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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

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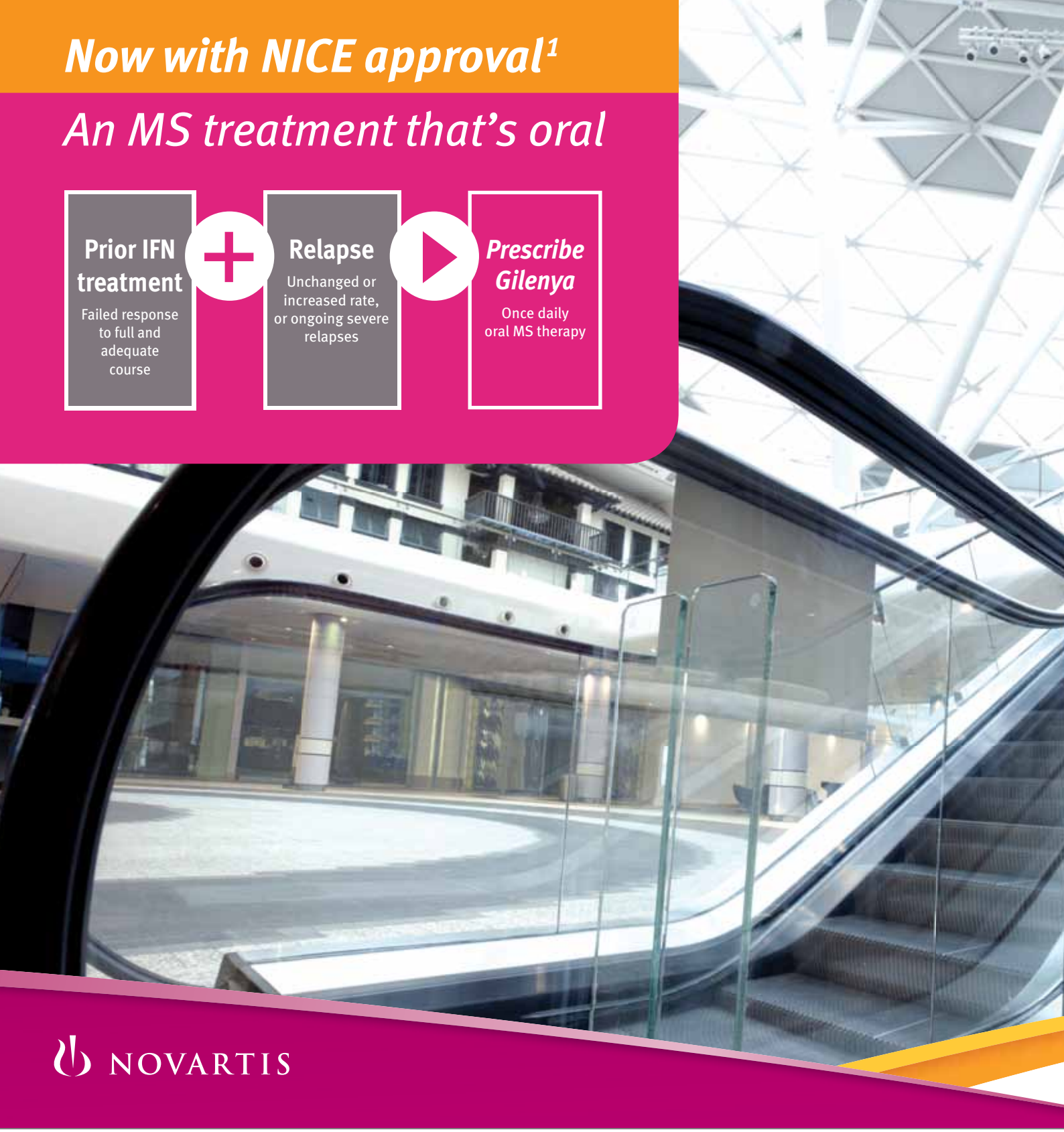

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- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

Dosage: Adults: Treatment should be initiated and supervised by a physician experienced in multiple sclerosis. One 0.5 mg capsule to be taken orally once daily. Patients can switch directly from beta-interferon or glatiramer acetate to Gilenya provided there are no signs of relevant treatment-related abnormalities, e.g. neutropenia. Use with caution in patients aged 65 years and over. No dose adjustments required in patients with mild to severe renal impairment or mild to moderate hepatic impairment. Exercise caution in patients with mild to moderate hepatic impairment. Do not use in patients with severe hepatic impairment (Child-Pugh class C). Use with caution in patients with diabetes mellitus due to an increased risk of macular oedema. **Contraindications:** Known immunodeficiency syndrome, patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies), severe active infections, active chronic infections (hepatitis, tuberculosis), known active malignancies, except for patients with cutaneous basal cell carcinoma, severe liver impairment (Child-Pugh class C), hypersensitivity to the active substance or to any of the excipients. **Warnings/Precautions:** *Bradyarrhythmia:* Initiation of treatment results in a transient decrease in heart rate (HR), which may be associated with atrioventricular block. Patients should have an ECG pre-dose, 6 hours post dose and observed for 6 hours with hourly HR and BP. Continuous ECG monitoring is recommended for 6 hours. In the event of bradyarrhythmia-related symptoms, initiate appropriate clinical management and monitor overnight. Also monitor overnight if at 6 hrs: HR ‹45 bpm, new onset 2nd degree heart block or higher, QTc ›500 msec, or 3rd degree heart block at any time. If HR is lowest at 6 hrs monitor for ›2 hrs until HR increases. The same precautions apply if Gilenya is discontinued for more than 2 weeks. Do not use Gilenya in patients with Mobitz type II or higher AV block, sick-sinus syndrome, sino-atrial block, symptomatic bradycardia, recurrent syncope, QTc ›450 msec significant cardiovascular disease, or severe sleep apnoea unless in consultation with a cardiologist and monitored overnight. Gilenya should not be given to patients taking beta blockers, HR lowering calcium channel blockers or other HR lowering substances (e.g. digoxin, diltiazem, ivabradine) unless in consultation with a cardiologist. *Infections:* Reduction of the lymphocyte count to 20-30% of baseline values occurs with Gilenya. Perform a complete blood count (CBC) at baseline and periodically during treatment, and in case of signs of infection, stop Gilenya until recovery if absolute lymphocyte count ‹0.2x10^9/L is confirmed. Consider VZV vaccination of patients without a history of chickenpox or VZV antibody negative patients prior to commencing Gilenya. Gilenya may increase the risk of infections. Employ effective diagnostic and therapeutic strategies in patients with symptoms of infection while on Gilenya and for 2 months after discontinuation. *Macular oedema:* Macular oedema with or without visual symptoms has been reported in patients taking Gilenya. Perform an ophthalmological evaluation 3-4 months after Gilenya initiation. Evaluate the fundus, including the macula in patients reporting visual disturbances. Perform ophthalmological evaluation prior to initiating therapy and periodically thereafter in patients with diabetes mellitus or a history of uveitis. Discontinue Gilenya if a patient develops macular oedema. *Liver function:* Do not use Gilenya in patients with severe pre-existing hepatic injury (Child-Pugh class C). Delay Gilenya initiation in patients with active viral hepatitis until resolution. Recent transaminase and bilirubin levels should be available before initiation of Gilenya. Monitor liver transaminases at months 1, 3, 6, 9 and 12 and periodically thereafter. Institute more frequent monitoring if transaminases rise above 5 times the ULN, including serum bilirubin and alkaline phosphatase (ALP) measurement. Stop Gilenya treatment with repeated confirmation

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of liver transaminases above 5 times the ULN and only re-commence once liver transaminase values have normalised. Patients with symptoms of hepatic dysfunction should have liver enzymes checked and discontinue Gilenya if significant liver injury is confirmed. Resume Gilenya only if another cause of liver injury is determined and if the benefits of therapy outweigh the risks. Exercise caution with Gilenya use in patients with a history of significant liver disease. *Serological testing:* Peripheral blood lymphocyte counts cannot be utilised to evaluate the lymphocyte subset status of a patient treated with Gilenya. Laboratory tests involving the use of circulating mononuclear cells require larger blood volumes due to reduction in the number of circulating lymphocytes. Blood pressure effects: Gilenya can cause a mild increase in blood pressure. Monitor blood pressure regularly during Gilenya treatment. *Respiratory effects:* Use Gilenya with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease due to minor reductions in values for forced expiratory volume (FEV_1) and diffusion capacity for carbon monoxide (DLCO). *Prior immunosuppressant treatment:* No washout is necessary when switching patients from interferon or glatiramer acetate to Gilenya assuming any immune effects (e.g. neutropenia) have resolved. Exercise caution when switching patients from natalizumab to Gilenya owing to the long half life of natalizumab and concomitant immune effects. *Stopping therapy:* Gilenya is cleared from the circulation in 6 weeks. Caution is indicated with the use of immunosuppressants soon after the discontinuation of Gilenya due to possible additive effects on the immune system. **Interactions:** Anti-neoplastic, immunosuppressive or immune-modulating therapies should not be co-administered due to the risk of additive immune system effects. Exercise caution when switching patients from long-acting therapies with immune effects, e.g. natalizumab or mitoxantrone. No increased rate of infection was seen with concomitant treatment of relapses with a short course of corticosteroids. Vaccination may be less effective during and for up to 2 months after Gilenya treatment. Avoid use of live attenuated vaccines due to infection risk. Due to additive effects on heart rate, Gilenya should not be given to patients receiving beta blockers, or class Ia and III antiarrhythmics, calcium channel blockers, digoxin, anticholinesteratic agents, pilocarpine or other HR lowering substances. Caution is indicated with substances that may inhibit CYP3A4. Co-administration of fingolimod with ketoconazole increases fingolimod exposure. No interaction has been observed with oral contraceptives when co-administered with fingolimod. **Fertility, pregnancy and lactation:** There is potential for serious risk to the fetus with Gilenya. A negative pregnancy test is required before initiation of Gilenya. Female patients must use effective contraception during treatment with Gilenya and for 2 months after discontinuation. Discontinue Gilenya if a patient becomes pregnant. Fingolimod is excreted into breast milk. Women receiving Gilenya should not breast feed. Fingolimod is not associated with a risk of reduced fertility. **Undesirable effects:** *Very common (≥1/10);* Influenza viral infections, headache, cough, diarrhoea, increased alanine transaminase (ALT), back pain. *Common (≥1/100 to <1/10);* herpes viral infections, bronchitis, sinusitis, gastroenteritis, tinea infections, lymphopenia, leucopenia, depression, dizziness, parasthesia, migraine, blurred vision, eye pain, bradycardia, atrioventricular block, hypertension, dyspnoea, eczema, alopecia, pruritus, asthenia, increased gamma-glutamyl transferase (GGT), increased hepatic enzymes, abnormal liver function test, increased blood triglycerides, decreased weight. *Uncommon (≥1/1,000 to <1/100);* pneumonia, macular oedema, decreased neutrophil count. **Packs and price:** Perforated unit dose blister packs containing 7 x 0.5 mg hard capsules: £367.50. Blister packs containing 28 x 0.5 mg hard capsules: £1470. **Legal classification:** POM. **Marketing Authorisation Holder:** Novartis Europharm Ltd, Wimblehurst Rd, Horsham, W Sussex, RH12 5AB, UK. **Marketing Authorisation Numbers:** 7 x 0.5 mg hard capsules: EU/1/11/677/001, 28 x 0.5 mg hard capsules: EU/1/11/677/005. **Date of last revision of prescribing information:** June 2012. **Full Prescribing Information available from:** Novartis Pharmaceuticals UK Ltd, Frimley Business Park, Frimley, Surrey, GU16 7SR. Tel: (01276) 692255 Fax: (01276) 692508.

Adverse events should be reported. Reporting forms and information can be found at http://yellowcard.mhra.gov.uk. Adverse events should also be reported to Novartis (01276) 698370.

Reference: 1. National Institute for Health and Clinical Excellence. Final appraisal determination. Available at: http://www.nice.org.uk/nicemedia/live/12170/58500/58500.pdf Accessed on 21/05/2012.

Date of preparation: June 2012 Code: FIN12-CO70

Martin Turner and Gwenaëlle Douard provide us with a stimulating account on recent thoughts about MND and how the loss of inhibitory interneurons may underlie some aspects of the disease. They discuss all this in the context of some of the known associations between MND and athleticism and this review certainly gets you thinking about neurodegenerative conditions in a completely new way.

The concept of involuntary musical imagery and a spectrum of musical symptoms is introduced to us by Lassi Liikkanen from Finland. It appears to be prevalent in that it occurs at least once a week in 90% of Finnish internet users who filled out an online questionnaire (presumably not during the Olympic closing ceremony). This imagery is not just about sticky tunes or unshakeable earworms, but can include palinacousis: 'the auditory illusion of persistence of sound impressions after cessation, sometimes music', and musical obsessions.

Stephen Price and colleagues in the article for the Neurosurgical series, take us through the diagnosis and treatment of high grade gliomas – tumours that carry with them a dire prognosis. They explain how better defining molecular markers expressed within tumours has helped to better predict their behaviour and responsiveness to therapy. This excellent up-to-date account also looks to the future and agents that may prove useful in the clinic including a range of targeted therapies, some of which will hopefully be approved for use both in Europe and the US!

Alys Mikolajczyk and Andrew Bateman in the article for the Rehabilitation Section of ACNR discuss some of the more subtle, but clinically relevant, consequences of stroke in terms of emotional and affective problems. They discuss how common these problems are and how they can be approached through psychodynamic counselling by taking us through a study they conducted in 15 patients.

Ray Chaudhuri in a Brittania sponsored article discusses the use of apomorphine and DuoDopa® in patients with advanced Parkinson's disease and how these two therapies match up in terms of helping all aspects of the disorder, not just the motor features of these conditions.

Finally, Suffolk artist Jane Southgate weaves together neuronal strands in her art that she describes in her short article.

We have a large collection of conference reviews in this issue and our usual journal and book reviews, and as usual we hope you enjoy this issue of ACNR. ◆

Roger Barker, Co-Editor.

Roger Barker, Co-Editor,
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Cover picture: "In Search of the Big Fish" by Anna Sendelbeck, winner of the Jury Prize in the "The Lab Through Your Eyes" category, FENS student committee competition 2012.

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FENS Photography Winners Announced

A Scientific Photography contest with "Scientific Phenomena" and "The Lab Through Your Eyes" categories was launched by the FENS students' committee for the first time at the 8th FENS Forum in July. The aim of the initiative was that young scientists should show science in a new way. The prizes were sponsored by Olympus, Mente y Cerebro magazine and ACNR. Congratulations to the winners of this first contest and thanks to all the scientists who sent their photographs.

Scientific Phenomena category: winner of the Jury Prize – "Fight and Surrender" by Carmen Agustín Pavón. Vox Pop Prize – "Happy Hippos" by Chris Henstridge.

The Lab Through Your Eyes category: Jury Prize – "In Search of the Big Fish" by Anna Sendelbeck (see cover picture of ACNR this issue). Vox Pop - "PhD Title Recipe" by Marco David Brockmann.

You can see all the photographs in an exhibition on the Jump the FENS 2012 Facebook page.

Nominations for UKABIF Awards 2012

Do you know someone who deserves recognition for the innovative or inspirational work that they do in the field of Acquired Brain Injury (ABI)? If you do, then nominate them now for one of two prestigious United Kingdom Acquired Brain Injury (UKABIF) Awards.

The UKABIF Award for Innovation is open to individuals or organisations that make a difference in ABI; innovation by a lawyer/law firm, clinician, care provider, social care worker, educational or voluntary sector provider or registered charity. The Stephen McAleese Award for Inspiration is for an individual in the field of ABI.

To enter simply complete the form that can be found on the UKABIF website: www.ukabif.org.uk. The deadline for entries is the 19th October 2012.

Naomi Gilbert

Hena Ahmad

Ed Roberts

Naomi Gilbert joins the TNA

Naomi Gilbert has joined the Trigeminal Neuralgia Association UK as their new CEO. Naomi trained as a nurse at Guy's Hospital and went on to become a surgical ward sister at St George's Hospital in Tooting and then a nurse teacher. Following two years monitoring clinical trials at a major pharmaceutical company, Naomi moved into the voluntary sector.

Further information from http://www.tna.org.uk/news.php

New Appointments at Imperial College London

Dr Hena Ahmad joins the Neuro-Otology team in September. She is currently working at Charing Cross Hospital and will be looking at the use of non-invasive brain stimulation techniques in understanding the brain mechanisms underlying symptoms in patients with dizziness and eye movement problems.

Dr Ed Roberts has recently joined the Neuro-Otology team as a post-doctoral researcher looking at the cerebral cortical mechanisms involved in chronic dizziness using brain stimulation and magnetic resonance imaging techniques.

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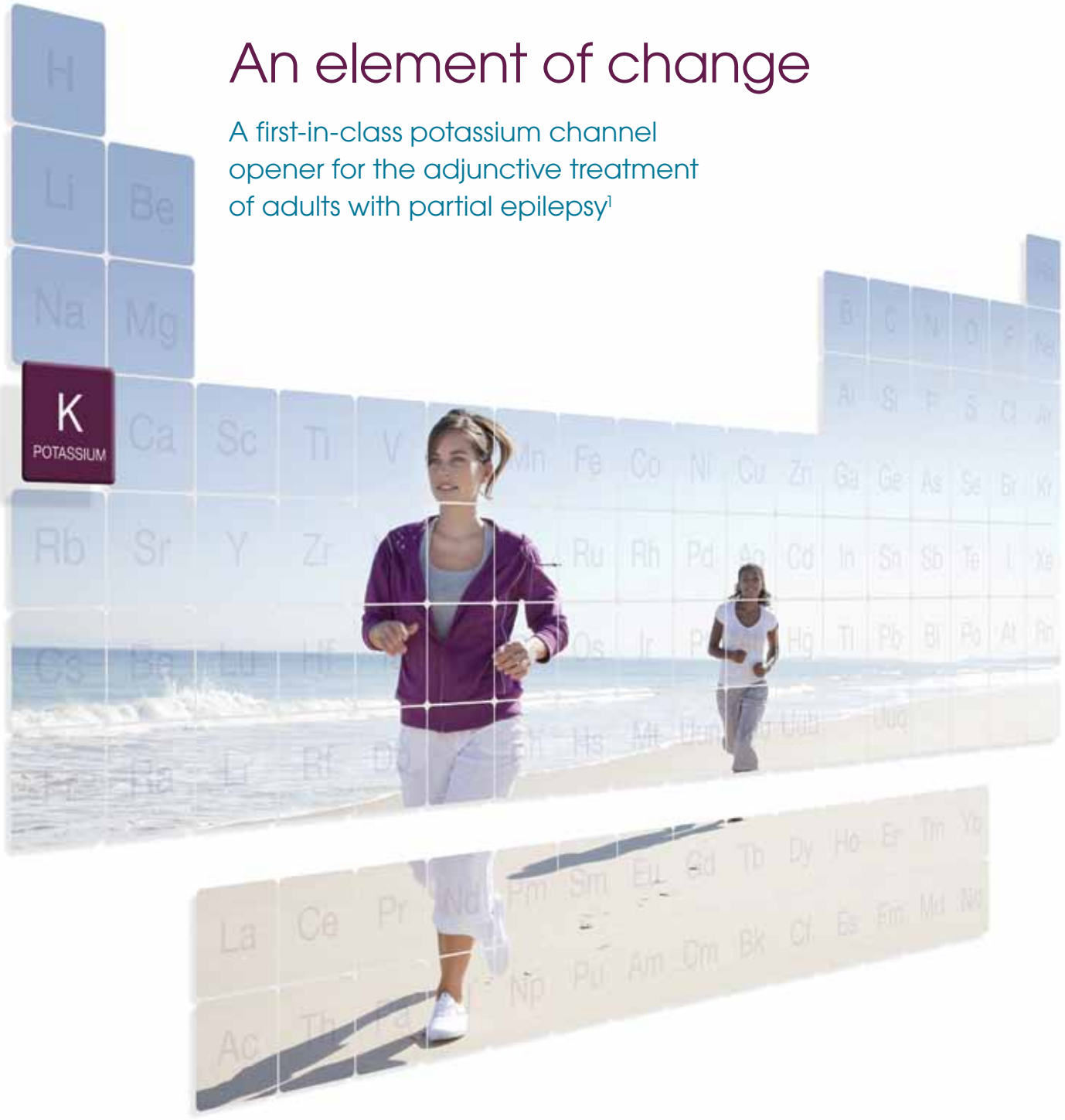

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Editorial board and contributors

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

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

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

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

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

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

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Faulty brakes:

An inhibitory neuronal deficit in the pathogenesis of motor neuron disease

Martin R Turner, MA, MBBS, PhD, FRCP,
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Gwenaëlle Douaud, PhD,
is a senior post-doctoral scientist at the Oxford University FMRIB Centre. She works on the integration of advanced MRI modalities to explore the pathogenesis of Huntington's and Alzheimer's disease in addition to MND. Her most recent focus is on movement disorders and the role of circuit changes in the basal ganglia.

