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapse activity. **Dosage and administration** Initiate under supervision of a physician experienced in the treatment of multiple sclerosis. Administer by subcutaneous injection. Recommended dose: Weeks 1 and 2: 8.8µg three times per week (TIW); weeks 3 and 4: 22µg TIW; week 5 onwards: 44µg TIW (22µg TIW if patients cannot tolerate higher dose). RebiDose pre-filled pen is for single use and should only be used following adequate training of the patient and/or carer. Follow the instructions provided in the package leaflet. Rebif solution for injection in cartridge is for multidose use and should only be used with the RebiSmart autoinjector device following adequate training of the patient and/or carer. Follow the instructions provided with the RebiSmart device. Limited published data suggest that the safety profile in adolescents aged 12–16 years receiving Rebif 22µg TIW is similar to that in adults. Do not use in patients under 12 years of age. Prior to injection and for 24h afterwards, an antipyretic analgesic is advised to decrease flu-like symptoms. Evaluate patients at least every second year of the treatment period. **Contraindications** History of hypersensitivity to natural or recombinant interferon beta, or to any of the excipients; treatment initiation in pregnancy; current severe depression and/or suicidal ideation. **Precautions** Inform patients of most common adverse reactions. Use with caution in patients with previous or current depressive disorders and those with antecedents of suicidal ideation. Advise patients to report immediately any symptoms of depression and/or suicidal ideation. Closely monitor patients exhibiting depression and treat appropriately. Consider cessation of therapy. Administer with caution in patients with a history of seizures and those receiving anti-epileptics, particularly if epilepsy is not adequately controlled. Closely monitor patients with cardiac disease for worsening of their condition during initiation of therapy. Patients should use an aseptic injection technique and rotate injection sites to minimise risk of injection site necrosis. If breaks in skin occur, patients should consult their doctor before continuing injections. If multiple lesions occur, discontinue Rebif until healed. Use with caution in patients with history of significant liver disease, active liver disease, alcohol abuse or increased serum ALT. Monitor serum ALT prior to the start of therapy, at months 1, 3 and 6 and periodically thereafter. Stop treatment if icterus or symptoms of liver dysfunction appear. Treatment has potential to cause severe liver injury including acute hepatic failure. Full haematological monitoring is recommended at months 1, 3 and 6 and periodically thereafter. All monitoring should be more frequent when initiating Rebif 44µg. New or worsening thyroid abnormalities may occur. Thyroid function testing is recommended at baseline and if abnormal every 6–12 months. Use with caution in, and closely monitor patients with, severe renal and hepatic failure or severe myelosuppression. Serum neutralising antibodies may develop and are associated with reduced efficacy. If a patient responds poorly and has neutralising antibodies, reassess treatment. Use with caution in patients receiving medicines with a narrow therapeutic index cleared by cytochrome P450. Women of childbearing potential should use effective contraception. Limited data suggest a possible increased risk of spontaneous abortion. During lactation, either discontinue Rebif or nursing. 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 8.8µg and 22µg: 6 (0.2ml) + 6 (0.5ml) syringes – £552.19. Rebif 22µg: 12 syringes (0.5ml) – £624.77. Rebif 44µg: 12 syringes (0.5ml) – £813.21. Rebif 8.8µg and 22µg: 6 (0.2ml) + 6 (0.5ml) pens – £552.19. Rebif 22µg: 12 pens (0.5ml) – £624.77. Rebif 44µg: 12 pens (0.5ml) – £813.21. Rebif 8.8µg/0.1ml and 22µg/0.25ml: 2 cartridges – £406.61. Rebif 22µg/0.5ml: 4 cartridges – £624.77. Rebif 44µg/0.5ml: 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, Bedford Cross, Stanwell Road, Feltham, Middlesex, TW14 8NX. 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Date of Preparation: August 2010

REB10–0231

tinued to attend the monthly meeting of the French Neurological Society, which he had helped to found in 1899. In 1930 it became more difficult for him to move around; after Henri had died, in the autumn of 1931, he lost interest in life. He passed away on October 29, 1932. He was buried with his relatives at the Polish cemetery in Montmorency.

The plantar reflex had been known to physicians since 1868, but only as a flexion response of the entire leg. Subsequently this synergistic response was rediscovered a number of times, each time under a different name. Sometimes movements of the toes were noted as part of the synergy, in one direction or another. The authors in question attached little importance to these observations, yet some later ‘historians’ would misinterpret these as prior discoveries. Babinski was the first to study the responses of the toes in a systematic fashion. His initial report was brief, reflecting an oral communication before the Société de Biologie. He had undertaken a systematic study of hemiplegic patients, with the aim of finding objective signs that were characteristic for organic disease and thus could help in distinguishing it from hysterical hemiplegia. His efforts resulted in a large series of signs, to all of which he devoted a separate publication. The toe reflex was only one of these new signs, though it would prove by far the most important. Babinski observed that in normal subjects stroking of the sole of the foot resulted in a downward movement (flexion) of the toes, together with flexion in the ankle, knee and hip, whereas in patients with hemiplegia the toe response was ‘transformed’: the toes went up (extension), especially the big toe. Before that he had found the organic contracture of the hand (1893). After the ‘toe phenomenon’ followed hypotonia of the arm (1896), weakness of the platysma muscle (1900), involuntary hip flexion on rising from a supine position (1900), involuntary pronation of the arm (1907) and abnormal passive movements of the arm during movements of the trunk (1909).

One year later, in 1897, Babinski associated the ‘toe phenomenon’ (‘phénomène des orteils’) specifically with dysfunction of the pyramidal tract. At the same time he drew a parallel with the plantar reflex in newborns, in whom the pyramidal system is not yet fully developed. The next year he provided more details, in an article structured as a clinical demonstration. Importantly, he had now observed the abnormal toe sign not only in structural but also in metabolic disorders: epilepsy, intoxication with strychnine, or meningitis. The term ‘Babinski sign’ was first used in 1898, by the Belgian neurologist Arthur van Gehuchten (1861–1914).

The pathophysiology of the phenomenon is different from the ‘transformation’ Babinski initially envisaged. Paradoxically, the toe extensors – and not the flexors – take part in the flexion synergy, as shown by Sherrington’s work in spinal animals. In a physiological sense the toe extensors (anatomical term) are actually flexors, as they shorten the limb on contracting. As the pyramidal tract becomes fully myelinated, between the first and second year of life, two functional changes occur. Firstly the influence of the pyramidal tract, strongest on distal muscles, and – in the leg – on flexors (in a physiological sense), excludes the upgoing movement of the great toe from the shortening synergy of the leg. Secondly, this suppression clears the way, so to speak, for the normal (downward) response of the toes; that response stands on its own as a monosegmental skin response, very similar to abdominal skin reflexes. With lesions of the pyramidal system the ‘neonatal’ state of affairs returns.

The great acclaim that befell the Babinski sign has prompted many epigones to stake their claim with regard to sites of stimulation other than the sole. In the pursuit of everlasting fame all eyes were on the toes alone. Many lost sight of the principle that pathological toe response was part and parcel of a complex synergy: on the efferent side many flexor muscles of the leg are involved, and on the afferent side the synergy can be elicited from a multitude of skin sites. Also, in the day-to-day interpretation of plantar responses, it is useful to take account of the flexion synergy of the leg: an upgoing toe is a Babinski sign only if it is accompanied by activity in other flexor muscles of the leg. ♦



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Intramedullary Spinal Cord Tumours: diagnosis, treatment, and outcomes

Intramedullary tumours are lesions that usually arise directly from the neural tissue of the spinal cord. They are unique amongst all spinal column masses in that they require incision of the spinal cord for surgical access. Intramedullary tumours of the spine make up 2-4% of all central nervous system tumours and are a rare cause of spinal cord dysfunction.¹ Tumours of the spinal column may be classified by location as extradural, intradural, or intramedullary. Amongst all masses of the spinal column, intramedullary tumours are the least common to be encountered in the general public.

Their rare incidence commonly results in misdiagnosis and improper diagnostic workup, resulting in delayed diagnosis. More common clinical entities such as arthritic spinal myelopathy, multiple sclerosis, or even aortic dissection can be confused with intramedullary tumours as they may have similar clinical and radiographic presentations.

Deferred diagnosis and treatment can lead to progressive paralysis, urinary and faecal incontinence, as well as reduced survival. Imaging and surgical technologies were inadequate to diagnose or treat these tumours without serious morbidity in the past. Today, convenient high resolution MRI as well as improved surgical adjuvants and techniques have allowed for significantly improved resection and overall neurological outcome. Most patients can now undergo definitive diagnosis and treatment without significant long-term loss of spinal cord function. Thus, awareness of this clinical entity and early diagnosis and treatment is paramount to avoid disability.

Clinical Presentation

Intramedullary spinal cord tumours (IMSC) have a myriad of presenting signs and symptoms, making a simple diagnostic algorithm difficult. The temporal course of these lesions is widely disparate, with occasional patients presenting with acute neurologic deficits and others with a protracted course. Most series demonstrate that the most common presenting complaint is either local dull pain or radicular pain, often associated with some degree of lower extremity numbness.^{2,3} The finding of local back pain when lying flat in bed (nocturnal pain) is highly suggestive of tumour, especially if this pain wakes the patient from sleep; however, these alerting symptoms are often absent. Motor weakness is also common, although it usually presents later than pain or sensory disturbances. The Brown-Sequard syn-

drome, hemiparesis ipsilateral to the lesion with loss of pain and temperature sensation on the contralateral side, has also been reported in patients with IMSC. Tumours of the cervical or thoracic spine may lead to lower extremity spasticity. Urinary retention and incontinence are more common in lower cord tumours, although urinary symptoms may be late sequelae of any lesion. Faecal incontinence is much less common. It is important to note that all patients with signs of new or unexplained myelopathy such as spasticity, hyperreflexia, incoordination, or gait disturbance should have further imaging of the spine and appropriate neurological follow-up.

Differential diagnosis

The differential diagnosis of the most common presenting signs and symptoms include IMSC, intradural extramedullary spinal tumours, epidural spinal tumours, myelopathy due to degenerative disease, cord infarct, vascular lesions such as spinal arteriovenous malformations and dural arterio-venous fistulae, the inflammatory processes such as multiple sclerosis, transverse myelitis and sarcoid. Perhaps most challenging for the general practitioner is differentiating between degenerative spinal canal stenosis, a relatively common condition, and IMSC (or other spinal tumours), which are relatively rare. The medical history is often helpful, as patients with degenerative disease tend to have years of waxing and waning pain, frequently accompanied by radicular symptoms. Patients with lumbar stenosis often complain of postural back or radicular pain, worst in torso extension (i.e. ascending stairs) and less painful in torso flexion (i.e. pushing a shopping cart). Neurogenic claudication (radicular pain and paraesthesias or numbness with ambulation) due to lumbar spinal stenosis is characteristically relieved by several minutes of sitting, while the radicular pain due to IMSC is usually not precipitated by walking nor relieved by rest.

Imaging

T1- and T2-weighted MRI with and without gadolinium is the imaging modality of choice for suspected IMSC. MRI allows the clinician to narrow the broad differential diagnosis listed above, and interpretation by an experienced neuroradiologist is helpful. Ependymomas and astrocytomas have similar imaging characteristics and a definitive diagnosis is only made intraoperatively with a tissue sample. Thus, the role of MRI is not to distinguish between differ-

Table 1: Differential diagnosis of spinal cord dysfunction or clinical myelopathy with prevalence of the disease in the general population. Note: not all persons will manifest symptoms or require medical attention in some disease states.

Diagnosis	Prevalence of Disease
Cervicothoracic spondylosis	13%
B12 deficiency	1%
Normal pressure hydrocephalus	0.5%
Multiple sclerosis	0.14%
Syringomyelia	0.008%
ALS	0.002%
Extrinsic tumours of the spine	0.0003%
IMSCT	0.00001%
Spinal cord infarction	unknown

Table 2: Symptoms and signs associated with intramedullary spinal cord tumours.

Symptoms
Gait Imbalance
Upper or lower extremity weakness
Upper or lower extremity numbness
Urinary incontinence
Nocturnal back pain
Hand incoordination
Burning dysaesthesias
Sudden paraparesis or quadraparesis
Signs
Spasticity
Hyperreflexia
Upward Babinski sign
Objective bilateral weakness
Sensory level
Positive Hoffman's sign

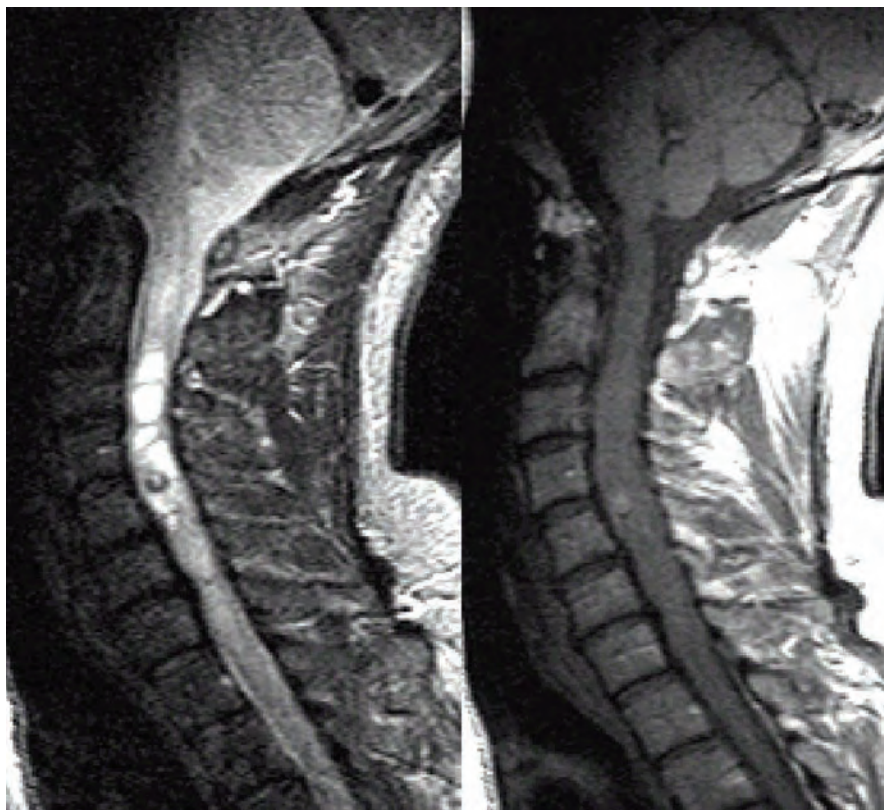


Figure 1. An ependymoma of the cervical spine on MRI T2 image (left) and T1 with contrast (right). Note the associated syrinx seen on T2, contrast enhancing mass on T1, and overall expansion of the cord.

ent IMSCT types, but to rule out lesions such as infarct, and auto-immune and inflammatory diseases which will not benefit from surgical intervention. Non-IMSCT lesions tend to have little or no cord enlargement or oedema, thus differentiating them from IMSCT. If the patient is relatively stable and the MRI is equivocal, repeat imaging after one month should show decreased oedema and mass effect in acute auto-immune lesions.⁴

Sequences in the sagittal and axial planes are most useful in pre-operative planning. Enhancement on T1-weighted gadolinium sequences is common, despite the low-grade

nature of most IMSCT. Associated cysts are also common with IMSCT, and may appear similar to tumour on T1 and T2-weighted images but can be differentiated from tumour by their lack of gadolinium enhancement.⁴ IMSCT at any level may be associated with a syrinx; these are especially common in IMSCT of the cervical spine. Once an IMSCT is demonstrated on MRI, prompt referral to a neurosurgeon is warranted. Patients in which MRI is contraindicated may benefit from CT myelography, although this modality is much less useful than MRI. Plain films do not have a significant role in the evaluation of suspected IMSCT.

Treatment

Referral to a neurosurgical specialist for treatment and management of intramedullary masses is very important. This is because, with very few exceptions, all newly diagnosed intramedullary masses require total or sub-total resection or biopsy for tissue diagnosis. Additionally, the surgeon may be able to provide adequate decompression of the spinal cord to avert progression of neurological compromise. It is also possible that a complete surgical resection, if possible, may result in the definitive treatment of many of the tumours of the spinal cord known to be pathologically benign.

Surgery for the resection of intramedullary tumours involves the exposure and decompression of the spinal cord, usually through a multilevel laminectomy followed by a midline dorsal dural opening. Localisation of the laminectomy can be performed using spinal needles and spinal imaging (image intensifier) in the operating theatre. Opening of the spinal cord in order to access the spinal tumour is commonly done through a longitudinal, midline incision. This is done to avoid transection of the white matter tracts of the dorsal columns and avoid disturbing motor and cerebellar long tracts found laterally and ventrally in the spinal cord. Intraoperative ultrasound is commonly employed prior to myelotomy to accurately localise the spinal cord lesion and minimise the extent of the incision.⁵

Modern surgical techniques and adjuncts employed during surgery have led to improved neurological outcomes and survival from intramedullary tumours. The employment of the operative microscope as well as ultrasonic aspiration devices during the exposure and resection of the tumour



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neurotoxin type A or to any of the excipients, generalised disorders of muscle activity (e.g. myasthenia gravis, Lambert-Eaton syndrome) and presence of infection at the proposed injection site. Dysphagia has also been reported following injection to sites other than the cervical musculature. **Warnings and Precautions:** Adrenaline and other medical aids for treating anaphylaxis should be available. Xeomin® contains albumin a derivative of human blood. Prior to administration the physician must make himself familiar with the patients anatomy and any changes due to surgical procedures. Side effects related to spread of botulinum toxin have resulted in death which in some cases was associated with dysphagia, pneumonia and /or significant debility. Patients with a history of dysphagia and aspiration should be treated with extreme caution. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise. Xeomin® should be used with caution if bleeding disorders occur, in patients receiving anticoagulant therapy, patients suffering from amyotrophic lateral sclerosis or other diseases which result in peripheral neuromuscular dysfunction and in targeted muscles which display pronounced weakness or atrophy. Reduced blinking following injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defects and corneal ulceration. Careful testing of corneal sensation should be performed in patients with previous eye operations. Xeomin® as a treatment for focal spasticity has been studied in association with usual standard care regimens, and is not intended as a replacement for these treatment modalities. Xeomin® is not likely to be effective in improving range of motion at a joint

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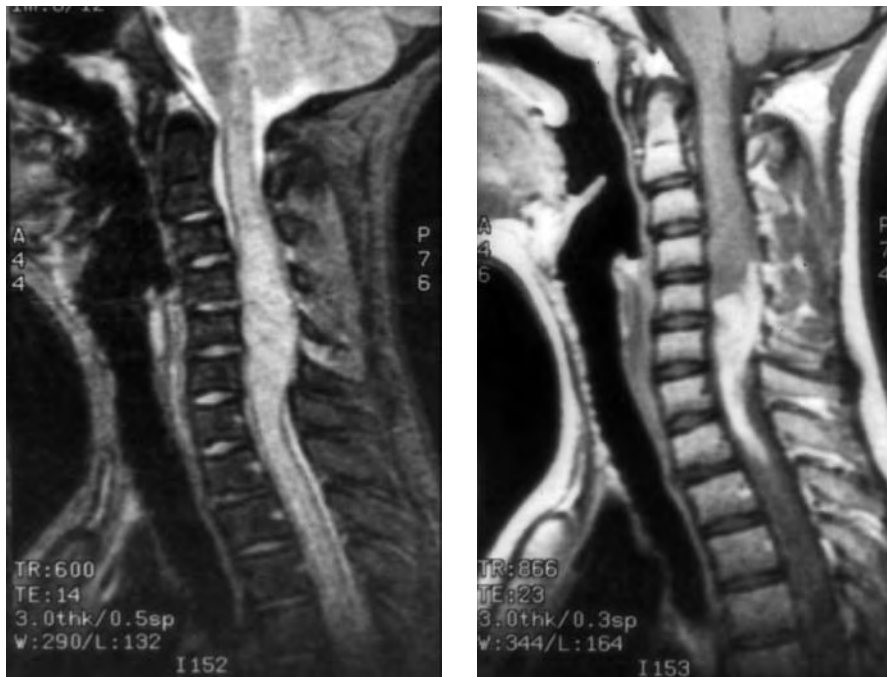


Figure 2. A fibrillary astrocytoma of the cervical spine on T2 (left) and T1 with contrast (right). Note the indistinct cord oedema, expansion and partial contrast enhancement.

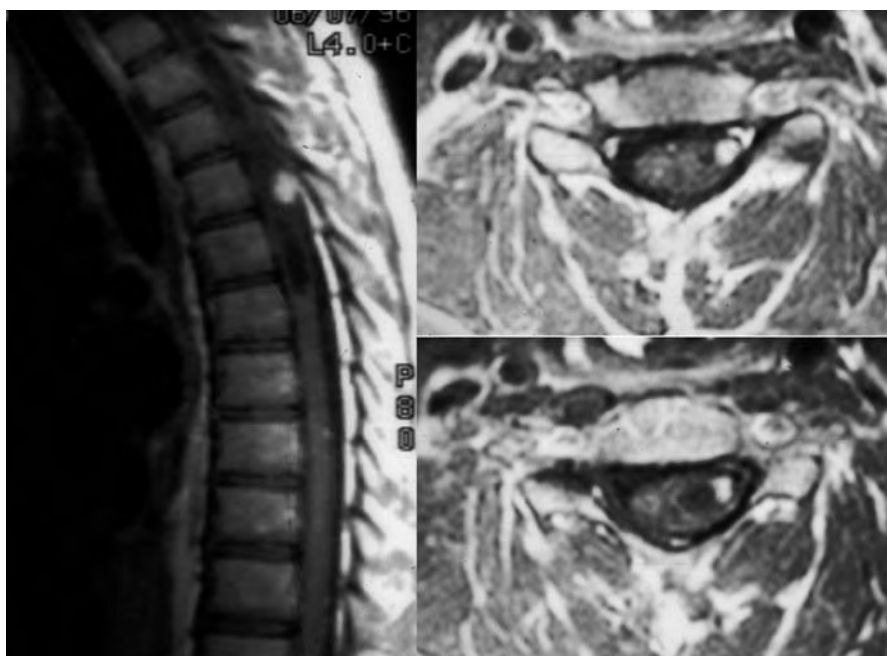


Figure 3. A haemangioblastoma of the thoracic spine on T1 with contrast in sagittal (left) and axial sections (right). Note the enhancing tumour nodule with associated cyst.

have resulted in an overall neurological morbidity rate of 34% for this type of surgery in current cohorts with most patients improving within 1 month of surgery.⁶ Active neuromonitoring during the surgical case has also been a technical advance employed during resection. Combined use of somatosensory evoked potentials (SSEPs) and motor evoked potentials (MEPs) has been shown to reduce surgical morbidity by providing feedback to the surgeon when resection manoeuvres or effects of anaesthesia during the surgery are putting the spinal cord viability at risk.⁷

Currently, most neurosurgeons tailor their resections depending on visualised anatomic planes, neuromonitoring changes, and results of intraoperative histology. The presence of a visualised plane between the tumour tissue and the tissue of the spinal cord greatly improves overall resection, neurological outcome, and overall survival.⁶ The presence of a syrinx that is continuous with the tumour plane also improves overall neurological outcome.^{6,8} The loss of greater than 50% of MEP signals during the case is sensitive for the appearance of significant motor deficits post-operatively.^{7,9} Another neuromonitoring adjuvant, D-wave monitoring, is often employed during surgery and has been shown to correlate with neurological outcome after surgery when used to tailor resections.⁷

Non-surgical treatments for intramedullary tumours are largely relegated to patients with diffuse inoperable tumours, those with known incomplete resection, recurrent tumours, or those who could not tolerate surgery or have such a poor prognosis from their primary disease process that surgery would be an ineffective intervention. Historically, external beam radiation has been employed as a treatment for these patients. There exists favourable evidence that radiation likely increases the progression free survival of patients with low grade astrocytomas and ependymomas after partial resection.^{10,11} However, evidence is limited on the overall effectiveness of radiation for patients with new progression or malignant pathologies. Although there is an expectation that chemotherapeutic agents may be effective in the treatment of malignant astrocytomas of the spinal cord, there is no evidence that they improve overall survival.

