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WIN
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Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Teva Pharmaceuticals Ltd on telephone number: 01296 719768.
**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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David J Burn is the editor of our Conference News Section and is Professor in Movement Disorder Neurology & Honorary Consultant, Newcastle General Hospital. He runs Movement Disorders clinics in Newcastle-upon-Tyne. Research interests include progressive supranuclear palsy and dementia with Lewy bodies. He is also involved in several drug studies for Parkinson’s Disease.

Andrew Lunn is the editor of our Case Report Section. He is a Consultant Neurologist at the Walton Centre for Neurology and Neurosurgery in Liverpool, with a particular interest in dementia and cognitive disorders. He is also an Honorary APO Non-Clinical Lecturer in the History of Medicine at the University of Liverpool.

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Nicki Cohen is ACNR’s Neuropathology Editor. She is a Specialist Registrar in Neuropathology at Southampton and has a DPhil in Neuroscience. Her research interests lie in CNS stem cell biology, and the brain’s response to injury.

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

Heather Angus-Leppan is ACNR’s ABN representative on the Editorial Board. She is Head of the Neurology Department at Barnet Health and Consultant Neurologist. She is the Honorary Consultant Neurologist to the Royal Free Hospital. Her research interest lies in the field of neurology and research in the Institute of Neurology at University College London. She is a member of the SAC in neurosurgery.

International editorial liaison committee

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

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

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

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

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**Professor John Hardy joins the ranks of science greats**

Professor John Hardy (Reta Lila Weston Institute of Neurological Studies & the Department of Molecular Neuroscience, London) has been recognised for his exceptional contribution to science with his election to the Fellowship of the Royal Society. Fellows of the UK’s national academy of science are leaders in the fields of science, engineering and medicine.

**Professor Miller awarded John Dystel Prize**

Professor David Miller, ION, London has been awarded the John Dystel Prize for Multiple Sclerosis Research. Sponsored by the American Academy of Neurology and National Multiple Sclerosis Society, the John Dystel Prize recognizes outstanding contributions to research in the understanding, treatment, or prevention of multiple sclerosis. The prize is intended to recognize significant and exciting contributions by investigators, not to be a lifetime achievement award.

**Excellence in Clinical Research**

Dr Helen Ling (Reta Lila Weston Institute of Neurological Studies, London) has won the International Movement Disorder Society’s 2009 Junior Award for excellence in clinical research. This is in recognition of her innovative research regarding diagnostic accuracy in 18 cases of pathologically confirmed corticobasal degeneration, a progressive neurological disorder characterised by nerve cell loss and atrophy of multiple areas of the brain.

**PDS awards Training Fellowship**

The Parkinson’s Disease Society (PDS) has awarded a Training Fellowship for just over £70,000 to Dr Ashwani Jha at the Institute of Neurology, London, to investigate what part of the brain is associated with specific symptoms of Parkinson’s. As part of Professor Peter Brown’s team, Dr Jha will carry out research with a group of 25 people with advanced Parkinson’s. They will measure the electrical activity on the surface of the brain with a specialized scanner and deep inside the brain by using surgically placed electrodes implanted for Deep Brain Stimulation (DBS). They will then investigate how the electrical signals vary within the group and how this may relate to their individual symptoms. Creating disruptions in specific brain regions should replicate or possibly improve some of the symptoms and will help understand what parts of the brain are responsible for them.

**Basic Science In Epilepsy Award (£1,000)**

To be awarded at the Annual Scientific Meeting of the ILAE UK Chapter in Sheffield from 7th to 9th October 2009. The award is open to any basic scientist or health professional employed at lecturer level or below (or NHS equivalent) and working in the field of epilepsy research within the UK. Entrants must be 40 years of age or under on 31st December 2009. Informal enquiries to Juliet Solomon, ILAE UK Chapter Secretariat, Email: j.solomon@ion.ucl.ac.uk. Entries close: Friday 31st July 2009 at 5.00pm.

**The Forbes Norris Award 2009 (£1,000)**

This Award was inaugurated by the International Alliance of ALS/MND Associations in memory of Dr Forbes (Ted) Norris, a neurologist dedicated to helping people with ALS/MND. For more information Email: alliance@alsmndalliance.org

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Do you know of any awards or appointments which should be featured on this page? Please email details to Rachael@acnr.co.uk by 10th August for the Sept/Oct issue of ACNR.
also be seen in which of the following disorders: motor neuron disease and multiple sclerosis, may being seen with stroke and in incontinence'), in addition to (pseudobulbar affect, ‘emotional pathologic laughing and crying answer the following:

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Pregnancy: Zonegran must not be used during pregnancy unless clearly necessary in the opinion of the physician, and only if potential benefits justify risk to the foetus. Specialist advice should be given to women who are likely to become pregnant in order to consider the optimal treatment during pregnancy. Women of childbearing potential must use contraception during treatment and for one month after discontinuation. Lactation: Zonisamide is excreted into breast milk. A decision must be made to either discontinue Zonegran or stop breast-feeding. Breast-feeding should not be resumed until one month after stopping Zonegran. Warnings and Precautions: Serious rashes occur in association with Zonegran therapy, including cases of Stevens-Johnson syndrome. Zonegran contains a sulphonamide group. Serious immune based adverse reactions are associated with the sulphonamide group, e.g. rash, allergic reaction, major haematological disturbances including aplastic anaemia, which very rarely can be fatal. Closely supervise and consider discontinuation in patients with unexplained rash. Cases of agranulocytosis, thrombocytopenia, leukopenia, aplastic anaemia, pancytopenia and leucocytosis have been reported. Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. The mechanism is not known and the available data do not exclude the possibility of an increased risk for Zonegran. Patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients and caregivers should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge. Kidney stones have occurred. 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Drug Interactions: No clinically relevant pharmacokinetic effects on carbamazepine, lamotrigine, phenytoin, sodium valproate, oral contraceptives (ethinylestradiol or norethisterone). Insufficient data with carbonic anhydrase inhibitors, e.g. topiramate. Zonegran was not affected by lamotrigine or CYP3A4 inhibitors. Caution with drugs which are P-gp substrates. Avoid concomitant administration with drugs causing urolithiasis. Zonisamide is metabolised partly by CYP3A4, N-acetyl-transferases and conjugation with glucuronic acid; therefore caution with substances that can induce or inhibit these enzymes. Side effects: The most common adverse reactions in controlled, adjunctive-therapy studies were somnolence, dizziness and anorexia. Adverse reactions associated with Zonegran in clinical studies and post marketing surveillance: Very common effects (≥1/10): anorexia, agitation, irritability, confusional state, depression, ataxia, dizziness, memory impairment, somnolence, diaphoresis, decreased bicarbonate. Common effects (1/10 < ≥1/100): ecchymosis, hypersensitivity, affect lability, anxiety, insomnia, psychotic disorder, bradyphrenia, disturbance in attention, night terrors, parasthesia, speech disorder, tremor, abdominal pain, constipation, diarrhoea, dyspepsia, nausea, rash, nephrolithiasis, fatigue, influenza-like illness, pyrosis, weight decreased. Uncommon (≥1/1000, <1/100): pneumonia, urinary tract infection, hypokalaemia, anger, aggression, suicidal ideation, suicidal attempt, convulsion, vomiting, cholecystitis, cholelithiasis, calculus urinary. Very Rare (<1/10,000 including isolated reports): agranulocytosis, aplastic anaemia, leucocytosis, leucopenia, lymphadenopathy, pancytopenia, thrombocytopenia, metabolic acidosis, hallucination, amnesia, coma, grand mal seizure, myasthenic syndrome, neuroleptic malignant syndrome, status epilepticus, dyspnoea, pneumonia aspiration, respiratory disorder, pancreatitis, hepatocellular damage, anhidrosis, erythema multiforme, purpura, Stevens-Johnson syndrome, toxic epidermal necrolysis, rhabdomyolysis, hypophosphonemia, renal failure, urinaria abnormality, blood creatine phosphokinase increased, blood creatinine increased, blood urea increased, liver function tests abnormal, heat stroke. Isolated cases of Sudden Unexplained Death in Epilepsy Patients (SUDEP). Post-marketing data suggests patients aged 65 years or older report a higher frequency of Stevens-Johnson syndrome and Drug Induced Hypersensitivity syndrome. Legal Category: POM. Presentation: PVC/PCTFE/aluminium blisters. Basic UK NHS cost: Zonegran 25 mg: packs of 14 £8.82, Zonegran 50 mg: packs of 56 £47.04, Zonegran 100 mg: packs of 56 £62.72, Irish price to wholesalers: Zonegran 25 mg: packs of 14 £10.95, Zonegran 50 mg: packs of 56 £58.07, Zonegran 100 mg: packs of 56 £67.59. Marketing authorisation numbers: Zonegran 25 mg: EU/10/04/307/001, Zonegran 50 mg: EU/10/04/307/003, Zonegran 100 mg: EU/10/04/307/005. Marketing authorisation holder: Eisai Ltd, European Knowledge Centre, Mosquito Way, Hatfield, Hertfordshire, AL10 9SN. Date of preparation: February 2009. Adverse events should be reported. Reporting forms and Information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Eisai Ltd on 020 8600 1400/0845 676 1400 or Lmedinfo@eisai.net.

Date of Preparation: May 2009 ZON-UK22676
About 50 years ago, our understanding of how the cerebral cortex is organised was revolutionised by the development of single cell recordings in the sensory cortices of animals. This pioneering work by Vernon Mountcastle, Tom Powell, David Hubel and Torsten Wiesel led to the concept of cortical columns. In this issue of ACNR, R Quian Quiroga discusses how this technology has now been used to study the human brain in patients undergoing epilepsy surgery, with results that reveal how and where we store memories and semantic knowledge.

Of late, mutations in the mitochondrial DNA-polymerase gamma gene (POLG) have been recognised as causing neurological disease. In this issue, one such presentation is discussed in this context—namely MSCAE [mitochondrial spinocerebellar ataxia and epilepsy]. In their article, Charalampos Tzoulis and Laurence Bindoff present the background to the genetic basis of this condition, before discussing the clinical phenotype, investigation of it and its management. In particular they highlight the helpfulness of MRI and the need to think about the diagnosis in the first place, so that the gene can be sequenced.

The neurosurgery article takes as its topic the vexed issue of AVMs and how they can best be treated. The authors clearly lay out the therapeutic options and conclude that “The management of a patient with an AVM is an individualised pathway that requires the multidisciplinary input of a neurovascular surgeon, an oncologist and a stereotactic radiosurgeon.” However, they also acknowledge there is much that is not known about the natural history of different types of AVMs, which makes the decisions on treatment options not as straightforward as one would wish.

For those who understood the basic MRI article by Justin Cross, now comes the advanced one dealing with ADC maps, FA, DTI, DWI, MRS and fMRI. This article combines just the right mix of physics and clinical application, such that all these acronyms will have meaning.

“Telemedicine is the assessment, diagnosis, direct treatment, education, monitoring and support of patients at remote sites via telecommunications, ranging from the plain old telephone service (POTS) to real-time videoconferencing through the Internet.” Dr Elsie Hui discusses how this technology has evolved and can be used to deliver telerehabilitation. This approach, if successful, would have a major impact on freeing up hospital services for inpatient care whilst ensuring that patients after discharge continue to receive appropriate rehabilitation. In addition it will allow health care systems to reach out into traditionally deprived areas. This is a most exciting area of development in health care delivery and raises many possibilities.

Helen Beaumont gives a very graphic description of how corticobasal degeneration affected her husband Clive, with major changes in his personality early on in the presence of a well-preserved motor system. This moving account is motivation for anyone working in this area, to find a cure and better treatments for this type of progressive neurodegenerative disorder.

We also have our usual collection of reviews and conference reports. If you would like to contribute please do get in touch. ♦
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Single-Neuron Recordings in Epileptic Patients

**Rodrigo Quian Quiroga**

is a Professor of Bioengineering and the head of the Bioengineering Research Group at the University of Leicester. He graduated in Physics at the University of Buenos Aires, Argentina and obtained his PhD in Applied Mathematics at the University of Luebeck, Germany. Before joining the University of Leicester as a lecturer in 2004, he was a post-doctoral fellow at the Research Center Juelich, Germany, and a Sloan fellow at the California Institute of Technology, USA. His main research interest is on the study of the principles of neural coding, especially for visual perception and memory, by analyzing single-cell recordings in epileptic patients.

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**Abstract neurons in the human medial temporal lobe**

With the same experimental setup described above, several improvements allowed the identification of much larger number of neurons, especially those that fire very sparsely and are usually hard to detect. These developments led to the finding of neurons with invariant visual responses in the human MTL. For example, a neuron in the hippocampus fired consistently to presentations of 7 different pictures of the actress Jennifer Aniston and not to about 80 pictures of other persons or objects. Another hippocampal neuron fired selectively to different pictures of the actress Halle Berry and even to the presentation of her name written in a computer screen. These findings show a very sparse, explicit and abstract representation by MTL neurons.

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**Intracranial recordings in epileptic patients**

Epilepsy is one of the most common neurological disorders affecting almost 1% of the population. Patients suffering from epilepsy that do not improve with medication may be considered for resective surgery and, based on clinical criteria combined with neuroimaging and video-telemetry, may be implanted with intracranial electrodes to accurately localise the seizure originating area – the ‘ictal onset zone’ – and evaluate the prognosis of the potential surgical intervention. Although the mechanisms of epileptic seizures are still far from being completely understood, intracranial electroencephalographic (EEG) recordings have given invaluable information, among others, to identify electrophysiological patterns at seizure onset, to determine the seizure focus and the routes of seizure spread, etc. Besides their clinical importance, intracranial recordings also allow the study of neural activity in the living human brain, thus providing unique insights about different brain functions.