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Introduction

Motor neuron disease, in its commonest clinical form amyotrophic lateral sclerosis (ALS), is characterised by the degeneration of upper motor neurons (UMNs) of the corticospinal tract (CST) and lower motor neurons (LMNs) of the brainstem nuclei and spinal cord anterior horns.[1] It is recognised to have clinical, pathological and, in cases with an intronic hexanucleotide repeat expansion in C9ORF72, genetic overlap with frontotemporal dementia (FTD).[2] Half of MND patients die within three years of symptom onset, typically via respiratory failure. There is no specific test for MND, and diagnosis is based on clinical features, with an average delay from symptom onset to diagnosis of one year.

To ask "what is the cause of MND?" is to underestimate the emerging pathogenic complexity. Only 5% of cases report a family history. Cytoplasmic inclusions of the ubiquitinated 43 kDa transactive-region DNA-binding protein, TDP-43, superficially appear to be the unifying hallmark for the 95% who have apparently sporadic MND. However, TDP-43 inclusions are notably absent in the 20% of familial cases associated with mutations of SOD1, despite being clinically indistinguishable from other MND patients. Thus, there appear to be multiple discrete 'tributaries' flowing towards a common 'waterfall', beyond which there is a typically rapid, relatively selective motor neuronal degeneration. In the vast majority of apparently sporadic cases, MND is likely to involve multiple genetic influences operating at a low level individually, combined with as yet poorly-defined environmental factors.

The brain in MND

Case reports of MND with brain involvement beyond the motor cortex can be found in the early 20th Century literature, now recognised as MND associated with FTD, largely of the behavioural variant. Later post mortem studies confirmed widespread cerebral involvement in MND even without frank dementia.[3] A spectrum of cognitive dysfunction, predominantly of a dysexecutive nature, and detectable in at least a third of MND cases without frank FTD, emerged over the following decades, cemented by the finding of the common TDP-43 histological signature.[4]

Aberrant axonal transport is one of several major themes in MND pathogenesis,[5] in which a LMN 'dying back' is then presumed to account for the consistent involvement of the CST, noted even in apparently clinically LMN-only cases. However, the early occurrence of cognitive impairment in some cases of ALS, and a rare UMN-only variant of MND (primary lateral sclerosis) often associated with severe atrophy of the motor cortex and strikingly absent LMN pathology, support a top-down 'dying forward' process. Combined clinical and post mortem analysis supports a main focus of pathology at the site of symptom onset, with contiguous spread through UMN and LMN populations.[6] A clear primacy of one over other remains uncertain, with the increasing sense that the disease must be understood as a whole 'system' degeneration that includes the brain at some level in all cases.

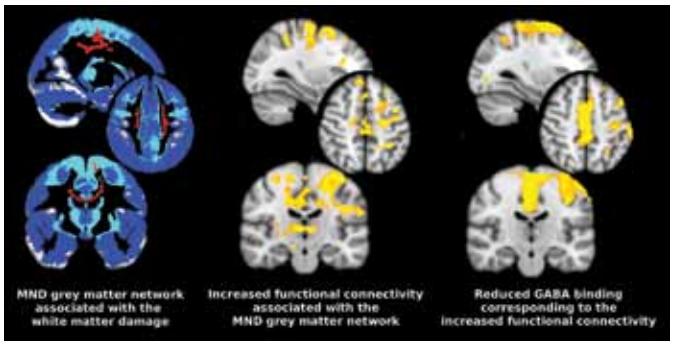
Excitotoxicity and cortical hyperexcitability in MND

Raised levels of CSF glutamate, and abnormalities of glutamate transport and reuptake in human post mortem tissue as well as animal models of MND, underpin an excitotoxic theme of pathogenesis, in which over-stimulation of motor neurons results in eventual calcium-mediated cell death.[5] An alternative or contributory mechanism might be a reduction in inhibitory neuronal influences. Cortical and spinal cord interneuronal local circuits are found intimately associated with both the UMN and LMN populations respectively, and a diverse range of evidence supports a role for their involvement in pathogenesis.[7] Paired transcranial magnetic stimulation can be used to explore cortical inhibitory circuits, and studies in MND demonstrated a reduction in the normal inhibitory response seen at short interstimulus intervals.[8] An adapted threshold-tracking method to assess this reduction in short-interval intracortical inhibition has demonstrated specificity for MND over mimic disorders.[9] Furthermore, this methodology provided pivotal evidence for an increase in cortical hyperexcitability prior to the development of symptoms in carriers of SOD1 mutations.[10]

Neuroimaging evidence for an 'interneuronopathy' in MND

Pioneering in vivo cortical studies in MND employed activation positron emission tomography (PET), observing an extended area of cortical activation in response to a motor task. It was suggested this "boundary shift" might reflect loss of inhibitory local circuits.[11] Application of the PET ligand flumazenil confirmed widespread cerebral reductions in γ-amino butyric acid (GABA)-A receptor binding in MND, crucially with relative preservation in those with a consistently more slowly progressive familial form of the disease (matched for disability and UMN involvement).[12]

Blood oxygenation level-dependent (BOLD) functional MRI involving a motor task, confirmed the original activation PET findings (reviewed in [13]). However, it is now possible to analyse the spontaneous fluctuations in BOLD signal that occur at rest (as opposed to during a motor task). This is being explored as a potentially sensitive in vivo marker of pathology in several neurodegenerative disorders. Diffusion tensor imaging (DTI) is an established MRI technique that can be used to



Left panel: MND grey matter network (in blue) directly associated with the white matter damage identified using DTI (in red).
Middle panel: Within the MND grey matter network, there was an increased functional connectivity using resting-state functional MRI - an increased synchronisation of the spontaneous fluctuations of the BOLD signal between the regions of the brain involved (in yellow).[15]
Right panel: The regions showing increased functional connectivity have some spatial overlap to the reduced GABA binding found in a previous study using flumazenil PET (in yellow).[12]

define the characteristic structural white matter tract involvement in MND, which consistently involves the CST and corpus callosum,[14] but also extra-motor frontal lobe pathways. The grey matter projections from these damaged white matter tracts were mapped using tractography in order to explore the resting-state functional changes in relation to an 'MND-specific' cortical network.[15] Unexpectedly this revealed increased functional connectivity within the structurally degenerating cortical network. Furthermore, this network overlapped strikingly with areas previously noted to show reduced GABA binding[12] (Figure). Whilst a 'compensatory' explanation cannot be entirely dismissed, it was noteworthy that those with faster rates of disease progression showed greater functional connectivity, raising the possibility that loss of inhibitory neuronal influences might directly contribute to the pathogenic cascade in MND.

Is there a potential MND brain architecture?

Osler noted that: "It is much more important to know what sort of patient has a disease, than what sort of disease a patient has." Case-control studies of the strong anecdotal observation of pre-morbid athleticism among those developing MND have been inconclusive. The significant increased occupational risk of MND associated with professional football and military service superficially fits with greater athleticism, and a significantly reduced vascular risk profile has also been noted among MND patients and relatives.[16] Debate continues over exercise as a direct precipitant of disease, versus athleticism as an associated phenotype. Developmental factors must also be considered, with MND patients noted to have a surrogate marker for high intrauterine testosterone exposure (also common among athletes) in the form of reduced 2D:4D digit ratio.[17]

With these data in mind, though entirely speculatively, it is conceivable that athleticism might in part reflect a particular cerebral architecture, which may in turn be a preferred substrate for MND in a minority. Eisen speculated on the relatively rapid human neocortical development associated with opposable thumbs and bipedalism as holding potential importance for the pathogenesis of MND.[18] Distinct patterns of structural and functional brain network organisation in healthy individuals have already been linked to the stereotyped patterns of neurodegenerative diseases.[19] Aptly summarised: "What wires together, dies together".[20]

Hand dominance has been linked to reduced inhibitory influences in the contralateral hemisphere, and so the finding of significantly increased concordance of site of onset and handedness in those with upper limb-onset MND might reflect inhibitory, interneuronal organisation, rather than an activity-driven mechanism.[21] In this way, a less inhibited, or perhaps more functionally connected motor cortex, with all its evolutionary advantage in terms of physical performance in youth, might somehow be more vulnerable, perhaps more permissive of spread of pathology, or otherwise define variable rates of progression in MND.

Primary prevention of MND?

Speculation aside, it is likely that the development of clinical symptoms in MND represents the late stages of long-standing pathological processes. Indeed the primary reason for the failure of so many of the candidate therapies for MND may be their administration in a relatively intractable phase of pathology. Although a minority of cases, those asymptomatic individuals carrying single genetic mutations linked to the development of MND offer a valuable opportunity to study the earliest changes. The observation of a similar pattern of metabolic changes in the cervical spinal cord of presymptomatic SOD1 mutation carriers compared to those with established disease,[22] marks a major conceptual shift in where pathology in MND begins, and brings it in line with observations in Alzheimer's, Parkinson's and Huntington's Diseases.

High-field MR spectroscopy can now be used to specifically demonstrate reduced GABA within the motor cortex in MND patients.[23] In combination with other advanced MRI techniques, the refinement of a cortical 'disinhibitory signature' in presymptomatic cases will be an important step towards the long-term aspiration of primary prevention. For the larger apparently sporadic and symptomatic group, identifying such a signature has the potential to reduce diagnostic delay, and permit earlier administration of therapy, one strategy for which might be boosting inhibitory interneuronal function. ◆

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Involuntary Music Among Normal Population and Clinical Cases

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There is a new topic in general psychology called involuntary musical imagery (INMI).[1,2] It is of great potential interest to practitioners of clinical neuroscience because of its notable similarities to clinical involuntary music phenomena. INMI is defined as a conscious experience of reliving a musical memory without deliberately attempting to do so. It is also known by other colloquial names such as earworms, sticky tunes, or tune in the head phenomenon. In this paper I review recent empirical findings on the topic of involuntary music, highlighting how the findings from INMI research in the normal population[1] may support the diagnosis of involuntary music in clinical practice.

It is proposed here that involuntary music involves a continuum of musical imagery phenomena, like the perceptual continuum proposed for hallucinatory perceptions.[3] These phenomena range from common, "normal" involuntary music to pathological conditions (see Figure 1), such as musical obsessions,[4] hallucinations,[5] and palinacousis.[6] This review includes involuntary phenomena from three disciplines: general psychology (specifically music), clinical neuroscience and psychodynamic psychology.

Involuntary music in general psychology

The human capacity to imagine sounds is generally called auditory imagery,[7] and musical imagery when it involves music.[8] Involuntary musical imagery is considered to be a manifestation of musical imagery[7] with uncontrolled onset of imagery.[9] This review is focused on INMI. As a subjective experience, INMI involves insight that the music is self-generated and its quality is not very vivid, in comparison to the perception of stimulus.

The first psychology paper related to INMI came out in 2004 when Kvavilashvili and Mandler[10] reported a series of studies on involuntary semantic memories. Melodies were found to be the most frequently recurring memory type which people recall unintentionally. Since this seminal work, researchers have been interested in the frequency and duration of involuntary music,[1,11] along with the phenomenology,[1] triggers,[2] and dynamics of INMI.[9]

There is a high prevalence of INMI in everyday life. An experience sampling study of musicology majors[11] revealed that the students are deeply immersed in both voluntary and involuntary imagined music throughout the day. A questionnaire study of over 11,900 Finnish Internet users found that almost 90% of respondents experienced INMI every week (see Figure 2).[1] In another recent study, a diary method was used for data collection over a four week period.[12] The INMI episodes lasted 25 minutes in average and happened more than once a week.

The conscious experience of INMI varies considerably between people. For instance, despite the higher likelihood of certain songs being reported as INMI, the songs are very idiosyncratic overall.[9] In the Beaman and Williams[12] diary study, 74% of INMI reports involved a unique song. The songs can be old, contemporary, or even completely novel.[1] Experiences of new, self-generated songs are more typical among musically-educated people.[1,11] Features of the musical experience have also been examined. In the study of Finnish internet users,[1] an INMI episode was typically contemporary, lyrical, and involved only a fraction of a song, presumably the chorus. The study found that the frequency and characteristics of the experience are influenced by age, gender and musical dispositions. Women reported experiences more often as did the younger cohorts. The frequency of musical activities correlated positively with the frequency of INMI experiences.

The causes of INMI are pretty much as yet unknown. The hypotheses often involve the function of memory, in terms of enforcing and decaying activation in semantic memory networks.[9,10] It is hypothesised that the activation of memory through recall, recognition, or cross-modal memory associations can evoke these experiences immediately or after a delay. A study of INMI triggers identified several common categories of triggers.[2] Exposure to music, recent and repeated, was the most prominent category, but cross-modal associations to music, and affective states were also repeatedly mentioned by subjects. Further evidence about the role of memory activation comes from the only experimental study of

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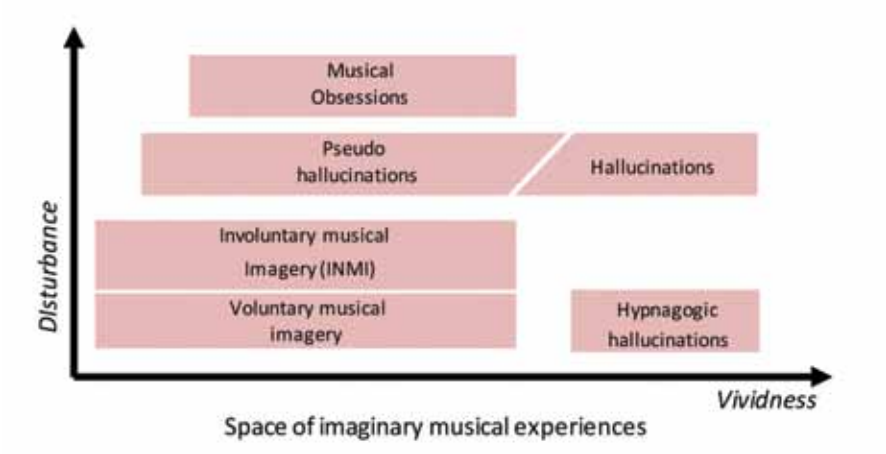

Figure 1: Hypothetical space of imagery-based involuntary music phenomena, ranging from normal (lower left) to clinical (upper right). The axes of the space are two perceptual categories: vividness (x-axis) and disturbance (y-axis) of imagery.

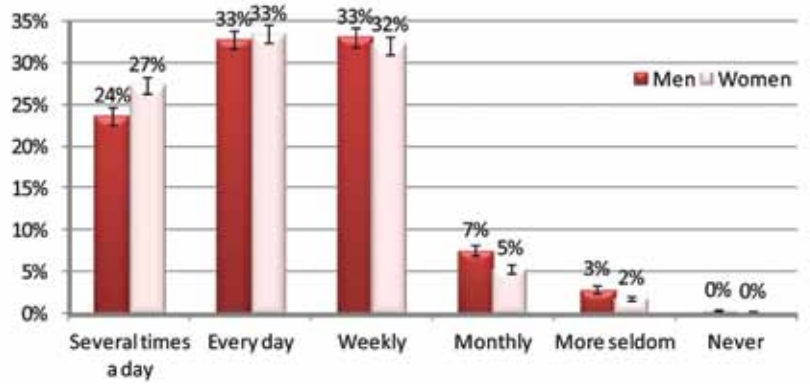

Figure 2: Self-reported, retrospectively assessed frequency of INMI experiences in the everyday life of 11,910 Finnish internet users. Error bars mark 99% confidence interval for the proportion. Modified from (1).

INMI published thus far.[9] Using a novel induction technique, it was found that the proportion of recently processed music among INMI reports increased in response to cueing. Familiarity with music was a necessary but not a sufficient condition for the emergence of INMI. The relative freshness of the song was important for its later induction, contemporary songs being more powerful cues than classic ones. The interpretation was that the repeated activation facilitates later, intentional or unintentional, imagination of music.

Involuntary music in clinical neuroscience

Several conditions in neurology and psychiatry involve symptoms very much like INMI, but are much more pronounced. For this review, I have included the most relevant phenomena with a known cause: peripheral nervous system, brain damage and functional diseases.[13] Additionally, intoxication and epilepsy are known to sometimes trigger these symptoms.[5] A rare phenomenon known as palinacousis has also been documented.[6] It involves an auditory illusion of persistence of sound impressions after the cessation of the auditory stimulation, sometimes music. This condition is related to brain damage and epilepsy and should not be confused with other types of involuntary music.

Involuntary music is sometimes associated with obsessive-compulsive disorder (OCD) and schizophrenia. For OCD, so-called musical obsessions[4,14] in the absence of other psychopathological symptoms, can be an adequate criterion for diagnosis when accompanied by subjective distress and dysfunction. For instance, Zungu-Dirway and colleagues[4] described two patients who perceived the internally created music as intrusive, irritating and disruptive of other thought. The sole difference in the phenomenology of musical obsessions to INMI is their noticeable disruptiveness.

Hallucinations, including musical ones, are typical in schizophrenia. Musical hallucinations are more common than musical obsessions, even though they occur in less than 0.2% of hospital populations and typically involve elderly females.[5] Among the researchers studying schizophrenia, there has been a long discussion about musical hallucinations and pseudo-hallucinations.[15] For instance, Terao and Ikemura[16] disagreed with the aforementioned musical obsessions diagnosis.[4] They preferred to call the condition pseudo-hallucinations because the hallucinations (music) were perceived in the subjective space and were under limited conscious control.

Reduction or loss of hearing can trigger auditory hallucinations.[5,17] This is sometimes called an auditory Charles Bonnet syndrome or auditory release hallucinations. The common denominator with these often elderly people is that their otherwise impoverished auditory consciousness becomes occupied with hallucinatory perceptions, in some cases music. Subjects usually have insight into the hallucinatory nature of their experiences. These conditions seem to relate to a lack of excitation to cortical auditory areas and limbic regions, as if the intact auditory cortices have become hypersensitive due to sensory deprivation.[17] Brain damage or brain stimulation can alter normal musical processing and create involuntary music experiences. For instance, a brain stem lesion induced a temporary hearing loss and accompanying musical hallucinations in a middle-aged man.[18]

Involuntary music in psychodynamic psychology

Freud was known for his indifference to music, unlike many of his followers. For instance, Reik, a psychotherapist and a scholar, was convinced that involuntary musical memories had a function in the service of psychoanalysis.[19] He believed that the INMI experiences of the analyst and the patient carried a hidden message about the workings of psyche, which the analyst could perceive and benefit from in the clinical work. Another hypothesis on the function of INMI portrays music as a substitute for the presence of a mothering person, comparing the role of music to the role of dreams in Freud's theory. This idea finds some support in the trends of popular culture. Hannet[20] studied the lyrical contents of 2111 "hit songs" from the first half of 20th century. Of those, 69% were classified as romantic love songs. The domination of love songs in the sample was interpreted as reflecting the universal need for love and passion, particularly that the popular lyrics express "unconscious infantile attitudes... or partial attachments to the image of preoedipal mother," according to Hannett.[20]

Implications for practice

This review has illustrated involuntary music phenomena from harmless, common forms to troublesome clinical conditions. I proposed that there is a continuum[3] of phenomena of involuntary music, with a variable degree of commonality and severity. It seems that the phenomenology of INMI and music-related mental disorders have much in common. INMI presents a case of intact self and reality monitoring (insight), but inadequate control of conscious thought. Regarding the latter, there is little evidence to support the suggestion that the use of mental coping strategies,[12] for instance intentionally replacing an INMI

song with another (musical displacement strategy), are effective in modulating the frequency, duration, or disruptiveness of INMI.

An important characteristic of INMI is high inter-individual variability. Even though nearly everyone has experienced it, the frequency and the nature of the experience is different from person to person.[1] It is noteworthy that the majority of people experiencing INMI several times a day find it compatible with everyday life.[1,12] An interesting parallel between INMI[1] and musical hallucinations[13] is the female preponderance, although this is not characteristic of mental illness such as schizophrenia in general. For clinical practice, it is important to understand that even nearly constant, involuntary musical imagery may not indicate mental disorder if it does not impede everyday life. I believe future work on the topic is needed to clarify diagnostic criteria for OCD and schizophrenia to distinguish their features from "normal" INMI. Thus far, brain research techniques successfully used for imaging voluntary imagery and hallucinations have not been able to capture INMI, but we can hope future efforts will bring insights from the neural level to help diagnose involuntary music phenomena. ◆

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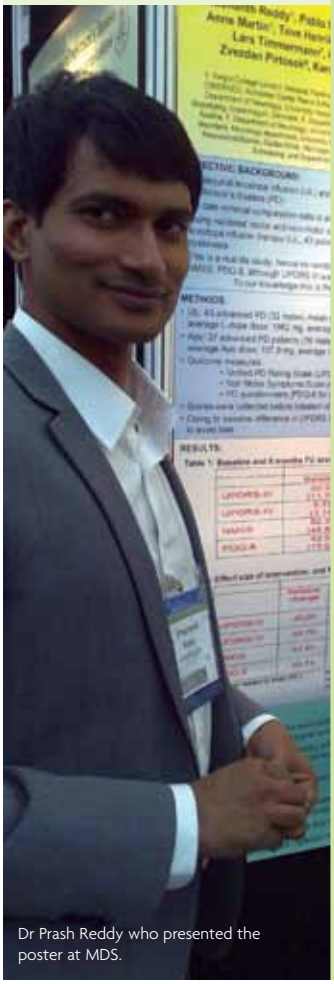
The EuroInf survey

Prof Ray Chaudhuri, who spoke at the webinar, is a neurologist with expertise in movement disorders and non-motor issues, particularly in relation to Parkinson's disease. Based at the National Parkinson Foundation Centre of Excellence at King's College Hospital, King's College, London, he works for King's Health Partners, which includes London's King's College Hospital, and St Thomas's and Guy's Hospitals.