Table 3: Radiographic differential diagnosis of an intramedullary lesion.

Diagnosis/Characteristics	Cord Expansion	Contrast enhancement	Well circumscribed	Heterogeneous Signal	Cord oedema
Ependymoma	+	+	+	-	-/+
Astrocytoma	+	+	-/+	-	-/+
Haemangioblastoma	+	+	+	-	+
Cavernoma	+	+	+	+	-/+
Multiple sclerosis	-/+	-/+	-/+	-	+
Transverse myelitis	-/+	-/+	-	-	+
Spinal cord infarct	-/+	-	+	-	+
AV fistula	-	-	-	-	+

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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 which should be increased to 800 mg once daily after one or two weeks. The dose may be increased to 1200 mg once daily. Withdraw gradually to minimise the potential of increased seizure frequency. **Elderly patients:** Caution (See SmPC). **Children and adolescents <18 years of age:** Not recommended. **Patients with renal impairment:** The dose should be adjusted according to creatinine clearance (CL_{CR}) (see SmPC). Not recommended in severe impairment. **Patients with hepatic impairment:** No dose adjustment in mild to moderate impairment. Not recommended in severe impairment. **Contra-Indications:** Hypersensitivity to the active substance, other carbamide 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. If women receiving Zebinix become pregnant or plan to become pregnant, the use of Zebinix should be carefully re-evaluated. Minimum effective doses should be given. Zebinix interacts with oral contraceptives. An alternative, effective and safe method of contraception should be used 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:** Zebinix has been associated with some CNS reactions such as dizziness and somnolence. Concomitant use with oxcarbazepine is not recommended. Rash has been reported. If signs or symptoms of hypersensitivity develop, Zebinix must be discontinued. Presence of HLA-B*1502 allele in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing Stevens-Johnson syndrome (SJS) when treated with carbamazepine. Screening for this allele should be undertaken in such individuals. Serum sodium levels should be examined before and during treatment in patients with pre-existing renal disease or in patients concomitantly treated with medicinal products which may lead to hyponatraemia. Serum sodium levels should be determined if clinical signs of hyponatraemia occur. If clinically relevant hyponatraemia develops, discontinue Zebinix. Use in primary generalised seizures is not recommended. 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. Appropriate treatment should be considered. **Drug interactions:** In vitro eslicarbazepine is a weak inducer of CYP3A4 and UDP-glucuronyl transferases. In vivo eslicarbazepine may have an inducing effect on the metabolism of medicinal products which are mainly eliminated by metabolism through CYP3A4 or conjugation through the UDP-glucuronyl transferases. When initiating or discontinuing treatment with Zebinix or changing the dose, it may take 2 to 3 weeks to reach the new level of enzyme activity. Time delays must be taken into account when Zebinix is being used just prior to or in combination with other medicines that require dose adjustment when co-administered with Zebinix. Eslicarbazepine has inhibiting properties with respect to CYP2C19. Interactions can arise when co-administering high doses of eslicarbazepine acetate with medicinal products that are mainly metabolised by CYP2C19. Phenytoin: concomitant use may require an increase of Zebinix dose and a decrease of phenytoin dose. Lamotrigine and topiramate: no dose adjustments are required. However, clinical review should be considered. Valproate and levetiracetam: Concomitant administration with valproate or levetiracetam appeared not to affect the exposure to eslicarbazepine but has not been verified by conventional interaction studies. Carbamazepine: Concomitant treatment with carbamazepine increased the risk of the diplopia, abnormal coordination and dizziness. An increase in other adverse reactions caused by co-administration of carbamazepine and eslicarbazepine acetate cannot be excluded. Carbamazepine increases eslicarbazepine clearance. Zebinix slightly increases the clearance of carbamazepine. Oral contraceptives: Interacts with the oral contraceptive. Women of childbearing potential must use adequate contraception during treatment with Zebinix, and up to the end of the current menstruation cycle after the treatment has been discontinued. Warfarin: Zebinix has been shown to decrease exposure to S-warfarin. There are 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. 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. Uncommon (≥1/1,000 to <1/100): anaemia, hypersensitivity, hypothyroidism, increased appetite, decreased appetite, hyponatraemia, electrolyte imbalance, cachexia, dehydration, obesity, insomnia, apathy, depression, nervousness, agitation, attention deficit/hyperactivity disorder, confusional state, mood swings, crying, psychomotor retardation, stress, psychotic disorder, memory impairment, balance disorder, amnesia, hypersomnia, sedation,

aphasia, dysaesthesia, dystonia, lethargy, parosmia, autonomic nervous system imbalance, cerebellar ataxia, cerebellar syndrome, grand mal convulsion, neuropathy peripheral, sleep phase rhythm disturbance, nystagmus, speech disorder, dysarthria, hypoaesthesia, ageusia, burning sensation, vision disturbance, oscillopsia, binocular eye movement disorder, ocular hyperaemia, saccadic eye movement, eye pain, ear pain, hypoacusis, tinnitus, palpitations, bradycardia, sinus bradycardia, hypertension, hypotension, orthostatic hypotension, dysphonia, epistaxis, dyspepsia, gastritis, abdominal pain, dry mouth, abdominal discomfort, abdominal distension, duodenitis, epigastric discomfort, gingival hyperplasia, gingivitis, irritable bowel syndrome, melaena,odynophagia, stomach discomfort, stomatitis, toothache, liver disorder, alopecia, dry skin, hyperhidrosis, erythema, nail disorder, skin disorder, myalgia, back pain, neck pain, nocturia, menstruation irregular, asthenia, malaise, chills, oedema peripheral, adverse drug reaction, peripheral coldness, blood pressure decreased, weight decreased, blood pressure diastolic decreased, blood pressure increased, blood pressure systolic decreased, blood sodium decreased, haematocrit decreased, haemoglobin decreased, heart rate increased, transaminases increased, triglycerides increased, triiodothyronine (T3) free decreased, thyroxine (T4) free decreased, drug toxicity, fall, joint injury, poisoning, skin injury. For rare side effects see SmPC. When treated concomitantly with carbamazepine, diplopia, abnormal coordination and dizziness are reported more frequently. Use of Zebinix is associated with an increase in the PR interval. Adverse reactions associated with PR interval prolongation may occur. No second or higher degree AV block was seen in Zebinix treated patients. Rare adverse reactions such as bone marrow depression, anaphylactic reactions, severe cutaneous reactions (e.g. Stevens-Johnson Syndrome), systemic lupus erythematosus or serious cardiac arrhythmias did not occur during clinical studies. However, they have been reported with oxcarbazepine and their occurrence during treatment with Zebinix cannot be excluded. **Legal Category:** POM. **Basic UK NHS cost:** Zebinix 800 mg: pack of 30 £154.20. **Marketing authorisation numbers:** EU/1/09/514/012-020. **Marketing authorisation holder:** Bial-Portela & C^o, 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:** July 2009.

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Outcomes

Neurological outcome from surgery is highly correlated with preoperative deficits. Patients with fewer preoperative symptoms are more likely to have good postoperative neurological outcomes.^{6,12} Factors predictive of worse postoperative neurological outcomes include thoracic location, advanced age and the presence of urinary symptoms.^{6,12} Up to one third of all patients have a significant, acute deterioration in neurological function after surgery, with nearly half returning to their preoperative status within a month of surgery.⁶

The most important predictor for tumour recurrence and survival is pathology. Malignant astrocytomas of the spinal cord have an overall recurrence rate of greater than 95%, with outcome unaffected by extent of surgery.^{13,14} Complete resection of ependymomas and haemangioblastomas, however, carry a very favourable outcome, with recurrence rates less than 10% over a ten year period.^{15,16} Extent of resection does not necessarily

correlate with progression-free survival in low grade astrocytomas, however, a growing body of evidence suggests that an increased extent of resection is beneficial to overall neurological outcome in this group of patients.¹⁷ Surgeons are commonly less aggressive with resections if intraoperative histology during the case indicates a diagnosis of astrocytoma and are conversely more aggressive for ependymomas and hemangioblastomas.

Given the greatly improved survival of many of the intramedullary tumour patients, the addition of spinal fusion techniques with internal rod or plate fixation has also been investigated to prevent long-term spinal deformity from the surgery. The presence of preoperative scoliosis, syrinx, long-standing neurological deficit, or cervicothoracic junction location has been correlated with the development of postoperative spinal deformities that can be functionally limiting.¹⁸ Thus the use of osteoplastic laminoplasty or preemptive internal spinal fixation

with fusion has been favourably applied with improved prevention of postoperative spinal deformities in children.¹⁹

Currently, outcome-modifying treatments for malignant astrocytomas of the spinal cord do not exist. Patients are empirically treated with postoperative radiation with or without chemotherapy with universally poor results. Aggressive resection, including cordotomy, has not yielded any benefit to outcome and most die of complications of paralysis or progression of disease.

Conclusion

Intramedullary spinal cord tumours are rare but important clinical entities that now can be easily diagnosed and often effectively treated. Importance should be given to recognising clinical and radiographic findings that are associated with these tumours. Surgical advances have now made many of these tumours treatable with acceptable long-term neurological outcomes. ♦

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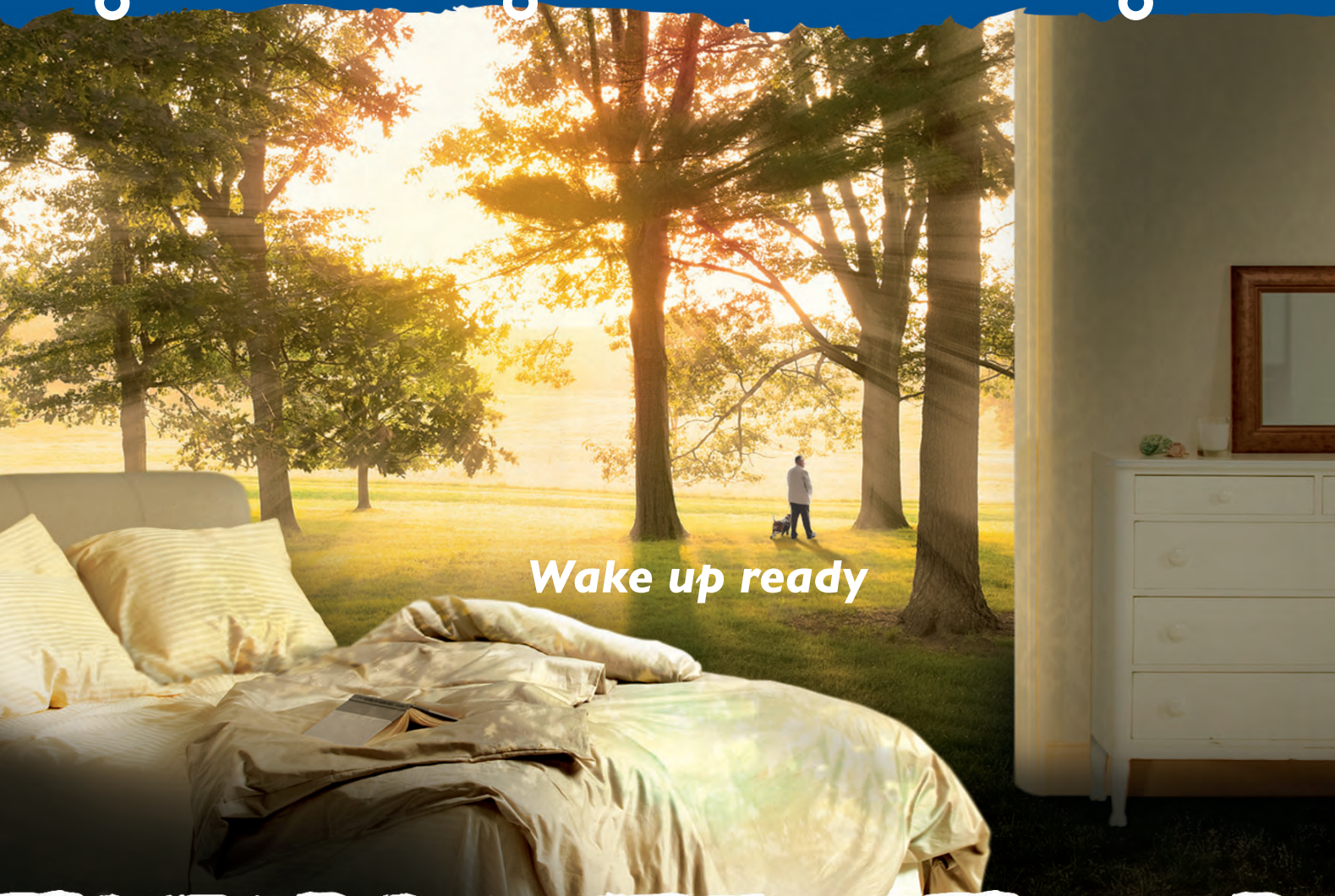
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Parkinson's Disease: personal experience

I first developed some left leg discomfort. I thought I had nerve root pressure, probably L5, just before we were about to go on holiday to Zimbabwe, in 1991. This settled and I had an enjoyable holiday.

In 1995 I decided that I was too heavy and needed to lose weight. I reduced my calorie intake largely by cutting fat and carbohydrate. I also started jogging and competed at a low level in some 10K races. I lost 2 stones in 2 years.

When I was running, one of my daughters commented that when I ran I moved my left arm much less than my right. Pursuing this I found that my shoe wear was asymmetrical and that I scuffed the front of my left shoe.

By 2000 I had a slight limp when I walked, and had cold sensitivity affecting my hands and feet. I also had some hypertension, treated with beta blockers, and some haematuria with urinary frequency and urgency, and Dupuytron's contracture, worse on the left side. The motor function of my left side gradually deteriorated and I became increasingly fatigued.

In 2003 I was working as Clinical Director and Consultant Orthopaedic and Trauma Surgeon and I went to see a consultant neurologist whom I knew, who agreed with my diagnosis of Parkinson's, and the diagnosis was supported by the results of SPECT and MRI scans.

Comment

People always ask "When did your Parkinson's begin?". It is extremely hard to be precise. The list of possible symptoms is so extensive. Was my leg pain in 1991 related to my PD?

The old physicians' observations were very shrewd. I wonder how many orthopaedic surgeons presently consider PD as a possible cause of shoulder pain, or of loss of manual dexterity as exemplified by diminishing guitar playing ability? I for one certainly did not.

Initial reactions

My initial reactions were probably fairly typical of most professionals:

1. "Why me?"

This is not helpful! Faith and religion may offer comfort, but not therapeutic opportunities.

2. Denial

I think there are two aspects. Firstly, denial that the diagnosis is correct.

Comment

This is where the SPECT and PET scans are so helpful in providing strong support for the clinical diagnosis. I think we have

become so used to the editors of medical journals not accepting clinical observations as evidence that we need a body of investigations to support the clinical diagnosis which is correctly made. Whilst it may be argued that PET and SPECT scans are not by themselves diagnostic of PD, I think they are very persuasive evidence, and that one or other should be done when the patient is a clinician.

The second aspect of denial is denial of the prognosis and denial of the fact that at present there is no known treatment which prevents the continuing loss of brain cells in the basal ganglia and elsewhere. I initially trawled the literature extensively. In my queries I was extra-ordinarily well served by my general practitioner, who patiently discussed with me papers from conference proceedings whose titles had been written mainly with a view to ensuring continued research funding.

Most apparently hopeful leads turned out to be isolated reports about work on laboratory animals. Most of the work on stem cells emphasised the vast number of factors which had to be evaluated before they could be used reliably in clinical disease. Even an orthopaedic surgeon with a strongly empirical approach could see no work that seemed terribly hopeful in the short to medium term.

Initial treatment

My initial treatment was started at the local neurology unit and rapidly handed over to the Movement Disorder Clinic.

I started ropinirole, which certainly helped my motor function, but caused me to be very nauseated, a symptom which was reduced to squeamishness with domperidone. I have returned to ropinirole after trying various alternative dopamine agonists, and am grateful for the slow release Requip XL, with which I have no problem with nausea.

One of my orthopaedic colleagues suggested I would limp less if I used an AFO (ankle splint), and I found its intermittent use helpful for prolonged standing and walking.

Work

After a couple of months I returned to work, where I was met by the Unit Administrator who said he had discussed my return with my successor as Clinical Director and they had decided that I could do outpatient and clinical work but not operate. I could understand this and did not contest their decision in any way and pursued early retirement through the Personnel Department. I was granted early retirement when on annual leave. I said I would prefer to work the last

four weeks before retirement in order to wind up my clinical work. The irony of the whole situation at this time is perhaps best summarised by the comment from Personnel that I could do so if I wished, it did not matter to them.

Continued medical treatment

I was enrolled in a clinical trial of Sanofi SR567667B which continued for about two years. I had PET scans at the beginning and the end. I do not recall any discussion of the scans, but the trial ended and I was informed that the drug was ineffective in preventing progression of the disease.

Comment

I sought involvement in this trial and certainly found the resulting increased contact with the local nurse specialist very helpful. I think all medically qualified patients should participate in trials whenever possible.

The route to surgery

At the end of the trial my tremor, walking, and urinary frequency had all become worse on the maximum dose of ropinirole, and I started Sinemet: and then propranolol which I stopped because it made me too sleepy. At this time I was unconvinced that selegiline made any difference.

Drug therapy was getting rather cumbersome by orthopaedic standards, and I came to appreciate my neurologist's approach and opinion that one change a fortnight was enough.

I had been reading about deep brain stimulation for Parkinson's disease. It seemed to me that the results at that time indicated that the best results showed sustained improvement for about five years. By now I had a great respect for my neurologist's opinion, so I asked him the question "If he were me, would he consider DBS?". His reply was "Yes, he would, let's get a surgical opinion."

I asked him if it were not a little scary, having someone poke around in his mid-brain for several hours to which he replied "Not nearly as scary as having a hip replacement"...so off down the road towards surgery I went.

Surgical treatment

The local neurosurgical unit had at that time done only a handful of cases of DBS for Parkinson's. At this point a number of things came together. Firstly, I had been involved in some research follow-up at my old university. Secondly, a friend of my daughters' had worked for Medtronic, manufacturers of the commonest stimulators. The advice from both sources was to see the same surgeon and I ended up under his care as a participant in the PD Surg trial.

I was admitted for assessment to the neurosurgical unit in October, three years after initial diagnosis. Fortunately most of the assessment was done by the excellent specialist nurses, as the neurologist was on annual leave. My luck held and I was allocated to the early surgery group.

The unit was transferring to a new unit and after several cancelled dates I was admitted for surgery in April 2007.

All the surgery was done on the same day. I have three memories of it. The first is being asked to move my hands by the surgeon, the second is being transported around many corners for a scan, and the third is having a sore throat after the anaesthetic.

After surgery the next morning was incredible. For the first time for several years I felt as if I did not have PD. I was warned this effect was temporary. A few days' later the first settings of the stimulator were made. About five days post-op I went home.

About 10 days after surgery my scalp wounds leaked suddenly and extensively over the pillows.

This occurred again the next night. I was concerned about infection. I phoned the unit where my surgery had been done and was advised to come to the unit forthwith. I got there at 10.00pm on a Sunday night. The Registrar had changed and suggested a couple of sutures and a guest house. The ward

staff had informed the surgeon I had not turned up. The bacteriologist said there was no point in plating a wound swab. Not a good day.

I was allowed to stay after the staff nurse argued with the registrar that there was a lot of discharge from my wound, and did he know that I had just retired as an orthopaedic consultant.

Comment

Over the period of my investigation and treatment I became firmly of the opinion that you should tell everyone that you are/were medically qualified. I think it is unfair on the staff not to, and it explains some of your attitudes and opinions. It also helps to get the systems to work on your behalf.

My wound settled after a course of i/v antibiotics, and has remained healed since that time. The bacteriologists remained unhappy. I have some sympathy with their position, but from a personal point of view, I would rather have a course of possibly inappropriate antibiotics than a cerebral abscess with a cultured organism.

Postsurgical course

My tremor has been virtually eliminated since the operation and this fact alone has enabled me to continue doing assessments and committee work, and to continue to travel and

drive. In summary, my quality of life has been enhanced for at least three years by the surgery. In addition, my medication has been reduced to about half its pre-surgery level.

What has not been affected by the surgery are the autonomic symptoms, like cold sensitivity, and urinary frequency.

I did not suffer any loss of balance or deterioration of speech after my operation.

My overall motor function has been maintained by skilled adjustment of the stimulator settings every six months or so by the PD nurse specialist at the neurosurgical unit, who has been looking after me. I no longer walk for pleasure, but I remain independent, and my upper limb motor function is adequate for using a keyboard, writing, and using hand tools for car maintenance and DIY.

Comment

I am extremely grateful to the medical professionals who enabled me to undergo successful DBS. In a progressive disorder it has enabled me to improve my motor function and so continue to do the things I want or need to do.

Also important for someone like myself, I now feel that I have tried every line of treatment open to me.

Lastly, I must thank my wife and daughters for their tolerance, encouragement and support all along the way. ♦

NEW LOOK AND VISION FOR PARKINSON'S UK

Earlier this year, the Parkinson's Disease Society changed its name to Parkinson's UK. The new name and fresh new identity was developed alongside a bold strategy, with access to specialist Parkinson's nurses and high quality care a top priority.

The charity's vision for the future – to find a cure, and improve life for everyone affected by Parkinson's – has been shaped by the opinions and views of people affected by Parkinson's. To help achieve these ambitions, the charity has set an ambitious fundraising target of more than £110m over the next five years.

For the last forty years, Parkinson's UK has been working to improve life for everyone affected by Parkinson's. The charity has invested more than \$45m in groundbreaking research, secured 289 specialist Parkinson's nurses, and provided vital information and support to thousands of people across the UK.

Campaigns such as Fair Care for Parkinson's have strengthened the voice of people affected by Parkinson's. But there is still more work to be done to find a cure, and still many people affected by Parkinson's in the UK who are not getting access to high quality care, support and information.

Low public awareness and a lack of knowledge about Parkinson's amongst many GPs and health professionals, as well as the general public, were also key factor in the charity's decision to re-brand.

Creative communications consultancy The Team, were tasked with developing the new brand. They came up with a bold, inspirational identity that puts people with Parkinson's at the heart of the new look. Photography of real people affected by Parkinson's (rather than models), feature heavily. They display personal messages of hope and determination, designed to reach out to new audiences, as well as inspiring existing supporters.

Central to Parkinson's UK's vision is continued campaigning for access to nurse specialists, and improved quality of care is a key area for future plans.