For clinical reasons, intracranial recordings are often done in the medial temporal structures. The medial temporal lobe (MTL) comprises the hippocampus, amygdala, entorhinal cortex and parahippocampal cortex. These areas are known to be involved in higher level cognitive processes, such as memory formation, and it is therefore very interesting to study how neurons in the MTL behave in different tasks and conditions. However, for neuroscientists interested in studying the principles of neural coding, the main limitation of intracranial EEG recordings arise from the fact that the EEG is a measure of the average electrical activity of large neuronal populations and, consequently, they only give indirect and ambiguous evidence of the behaviour of single neurons. Ideally, to get a deeper understanding of how neurons encode information in these areas, one would like measure the activity of single-neurons directly.

**Single neuron recordings in humans**

Using tungsten microelectrodes implanted during surgery in epileptic patients undergoing anterior temporal resections, just before the tissue removal, Ojemann and colleagues recorded single cells while the patients performed language tasks, such as object naming and word reading. In this pioneering study, these authors found that single cells significantly changed their firing, thus showing some relation with language and memory. Using microwires placed at the end of intracranial depth electrodes, a recording setup was developed at the University of California, Los Angeles (UCLA) that allows not only the recording of intracranial EEG but also of multiple single-neurons and local field potentials i.e. the mean field potential generated by the activity of neurons and synapses in the vicinity of the recording electrode. The possibility of recording multiple single neurons in these areas allows the extraordinary opportunity to study directly the neural correlates of different brain functions in conscious human subjects, who – in contrast to animals – can give detailed feedback of their experience and behaviour. Moreover, human subjects can just be asked to perform a certain task and, at least in general, do not need extensive training as in the case of animals. In this respect, it should be noted that monkeys are usually overtrained to perform a task, a fact that may affect the interpretation of results since these could be attributed to the particular behaviour under study or to training effects.

With the human single neuron recording setup developed at UCLA, it was shown that the firing of single neurons in the hippocampus and the amygdala discriminated faces from inanimate objects. A following study demonstrated the presence of category-specific neurons in the human MTL: a neuron responding to faces, another one responding to animals, etc. In another study, subjects were asked to imagine previously seen images and it was found that MTL neurons selectively changed their firing according to the image that was imagined. Interestingly most of the visually responsive neurons had the same selectivity when pictures were imagined – i.e. in the absence of the visual stimuli – thus suggesting that in MTL there is a common substrate for processing visual information and visual recall.
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Neural correlates of conscious perception

By progressively shortening the stimulus duration (264ms, 132ms, 66ms and 33ms) and showing the pictures at the threshold of recognition, it has recently been shown that the MTL neurons described above can follow the conscious perception of the pictures with ‘all-or-none’ responses. For example, Figure 1 shows a single-unit in the right entorhinal cortex of a subject that fired selectively to pictures of the World Trade Center from a nearly silent baseline activity the neuron responded with up to 10 spikes per second. The response of this neuron to the other 15 pictures shown in this experiment was not significant. The patient reported not recognising the picture of the World Trade Center in all trials with 33ms duration and in eight trials with other durations (in red). Corresponding with the behavioral report, there was no observable response during trials where the picture was not recognised. The difference between recognised and non-recognised trials was remarkable for the 66ms presentations, where it is clear that the neuron fired in an “all or none” fashion. In fact, for the three trials in which the picture was recognised, the neuron fired five to eight spikes between 300ms and 1000ms after stimulus onset and for the five trials in which the picture was not recognised the neuron did not fire a single spike.

What is the function of these MTL neurons?

Given the relatively long latency of the human MTL responses reported here – at about 300ms – it is highly likely that these neurons are not part of the recognition process per se. This is in agreement with lesion studies in the hippocampal formation and substantial evidence from patient H.M. and others. In fact, patient H.M. – the most studied patient in neuroscience history – was subject to a bilateral hippocampal resection, which at the time (in the 1950s) was thought to cure him from his epilepsy. After surgery, H.M. seemed to have a completely normal behaviour without the hippocampus, given his intact ability to recognise different people, but it soon became apparent that he was not able to form new memories. The fact that the MTL cells described here have very strong and abstract visual responses is in line with the interpretation that they may be underlying the link between consciously perceived inputs and memory, since we tend to remember concepts rather than irrelevant details.

Conclusion

Recordings in patients suffering from epilepsy, implanted with intracranial electrodes for clinical reasons, have provided invaluable information about normal and pathological brain function. Here we have shown how much information can be obtained from single neuron recordings while awake and behaving patients perform different perceptual and cognitive tasks. The recordings described here were in the medial temporal lobe structures, which are crucial for memory processes. But this approach in not limited to the medial temporal lobe, since similar type of recordings are possible (and clinically justified) in other cortical and subcortical structures, such as the subthalamic nuclei for deep brain stimulation. The possibility of recording the activity of single neurons in these areas opens a window of new opportunities to directly tackle some of the most important and, so far, elusive questions in neuroscience.

REFERENCES

6. H.M. – the most studied patient in neuroscience history – was subject to a bilateral hippocampal resection, which at the time (in the 1950s) was thought to cure him from his epilepsy.
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Precautions

Inform patients of most common adverse reactions. Use with caution in patients with previous or current depressive disorders and those with antecedents of suicidal ideation. Advise patients to report immediately any symptoms of depression and/or suicidal ideation. Closely monitor patients exhibiting depression and treat appropriately. Consider cessation of therapy. Administer with caution in patients with a history of seizures and those receiving anti-epileptics, particularly if epilepsy is not adequately controlled. Closely monitor patients with cardiac disease for worsening of their condition during initiation of therapy. Patients should use an aseptic injection technique and rotate injection sites to minimize risk of injection site necrosis. If breaks in skin occur, patients should consult their doctor before continuing injections. If multiple lesions occur, discontinue Rebif until healed. Use with caution in patients with history of significant liver disease, active liver disease, alcohol abuse or increased serum ALT. Monitor serum ALT prior to the start of therapy, at Months 1, 3 and 6 and periodically thereafter. If hepatitis with or without icterus, severe liver injury, anaphylactic reactions, angioedema, erythema multiforme, erythema multiforme-like skin reactions, aspergillosis, thromboembolic events, suicide attempt, Stevens–Johnson syndrome, dysphonia. Consult the Summary of Product Characteristics for more information relating to side effects. Legal category: POM.