Dr Prash Reddy who presented the poster at MDS.

Speaking at an interactive webinar, Professor Ray Chaudhuri discussed the European Infusion (EuroInf) survey, part of the EUROPAR project endorsed by the EPDA and involving over 14 centres across Europe. This survey was presented as a poster at the MDS meeting in Dublin and also presented as one of the highlights at the Dublin congress earlier this year in June. This ongoing multicentre observational study across several centres in the UK and Europe compares the two infusional therapies for advanced Parkinson's disease - subcutaneous apomorphine and intrajejunal levodopa.

The study focuses on motor and non-motor symptoms and their cumulative effect, namely quality of life. While not a randomised placebo-controlled study, the outcome measures used (UPDRS III and IV for motor symptoms, NMSS for non-motor symptoms and PDQ-8 for quality of life) reflect good clinical practice in a 'real-life' population. Aiming ultimately to have 50 patients in each treatment arm, the study has already recruited over 40 patients on levodopa and 37 on apomorphine. Because the two groups do not match identically, the study looks at the effect size of the two interventions and numbers needed to treat.

With regard to inclusion criteria, these reflect existing clinical practice across Europe for treatment with advanced therapies, said Professor Chaudhuri. Not included are patients who are demented or have significant cognitive problems, those with a diagnosis other than Parkinson's disease or where the Parkinson's diagnosis is uncertain, and patients whose response to levodopa is failing. Patients included in the study are therefore essentially those considered fit for further therapy in whom deep brain stimulation using the subthalamic nucleus or globus pallidus internus is not appropriate.

Summarising the observations from the EuroInf survey Professor Chaudhuri outlined that infusions of both apomorphine and levodopa worked well in terms of UPDRS-III, but apomorphine had a very strong effect on motor symptoms, perhaps not surprisingly since previous studies have shown that apomorphine can often quite dramatically return a patient who is otherwise 'off' and bradykinetic to essentially normal motor function. In addition, the study found that apomorphine improved certain non-motor symptoms, though the effect on dyskinesias was not quite as good as might have been expected, perhaps because apomorphine therapy was given as monotherapy in only a few centres and was often associated with concomitant use of oral dopaminergic treatment. Levodopa on the other hand was generally given as monotherapy. However, the effect of apomorphine on the non-motor symptoms scale, as well as on quality of life, was as strong as in the levodopa arm.

Addressing the availability of infusion treatments Professor Chaudhuri noted that even in well established Parkinson's disease treatment centres the number of patients receiving these therapies is low. Clearly a significant number of patients suitable for apomorphine or levodopa are not being offered these interventions. This may be due to non-availability of the relevant expertise or the supporting services required, but perhaps also because clinicians are not familiar with these treatment strategies. By contrast, deep brain stimulation is a well recognised therapeutic option with a good evidence base from randomised controlled trials. However, to Professor Chaudhuri's knowledge, deep brain stimulation therapy has yet to be examined holistically using the validated non-motor scale used for apomorphine and levodopa in the EuroInf survey. For patients who cannot undergo deep brain stimulation because of their age, or because they have cognitive impairment or depression, infusion with apomorphine or levodopa provides an alternative therapeutic option.

Looking to the future the aim is therefore to add a third arm to the EuroInf survey to compare a matched group of patients undergoing deep brain stimulation, as well as a fourth comparator arm comprising patients who have not received any of these advanced therapies and who instead continue on conventional best medical therapy. Such a cohort exists in the UK, where funding streams are somewhat different to other countries in Europe. Professor Chaudhuri stressed that access to treatment with apomorphine, levodopa and deep brain stimulation is very variable. A good state-of-the-art Parkinson's disease centre should be able to provide access to all three therapies, based on informed patient choice. This is not currently the case. Patients can be influential here. Professor Chaudhuri noted that, empowered by initiatives such as expert patient groups, patients are becoming better educated about Parkinson's disease and its potential treatments. In addition, the media has considerable influence in this area.

Impulse control disorders continue to be a major topic of discussion in Parkinson's disease. Professor Chaudhuri outlined that the relationship between impulse control disorders and oral therapy, particularly dopamine agonist therapy, remains unclear. However data from his own group suggest that the rate of impulse control disorders occurring with longer-acting dopaminergic therapies, particularly dopamine agonists, is actually low compared to the overall prevalence. Single infusional therapies (as possible with apomorphine) appear not to be associated with a high rate of impulse control disorders. Professor Chaudhuri stressed that this is an anecdotal observation, however, which needs to be supported by evidence from a controlled study or data from a large case series like the EuroInf survey.

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Psychodynamic Counselling after Stroke:
A pilot service development project and evaluation

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The benefit of 1:1 psychodynamic counselling and couples counselling to people who have suffered from stroke was investigated in this pilot service development project. This work aimed to demonstrate the importance of provision of stroke psychological services in the community and explore the issues that arose in the course of therapy provided with individuals and couples seen in the course of a year.

Method: seven individuals and four couples were seen. Response to therapy was measured using The Depression, Anxiety and Stress Scales.[1]

Findings: With this small sample of participants, pre-assessment and post-assessment evaluation showed positive changes on the DASS. Assessments revealed high severities of stress, anxiety and depression post-stroke. Important and recurring themes of grief, loss, attachment, dependency, death anxiety and fear are shown.

Discussion: This work adds to the well known need for increased specialist psychological support for those experiencing moderate – severe mood difficulties following stroke by illustrating the appropriateness of this specific clinical approach. In addition, the value of long-term support groups were shown as a lifeline and focus for a person's week.

Introduction

Long-term disability is experienced by a third of people living in England who have had a stroke. This disability includes psychological difficulties following a stroke. There are 900,000 people in England who have had a stroke, and 300,000 of these people are living with moderate to severe disabilities. Stroke is the third largest cause of death.[2] Advances in acute care mean that we are seeing improved survival and reduced morbidity. However, this means that some of the subtler consequences of stroke are now more apparent in the day to day interactions with clinicians. In particular the cognitive and emotional consequences of stroke are increasingly recognised by clinicians and service users who are seeking help for these problems.

There are a range of long-term difficulties that follow stroke that can impact on a person's mood. It is well recognised that the consequences of a stroke can be experienced as a massive, traumatic event in a person's life. It can cause feelings of crisis and suicide, and dramatic changes to a person's physical, emotional and social well-being.[3] Following the shock of a stroke, a person can feel anxious, stressed and depressed. Patients report statements such as "you feel like you want to stay in bed and can't face things anymore," "Tasks that were simple take so much effort and concentration," "It is easy to cry and hard to control," "You can be snappy and not mean to be," "You want to avoid people, because you don't want anyone to see you," "It feels devastating," "It feels like you've lost yourself."

These are compelling reasons why any therapist would wish to seek to reconsider the services provided alongside existing services. Typically in the UK at present it is routine for physiotherapy, speech and language therapy, and occupational therapy services to be provided. There has been relatively less attention to the psychological needs of patients in commissioning guidelines despite a longstanding recognition of the need to provide such services.[4]

Psychodynamic counselling is an approach that enables a person who is struggling to cope with life to have space to explore their feelings, and find ways to recover from depression, stress and anxiety. Counselling supports people to move from stages of crisis to develop realistic goals and make adjustments to their self-concepts.[5] This process can be exceptionally challenging and can feel like a fight and a battle to keep going.

Psychodynamic counselling also reflects on past experiences that have relevance to difficult recent life events. For example, a husband being unable to provide for his family triggered feelings about a past relationship that had not been talked about and grieved for.

There are past studies that look at psychotherapeutic interventions for working with stroke. For example, Cunningham's case study[6] describes the use of personal construct therapy with severe aphasia. Oliveira et al[7] discuss in detail psychodynamic work with physically disabled patients. There is also plenty of literature looking at psychotherapeutic approaches to pain.[8] In addition, Wilson et al's work on neuropsychological rehabilitation covers various approaches including social and personal identity, systemic family therapy, and narrative therapy.[9] This pilot service has focused on the use of another psychotherapeutic approach called psychodynamic counselling. Many aspects of general psychodynamic theory can be useful when working with those experiencing strokes. In this short introductory review we will highlight a

number of themes including grief, loss, mourning, attachment and fear.

A key theme is grief and mourning. After a stroke, a person can feel lost. Counselling tries to help a person rediscover parts of his or herself that feel lost. Stroke specific psychodynamic counselling helps a person to talk about their sense of loss after their stroke and to encourage a person through their rehabilitation. It also aims to help a person find resilience to cope with the long-term consequences of a stroke. An added dimension of stroke experienced counselling is the provision of information about expected recovery, ability to answer some general medical concerns, and to refer on to other professionals such as medicines management.

Understanding unconscious object relations such as the 'lost object' is important to psychodynamic counselling. In relation to stroke, the lost object may be a part of the self.[10] Leader proposes 'Grief is our reaction to loss, but mourning is how we process this grief.' (p.26). He describes how we anticipate hearing a loved ones voice on the phone after they have died. This could be compared to someone thinking back to their pre-stroke self and seeing themselves back at work or driving the car. One hypothesis that underpins therapeutic interventions is that the more these memories are processed, feelings begin to improve. Through therapeutic conversations, the sense of discrepancy from 'pre-stroke' self may be reduced.[9] For some, this can be a long and difficult process after a stroke. The challenge for counselling following a stroke is to support a person to rediscover parts of their self and develop an adjusted self-concept. Many people also have loss in their lives where there is mourning still to be done. Counselling helps to look at the unconscious processes of grief and mourning to support people to recover from depression.[10]

Following a stroke, a person often feels a lack of confidence and insecurity in their sense of self and especially how they feel about their body. Blando[11] describes the outcomes of Fortner & Neimeyer's research (1999, p.90) that found higher death anxiety in older people with more psychological problems and a reduced sense of self. Feeling anxious about the prospect of death is known as death anxiety. Awareness of death can be a cause of anxiety particularly after middle age.[11] Near-death experiences such as suffering a stroke and the memories of the days following a stroke can evoke high anxiety. Death anxiety can restrict how someone engages with life, and this could include restrictions to their recovery and their ability to socialise.

Attachment is also important to any psychotherapeutic approaches. The trauma of a stroke can affect attachments, for example, there can be increased dependency on partners and new strong attachments to health care staff. The stroke may amplify previous attachment patterns such as 'anxious avoidant' and 'anxious resistant' attachment types (Blando, 2011, p.111-p.112). If someone feels vulnerable, they may feel as insecure as they did as a child. A stroke can cause a person to feel frightened. The support of others helps alleviate these feelings, and enables a person to cope better. There may especially be difficulties if a partner has died or a key attachment figure is unavailable. In psychodynamic working, the type of transference and attachment type can be closely associated.[11]

In light of these themes, this project was conceived following Speech and Language Therapist Alys Mikolajczyk's post-qualification training in Psychodynamic Counselling at Cambridge University Continuing Education. Funding from the local Stroke and Heart Network to implement this project was sought and approved because it was recognised that there was a lack of service descriptions and evaluation of work in this field locally, despite the need for psychological support outlined in The National Stroke Strategy for England (2007).

Method

This service was initially advertised to the rehabilitation team to support participants and their families experiencing low mood since a stroke. As a consequence, referrals mainly came from the neurological rehabilitation multidisciplinary teams, though all GP practices in the catchment area were sent a letter and leaflets. People could also self-refer. This service aimed to be flexible by seeing both individuals and couples, and aimed to be participant-led and flexible to circumstances. Domiciliary and outpatient sessions were offered.

The number of sessions offered was dependent on the outcome of the initial assessment and severity of anxiety, stress and depression that was shown. Initially up to twelve sessions were offered, though as the results will show this changed as the project progressed.

Participants

In total, 15 people have been seen over the time period of this project, seven people seen individually and four couples (see Table 1 for demographics). Due to the high severity of depression, anxiety and stress fewer people were seen than anticipated in the original grant application. At point of referral, 10 participants had experienced a stroke in the last two years, and one man experienced a stroke four years previously. Three participants were referred after a second stroke. All of these three participants reported that they had not received any psychological support after their first strokes and did not know that help existed.

Seven participants were over 65 years and 8 participants were under 65 years. Only one participant had severe speech difficulties, and two other participants had mild-moderate speech and language difficulties.

Outcome Measures:

The Depression, Anxiety and Stress Scales[1] were used with the majority of participants. 'The Visual Analog Mood Scales'[12] were used with only one couple. As Table 2 shows, overall outcome measures are very positive and encouraging. Individualised assessment and interview also helped to evaluate outcomes for participants, and for one participant a change questionnaire seemed appropriate.

Results

As this project developed, the level of anxiety and depression in this caseload was found to be moderate to severe. Seven of the people seen were experiencing at least one severe rating on the DASS (The Depression, Anxiety, Stress Scales). Four participants needed to be considered for risk issues due to suicidal ideation and one attempted suicide near to the start of therapy. With two participants, other services were involved, specifically psychiatry and a community psychiatric nurse in one case and the crisis team and mental health care coordinator in the other. More detailed cognitive assessment was also completed for two participants by a clinical psychologist specialising in stroke. These complex participants required more time investment and liaison with other professionals. As a consequence of the overall severity, only three participants were offered the originally-planned six sessions. All other participants were offered more sessions due to need, risk and multiple life issues. As Table 1 shows, in some cases this was substantially more (range 6-27 sessions), demonstrating the need for long-term treatment for some participants.

One referral was a self-referral from a man and his wife, who were looking for stroke related counselling due to this man's severe depression and emotionalism. All other referrals were from the multidisciplinary team and a PhD student. Couples were not always seen together and sometimes only the participant experiencing the stroke was seen. This was flexible to daily circumstances. As Table 1 shows, this service was mainly domiciliary, though three participants were seen both at their homes and as outpatients. Dominant concerns were losses in their lives such as loss of occupation, mobility, income, self-esteem, self-worth and loss of previous overall lifestyle.

It seemed that a psychodynamic approach was appropriate for most of the people seen. With participants 2, 7 & 11 however (See Tables above), the psychodynamic approach was not central. Participant 2 required a supportive client-centred relationship. She required companionship and was introduced to a support group during the duration of our sessions. Participant 7 was one of the later participants in the study and wanted further support to understand his stroke, including the type of stroke he experienced four years previously. He required factual information about his stroke and needed to talk about his difficul-

Findings: Table 1 – Demographic Table

Couple/Individual	Age of person with Stroke	Time Post-Stroke	Location	Number of sessions and Total Face – Face Hours	Referred by	Themes of the Counselling
1. Individual: Female	81	5 months Left middle Cerebral Artery	Home visits	6 Sessions + 1 cancelled session	Speech and Language Therapist	Isolation and loneliness. Loss of mobility and social circle.
2. Individual: Female	85	7 months Haemorrhagic Stroke	Home visits	6 sessions	PHD Student	Loss. Relationship pressures.
3. Individual: Female	64	3 months Right Posterior MCA Infarct	Home visits	14 sessions (in addition, some gaps and breaks)	Physiotherapist	Multiples losses. Boredom. Massive impact of visual losses.
4. Individual: Female	67	6 months Right Haemorrhagic Stroke	Home visits and outpatient sessions	13 sessions	Ward Consultant	Multiples losses. Grief and Mourning. Attachment. Fear. Pain. Rehabilitation support and advice.
5. Individual: Female	51	2 months post 2nd Stroke	Home visits	10 sessions	Occupational Therapy	Anxiety. Loss. Family issues. General stroke support and advice.
6. Individual: Male	51	7 months Since 2nd Stroke	Home visits	17 sessions	Occupational Therapy	Boredom. Self-image and sense of self. Multiple losses. Feeling inadequate. Pain.
7. Individual: Male	68	Left Parietal Infarct	Outpatient and Home visits	6 sessions	PHD Student	Understanding stroke. Confidence. Reading and writing. Loss. Pain.
8. Individual sessions and couple sessions: Husband had stroke	52	23 months post stroke	Outpatients sessions and a few Home visits	27 sessions (plus some breaks/holiday and 2 sessions cancelled)	Self-referral	Acceptance of stroke. Multiple losses (occupation, movement, social, hobbies). Grief and mourning. Dependency. Fear. Vulnerability. Death Anxiety.
9. Individual and couple sessions Husband had stroke	73	2 months Left basal ganglia haemorrhage.	Home visits	13 sessions	Occupational Therapy	Communication difficulties. Fear. Frustration. Tiredness. Dependency.
10. All couples: Husband had stroke	52	1 month post 2nd Stroke	Home visits	9 sessions	Speech and Language Therapy	Loss. Rehabilitation and expectations. Social anxiety and confidence.
11. All couples Husband had stroke	75	10 months post Left MCA Stroke	Home visits	9 sessions	Speech and Language therapy	Pervading unpredictable low mood. Loss. Confidence. Self-esteem. Attachment.

Findings: Table 2 – Baseline and Outcome Measure Table

Participant	Depression, Anxiety and Stress at Initial Assessment			Depression, Anxiety and Stress at End of sessions		
1	Extremely Severe	Moderate	Moderate	Normal	Normal	Mild - Normal
2	Refused to complete outcome measure questionnaires					
3	Extremely Severe	Moderate	Severe	Moderate	Normal	Normal
4	Extremely Severe	Extremely Severe	Extremely Severe	Moderate	Severe	Moderate
5	Extremely Severe	Extremely Severe	Severe	Mild	Extremely Severe	Moderate
6	Extremely Severe	Extremely Severe	Extremely Severe	Still high. Under Mental Health Teams.		
7	Normal	Normal	Normal	Not repeated. Needed factual information about stroke not previously received.		
8	Extremely Severe	Mild	Moderate	Severe	Normal	Mild–moderate
9	Normal	Moderate	Normal	Mid–Normal End–moderate	Normal Normal	Mid–Normal Normal
10	Normal	Moderate	Moderate–Severe	Mid–Normal	Mid–Moderate	Mid–Mild
11 (VAMS Used)	Scored differently to DASS, some improvement seen especially on measures of anger and tension.					

ties. This participant also required further speech and language therapy guidance for reading and writing, and work on confidence. Participant 11 (a couple) required a mixture of some psychodynamic counselling in the early sessions but also communication advice and support. The couple also benefitted hugely from the long-term support groups they attended (an aphasia support group in their locality). With this couple, their mood deteriorated when a support group was having break due to staffing problems. In this case, it seemed that long-term conversational support was more valuable than counselling as it provided opportunity to get out of their home and socialise. For all these three participants (2, 7, 11), negative mood could be linked to level of conversational support available to them.

Level of daily activity was a recurring theme for many participants. Reduced ability to participate in daily activities and boredom at home has been a pattern for participants and negatively reinforced low mood. This has shown the crucial need for long-term support

groups and health professionals to support transition back to accessible social and pleasure activities if possible, before discharge from therapy.

Two of the participants experienced severe physical pain during the course of the sessions. It was clear that this influenced their mood and could be associated with suicidal thoughts. Pain management was shown to be crucial for these participants. For client 6, improvements were harder to see on the DASS and were unchanging on objective outcomes. This participant however began to demonstrate positive changes, and though he rated 'I felt I had nothing to look forward to' highly (3), he had described looking forward to a trip out and his socialisation was improving. In addition, suicidal comments stopped during the sessions.

Most participants were able to complete the outcome measures, though help was required by one participant to be clear about the meaning of elements of the rating scale. This help was by writing out the choices of 0-3 in a larger font and by giving reminders for each question. With the Visual Analog Mood Scale, the scales were completed together with the couple and differences were discussed as the scales were completed. Sometimes these differences were not anticipated, so this was in itself useful to the counselling work.

Discussion

Importantly this service development project has identified people experiencing moderate to severe stroke associated depression, stress and anxiety. Most of these people were already on antidepressants and were in need of psychological support after stroke. It seems to us convincing that there is a need for a service such as this, especially when some risk of suicide has been shown. More specifically for most of these people, support was needed for their feelings of grief, loss, death anxiety and fear.

With the majority of participants, there were multiple issues as well as a stroke. In some cases, a person's stroke brought out other issues that were repressed and that had not been spoken about before. In other cases, the stroke had coincided with other life issues, such as the loss of parents and businesses, and with the poor health of a family member.