Parkinson's UK is demanding 100 per cent coverage of Parkinson's nurses in the UK by 2015. To achieve this, the charity will continue its efforts to influence local service planners and commissioners to provide comprehensive services for people with Parkinson's, and continue to campaign hard to make sure that national standards of Parkinson's care are implemented across the UK.

Lesley Carter, Head of Influence and Service Development at Parkinson's UK, explains: "Parkinson's nurses are critical to the care of people living with the condition, but the current postcode lottery of care means that many people with Parkinson's are missing out.

Parkinson's nurses help people manage their medication, offer advice and information about living with Parkinson's, and give emotional support to both the patient and their carer."

Another top priority is promoting training and information resources to all health professionals, and encouraging more effective information sharing between local services to drive up standards and encourage best practice.

It is hoped that the overall result will be a greater understanding of Parkinson's amongst health and social care professionals, changed attitudes, and the delivery of better care for all people affected by Parkinson's.



Parkinsons.org.uk

SWEDD for the General Neurologist



Nin Bajaj

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He was appointed Consultant Neurologist at Nottingham University Hospitals in 2002, specialising in movement disorder. He was the Lead Clinician for the Hospital Doctor Parkinson's Disease team of the year in 2007. Dr Bajaj is currently Clinical Director of the National Parkinson Foundation Centre of Excellence in PD between Derby Hospitals NHS Foundation trust and the University of Nottingham.

His ongoing research interests are in SWEDD, and the application of high field MRI and proteomics in the diagnosis of movement disorders and allied neurodegenerative conditions.

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A pleasant spring morning in a London Square was the setting of the first ever SWEDD-UK meeting. The event was made possible with generous support from the Dementias and Neurodegenerative diseases network (DeNDRoN).

Many of you will be forgiven for never having heard of SWEDD. This article, summarising the proceedings of the meeting, and detailing the aims of the UK consensus group, should tell you all you need to know. For those of you who want to know more, there has been a detailed recent review.¹

What is a SWEDD and why should I care?

Scans without evidence for dopaminergic deficit (SWEDD) is the term originally coined to describe a group of patients that puzzled the movement disorder establishment. At the time this term was coming into use, a number of studies comparing post-mortem diagnosis of Parkinson's disease with the clinical diagnosis in life had already confirmed our widely held belief that our clinical skills were excellent and indeed, over the course of studies held a decade apart, were improving.^{2,3}

A number of clinical trials held against this backdrop of high confidence in our clinical diagnostic skills, were attempting to use nuclear medical imaging techniques [18F-dopa PET or β -carbomethoxy-3 β -(4-iodophenyl)nortropine single photon emission computed tomography (β -CIT SPECT)] as a biomarker to assess disease progression.^{4,6} The use of these imaging techniques as disease biomarkers in PD has since come under considerable criticism, but the role of these techniques in distinguishing PD from benign tremor disorders has been endorsed, inter alia, by NICE.⁷ These trials all sought to recruit patients with PD, either relatively early or later in the disease course, referred from movement disorder specialists in the USA, UK and Europe. The trials organisers were surprised to note a consistently high normal functional imaging scan ranging from 4% for later disease course trials to 15% for early disease course trials. Initially a number of explanations were considered to explain this anomaly, including poor diagnostic accuracy of the scans and poor diagnostic accuracy of the clinicians. Subsequent long term follow-up of these patients however was notable for no initially normal scans becoming abnormal with time and for blinded clinician review of the video-tape of patients confirming the initial clinical presumption that these patients looked like they had PD.^{8,9} Furthermore, more recent olfaction studies have shown near normal olfaction scores in SWEDDs patients whereas PD patients are notable for impaired olfactory function.¹⁰ A number of studies looking at diagnostic accuracy of SPECT scanning have also confirmed a high clinical concordance between the scan findings and clinical opinion with sensitivity (93%) and specificity (95%) of

detection of the pre-synaptic dopaminergic deficit typical of PD.¹¹

Although the term SWEDD is relatively recent in usage and has emerged from the clinical trial literature, clinicians have always been aware of PD mimics where the parkinsonism is not of a pre-synaptic, dopaminergic deficiency origin. Thus the term SWEDD can really be levelled at any patient that looks as if they have PD but where subsequent functional imaging assessments do not confirm this. SWEDD phenotypes will therefore vary in much the same way as PD phenotypes do. There are two broad PD phenotypes, akinetic-rigid (also known as postural instability gait disorder variant-PIGD) and tremor dominant (also known as tremulous PD).¹² In the same way, SWEDDs patients can be subdivided into tremor dominant and non-tremor dominant (or tremor absent) subtypes. These subtypes are summarised in Tables 1 and 2.

Most causes of SWEDDs are sufficiently uncommon to be rare causes of clinical mis-diagnosis outside the most specialised of units. It is the common causes of SWEDDs that the clinical readers of this article need to be most wary of. Some common causes of SWEDDs give other clues- vascular parkinsonism is relatively common but most cases of vascular parkinsonism do not look like typical PD. The classic vascular PD case may have step-wise progression (reviewed in 13), be predominately lower body, show no response (or poor response at standard doses) to levo-dopa and have an MRI brain showing extensive leukoariopathy especially in the basal ganglia. Tardive cases are common but are usually referred from concerned psychiatrists and are obviously on neuroleptic drugs – similarly a drug history of valproate exposure requires little detective work to come up with this as a diagnostic consideration.

The commonest cause of SWEDD that would trouble the general neurologist and even the movement disorder expert are those harbouring a tremulous but benign condition where parkinsonian features are a common occurrence. This is where adult onset dystonic tremor, indeterminate tremor and perhaps essential tremor (ET) need to be considered. Whether ET should be considered at all as a cause of SWEDD is controversial, and indeed was one of the topics debated by our experts in the SWEDD-UK meeting (see proceedings following), but there is sufficient reference to this in the current literature that for the moment, we have retained it. Under the 1998 Movement Disorder Consensus Statement on Essential Tremor,¹⁴ other neurological features e.g. dystonia, are exclusion criteria for definite ET and thus ET masquerading as SWEDD should not occur, but given the prevalence of ET, dual pathology with parkinsonism secondary to the ageing process, cerebrovascular disease or concomitant medications, is likely to occur.

Table 1. Causes of non-tremor dominant SWEDD phenotype

Non-Tremor Dominant SWEDD	References
Tardive (neuroleptic) induced	18
Vascular Parkinsonism	13, 19
Brain Neoplasm	20, 21
Carbon Disulphide	22
Manganism	23, 24
Huntington's disease	25

As a proof of principle that tremulous SWEDDs patients are the really troublesome diagnostic conundrums and to emphasise clinical diagnostic error rate, we recently assessed the ability of two of the UK's leading movement disorder experts to clinically distinguish a series of tremulous SWEDDs from TDPD on blinded videotape analysis. Many will argue that videotape analysis is not the same as seeing a patient in clinic, but we already know from the SWEDD literature that even seeing patients in person, in the clinic setting, can give a false positive error rate of up to 15% for PD. Furthermore, videotape diagnosis of movement disorder is something that we experts indulge in at numerous video Olympics sessions held around the world and there is a literature validating the diagnostic accuracy of video consultation.¹⁵

So how did our experts do? Well, you can soon read for yourself but with a specificity for the diagnosis of PD ranging from 79-85%, and sensitivity of 72-93%, their performance was respectable but not as good as either of them

Table 2. Causes of tremor dominant SWEDD phenotype

Tremor-Dominant SWEDD	References
Adult onset Dystonic Tremor	17
Essential Tremor	26
Psychogenic Tremor	27
Fragile X premutation	28
Valproate Toxicity	29

would have liked.¹⁶ To spare the blushes of our experts, the entire audience at the British and Irish Movement Disorder Meeting in London 2009, and the assembled panel at SWEDD-UK were subjected to similar blinded analysis of tremulous parkinsonian patients. Needless to say, the diagnostic accuracy of both audiences was sub-optimal and really serves to highlight the following point: tremulous SWEDD cases are not uncommon, you will all come across them in your clinics and even the very best among you will make diagnostic mistakes. If you have diagnostic doubts, you should consider ordering an FP-CIT or PET scan for diagnostic clarification.

Making SWEDD obsolete

Having taken the time to publicise the term SWEDD for the general neurological community, one of the aims of the SWEDD-UK meeting was how to eliminate SWEDD from our practices. After all, there are clinical clues to spotting some causes of SWEDD and we have detailed these already, such as the lower body phenotype of

most vascular PD cases and the very symmetrical parkinsonian appearance of tardive PD cases.

Are there clinical clues or "tells" that would make us consider an alternative diagnosis and save us from making a false positive diagnostic error of PD? This consideration was the subject of a paper from Schneider and colleagues¹⁷ noting the frequency of dystonic features in a cohort of SWEDDs patients which would allow their re-classification as adult onset dystonic tremor. Although this paper was a real landmark in the understanding of tremulous SWEDD, it is unlikely to be the end of this story. One finding that emerged strongly from the mis-diagnosis between TDPD and tremulous SWEDD by our two movement disorder experts¹⁶ was the frequency of dystonic features in drug naïve, adult onset TDPD, which markedly reduced the usefulness of identifying dystonia as the discriminating feature between these two conditions. Furthermore, discussions following on from the publication of the original paper,¹⁶ have highlighted that one man's dystonia may not be another's, and that subtle head tilt and thumb hyperextension as hints to dystonia may lead to over-interpretation of the signs. Still, the identification of dystonic features is useful and would certainly save the more typical dystonic tremor patient from being mis-diagnosed as TDPD. Whether the lessons we have learnt from functional imaging will inform our clinical practice to such a degree as to render these scans obsolete is another matter altogether. I rather feel that SPECT scanning for the uncertain parkinsonian patient is here to stay.

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SWEDD-UK Meeting Report

Friday, 30th April 2010

**Minutes compiled by K Peall*,
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Present:

Dr Nin Bajaj, Chair (Institute of Neuroscience, Nottingham University Hospitals) – (NB)

Dr Donald Grosset (Institute of Neurological Sciences, Glasgow) – (DG)

Dr Huw Morris (MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University; Department of Psychological Medicine and Neurology, Cardiff University and University Hospital of Wales, Cardiff) – (HM)

Dr Kathryn Peall (MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University; Department of Psychological Medicine and Neurology, Cardiff University and University Hospital of Wales, Cardiff) – (KP)

Prof Niall Quinn, (UCL Institute of Neurology) – (NQ)

Dr Peter Bain (Charing Cross Hospital) – (PB)

Prof Andrew Lees (UCL Institute of Neurology) – (AL)

Dr Mark Edwards (UCL Institute of Neurology) – (ME)

Dr Laura Silveira Moriyama (via conference link, UCL Institute of Neurology) – (LS)



SWEDD-UK team, left to right: Dr Peter Bain, Charing Cross; Dr Michael Edwards, UCL; Professor Niall Quinn, UCL; Dr Donald Grosset, Southern General, Glasgow; Dr Nin Bajaj, Nottingham University Hospital; Dr Kathryn Peall, Cardiff University; Professor Andrew Lees, UCL; Dr Huw Morris, Cardiff University.

The meeting was chaired by Nin Bajaj (Nottingham) who gave an overview of the aims of the SWEDD-UK group. The meeting was funded as a working party of the Dementia and Neurodegenerative Disease Research Network (DeNDRoN). The SWEDD-UK group is open to all UK researchers and clinicians working on the area of “scans without evidence of dopaminergic deficit” (SWEDD). The aims of this meeting were to come to a greater understanding of the type of patients that might be mistaken clinically for Parkinson's disease (PD), but have SWEDDs, and to discuss ideas for future network research studies on this group of patients.

Background

The acronym SWEDD, which stands for a “Scan Without Evidence of Dopaminergic Deficit” was first introduced¹ to describe patients who had been entered into therapeutic trials on the basis that they were thought to have Parkinson's disease (PD) by their neurologist, but were found to have normal presynaptic nigro-striatal dopaminergic imaging. This issue affected 4-15% of subjects scanned in several studies, amongst patients thought to have PD.^{2,3}

These patients with SWEDDs had no benefit from active medications in these drug trials and follow-up presynaptic dopaminergic system imaging demonstrated that the scans continued to be normal up to 4 years later, with negligible deterioration in clinical features, thus casting considerable doubt on the diagnosis of Parkinson's disease.¹ The issue then arose as to what are the correct diagnoses in these SWEDDs patients, given that they are unlikely to have Parkinson's disease.

Schneider et al. (2007)⁴ reported that dystonic tremor can masquerade as Parkinson's disease. This suggests that some SWEDDs patients in these clinical trials may have had a dystonic tremor syndrome rather than PD. Additional possible causes of likely SWEDD should also be considered. Furthermore, there are no published reports of the SWEDDs patients from the trials being re-examined clinically to re-assess the original diagnosis, although some of the original tapes have been reviewed.

For the purposes of clarity the SWEDD-UK group recommend that the term SWEDD is used to indi-

cate that the patient was entered into a therapeutic trial for Parkinson's disease but had normal presynaptic dopaminergic imaging. This was the original use of the term. We propose the term clinical SWEDD to indicate the broader usage of the term that has subsequently developed: namely the situation in a clinical practice scenario where a patient suspected to have Parkinson's disease and subsequently has normal presynaptic dopaminergic imaging.

Clearly, the nature of SWEDD is an evolving subject and further work is necessary to more fully understand the diagnoses and natural histories of these patients.

Presentations

1. Overview of SWEDD – Definition of term; Types of SWEDD; Frequency in Clinical Studies – Dr Donald Grosset (Institute of Neurological Sciences, Glasgow)

The term SWEDD was initially coined by John Seibyl to refer to a normal putaminal presynaptic dopaminergic scan in a patient clinically considered to have Parkinson's disease. Subsequent usage of the term SWEDD has broadened to describe any patient with a tremor and/or parkinsonism phenotype, in whom such imaging shows a normal result.

The Benamer et al study of 2000⁷ involved patients apparently fulfilling diagnostic criteria for idiopathic Parkinson's disease (IPD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), or essential tremor (ET). Patients were included from early to later disease stages. Among the 158 patients with a clinical diagnosis of degenerative parkinsonism, 4 (2.5%) were identified as having SWEDD.

Within this study, patients with a clinical diagnosis of early (hemi-) Parkinson's disease showed bilaterally abnormal FP-CIT SPECT scans in all but one case. This patient had a clinical diagnosis of PD and was on L-dopa therapy; later clinical observations allowed complete withdrawal of antiparkinson medication and he was re-classified as dystonic tremor.

The rates of SWEDDs in the clinical studies (ELL-DOPA, REAL-PET, CALM-PD, European FP-CIT)^{3,5} of patients diagnosed as having PD have varied from just over 2% of 103 cases (European FP-CIT study)⁵ to 14.7% of 142 cases (ELL-DOPA)³. The rate of SWEDD was high-

er when studies recruited patients with a shorter diagnosis duration.

Discussion

NQ: It would be interesting to know who has seen these patients' videos. How many were tremulous and how many non-tremulous? There has been no systematic review of the patients' clinical diagnoses, so it would be helpful to re-review these videos, ideally in a double-blinded video assessment.

PB: The whole diagnostic term SWEDD is dependent upon the reporting of a normal scan. Therefore this requires some standardisation as to what a normal scan constitutes. What type of scan is needed? Does the scan need to be visually or quantifiably normal? Should there be a requirement for two individuals to report the scan? If so, should they be blinded? And does there need to be a consensus between the two for the reporting of an abnormal/normal scan?

2. Are many SWEDDs adult onset dystonic tremor patients? – Professor Niall Quinn, UCL Institute of Neurology, London

The purpose of scans looking for dopaminergic deficit is to reveal, when it is not clinically obvious, whether an individual has a lesion in their nigrostriatal tract. Theoretically almost the entire population potentially have SWEDDs, but only become a subject with a SWEDD when a presynaptic dopaminergic scan is performed and deemed to be normal.

The entry of patients into the SWEDDs arena can occur from varying backgrounds and amongst these are patients with tremor syndromes in whom there is uncertainty whether they have PD instead of, or in addition to, essential tremor (ET) or dystonic tremor (DT). In the Movement Disorder Society Consensus Statement (1998)⁹ dystonia is an exclusion criterion in the diagnosis of ET. However, Jankovic et al (1991)⁹ had earlier reported dystonia in 47% of his clinic population with a diagnosis of 'ET' (27% spasmodic torticollis, 7% blepharospasm, 14% writer's cramp, 4% segmental dystonia) and today many patients with DT are misdiagnosed with ET.¹⁰

Adult onset dystonic tremor (AODT) is also sometimes mistaken for PD. The original paper on AODT included 10 patients.⁶ Clinical features included asymmetric resting arm tremor, including thumb tremor, reduced arm swing, hypomimia, jaw tremor and leg tremor. However, there was no fatiguing or decrement of alternating movements and a normal FP-CIT SPECT scan was obtained in all 10.

Subjects with classical ET would not merit an FP-CIT scan, but those with 'ET' or DT in combination with jaw tremor, rest tremor, leg tremor, very asymmetric or unilateral tremor, reduced arm swing or facial hypomimia may merit a scan if there is a suspicion of PD, but the scan will not differentiate ET from DT. How many subjects with SWEDDs have DT depends upon a physician's clinical experience and acumen, and their threshold for ordering scans. All one can say is that DT patients more frequently than ET patients have atypical features that may hint at PD, but still most of these should not need scans to formulate a diagnosis. The lower the threshold for ordering FP-CIT scans, the more SWEDDs with DT there will be.

Patients with unusual tremor features but no evidence of overt dystonia e.g. isolated head/vocal tremor, jaw tremor, unilateral tremor etc probably do not have ET. Some may later turn out to have DT, when evidence of dystonia subsequently develops. These individuals should, at present, be called "indeterminate tremor".

Chouinard et al (1997)¹¹ conducted a survey of movement disorder specialists' views on the diagnosis

of ET. 70% would diagnose ET in a patient with isolated voice tremor, and 81% with isolated head tremor. It would be interesting to repeat a similar questionnaire study amongst 'movement disorder specialists' today. The MDS certainly needs to revisit and revise its definitions for both ET and DT.

Discussion

NQ: I would suggest that the term dystonic tremor should encompass both tremor in a body part that is affected by dystonia and tremor associated with dystonia (tremor in a body part not affected by dystonia but the patient has dystonia elsewhere). Essential tremor is a bilateral, largely symmetrical postural or kinetic tremor involving hands and forearms that is visible and persistent. Additional tremor elsewhere may occur but should follow, and be less severe than, the arm tremor. Exclusion criteria include dystonia, parkinsonism, other known causes of tremor e.g. neuropathy or isolated position- or task-specific tremors, or isolated tremor sparing the arms. Indeterminate tremor is the presence of postural or kinetic tremor (sometimes with additional rest tremor) accompanied by other neurological signs of uncertain significance e.g. mild extrapyramidal features, but without sufficient parkinsonism or dystonia to make a diagnosis of PD or dystonic tremor. Monosymptomatic rest tremor is rest tremor without sufficient parkinsonian or dystonic features to entertain a diagnosis of PD or dystonic tremor. Benign tremulous PD is part of tremor-dominant PD, but cannot be diagnosed in the absence of true bradykinesia or the presence of a normal FP-CIT scan.

HM: Many PD patients, especially those with a younger age of symptom onset have dystonia in addition to tremor. Rather than looking at some of the older videos used as examples of each tremor type, there is a good case for developing a new teaching library indicating the typical features of essential and dystonic tremor with consensus between movement disorders experts across the world.

3. The definition of dystonic tremor; revisiting the definition of essential tremor (can ET patients ever present as SWEDDs?); re-defining atypical tremor and monosymptomatic tremor – Dr Peter Bain

Tremor can be classified as rest, postural or kinetic, the latter including simple kinetic, intention, task specific, position specific and intention tremor or by aetiology according to the underlying disease.¹² Currently the most widely used definitions are those in the 'Consensus Statement of the Movement Disorder Society on tremor,'⁸ which proposed the following definitions:

Classic essential tremor: defined by inclusion and exclusion criteria. Inclusion criteria: bilateral, largely symmetrical postural or kinetic tremor involving the hands and forearms that is visible and persistent. Additional or isolated tremor of the head may occur but in the absence of abnormal posturing, although inclusion of this has been heavily disputed. Exclusion criteria: presence of other neurological signs (e.g. dystonia), known causes of enhanced physiological tremor (e.g. drugs), historic or clinic evidence for psychogenic tremor or convincing evidence for a stepwise onset or deterioration of tremor. The presence of primary orthostatic tremor, isolated voice tremor, isolated position specific or task specific tremor, isolated tongue or chin tremor or isolated leg tremor.

In developing these criteria it was acknowledged that:

- The 5 and 3 year time frames used in the previous TRIG criteria had been removed
- There was no mention of tremor severity

- That essential tremor may affect body parts other than the hands
- Intention tremor and much more rarely rest tremor may be present
- Re-classification of 'possible ET type 1a' from the TRIG criteria under the respective neurological criteria e.g. parkinsonism tremor syndromes, dystonic tremor syndromes, neuropathic tremor syndromes

Dystonic Tremor Syndromes

The following classification was proposed:

- Dystonic tremor – occurs when dystonia and tremor affect the same body part. These are often focal with irregular amplitudes and variable frequency. Predominantly postural/kinetic and not usually seen with complete rest. They may have geste antagoniste
- Tremor associated with dystonia – tremor that occurs in a body part unaffected by dystonia, although there is evidence of dystonia elsewhere.
- Dystonia gene associated tremor – isolated tremor in patients with a dystonic pedigree e.g. isolated head tremor in a patient with first-degree relatives with spasmodic torticollis

Epidemiological research has also shown the dystonic tremor syndromes to have a bimodal age of onset similar to that of essential tremor. Approximately 49-60% have a first degree relative with a form of tremor. In terms of treatment, these patients tend to have a negative response to levodopa and approximately 70% showing a response to alcohol.

Marsden's dystonic tremor

Referred to by Marsden as dystonic tremor, and consisting of a jerky tremor often occurring in flurries without overt dystonia. This form of tremor was not included in the MDS consensus statement.

Monosymptomatic rest tremor

Characterised by:

- Pure or predominant rest tremor of at least 2 years duration
- No additional signs of bradykinesia, rigidity, or problems with stance/stability sufficient to make a diagnosis of Parkinson's disease.
- Features of the tremor component of this group are essentially identical to parkinsonian tremor
- Positron emission tomography (PET) scans of some patients in this group show evidence of dopaminergic deficit

Indeterminate Tremor Syndrome

These patients satisfy the criteria for classical essential tremor but also exhibit other neurological signs of uncertain significance, but insufficient to make a specific diagnosis. This term also allows clinicians to remain open minded about the diagnosis and avoids making an incorrect diagnosis and prevents the possibility of conflicting diagnoses. This category also includes the 'possible ET type 1b' category from the TRIG criteria.

Unclassified Tremor

Those tremors that cannot be classified should be labelled unclassified and described phenomenologically.

Discussion

NQ: The bimodal age of onset distribution described in the dystonic tremor syndromes is reminiscent of that of dystonia, where DYT1 and DYT6 mutations are found predominantly in younger, but not in older, subjects.

DG: Although much discussion of the differences between essential and dystonic tremor has taken place, it must be noted that ultimately both of these patient groups could be classified as SWEDDs.

4. Mis-diagnosis in tremulous PD – *Dr Nin Bajaj*

Two pairs of videos were shown and the group asked to comment on whether they felt the individuals had Parkinson's disease or not. The assembled panel of experts performed poorly in their clinical ability to predict which patient had PD or not on the basis of the videos shown. The clinical diagnosis of PD had been assigned by NB based on FP-CIT scan result, prolonged clinical follow-up (3 years) and in all PD patients and many non-PD patients, response to dopaminergic therapy.