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References


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The Syndrome of Mitochondrial Spinocerebellar Ataxia and Epilepsy caused by POLG mutations

Introduction

DNApolymerase γ (pol γ) is the enzyme that replicates and repairs the mitochondrial DNA (mtDNA), the small, maternally inherited genome found inside mitochondria that encodes 13 subunits of the respiratory chain. Pol γ is a heterotrimer composed of one catalytic subunit (pol γA), and two accessory subunits (pol γB). Pol γA comprises a polymerase (replicating) domain and an exonuclease (proof-reading) domain, separated by a large linker region. The linker domain is the binding site of the accessory subunits, which enhance substrate affinity and processivity of the catalytic subunit.3

Over 120 pathogenic mutations have been described in the gene encoding the catalytic pol γ subunit (POLG) and these are associated with a wide spectrum of neurological syndromes ranging from adult onset myopathies to severe infantile encephalopathies. Specific disorders include autosomal recessive and dominant progressive external ophthalmoplegia (PEO), Alper’s syndrome, parkinsonism, and the syndrome of mitochondrial spinocerebellar ataxia and epilepsy (MSCAE).1,4 This review will focus on MSCAE.

Pathophysiology

MSCAE is inherited as a recessive disorder most commonly associated with the mutations c.1399G>A, p.A467T or/and c.2243G>C, p.W748S in the linker region of pol γA. The A467T interferes with the catalytic subunit's intrinsic polymerase activity and binding to the accessory subunit, resulting in severely reduced efficiency of mtDNA synthesis.3 The pathomechanism of the W748S mutation has yet to be revealed, but it is possible that this too has a similar effect. Irrespective of the mechanism, these mutations ultimately lead to secondary damage of the mtDNA in the form of point mutations, multiple deletions and quantitative depletion,5 making pol γ induced disease a paradigm for mtDNA disease.

Epidemiology

The A467T and W748S were each introduced in the European populations by an ancient common founder. The reported carrier frequency for the A467T is 1% in Norway, 0.69% in the UK, 0.6% in Belgium, 0.5% in Sweden, and <0.2% in Finland. The carrier frequency of the W748S has been estimated to be 1% in Norway and 0.8% in Finland. Both sexes are equally affected by the disease.6,7

History and clinical features

The age of onset varies between 1.5 and 45 years, with most patients presenting in their teens at a mean age of 19 years. The most common presenting features in order of decreasing frequency are progressive gait unsteadiness, epileptic seizures, and headache, often with migraine features. Ataxia is universally present and results from a combined cerebellar and peripheral sensory dysfunction, producing a clinical picture with nystagmus, scanning dysarthria, midline and appendicular ataxia. The vast majority of patients (98%) also develop features of a peripheral neuropathy with diminished tendon reflexes and glove and stocking sensory impairment. Ptosis and PEO develop late, at a mean age of 33 years. Progressive cognitive decline is common. A few patients develop gastrointestinal dysmotility with chronic abdominal pain, diarrhoea or pseudo-obstruction (Table 1). Epilepsy affects the majority of patients (63%) and, although it usually manifests either at disease onset or shortly after, it may start as late as several decades after the onset of the ataxia. A variety of clinical seizure types are seen, including partial simple or complex visual and motor seizures and generalised tonic-clonic (GTC) seizures. Commonest are simple partial motor seizures involving an upper limb and the head/neck region and these often evolve into epilepsia partialis continua (EPC), which may last for up to several months. Visual seizures are common and patients usually describe flashing coloured lights in one or both visual hemifields. Primary and secondary GTC

Table 1: Clinical features of MSCAE.8

<table>
<thead>
<tr>
<th>Sign/symptom</th>
<th>Present/evaluated</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia</td>
<td>68/68</td>
<td>100%</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>62/63</td>
<td>98</td>
</tr>
<tr>
<td>Headache</td>
<td>29/35</td>
<td>83%</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>43/68</td>
<td>63%</td>
</tr>
<tr>
<td>PEO</td>
<td>35/68</td>
<td>51%</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>35/68</td>
<td>51%</td>
</tr>
<tr>
<td>Liver failure</td>
<td>15/50</td>
<td>30%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>6/68</td>
<td>9</td>
</tr>
</tbody>
</table>

Liver failure was associated with the use of sodium-valproate in all but one patient.1,8

Acknowledgments

The authors express their gratitude to Professor Bernt Engelsen for providing the EEG data.

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seizures are frequent as is GTC status epilepticus [9, 14, unpublished data]. Patients with epilepsy experience episodes of clinical exacerbation with severe seizures and rapidly progressing encephalopathy (EE episodes). These start either acutely with epileptic seizures or insidiously with gradual mental and personality changes that may precede the onset of seizures by days to weeks. EE episodes may last from a few days up to several months (usually two to three months) and are clinically characterised by progressive encephalopathy, disturbed consciousness ranging from confusion to deep coma, and severe epilepsy with multiple daily seizures and frequent partial or generalised status epilepticus. EE episodes are associated with significant morbidity and mortality. In a series of 30 episodes in 26 patients, 14 proved fatal [unpublished data]. Survivors suffered severe and permanent disability as a result of accelerated decline of motor and cognitive skills and/or cortical visual loss. Liver involvement may occur ranging from asymptomatic biochemical findings to fulminate and fatal hepatic failure. Liver failure in MSCAE is usually, but not always, precipitated by exposure to the anti-epileptic drug sodium-valproate [1, 9, 14, unpublished data].

Course and survival
The course of MSCAE is invariably progressive. The rate of progression and mortality are highly variable and linked to two factors: genotype and epilepsy. Survival is worse in patients carrying the A467T and W748S mutations (compound heterozygous) and best in A467T homozygotes. The presence of epilepsy is the most important clinical prognostic factor as it is associated with significant morbidity and mortality as a result of EE episodes. In a study of 35 patients by the authors, mortality was 77% in patients with epilepsy (26 patients) with a median survival of 20 years, while no deaths occurred in the group without epilepsy (nine patients) [1, unpublished data].

Investigations

Neuroimaging
Magnetic resonance imaging (MRI) showing high T2 signal abnormalities in the thalamus, cerebellar cortex or white matter and inferior olivary nuclei is highly suggestive of MSCAE (Figure 1, Table 2). During EE episodes, MRI may reveal hyperintense cortical lesions involving the occipital, frontal or parietal regions. These acute lesions evolve dynamically and may expand or regress reflecting the clinical course and severity of the episode (Figure 1C, E, F, Table 2). If performed early enough, diffusion imaging shows initially restricted cortical diffusion, which gradually increases, consistent with a transition from cytotoxic to extracellular cortical oedema. Progressive cerebellar and cerebral atrophy is commonly seen (Figure 1A). Magnetic resonance spectroscopy of fresh cortical lesions shows decreased N-acetyl aspartate spectra and high lactate levels [unpublished data].
As soon as first line oral dopamine agonists start to fail, go directly to APO-go

Trying subsequent oral medication once your PD patient’s first line dopamine agonist begins to fail, resulting in increasing motor complications, can be a time of frustration and disappointment for you and your patient – compromising their optimum quality of life.