Examples of issues for participants covered in this counselling work:

- Recent loss of a mother and similarities in medication and mobility to mother.
- Forced retirement, loss of job, loss of business.
- Loss of mobility and some participants already had losses prior to stroke, such as impaired vision.
- Other medical challenges such as epilepsy, heart attacks, arthritis.
- Difficult family relationships e.g. step-relationships, fostered children.
- Previously undisclosed abuse.
- Losses of siblings at a younger age.
- Previous relationship break-ups and divorce.

The trauma of stroke has been central to all the counselling, but exploration of relevant and related issues such as those mentioned above were vital for counselling to be beneficial.

Accessible services that doctors and health professionals know about and know how to refer to are crucial for those experiencing strokes. For three participants that did not have access to psychological support services after their first strokes, we can question whether their assessment outcome measures would have been better at the start of this pilot. A referral pathway for psychological support needs to be clear to all GP services, as some participants' needs after their first stroke were not recognised and there were limited services to refer to. Some participants said, "I didn't know services existed; I didn't get any help after my first stroke."

We argue that commissioning of Stroke-specialist psychological services is needed for long-term post-stroke. Without this there will remain poor service provision, such as failing to meet The National Stroke Strategy for England (2007) guidelines.[13]

A harder element to articulate in a service development project is the observation that psychodynamic counselling 'felt' appropriate to the counsellor for the majority of participants, especially participants, 3, 5, 6, and 8. It was also felt some participants could have continued to benefit from longer term sessions. One reason was because the dynamic of the sessions seemed appropriate in terms of the application of psychodynamic theory and the rapport, transference and interpretation of feelings and emotions that evolved.

This service evaluation has shown the value of a stroke experienced counsellor. For example some of the counselling was aimed at helping the individuals to understand 'what is normal' after stroke. The counselling provided included sharing of expert knowledge about stroke and gave support and understanding of rehabilitation. Tiredness was a recurring issue with most of the participants seen. In particular, partners understanding issues such as tiredness was important. 'The Stroke and Aphasia Handbook'[14] was a much appreciated resource and reading about these issues was reassuring for some people.

The DASS was shown to be a good accessible outcome measure for these clients as it directed assessment and understanding of the degree of stress, anxiety and depression. It is interesting to note from the results that the counselling appeared to be more effective at reducing depression than anxiety for participants 4, 5 & 10. With a psychodynamic approach, depression and stress showed greater improvements. It is indicated that further sessions may be needed to reduce anxiety.

At the outset of this project, some group work with participants was anticipated, such as a carers' group. 1:1 work and couples sessions were however shown to be the most appropriate for this particular group of participants.

This service development project and evaluation has identified that increased psychological support is needed for people following strokes who have moderate-severe depression, stress and/or anxiety. This small evaluation project demonstrates that increased clinical psychology provision and/or provision of counsellors/psychotherapists specialising in stroke are needed as part of a permanently funded service. This service has shown that 15 participants needed – and benefited from –

Individual case study with more details of this counselling service.

Case Study, illustrating how losses are discussed in therapy.

Participant 4 (from Tables 1-2, female, aged 67) was on antidepressants and despite this stress, anxiety and depression were rated as extremely severe initially. There was some risk of self-harm due to low mood and at one point clear suicidal ideation. Losses were multiple, not only severe mobility losses due to her stroke, but loss of occupation and grief for her mother who had recently died.

Sessions were focused on the mourning her mother, alongside her own mourning of previous role. In addition, the counselling was supportive and client-centred and followed her through her rehabilitation when the level of recovery was uncertain.

There was clear reliance on attachment figures with strong dependency in the first year post stroke. As the sessions progressed, there was less dependency. In our final sessions, she stated, "I'm not worried of sitting alone. Not terrified anymore."

Outcomes improved from extremely severe to lower levels as shown in Table 2. She was later referred back for a further four sessions due to concern from another health professional that her levels of depression had deteriorated again. She was however maintaining improvement well. Her level of depression had however been extremely severe initially and some level of enduring depression was likely. This is interesting as it shows different perceptions of depression. Participant 4 felt that the counselling was very beneficial to her and described it as, "A relief through a difficult time." Since these sessions, follow-up appointments have indicated that she has maintained the gains that she made.

psychological support that was previously unavailable. This service development project and evaluation was completed in one day per week for a year including travel and administration. If services such as this are continued, further people having strokes could benefit. This will have benefits for the health and well-being of those experiencing strokes and their families, and positive benefits to rehabilitation outcomes.

Conclusion

This service development project and evaluation has identified and filled an unmet need for psychological provision after stroke in this locality. All the participants were appreciative of the service and felt that they benefited.The results show that participants' overall mood improved after receiving this service. The DASS was an appropriate measure to assess mood and enabled changes in stress, anxiety and depression to be assessed and evaluated.

Psychodynamic counselling was shown to be a potentially effective psychotherapeutic approach and a valuable extension to the community multidisciplinary rehabilitation approach. This evaluation adds further to the literature and evidence base of the effectiveness of psychotherapeutic approaches with stroke. It has also been identified that the commissioning of a well-structured psychological support service is needed. Anticipated benefits are likely to include: reduced demand on GPs due to reduced risk, supporting GPs to meet higher ratings on their quality and outcomes framework and therefore making cost savings, and the provision of a high quality service that meets the quality markers of The National Stroke Strategy (Department of Health, 2007).

Helping to support a person to feel better about life can only be valuable, and therefore this has been a very worthwhile project. One participant's positive feedback through a change questionnaire made the following comments about the counselling sessions.

"A relief through a difficult time"
"I couldn't have stayed in hospital if I didn't have you."
"Not worried if sitting alone. Not terrified anymore."

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An Artist's View of the Brain

Jane Southgate
gained her BA at Chelsea School of fine art and has worked as a professional artist from her studio in Suffolk for the last 17 years. She regularly exhibits, undertakes commissions and runs workshops for a variety of different groups. Her work is generally three-dimensional and often contains a textile element.

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There is always a biological element in my work, usually human but not exclusively, however lately I have been fascinated by the brain. This interest arose after the death of a family member from a brain tumour. As an artist, the majority of my work involves life cycles and has at times addressed pregnancy, the lifecycle and nesting of birds, reclamation and recycling, decay and new life within the natural world. I wasn't looking for answers, reasons or even explanations linked with this event. It merely highlighted to me what an amazing and fascinating organ the brain is. Initially I concentrated on the theoretical concepts, I am enthralled by how we can be ourselves, have our own individual personality and yet everything we are, do and think has been explained by some as merely a process in the brain, how can this be all we are? How can electro-chemical reactions within our brains make me an artist and you a neurologist? And where does the spirit of each of us come from, and reside, within that amazing network of firing synapses? Well, these questions I still can't answer and they still fill me with awe. I have, however, been learning more about the physical construction of the brain and, as a sculptor who frequently works with textiles, this grasping at an understanding of the fabrication of the brain holds another area for amazement.

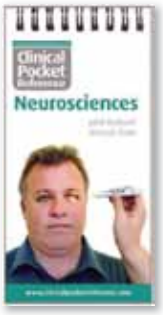
In order to explore my thoughts and findings I began making papercuts of the outer appearance of the brain, that beautiful folded and pleated, almost quilted surface. I followed this with a papercut of an artistic interpretation of neurons. Neurons, it seems to me, really are the thread of our thoughts. Their delicate spidery dendrites and axons have a truly textile, woven quality to them. For this very reason I crocheted a neuron, but this wasn't delicate enough and I felt it lacked the fantastically fragile appearance of the real thing. This led me into an experiment of embroidering neurones onto dissolvable fabric so that I could make a neuron lace. I was happier with the results but currently I am trying to find a way of making them more three-dimensional as the flat lace doesn't do justice to the the neural networks and interconnections. I have embroidered a side view of the brain and upper brainstem, and made a quilted version although I intend to work on this quilting effect much more as my first attempt doesn't embody the sumptuous depths of the crenellations that I want to capture. I have just finished knitting myself a brain. I took my knitting in my bag with me wherever I was going for the last few weeks so I could work on it whenever I had a few minutes. It was fantastic fun to see people's reactions as they often stopped me to ask what it was I was knitting. I am trying to design a way to make a very loose 3-D weaving based on images of thought pathways and digitally recoloured photographs of neuron interconnections especially the gorgeous

Knitted brain

'Brainbow Mouse' images by Jean Livet, Joshua R Sanes and Jeff Lichtman but it is proving to be rather demanding. Having recently visited the Wellcome Trust to see 'Brains: The Mind as Matter' exhibition I was captivated by the fantastic drawings of Santiago Ramon y Cajal. I am hoping to create a body of work that will be exhibited together in order to inspire other peoples' interest and exploration into this fascinating organ. Particularly, I hope to encapsulate a sense of its visual beauty in physical construction, externally and internally, not just its vast, assorted and amazing functions. ◆

Neuron lace

Clinical Pocket Reference: Neurosciences



From a nurse's perspective, I would recommend this booklet as a handy reference guide to neurological aspects of nursing care. It is of a convenient size, to fit into uniform pockets. Its spiral binding and waterproofed card make it hard wearing and practical for use on a daily basis within the workplace.

The Pocket Reference will be ideal for nurses working in general hospital, general practice or community settings who encounter patients with neurological diseases (either as the patient's primary diagnosis, or as a co-existing condition). Student nurses will find it a great introduction to Neuroscience Nursing, as would more experienced nurses moving into Neurology and Neurosurgery work for the first time.

The booklet provides an easy guide to neuroscience practice, divided into three sections. Section 1 gives an introduction to the nervous system including diagrams and definitions of the central and peripheral nervous systems, the motor and sensory pathways. Section 2 is a very comprehensive guide to neurological assessments explaining how to do and how to document. Section 3 introduces common neurological disorders by describing the conditions, explaining signs and symptoms, outlining possible investigations and possible treatment. Importantly, within this section, there are references to appropriate NICE guidelines and tips on where to go for more information.

The format is clear, logical and easy to read. Its brevity means that it will be most useful as a reference for general nurses and nurses new to the, often complicated, field of Neuroscience. However, the guide's referencing and bibliographies mean that it would also be a useful acquisition for more experienced nurses and other practitioners. ◆

Authors: Juliet Bostwick and Deborah Slade
Published by: Clinical Pocket Reference, Oxford
Price: £9.99
ISBN: 978 0 9543065 7 1

Reviewed by: Kerry Mutch, RGN, BSc (Hons) MSc, Specialist Nurse (Neuromyelitis Optica), Walton Centre Foundation Trust, Liverpool.

Neuro-oncology Part 1

Handbook of Clinical Neurology (Volume 104)

This book boasts a stellar authorship from the world of neuro-oncology with chapters written by many of the current leading lights in the field from around the world. Part I contains an overview of basic principles including pathogenesis and epidemiology of CNS Tumours and the basic principles of therapy including surgery, chemotherapy, radiotherapy, symptom management and the role of clinical trials. Each chapter is succinct and very readable. There are extensive references for those looking for more detail. Volume II promises a more detailed exploration of specific tumour types and neurological complications of systemic cancer.

Although most likely to appeal to those with a special interest in neuro-oncology, the sections on neuro-imaging and principles of therapy are of wider appeal.

There are few, comprehensive and up-to-date works in the area of neuro-oncology and this book goes a long way towards filling that gap and I would highly recommend it. ◆

Editors: Wolfgang Grisold and Riccardo Soffietti
Published by: Elsevier
Price: £162.65
ISBN: 978-0444521385

Reviewed by:
Simon Kerrigan, Neurology Registrar, Edinburgh Centre for Neuro-oncology, Western General Hospital, Edinburgh.

Primer on Multiple Sclerosis (OUP)

This book provides a comprehensive review of multiple sclerosis (MS) and, pretty much, everything related to it. It covers historical aspects, basic science, clinical practice, psychosocial issues, and provides a glimpse into the future of MS research. All the chapters are easy to digest and benefit from experience and expertise of an impressive list of contributors.

The primer begins with a fascinating review of the history of MS. We are taken through an evolutionary narrative from initial misconceptions to Charcot's illuminating account. The numerous and, in many cases, agonisingly painful treatments of the past are described, with chronological progression to treatments more familiar in modern day practice. There are nostalgic moments too: 'beef steaks twice daily with London porter beer' offered to Augustus d'Este in the early 19th century sounds more appealing, albeit (slightly) less efficacious, than weekly injections of Avonex!

A concise overview is provided on MS Genetics, highlighting current understanding of genetic and epidemiological factors, bringing together knowledge attained from years of linkage and association studies and the explosion of information from genome-wide association studies. The ever controversial topics of viral aetiology and vitamin D are also explored.

The initial part of the Neuropathology section may have been 'common knowledge', but covered aspects of demyelination, remyelination, and axonal loss of interest to me as a trainee. I was pleased to see that the section on diagnosis was not just a review of the Revised Mcdonald Criteria, or a lesson in lesion-counting. Specific chapters were also included on supportive paraclinical tests (imaging, CSF, and evoked potentials) and their utility. Given the date of publication, the most recent (2010) revisions to the criteria were not included.

A large section of the book is devoted to the clinical manifestations of MS. Challenging clinical scenarios such as cognitive impairment, fatigue, pain, sexual dysfunction, and reproductive issues are covered in informative chapters. We are taken on a whistle stop tour of paediatric multiple sclerosis in a level of detail 'just right' for neurologists in adult practice. The review of immune therapies very neatly summarises relevant trials.

Exactly as it says on the cover, 'Primer on Multiple Sclerosis' provides a second-to-none reference for trainees intending to work in the field of MS Neurology or for general neurologists with a significant MS workload, which probably covers most of us. ◆

Editors: Barbara S Geisser
Published by: Oxford University Press
Price: £45.00
ISBN: 978-0195369281

Reviewed by:
Saif Huda,
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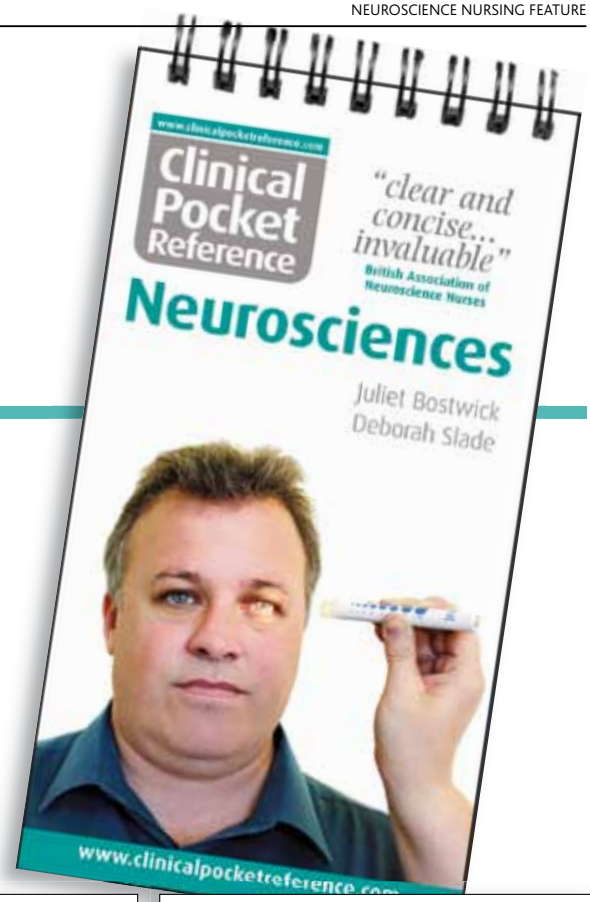
Clinical Pocket Reference **Neurosciences**

Authors: Juliet Bostwick and Deborah Slade, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford.
ISBN: 978 0 9543065 7 1



This new handbook provides practical support for the nurse caring for patients with neurological conditions. Trainees will find this an essential learning and reference tool, while trainers and mentors will find the book invaluable as a training aid. Neuroscience nurses will find this a useful update on key topics.

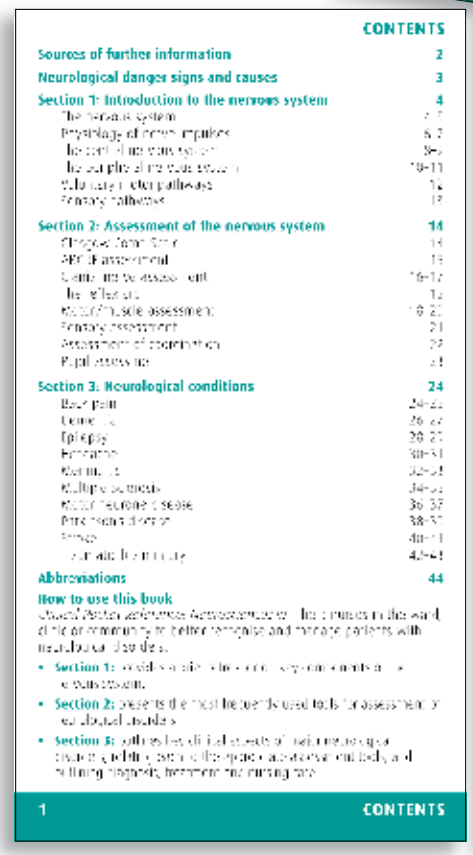
Reviewer's comments:

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

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

ACNR

ACNR are publishing selected content from Clinical Pocket Reference: Neurosciences over the next few issues... neuroscience nurses will find this a useful aide memoire. Keeping a copy on the ward will be ideal for reference and teaching.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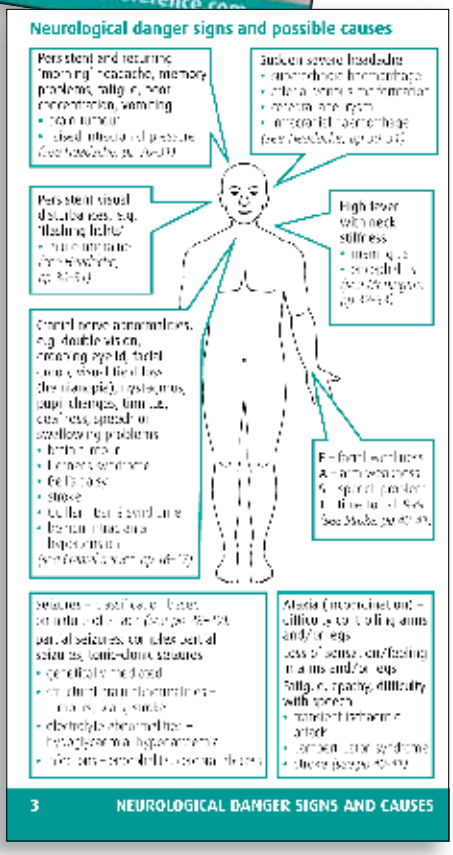

3 NEUROLOGICAL DANGER SIGNS AND CAUSES

High Grade Gliomas: Pathogenesis, Management and Prognosis

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did his basic Neurosurgical training in Malaysia and completed his training in Addenbrooke's Hospital, Cambridge in 2011. He is currently a junior consultant neurosurgeon in University Malaya, Malaysia. His clinical interest lies in neuro-oncology and skull base surgery.

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Stephen Price
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High grade gliomas are the most common type of brain tumours, accounting for up to 85% of all new cases of malignant primary brain tumours diagnosed every year. They carry a very large disease burden with greatest years of life lost for any cancer. Despite recent advances in the understanding of pathogenesis and management, the median survival still ranges between 12 to 18 months. Surgery along with adjuvant chemo and radiotherapy remains the mainstay of management. This review summarises the diagnosis and management as well as recent advances in the understanding and treatment of high grade gliomas.

Introduction

The term high grade glioma(HGG), is usually used to describe WHO grade III and IV tumours. The incidence of these tumours is approximately 5/100,000 person years in Europe and North America.[1] Of these, glioblastomas account for 60 to 70%, anaplastic astrocytomas for 10 to 15%, anaplastic oligodendrogliomas and anaplastic oligoastrocytomas for about 10%, while anaplastic ependymoma and anaplastic ganglioglioma make up the rest.

There has been a recent increase in incidence of HGGs in the Western world, particularly in the elderly population. This probably reflects the easy availability of vastly improved diagnostic imaging.[2] The median age of onset is 45 for Grade III and 60 for Grade IV tumours.[3] There is a 40% greater incidence among males.[4]

In the majority of cases, no causative factors can be attributed. However, exposure to ionising radiation, such as from treatment of previous cancer is an established risk factor.[5] Many other factors have been studied including head injury, foods with N-nitrose compounds, electromagnetic fields, smoking and most recently usage of cellular phones, all of which have not been shown to be risk factors in the development of HGG.[6-8]

Approximately 5% of patients with HGG have a family history of gliomas.[9] Some of these are familial and associated with genetic syndromes such as neurofibromatosis types 1 & 2, Li-Fraumeni syndrome and Turcot's syndrome. Recent studies have also shown links between DNA repair genes and tumour aggressiveness.[10-12]

Presentation

Most patients with HGG present with signs and symptoms of raised ICP from mass effect, oedema or haemorrhage. These frequently manifest as headaches, nausea & vomiting, reduced visual acuity, diplopia, drowsiness and confusion.[13] Other presentations include focal neurological deficits, symptoms which are dependent on the location of the tumour such as aphasia, limb weakness, altered sensorium and neurocognitive defects including disinhibition and personality changes.[14] Approximately 50% of grade III and 25% of Grade IV tumours present with seizures compared to 80% of low grade gliomas.