A study by Hughes and Lees¹³ suggested that movement disorder specialists had a sensitivity of 91.1% and specificity of 98.7% in diagnosing PD. However, Meara et al¹⁴ found a diagnostic accuracy of only 53% when examining this at a community level.

Bajaj et al¹⁵ showed two blinded experienced movement disorder experts videotaped examinations of 15 TDPD and 23 SWEDDs patients. Both experts had both high false positive (17.4 to 26.1%) and negative rates (6.7 to 20%) for the diagnosis of PD.

Discussion/Remarks

NB: Dystonic features are not uncommon in drug naive TDPD patients, making the distinction from dystonic tremor more difficult. This particularly applies to some untreated young-onset PD cases, but in these patients true bradykinesia is also present. Subtle dystonic features such as thumb hyperextension, mild head tilt, subtle dinner-forking of the hand and mild shoulder elevation, are not sufficiently discriminating to indicate dystonia.

DG: There is great difficulty in making a decision with regards to bradykinesia in isolation. A clinical decision is usually made based upon the whole picture e.g. clinical history, time course, additional features etc.

NQ: It is usually easy to determine if true bradykinesia is present after relatively few repetitions of a movement. However, how many finger or toe taps should patients be required to perform to be certain that bradykinesia is absent? In uncertain cases, I would usually ask a patient to perform up to 64 in each extremity before being certain that there is no bradykinesia in that extremity. I would also place a caveat on making or excluding diagnoses on the basis of videotape samples, which are not fully representative of a more prolonged full examination of the subject.

HM: The MDS-modified UPDRS scoring system suggests only 10 finger taps in each hand.

AL: If the FP-CIT scan signal was reduced on one side but deemed to be normal on the other, would people be happy to make a diagnosis of PD?

DG: This would require the ratios between the two sides to be measured and compared before making a final decision.

NQ: I would not feel happy making a diagnosis of PD on this basis, as the scan should be abnormal on both sides, albeit asymmetrically so. In this setting I would also request an MRI scan for further information on the region.

NB: Several studies have addressed the error rate in the diagnosis of PD e.g. the Meara community study found a misdiagnosis rate for PD of around 50%. Key contributing factors to false positive diagnoses of PD are discrepancies in the application of the definition of bradykinesia and the prevalence of parkinsonian features such as facial hypomimia and reduced arm swing in SWEDDs patients. It is possible for SWEDDs patients to have one or more of the essential criteria for step 1 of the Queen Square Brain Bank Criteria (QSBBC) for PD, but rarely true bradykinesia, as defined by progressive fatiguing and

decrement of repetitive alternating movements. The classical tremor phenotype of PD with asymmetrical rest tremor, re-emergent postural tremor and less prominent kinetic tremor may not be so true of tremor-dominant PD phenotypes, hence causing diagnostic confusion with other tremor syndromes.

5. The Queen Square Brain Bank Criteria in the age of SWEDD – *Professor Andrew Lees (UCL Institute of Neurology, London)*

Recent suggested criteria for diagnosing Parkinson's disease have included the triad of:

- Impaired sense of smell
- Rapid Eye Movement (REM) sleep behaviour disorder
- Refractory constipation

Referring to the original QSBBC,¹⁶ bradykinesia is arguably the most important feature, especially in younger patients where it may be the only feature.

Within the initial Brain Bank series for PD there were 730 cases, of which only 7 were found to have no evidence of neurodegenerative disease related to PD. Are these individuals pathological correlates of SWEDDs? Reviewing the clinical data, all 7 patients had tremor as a dominant feature

In the modern era, with use of FP-CIT scans, there is much variability in reporting methods with some preferring a visual stage scoring system and others quantitative analysis. This in itself can lead to diagnostic uncertainty, especially when the scan result conflicts with the clinically expected outcome.

Discussion

AL: As the term SWEDD is dependent on correct interpretation of functional imaging data, we propose regular external audit of all nuclear medicine facilities carrying out such tests. Random scans should be exchanged for blinded external review to assess concordance with reference standards.

6. Olfaction in SWEDDs patients – *Dr Laura Moriyama, UCL Institute of Neurology*

The causes of smell loss are multifactorial, including:

- Decline with age
- Gender (women out perform men)
- Damage to epithelium from previous cold/flu
- Head trauma: fracture of axons passing through the cribriform plate
- Neurodegeneration: severe deficit in Alzheimer's Dementia (AD) and PD, with mild/moderate deficit in various other diseases.

In PD, 70-90% of patients have objective smell loss and although self-reporting is often not reliable, smell tests may help in the early detection of PD. The severity of failure of smell identification is not related to disease duration, disease severity or PD treatment.¹⁷

Smell tests conducted upon patients with ET showed a possible mild deficit in the earlier papers,^{18,20} but with no deficit reported in more recent papers.^{21,22}

Silveira-Moriyama et al²³ reported smell testing in 21 SWEDDs patients. University of Pennsylvania Smell Identification Test (UPSIT) scores within this group differed significantly from those with idiopathic PD and more comparable with controls, ET and dystonia. UPSIT tests were also performed on 41 SWEDDs patients from the Nottingham area, with mean disease duration of 16 years, mean age 66.8yrs and mostly tremor dominant in terms of clinical symptoms. Again in this cohort the SWEDDs group out-performed PD group in terms of olfaction.

When the results of the London and Nottingham cohorts were combined, age and gender had a statistically significant load. Statistical analysis of UPSIT scores showed the SWEDDs group to differ significantly from PD and control groups, but without significant difference between ET and DT groups.

Future directions for smell testing within the SWEDD cohort:

- Smell test more subjects with tremors (ET, DT, SWEDD), cost of a UPSIT test is approximately 10 times less than that of a FP-CIT scan
- Go back to the SWEDD cohort and use clinical insight to determine if SWEDDs patients are a heterogeneous group i.e. those with smell deficits and those without.
- Carefully collect clinical/phenomenological data on SWEDDs patients: might they also be neurodegenerative?
- UPSIT tests may be more sensitive than Sniffin' Sticks, especially in those with milder deficits
- Develop a database of UPSIT scores for control and PD subjects, also very important to test local controls.

7. Handwriting and Spiral Analysis in SWEDDs patients – *Dr Peter Bain*

As clinical distinction of SWEDDs patients from PD, especially in early disease stages, can be challenging, careful analysis of the phenomenology of both conditions is called for. With this in mind, comparisons of handwriting examples and spiral drawings were carried between SWEDDs patients and PD cohorts.

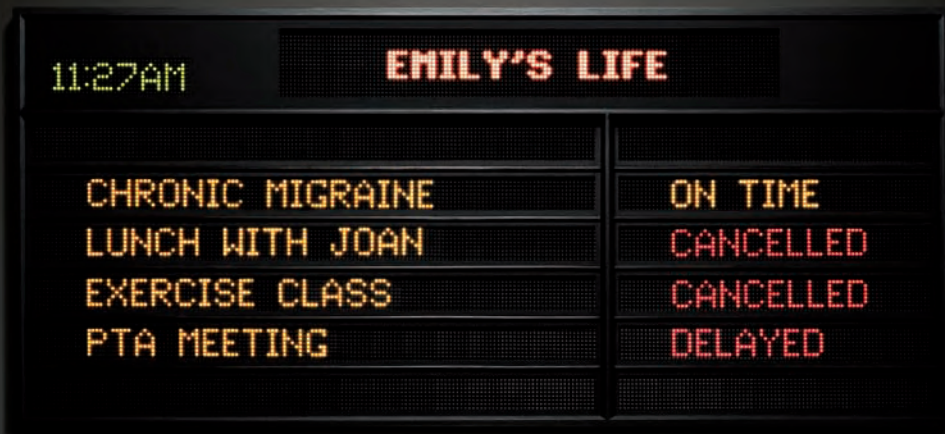
Recent work by Bajaj et al²⁴ compared handwriting samples from 8 tremor dominant PD patients and 20 dystonic SWEDDs (diagnosis based upon FP-CIT SPECT, longitudinal clinical data and response to dopaminergic treatment). Handwriting examples were then reviewed by 3 individuals, blinded to clinical details, and asked to diagnose PD or non-PD in each case. The results showed mean sensitivity of 37.5% and specificity of 63.3%. Micrographia, in the tremor dominant PD cases, was diagnosed in 1 patient by all 3 reviewers, 2 patients by 2 reviewers, 2 cases by 1 reviewer, and deemed not present in 3 cases. Eight of 20 cases (40%) of the SWEDDs cases were described as having 'large jerky childish writing'. Overall these results suggest that visual inspection of handwriting is not a good method of discriminating between these two conditions.

Previous work comparing spirals drawn by PD and ET patients showed those drawn by PD patients to be significantly smaller in diameter, denser and less tremulous than those drawn by patients with ET.²⁵ Using similar criteria,²⁶ Bajaj et al²⁷ compared 65 tremor dominant PD and SWEDDs patients. This found no significant difference in tremor severity however, those drawn by tremor dominant PD patients were significantly smaller in diameter and denser than SWEDDs patients. The most sensitive method was the spiral 3 turn-diameter (75%) and spiral density the most specific (83%), thus suggesting that spirometry may have some role in distinguishing between the two.

8. Tremulous patients misdiagnosed as PD – clinical and physiological characteristics of tremulous SWEDDs patients – *Dr Mark Edwards (UCL Institute of Neurology)*

There are multiple differential diagnoses for both rest tremor and action tremor e.g. Parkinson's disease, benign tremulous Parkinson's disease, DT for the former and ET, cerebellar tremor, and tremor associated with dystonia for the latter.

The main problems are that clinical features of tremor syndromes overlap and there is disagreement over which features are valid. In addition simple tremor parameters overlap and do not distinguish patients on an individual level. On one level it could be thought that this argument was academic, however, it does have an impact upon clinical care as it causes a stagnation of pathophysiological understanding and a contamination of clinical trials.



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in some cases). Other adverse events reported include dysarthria, abdominal pain, vision blurred, pyrexia, focal facial paralysis, hypoaesthesia, malaise, myalgia, pruritis, hyperhidrosis, diarrhoea, anorexia, hypoacusis, tinnitus, radiculopathy, syncope, myasthenia gravis, erythema multiforme, dermatitis psoriasiform, vomiting and brachial plexopathy. Also, rare reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Rare reports of serious and/or immediate hypersensitivity (including anaphylaxis, serum sickness, urticaria, soft tissue oedema and dyspnoea) associated with BOTOX[®] use alone or in conjunction with other agents known to cause similar reaction. Very rare reports of angle closure glaucoma following treatment for blepharospasm. New onset or recurrent seizure occurred rarely in predisposed patients, however relationship to botulinum toxin has not been established. Needle related pain and/or anxiety may result in vasovagal response. **Basic NHS Price:** 50 Units: £77.50, 100 Units: £138.20, 200 Units: £276.40. **Marketing Authorisation Number:** 50 Units: 426/0118, 100 Units: 426/0074, 200 Units: 426/0119. **Marketing Authorisation Holder:** Allergan Ltd, Marlow International, The Parkway, Marlow, Bucks, SL7 1YL, UK. **Legal Category:** POM. **Date of preparation:** July 2010. Further information is available from: Allergan Limited, Marlow International, The Parkway, Marlow, Bucks SL7 1YL.

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The predominant questions surrounding tremulous SWEDDs patients are:

- a. How can we stop diagnosing these patients as having PD?
- b. What is the underlying cause of their tremor?

Recent work by Schwingschuh et al²⁸ attempted to answer some of these questions. They attempted to define the clinical characteristics, both motor and non-motor, of 25 SWEDDs and 25 tremor dominant PD patients. There was then an assessment of the tremor itself using accelerometry comparing PD, patients with SWEDDs, dystonic tremor and essential tremor. There was a further assessment using a specialised electrophysiological method (paired associative stimulation) which assesses the ease with which one can cause plastic changes within the motor system. Previous studies using this technique have found that patients with PD (off treatment) show a very limited response whereas patients with dystonia show an exaggerated response. It had not previously been applied to people with ET.

Results of the clinical investigation suggested:

- a. hypomimia, re-emergent postural tremor, decrement and fatiguing of repetitive hand movements, main tremor at rest were discriminating features in favour of tremor dominant Parkinson's disease.
- b. head tremor and the presence of dystonia favoured a diagnosis of SWEDD.
- c. Non-motor symptoms according to NMSQuest scores, were more prevalent amongst PD patients
- d. TDPD patients tended to respond better to medical therapy with levodopa treatment performing the best. The best group of drugs amongst the SWEDD cohort were anticholinergics.

Accelerometry results suggested an overlap amongst both groups and did not readily distinguish SWEDD patients from TDPD.

The paired associative stimulation test confirmed previous studies with an exaggerated response in patients with dystonic tremor and a subnormal response in patients with PD. Patients with ET were not different from normal controls. However, tremulous SWEDDs patients showed an exaggerated response to paired associative stimulation similar to that seen in patients with dystonic tremor.

Therefore overall tremulous SWEDDs patients have a clinical overlap with TDPD patients but lack re-emergent tremor upon posture, have a dominant tremor upon posture, involvement of head with tremor, lack true bradykinesia and lack non-motor symptoms. Using simple accelerometry, it is not possible to differentiate tremulous SWEDDs patients from other causes of tremor such as PD or ET. However, their response to an experimental plasticity protocol clearly separates them from the response seen in ET and PD, and is similar to the abnormal response seen in dystonic tremor. This is additional evidence that a major cause of SWEDDs in tremulous patients could be adult-onset primary dystonia.

9. Comparison of Clinical Characteristics of TDPD with tremulous SWEDDs patients- the Nottingham experience – Dr Nin Bajaj

Ongoing work comparing the clinical characteristics of SWEDDs cohorts with TDPD cohorts in the Nottingham/Derby area has found these clinical features to be statistically more prevalent in TDPD cohorts:

- a. Dependent tremor upon walking
- b. Bradykinesia
- c. Stooped posture
- d. Pill-rolling tremor
- e. Arm flexion
- f. Reduced arm swing when walking

In contrast SWEDDs patients were found to have a significantly greater incidence of:

- a. Subtle dystonic features e.g. thumb or little finger hyperextension
- b. Positive family history of either tremor or PD
- c. Head tremor
- d. Flurries

10. Tremor Genetics – Where is Dystonia tremor

Genetics? – Dr Huw Morris, University Hospital of Wales, Cardiff

Mendelian tremor conditions subgroups defined on Online Mendelian Inheritance in Man (OMIM) under the term 'tremor genetics' include: familial myoclonic cortical tremor with epilepsy (FCMTE), geniospasm, Myoclonus Dystonia Syndrome, Fragile X tremor ataxia syndrome, Essential tremor (ETM 1, 2, 3 & unlinked families), however, there isn't a defined category locus for familial dystonic tremor. It seems likely that some families defined to have familial essential tremor will have familial dystonic tremor and the main family linked to chromosome 6 by Shatunov and colleagues had a high proportion of individuals with features of dystonia.

ETM 1, 2 and 3^{29, 31}

Although there is now a well replicated common risk association in essential tremor (LINGO1) it seems surprising that to date progress in identifying Mendelian ET genes has been slow. This may relate to the overlap and diagnostic confusion with dystonic tremor, The main difficulties with research to date is ascribing an explanation to the differing degrees of variation in penetrance, and the existence of phenocopies within families and variation in allelic transmission possibly playing a role. The identification of SWEDDs patients within Parkinson's disease clinics highlights the diagnostic uncertainty in some patients, and the identification and characterisation of Mendelian families with dystonic tremor will clarify the situation, and provide insights into pathogenesis.

Discussion

NB: What is the definition of SWEDDs?

AL: Response: a patient suspected of having parkinsonism has gone on to have a nuclear imaging scan, usually FP-CIT, which has subsequently been reported as normal. This group of patients could then be subdivided into tremulous and non-tremulous forms.

NQ: Using a scan result to make a clinical diagnosis appears to be moving in the wrong direction. Instead we should be beginning with the characteristics of the tremor and attempting to differentiate TDPD/ET/DT on clinical grounds, and using scans only in clinically uncertain cases.

DG: Clinical differentiation is often very difficult and FP-CIT scans have opened a new arena where patients

have an unexpectedly normal scan. Therefore we have a need to try and analyse these cases and work out why this may be the case.

PB: SWEDDs patients are likely to be a heterogenous group. In addition there may be medicolegal implications of the diagnosis of SWEDD in terms of prognosis versus PD.

NB: We need to consider formal drug trials in dystonic tremor which can be a very debilitating condition. There is a need for large scale trials assessing the effects of e.g. propranolol, primidone, benzodiazepines, anti-cholinergics and newer drugs such as levetiracetam. There are also anecdotal reports of deep brain stimulation surgery being helpful in case studies- again we need formal trials to decide which surgical target might be best

ME: We could consider a trial of alcohol substitutes e.g. 1-octanol

NB: I often find the tremor component of tremor dominant PD does not respond well to L-dopa whereas the bradykinesia does. What is the experience of others?

NQ: I think virtually all PD patients with tremor will respond to L-dopa, but some will need unacceptably high doses.

AL: It will often take more than 1 year of treatment at high doses before any improvement to the tremor component is seen in tremor dominant PD. However, I agree with NQ that the rest component of the PD tremor responds better to L-dopa than the postural or kinetic components.

AL and NQ: Neither have seen DT respond to L-dopa, not even the rest component of DT.

ME: In addition to the suggestions above there is also need for an epidemiological study to determine who is being misdiagnosed with PD and why. We should begin by attempting to correlate all reported SWEDDs cases thus far and attempt to determine their clinical features. Their clustering of numbers may reflect a referral bias to specialist centres.

NB: Access to FP-CIT scan is very variable throughout the country and the approaching decade of austerity may further lessen its availability. Instead, maybe we should be focusing upon re-learning of clinical skills to improve diagnosis.

DG: We should aim to provide reassurance to other neurologists that diagnosis of PD and differentiation from SWEDDs cases can often be difficult and mistakes will be made even by the most experienced movement disorders experts.

Locus	Area	Author	Comments
ETM1	3q13	Gulcher 1997	Icelandic - 16 families; individual lod score 1.4, TRIG criteria
ETM2	2p24: Lod 5.92	Higgins 1997	Main family Czech, no features of dystonic tremor
ETM3	6p23: Lod 3.28	Shatunov 2006	3 affected members did not have disease haplotype, 8/14 dystonia

HM: Patients with PD should have bradykinesia but this can be difficult to determine in the presence of tremor. A normal FP-CIT scan makes the diagnosis very unlikely and should prompt the consideration of other diagnoses, including dopa responsive dystonia and psychogenic tremor, in addition to dystonic and essential tremor.

ME: What is the aim of clarifying the issues surrounding SWEDDs cases? Is it for clinical reasons e.g. review of patients within 6 months of initial consultation and a trial of treatment? Is it research i.e. need for accurate classification of disorders when carrying out therapeutic or genetic studies? Or is it a question of health economics and not giving expensive PD treatments to patients who do not have the disorder?

NB: We need to address the issue of variability in the techniques used for FP-CIT scan reporting. Visual methods using a 0-3 scale are prevalent, alternatively quantitative analysis is used in some centres. We need to standardise how scans are read and reported. We should possibly introduce blinded reading of other centre's scans. There should also be a system of regular external audit for quality assurance purposes.

HM: Scans should be interpreted as part of the overall clinical picture. All FP-CIT scans should be re-reviewed as standard, followed by an additional blinded review. There should also be a system in place to deal with questionable scans. Nuclear medicine experts should also be blinded to the clinical features of the case.

NB: What is everyone's view on serial FP-CIT scans? If so, how many? And at what frequency? Should part of the criteria include consistent abnormality and should degree of abnormality be graded?

DG: Current evidence suggests approximately 1 in 200 scans are difficult to interpret. Generally it is suggested that these scans should be repeated 1 year later if

it is clinically indicated. Our own approach is to defer repeat scanning for longer, to maximise the chance of detecting a change between sequential studies; we generally use an 18 month interval.

Consensus amongst the group: significant clinical heterogeneity amongst TDPD patients. Some TDPD patients are truly benign with slow progression over decades.

AL: Is monosymptomatic rest tremor a forme fruste of PD?

NB: Do we believe that ET can lead to PD?. Statistically there must be patients with ET who also have PD.

NQ: There is inherent bias in the patients who attend clinic. We are much more likely to see those with ET who then develop PD than those who don't.

NB: Generally the ET definition from 1998 has stood the test of time and should be adhered to.

NQ: Would disagree with component regarding isolated head tremor, which I don't consider as ET. However, this argument may simply be tautological. If it is decided that ET constitutes a family of separate conditions, then this may be one of them.

AL: Predominant problem is that people are not using the criteria appropriately.

ME: Concerns with the number of people being labelled with dystonic tremor, often when they have very little dystonia that is visible clinically.

HM: Future research should include further delineation and study of dystonic tremor as a clinical entity, a prospective review of diagnoses and outcomes in patients with parkinsonism/tremor and SWEDDs, evaluation of the assessment of bradykinesia in challenging clinical situations.

Conclusions

The use of new clinical diagnostic techniques has a tendency to broaden recognised clinical phenotypes, something that has already been seen with the use of molecular genetic techniques. In a similar way, the widespread use of presynaptic dopaminergic imaging has allowed us to recognise and start to categorise syndromes resembling PD. The use of these imaging techniques has not only increased our awareness of the variability within the phenotype of PD but also has made us re-visit the tremulous syndromes that can resemble PD and hopefully re-define these in a more systematic way.

These other tremulous syndromes, although often more benign in outlook, can also be more difficult to treat symptomatically than PD itself, and future directions for the study of SWEDD should include drug trials and surgical therapy trials investigating better treatment options in SWEDDs cases. Furthermore, the high prevalence of a positive family history in these benign tremulous disorders should allow genetic studies giving further insight into the aetiopathogenesis of these disorders.

The high prevalence of SWEDD across clinical trials to date should also raise the question as to whether to incorporate presynaptic dopaminergic imaging into all PD clinical trials, with scan abnormality as an obligatory inclusion criteria. This may also serve to make trials more representative of PD as a whole perhaps increasing the inclusion of more tremulous PD patients that have always represented more of a clinical challenge diagnostically and may therefore have been referred for trial inclusion less regularly than their akinetic-rigid counterparts. The identification of all SWEDDs cases in trials of this sort and across clinical departments in general could lead to a registry/database of SWEDDs patients allowing both external review of these subjects and further research in this fascinating and important area of movement disorder research. ♦

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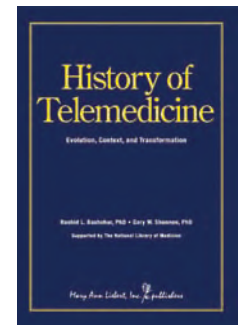
History of Telemedicine. Evolution, Context, and Transformation

Telemedicine is a technologically based modality of care which, as this thorough history shows, has been around for centuries as an alternative to “in-person” care, predicated on the technologies available at the time to provide connectivity. However, this is essentially a 20th century-and-onwards story (transmission of an ECG was first achieved by Einthoven in 1905) and most particularly the last twenty years, although pioneering projects predated this. These studies have shown the technical feasibility of telemedicine, but hard evidence of its efficacy in addressing issues of cost, quality and access has been difficult to establish unequivocally, partly related to methodological issues.