For responsive patients with Early Complex PD, APO-go CDS is a highly effective, rapid-acting drug that, combined with Britannia’s extensive Package of Care, can maintain your PD patients’ independence.

Prescribing information can be found overleaf.
Neurophysiology

Electrophysiology in patients with epilepsy shows a primary occipital focus with generalisation during status epilepticus. Extra-occipital epileptogenic foci are also seen and these often correlate with extra-occipital frontal or parietal cortical lesions. Nerve conduction studies show a predominantly aural sensory peripheral neuropathy (Figure 2).16

Biochemistry and histology

Elevation of lactate in blood or CSF is an inconsistent feature and blood chemistry is otherwise unremarkable with the exception of liver function tests in patients with liver involvement. Muscle histology may reveal cytochrome oxidase negative fibres, but is often normal, especially when taken early during the course of the disease.

Therapy

No disease modifying treatment exists for MSCE. The cornerstone of management is antiepileptic treatment. Achieving satisfactory seizure control in MSCE is, however, a challenging task. Our experience suggests that monotherapy can be effective initially, but high dose polytherapy regimes are usually needed, particularly once the patient has an EE episode. No specific drug combination has shown an advantage and the choice of individual agents should be individualised for each patient and based on clinical response. Sodium-valproate is strongly contraindicated due to a significant risk for development of severe liver failure. Status epilepticus is often refractory to conventional treatment protocols and we have a low threshold for initiating generalised anaesthesia.16

REFERENCES


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Pre-senile Dementia

We were well down the road before we even knew it existed. Clive’s diagnosis of “pre-senile dementia” came in November 1993, but I had noticed the first signs in the summer of 1988; the first major row at work came in spring 1991, and redundancy in autumn 1992. By 1993 Clive was incapable of applying for a job, never mind doing one, and yet in the summer he was told there was nothing wrong with him, and by November a different consultant diagnosed the dementia. The consultant never saw Clive to tell him the diagnosis. He told me over the phone, and referred us back to our GP for more information.

Clive was diagnosed just after his 46th birthday. Our children were 4 and 5. I met Clive at university. He was just 46; their children were four and five. She has since helped found The Clive Project, which provides support for people with young-onset dementia, written a book ‘Losing Clive’, ISBN 978-1843304803 and will shortly start a PhD researching methods for early diagnosis of dementia.

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OX14 1JG, UK.

Helen Beaumont’s life changed track when her husband was diagnosed with pre-senile dementia. He was just 46; their children were four and five. She has since helped found The Clive Project, which provides support for people with young-onset dementia, written a book ‘Losing Clive’, ISBN 978-1843304803 and will shortly start a PhD researching methods for early diagnosis of dementia.

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Case Studies in Neurological Rehabilitation

This innovative new book provides current, highly practical and enjoyable test to refer to when dealing with the usual mix of cases seen in a typical neurological rehabilitation service. The material is presented as case histories to set the scene for a discussion of a complex neurological rehabilitation issue. Almost all similar book titles present clinical cases as diagnostic challenges. What is unique about this book's approach is its presentation of cases as management challenges. Most cases seen in neurological rehabilitation services are already diagnosed but nonetheless difficult because of their complexities. The cortical blindness case is a good example. The patient's visual impairment is probably the least of his problems as the cognitive, behavioural, sleep etc are the prime causes of disability and handicap. The author presents the cases in an uncomplicated way, allowing non-medically trained clinicians to follow the arguments with ease.

There are three parts. The first part is on the basic principles of service delivery. This part is short and presents a relatively narrow view. Readers from overseas may find the material useful but it lacks originality.

The second part is based on case studies and is subdivided into thirteen sub-sections to cover all the major issues that neurological rehabilitation clinicians face routinely. There are forty-five case histories with different types of management problems. Each section consists of brief case histories followed by a well-written commentary highlighting all the must-know points. This extremely useful section contains explanations, classifications, criteria for diagnosis and proposed guidelines and management options. Most of the topics use tables, which aid understanding and recall. All topics end with a brief but relevant further reading suggestion list.

The second part is the real strength of this book as it provides clear practical advice about day-to-day complex neurological rehabilitation cases in a simple and easy way.

The quality of the commentaries varies with good, insightful cases such as aphasia, thromboprophylaxis and pontine myelolysis and other cases with relatively limited scope, such as locked-in syndrome (ignoring low consciousness states as differential diagnosis) or ataxia. I could not understand the absence of a case dealing with memory impairment despite the excellent coverage of the other main cognitive rehabilitation issues.

This weakness is probably common to all similar books with a single authorship as the author only feels comfortable dealing with the areas of his specialist interest.

The book concludes with 50 multiple-choice questions covering issues, which are probably too brief to warrant a full case discussion. This part is very helpful for trainees preparing for European/North American board examinations.

Overall this is a well-written, interesting and handy practical guide that would be useful for any clinician dealing with long-term neurological conditions whether s/he is a doctor, therapist or nurse.

Vascular cognitive impairment in clinical practice

Vascular dementia (VaD) and vascular cognitive impairment (VCI) are mysterious conditions for those neurologists with an interest in cognitive disorders who almost never make these diagnoses, and hence believe them to be rarities, whereas old age psychiatrists seem often to use these labels (age mix of cases may explain some of the difference). Perhaps the problem lies in the textbook dichotomisation of Alzheimer's disease (AD) and VaD as distinct disorders, whereas Kwivelto and colleagues (p178-91) argue in this volume for a more ‘integrative etiology’ with a continuum running from pure AD to pure VaD through entities such as ‘AD with vascular lesions’ and ‘VaD with AD changes’. The heterogeneity of VaD/VCI, with various subtypes, is of course well-recognised.

Various lines of evidence support this approach: the shared vascular risk factors for AD and VaD (p155-65), the evidence for cholinergic deficits in VaD (e.g. p196), neuropathological studies (e.g. MRC CFAS) showing that mixed pathology is the rule in demented elderly, evidence for the modulation in a synergistic manner of AD-related clinical expression by vascular lesions (e.g. the Nun study), and the modest efficacy of ChEI in VaD (p196-8, though not of course sanctioned by NICE).

Elsewhere this well-presented volume covers diagnosis (clinical, cognitive, structural and functional imaging) and pathophysiology (large vessel, small vessel, white matter changes, amyloidosis) of VCI. Treatment however remains problematic with a paucity of controlled studies addressing functional decline (p200-5) and behavioural symptoms (p206-19).

Primary and secondary prevention measures, perhaps facilitated by predicting risk of dementia in 20 years time (p161), may be the best hope for future national dementia strategies, with emphasis being appropriately placed on a lifelong lifestyle approach. Hence this book may be recommended not just for the VaD/VCI cognoscenti, but for all those concerned with the diagnosis and management of dementia syndromes.◆
For the treatment of patients with Parkinson’s disease and end-of-dose motor fluctuations not stabilised on their current levodopa/DDCI treatment.