Imaging

The initial imaging modality is usually a contrast enhanced Computed Tomography (CT). However, Magnetic Resonance Imaging (MRI) is more sensitive than CT and is now the imaging modality of choice for all patients with brain tumours – especially if considered for surgery.

HGG typically appear as irregular, ill-defined masses with associated vasogenic oedema on both CT and MR. Enhancement typically is around the rim of the mass with a central area of non-enhancing tissue. Enhancement per se, cannot be taken as a diagnostic feature as between 30-50% of anaplastic tumours fail to enhance on CT,[15] and 16% fail to enhance on MRI.[16] In addition, 20% of low grade gliomas (typically oligodendrogliomas) enhance on CT[15] and 35% enhance on MRI[16] (see Figure 1).

Identification of tumour margins is not possible with conventional imaging. Both post mortem and biopsy studies have shown tumour

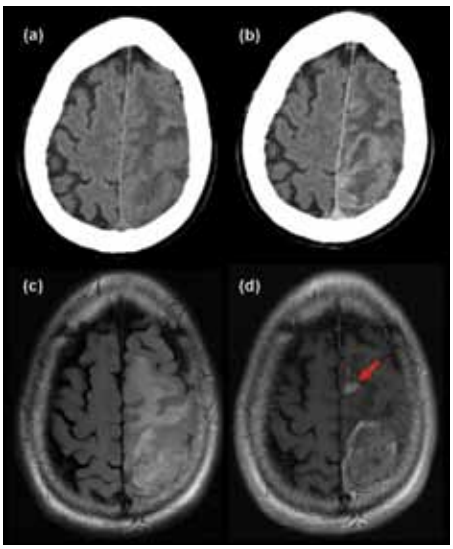

Figure 1: Imaging of a glioblastoma. (a) An unenhanced CT and contrast enhanced CT (b) show the lesion and the oedema. The latter is better identified on the FLAIR imaging (c). Contrast enhanced T1-weighted imaging shows a small focus of enhancement separate from the main body of the tumour that was not identified by other methods.

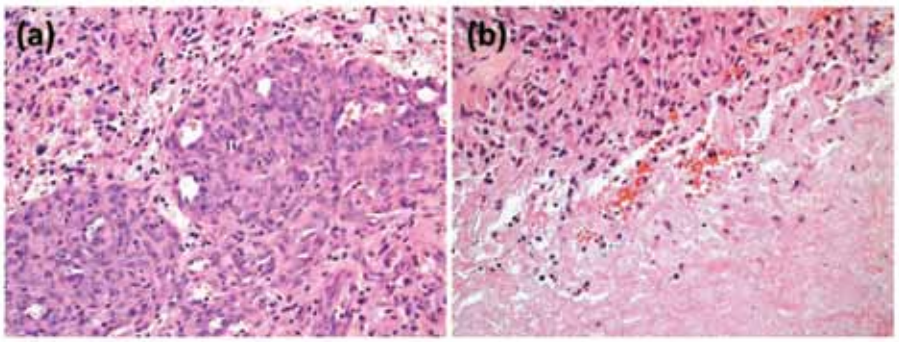

Figure 2: Histology of a glioblastoma. (a) shows the microvascular proliferation and (b) shows evidence of tumour necrosis – the presence of either of these factors in an astrocytic tumour is sufficient to make a diagnosis of glioblastoma. (Picture courtesy of Dr Kieren Allinson, Addenbrooke's Hospital, Cambridge).

extends beyond the margin on CT,[17-20] contrast-enhanced T1-weighted MRI[20-21] and T2-weighted MR.[20-23] These techniques cannot determine the margin or the invasiveness of these tumours. Advanced imaging methods have been developed for assessment of these tumours. These are being used in clinical practice and are summarised elsewhere.[24]

Post-operative MRI is the only method of objectively assessing the extent of resection. Studies have shown it identifies more cases of incomplete resection compared to the judgement of the surgeon.[25] Imaging within 72 hours avoids the post-operative changes that occur later.

Histology

High grade gliomas arise from supporting glial cells in the brain. The predominant cell type determines the pathological classification. Tumours are graded according to the World Health Organisation (WHO) grading system (Grade I to IV).[26] HGGs comprise of WHO grade III and IV tumours. Multiple subtypes have been identified which may alter response to treatment and prognosis. These include subtype III which comprises anaplastic astrocytoma, oligoastrocytoma, anaplastic oligoastrocytoma as well as subtype IV which includes glioblastoma, glioblastoma with oligodendrocyte component and gliosarcoma.[27]

Grade III tumours are diffusely infiltrating astrocytomas with focal or dispersed anaplasia and a marked proliferative potential with increased cellularity, distinct nuclear atypia and high mitotic activity while Grade IV tumours show cellular polymorphism, nuclear atypia, brisk mitotic activity, vascular thrombosis, microvascular proliferation and necrosis (see Figure 2).

Grading is determined by the most malignant part of tumour, which makes it essential for adequate sampling to determine the proper grade, especially in biopsy procedures.

Molecular markers and their significance

One of the biggest advances in high grade glioma management has come in the form of molecular markers. Three particular markers have been well studied over the past few years.

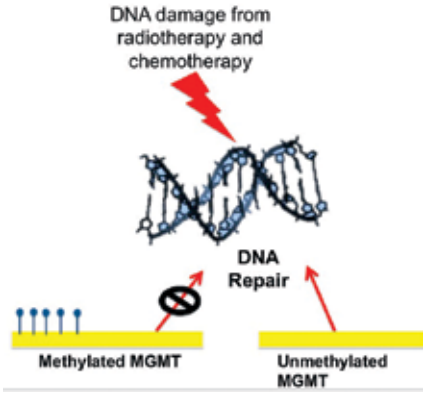

Figure 3: Methylation of MGMT inhibits repair of DNA damaged by both radiotherapy and chemotherapy drugs.

1. MGMT Methylation Status

The MGMT gene encodes O-6-methylguanine-DNA methyltransferase enzyme – a DNA repair enzyme that removes alkyl groups from the O-6 position of guanine, an important site of DNA alkylation. MGMT methylation status has been used to prognosticate response to alkylating chemotherapeutic agents like Temozolomide. In the methylated form, it is non-functional (i.e. the enzyme is not produced) thus limiting DNA repair, cf. Figure 3). Two recent retrospective studies by Hegi et al[28] and Stupp et al[29] analysed this particular molecular marker and found the methylation phenomenon present in up to 45% of cases of GBM. Further, in the presence of methylation, median survival for radiotherapy with Temozolomide was significantly longer than radiotherapy alone (21.7 months, 95% CI 17.4-30.4 vs 15.3 months, 95% CI 13.0-20.9; P=0.007). In comparison, the difference in survival in the unmethylated group was insignificant (11.8 months, 95% CI 9.7-14.1 vs. 12.7 months, 95% CI 11.6-14.4). As the methylated group with radiotherapy alone has better survival than either unmethylated groups, it suggests MGMT methylation functions as a prognostic marker rather than a predictive marker. A prospective analysis by Weller et al shows an improvement in both progression free survival (7.5 months vs 6.3 months) and overall survival (18.9 months vs 11.1 months).[30] MGMT methylation status assessment is not without its problems – multiple sites for mutation have been identified making this marker difficult to assess. In addition, the results are semi-quantitative with no clear cut off to define positive or negative status, resulting in non-standard interpretation of test results.

2. IDH-1 Mutation

The IDH-1 gene encodes the enzyme isocitrate dehydrogenase (IDH-1) gene that converts isocitrate to α-ketoglutarate within the Krebs cycle. This stage generates NADPH that appears to be important in dealing with cytotoxic oxidative stresses. Mutation of this gene results in an alternative metabolism of isocitrate to 2-hydroxyglutarate. Mutations cause a 10 fold increase in the production of 2-hydroxyglutarate.[31] Accumulation of 2-hydroxyglutarate also leads to the breakdown of HIF-1α, a factor important for generating a malignant cell phenotype.

Mutation of IDH-1 gene was found in 12% of GBM patients and seems to confer a better median survival, (3.7 years vs 1.1years).[32] Weller et al reconfirmed this via the German Glioma Network study which found IDH-1 mutations in 16/286 patients (5.6%). They also found an improvement in both progression free survival (16.2 months vs 6.5 months) and overall survival (30.2 months vs 11.2 months).[30] As with the MGMT mutation, IDH-1 mutation is prognostic rather than predictive.[33] Virtually all mutations (96%) are a point mutation involving arginine 132. This allows an immunohistochemistry test on paraffin embedded tissue.

3. Chromosome 1p19q Loss in Oligodendroglial Tumours

One of the commonest chromosomal abnormalities seen in oligodendrogliomas is the concurrent loss of part or all of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q). Cairncross et al showed loss of 1p19q in 50-70% of anaplastic oligodendrogliomas.[34] This mutation had an improved survival with chemotherapy and was originally thought to be predictive of chemosensitivity. Results from a trial of radiotherapy vs chemoradiotherapy showed the radiotherapy only arm with 1p19q loss did better than the chemoradiotherapy arm without loss of 1p19q suggesting again the prognostic nature of these molecular markers.[35]

Pathogenesis

Glioblastomas develop either as primary tumours or arise from pre existing low grade gliomas (Table 1). These primary and secondary GBMs constitute separate and distinct disease entities. They affect different epidemiological groups and carry different prognoses.

Primary gliomas usually are of a de novo manifestation involving older patients with a shorter clinical history. On the other hand, secondary gliomas are usually part of a malignant progression from low grade to high grade

Table 1: Differences between Primary and Secondary GBM's

	PRIMARY (de novo)	SECONDARY
Definition	No clinical or pathological evidence of pre-existing lesion	Malignant progression from lower grade tumour
Age	Typically older (mean 55 years)	Typically younger < 45yrs
Genetics	Early EGFR overexpression	Early p53 mutation and PDGF overexpression. V early IDH-1 mutation
Clinical	Probably worse outcome	Better survival (esp. if IDH-1 mutation)

involving younger patients with a variable interval between 1 to 10 years.

Large numbers of genetic abnormalities have been found in gliomas. These genetic abnormalities increase as the grade of glioma increases. Most of these abnormalities affect entry into cell cycle or inhibit apoptosis via multiple pathways, which is discussed in depth elsewhere.[36]

Recent data from the Cancer Genome Project suggests genetic abnormalities can classify GBM's into four categories[37]:

- CLASSICAL – amplification of EGFR
- MESENCHYMAL – NF1 deletion
- PRONEURAL – mutations of PDGFR-A and IDH-1
- NEURAL – expressed neuronal markers

The proneural group showed improved survival, but interestingly showed no survival advantage with chemoradiotherapy vs. radiotherapy alone. Further work is underway to understand the significance of this classification for individual patients.

Management

HGGs are best managed using a multi-disciplinary team (MDT) approach. Options for management span the spectrum from conservative treatment, to surgery and adjuvant therapy. The main thrust of management is diagnosis and prolongation of progression free survival.

Dexamethasone is vitally important in controlling cerebral oedema associated with tumours. The response to steroids can be extremely rapid. Failure to improve with steroids suggests radical surgical resection may cause a worsening neurological deficit.[38] The role of steroids, their complications and dosing in neuro-oncology has been recently reviewed elsewhere.[39]

Conservative management is a valid option in patients with a poor prognosis as identified by age and poor performance status. In this situation good palliative and supportive care is important.

Surgery

Surgery ranges from diagnostic biopsy to debulking to gross total resection.

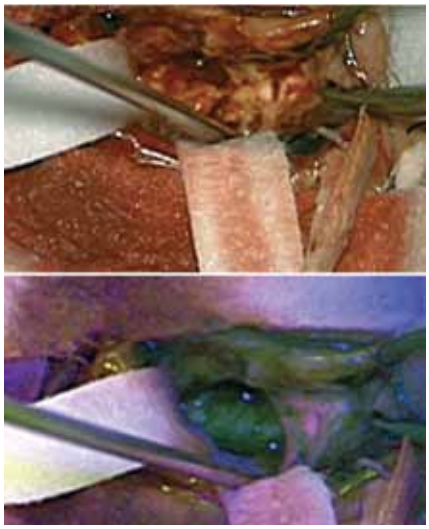

Figure 4: An intra-operative image of a resection of a glioblastoma under white light (upper panel) and blue light (bottom panel) after administration of 5-ALA. With blue light the tumour can be seen as pink fluorescence in an area that looked relatively normal with white light.

1. Tumour Biopsy

Biopsies are minimally invasive, well tolerated and suitable for lesions of any site or size. Biopsy is usually considered when the risks of resection outweigh the benefit.[40] It is best utilised in cases where initial diagnosis may influence subsequent management. However, it has its pitfalls in the form of sampling error especially in small or heterogeneous samples. To reduce the risk of non-diagnostic biopsies, image-guidance is routinely used to guide biopsies.

2. Tumour Resection

Debulking surgery is beneficial in reducing the tumour load and thus the side effects of raised intracranial pressure and providing a more representative histological sample. Whether it provides an improvement in survival is controversial. The Cochrane review of the literature has highlighted the lack of quality studies in this area.[41] Retrospective studies have suggested that gross total resection as defined by post operative MRI findings of more than 98% tumour resection, has shown better quality of life and progression free survival.[42] The median survival, according to one study, improved from 8 months for subtotal resection to 13 months after gross total resection (GTR).[43] This was reconfirmed by Pichlmeier et al whose RPA analysis revealed survival benefit was greatest in patients with higher RPA scores (i.e more severe baseline disease based on age, performance status, neurology and mental status). The median survival for GTR vs incomplete resection was 17.7 vs 12.9 months for RPA IV and 13.7 vs 10.4 months for RPA V.[44] The problem with GTR remains balancing maximal resection against potential neurological deficits.

5-ALA is a new surgical adjuvant used to identify glioma tissue under blue light (see Figure 4). 5-ALA is taken up and is converted in the normal heme biosynthesis pathway. In tumours there is a deficiency of the ferrochelatase enzyme that leads to the accumulation of the fluorophore protoporphyrin IX that fluoresces under blue light. The use of 5-ALA enables more complete resections of contrast enhancing tumour, leading to improved progression free survival in patients with malignant glioma. Stummer et al showed a 29% increase in complete resections rates in the 5-ALA group as opposed to the white light group. The 5-ALA group also had a higher 6-month progression free survival than the white light group (41% vs 21.1%).[45]

Another adjuvant to surgery has been local therapy with BCNU loaded wafers. These wafers provide a method of local delivery of high concentration chemotherapeutic agent bypassing the blood brain barrier. The use of these agents remain controversial though, as questions have been raised about their efficacy as well as side effects including CNS and wound infection rates as high as 28%.[46,47] However, there is substantial evidence for the use of BCNU wafers in adjuvant treatment. A retrospective review on BCNU wafer implanta-

MGMT methylation and mutation of the IDH-1 gene are both prognostic factors associated with better progression free survival and long term outcome

Table 2 Recursive partitioning analysis (RPA) of GBM survival based on Karnofsky performance status (KPS), the age of the patient, and treatment[53]

RPA class	Definition	Historical Median Survival Time	Historical 1-Year Survival
III	Age < 50, KPS ≥ 90	17.1 months	70%
IV	Age < 50, KPS < 90 Age > 50, KPS ≥ 70, surgical removal with good neurologic function	11.2 months	46%
V + VI	Age ≥ 50, KPS ≥ 70, surgical removal with poor neurologic function Age ≥ 50, KPS ≥ 70, no surgical removal Age ≥ 50, KPS < 70	7.5 months	28%

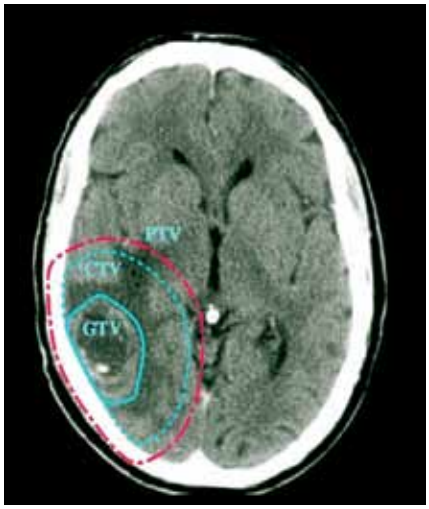

Figure 5: An example of radiotherapy treatment volumes. The enhancing tumour is outlined as the gross tumour volume (GTV). A 2.5cm margin is then applied to account for the infiltrating margin and is referred to as the clinical target volume (CTV). A further 0.5 cm margin for set up error is then applied, the patient target volume (PTV). The areas outside the GTV will include normal brain at risk of radiation injury. (Picture courtesy of Dr Neil Burnet, Addenbrooke's Hospital, Cambridge).

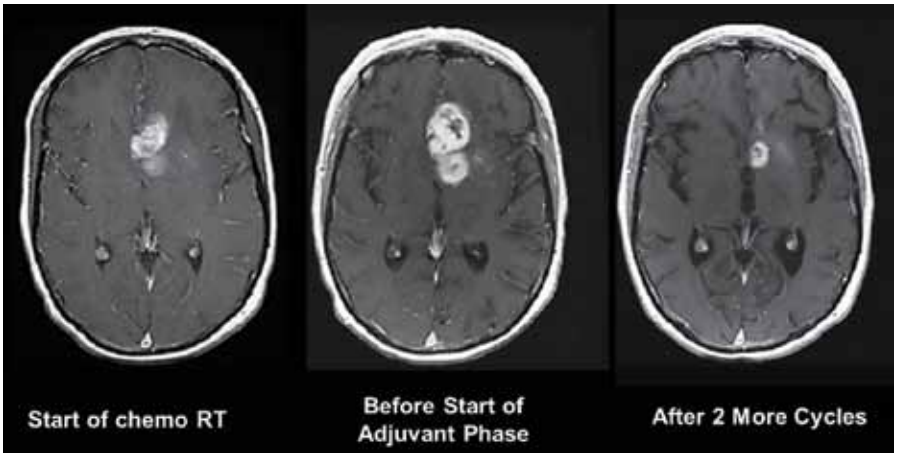

Figure 6: An example of pseudoprogression in a patient with a glioblastoma being treated with concomitant Temozolomide and radiotherapy. Before starting the adjuvant phase the tumour appears to have enlarged in size. This is not true progression but pseudoprogression as continuation of adjuvant Temozolomide shows excellent response after two more cycles.

tion in combination with TMZ and radiotherapy in newly diagnosed GBM revealed a median survival of 20.7 months with a two year median survival of 36%.[48]

Radiotherapy

Radiotherapy has been the mainstay of adjuvant therapy for high grade gliomas since multiple studies from the 1970s showed a survival benefit.[49] However, attempts to improve on the initial benefits by increasing dosage of radiation has failed to have any success. Unfortunately the therapeutic window for radiotherapy to the brain is narrow and there is an increased incidence of radiation necrosis with increased radiation dose. Part of the reason for this is the inability of conventional imaging to identify infiltrating tumour. As a result radiotherapy planning outlines the obvious tumour as the Gross Tumour Volume (GTV). A 2.5cm margin is then applied to form the Clinical Target Volume (CTV). A 0.5cm margin is added to account for set up errors and patient movement to form the Planning Target Volume (PTV). In other words, a 3cm margin is applied around the tumour that will contain normal brain. To reduce the risk of radiation necrosis the dose is therefore limited (see Figure 5).

Although various radiotherapy regimes have been proposed, traditionally two are used in HGG:

1. ***Radical radiotherapy:*** gives 60 Gy dose over 30 daily fractions.
2. ***Short Course/Palliative Radiotherapy:*** gives 30 Gy over two weeks in six fractions. As there is little planning patients can start treatment very quickly and it is well tolerated. It is useful where patients are acutely deteriorating.

Cytotoxic Chemotherapy

PCV was the standard adjuvant chemotherapeutic regime in use until the advent of Temozolomide. PCV is nitrosurea based chemotherapy providing a small survival benefit; a 5% increase in two year survival rates.[50] The treatment involves a 10 day oral course of procarbazine, a single oral dose of CCNU and a single intravenous infusion of vincristine given in six weekly cycles.

The introduction of Temozolomide has provided some improvement in survival. It is given orally over five consecutive days within a 28 day cycle. Leucopenia and thrombocytopenia are commonly associated side effects of this treatment. The combination of radical radiotherapy and daily, concomitant Temozolomide followed by six cycles of adjuvant Temozolomide has significantly altered the prognosis of GBM. Stupp et al. in a multicentre trial showed that at a median follow up of 28 months, the median survival was 14.6 months in radiotherapy plus TMZ group as compared to 12.1 months with radiotherapy alone. The two year survival rate was 26.5% vs 10.4% while a five year review of the same population has revealed 9.8% survival at five years in the TMZ group compared to 1.9% in the radiotherapy group.[29] This represents a significant advance over previous survival statistics in high grade glioma. The MGMT status was found to be the single most important predictive factor for a favourable outcome.