This book is a fascinating read. The focus is, perhaps understandably in view of the authors’ interests, largely American. There is little concerning teleneurology (pp 159, 162, 172, 252-3, 274, 379) or neurosurgery pp 286, 374, 385), in sharp contrast to telepsychiatry, which seems to have been taken up enthusiastically, perhaps because there is no “necessity to physically lay hands on the patient” (p390) and also because patients may find that it “diminished the emotional intensity of divulging personal information” (p235). Visually oriented specialties such as radiology, pathology and dermatology are frequent users of telemedicine. (Those interested specifically

in neurological applications of telemedicine might consult Wootton R, Patterson V (eds.). *Teleneurology*. London: RSM Press, 2005; I am also aware of real-time teleneurology clinics being conducted in Aberdeen).

The fine detail of telemedicine projects in Texas, Arizona or Alaska will not be to everyone’s liking, nor perhaps the administrative aspects of setting up such programmes (there is a risk to the reader of acronym fatigue). I would like to have read something about patient-directed health behaviour with respect to internet searching. Nonetheless, this volume stands as a useful summary of the origins of telemedicine. ♦



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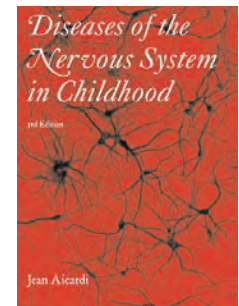
Diseases of the Nervous System in Childhood (3rd Edition)

It is 10 years since the publication of the 2nd edition of Aicardi’s famous text book, which is considered by many paediatric neurologists to be the standard text book of paediatric neurology. Aicardi is one of the most well known contemporary paediatric neurologists and for this reason he has recruited many other authors who are very well known in their fields to contribute to the book, including the two co-authors, Martin Bax and Christopher Gillberg. In the last edition, Aicardi wrote most of the chapters himself; however in the 3rd edition, he is joined by 16 other authors, which, he explains is necessary due to the tremendous volume of new information available. The book is enormous and contains almost 1000 pages. It is split into 11 different sections, with several chapters in each. Information is easy to find. There are many useful tables, diagrams, photographs, radiology images and even some colour images of fundi.

The book’s audience would be mainly paediatric neurologists, general and developmental paediatricians and their trainees. Adult neurologists and trainees and geneticists would also find it useful. Whilst it may be very nice to own such a large and impressive looking text book, I do wonder about their purpose in the days of the internet. Is it worth investing in a book like this these days? I decided to put it to the test, by looking

up several recent topics that I had done internet searches for. These all related to children I was managing who had various neurological presentations and disorders. The first was some general information about the neuronal ceroid lipofuscinoses, a common cause of regression in childhood. I found a good review published in 2009 and compared the information in the book to that. The book was useful and covered everything that I was looking for. The electron microscopy photographs of the abnormal inclusions helped me interpret those sent to me by the lab for my patient. The review was also good but I felt the overview in the book was superior. The second topic was inherited brain-specific folate transport defects, a very rare group of disorders which are only recently described. The book contained very little on this subject, which is not surprising so this time the paper was more useful. The third topic was infantile neuroaxonal dystrophy. I wanted to read about the clinical features as I was considering this as a diagnosis for one of my patients. The most recent review I could find was published in 2004 but it was very useful and gave me the information I needed. Again, the book gave equally good information, particularly the early features and MRI findings so I felt the information in the book and paper were pretty equal.

In summary, Aicardi’s book is considered to be a classic paediatric neurology text along with probably 2 or 3 others. I think the author set out clear objectives for this latest edition and these have definitely been met. The most valuable feature of the book is the depth of clinical information covered. However, the most common reason for using a book like this may be to help in the investigation of a child where the diagnosis is still unknown. So what may have been helpful is to somehow give a differential diagnosis for diseases that you may be considering using the clinical features that you have found on examination or on early investigations. One possible way of doing this would be to use the index to link all conditions together that share particular features, for example particular MRI abnormalities. The other drawbacks are obvious. Textbooks are to some extent out of date as soon as they are published and I would always undertake a literature review on top of looking up a topic in this book when looking for information about a particular disorder or disease. Having said that, the book is very useful and should be available to all trainee doctors coming through a busy tertiary unit. My copy will end up in our library where I hope it will be used for this exact purpose. ♦



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Diagnostic Approach to an Adolescent with Myoclonus



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Adolescence is a period of considerable change in a young person's physical and emotional needs. It is a time when they are gaining independence and making choices about education, driving and future careers. When a young person presents with new onset neurological symptoms or signs it impinges on this independence. Epilepsy and neurodegenerative disorders may well be a lifelong diagnosis, with many disease processes having evolving signs and symptoms and thus posing a significant diagnostic challenge. Adult neurologists may be presented with a teenager with myoclonus and this article describes a practical approach to its diagnosis.

Myoclonus

Myoclonus is characterised by sudden, brief, shock like movements which are caused by involuntary muscle contraction with brief electromyographic bursts (positive myoclonus) or sudden cessation of muscle contraction associated with a silent period in the EMG discharge (negative myoclonus). It may occur as an epileptic or a non-epileptic event. It can be an isolated finding or occur as a symptom of many diseases. Myoclonus needs to be differentiated from tics, tremors, exaggerated startle (hyperekplexia) and chorea.

Myoclonus

- Sudden involuntary muscular contraction
- generally brief - <50-100 ms in duration
- sudden onset and offset- 'lightning like'
- cannot be suppressed
- may be focal, multifocal or generalised
- less variable than tics

Tics

- Involuntary repetitive movements of skeletal or oropharyngeal muscles
- brief or prolonged
- variable pattern and site
- more complex movements
- can be suppressed

Tremor

- rhythmic oscillation of part of body (usually limb)
- can be worse with action (cerebellar dysfunction) or be present at rest

Chorea

- Sudden, irregularly timed spontaneous movements that tend to affect proximal limbs, trunk and facial muscles.
- exacerbated by mental concentration or stress

Epileptic syndromes with myoclonic seizures

Adolescents presenting with myoclonus may have one of a number of epileptic syndromes or neurological conditions with poor prognosis. They generally fall into two categories:

1. Idiopathic generalised epilepsies (IGE) –
 - Juvenile myoclonic epilepsy (JME)
 - Juvenile absence epilepsy (JAE)

2. Progressive myoclonic epilepsies (PME)

The five principal causes are:

- Unverricht Lundborg disease
- Lafora disease
- Myoclonic epilepsy with ragged red fibres (MERRF)
- Neuronal ceroid lipofuscinosis (NCL)
- Sialidosis

Idiopathic generalised epilepsies

Myoclonic (cortical) seizures are just one of many seizure types seen in IGE. In JME myoclonic jerks may occur in variable frequency with minimal absences – unlike JAE where absences are the predominant seizure type. Generalised tonic – clonic seizures can occur in both JME and JAE. The majority of adolescents respond well to treatment though there is a high relapse rate on stopping medications, hence the need for prolonged treatment.

Table 1: Causes of non epileptic myoclonus¹

Non epileptic (subcortical myoclonus)	Non epileptic, non myoclonic phenomenon
Benign neonatal sleep myoclonus	Tremor
Opsoclonus myoclonus syndrome	Tic
Psychogenic (worsens with stress)	Chorea
Drug induced myoclonus	

Table :2 PME – Clinical features and EEG changes in PME

Disease	Age of onset	Seizure pattern	Neurological signs	EEG
Unverricht disease	6-15 years	Myoclonus and GTCS Absences can occur	Initially normal examination. Later mild progressive ataxia, inco-ordination, intention tremor, dysarthria and usually mild dementia	Initially normal or mimics IGE Later abnormal and highly photosensitive
Lafora disease	6-19 years, can begin in early adulthood	Myoclonic and occipital seizures, occasionally GTCS, atypical absences, atonic seizures	Cognitive signs may present early, progresses to spastic quadriparesis and constant myoclonus	Initially normal Later generalised or focal predominately in the posterior regions, with photosensitivity
Juvenile NCL (NCL Type 3), Batten's disease	4-10 years	Myoclonus is mild, GTCS can occur	Starts with visual failure, gradually develop dementia and extrapyramidal signs, psychoses and hallucinations. Pigmentary retinopathy occurs	Slow background with generalised spike and wave, accentuated during sleep but not with photic stimulation
Sialidoses Type 1 and Type 2	Adolescence	Facial especially perioral myoclonus, persisting in sleep, GTCS	Type 1 – gradual visual failure, ataxia, cherry red spot on fundoscopy Type 2 – coarse facial features, corneal clouding, hepatomegaly, skeletal dysplasia, learning difficulties	Background shows low voltage fast activity with slowing with dementia
MERRF	Early childhood to late adulthood	Myoclonus, focal seizures may occur	Ataxia, mild myopathy, cognitive impairment, pigmentary retinopathy	Slow background activity with generalised or focal polyspike waves

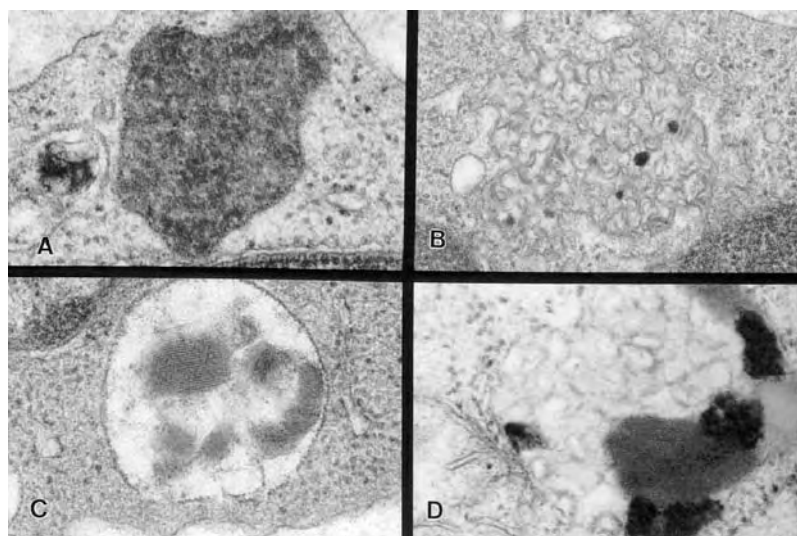


Figure 1: Electron microscopy – Buffy coat preparation (leucocytes) showing various inclusion bodies in NCL. (A) Granular osmiophilic deposits in infantile NCL, (B) Curvilinear inclusions in classical late infantile NCL, (C) Finger print inclusions in Juvenile NCL, (D) Mixed granular, curvilinear and finger print inclusions in juvenile NCL.

Juvenile myoclonic epilepsy

The age of onset of the myoclonic jerks is usually 14-15 years. Jerks occurring after awakening are a prominent feature and should be directly asked about. There may be a history of clumsiness or frequently dropping things due to jerks affecting the upper limbs. The absences are atypical and often associated with impairment of cognition and eyelid flickering. The EEG shows 3-6 Hz generalised spike wave discharge associated with photosensitivity. A third of patients may also show focal EEG abnormalities. Response to valproate and levetiracetam is good. Clonazepam at night is the most effective treatment for the myoclonic jerks. Carbamazepine and lamotrigine may worsen the myoclonic jerks.

Juvenile absence epilepsy (JAE)

JAE usually presents between 9-13 years (age range 5-20 years). The absence seizure is more prominent than the myoclonic jerks. The absences occur from 1-10 per day and are associated with mild impairment of consciousness and automatisms. They last between 4-30 seconds (average 16 seconds). The myoclonic jerks do not have the same circadian rhythm as JME, tending to occur more in the afternoon. The EEG shows 3-4 Hz generalised spike wave discharge and may show focal features. Sodium valproate and lamotrigine are the two main drugs of choice in this condition.

Progressive myoclonic epilepsies

Progressive myoclonic epilepsies are rare genetic disorders, usually autosomal recessive, characterised by myoclonic jerks, tonic clonic seizures and progressive neurological deterioration especially cerebellar signs and dementia. The myoclonus is exacerbated by stimuli (action myoclonus)² such as light, sound, touch and emotional strain and is multifocal, involving the face, distal limbs and sometimes the proximal muscles causing recurrent falls. Each of the different neurological disorders may have additional clues to aid in diagnosis. The clinical characteristics and EEG of the five most common PME are highlighted in Table 2.

Rarer causes of PME include dento-rubral – pallidolusian atrophy, non-infantile neuronopathic Gaucher's disease, atypical inclusion body disease, neuroaxonal dystrophy, late infantile or juvenile forms of GM2 – gangliosidosis, Panthothenate kinase associated neurodegeneration, and the childhood form of Huntington's chorea. SSPE can also rarely have myoclonus as a clinical feature.

The investigation of progressive myoclonic epilepsy can be extensive. A step wise approach to the diagnosis is outlined below:

Initial investigations

1. Biochemical – electrolytes, liver function tests, lactate and pyruvate (plasma and CSF)
2. Blood – light microscopy shows vacuolated lymphocytes and electron microscopy³ shows finger print inclusion bodies (Figure 1) in juvenile NCL
3. Fundoscopy may show a pigmentary retinopathy
4. EEG – normal initially later becoming abnormal, with many conditions associated with photosensitivity
5. ERG/VEP – become smaller while the SSPE may increase in amplitude in juvenile NCL
6. Brain imaging – initially the MRI can be normal or nonspecific. Later cerebral or cerebellar

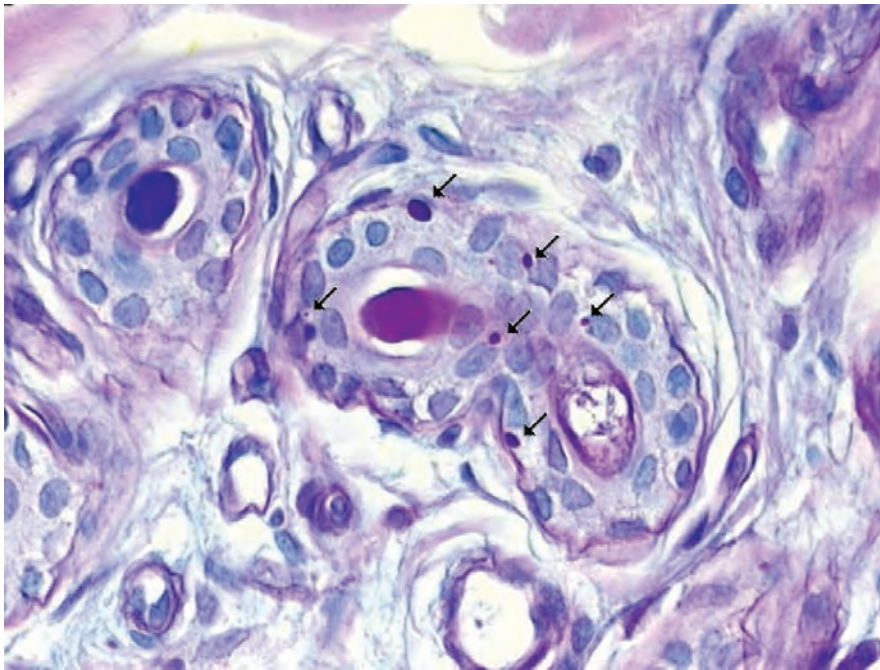


Figure 2: Skin biopsy of an eccrine sweat gland in Lafora body disease showing PAS - positive Lafora bodies (arrows).

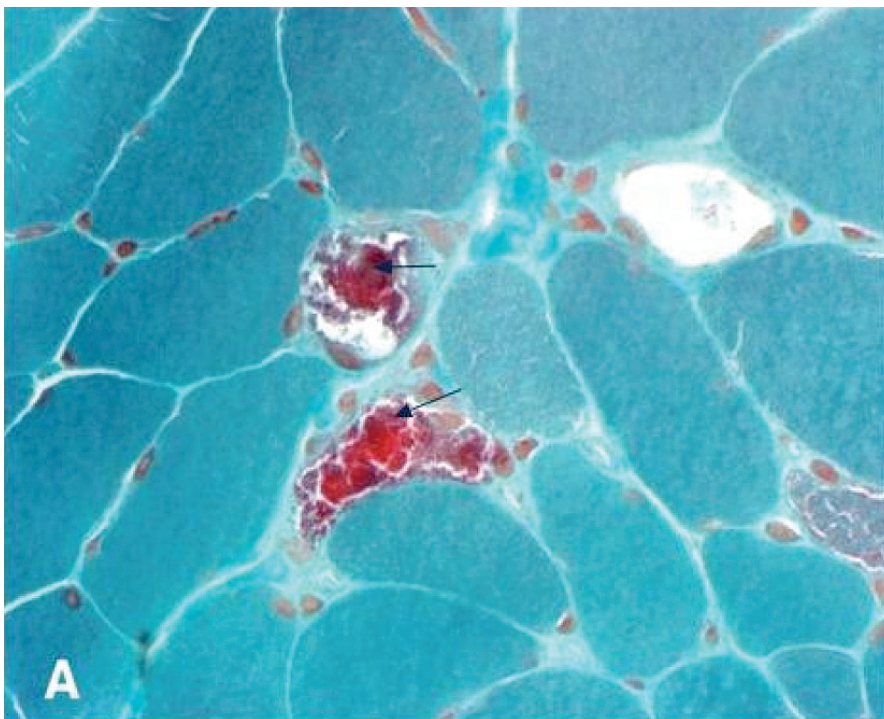


Figure 3: Muscle biopsy (Modified Gomori trichrome stain) showing ragged red fibres in MERRF.

atrophy occurs in juvenile NCL and sialidosis. Brain atrophy and basal ganglia calcification has been reported in MERRF

Second line investigations

1. Skin biopsy (Figure 2) – for Lafora disease the biopsy should be deep enough to include entire sweat gland ducts. The axilla should be avoided as a site for biopsy, because PAS – positive bodies may normally occur there.⁴ Electron microscopy of the biopsy reveals lipopigments in the case of NCL.
2. Muscle biopsy (Figure 2) – to look for ragged red fibres in MERRF
3. Enzyme analysis – neuraminidase deficiency in leucocytes or fibroblasts in sialidosis. Enzyme analysis for PTT1 or TPP -1 in juvenile NCL may need to be done if the vacuolated lymphocytes are negative and awaiting gene testing.⁵
4. Molecular genetic analysis – definitive diagnosis by mutation analysis is available for all the progressive myoclonic epilepsies (Table 3).

Summary

Myoclonic seizures in a teenager should be carefully evaluated in the form of history and clinical examination with observation or video of the seizures. It is important to look for any evidence of cognitive decline.⁶ Poor seizure control can be a clue to the progressive myoclonic epilepsies. New neurological signs that may develop are visual failure, pyramidal signs and extrapyramidal features such as chorea. Specific genetic testing is available but may need to be done after preliminary extensive investigations. Making the correct diagnosis and taking time to discuss the implications of this, is of the utmost importance for a young person at a sensitive period of transition. ♦

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Table 3 – Definitive diagnosis of PME			
	Inheritance	Chromosome locus	Gene
Unverricht disease	AR	Ch 21q22.3	CSTB
Lafora disease	AR	Ch 6q24 Ch 6p22.3	EPM2A NHLRC1
Juvenile NCL	AR	Ch 6p	CLN3
Sialidoses- Type 1	AR	Ch 6p21.3	NEU1
Type 2	AR	Ch20	NEU1
MERRF	Maternal	Mitochondrial DNA	MTTK

Combining EEG and Diffuse Optical Imaging: A New Approach to Monitoring Neonatal Seizures?



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Seizures in the newborn infant brain represent a major unsolved problem in neonatal medicine. Neonatal seizures are poorly classified, frequently under-diagnosed, and are difficult to treat. Estimates of incidence vary; a recent review placed the figure at between 1.8 and 3 per 1000 live births,¹ however, the risk for babies with a very low birthweight (< 1.5 Kg) is thought to be higher, between 10-11 per 1000.² In the term infant, hypoxic-ischaemic brain injury is the most common cause of seizures, although perinatal stroke is an increasingly recognized cause in the population group.³ In the preterm infant, haemorrhagic and ischaemic lesions as well as infection account for the majority of seizures.⁴ Neonatal seizures have been associated with adverse neurodevelopmental outcome, but there is continuing debate about the extent to which seizures can cause or aggravate brain injury themselves.^{5,6}

Traditionally, neonatal seizure has been diagnosed on the basis of clinical observation of changes in behavioural state, motor and autonomic function. It is now known that diagnosis by clinical observation alone dramatically underestimates the prevalence of neonatal seizure.⁷ This is because the majority of seizures, as diagnosed by EEG, do not manifest themselves clinically.

Video-EEG is rightly considered to be the gold standard for seizure detection, but even with EEG diagnosis can remain difficult because of the high-amplitude, discontinuous nature of neonatal EEG activity. It is also important to consider the case where classic clinical manifestations of seizure are apparent whilst the EEG remains seizure negative. Many of these events can be explained by paroxysmal 'nonepileptic' behaviours, but as EEG is known to have limited sensitivity to sub-cortical neurons there remains an important question: do neonates who exhibit clinical manifestations but lack electrographic expression of seizure have a sub-cortical seizure focus, which EEG cannot detect?

Diffuse Optical Imaging

Diffuse optical imaging (DOI) uses the relative absorption of two or more wavelengths of near-infrared light to measure changes in the concentration of oxyhaemoglobin and deoxyhaemoglobin in tissue. If enough light sources and detectors are arranged at the scalp, it is possible to produce three-dimensional images of

changes in blood volume and oxygen saturation in both cortical and sub-cortical regions of the brain.⁸ Indeed, three-dimensional, whole-head diffuse optical imaging has been performed in both healthy and brain-injured neonates.^{9,10}

The application of DOI techniques has become increasingly common in the last 15 years in both clinical and research environments. Diffuse optical imaging is often used to investigate brain function in response to a particular external stimulus. The increase in metabolic demand of activated groups of neurons usually results in an over-compensation in localised cerebral blood flow. This haemodynamic response to stimulation gives rise to the blood-oxygen level dependant (BOLD) signal observed in functional magnetic resonance imaging (fMRI) and is also what allows DOI to localise and quantify functional activation in the brain. However, DOI has several important advantages over fMRI. Diffuse optical imaging can be performed at the bedside, which makes it particularly suited to studies of vulnerable infants, it is silent, does not affect neonatal developmental care procedures and it is relatively inexpensive.

Diffuse optical imaging techniques have been used to study healthy neonatal brain function in response to a variety of visual¹¹, auditory¹² and somatosensory¹³ stimuli. However, an external stimulus is by no means necessary; DOI has been used to monitor continuous changes in blood volume and oxygen saturation¹⁴ including studies in neonates with hypoxic-ischaemic encephalopathy.¹⁵

Combining EEG and DOI

Electroencephalography is the oldest method of non-invasively interrogating brain function, and has survived as a technique because it can provide a vast amount of clinical information whilst being easy to perform at the bedside. It has, however, had its clinical usefulness limited by the advent of structural imaging techniques, particularly x-ray CT and MRI. This is because despite having far superior temporal resolution (sample rates routinely reach 2 KHz) the nature of scalp EEG severely limits its spatial resolution. Where once EEG was used to investigate all manner of cerebral disease, it now has one dominant clinical purpose; the study and diagnosis of epileptic disorders.