Stalevo with caution, provided the intra-ocular pressure is well controlled

- Most common: dyskinesias including choreiform, dystonic and other involuntary movements, nausea. Also mental changes, abnormalities of behaviour, psychiatric adverse events, conjunctival hyperemia, other eye disorders. Rare: visual disturbances, photosensitivity reactions, keratitis, conjunctivitis. Very rare: retinal detachment, uveitis. Rare and very rare: decreased vision, cataract, eye pain, eye irritation, eye injury, eye oedema, eye infections. Very rare: endophthalmitis, ocular haemorrhage. Rare: eye disorder, conjunctival hyperemia, ocular haemorrhage, eye pain.

- Most common: nausea, vomiting, diarrhoea, flatulence, bloating, constipation. Common: abdominal pain.


- Most common: weight gain, oedema. Common: peripheral oedema, oedema of the hands and/or feet. Very rare: obesity. Rare: oedema of the hands and/or feet.


- Most common: depression, anxiety, insomnia, irritability, hostility, aggressiveness, aggressivity, euphoria, libido decreased, sexual dysfunction, suicidal ideation, personality disorder. Common: agitation, anxiety, depression, disturbance of mood, aggression, hallucinations, delusions, depression, anxiety, insomnia, irritability, hostility, aggressiveness, aggressivity, euphoria, libido decreased, sexual dysfunction, suicidal ideation, personality disorder, obsessive-compulsive disorder, mania, thought disorder, aggression, irritability, hostility, aggressiveness, aggressivity, euphoria, libido decreased, sexual dysfunction, suicidal ideation, personality disorder, obsessive-compulsive disorder, mania, thought disorder, aggression, irritability, hostility, aggressiveness, aggressivity, euphoria, libido decreased, sexual dysfunction, suicidal ideation, personality disorder, obsessive-compulsive disorder, mania, thought disorder, aggression, irritability, hostility, aggressiveness, aggressivity, euphoria, libido decreased, sexual dysfunction, suicidal ideation, personality disorder, obsessive-compulsive disorder, mania, thought disorder.


- Most common: weight gain, oedema. Common: peripheral oedema, oedema of the hands and/or feet. Very rare: obesity. Rare: oedema of the hands and/or feet.

- Very rare: hepatitis, colitis. See SPC for further details.
Diffusion weighted imaging

Physics

In diffusion weighted pulse sequences, magnetic resonance signal is generated in proportion to the freedom with which protons are able to move. When restricted by macromolecules and cell membranes, protons move more slowly than when in aqueous solution. Diffusion weighted imaging (DWI) sequences use radiofrequency pulses and magnetic gradients to dephase protons. After a short interval, an exactly opposite pulse and gradient is applied which returns the protons into phase. Protons that have moved in the interval do not generate signal, so that DWI intensity is proportional to the amount that protons have diffused during the imaging process (Figure 1).

Post processing of diffusion weighted images

Raw diffusion weighted images (Figure 2) are presented as unweighted (B=0), Antero-Posterior gradient, Left-Right gradient, Supero-Inferior gradient and combined (B=1000) images.

Apparent diffusion coefficient (ADC) maps (Figure 3) differentiate signal generated by restricted diffusion of protons from T2 effects (T2 ‘shine through’). ADC is a scalar quantity and does not reflect the asymmetry or direction of diffusion.

Fractional anisotropy, FA (Figure 4) is a tool for quantifying the extent to which diffusion is restricted asymmetrically (anisotropically). At the time that workers were investigating DWI in stroke, it was observed that the sig-
nal obtained depended on the direction in which the diffusion imaging gradient was applied. This is because axons tend to be arranged in parallel tracks and cell membranes/myelin allow proton diffusion along axons but not across the myelin sheath.

FA varies from 0 (spherical pattern of diffusion=perfectly isotropic) to 1 (diffusion restricted to a single linear direction=perfectly anisotropic). Heavily myelinated structures such as the corpus callosum have a high FA (0.90), unmyelinated regions such as cortex have a low FA (0.20) and water has an FA of 0. Note that FA is a scalar quantity and does not take account of the direction in which diffusion is occurring, only the extent to which diffusion is asymmetric.

FA can be used to map normal fibre tracts and is a sensitive method for detecting abnormal white matter. White matter pathology affects myelination and reduction in FA can be detected before signal change can be seen on other sequences such as T2 weighted imaging.

**Diffusion Tensor Imaging, DTI** (Figure 5) combines diffusivity with the direction in which diffusion is restricted to give a parameter that has magnitude and direction (a tensor). By applying sufficient diffusion gradients (a minimum of 6 directions as well as an unweighted, b=0 image) a map of the direction of axons throughout the brain can be obtained. This anatomical data is useful in surgical planning so that important white matter tracts close to tumours can be avoided.

**Clinical applications of DWI**

**Stroke** (Figure 6): The first clinical application that was found for DWI was in the field of stroke imaging. Restriction of proton movement in acutely ischaemic tissue occurs because of failure of membrane pumps and consequent neuronal swelling. This results in an increase in the ratio of intracellular to extracellular space. Proton diffusion is restricted in the intracellular space because of protein content, intracellular organelles and lipid membranes. It has been shown that tissue which shows restricted diffusion has suffered irreversible damage and will not recover even if perfusion is restored, making DWI a useful discriminator of patients who will benefit from thrombolytic and other acute interventions.

**Abscess** (Figure 7): Conventional sequences cannot always distinguish a cystic tumour from an abscess. Diffusion weighted imaging can be helpful when an abscess is a possibility.

**CJD** (Figure 8): DWI helps confirm the diagnosis of Creuzfeld-Jakob disease (CJD). In sporadic CJD, there is restricted diffusion in the cortex and basal ganglia. In new variant CJD, there is signal change in the posterior thalami (pulvinar sign).

**Epidermoid** (Figure 11): These masses arise from congenital remnants of cutaneous ectoderm within the cranial cavity. They contain keratin which returns high signal intensity on DWI which helps to distinguish them from similar appearing lesions such as arachnoid cysts.

**Functional MRI**

**Physics**

Functional MRI (fMRI) generates contrast on images on the basis of different oxygen levels and is also known as BOLD (Blood Oxygen Level Dependent) imaging. As regions of the brain become active, their demand for blood supply increases and surrounding vessels dilate resulting in a local increase in oxyhaemoglobin levels. This causes a small reduction in intensity on T2 weighted images which is detected by the MRI equipment. Acquisitions are made before and after a specific task which may be:

- Sensory - visual (lights, faces, scenes etc)
- Auditory (voice, sound)
- Somatosensory (cutaneous stimulation)

- Motor - finger, toe movement

- Cognitive - recall, arithmetic, word finding

The images viewed are statistical maps showing areas with significantly reduced signal after the task. These areas are shown in colour on an anatomical image of the subject’s brain.
Clinical applications
Although primarily a research tool, fMRI can be useful for surgical planning:
– to localise memory function in children undergoing temporal lobe resection for seizures.
– to minimise post-operative deficits in cases where brain tumours are close to neurologically eloquent areas of cortex (Figure 12).