It is now well recognised that MR appearances immediately after chemoradiotherapy can show apparent progression of disease–22% of patients in the study reported by Stupp et al did not receive the adjuvant chemotherapy phase due to presumed tumour progression. Subsequent imaging shows that these changes either stabilise or improve. This pseudoprogression is more commonly seen in patients with methylated MGMT and is thought to represent a good prognostic sign of response to therapy (see Figure 6).

Treatment at Tumour Progression

Despite the best management, virtually all patients with HGG will develop recurrence of tumour at some point. Salvage therapies may be considered depending on the patient's clinical condition. These may include:

1. ***Surgery:*** Re-operation is associated with higher morbidity and mortality than for the original operation. However, it is an option in patients with a long progression free survival who have tumour that is maximally resectable. Insertion of carmustine wafers at this stage has been shown to improve survival.[51]
2. ***Radiotherapy:*** There has been some suggestion that the toxicity of re-irradiation has been overestimated. Re-irradiation is

an increasingly used option with precise fractionated radiotherapy being the optimal technique. There has also been some suggestion that for accurate, focal radiotherapy to a recurrent tumour, radiosurgery may be considered. On average, time to secondary progression is in the range of several months.

3. ***Cytotoxic Chemotherapy:*** Conventional chemotherapy regimens also improve time to secondary progression; however the efficacy is only modest and treatment related toxicities like myelo-suppression occur very frequently.[52] Recent Phase III Trials have failed to show that Temozolomide has a survival advantage over PCV regimes.

Prognosis

Despite advances in management, a diagnosis of HGG still carries a dismal prognosis. The median survival without any treatment is less than six months, but with treatment, this increases up to 18 months. Increasing age, poor initial neurology, poor general condition as evidenced by Karnofsky Performance score (KPS) and absence of MGMT methylation have all been associated with poor survival.[53] [Table 2: RPA of GBM survival based on KPS, the age of the patient, and treatment]

Patients who undergo surgery and chemoradiotherapy have shown better long term benefits. Why certain groups of patients survive longer than others is still unknown. Death is usually due to cerebral oedema and raised intracranial pressure.

The future

Targeted molecular therapies are an exciting prospect currently at various stages of research and development. These are drugs that target the oncogenic pathways in gliomas either by interacting with receptors or affecting a downstream target. Clinical trials of drugs blocking the epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), phosphatidylinositol 3-kinase (PI3K) and related pathways and the SRC related pathways have so far been disappointing. It is clear that monotherapy will have little effect and trials combining treatments are now underway as summarised by Wick et al.[54] The reason for this poor response is thought to be the fact that multiple receptor tyrosine kinases are activated in the development of a glioma, so blocking one receptor has little effect on the overall pathway.[55] Combinations of targeted therapies are likely to be the way forward.

One targeted therapy of particular interest blocks the vascular endothelial growth factor pathway involved in tumour angiogenesis. A large non-randomised phase 2 study of Bevacizumab at recurrence showed a high response rate (progression free survival at six months 46%; overall survival at six months 77%).[56] This trial paved the way for FDA approval. But the non-randomised nature of the study and non-standard endpoints has made the European Medicines Agency (EMEA) reject its use in Europe. One of the problems with studies using anti-angiogenic agents is the marked decrease in enhancement due to closure of the blood-brain barrier. This so called pseudoresponse does not predict the response to these agents, and subsequent progression can occur with no apparent contrast enhancement.[57] ◆

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The Eighth Congress on Mental Dysfunctions and other Non-Motor Features in Parkinson's Disease

Conference details: 3-6 May, 2012, Berlin, Germany.
Reviewed by: Professor Amos D Korczyn, Tel Aviv University.

Remarkable success in treating the key motor problems of Parkinson's disease (PD) has been achieved over the past fifty years, with drugs, mainly levodopa and later dopamine agonists, as well as with surgical approaches, particularly deep brain stimulation. However all these therapies, important as they are, provide only symptomatic relief and none affects the progression of the underlying pathology.

As therapy of motor features improved, more attention has been paid to other manifestations of the disease. Although James Parkinson claimed that "the senses are unaffected", in fact most PD patients manifest early cognitive changes and most progress to full blown dementia in later stages of the disease. Autonomic changes are also common and affect quality of life of the patients. These frequently start with constipation but other systems become affected as well. Orthostatic hypotension may

interfere with standing and walking. Sleep changes pose problems for the patient, bedfellow and physician. Many people develop REM-sleep behaviour disorders years before the appearance of motor manifestations, which are expressed as vivid dreams, frequently frightening. Unlike normal dreams, in which the person is unable to move, in PD the motor system is not inhibited and the patient may enact the dream, sometimes with violent movements which may hit the spouse. Some patients complain of insomnia. Affective changes, particularly depression, are also common in PD. These are not only a reaction to the motor problems. In fact these, like the autonomic manifestations, can appear years before the tremor, rigidity or bradykinesia first show. The sensory system is also affected in PD. Patients may develop pain, visual changes, and particularly anosmia fairly early on. In addition to these changes, which are part of the underlying disease process, there are many iatrogenic non-motor problems which PD patients develop. Most intriguing is the newly described impulse control disorder and the associated dopamine dysregulation syndrome.

Many of these topics are not covered sufficiently in international meetings, where industrial support leads the organisers to focus on issues which are of interest to the sponsors.

Therefore there was a growing need for specialised congresses. The first in this series took place in Jerusalem, Israel in 1994. In the past few years, as interest grew and attendance increased with it, the congresses became more regular, increasing to biannually and now annually.

The eighth congress in Berlin attracted about 800 participants, including neurologists, psychiatrists, geriatricians and basic scientists. The faculty included eminent scholars from around the world who participated in plenary talks, symposia and discussions. There were also hundreds of free communications and posters, where young clinicians and scientists were able to face the distinguished leaders in the field.

There was extensive discussion of new developments in the field, the understanding of non motor aspects not only of PD but also of other movement disorders such as Huntington's disease, Gilles de la Tourette syndrome and many others. Psychological and biological markers of cognitive decline in PD were presented, and the Pathogenesis of them deliberated at length. ◆

The full program of the Congress can be seen at www.kenes.com/MDPD, where details can also be found of the 9th MDPD Congress, which will be held in Seoul April 18-21, 2013.

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

2012

September

16th Congress of the European Federation of Neurological Societies
8-11 September, 2012; Stockholm, Sweden
T. +41 22 908 04 88, E. headoffice@efns.org
www.efns.org/efns2012

Cognitive Behavioural Approaches to Physical Rehabilitation: Intermediate level
18 Sept, 2012; Derby, UK
T. 01332 254679, E. ncore@derbyhospitals.nhs.uk
www.ncore.org.uk

Neurological Upper Limb for Occupational Therapists
19 Sept, & 10 Oct, 2012 Derby, UK
T. 01332 254679, E. ncore@derbyhospitals.nhs.uk
www.ncore.org.uk

Imperatives in Regional Anaesthesia: Current hot topics and future developments Workshop sessions and lectures
24th and 25th September, 2012;
The Royal College of Anaesthetists, London, UK
Anna Mawe, Event Coordinator,
T. 0114 2259057/36, E. anna.mawe@bbraun.com

Multiple Sclerosis: MS Trust Study Day on Postural Management
25th September 2012; Leeds U.K.
(Advanced Level)
E. education@mstrust.org.uk
www.mstrust.org.uk/professionals/

11th Annual Brain Injury Legal Seminar A Changing Legal Landscape - the View from Acquired Brain Injury
26 September, 2012; Birmingham, UK
www.biswg.co.uk for the full programme and booking form
Contact Chloe Hayward info@biswg.co.uk,
T. 07501 483989.

Squeezing the best out of stroke care
27 September, 2012; London, UK
Conference Department
T. 020 3075 1436/1300/1252,
E. conferences@rcplondon.ac.uk

October

The Intoxication of Power: From neurosciences to hubris in healthcare and public life
9 October, 2012; London, UK
Ruth Cloves, Senior Events Co-ordinator,
Psychiatry Section, Royal Society of Medicine. E. psychiatry@rsm.ac.uk;
T. 44 (0)20 7290 2985
www.rsm.ac.uk/psychiatry

Complex Epilepsy Conference In collaboration with Matthew's Friends
12 October, 2012; Solihull, UK
T. 01342 832243 ext 296,
E. epilepsytraining@youngepilepsy.org.uk

Sleep and Sleep Disorders from a Neurological Perspective
24th Oct, 2012;
Royal College of Physicians of Edinburgh
E. info@p-cns.org.uk
www.p-cns.org.uk

Practical Skills in Managing Fatigue
25th Oct, 2012; Bedford Lodge Hotel, Newmarket
E. info@communitytherapy.org.uk
www.communitytherapy.org.uk

November

Putting epilepsy first – supporting individuals with epilepsy in primary care
2 November, 2012: London UK
E. rona.eade@epilepsysociety.org.uk
www.epilepsysociety.org.uk/epilepsyfirst

Managing Cognitive Impairment
7th November, 2012; Bedford Lodge Hotel, Newmarket
E. info@communitytherapy.org.uk
www.communitytherapy.org.uk

Assessment and Treatment of the Thorax in Neurology
14th November, 2012; Derby, UK
T. 01332 254679
E. ncore@derbyhospitals.nhs.uk
www.ncore.org.uk

8th Essential Neuro MRI Study Day One day course in how to interperet MRI Brain & Spine
17 November, 2012; Liverpool, UK
Limited places. Kath Tyler, T. 07799 723 925,
E. essentialneuromri@hotmail.co.uk

Delivering Community Rehabilitation – Learning from Experience
28th November 2012;
Hippodrome, Birmingham
E. info@communitytherapy.org.uk
www.communitytherapy.org.uk

MS Trust Specialist Health Professionals Master Class: Sexuality in MS
29th November, 2102; London
E. education@mstrust.org.uk
www.mstrust.org.uk/professionals/

December

UK Stroke Forum
4-6 December, 2012; Harrogate, UK
T. 01527 903913
E. ukstrokeforum@stroke.org.uk

2nd Annual Regulatory Cells in Autoimmunity event: Analysing and moderating function
6 December, 2012; London, UK
T. 07507 799380
E. enquiries@euroscicon.com
www.regonline.co.uk/autoimmune2012

2013

February

Biomarkers for Brain Disorders: Challenges and Opportunities
3-5 February, 2013; Cambridge, UK
https://registration.hinxton.wellcome.ac.uk/display_info.asp?id=303
E. Lucy Criddle,
l.criddle@hinxton.wellcome.ac.uk

Basic Applied Neurophysiology
13th February, 2013; Derby, UK
T. 01332 254679
E. ncore@derbyhospitals.nhs.uk
www.ncore.org.uk

May

MS Frontiers: Bringing the research community together to beat MS
9-10 May, 2013; London, UK
T. 020 8438 0941
E. conferenceadmin@mssociety.org.uk
www.mssociety.org.uk/frontiers

June

New Avenues for Brain Repair: Programming and Reprogramming the Central Nervous System
June 10-11, 2013; Cambridge, US
E. events@abcam.com

ABN National Meeting

Conference details: 28-31 May, 2012, The Brighton Centre, Brighton, UK. ***Reviewed by:*** Seán J Slaght.

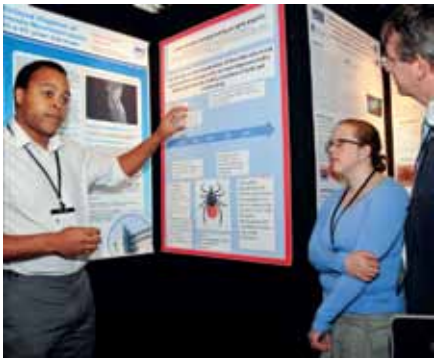
The ABN were welcomed to Brighton for four days of glorious sunshine and a stimulating mix of teaching, scientific breakthroughs and case study conundrums. This year the ABN conference was brought right up to date with a conference app for smart phones and a dedicated twitter feed.

The conference opened on Monday the 28th with the medical student road show in parallel with the Specialist Registrar teaching session. The Registrar session, attended by over 70 trainees, kicked off with small group teaching on prescribing in epilepsy. There were then seminars on 'Neurology on the ITU' from Lionel Ginsberg, 'How to interpret the EMG' from David Allen and 'Dementia' from Jonathan Schott. The day was rounded off with Jeremy Isaacs describing how to get (and keep!) a first consultant job and Trevor Pickersgill showing how to negotiate a job plan once you have got it.

The main conference opened the following day and started with a teaching session on epilepsy, with Mark Manford reminding us of the importance of taking a good history, Tejal Mitchell exploring the use (and misuse) of the EEG and John Duncan describing advances in imaging technology allowing refined diagnosis and more targeted epilepsy surgery. Parallel sessions on improving neurology services and neuromuscular platform presentations came next. Michael Pearson gave the perspective of a Respiratory Physician on improving outcomes for patients by using national audit data to drive service change.

The 18th Gordon Holmes Lecture was delivered by John Leigh from Cleveland, Ohio describing the neuronal control of eye movements and their use as research tools. The afternoon teaching session covered head injury, an area often neglected by neurologists. We learnt about the acute management of head injury and the on going efforts to improve this, using clinical trials, from Maxwell Damian, the surgical options from neurosurgeon Peter Hutchinson and the long term consequences of head injury from Richard Greenwood. This was followed by parallel platform sessions on neurodegeneration and multiple sclerosis. The Neurolympic Challenge drew the day to a close. Quiz Master Phillip Smith pitted the regions against each other with the team comprising Scotland and Northern Ireland reigning supreme. The trainees' dinner was held at Al Duomo restaurant.

Wednesday started early with a stimulating breakfast with neuro-ophthalmology experts followed by a teaching session on degeneration and regeneration of the nervous system. Parallel platform sessions followed on epilepsy and cerebrovascular disease. A highlight was the discovery by Lilleker and Mohanraj of anti-VGKC complex antibodies in a small proportion of patients with unexplained refractory epilepsy, who became seizure free following immunomodulatory treatment. Walking tours of the posters followed lunch. Then the ABN Medallist, Mark Wiles, told us about learning neurology and that pyramidal pattern weakness does not exist. The day was rounded off with a movement disorders video session with many excellent videos including a case from Chris Allen of paroxysmal exercise-induced dystonia secondary to demyelination. The ABN Gala dinner at the Corn Exchange, Brighton Dome was well attended and was a great opportunity to unwind and digest the conference's offerings so far.



The final day of the conference started with the ACNR sponsored case presentation competition where we were reminded that common diseases may present in atypical ways and sometimes, rare diseases can present like they are supposed to. Hugh Adler won the case presentation prize for his description of a patient with Ophelia syndrome associated with anti-mGluR5 antibodies. The plenary lecture from Iain McGilchrist looked at how the two hemispheres work in very different ways resulting in a kind of power struggle in our interaction with the world.

Brighton has a high incidence and prevalence of HIV and so it was fitting that the morning teaching session looked at this now manageable infection. Hadi Manji explained the effect of HIV on the brain, and, in particular, premature cognitive decline. Nick Davies categorised the immune reconstitution syndrome and Martin Fisher described his 30 years experience of dealing with the epidemic in Brighton. We were reminded of the importance of offering HIV testing to all patients with neurological symptoms, as this is now an infection that can be controlled. The final teaching session of the conference was an overview of antibody-mediated neurology, an area where our knowledge is rapidly expanding and our understanding of the clinical phenotypes of each antibody and how to treat them deepening.

The clinicopathological conference was a complex case with many a red herring, but expertly discussed by Peter Enevoldsen. The audience was able to participate via twitter or text, but none clinched the final diagnosis of primary angiitis of the central nervous system.

An excellent conference attended by over 550 neurologists, trainees and medical students from across the UK and beyond. The level of poster and platform presentations was high and there were excellent opportunities to meet and socialise with old colleagues, in the glorious south coast sunshine. The Charles Symonds prizes for best platform presentation was won by Michaela Simoni and for best poster by Tim Shakespeare. As mentioned before, Hugh Adler won the case presentation prize. I am certainly looking forward to Glasgow 2013! ◆

British Society of Rehabilitation Medicine Conference

Conference details: 14-15 June, 2012; Southampton, UK. ***Reviewed by:*** Dr John Burn, Rehabilitation Consultant, Poole General Hospital.

The Major Trauma Centre (MTC) initiative has thrust rehabilitation into the limelight and it was the focus of this year's meeting. The identification of patients who need specialist services will be a particular responsibility of Rehabilitation Medicine (RM) specialists. Presentations from both Manchester and London described a cultural change whereby RM specialists were forming an integral part of acute trauma teams and moving patients quickly on to appropriate rehabilitation facilities. To do this well services need to be available on the acute site and RM physicians need to acquire new skills, particularly in musculoskeletal conditions. There was extensive discussion on the requirements for 'Rehabilitation Prescription'. Well organised MTCs are securing this not only for patients with an Injury Severity Score (ISS) of > 15 but also for > 8 (three fractured ribs) thus securing more 'best practice tariffs'. These monies will have to be invested in enhanced services for this not just to be a paper exercise.

The conference brought unfamiliar specialisms to the BSRM. Mr Michael Fox from Stanmore described surgical approaches to brachial plexus injury and Dr Chris Lowe from Poole Hospital described continuing problems after Critical Care. Survival is reduced for 15 years after ARDS and this is determined principally by weakness. This affects almost 50% of

patients and, although not completely understood, is detectable as a reduced 6 minute walking distance for at least 5 years afterwards. There are recommendations for early mobilisation but little supporting evidence as yet.

Public awareness of rehabilitation has been enhanced by the work amongst veterans at Headley Court. Prof Greenberg, visiting professor of psychiatry, gave a robust defence of the psychological management of British service personnel. Despite, or maybe because of, fewer mental health personnel, the rate of PTSD is significantly less than in the US army and, although peaking at 6% at 4 years, appears to decrease subsequently. The incidence of PTSD is less for the majority of combatants who describe their leadership as good or very good or who have fewer stresses at home. Early (less than 4 year) army discharges or reservists are more at risk. There is no significant increase in suicide or imprisonment but rates of alcohol abuse are frighteningly high: up to 25%.

Spiritual care was introduced into a BSRM meeting by Dr Collicut, both a neuropsychologist and an Anglican priest. She distinguished religion from spirituality by describing three axes of Transcendence, Meaning and The Sacred. Traumatised patients face keen questions of meaning (why me?) but often because of cognitive and physical problems are less able spiritually to address them. Spiritual help cannot be left to faith practitioners but crosses professional boundaries. She suggested focusing on Shalom (wholeness/peace) through supporting dignity and identity, conveying hope, and expressing solidarity and loving kindness.

The conference finished with a symposium on the definitions and management of minor brain injury. We were encouraged to move beyond the dualisms of 'is it structural or emotional?', and address the combined problems of patients using a number of treatments that can be practised in the clinic.

In all, a broad and satisfying conference that demonstrated to visitors and members alike the increasing range of the specialty. The next conference, from 7th – 9th November 2012, will be hosted by colleagues in Belfast and will include presentations on teleneurology, assistive technology, transcranial magnetic stimulation and the transitional rehabilitation of children with cerebral palsy. ◆

PREVIEW The Fifth Practical Cognition Course

Course details: 1-2 November, 2012, Newcastle upon Tyne, UK.

This very successful course is for consultants and trainees in neurology, psychiatry, neuropsychology and rehabilitation medicine who want to develop their practical expertise in cognitive assessment and relate this to clinically relevant neuroscience. There will be a practical introductory session to cognitive assessment followed by four sessions of case presentations discussing the assessment, diagnosis and management of common cognitive syndromes. The course begins and ends with the patient. Case presentations will feature video material illustrating disorders that clinicians may encounter in daily practice. Each session will also include a talk from an invited expert, who will provide a framework for understanding the clinically relevant neuroscience. The case presentations and talks are highly interactive and lively discussion is encouraged.

This year's programme will cover memory, sleep and cognition, hallucinations and motor function and cognition. Our highly acclaimed speakers include Kirsty Anderson (Newcastle), David Burn (Newcastle), Tom Kelly (Newcastle), Andrew Larner (Liverpool), Sinéad Mullally (UCL) and Peter Woodruff (Sheffield). The course is organised by neurologists Tim Griffiths (Newcastle) and Chris Butler (Oxford), sponsored by the Guarantors of Brain and will be accredited for CME points.

The course will be held in the Beehive conference centre on the main campus of Newcastle University within the city. The registration fee includes a superb dinner on the first evening at the Quayside in Newcastle.

The Practical Cognition course has received highly enthusiastic feedback in previous years. Participants have enjoyed the practical approach to an area of clinical work that is extremely important but often neglected in postgraduate education. Here are links to reviews of last year's course by a trainee psychiatrist [http://careers.bmj.com/careers/advice/view-article.html?id=20006682] and consultant neurologist [http://www.acnr.co.uk/contents11-6.htm].