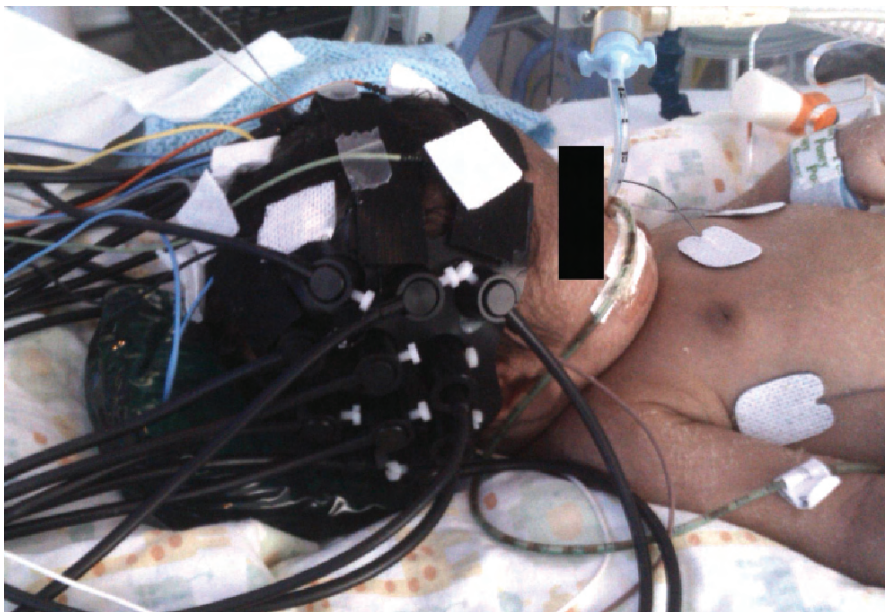
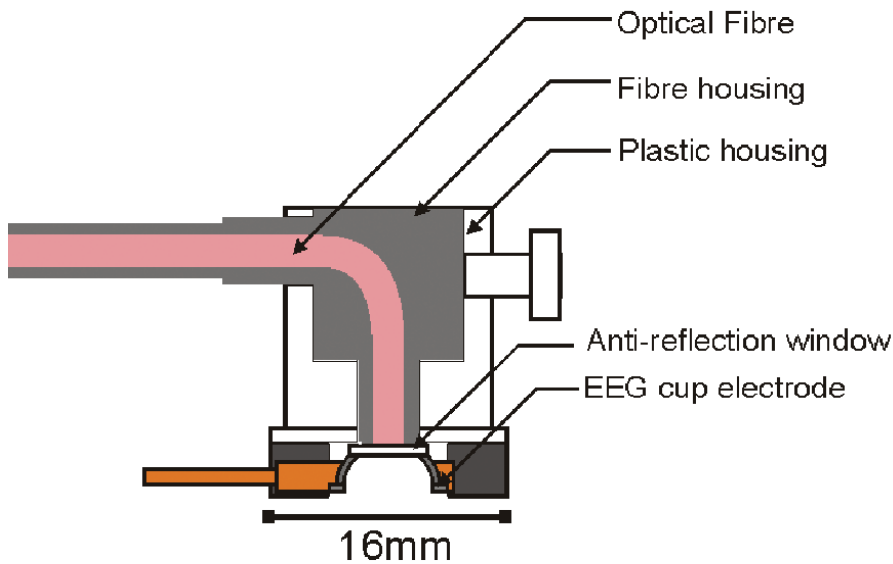


Figure 1a (Top): The opto-electrode probe design. b (Bottom): An EEG-DOI experiment being performed in neonatal intensive care. The black optical fibres and coloured EEG leads can be seen.

Combining EEG and DOI has several advantages because the two systems are complementary in nature. Whilst EEG measures the overall electrical activity of groups of neurons, DOI measures the haemodynamic response to this activity. A combined system will therefore allow the relationship between these two signals (broadly referred to as neuro-vascular coupling) to be studied directly. A better understanding of neuro-vascular coupling in the neonate, particularly under conditions of encephalopathy may well have clinical applications. The spatial resolution of DOI is good, comparable to that of fMRI. Given the excellent temporal resolution of EEG, a combined EEG-DOI system has the advantage of good spatio-temporal resolution, a characteristic which is rare in non-invasive functional imaging techniques. Unlike EEG and fMRI, EEG and

DOI do not interfere with one another, making it less technically challenging to obtain simultaneous measurements. Both EEG and DOI are totally non-invasive, can be performed at the bed side and are not overly sensitive to movement artifacts. It is for these reasons that a combined system is well suited to the study of vulnerable patient groups, particularly neonates in intensive care. The importance of a combined electrophysiological and optical approach to the future of neonatal neuromonitoring was recently highlighted in a review by Toet and Lemmers.¹⁶ In order to facilitate simultaneous EEG and DOI, an integrated optical-electrical probe has recently been developed at the Biomedical Optics Research Laboratory at UCL.¹⁷ This probe combines a modified EEG cup electrode and an optical fibre bundle, as shown in Figure 1a. The probe

design maximises the number of optodes and electrodes which can be placed on a given area of the scalp (which is vital in neonatal studies) whilst maintaining the standard clinical electrode application method. This probe design has allowed full neonatal EEG to be performed simultaneously with diffuse optical imaging of the temporal lobes for the first time (Figure 1b).

DOI and EEG to study seizures

There are several reasons why EEG-DOI has great potential in the clinical monitoring of neonatal seizures. First, as each system measures a different neurophysiological response, an additional indication of seizure onset and measure of seizure burden will be provided beyond that of EEG alone. Second, a combined system will significantly improve localisation of a partial seizure focus. Third, seizure-induced failures in cerebrovascular function can be directly observed in real time¹⁸, and fourth, the addition of DOI will allow regions of the brain to be interrogated which, because of their depth or orientation, are essentially invisible to EEG. Given that sub-cortical seizure foci have been observed which do not manifest themselves electrographically¹⁹ we believe a combined system could be of great clinical benefit.

Combined EEG and DOI methods have already been used to study functional activation and neuro-vascular coupling in adults²⁰, but the use of such systems in the study of epilepsies is also becoming increasingly common. Between 1997 and 2000, Watanabe et al. successfully employed EEG-DOI techniques in a study of 28 adult patients exhibiting partial seizure.²¹ In 2008 the haemodynamic response to absence seizures in children was characterised²² and EEG-DOI methods were used to detect seizure focus in a child prior to surgery.²³ The haemodynamic response to non-epileptic discontinuous neonatal EEG activity has been studied using EEG and simplified diffuse optical techniques²⁴ and last year, similar methods were used to produce the first ever study of a seizing neonate.²⁵ This study was the first to show that a haemodynamic response can be observed in response to neonatal seizures.

While both techniques are independently well established, there remain several important questions which must be answered before a combined EEG-DOI system can begin to be clinically implemented. It has to be determined whether neonatal seizures produce a truly robust and identifiable haemodynamic response, and that response must be carefully characterised. It will then be necessary to examine whether a combined EEG-DOI system can more reliably identify seizure events than EEG alone, or indeed whether it is possible for EEG-DOI to identify seizure events which EEG misses altogether. Nevertheless this integrated approach to seizure detection and classification may yield important and novel information on brain activity in this high risk population. ♦

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- Gallagher A, Lassonde M, Bastien D, et al. *Non-invasive pre-surgical investigation of a 10 year-old epileptic boy using simultaneous EEG-NIRS*. *Seizure*. 2008;17(6):576-82.
- Roche-Labarbe N, Wallois F, Ponchel E, Kongolo G, Grebe R. *Coupled oxygenation oscillation measured by NIRS and intermittent cerebral activation on EEG in premature infants*. *NeuroImage*. 2007;36(3):718-27.
- Wallois F, Patil A, Kongolo G, Goudjil S, Grebe R. *Haemodynamic changes during seizure-like activity in a neonate: A simultaneous AC EEG-SPIR and high-resolution DC EEG recording*. *Neurophysiologie Clinique/Clinical Neurophysiology*. 2009;39(4-5):217-27.

RAatE 2010

Recent Advances in Assistive Technology & Engineering Conference and Exhibition

Monday 29 November 2010,

University of Warwick Conference Centre, Coventry, CV4 7AL

RAatE 2010 is the only UK conference focused on the latest innovations and developments in Assistive Technology. This conference will be of interest to everyone who uses, works with, develops or conducts research on Assistive Technologies (AT). This year's event is run in association with the Health Design & Technology Institute at Coventry University. The HDTI seeks to develop new products and new systems of care provision for the assisted living sector.

RAatE 2010 is delighted to announce this year's keynote speaker as Dr. Martin Ferguson Pell, the Dean of the Faculty of Rehabilitation Medicine at the University of Alberta, Canada. Dr. Ferguson Pell's background is in Biomedical Engineering and he is a registered Clinical Scientist. He has extensive experience working in clinical academic settings developing engineering solutions to overcome barriers experienced by people with physical disabilities.

Paper presentations and Workshops at **RAatE 2010** will include:

- Case Studies of Successful Interventions
- Care for Older People, People with Dementia and Children in Rehabilitation following Stroke
- Healthcare & Telehealth
- Innovative Access & Innovative Wheelchair Control
- Assisted Living Support

To book your place at **RAatE 2010** register online at www.raate.org.uk Cost is £125 inclusive of VAT.

For more information on sponsorship opportunities or to book an exhibition stand please contact hdti.info@coventry.ac.uk



The British Neuropsychiatry Association

Neurology and Psychiatry SpRs Teaching Weekend

10/11/12 December 2010, St Anne's College – Oxford

Topics to include: Neurological and psychiatric history taking and examination • Investigations (MRI, EEG) • Psychological presentations of neurological disorder • 'neurological' presentations of psychological disorders and the biological basis of psychiatric symptoms.

Course Fee: £250 (Includes two nights' bed & breakfast, lunches, morning and afternoon coffee/tea and Friday night dinner).

24th Annual General Meeting

10/11 February 2011

With a joint meeting, 9 February, with the **Section of Neuropsychiatry, RCPsych**
Venue: The Institute of Child Health, Guilford St, London

Topics to include: Sleep (SoN/BNPA) • Neuropsychiatry of Parkinson's Disease • Neuropsychiatry and the New Genetics.

For outline programme and registration form visit:

www.bnpa.org.uk

For details of exhibition/sponsorship opportunities, contact: Jackie Ashmenall on

Phone/Fax: 020 8878 0573/Phone: 0560 1141307

Email: admin@bnpa.org.uk or jashmenall@yahoo.com

To list your event in this diary, email brief details to John Gustar at editorial@acnr.co.uk by 6th October, 2010

2010

SEPTEMBER

3rd International Congress Biotechnologies for Spinal surgery
1-4 September, 2010; Amsterdam, Netherlands
E. meisel@bergmannstrost.com
www.biospine.org

Cambridge Memory Disorders Workshop
2-3 September, 2010; Cambridge, UK
T. 01223 217557
E. fiona.aschmann@addenbrookes.nhs.uk
www.ozc.nhs.uk

Computers for Therapy, one day course
6 September, 2010; London UK
T: 0208 780 4500 x5140
E: pdenning@rhn.org.uk
www.rhn.org.uk/nec_001.asp

PRION2010 – From Agent to Disease
8-11 September, 2010; Salzburg, Austria
E. Herbert.budka@meduniwien.ac.at
www.prion2010.org

17th International Congress of Neuropathology
11-15 September, 2010; Salzburg, Austria
Brigitte Millán-Ruiz, T. 43 1 404 005 573
E. brigitte.millan-ruiz@meduniwien.ac.at

Evaluation of Social Interaction
12-14-September 2010; Derby, UK
T. 01332 254679
www.ncore.org.uk

14th International Conference on Intracranial Pressure and Brain Monitoring
12-16 September, 2010; Tübingen, Germany
E. icp2010@conventus.de
www.icp2010.eu

Parkinson's Disease SpR Masterclasses
13-17 September, 2010; Central England, UK
T. 01872 225552
E. info@redpublish.co.uk
www.redpublish.co.uk/courses

School AMPS
13-17-September 2010; Derby, UK
T. 01332 254679
www.ncore.org.uk

Introduction to MOHO
14 September 2010; Derby, UK
T. 01332 254679
www.ncore.org.uk

Health Care Records on Trial
15 September 2010; Derby, UK
T. 01332 254679
www.ncore.org.uk

Understanding & Managing Occupational Stress
16 September 2010; Derby, UK
T. 01332 254679
www.ncore.org.uk

Congress of Neurological Surgeons Annual Meeting
16-21 September, 2010; San Francisco, USA
Congress of Neurological Surgeons
T. +847 240 2500,
F. +847 240 0804
E. info@ICNS.org
www.neurosurgon.org

OZC – Understanding Brain Injury
17 September, 2010; Ely, UK
T. 01353 652173
E. Rachel.everett@ozc.nhs.uk

Evolving MS Services
17 September, 2010; Maidstone, UK
T. 0208 438 0809
E. pcrossman@mssociety.org.uk

Understanding and Dealing with Behaviour Problems following ABI
17-18 September, 2010; Gatwick Airport, London, UK
E. enquiries@braintretraining.co.uk
www.braintretraining.co.uk

Clinical Reasoning in Soft Tissue Repair: Using the evidence to maximise recovery using manual therapy, exercise and electrotherapy
18 September, 2010; Bath, UK
www.physiouk.co.uk

Second Meeting of the European Societies of Neuropsychology
22-24 September, 2010; London, UK
E. dana.samson@nottingham.ac.uk

An Introduction to Bobath Concept (Module 1)
23-24-September 2010; Derby, UK
T. 01332 254679
www.ncore.org.uk

14th Congress of the European Federation of Neurological Societies (EFNS 2010)
25-28 September, 2010; Geneva, Switzerland
T. 41 229 080 488
E. efns2010@kenes.com

Neuro Upper Limb for OT's
28 September 2010; Derby UK
T. 01332 254679
www.ncore.org.uk

2nd World Parkinson Congress
28 September–1 October, 2010; Glasgow, UK
T. Elizabeth Pollard, (001) 212.923.4700
E. info@worldpdcongress.org

10th Annual Brain Injury Legal Seminar
30 September, 2010; London, UK
T. 07501483989
E. chloe_hayward@hotmail.com

3rd National Autism and Depression Conference
30 September–1 October, 2010; London, UK
E. anne.haylock@markallengroup.com

Molecular and Functional Imaging in Clinical Practice
30 September–1 October 2010; London, UK
www.bir.org.uk

20th Alzheimer Europe Conference
30 September – 2 October, 2010; Luxembourg
E. info@alzheimer-europe.org
www.alzheimer-europe.org/conferences/luxembourg-2010

OCTOBER

6th International Symposium on Neuroprotection and Neurorepair
1-4 October, 2010; Rostock Germany
T. +49 (0)341240596-50
F. +49 (0)341240596-51
E. johannes.boltze@izi.fraunhofer.de

19th Symposium Neuroradiologicum
4-9 October, 2010; Bologna, Italy
E. marco.leonardi@symposiumneuroradiologicum.org
www.symposiumneuroradiologicum

Global Symposium on Dietary Treatments for Epilepsy and other Neurological Disorders
5-8 October, 2010, Edinburgh, UK
E. Julie@matthewsfriends.org

AANEM Annual Scientific Meetings
6-9 October, 2010; Quebec City, Quebec, Canada
T. + (507) 288-0100,
F. + (507) 288-1225
E. aanem@aanem.org

European Life Science meeting: Induced pluripotent stem cells: production and utility in regenerative medicine
7 October 2010; Hertfordshire, UK
E. enquiries@euroscicon.com
www.regonline.co.uk/IPSO9

CBT
7 October 2010; Derby, UK
T. 01332 254679
www.ncore.org.uk

Neuro Upper Limb for OT's
8-October 2010; Derby, UK
T. 01332 254679
www.ncore.org.uk

Discussion Workshop: Improving Immunohistochemistry 2010
8 October, 2010; Welwyn Garden City, UK
E. enquiries@euroscicon.com
www.regonline.co.uk/workihc2010

ABN Annual General Meeting
11-14 October, 2010; Bournemouth, UK
E. karen.reeves@theabn.org

Assessment & Treatment of a client with Perceptual & Cognitive Dysfunction
12-13 October 2010; Derby, UK
T. 01332 254679
www.ncore.org.uk

7th World Stroke Congress
13-16 October, 2010; Seoul, Korea
T. +41 22 908 0488 x966
E. dhuriel@kenes.com
www.kenes.com

2010 Congress of the European Committee for Treatment and Research in Multiple Sclerosis
13-16 October, 2010; Gothenburg, Sweden
T. +41 61 265 4464
E. secretariat@ectrims.eu

An Introduction to Bobath Concept (Module 2)
14-15 October 2010; Derby, UK
T. 01332 254679
www.ncore.org.uk

Positioning for Function, two day course
14 - 15 Oct 2010, London UK
T. 0208 780 4500 x5140
E. pdenning@rhn.org.uk
www.rhn.org.uk/nec_001.asp

Discover the Thorax with LJ Lee
15-17 October, 2010; Sutton, UK
www.physiouk.co.uk

Thoracic Outlet Syndrome: Assessment, Differential Diagnosis and Hands on Treatment
16 October, 2010; Bristol, UK
www.physiouk.co.uk

Practical Neuro-Linguistic Programming
18-19 October 2010; Derby, UK
T. 01332 254679
www.ncore.org.uk

British Neuropsychological Society Autumn Meeting
20 October, 2010; London, UK
E. dana.samson@nottingham.ac.uk

42nd Danube Symposium and 10th Congress of the European Society of Clinical Neuropharmacology
October 21–24, 2010; Zagreb, Croatia
E. danube@nepsy.szote.u-szeged.hu
www.szote.u-szeged.hu/neur/danube
www.esncp.org

UKNG Education/Update: Ischaemic Stroke
22 October, 2010; London, UK
E. Annie.Sellar.sellarannie@hotmail.com

10th International Congress of Neuroimmunology
26-30 October, 2010; Barcelona, Spain
Francesca Mariani,
T. 39 0 65 193 499,
F. 39 0 65 194 009
E. mariani@eemservices.com

4th World Congress on Controversies in Neurology (Cony)
October 28–31, 2010; Barcelona, Spain
E. cony@comtecmed.com
www.comtecmed.com/cony

Neurology Symposium
27 October, 2010; Edinburgh, Scotland
E. patricia@oncologynews.biz

2nd European Headache and Migraine Trust International Congress (EHMTIC)
October 28–31, 2010; Nice, France
E. sgampel@kenes.com
www2.kenes.com/ehmtic/Pages/Home.aspx?refl=dbl

The 4th World Congress on Controversies in Neurology (CONY)
28-31 October, 2010; Barcelona, Spain
E. info@comtecmed.com
www.comtecmed.com/cony

NOVEMBER

Management of Adult Central Nervous System Tumours
3 November, 2010; London, UK
www.bir.org.uk

International Symposium on Nitric Oxide-Cyclic Signal Transduction in Brain
4-6 November, 2010; Valencia, Spain
E. catedrag@cac.es
www.fundacioncac.es/catedrag

Clinical Reasoning in Soft Tissue Repair: Using the evidence to maximise recovery using manual therapy, exercise and electrotherapy
6 November, 2010; Edinburgh, Scotland
www.physiouk.co.uk

MS Trust Annual Conference 2010
7-9 November, 2010; Kenilworth, UK
T. 01462 476700
E. info@mstrust.org.uk

OZC – Communication, Assessment and Rehabilitation
11 November, 2010; Ely, UK
T. 01353 652173
E. Rachel.everett@ozc.nhs.uk

UKABIF Annual Conference
11 November, 2010; London, UK
T. 01752 601318
E. ukabif@btconnect.com

An Introduction to Bobath Concept (Module 3)
11-November 2010; Derby, UK
T. 01332 254679
www.ncore.org.uk

How to do Cognitive Rehabilitation
13 November, 2010; Gatwick Airport, UK
E. enquiries@braintretraining.co.uk
www.braintretraining.co.uk

NanoBioTech-Montreux 2010
15-17 November, 2010; Montreux, Switzerland
www.nanotech-montreux.com

The West of England Seminars in Advanced Neurology (WESAN)
18 & 19 November, 2010; Exeter, UK
E. cgardnerthorpe@doctors.org.uk

3rd International Conference on Fixed Combination in the Treatment of Hypertension, Dyslipidemia and Diabetes Mellitus
18-20 November, 2010; Brisbane, Australia
T. +41 (0)22 5330 948
F. +41 (0)22 5802 953
E. fixed2010@fixedcombination.com

41st Rio International Eating Disorders and Obesity Conference
19-20 November, 2010; Rio de Janeiro, Brasil
E. anne.haylock@markallengroup.com

Electrotherapy Update: Current Concepts in Electrical Stimulation (Study Day 1)
20 November, 2010; Farnborough, UK
www.physiouk.co.uk E90

Electrotherapy Update: Current Concepts in Tissue Repair (Study Day 2)
21 November, 2010; Farnborough, UK
www.physiouk.co.uk

After Meningitis - the impact of meningitis and meningococcal septicaemia
23 November, 2010, Solihull, UK
T. 01453 769032
E. susette@meningitis-trust.org

Evolving MS Services
26 November, 2010; Liverpool, UK
T. 0208 438 0809
E. pcrossman@mssociety.org.uk

1st Oxford Integrated Neurology Course

Conference details: 30 June-2 July, 2010; Oxford, UK. Reviewed by: Dr Michal Rolinski, FY2, Oxford, UK.

The British summer was in full bloom as 27 consultants, 21 trainees (at least half ST3 and above) and 2 GPs descended on Oxford for the inaugural Oxford Integrated Neurology Course; a three-day course aiming to cover numerous neurological topics in a mixture of scientific and clinical perspectives (and with 15 CPD points on offer). Set in St Anne's College, across the road from the historic Radcliffe Infirmary, the course provided an intimate setting for the audience to interact with the expert faculty, sparking interesting questions and insightful discussion.

After words of welcome from Head of Department Professor Christopher Kennard, the course began with Professor Sarah Tabrizi from the Institute of Neurology giving a fascinating introduction into the crucial role of protein misfolding in neurodegenerative diseases. As well as discussing the recent discoveries in the fields of motor neuron disease (MND), Huntington's and prion diseases, preclinical developments in cognitive impairment were also featured, a topic then developed further by Prof Gordon Wilcock, sharing with us his years of experience diagnosing dementia. The afternoon continued with Dr Allyson Parry discussing the interaction between neurology and oncology, highlighting three cases where, not only the neoplastic process, but also the treatment led to severe, and challenging neurological presentations. The same could be said for the cases presented by Professor Tom Solomon from the University of Liverpool, who gave a comprehensive and entertaining account of the controversies surrounding the entity known as chronic Lyme disease, which certainly got the discussion flowing.

After a brief account of the rich history of Medicine and Neuroscience at Oxford from Professor Alastair Buchan, (Head of the Medical Sciences Division at Oxford University), the first day ended with the audience treated to a guest lecture by Professor Marcus du Sautoy, the Oxford University Simonyi Professor for the Public Understanding of Science. With his back-




ground in mathematics, he showed us the journey involved in the making of a BBC Horizon programme attempting to explore the nature of consciousness.