Magnetic resonance spectroscopy (MRS)

Physics
Spectroscopic signals are obtained from hydrogen nuclei in organic molecules. The technique relies on subtle alteration (‘shift’) of the resonant frequencies of hydrogen nuclei because of the effect of adjacent nuclei and electrons in the molecule. Spectra are presented as plots of amplitude against parts per million shift in resonant frequency.

Principal metabolites detectable on clinical MRS are:

N-Acetyl Aspartate (NAA) – is a marker for neurones and is decreased in conditions that cause axonal or neuronal cell loss. There are a few metabolic conditions in which too much NAA is produced (eg Canavan disease).

Creatine (Cr) – is a marker of the intracellular energy stores and is relatively constant in most disease processes. Other metabolites may be compared to the Cr peak.

Choline (Cho) – is a marker of cell turnover since it is an important constituent of cell membranes. Rapidly dividing tumours, particularly those with small cells (high surface area to volume) content choline peaks.

Clues about the grade of a glioma, although not accurately enough to avoid biopsy in most cases.

Alzheimer’s disease (Figure 14) – Myo inositol is a breakdown product of myelin and is seen in Alzheimer’s disease more commonly than in other forms of dementia. It may also be seen in malignant tumours.

Stroke (Figure 14) – The striking feature in stroke is loss of NAA. Choline may be raised in this condition. Ischemic penumbra shows relatively normal spectra. Spectroscopy is not widely used in stroke imaging because of the relatively long time an acquisition requires.

Metabolic diseases (Figure 14) – Some leukodystrophies (eg. Canavan disease, adrenoleukodystrophy) can be diagnosed and the effect of treatment can be assessed using MRS.

Figure 9: Astrocytoma Grade 3
(a) T2 weighted image (FSE, TR=4000 msec, TE=100 msec, slice=6 mm) and (b) Diffusion Weighted image (EP, TR=6000 msec, TE=98 msec, slice=5 mm) show a cystic mass in the right temporal lobe with an enhancing mural nodule (arrow head).

Figure 10: Acute Disseminated Encephalomyelitis (ADEM)
(a) T2 weighted image (FSE, TR=4000 msec, TE=111 msec, slice=6 mm) and (b) Diffusion Weighted image (EP, TR=6000 msec, TE=98 msec, slice=5 mm) shows multiple high intensity lesions in cerebral white matter in keeping with demyelination. (c) ADC map demonstrates the presence of restricted diffusion rather than T2 shine through (arrow head).

Figure 11: Epidermoid
(a) T2 (FSE, TR=3000 msec, TE=105 msec, slice=6 mm) and (b) Diffusion weighted (EPI, TR=10000 msec, TE=111 msec, slice=6 mm) show high intensity on a suprasellar epidermoid (arrow heads). These are characteristically high intensity on DWI in contrast to arachnoid cysts which usually low intensity.

Figure 12: Functional MRI. Pre-operative study for planning of right superior frontal tumour resection. The patient has been given the task of toe movement. a) Axial image, patient moving right toe. There is activation in the medial left precentral gyrus. b) Axial image, patient moving left toe. Activation is more diffuse and bilateral with some activity seen on the periphery of the right frontal tumour.

Figure 13: Spectroscopy. Grade III glioma.
(a) Control. The NAA peak at 2.0 ppm is approximately twice the amplitude of the Choline and Creatine peaks.
(b) Tumour. The NAA peak is reduced and the Choline peak is greater in amplitude compared to Creatine.
(c) Alzheimer’s disease. The most striking feature in this spectrum is the presence of myo-inositol. In later stages of the disease, NAA is reduced. (d) Infarct. There is reduction of Choline, Creatine and NAA with a prominent lactate peak. Some infarcts may show increased Choline.
(d) Canavan disease. There is a raised NAA peak and this finding is almost pathognomonic for this condition.
Telemedicine in Neurorehabilitation

Telemedicine is the assessment, diagnosis, direct treatment, education, monitoring and support of patients at remote sites via telecommunications, ranging from the plain old telephone service (POTS) to real-time videoconferencing through the Internet (Table 1). Telerehabilitation, one of the numerous applications of telemedicine, was initially utilised to provide home-based physical therapy to disabled stroke patients, who, due to their physical limitations, had particular difficulty in travelling to urban rehabilitation facilities. With computers and the Internet becoming an integral part of our daily lives, telerehabilitation may be extended beyond the hospital and into the community or the patient’s home, whereby health care providers can continue to monitor patients’ progress, identify areas in need of improvement before complications set in, and ultimately improve function and minimise disability and costs.

Telemedicine has been applied with success in the field of neurology, from acute stroke management to consultations with specialist neurology centres. Moreover, the role of telemedicine in rehabilitation and management of chronic neurological diseases such as stroke, multiple sclerosis, brain or spinal injury, Parkinson’s disease and dementia has been studied.

Clinical applications of telerehabilitation

Stroke
The role of intensive multidisciplinary rehabilitation following stroke is well established. Conventional physiotherapy targeting major motor deficits following stroke could be delivered via teleconferencing. The author conducted a study in which stroke rehabilitation in a group format was provided via teleconferencing at a community social centre for seniors. Significant improvement was seen in physical (Berg Balance Scale) and psychosocial (Medical Outcomes Study Short Form (SF-36), State Self-Esteem Scale) outcomes as well as the Stroke Knowledge Test.

Task-specific approaches that deal with lost abilities, for example, hand function, are also important in stroke rehabilitation. Robotic devices and virtual reality software can facilitate training of motor function and coordination in the limbs. A web-based monitoring and feedback system allows patients to continue training at home, while their therapist can monitor their progress and make gradual modifications to their exercise prescription (Figures 1 and 2).

Parkinson’s disease
In the United States, the Parkinson’s Disease Research, Education, and Clinical Centers (PADRECC) operated by the Veteran’s Health Administration (VHA) have established telerehabilitation services to provide expert medical care and education to patients, carers as well as health care providers located some distance from a PADRECC.

Step counting is an important index in motion monitoring and rehabilitation in Parkinson’s disease. However, commercial pedometers are confounded by the abnormal movement style in this condition and rendered inaccurate. Giansanti’s group from Italy has developed a new wearable step counter based on calf muscle expansion during walking. The step counter device collects and transmits data from the patient at home back to the therapist. Remote telemonitoring and telerehabilitation could thus be offered to patients with Parkinson’s disease as well as a number of conditions requiring motion rehabilitation (for example, stroke or weight-reduction programs).

Table 1: What is Telemedicine?