Bookings can be made online (www.practicalcognition.com) or by telephoning Laura Pereira on 0191 222 8320. Places are limited and should be reserved early. ◆

The 10th European Congress of Neuropathology

Conference details: 6-9 June, 2012, Edinburgh, Scotland. ***Reviewed by:*** Dr Valerie Critcher, Specialist Registrar in Neuropathology at the Royal Hallamshire Hospital, Sheffield, UK.

An invitation from the European Confederation of Neuropathological Societies (Euro-CNS) and the British Neuropathological Society drew almost 400 participants from across the globe to the Edinburgh International Conference Centre for this Neuropathology Congress. The meeting was preceded by the Euro-CNS training course on Leukoencephalopathies.

Plenary Lectures

The programme included plenary lectures by eight distinguished speakers working at the forefront of neuroscience research and its application to improvements in diagnosis and treatment. In his talk on the molecular pathology of CNS tumours, Professor David Louis focused on developments in this rapidly expanding field that have been translated into valuable diagnostic and prognostic tools. An example was the use of MGMT promoter methylation to help distinguish glioblastoma recurrence from pseudoprogression during temozolomide therapy. Professor John Hardy discussed how advances in sequencing and DNA chip technology are being used to identify different types of genetic risk for neurodegenerative diseases, thereby increasing understanding of the aetiologies. Professor Richard Gilbertson described his laboratory's cross-species genomics approach to the subgrouping of CNS tumours. This is helping to explain why tumours of similar histopathological appearance may show very different biological behaviours. For example, ependymomas arising in the forebrain, hindbrain and spinal cord have distinct molecular profiles, reflecting their different stem cell type origins. Professor William Brown illustrated his techniques of creating three dimensional views of vascular networks to investigate the vascular changes in deep white matter in ageing, neurodegeneration and dementia. The increasing complexity and diversity of prion diseases were discussed by Professor Pierluigi Gambetti. He talked about the identification and characterisation of novel forms such as variably protease-sensitive prionopathy which is suggested to represent a sporadic form of Gerstmann-Sträussler-Scheinker disease. Professor Ingmar Blümcke described how the survey of over 5,000 surgical epilepsy specimens collected at the European Epilepsy Brain Bank has enabled correlation between histopathology, preoperative imaging and clinical response to surgery, which in turn is leading to more specifically tailored resection strategies. Developments in understanding the pathogenesis of lysosomal diseases were explained by Professor Steven Walkley. He showed that the complex role of lysosomes within a major metabolic regulatory network indicates that brain dysfunction in lysosomal diseases is not simply the consequence of abnormal storage of non-degraded materials. In the final lecture to the Congress, Professor Robin Franklin described the work in his laboratory on the biology of remyelination. The findings show that declining efficiency of remyelination with age is largely due to failure of stem cell differentiation. Evidence that the innate immune response has a key role in remyelination led to an interesting discussion on the effects of anti-inflammatory therapy in multiple sclerosis.

Seminars and Workshops

A total of 10 symposia and 7 workshops provided platforms to discuss aspects of research and diagnostic practice related to a wide range of neurological/neurosurgical disorders. There were sessions dedicated to regenerative neuroscience and to brain inflammation. A personal highlight was the lecture by Professor Arie Perry in which he presented a very practical approach to the subtyping of glioblastomas, with emphasis on the clinical relevance of making the distinctions.

Posters

Over two hundred posters, grouped into ten themes, were displayed in the exhibition hall throughout the Congress, giving ample opportunity for viewing. The standard was high and twenty-six poster presenters were invited to give oral presentations within the above symposia and workshops. In addition, there were two plenary poster discussions. For these, eight discussants were asked to reflect on what they had found of interest among the posters. I enjoyed the different approaches taken by the eight individuals to present their choices and seeing which strategies had most success in promoting audience participation in the ensuing discussions.

A friendly encounter between congress participants in the exhibition hall.

Social Events

The large exhibition hall provided a place to encounter old friends and make new acquaintances. On day two the delegates were treated to an exclusive evening reception in Edinburgh Castle. This included a chance to view Scotland's Crown Jewels and experience the stirring sounds of a pipe band through the mist over Crown Square. The Gala Dinner was held in the newly refurbished National Museum of Scotland, surrounded by the eclectic Window on the World exhibition in the Grand Gallery. Entertainment was provided by the excellent Kilter Ceilidh Band and I observed that many eminent neuropathologists are also adept at Strip the Willow and other traditional dances performed that night.

Conclusions

The scientific programme was scheduled so that in general sessions with a bias towards clinical diagnostics ran alongside those with a more dedicated research content. This allowed delegates to select the topics most relevant to their areas of interest and there was truly 'something for everyone' throughout the Congress. Inevitably clashes occurred and so we hopped between the auditoria to catch the anticipated highlights from each symposium and workshop. Some of the sessions suffered from less than strict timekeeping, thus limiting the opportunities for discussion and one of the plenary poster sessions had to be cut short. In the welcome addresses there had been references to the inclement weather and to the recent outbreak of Legionnaires' disease in Edinburgh. Nonetheless I am sure that most delegates remained within the Conference Centre each day not because of these external factors but as a consequence of such an informative and enjoyable meeting. ◆

The Abstracts of the 10th European Congress of Neuropathology are published in: Clinical Neuropathology. 2012;31(4):232-5.

Details of future Euro-CNS events, including the neuropathology training courses, can be found at: www.euro-cns.org

Epilepsy Nurses Association (ESNA) conference 2012

Conference details: 13-14 May 2012, Nottingham. ***Reviewed by:*** Phil Tittensor, Lead Epilepsy Nurse, Department of Neurology, Stafford Hospital, UK.

2012 marked the 20th anniversary of the formation of ESNA. In that time the organisation has expanded from an initial handful of pioneering epilepsy nurses to the two hundred and forty or so that make up its current complement. ESNA is now recognised both nationally and internationally as the leading voice of epilepsy nursing in the UK. Its views influence health care policymakers and the organisation has been at the forefront of efforts to establish the necessity of an epilepsy specialist nurse as part of a comprehensive multidisciplinary service.

ESNA holds a biennial scientific conference which this year was hosted by the well appointed Nottingham Belfry hotel. Delegates were treated to an outstanding series of platform presentations from both medical and nursing leaders in the field. Generous sponsorship from a number of pharmaceutical companies, most notably Eisai and GlaxoSmithKline made the conference affordable for delegates without the need to compromise on venue or content.

The Sunday afternoon sessions began with Prof Matthew Walker and Dr Sunny Philip delivering a generalised epilepsies symposium. Prof Walker took delegates candidly through the proposed new International League Against Epilepsy (ILAE) epilepsy classifications while Dr Philip looked at syndromic classification and the thorny issue of when to withdraw medication. A further paediatric specific session was held on day two when Dr Robert Robinson gave delegates an overview of catastrophic encephalopathies.

There followed a neuro-oncology symposium presented by Dr Doug McCorry and Prof Garth Cruickshank. Prof Cruickshank presented work in progress to examine whether Valproate might be a useful tool in modifying tumour progression as well as treating resultant seizures.

Much of the first afternoon was given over to nurse led care innovation. Malissa Pierri presented her work which examined different healthcare models in the UK, America and Australia. Nurses in all three countries were at the forefront of patient care, streamlining the patient experience from first seizure through to diagnosis and treatment. Service delivery varied enormously between the models but the crucial role of the epilepsy specialist nurse was evident across all three. Each country's nurses were clearly working at an advanced level and Malissa's talk dovetailed nicely into a presentation on what is arguably the greatest step forward in epilepsy specialist nursing since its inception. Doctors in particular, with their rigid development programme find it very difficult to work out the level at which an individual nurse is working as the majority have very similar titles (usually a play on the phrase 'epilepsy specialist nurse'). Yvonne Leavy presented a framework of adult epilepsy nursing competencies which for the first time sets out what can be expected of a nurse working at novice, competent or expert level. Competencies for paediatric epilepsy nurses have been around for a few years but conference heard that they are in the process of being updated. Brand-new competencies for epilepsy nurses working in the field of learning disability are also being developed and are scheduled for launch later this year.

At this point, conference indulged itself in a little nostalgia. Carina Mac and Lorraine Reynolds were both epilepsy specialist nurses in the early 1990s (incidentally both are still practising although Carina has a managerial role these days) and are founder members of ESNA. They took delegates on a light-hearted look back at the organisation over the last 20 years with plenty of photographs illustrating the ageing process and questionable fashion sense!

The evening began with a drinks reception followed by an excellent gala dinner punctuated by awards ceremonies for the best poster in conference and the 'achievement in epilepsy' (ACE) awards. The biggest cheer of the night was reserved for Ena Bingham, epilepsy specialist nurse from Belfast who has recently received an MBE for services to epilepsy and who was made an honorary life member of ESNA.

Day two opened with a transient loss of consciousness symposium. The diagnosis of epilepsy can be extremely tricky and the differentials between it, non epileptic seizures, vasovagal syncope and cardiac causes of loss of consciousness were covered by Dr Richard Grunewald and Dr Sanjiv Petkar. The theme of nonepileptic seizures was to be taken up later in the day by Catherine Crow with a fascinating overview of conversational analysis which examines how patients with different diagnoses describe their seizure episodes.

Ena Bingham (left) showing her MBE to delegates and receiving her honorary membership from the ESNA Chair Mel Goodwin.

Their presentations were followed by an examination of the treatment of seizures in the accident and emergency department. Prof Tony Marson gave delegates an overview of the recent national audit of seizures management in hospital (NASH) while Vicky Myson presented an audit of an innovative nurse led first seizure service operating in Cardiff.

Nurses are always keen to learn about approaches that improve seizure control. In common with many conferences, a session was given over to 'rational poly-therapy'. This title can be a poisoned chalice for speakers but delegates pretty much universally praised Prof Mike Kerr for his rather unique stance with an emphasis on demonstrating to patients both the knowledge of the practitioner and the theory behind combining antiepileptic drugs with different modes of action. The message was not so much innovative treatment but rather innovative presentation.

The day concluded in somewhat unusual style for an epilepsy conference. Mr Doug Feeny is a barrister specialising in medicolegal cases. He used two hypothetical case scenarios involving people who have epilepsy but also lack capacity to illustrate current legislation and considerations that all practitioners need to be aware of when planning the treatment and management of people with epilepsy.

The ESNA conference 2012 represented a celebration of epilepsy nursing in the UK. Twenty years ago the handful of original epilepsy specialist nurses may never have really believed that there would now be an epilepsy nurses organisation with a membership of over 260 and a national voice in decisions relating to epilepsy care, or that both NICE and SIGN guidelines would identify epilepsy specialist nurses as integral to high quality care provision. That the organisation can now hold a conference of such quality is tribute in itself to the drive and determination of epilepsy nurses. It must also be recognised that this development process has received incredible support from our medical colleagues as evidenced by the faculty list from this excellent meeting. By working together, we can make the next twenty years even more successful to the benefit of all people with epilepsy. ◆

Neuroradiology and Functional Neuroanatomy: Correlating Anatomical, Brain Imaging and Clinical Studies

Conference details: 16-19 April, 2012, London, UK. ***Reviewed by:*** Dr Sathiji Nageshwaran (Foundation Trainee, North Central Thames Foundation School), Dr Imran Noorani (Foundation Trainee, Southampton University Hospital Trust).

For the 12th year running the Neuroradiology and Functional Neuroanatomy course was held at The Hospital for Neurology and Neurosurgery in Queen Square, arguably the home of British neurology. All attendees were hoping to gain a better grasp on the complex disciplines of neuroanatomy and neuroimaging. We were not disappointed.

Why attend and who is it for?

We decided to attend the course as we are applying for neurosurgery and neurology specialty training posts and this course is ideal for building on our knowledge and understanding the anatomy and imaging of the nervous system, essential for our practice. There were a number of other neurosurgery, neurology and neuroradiology trainees in the audience, ranging from very junior to more senior level. The majority of attendees, however, were neuroscience researchers including PhD students and post-doctoral researchers.

Course Preparation

A basic understanding of neuroanatomy was essential and can make the course far more accessible. There was frequent reference to Nieuwenhuy's The Human Central Nervous System with its excellent illustrations but a simple text such as Crossman & Neary Neuroanatomy: An Illustrated Colour Text covers many of the introductory topics.

Course Organisation and Structure

The course was organised by Professor Thomas Naidich (Neuroradiology Mount Sinai, New York), Professor Christopher Yeo (Behavioural Neuroscience, UCL) and Professor Tarek Yousry (Lysholm Department of Neuroradiology, Queen Square). The course was held over 4 days and consisted of a mixture of interactive lectures and practical sessions. Lectures covered a host of topics from basic neuroanatomy, the evolution and development of the nervous system, cellular and chemical structure of various brain regions and talks on MRI, fMRI and tractography.

Prof Thomas Naidich

Prof Christopher Yeo

Prof Tarek Yousry

Lecture Highlights

Following the welcome address, day one began with Professor Naidich discussing the surface anatomy of the brain on MRI. The interactive lecture had all those in the auditorium chanting key landmarks of gyri and sulci throughout, which made for enjoyable and surprisingly effective learning. When reviewing brain MRI in a clinical setting it is often difficult to orientate oneself to the depth of the slice and the specific area of the brain affected by a lesion (for example many can identify the pre- and post-central gyrus on lateral sagittal views but this is difficult on midline sagittal sections). Through highlighting several reference points, which exhibit minimal variation between patients/subjects, and their relation to key areas such as the motor strip, we were able to systematically work through and orientate ourselves to key brain regions in different MRI planes.

We then considered imaging of normal and abnormal brain development and the embryological development of the cerebral hemispheres (Professor Griffiths, Sheffield). This covered the fundamentals of brain development and discussed the pathophysiology and nomenclature of abnormal hemisphere development. Professor Valvanis (Zurich) talked about the evolution of the brain and lessons that came from neuroimaging.

The anatomy of movement, vision, sleep and balance were covered in different sessions by experts in each field across the 4 days. All assumed basic background knowledge and then built upon this, finally covering controversial and frontier aspects in each field.

Imaging – Hands-On PACS

One of the highlights of the course was the 'Hands on PACS' sessions, where we were able to discuss clinical cases, practice using the PACS systems with specialist advice and test our ability to report MRI studies. In these sessions, cases were compiled with presenting symptoms and questions posed, asking us to localise the lesion (and confirm this on MRI), describe the lesion and attempt to make a diagnosis. A mixture of pathologies were presented, ranging from tumours and stroke to neuromigrational abnormalities.

Dissection - Hands-On Anatomy

The two 'Hands-on Anatomy' sessions were held at nearby University College London. Professor Yeo and Professor Naidich led the anatomy demonstration. In these sessions specimens were studied working from the surface anatomy towards deep structures discussed in lectures earlier that day, such as the basal ganglia. This helped orientate and bring to life the morning's teaching sessions. Following this we were able to handle prepared brains in small groups to further familiarise ourselves with the anatomy. Several senior faculty members were available to provide individualised teaching and answer questions. These sessions were incredibly useful: allowing students to reinforce earlier lessons and visualise the 3 dimensional concepts. We were however not able to undertake our own dissection.

Conclusions

The course was very well organised, the lecturers and demonstrators were highly enthusiastic, and the content certainly helped us on our way towards a better understanding of neuroanatomy and neuroradiology. Moreover, the neuroscience lectures broadened our knowledge of current hot topics in research. With the themes varying each year, it would certainly be worthwhile to attend the course in order to keep one's knowledge up-to-date. ◆

7th World Congress for Neurorehabilitation 2012

Conference details: 16-19 May, 2012, Melbourne, Australia ***Reviewed by:*** Louise Blakeborough, on behalf of the World Federation for Neurorehabilitation.

The WCNR attracted neurorehabilitation clinicians and therapists from 55 countries. More than 1800 health professionals attended the meeting in Melbourne's award-winning Congress Centre, where there were 650 submitted abstracts, and over 300 posters.

The Congress was held in conjunction with the 35th Annual Brain Impairment Congress for the Australian Society for the Study of Brain Impairment (ASSBI) and the 20th Annual Scientific Meeting of the Australasian Faculty of Rehabilitation Medicine, The Royal College of Australasian Physicians (RACP). The Congress included 12 half-day workshops, 'Meet the Professor', breakfast sessions and a scientific programme covering international research, discovery and innovation in all the major areas of neurorehabilitation including traumatic brain injury, multiple sclerosis, stroke, spasticity management and neuro-oncology. In addition there were 17 World Federation for NeuroRehabilitation (WFNR) Special Interest Group Meetings taking place concurrently.

In the Opening ceremony, Professor John Olver, Convenor and Chairman of the Organising Committee and WFNR Regional Vice-President for Australia, New Zealand and Oceania welcomed delegates. The meeting officially opened with The 2nd Michael Barnes Lecture, established in recognition of the visionary leadership and dedication of the founding President and delivered by Professor Randolph Nudo, Director of the Landon Centre on Aging and Professor in the Department of Molecular and Integrative Physiology at the Kansas University Medical Centre, USA. Neuroplasticity occurs on a variety of levels, ranging from cellular changes due to learning, to large-scale changes involved in cortical remapping in response to injury. It provides the scientific basis for the treatment of acquired brain injury with goal-directed therapeutic programmes in the context of rehabilitation. The adult brain is not 'hard-wired' with fixed neuronal circuits. Cortical and subcortical rewiring of neuronal circuits occurs in response to training and injury; this active, experience-dependent re-organisation of the synaptic networks of the brain involves multiple inter-related structures including the cerebral cortex. Individual connections within the brain are constantly being removed or recreated, largely dependent upon how they are used. If there are two nearby neurons that often produce an impulse simultaneously, their cortical maps may become one. Professor Nudo encapsulated this concept by saying "Neurons that fire together, wire together". He outlined animal studies showing that if a tiny stroke is produced by blocking the blood flow to a small part of a monkey's motor cortex, the part of the body that used to move in response to electrical stimulation of that area of cortex moves when nearby areas of the brain are stimulated. Understanding this interaction between the damaged and undamaged areas provides a basis for better treatment plans in stroke patients. Functional imaging studies have shown that the brain can change its responses in human stroke patients in ways similar to that found in monkeys. This has also been shown by experiments using transcranial magnetic stimulation of the human cortex. "The challenge is to translate these results to the clinic" concluded Professor Nudo.

Tracey Mole and Professor Michael Barnes WFNR.

Current neuroprosthetic applications include Deep Brain Stimulation in Parkinson's Disease, the Cochlear Implant, Bionic Eye and epidural stimulation post-stroke. Professor Nudo is currently collaborating with engineers to develop micro-implantable devices for repairing neural circuits after stroke and traumatic brain injury.

Against the exciting developments in neuroplasticity and neuroprosthetic tools, there are frustrations due to the limits imposed by the biology of the brain, and the difficulty in doing human experiments that demonstrate the benefits of therapy. It has proved difficult for researchers carrying out rehabilitation trials to determine how much an improvement is due to a particular therapy, how much is placebo and how much is the 'normal' spontaneous partial recovery that follows stroke or brain injury. Professor Bruce Dobkin, Professor of Neurology and Director of the Neurologic Rehabilitation Program at the University of California, Los Angeles, USA highlighted the shortcomings of neurorehabilitation clinical trials. He illustrated his talk by looking at randomised control trials of body weight-supported treadmill training and robotic-assisted step training which did not produce better outcomes than a comparable dose of progressive over-ground training or exercise in disabled persons with stroke, spinal cord injury, multiple sclerosis, Parkinson's disease and cerebral palsy. Professor Dobkin suggested that the shortcomings require better strategies to assess the conceptual basis, design and outcome measurements for future trials of pharmacological, cortical stimulation, neural repair and other experimental neurorehabilitation interventions.

Professor Robert Teasell, Chair-Chief of the Department of Physical Medicine and Rehabilitation, University of Western Ontario, Canada pointed out that despite all the evidence available, clinical care for stroke patients is not generally delivered in accordance with established guidelines and this may negate the benefits of specialised, organised, interdisciplinary care. Stroke is increasing - it's a disease of older people – this was the recurring message throughout the Congress and Professor Teasell emphasised "the demographic crunch that is coming". The three key principles for stroke rehabilitation are a) organised stroke care, b) the earlier the better and c) intensity of therapy. Evidence is growing that rehabilitation has a significant impact on functional outcomes following stroke with improvements in discharge disposition and community reintegration. If the rehabilitation team adhere to guidelines the outcomes are better. "You can discover all you want but if you don't transfer it to the patient then it doesn't matter" said Professor Teasell, "the simple existence of research evidence doesn't automatically result in alterations in policy or clinical decisions".

Professor Michael Barnes presented the Early Career Development Awards in recognition of the most outstanding oral and poster presentations by a delegate. The Awards, totalling AU$6000, were donated by the Melbourne Convention and Visitors Bureau. The recipients of the Poster Awards were Louisa Ng (Australia) and Corina Schuster (Switzerland). The recipients of the Oral Presentation Awards were Camila Fiore (Australia) and Mayowa Owolabi (Nigeria).