Day two had a clear aim to try to crack some of the big chestnuts in neurology, namely MND, stroke and multiple sclerosis (MS). Dr Kevin Talbot gave us an invaluable guide to approaching a patient with possible MND challenging us not to be afraid to rely mainly on clinical judgement, before Professor Chris Shaw divulged the recent exciting developments in the genetics of this disease. Controversy was once again in the air when course co-organiser Dr Ursula Schulz attempted (successfully, in my opinion!) to dismiss the common myth of vertebrobasilar insufficiency, a topic that certainly struck a chord with special guest Professor Louis Caplan ahead of his fascinating seminar on under-recognised stroke types. With audience participation strongly encouraged, there was no place to hide from committing to a diagnosis after each case history! Any Oxford and Cambridge rivalry seemed put aside as Dr Andrew Weir gave a


very wise talk on the evidence-based practicalities of managing people with clinically isolated syndromes, followed by Dr Alasdair Coles' on novel disease modifying therapies in MS. Dr Weir was once again in action as he presented one of the three Oxford Grand Round Archive cases chosen by course co-organiser Dr Martin Turner to surprise, inspire and, as was demonstrated by the entirely unexpected case of 'surfer's myelopathy', completely perplex the audience. Just before retiring for a glass of fizz on the lawn at Trinity College, followed by the course dinner at the historic hall, Professor Michael Swash gave us a fascinating and insightful run-through of the key pioneers that still influence neurology today.

The final day centred on epilepsy and movement disorders. The sessions began with Dr Michael Johnson describing some of the evidence-poor challenges related to use of add-on antiepileptic medications. When the drugs don't work, Professor Mark Richardson then demonstrated the role that could be played by current and novel neurosurgical intervention. Deep brain stimulation was a theme then also discussed by Dr Ralph Gregory, who addressed the problem of what is available when the L-dopa 'honeymoon' is over. Dr Michele Hu, addressing the often-feared topic of movement disorder semiology through videos, rounded off the course. After re-fuelling for the last time at the St Anne's lunch hall, the event was brought to a close with a rare opportunity to discover some of the historical places and artefacts mentioned by Professors Buchan and Swash first hand, on a medical tour of Oxford led by the two of the University's historians.

The course set out to interweave basic science and clinical practice, and this aim that was well met. The organisers successfully set out to find speakers that would not only be able to update the delegates on the latest research but also bring it to life through their clinical practice. There was something inspiring for everyone, whether an experienced consultant or like me, at the start of my neurological career. ♦



ASSOCIATION OF BRITISH NEUROLOGISTS



One day Autumn Meeting of the Association of British Neurologists

Royal College of Physicians in London on Thursday 30th September 2010

The programme will consist of four short courses, with parallel sessions of free communications based on submitted abstracts, and two plenary lectures.

To Register

Complete the online form found on www.theabn.org from 1st July.

£125 – ordinary members

£50 – trainees

This includes all meals and refreshments. A dinner will be held in the evening for an additional charge.

14th EFNS Congress

Conference details: 28-25 September, 2010; Geneva, Switzerland.

PREVIEW

1924 abstracts submitted to 14th EFNS Congress, Geneva, Switzerland

The call for abstracts to be submitted for presentation at the 14th EFNS Congress in Geneva, Switzerland, September 25-28, 2010, was answered with a strong response of more than 1900 contributions. This number again demonstrates the high scientific quality of the topics dealt with at the EFNS congresses.

Don't miss the...

- EFNS Lecture on Clinical Neurology
Thomas Brandt, Munich, Germany
"Out of Balance"

Tuesday, September 28, 2010, 12.00 – 13.00

- Uschi Tschabitscher Prize – Tournament for Young Neurologists

The 2010 participants and winners of a travel grant to Florence and a free congress registration are:

Tournament 1 – Clinical neurology

Sunday, 26 September 2010, 11:00-12:30h

- Bartosz Karaszewski, Gdansk, Poland
- Dacia Dalla Libera, Milano, Italy
- Maja Kojovic, London, UK
- Marcel Heers, Erlangen, Germany
- Pasquale Striano, Genova, Italy
- Jordi Díaz-Manera, Barcelona, Spain

Tournament 2 – Basic neurology

Monday, 27 September 2010, 11:00-12:30h

- Juan Carlos Sanchez-Mansó, London, UK
- Lucas Schirmer, Göttingen, Germany
- Yana Motuzova, Minsk, Belarus
- Marte Bjørk, Trondheim, Norway
- Renuka Natarajan, Tampere, Finland
- Cathryn Poulton, Rotterdam, The Netherlands

Please register **NOW** for the teaching courses at €15 per course.
Only a limited number of tickets are available!
www.efns.org/efns2010

World Parkinson Congress welcome letter from Steve Ford

Conference details: 28 September-1 October, 2010; Glasgow, UK. Reviewed by: Steve Ford, Chief Executive, Parkinson's UK

PREVIEW

The UK is a world leader in the field of Parkinson's research and clinical practice. The World Parkinson Congress (WPC) will take place this September in Glasgow. As a member of the Steering Committee, I am delighted to extend this invitation to you to attend.

It will be the first time that the World Parkinson Congress has come to the UK. As you read this you may be thinking "not another research conference about Parkinson's", and it's true that conferences which highlight Parkinson's research take place with some frequency.

What makes the World Parkinson Congress stand out is that it unites the international Parkinson's research community, and is aimed not just at scientists and researchers, but at everyone involved with Parkinson's, including those living with the condition, their carers, clinicians and health care professionals.

The WPC will have a truly international flavour, with over 3,000 delegates from around fifty countries representing all areas of Parkinson's, joining together with a common purpose. There will be something for everyone, from experienced researchers and those starting out in their careers, to health care professionals with a special interest in Parkinson's.

What's in the programme?

A wide range of topics will be covered over four days. Sessions and workshops will cover the best in scientific research that is helping to advance our understanding of the development of the condition itself, as well as translational and clinical science that will help slow

the progression of the condition and ease its impact on those with Parkinson's.

The Congress will also focus on all aspects of life with Parkinson's, including treatments, alternatives to drugs, clinical trials, neuroprotection, non-motor symptoms, gene therapy, deep brain stimulation, speech and movement therapies and the role of exercise.

For anybody with a passionate interest in advancing their understanding of Parkinson's, this is the conference for you.

Who will be speaking?

International speakers will host sessions, and a number of researchers who have received funding from Parkinson's UK will be showcasing their work.

Our Director of Research, Dr Kieran Breen, will be co-chairing sessions on biomarkers and brainbanking, and gene and cellular therapies with Deniz Kirik from Sweden. Deniz will also be a keynote speaker at Parkinson's UK's own research conference in York this November.

There will be plenty of opportunities to network at the fringe sessions. The World Parkinson Congress also gives the opportunity for people with Parkinson's to meet and hear first hand from the scientists and clinicians who have chosen to work in the neurosciences.

For those looking to relax, an optional tour includes a visit to sample the delights of Glengoyne Distillery.

On behalf of everyone involved in putting together the World Parkinson Congress, we look forward to meeting you in Glasgow. ♦



The World Parkinson Congress will run from September 28–October 1, 2010 at the Scottish Exhibition & Conference Centre, Glasgow. Find out more at www.worldpdcongress.org.

Parkinson's UK Research Conference, 1-2 November 2010, Royal York Hotel, York.
For more information visit parkinsons.org.uk

Acquired Brain Injury Behind Closed Doors – unspoken issues and possible solutions

Conference details: 11 November 2010, 2010; London, UK.

PREVIEW

The UKABIF Annual Conference 2010 is shaping up to offer another unmissably informative day. The conference, which has become the key event in the brain injury calendar, attracts a wide range of clinicians, personal injury lawyers, case managers and social care workers from a variety of settings and locations. Last year saw over two hundred delegates packing the halls of The Russell Hotel in London and this year's event is already selling fast.

The programme includes such eminent speakers as Dr Igo Krebs, who will be joining us from Massachusetts in the United States. He will deliver the keynote speech and talk about the revolutionary uses of robots in rehabilitation.

Penny Weekes, an occupational therapist specialising in acquired brain injury (ABI) in children, young people and their families will discuss the issues surrounding fatigue in teenagers post ABI. This will be complemented by a talk from Edinburgh based psychologist, David Johnson on the many areas specific to children with ABI.

Mr Antonio Bell of Southampton General Hospital will give an overview of hypopituitarism and other hormonal imbalances which will be followed by Joanna Lane's personal account of her son's hypopituitarism.

Dr Barbara Chandler will approach Sex and Relationship problems in more detail - an area which is enormously problematic for many



people with acquired brain injury but not one which is often explored and discussed.

Dr Howard Jackson will look at alcohol and substance abuse following ABI and finally Dr Huw Williams will talk about the work carried out by his team at The University of Exeter researching the links between crime and ABI.

Prof Mike Barnes, Chair of UKABIF said, "This conference aims to highlight the complexity of acquired brain injury and offer the delegates

some practical solutions to the issues that they face either in their own situation or that of their clients, patients or family members."

UKABIF will also take the opportunity to present the UKABIF Awards for Innovation – new this year – in the following categories:

- Innovation by a law firm in the field of ABI
- Innovation by a clinician in the field of ABI
- Innovation by a care provider in the field of ABI
- Innovation by a social care worker in the field of ABI
- Innovation by a voluntary sector provider or registered charity in the field of ABI

The Russell Hotel offers a fabulous venue for events of this kind with a spacious exhibition hall adjoining the large conference room. An exhibition will run alongside the conference and there will be ample time for networking during the day.

UKABIF would like to thank the sponsors: Pannone, The Oakleaf Group, Hunters Moor, The Portland Hospital, The Huntercombe Group and Voyage. ♦

The conference has CPD accreditation. For details about the programme and to book places please see the loose insert with this publication or book directly through our website:
<http://www.ukabif.org.uk/acquired-brain-injury-behind-closed-doors>.



EFNS GENEVA 2010

14TH CONGRESS OF THE EUROPEAN
FEDERATION OF NEUROLOGICAL SOCIETIES
GENEVA, SWITZERLAND, SEPTEMBER 25 – 28, 2010

Don't miss the opportunity to meet more than
5,000 neurologists and join us at the EFNS Congress in 2010.
The Preliminary Congress Programme is online now.

Organised in co-operation with the Swiss Neurological Society

Co-sponsored by the European Section of the Movement Disorder Society (MDS-ES)

Co-sponsored by the World Federation of Neurology (WFN)



For details please visit
www.efns.org/efns2010

EFNS 2010 c/o Kenes International Global Congress Organisers and Association Management Services
1-3 rue de Chantepoulet, P.O. Box 1726 1211 Geneva 1, Switzerland
PHONE +41 22 908 04 88 FAX +41 22 732 28 50 EMAIL efns2010@kenes.com WEB www.efns.org/efns2010



Royal College
of Physicians
Setting higher medical standards

This conference will be held at the *Royal College of Physicians*,
11 St Andrews Place, Regent's Park, London NW1 4LE

**NSF FOR LONG-TERM NEUROLOGICAL
CONDITIONS – FIVE YEARS ON**
*A JOINT CONFERENCE WITH THE BRITISH
SOCIETY OF REHABILITATION MEDICINE*
Thursday 25 November 2010

This conference aims to provide an update on the needs of people with long-term neurological conditions. It will renew the focus on the NSF standards as the key to providing improved services and look specifically at rehabilitation aspects. Speakers will review the evidence base, propose best-practice models for implementation and consider the issues around commissioning.

Audience: consultants in rehabilitation medicine, neurology/neurosurgery, geriatric medicine, palliative medicine, trainees, allied health and social care professionals, service providers and commissioners responsible for NSF implementation.

Further information is available on-line at
www.rcplondon.ac.uk/conferences or from:
Conference Department, Royal College of Physicians
Tel: 020 3075 1436/1300/1252.
Email: conferences@rcplondon.ac.uk



DATE FOR DIARY

11th Annual
UK Movement Disorders Meeting

Friday 15th and Saturday 16th October 2010
London, UK

Programme to be finalised. CPD approval will be sought

Chaired by

Prof Anthony Schapira,
Professor of Neurology,

*Institute of Neurology, UCL and Royal Free Hospital and
National Hospital for Neurology and Neurosurgery, Queen Square, London, UK*

Alongside an International Clinical Faculty

Accommodation will be provided for those delegates
who require it in order to attend the meeting.

As these meetings are very popular and
oversubscribed, please register early to avoid disappointment.
To register your interest in attending please e-mail: neurology@boehringer-ingenheim.com

Educational Meeting Sponsored by Boehringer Ingelheim Ltd
Date of preparation: November 2009
PPX1303



EUROPEAN CHARCOT
FOUNDATION
UNIVERSITY CLASSES VII

Focussed on Pathology
An Educational Programme on
Multiple Sclerosis

December 1, 2010, Fiuggi, Italy

Faculty:

M. Clanet, G. Comi, G. Edan, M. Esiri, F. Fazekas,
O. Fernandez, M. Freedman, C. Heesen, L. Kappos, T. Kuhlmann,
H. Lassmann, X. Montalban, J. Palace, P. Soelberg Sørensen

Call for Biogen Idec young investigators travel grants

The European Charcot Foundation is pleased to announce that Biogen Idec has provided an unrestricted educational grant to sponsor 20 young investigators with a travel grant of €1500, to attend the University Classes in Multiple Sclerosis VII.

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Dr Andrew J Larner

is the editor of our Book Review Section. He is a Consultant Neurologist at the Walton Centre for Neurology and Neurosurgery in Liverpool, with a particular interest in dementia and cognitive disorders. He is also an Honorary Apothecaries' Lecturer in the History of Medicine at the University of Liverpool.

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Neurological Signs: Lycanthropy



Werewolf: engraving by Lucas Cranach der Ältere, 1512.

I had always understood lycanthropy to mean the transformation of a human into a wolf (Greek: *lukos*=wolf, *anthropos*=man). Such animal-like behaviour has a long history.^{1,2} The mythical werewolves so beloved of the film industry aside, these cases, sometimes labelled “clinical lycanthropy” to emphasize the distinction, usually seem to be associated with psychiatric disorders such as psychosis or depression and have been understood as delusional disorders in the sense of self-identity disorder.³

I was somewhat surprised to read in a recent case report the word lycanthropy used to denote conversion to a pig.⁴ However, this was simply a reflection of my own ignorance, since in a review of over thirty published cases of clinical lycanthropy only a minority had wolf or dog themes.³ Hence the “animal-like behaviour” may encompass a broader phenotype than simply that of the wolf. (I have seen one patient with behavioural variant frontotemporal dementia who, according to his wife, used to bark like a dog.) Perhaps Gregor Samsa’s metamorphosis into a gigantic insect in Franz Kafka’s story *Metamorphosis* (*Die Verwandlung*, 1915) is therefore also an example?

This broader definition including the pig obviously stimulates a few literary reminiscences, perhaps first to come to mind being George Orwell’s *Animal Farm* (1945), wherein the pig Napoleon and his supporters gradually adopt human characteristics, walking on two legs.

Lycanthropy as pig conversion may perhaps be one of the oldest neuropsychiatric syndromes described in literature, not just the medical literature, since a possible example occurs in Homer’s *Odyssey* which may date from the 8th century BC, and be based on even earlier traditions of oral

story telling. In Book X, Odysseus and his men encounter the beautiful Circe, “a formidable goddess with a mortal woman’s voice”, on the island of Aeaëa:

Circe ... prepared them a mixture of cheese, barley-meal, and yellow honey flavoured with Pramnian wine. But into this dish she introduced a noxious drug, to make them lose all memory of their native land. And when they had emptied the bowls which she had handed them, she drove them with blows of a stick into the pigsties. Now they had pigs’ heads *and bristles, and they grunted like pigs; but their minds were as humans they had been before*. So, weeping, they were penned in their sties. Then Circe flung them some forest nuts, acorns, and cornel-berries – the usual food of pigs that wallow in the mud [my italics].

Odysseus’s men may not be alone, since “Prowling about the place were mountain wolves and lions that Circe had bewitched with her magic drugs”.⁵

John Wain’s short story *A message from the Pig-man* (1960) may perhaps be seen as within the same tradition, conveying a six year-old child’s anxieties about encountering the “Pig-man”, whom he imagines to be part man part beast.

As a footnote to this consideration of some of the interrelationships between pigs and men, Ambrose Bierce in his *Devil’s Dictionary* (1906) defined trichinosis, infection with the nematode worm *Trichinella spiralis* due to ingestion of undercooked pork containing encysted *T. spiralis* larvae, as “the pig’s reply to proponents of porcuphagy”. ♦

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EDITOR'S CHOICE

NICE does delirium

This short paper summarises NICE guidance on delirium (www.nice.org.uk/CG103). Although some may consider delirium the exclusive preserve of psychiatry, patients with neurological disease are at risk and hence neurologists will inevitably be involved in the diagnosis, prevention and management of delirium.

The guidance contains few surprises. There is pretty much consensus that prevention is better than cure, so much of the thrust of this document relates to identifying those at risk by repeated assessment of risk factors followed by implementation of interventions recognised to prevent delirium. In the paper, MMSE is advocated as a standardised and validated cognitive impairment measure which may be used. Once delirium is suspected, it seems that diagnosis requires "specialist clinical assessment" which may include use of more specific instruments such as the confusion assessment method (CAM). Management focuses on treatment of causes, reorientation of patients, and provision of a suitable care environment. Should pharmacotherapy be required, haloperidol and olanzapine get the nod (ben-

zodiazepines are not mentioned), albeit at the lowest clinically appropriate dose and with cautious titration. Referencing in the document is fairly much confined to other examples of NICE guidance (dementia, acute illness, violence, Parkinson's disease) rather than the evidence base per se. The Quick Reference Guide acknowledges in a footnote that haloperidol and olanzapine "do not have UK marketing authorisation for this indication".

Will this document improve the diagnosis, prevention, and management of delirium? Will anybody try to measure if it does? Certainly the goal of "a new culture of preventing delirium" is laudable, but, at risk of sounding old fashioned, perhaps more research into understanding the pathogenesis of delirium and better training might bear greater fruit?

– *AJ Larner, Cognitive Function Clinic, Walton Centre for Neurology and Neurosurgery, Liverpool, UK.*

Young J et al. Diagnosis, prevention, and management of delirium: summary of NICE guidance. *BMJ* 2010;341(7766):c3704.

Parkinson's disease: a stimulating read

Deep brain stimulation (DBS) is now a widely accepted treatment for motor complications of Parkinson's disease (PD). Globally about 50,000 patients have been treated since Benabid performed the first DBS operation on the subthalamic nucleus (STN) in the early 1990s. Despite its recent introduction, DBS is accepted by current NICE guidelines for PD as appropriate in selected patients, with typical PD patients being those with advanced disease and major motor complications. Acceptance by the relevant medical and patient communities is one thing, scientific proof of benefit another. In light of this, the PD SURG study, a UK collaboration, set out to provide class 1 scientific evidence of benefit in the form of a randomised controlled trial (RCT). The study, reported here, randomised 366 patients to surgery or best medical therapy, with entrants being those for whom surgical treatment was deemed appropriate because of the severity of their motor symptoms. Control arm patients were assigned to 'delayed surgery' – with optimal medical therapy prior to surgery at one year. The study was open-label rather than blinded (for obvious reasons), and used a quality of life scale (the PDQ-39) as the primary outcome measure. Rating via the PDQ-39 was felt to be more meaningful to patients than the other widely used scales – although the Unified Parkinson's Disease Rating Scale (UPDRS) was also employed as a secondary measure.

The study is preceded by two other RCTs for DBS in PD – a German-based study (Deuschl et al, 2006) and an American-based (Veteran's) study (Weaver et al, 2009). As both of these reported positive results for surgery at 6 months, a similar outcome from the PD SURG

trial could have been anticipated. Indeed, the PD SURG study also demonstrates a clear benefit for surgery over medical treatment, with benefits apparent in expected PDQ-39 domains: mobility; activities of daily living; and bodily discomfort. In parallel, surgical benefits in both OFF and ON motor scores (UPDRS III), and in the dyskinesia scale (UPDRS IV), were apparent. The downsides of surgery included more serious adverse events (including one death), and a non-significant trend to lower cognitive scores. Interestingly, the size of the overall PDQ-39 beneficial effect was smaller than found in the German and American trials, and reasons for this are considered. For example, a 'honeymoon' effect may be present at 6 months post surgery and may have faded somewhat by 1 year. A potentially more interesting difference is the higher use of apomorphine in the UK study (nearly one third of medical arm patients); this drug was not widely used in the other two RCTs and may offer better optimisation of medical therapy in non-surgical patients. The PD SURG study thus not only confirms that surgery is an appropriate treatment for selected patients with complicated PD, but also hints that apomorphine infusions might become more widely used as an alternative to surgery in centres where it is not already employed.

– *Philip Buttery, Cambridge Centre for Brain Repair, Cambridge University, Addenbrooke's Hospital, Cambridge and Queen Elizabeth Hospital, King's Lynn, UK.*

Williams et al. PD SURG Collaborative Group. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. *LANCET NEUROLOGY* 2010; 9:581-91.

Movement disorders: the shaking palsy

SWEDDS is the slightly unappealing name for 'subjects (with suspected Parkinson's disease) without evidence of dopaminergic deficit' and these cases have come to light with the advent of nuclear medicine techniques to visualise pre-synaptic dopaminergic terminals. Many such patients have been thought to have dystonic tremor (DT) on the basis of, sometimes subtle, dystonia (e.g. hyperextension of the thumb, prominent postural element) and lack of bradykinesia (with decrement). Bajaj and colleagues have examined the accuracy of movement disorder specialists in distinguishing tremor dominant Parkinson's disease (TDPD) from other tremulous movement disorders. 38 patients with clinically uncertain PD were included in this prospective study; all had [123I] FP-CIT scans and were followed up over 3 years. Two movement disorder specialists blinded to the scan results diagnosed patients with PD according to Brain Bank Criteria, DT according to published clinical features or ET according to consensus criteria. A third specialist gave the 'final diagnosis' according to SPECT result, history and clinical examination, and 3 years of follow-up. PD patients were treated in the usual way. The video diagnosis was compared with the clinical diagnosis/ SPECT results and the video reviewers were compared with each other.

A false positive diagnosis of PD occurred in 17.4 and 26.1%; and false negative 20% and 6.7% (after excluding 5 patients who were on dopaminergic therapy and thus easier to make a false negative diagnosis). The features leading reviewers to diagnose PD from the video (when the clinical follow up/SPECT supported another diagnosis) were fatiguable bradykinesia, facial hypomimia, reduced arm swing, gait impairment, hypophonic voice, rest tremor. It is possible that fatiguable bradykinesia is seen in DT due to motor flurries interrupting self-paced movements. Facial hypomimia could potentially be seen if the patient was depressed (this information was not given). False negative diagnoses (i.e. the reviewers thought the patients had other tremors but clinically and by SPECT, had PD) were due to dystonic features, myoclonic flurries, no fatiguable bradykinesia, no gait impairment, no pill rolling. Dystonic features can occur in PD and pill rolling and gait impairment are not absolute requirements for a diagnosis. Although bradykinesia is a Brain Bank Criteria requirement for PD, this may be a late feature in TDPD. Given the diagnosis was made by rating videos, rigidity could not, of course, be tested for. There was no difference in the latency of tremor between TDPD and ET/DT (i.e. the TDPD diagnosis cannot be made on the basis of 're-emergent tremor'). Inter-rater reliability was poor as has been noted in previous studies.

Thus the distinction between TDPD and ET/DT is difficult; made easier by clinical observation and SPECT. Practically, in clinically uncertain cases a watch and wait policy could be adopted, or the response to medication observed. With a dubious response to medication, SPECT would be valuable to ensure patients were not given inappropriate treatment. This diagnostic difficulty is more problematic for clinical studies however; previous studies on ET and DT may have included TDPD and vice versa.