The meeting closed with a presentation by Professor Anthony Burkitt on the development of the Retinal Implant for the Sight Impaired. The 'Bionic Eye' works by using electrical currents to stimulate nerves at the back of the eye. This Australian technology is targeted at two forms of vision loss; retinosa pigmentosa and age-related macular degeneration.

Commenting at the closing ceremony Professors Barnes and Clarke said: "The WFNR needs to position itself to address the challenges of acute to community rehabilitation so we can do the best possible rehabilitation for our patients. We should strengthen our teaching initiatives and awareness raising is key amongst politicians and the public". "In 15 years we have come a long way and we need to keep moving forwards. The WFNR's 32 National Societies cover half the world's population but there's 400 million people who are not getting any rehabilitation at all and we need to address this through education and training. There is reasonable evidence to suggest that low tech aids can provide some rehabilitation to the masses and we should work on the concept that something is better than nothing". ◆

Editor's Choice

A mutation for protection against Alzheimer's disease

The perceived importance of amyloid in the pathogenesis of Alzheimer's disease has fluctuated in the last 30 years. Deposition of amyloid is a pathological hallmark of the disease and suggests a central role for the protein in the disease. The association of Down's syndrome, trisomy 21, with Alzheimer's made the Amyloid Precursor Protein (APP) gene on chromosome 21 an obvious candidate gene for autosomal dominant Alzheimer's disease. Initial genetic linkage studies excluded APP as the site of the causative mutation. The subsequent realisation that Alzheimer's disease might be caused by more than one gene by John Hardy's group led to a re-examination of linkage results and the discovery that APP mutations can cause autosomal dominant Alzheimer's disease. Over 20 further pathological mutations in the APP gene have been described, however, APP mutations proved comparatively rare. Other genes, Presenilin 1 and APOE, stole much of the limelight. In Alzheimer's disease drug development, there was a clear rationale to developing treatments that influenced amyloid metabolism or deposition. These treatments have been developed and shown initial promise but, so far, have disappointed.

This paper is another step in the Alzheimer/amyloid story. Jonsson and colleagues utilised whole genome data from over 1500 Icelanders to look for sequence changes in the APP gene. They identified a coding mutation (A673T) which confers protection against Alzheimer's disease in their cohort and show that this mutation reduces the production of amyloidogenic peptides in vitro. Their controls were elderly (over 85 years of age) and had passed a cognitive assessment. Jonsson and colleagues found that the A673T mutation was also rarer in patients with less specific "cognitive decline". The results look robust and there seems little reason to suppose that they will not apply to a wider population than Iceland, but this remains to be shown. 0.6% of the control Icelandic population carry the mutation so the effect is significant although the protective allele may be rarer in other populations. This discovery will also encourage therapeutic approaches aimed at altering APP metabolism.

It is not surprising that these results apply also to patients with cognitive decline not diagnosed with AD. It highlights the spectrum that exists between the "normal" decline in memory with age, amnestic Mild Cognitive Impairment and Alzheimer's disease. The result supports the theory that very mild Alzheimer's pathology may be responsible for minor cognitive problems as people age. This observation highlights the question that already troubles Alzheimer specialists: of when a minor cognitive problem becomes a disease.

– Dr Jeremy Brown, Addenbrooke's Hospital and Queen Elizabeth Hospital, King's Lynn.

Jonsson et al. A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. Nature: 488, 96–99. Date published: (02 August 2012)

miRNA and ASO – The initial approach to treating genetic diseases in a new way

One of the holy grails of treating genetic disorders of the CNS is to target the abnormal gene itself and by so doing effect a cure without having to worry about off target effects. There have been two recent papers which are worth highlighting in this regard – one using a microRNA approach, the other an antisense oligonucleotide (ASO) strategy and both involving autosomal dominant trinucleotide repeat disorders.

In the first paper by Miyazaki et al in *Nature Medicine* (with a wonderfully clear News and Views commentary on it by Christopher Pearson), they concentrated on spinal bulbar muscular atrophy (SBMA) which is a slowly progressive lower motor neuron disorder of men. The disease is characterised by a CAG expansion in the androgen receptor, which then causes motor neuronal cell dysfunction and death through translocation of the mutant receptor within the cell. This has in the past led to attempts to block translocation using anti-androgen agents, although as a clinical therapy this creates obvious problems. In this new paper the authors looked at a transgenic model of this condition and found that one endogenous microRNAs in particular (the imaginatively named miRNA-196a) was upregulated and that by overexpressing it they could slow down the disease process. This they did using an AAV delivery system that selectively targeted the motoneurons. They then showed that miR-196a mediated its effects on the mutant receptor through a protein that is involved with mRNA processing (CELF2). This beautiful work shows how miRNAs are coming of age not only in terms of how they regulate networks of intracellular processes but how they can be recruited for treating disease.

In the second study the disease under attack is Huntington's disease, which has its CAG repeat in exon 1 of the huntingtin (htt) gene. This gene product causes extensive cell loss in the CNS but typically not until patients are in their 40s, although exactly when the disease process begins relative to clinical expression remains a subject of great interest (see TRACK-HD and PREDICT-HD studies). Obviously being able to switch off the mutant gene (mthtt) whilst leaving the normal htt to do its job has proven difficult, as has getting the silencing agent for the mutant htt in all cells for long period of times. This last point in particular has vexed the field but a recent paper by Kordasiewicz et al in *Neuron* (again accompanied by a lovely Preview by Lu and Yang) suggests that this might not be necessary as they showed that transiently knocking down mthtt could have long lasting benefits in animal models of disease. This implies that stopping the production of mthtt even if only for a short time may allow the cell to recover, regroup and fight another day, and thus whilst repeated injections of ASOs may be required, the frequency of administration may be less than once thought.

These papers highlight once more the skill of researchers to get to the heart of disease, and their ingenuity in how to do this. Obviously the challenge still remains as to how one can translate such findings into a much larger, longer living human patient – but slowly we are moving towards therapies that seek to truly switch off disease causing genes and their products.

– Roger Barker, Cambridge Centre for Brain Repair.

Pearson CE. Co-opting endogenous microRNAs for therapy. NATURE MEDICINE 2012;18:1011-2.

Miyazaki Y, Adachi H, Katsuno M et al. Viral delivery of miR-196a ameliorates the SBMA phenotype via the silencing of CELF2. NATURE MEDICINE 2012;18:1136-1141.

X-H Lu & X.W Yang. "Huntingtin Holiday": progress toward an antisense therapy for Huntington's disease. NEURON 2012;74:964-6.

Kordasiewicz HB, Stanek LM, Wancewicz EV et al. Sustained Therapeutic Reversal of Huntington's Disease by Transient Repression of Huntingtin Synthesis. NEURON 2012;74:1031-44.

Intramuscular midazolam for status epilepticus

Large studies of status epilepticus which change practice are hard to come by but this is one such. The study compared the outcome of treatment of status epilepticus with IM midazolam and IV lorazepam, which has been the gold standard since 1998. This massive effort included 3114 paramedics and 79 hospitals. Children estimated to be over 13Kg and adults were included and were treated if convulsive seizures had been continuing for over five minutes. Patients were excluded with major trauma, hypoglycaemia, cardiac arrest or HR<40. Essentially the question is does speed of access with an IM injection of midazolam 10mg in adults, using an autoinjector make up for speed of distribution of IV access of IV lorazepam 4mg (smaller doses were given to little people) given also that it is a different drug being administered. The short

answer to the question is yes, which means that we should be looking to change practice for emergency management to IM midazolam.

The primary outcome of the study was termination of seizures before arrival in the emergency department without the need for the paramedics to provide rescue therapy. The key secondary outcome was time from opening the box containing treatment to the termination of seizures. 448 patients were assigned to IM midazolam of whom 443 received the drug. 445 were assigned to IV lorazepam of whom 297 received the drug. Of the remainder, seizures stopped anyway in 95, before the drug was given and in 42 IV access could not be achieved. In the intention to treat analysis, treatment failure occurred in 26.6% of midazolam patients and 36.6% of lorazepam patients. Per protocol figures were 25.1% and 35.7% respectively. Midazolam also fared better on all secondary measures, except slightly longer hospital stays. Seizure recurrence within 12 hours was similar and only around 10% in both groups and hypotension was also similar. Although the time from giving the injection to cessation of seizures was slightly longer with midazolam, this was more than relative speed of IM access compared with IV access for lorazepam. The authors cautiously state that IM midazolam is non-inferior to IV lorazepam. With these data one might go further.

– Mark Manford, Addenbrooke's and Bedford Hospitals.

Silbergleit R, Durkalski V, Lowenstien D et al.
Intramuscular versus intravenous therapy for prehospital status epilepticus.
NEJM 2012;366:591-600.

A View to a Kill: Oligodendrocytes in ALS

It is the glia that are to blame, again. Recent revelations that astrocytes can trigger neuronal degeneration in amyotrophic lateral sclerosis (ALS) came as a surprise. Now, it seems that astrocytes are not alone in serving as a primary cause in neurodegeneration. Oligodendrocytes, normally providing insulation and nutritional support for axons, have currently come into the spotlight. Their primary involvement in multiple sclerosis has been long evident, leading to axonopathy and cortical neuronal loss following the disruption of the myelin sheath. However, their relatively normal initial appearance in neurodenerative disease has perhaps masked their significance in pathogenesis. A new paper published by Jeffery Rothstein's group reports a mechanism by which oligodendrocytes may contribute to early neurodegeneration in ALS patients, but somewhat unexpectedly, without the loss of myelin.

Youngjin Lee and colleagues have demonstrated that monocarboxylate transporter 1 (MCT1) is specifically enriched in oligodendrocytes in the mouse brain and spinal cord, providing potential energy support to neurons in the form of lactate. In vitro, the inhibition of MCT1 in oligodendocytes, either by antisense or by pharmacological methods, leads to selective motoneuron death in organotypic spinal cord slice cultures. This highlights the possibility that the inhibition of lactate transport by oligodendrocytes to neurones could be solely responsible for a neurotoxic effect. Indeed, the replacement of lactate in the culture medium reversed neurotoxicity. Similar results were noted also in vivo when MCT1 expression was downregulated by a specific small hairpin RNA (shRNA) packaged by a lentivirus.

Could the failure of providing lactate by oligodendrocytes play a primary role in toxicity in neurodegenerative diseases? The elegant series of experiments, in which MCT1 downregulation was induced selectively in oligodendrocytes, have provided proof of their direct involvement. The similar features of axon pathology seen in the mouse ALS model (SOD1 transgenic mice) and in mice affected by a single MCT1 allele deletion lent further support to such a notion. Thus it did not come as a surprise to learn that the motor cortex of human ALS patients show more than a 50% decline in MCT1 expression, similar to that seen in the spinal cords of the SOD1 transgenic mice.

This corroborating evidence may add another layer to the complexity of ALS pathogenesis, shifting the view to another potential killer cell in neurodegenerative disease. Perhaps there is more than meets the eye, and one may speculate that protective approaches designed to directly target neurones may not be sufficient.

– Andras Lakatos, Cambridge Centre for Brain Repair and Addenbrooke's Hospital, Cambridge.

Youngjin Lee et al.
Oligodendroglia metabolically support axons and contribute to neurodegeneration.
NATURE, Published online on 11 July 2012.

Infection and autoimmunity – an overlap in the brain?

NMDA-receptor antibody related encephalitis is now a well-recognised, clinically distinctive condition often seen in younger individuals with a good response to immunotherapies. Patients frequently develop fever and headache prior to, or during, their illness. Importantly, the antibodies are of the IgG class.

Pruss et al retrospectively show antibodies of IgG, IgA and IgM classes which are directed against the NMDA receptor in 13 of 44 (30%) patients with proven HSV encephalitis (HSVE). The diagnosis of HSVE appears robust in that patients had the typical symptomatology, CSF HSV PCR positivity plus a pronounced lymphocytosis, and classical temporal lobe changes on imaging.

Although the timing of available serum and CSF samples was understandably rather patchy and variable, it was apparent that some patients had NMDAR-Igs as early as four days after their diagnosis of HSV. By contrast, in other patients, NMDAR-Igs only appeared many weeks or months after the HSV symptom onset. This may suggest that in some cases, and slightly surprisingly, the antibodies are present in HSVE very early in the illness. In others, the antibodies may be part of a secondary immune response to the HSV-induced cell lysis.

However, the serum-CSF compartmentalisation of the antibodies, time-course of their appearance and the NMDA classes were often difficult to predict or pathophysiologically model. For example, one patient only had serum NMDAR-IgM ten days into their illness, these persisted and were accompanied by serum NMDAR-IgA after around one year but serum NMDAR-IgG or CSF NMDAR-IgG/A/M were never detected. Another case had serum and CSF NMDAR-IgA two weeks into their illness, the serum NMDAR-IgA persisted for an additional fortnight, and at around one year CSF showed no NMDAR-IgG/A/M and only serum NMDAR-IgM was present.

These data provide one potential rationale for the use of steroids in HSVE. They also suggest that infectious and autoimmune encephalitis may coexist. Although headache, fever and cognitive deficits do overlap, there are marked differences between many clinical and paraclinical features of HSVE and 'typical' NMDAR-IgG antibody encephalitis. While the presence of these antibodies in the setting of HSVE is intriguing, their role remains unclear. Nevertheless, these antibodies should certainly be measured in a prospectively collected series of HSVE. Reproducible findings may mean that in the future steroids are routinely added to acyclovir in the setting of HSVE.

– Sarosh Irani, Neurosciences Building, University of California, San Francisco.

Prüss H, Finke C, Höltje M, et al.
NMDA receptor antibodies in herpes simplex encephalitis.
ANNALS OF NEUROLOGY. Accepted manuscript online: 16 JUL 2012, DOI: 10.1002/ana.23689.

Fujifilm supports the world's busiest Wildlife Hospital

Fujifilm is a pioneer in diagnostic imaging and information systems for healthcare facilities, with a range of constantly evolving clinically proven products and technologies designed to assist medical and veterinary professionals perform more efficiently and effectively. The company have recently provided substantial support to Tiggywinkles - the world's busiest wildlife hospital who treat over 10,000 animal casualties, free of charge, every year. The hospital receives no government funding relying entirely on charitable donation to continue its work.

Tim Moran, Operations Manager for Tiggywinkles Wildlife Hospital said, "Thanks to substantial support from Fujifilm we were able to invest in the Company's state-of–the-art CR X-ray processing system which will allow us to diagnose casualties more efficiently. The equipment arrived just in time to help during the busy spring and summer months when thousands of sick and injured animals are brought to our busy Aylesbury facilities."

Mark van Rossum for Fujifilm, presented Tiggywinkles with their Fujifilm PRIMA CR system saying, "Fujifilm are pleased to be able to support the world renowned work that the animal hospital does by making this latest imaging technology available to them. As a result their patients will be diagnosed and treated much faster, increasing the hospital's capacity."

Stuart introduces new high capacity shaking incubator for cell culture applications

Stuart, the benchtop science equipment specialist, has unveiled a new addition to the company's SI Series of incubators. The new SI600 with built-in orbital shaker has a capacity of 115 litres – more than double that of the existing SI500 – and can accommodate up to six 2 litre Erlenmeyer flasks. Both of these benchtop systems are equipped with Biocote antimicrobial protection and are ideal for use in cell culture, especially suspension culture applications, with the larger SI600 supporting growing demands for larger scale production.

The SI600 incubator is designed for reliable, convenient operation. Like the SI500 it includes a unique retractable platform for effortless loading and unloading. Under normal use the platform is locked in place but can be drawn forward from the chamber to give easy to access to samples at the back.

Microprocessor control delivers long-term temperature stability, with forced air circulation ensuring uniformity throughout the incubator. Separate control of temperature and shaker speed guards against accidental temperature adjustment, while USB enabled communication allows long term tracking of the incubator temperature.

For more information see www.stuart-equipment.com

Shimadzu UK launches liquid chromatography mass spectrometer (LCMS)

Shimadzu UK has launched a high-end liquid chromatography mass spectrometer – the LCMS-8080 – which delivers best-in-class sensitivity, high quality data and fast cycle times. An extension of its Ultra Fast Mass Spectrometry (UFMS) range, the new model's high speed capabilities increase productivity in the laboratory by delivering accurate measurements, first time.

Ideal for users requiring information rich analyses, the LCMS-8080 can be used across a wide range of applications including food safety testing, drugs of abuse screening as well as in clinical, environmental and ADME laboratories. The instrument delivers high quality and accurate data over long periods of use.

The Coaxial Hot Gas Desolvation source is fundamental in delivering the LCMS-8080's enhanced sensitivity as it focuses the ion plume and improves ionisation efficiency. This is enhanced by Hot Source Induced Desolvation which removes solvent noise, followed by high performance pumping and a multi-orthogonal inlet. The LCMS-8080's class-leading sensitivity allows accurate quantitation of low level analytes.

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New brochure for Fujifilm's Console Advance

Fujifilm has published an eight-page, full colour brochure on their next generation Console Advance.

The brochure details the benefits of Fujifilm's Console Advance and includes information on all the new enhanced features, which make it an ideal option to integrate FDR and FCR Systems.

It is packed with features to streamline workflow and assist users to save time, including a new gradation design monitor and intuitive arrangement of operation buttons, helping users check and confirm information quickly and accurately, and advanced functions such as ROI image adjustment and auto-trimming.

The brochure also details additional optional functions including image stitching and precise enlargement, helping users get the best image possible first time.

The Console Advance automatically recognises the region of interest and applies the optimum image processing parameters to deliver reproducible, high quality images every time.

With connectivity to a range of other equipment via the hospital network, and being fully compatible with DICOM part 14, Fujifilm's Console Advance is the heart of an FDR/FCR System.

For a copy of the brochure, telephone Fujifilm on +44 (0)1234 326780.

Brain Tumour Tissue Banking – a new approach

Brain tumour tissue is difficult for researchers to access. Bureaucracy has led to banks being established which are closed to researchers; a review of just three centres that returned data on current archive holdings (dating back to 1970) revealed that the potential of a networked approach is clear to see – in excess of 50,000 surgical cases. Just sitting there.

Brainstrust is working alongside key clinicians to change this. The Charity is looking to build a UK wide network of brain tumour tissue banks, that will support a diverse range of brain tumour research projects.

The immediate objective is to link existing archives of brain tumour tissue in one virtual network. Phase 2 will support existing brain tumour tissue banks so that the surgical collection of brain tumour tissue has full consent and clinical data attached. Hospitals achieving this will then be able to link into the national network.

This project will provide the interface that is needed between researchers and brain tumour tissue, giving easy access to the right tissue, in sufficiently large numbers and of high quality.

To find out more, visit www.brainstrust.org.uk, or call 01983 292405.

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COPAXONE® (glatiramer acetate)
PRE-FILLED SYRINGE PRESCRIBING INFORMATION

Presentation – Glatiramer acetate 20mg solution for injection in 1ml Pre-filled Syringe. **Indication** – Treatment of patients who have experienced a well-defined first clinical episode and are determined to be at high risk of developing clinically definite multiple sclerosis (MS). Reduction of frequency of relapses in relapsing-remitting MS in ambulatory patients. In clinical trials this was characterised by at least two attacks of neurological dysfunction over the preceding two-year period. **Dosage and administration** – 20mg of glatiramer acetate (one pre-filled syringe) administered sub-cutaneously once daily. Children (12 - 18 years) No specific studies. Limited published data suggest the safety profile of 20mg administered sub-cutaneously once daily is similar to that seen in adults. Children (<12 years) Not recommended. Elderly No specific data. Impaired renal function No specific studies. Monitor renal function during treatment and consider possibility of deposition of immune complexes. **Contra-indications** – Known allergy to glatiramer acetate or mannitol (excipient). Pregnancy. **Special warnings and precautions** – Sub-cutaneous use only. Initiation to be supervised by neurologist or experienced physician. Supervise first self-injection and for 30 minutes after. One or more of vasodilatation, chest pain, dyspnoea, palpitations or tachycardia may occur within minutes after injection. These generally resolve spontaneously after a short time. If severe, treat symptomatically. Caution in patients with pre-existing cardiac disorders and review such patients regularly. Rarely convulsions and/or anaphylactic or allergic reactions. Rarely, hypersensitivity (bronchospasm, anaphylaxis or urticaria). If severe, treat appropriately and discontinue Copaxone. **Interactions** – No formal evaluation. Increased incidence of injection-site reactions with concurrent corticosteroids. Theoretical potential to affect distribution of protein-bound drugs, therefore concomitant use of these should be monitored. **Pregnancy and lactation** – Not to be used in pregnancy. Consider contraceptive cover. No data on excretion in human milk. **Undesirable effects** – Local injection site reactions (erythema, pain, mass, pruritus, oedema, inflammation, hypersensitivity, injection site atrophy). An immediate post-injection reaction (one or more of 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** – February 2012.

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

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

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