– **Wendy Phillips, Neurology Unit, Addenbrooke's Hospital, Cambridge, UK.**

Bajaj N et al. Accuracy of clinical diagnosis in tremulous parkinsonian patients: a blinded video study. JNNP 2010; online first June 14. See SWEDD feature this issue p.30

Measuring myelin-autoreactive T cells in multiple sclerosis: exchanging molecules

The importance of peripheral blood myelin-autoreactive T cells in multiple sclerosis (MS) is debated. Some studies report higher frequencies of these cells in MS patients than in healthy controls (Sun et al. J Immunol 1991) and others see no difference (Hellings et al. J Neurosci Res 2001). The conflicting conclusions reached by different studies may be partly explained by differences in experimental design and the nature of the experimental antigen used. Previous assays of antigen recognition by T cells were based either on cytokine production (for example interferon-gamma (IFN γ) enzyme-linked immunosorbent spot assay: ELISPOT) or proliferation of T cells in response to the antigen, which may both have

underestimated autoreactive cell frequency. In addition, both peptides and recombinant proteins from several different myelin antigens have been used. The nature of the autoantigen is crucial since different forms are processed separately by antigen-presenting cells and may have a reduced efficacy of activation of autoreactive cells.

To avoid such problems, this study describes a more physiological assay using whole myelin extract and a recently developed technique, T cell recognition of antigen-presenting cells by protein transfer (TRAP), which is based on trogocytosis: a phenomenon in which plasma membrane molecules are transferred from antigen-presenting cells by and to memory T lymphocytes after antigen recognition and binding. Compared to IFN γ ELISPOT, this method leads to much higher frequencies of autoreactive T cells and the whole myelin extract causes a larger increase in activated T cells than MBP peptide, so both the novel assay and the novel antigen boost the sensitivity of this analysis. Using this method, the authors report the frequency of whole myelin-autoreactive T cells to be far higher in MS than in healthy controls and to be stable over months in 3 patients and 3 healthy controls, and conclude that the difference in frequencies of myelin-autoreactive T cells may have been underestimated to date. The study requires replication, but this technique could shed light on the role of autoreactive cells in MS and other autoimmune diseases.

– **Suzanne Mosely, Department of Clinical Neurosciences, Cambridge University.**

Bahbouhi et al. T cell recognition of self-antigen presenting cells by protein transfer assay reveals a high frequency of anti-myelin T cells in multiple sclerosis BRAIN 2010; 133:1622-36.

Anti-epileptic cookies?

For those of you like me, for whom the endocannabinoid system was an unknown but anticipated pathway at the time they learned basic neuropharmacology, this paper provides a summary. CB1R is the commonest receptor and its activation inhibits synaptic transmitter release by means of modulating K⁺ or Ca²⁺ channels an inhibiting adenylyl cyclase. Endocannabinoids are released from the post-synaptic cell and spread retrogradely to have their effect on the presynaptic cell. Both the cannabinoid anandamide (AEA) and CB1R are expressed on GABAergic interneurons and glutamatergic neurons in the hippocampus. Cannabinoid release is greater with increased demand, and in numerous animal studies they have been shown to have anticonvulsive properties. In a minority of studies, they were proconvulsive and in a third group, seizures continued but the rats said that they were chilled about them. In this study, CSF was collected from 12 untreated patients who had suffered two or three temporal lobe seizures, diagnosed on electroclinical criteria with normal neuroimaging. Controls had CSF studies for other symptoms and were found to have no neurological diagnosis. The levels of anandamide (AEA) were significantly and markedly reduced in epilepsy patients but the levels of the other endocannabinoid 2-arachidonoylglycerol (2-AG) were no different to controls. From a human in vivo study, these are powerful data. The reduction of hippocampal cell populations in TLE may reduce the production of AEA and remove a seizure-suppressing effect of the cannabinoid. The question remains whether this can be replaced without the psychotropic effects of cannabinoids; after capsules, tablets and sprinkles, now it is time for the antiepileptic cookie.

– **Mark Manford, Neurology Unit, Addenbrooke's Hospital, Cambridge, and Bedford Hospital, Bedford, UK.**

Romigi et al. Cerebrospinal fluid levels of the endocannabinoid anandamide are reduced in patients with newly diagnosed temporal lobe epilepsy. EPILEPSIA 2010;51:768-72.

Epilepsy: what's in a name?

For an epilepsy drone like me, there is little as entertaining as a group of my sadly not that much older, but definitely better Queen Bees, sitting down for an expensive lunch, to define the limits and extent of

their own ignorance by producing a new classification, although I suspect that this noble attempt took at least until suppertime. In truth, the underlying principle behind this reclassification is an important one. That is to move from rigid definitions of epilepsies where they often seem artificial, to an aggregation of concepts underlying particular groupings. This seems to me a positive way forward, in that the classification you need is different when you are thinking about underlying pathology; localisation for the purposes of surgery; prognostication, or when you are thinking about pharmacological mechanisms which might be the target of specific drugs. This is perhaps best seen in the monogenic epilepsies which may be expressed as different electroclinical syndromes in different individuals. With the possible exception of pre-surgical localisation, we are some way away from the knowledge that we need in developing such a purpose-led classification, but this revision does lay a foundation.

Out go some treasured terms such as idiopathic (memorably defined by one of my undergraduate professors as “the idiots do not know the pathology”) and cryptogenic, a singularly meaningless term, which roughly translates as: “we think that there ought to be focal pathology but we're not sure”. In come some new terms such as genetic epilepsy, which seems to vary in meaning from: “we know the gene for this one”, to “it looks from the epidemiological studies as if genes are important here”. We also acquire a brutally honest “unknown epilepsy” for all the inevitable stragglers, which do not quite fit anywhere else. Electroclinical syndromes, such as Lennox-Gastaut syndrome, which have specific implications for management are maintained and an additional category of “constellations” rises appropriately from this lofty stargazing, which includes mesial temporal sclerosis and Rasmussen syndrome amongst others. It is recommended that the term benign is dropped from the names of epilepsies, on the basis that it is sometimes misleadingly optimistic but on the other hand, the term epileptic encephalopathy, denoting an adverse prognosis with cognitive decline is adopted, sadly reflecting inadequacies in our treatments. The group recognised epilepsies which they consider self-limiting, and those which they consider pharmacoresponsive, although it is increasingly clear that those conditions which we used to call idiopathic generalised epilepsy and which we are now being urged to consider genetic or unknown epilepsies, depending on your viewpoint, are less pharmacoresponsive than we think they are. Whilst I share the authors' frustration with the terms simple and complex, since they are almost impossible to differentiate accurately outside a video-telemetry suite, I think that in the era of the minimalist “txtmsg”, a move from “secondarily generalised” to “evolving to a bilateral convulsive seizure” is about as likely as Barack Obama filling his limo at a BP (sorry British Petroleum) gas station. The last revision of the classification was about five years ago and was completely ignored by the general neurology fraternity/soeurity, at least in the UK. I think this is because it has not been reflected in advances in management which need to incorporate a new classification. The proof of this pudding, and I hope it was a good one, will also be in the eating.

– **Mark Manford, Neurology Unit, Addenbrooke's Hospital, Cambridge, and Bedford Hospital, Bedford, UK.**

Berg et al. Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009 EPILEPSIA 2010;51:676-85.

IPSC for SCI?

The use of induced pluripotent stem cells (iPSCs) has really captured the imagination of clinicians, scientists and the public. These iPSCs are reprogrammed adult somatic cells, typically skin fibroblasts, that once generated can be differentiated into different cell fates using protocols that have been developed over the years. This allows such cells to be thought of as in vitro tools for studying disease as well as being a source of ethically neutral cells that could be used for neural repair. In a new paper, it has now been shown using the mouse system that iPSC cells can be used safely in models of spinal cord injury (SCI), namely there was no evidence of tumour formation and the cells made functional neurons, astrocytes and oligodendrocytes. In contrast different

iPS cells derived from this group, that were thought to be UNSafe based on their behaviour in nonobese/severe combined immunodeficiency mice, were just that when grafted into the contused spinal cord. Furthermore the SAFE iPSC cells did not only differentiate and not form tumours but also promoted functional recovery. Thus these cells may have some clinical application, although obviously there is still a long way to go before the human spinal cord could be treated with such an approach.

– **Roger Barker**

Tsuji O et al. Therapeutic potential of appropriately evaluated safe-induced pluripotent stem cells for spinal cord injury. PNAS 2010;107:12704-9.

Multiple sclerosis: location, location, location... does fingolimod trap T helper 17 cells within secondary lymphoid tissues?

T helper17 cells (Th17) are characterised by their secretion of interleukin-17 (IL-17) together with numerous other ‘pro-inflammatory’ cytokines and their expression of the transcription factor retinoic acid-related orphan receptor C transcript variant 2 (RORC2). Th17 cells have been implicated in a range of autoimmune diseases and there is growing evidence for a role of these cells in multiple sclerosis (MS). Th17 cells are increased in MS patients during active disease, though debate exists as to whether increased Th17 cells are seen in peripheral blood (Durelli et al. Ann Neurol 2009) or cerebrospinal fluid (Brucklacher-Waldert et al. Brain 2009). IL-17A positive T cells are found within MS plaques and not within ‘normal appearing white matter’ or control brain (Kebir et al. Nat Med 2007; Tzartos et al. Am J Path 2008). There is evidence that Th17 cells increase the permeability of the blood-brain barrier, easily migrate across, promote the migration of other T helper cells and directly kill human foetal neuronal cultures (Kebir et al., 2007).

Naive T helper cells primed with antigen and the necessary co-stimulatory signals develop into short-lived effector cells, a few of which develop into long-lived memory cells. Memory T cells can be classified as either effector memory T cells (which traffic through peripheral tissues and can respond rapidly) or central memory T cells (which traffic through lymph nodes and are capable of rapid proliferation). Recently Mehling et al investigated whether Th17 cells are effector memory or central memory T cells, and also the effect of fingolimod treatment on Th17 cells. Fingolimod is an oral sphingosine-1-phosphate-receptor modulator that prevents the passage of lymphocytes out of lymph nodes and the thymus (Matloubian et al. Nature 2004). In relapsing-remitting MS, two large phase III trials showed that fingolimod resulted in a greater reduction in annualised relapse rate compared to placebo (FREEDOMS) and interferon- β 1a (TRANSFORMS). In these trials patients receiving fingolimod developed approximately a 75% reduction in their circulating lymphocyte count, this reflected a reduction in both naive and central memory T cells, leaving a T cell pool dominated by effector memory T cells (Mehling et al. Neurology 2008).

This study by Mehling et al used peripheral blood from healthy controls (n=10) and relapsing-remitting MS patients who were untreated (n=7), treated with fingolimod (n=10) or treated with interferon- β (n=10). Using flow cytometry the authors demonstrated that the highest proportion of Th17 cells (identified by their putative surface markers CCR4+ and CCR6+) was found in the central memory (CCR7+CD45RA-) T cell pool and that very few Th17 cells were found in the effector memory (CCR7-CD45RA-) and naive (CCR7+CD45RA+) T cell pools. The number of IL-17 containing T helper cells (assessed by intracellular flow cytometry) was reduced in fingolimod treated MS patients (0.1%), compared to healthy controls (0.78%, p=0.002), untreated (0.86%, p<0.001), and interferon- β -treated (0.68%, p< 0.001) MS patients. T cells from fingolimod-treated patients (cultured and stimulated through their T cell receptor) secreted less IL-17 and expressed reduced levels of the Th17-specific transcription factor RORC2, compared to T cells from healthy controls, untreated MS patients or interferon- β -treated MS patients.

In conclusion, the authors suggested that Th17 cells are part of the central memory T cell pool that is retained by fingolimod within secondary

lymphoid tissues. This is the first published report of Th17 cells belonging to the central memory T cell pool. However, identification of central memory T cells is complex and can be done using several cell surface markers, of which only two were used in this study. It should also be noted that Th17 cells constitute a small percentage of T cells and are outnumbered by Th1 cells in both peripheral blood and MS lesions. Nevertheless, the existing evidence suggests a significant role of Th17 cells in MS and they are likely to remain a hot topic in MS research.

– **Claire McCarthy, Norfolk and Norwich University Hospitals NHS Trust, UK.**

Mehling et al. Th17 central memory T cells are reduced by FTY720 in patients with multiple sclerosis. NEUROLOGY 2010; 75(5):403-10.

Multiple sclerosis: imaging the clinically isolated syndrome at rest

It is an attractive theory that plasticity allows the brains of patients with multiple sclerosis to perform more effectively than their plaques of demyelination would otherwise allow, and might contribute to the disappointingly poor correlation and predictive value of current radiological parameters and measures of disability, both concurrent and future. So what do novel imaging techniques have to offer? It is known that task-related changes in neuronal metabolism are small, less than 5% compared to basal brain energy consumption. Functional magnetic resonance imaging can record changes in cerebral blood oxygenation level-dependent signal. It has been shown that the spontaneous fluctuations that occur in this signal whilst the brain is at rest are not random but specifically organised. The patterns of synchronous activity may represent networks significant in the functional architecture of the brain and have been correlated with neuro-physiological data. In this study the networks were identified by a form of independent component analysis. The approach avoids dependence on predefined regions of interest and allows multiple systems to be studied simultaneously: sophisticated algorithms analyse the fMRI data to identify components which demonstrate maximal statistical independence. Some of these components are then investigator rejected as reflecting noise not neuro-anatomical systems. In 6 of 8 networks identified, Roosendaal et al found increased synchronisation in patients with a clinically isolated syndrome (14 mean age 34.6) compared with both patients with relapsing remitting multiple sclerosis (31 mean age 39.1) and healthy controls (41 mean age 38.6). The patients with clinical isolated syndromes did not differ from the controls on cognitive assessment nor on measures of fatigue or depression. The patients with established multiple sclerosis had statistically significant cognitive impairments and increased depression, fatigue and anxiety scores, accompanied by grey matter atrophy and white matter diffusion imaging changes. The authors conclude that these results are consistent with a hypothesis of early but limited reorganisation. An earlier study by Rocca et al published in *Lancet Neurology* in 2005 recorded functional MRI changes during repeated rhythmic finger flexion of patients' (16 patients with clinically isolated syndromes, 14 with relapsing remitting multiple sclerosis without disability, 15 with mild disability and 12 patients with secondary progressive disease) unaffected dominant hands. The findings were of increasing recruitment of novel cerebral regions with disease progression. It is not easy to reconcile these studies.

MRI has numerous roles in multiple sclerosis, being routinely used to make the diagnosis through the confirmation of dissemination of lesions in space and time and to exclude other pathology, with additional roles in research. These roles have been assessed against established clinical and pathological standards. Demonstrating plasticity presents the challenge of going beyond established standards. However, in an approaching era of more effective but more toxic therapies accurate prognostication would be most valuable. I am left repairing to the resort of many a commentator – more work is needed...

– **Tom Button, Department of Clinical Neurosciences, Cambridge University, Cambridge, UK.**

Roosendaal et al. Resting state networks change in clinically isolated syndrome. BRAIN 2010; 133:1612-21.

Post-Traumatic Amnesia Time Will Tell

Post-traumatic amnesia (PTA) occurs in people who have sustained brain injuries. It is a phenomenon whereby new continuous memories are not formed and hence there is ongoing disorientation and agitation. It has long been known that the duration of PTA predicted outcomes – different retrospective analyses have used a variety of outcome measures and settings. Part of the difficulty lies in defining what constitutes a “good” outcome in this patient group. Discharge home? Independence? Consciousness? This Australian study has adopted a similar approach in reviewing a large cohort (638 patients) with documented duration of PTA (as measured by the Westmead PTA score – other scores are used, but that's another story!). These patients had their duration of rehabilitation and total hospital stay recorded as well as a functional independence measure (FIM) on discharge. The FIM is a detailed instrument that records functioning in a number of domains and, as such, is much more sensitive to change than cruder measures that have previously been employed (such as the Glasgow Outcomes Scale). Unfortunately, of the 638 head-injured patients, only 436 had a reliable PTA duration recorded via 3 consecutive complete Westmead scores. Another 175 were assigned a PTA “range” due to infrequent formal measurement of PTA. There are clear correlations between the duration of PTA and the length of stay in hospital. This cohort also demonstrates a strong correlation between PTA length and FIM score on discharge as well as the rate of recovery.

Although none of these findings are particularly surprising, the clear demonstration of the effect of PTA length on the rate and extent of recovery on discharge is helpful in clarifying how close monitoring of PTA in the early phases of recovery from a brain injury can be used to plan and guide rehabilitation further down the line. Patients being admitted to rehabilitation units should have the duration of their PTA clearly documented at the point of transfer to allow realistic long term goals to be set and to form the basis of sensible prognostic discussions.

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

Kosch Y et al. Post-traumatic amnesia and its relationship to the functional outcome of people with severe traumatic brain injury. BRAIN INJURY 2010;24(3):479-85.

What's your poison?

The story is very familiar; a good party, a late night and a bit too much to drink, an early start the next day and there but for the grace of God etc. But what about other legal drugs of abuse; high dose nicotine is pro-convulsive in animal studies and low dose may be protective and high dose methylxanthines are acutely convulsive. This study from the USA registered 120,000 female nurses in 1989 and followed up various health outcomes. 625 self-reported a seizure in response to a questionnaire, but a quarter were not subsequently contactable. Of the remaining 469, 44 said that they had made a mistake, 12 declined to give more information and 98 said that their seizure was prior to recruitment. Sixty-nine events were deemed uncertain, leaving 246 with seizure or epilepsy. Of these 45 gave no information regarding caffeine or alcohol. The caffeine questionnaire had categories from none to more than six cups per day. Rather few women consumed more than 15g of alcohol per day so the data from this analysis had wide confidence intervals. For smokers, there was a relative risk of seizures of 2.6 (CI 1.53-4.42). There was no association with the current daily number of cigarettes smoked but there was with pack years (RR 1.03 per pack year). It should be noted that obvious smoking-related causes of seizure such as stroke or tumour were excluded. There was no association with caffeine or with moderate alcohol consumption. This is a large study and, as a non-smoking, caffeine consuming, moderate drinker, I am convinced by this study that supports my lifestyle choices and I shall ignore its statistical problems. Time to put the kettle on.

– **Mark Manford, Neurology Unit, Addenbrooke's Hospital, Cambridge, and Bedford Hospital, Bedford, UK.**

Dworetzky et al. A prospective study of smoking caffeine and alcohol as risk factors for seizures or epilepsy in young adult women: Data from the Nurses' Health Study II. EPILEPSIA 2010;51:198-205.

Meiji Techno microscopes and accessories

Meiji Techno UK, one of the UK's leading suppliers of light microscopes and accessories, has announced the new line up of cost-effective microscopes. Excellent delivery backed with a limited lifetime warranty make Meiji a "must see" alternative for laboratories upgrading their microscope suites.

The all-new MT9900 Series Polarising Microscopes are perfect for the study of thin sections and other mounted samples. They come with a focusable Bertrand lens, a rotatable analyser in a sliding mount with 360° graduation and a 3-position slider with 1st order red, 1/4 wave plate and Brightfield imaging.

The EMZ-13VX has a coaxial vertical fibre optic illuminator which is excellent for observing flat, highly reflective specimens such as integrated circuits, semiconductors, wafers, polished metal specimens, solder balls, or magnetic recording heads.

The MT5000 Series biological microscopes feature larger F.N.22 eyepieces, top line U.Plan objectives, larger wider stage with low ergonomic controls and the choice of LED or 30W halogen illumination. They are available in Brightfield and Phase Contrast models. Darkfield and simple



polarised light accessories are available too.

The TC5000 Series Inverted Microscopes from Meiji Techno feature new improved infinity optics and computer aided design. Brightfield, phase contrast and epi-fluorescence models are available.

To learn more about the products and services in light microscopy, visit Meiji's website at www.meijitechno.co.uk

Sativex® for the treatment of spasticity due to Multiple Sclerosis

Sativex® (delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)), the first cannabinoid medicine derived from whole plant extracts from the cannabis sativa plant, was launched in the UK in June to treat spasticity associated with Multiple Sclerosis (MS) by Bayer Schering Pharma.

Available as a prescription only medicine and given as a mouth spray, the launch of Sativex® means that now, for people with MS experiencing the spasms and cramping associated with spasticity, there is another option to add to their standard treatment.

There are approximately 100,000 people with MS in the UK and spasticity is very common, affecting most people with the condition at some point.

Speaking about the availability of Sativex®, Pam Macfarlane, Chief Executive of the MS Trust said, 'We have been aware for a long time, based on comments from people with MS, that cannabis based medicines can significantly improve spasticity which is a common, complex symptom of MS. For this reason the MS Trust has campaigned for the availability of a licensed medicine that can be properly controlled and prescribed. We have also invested money and resources in developing the body of knowledge by funding clinical research into the effectiveness of cannabis based medicines. The launch of Sativex® is therefore a milestone for the NHS and the MS Trust, and we are delighted. It will now be down to specialist professionals to assess people and we hope that this can happen quickly'.

As with many medicines, Sativex® does not work for everyone. The clinical trials show that about half of all people who add it to their existing medication find that it can provide relief from the debilitating symptoms of spasticity associated with MS.

For more information contact Bayer on T: +44 (0)1635 563000.

Natalizumab demonstrates improvement of disability statusx

Study data recently published online in the European Journal of Neurology have demonstrated that patients with highly active Multiple Sclerosis (MS) treated with natalizumab (Tysabri) showed a confirmed improvement in EDSS score during the 11 month observational follow-up. (n = 45)

- 62% of patients showed no clinical and no radiological signs of disease activity
- 29% showed a rapid and confirmed EDSS improvement over 44 weeks natalizumab therapy
- A clinically meaningful improvement in ambulation speed was observed in approximately 30% of patients.

For more information contact Biogen on T: +44 (0)1628 501000.

Epilepsy nurses encouraged to take the right path

A new learning and development pathway programme has been produced for Nurses working at the National Centre for Young People with Epilepsy (NCYPE).

The national epilepsy charity has a world class medical centre – the Neville Childhood Epilepsy Centre – at Lingfield, Surrey. The centre provides a range of diagnostic, assessment and rehabilitation facilities to children and young people aged between 3 and 19.

The new pathway programme has been developed to ensure that nurses can continually develop their careers and advance their knowledge and skills during their time at the NCYPE. Secondments for nurses from the NHS

and other organisations are also available.

Head of Health Services at the NCYPE, Hayley Bath, said, "The new pathway programme is designed to help nurses at the NCYPE to get the best they can from their time with us. This in turn helps us to provide the young people coming into the Neville Childhood Epilepsy Centre with the best possible service."

"The experiential learning gained through supporting residential students on the NCYPE campus and the young people attending diagnostic, interdisciplinary and rehabilitation services is one of the more important elements of the programme."

"Ultimately, we want to improve and enhance

epilepsy services nationally to help meet the needs of the 60,000 young people with epilepsy in the UK."

The programme provides study days, master-classes and regular academic meetings for NCYPE nurses on campus. Nurses can also undertake the Professional diploma in Epilepsy Care through a distance learning package with Leeds Metropolitan University.

More information can be found on the health pages of the NCYPE website: www.ncype.org.uk/health



Confidence to take action everyday

COPAXONE® (glatiramer acetate)

PRE-FILLED SYRINGE PRESCRIBING INFORMATION

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

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

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

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

Date of Preparation: May 2010

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COPAXONE®
(glatiramer acetate)

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