<table>
<thead>
<tr>
<th>Means of communication</th>
<th>Information exchanged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telephone / Fax</td>
<td>Traditional consultation</td>
</tr>
<tr>
<td>Email</td>
<td>Photographs, digitalised radiographs, videos</td>
</tr>
<tr>
<td>Internet</td>
<td>Health web sites, on-line assessment +/- feedback or education, computer assisted rehabilitation programmes</td>
</tr>
<tr>
<td>Videoconference</td>
<td>Real-time, audio-video link</td>
</tr>
<tr>
<td>Suitable patient</td>
<td>Isolated, disabled, elderly</td>
</tr>
<tr>
<td>Health care provider</td>
<td>Limited resources or expertise, long travelling time</td>
</tr>
<tr>
<td>Setting</td>
<td>Patient’s home, primary care clinic, rural health facility, community elderly centres</td>
</tr>
<tr>
<td>Hardware and Infrastructure</td>
<td>I.T. hardware (personal computers, designated devices for transmitting clinical data, videoconferencing equipment); data transmission (integrated services digital network (ISDN) line, broadband [fixed or wireless])</td>
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Multiple Sclerosis
The progressive and disabling nature of multiple sclerosis means most patients have difficulty accessing health care facilities. Telemedicine can extend traditional outpatient services to patients from rural areas. A telemedicine network can link a regional centre specialising in multiple sclerosis with the primary health care provider of the patient, allowing discussion of the diagnosis, prognosis and goal setting. Web sites targeted at the disease allow patients and caregivers to access information and participate in therapy, training and support. Moreover, telemedicine has been used to manage complications of multiple sclerosis, including pressure ulcers, depression and gait disorders.9 In a study where frequent assessments by a wound specialist via teleconferencing enhanced usual care provided by a community nurse, improved healing rate and cost savings was achieved for home-dwelling patients with pressure ulcers.10

Mobility problems affect 60% of multiple sclerosis cases, and frequent monitoring of their physical status and adjustment of exercises and assistive devices in the home is important to prevent deterioration. Telemedicine was shown to be reliable in neurological evaluation and the assessment and management of falls.8

Dementia
It has been demonstrated that a videoconference link is as effective as face-to-face interviews in the assessment and diagnosis of dementia. A web-based information and support systems (e.g., AlzOnline, http://alzonline.phhp.ufl.edu/) as well as telephone and email access to specialist nurses can provide practical advice and emotional support to demented patients and their caregivers.17

A randomised controlled trial was conducted by the author’s group at the Chinese University of Hong Kong, in which 12 sessions of cognitive training were provided via videoconferencing or by face-to-face method. Significant cognitive improvement as measured by the Mini-Mental State Examination, Rivermead Behavioural Memory Test and Hierarchic Dementia Scale was observed in both treatment arms. The telemedicine group was as effective as the conventional treatment group, and well accepted by the clients.18

Other issues
Much of the experience in telemedicine came from the VHA, one of the largest health care organisations in the United States. Taking advantage of economies of scale, the VHA is able to service entire regions, sometimes comprising of several states. VHA facilities are connected by a highly developed information infrastructure which includes an electronic medical record system, medical imaging, videoconferencing and a large PC-based network.9

Costs and reimbursement
Despite considerable reductions in the price of commercial available videoconferencing units (e.g., Polycom®, Tandberg), start-up and maintenance costs are still relatively high. A British study calculated the average cost of a neurology outpatient to be £72 via teleconference whereas the conventional clinic visit cost £49.19 In 2001, the author reported costs per teleconsultation to nursing home residents ranging from USD3 for a nurse to USD15 for a dermatologist.20 To maximise cost-effectiveness, the telemedicine infrastructure should be a high-volume service, shared by multiple health care providers and serving as many remote sites or users as possible.

When transport & travel costs exceed treatment costs, tele-rehab may be the answer
In the United States, reimbursement mechanisms for telemedicine can be complex, as Medicare insurance only provides partial payment for teleconsultations compared with conventional face-to-face care episodes. Not surprisingly, telemedicine practice and research have predominantly been federal-funded demonstration projects, conducted by large health care organisations such as the VHA or Kaiser Permanente. In fact, the United Kingdom’s socialist health care model may be more conducive to the development of telemedicine.

Legal
Health care professionals’ licensure requirements may restrict the practice of telemedicine across state or country borders. As of 2002, twenty-six states in the United States have introduced licensure laws which actually make the practice of telemedicine more difficult across state lines. The VHA, however, allows all its practitioners to practice in any VHA facility within the country, hence allowing telemedicine to develop and expand within the organisation.

Privacy
It is important to protect the privacy or security of patient-identifiable information in all health provision settings, and telemedicine is no exception. Specific issues relating to telemedicine include the presence of non-clinical personnel (e.g., camera technicians) during consultations, and the handling or storage of patient information (e.g., clinical photographs, videos) separate from the conventional or electronic medical notes. Commercially available videoconferencing equipment has built-in encryption which ensures secure communication between the provider and patient during teleconsultations.

Acceptability
Telemedicine challenges the basic belief that all health care is best delivered face-to-face. It requires a shift in culture in both patients and health care professionals. Patient satisfaction towards various forms of telehealth has been consistently high, with common cited reasons such as improved access to specialists, reduced travel and associated costs, shorter waiting times for appointments and the opportunity to participate in health education or group therapy.

From the health provider’s perspective, satisfaction surveys are generally positive for the same reasons mentioned above. General practitioners and doctors in rural or deprived areas appreciated the educational aspect of telemedicine, where the support of specialists allows them to diagnose and manage patients with greater confidence. Nevertheless, the need to learn and adjust to a new technology and make changes in their daily work routine may explain the cynicism held by a minority of health providers.

Technical
In the infancy of telemedicine, the slow POTS connection meant that video quality was choppy with low resolution. This improved with integrated service digital network (ISDN) technology, which allowed the transmission of simultaneous voice and video data at a fixed rate of 128kBs within a network. More recently, as moderate to high bandwidth broadband networks became more widely available, teleconferencing applications can support real-time audio-video link at 768kBs or above. However, the bandwidth has to be monitored so that the image quality does not degrade with heavy network traffic. Store-and-forward clinical information such as photographs, CT scans and echocardiograms can be transmitted as e-mail attachments via lower bandwidth systems. Wireless telemedicine using satellite, 3G and other emerging wireless networking technologies is an attractive means for linking ambulances with hospital Emergency Rooms and in the provision of emergency medical care to soldiers in the battlefield.

In chronic disease management, mobile phones are becoming an important method of enhancing health provider-patient communication, monitoring health outcomes and delivering health interventions.

Conclusions
Telerehabilitation is an attractive method of delivering services to disabled patients without a need for both the patient and health care professional to be in the same location at the same time. It has a major role in providing remote rehabilitation to patients with chronic neurological conditions, and fills a service gap among those who have limited access to expert care. New telecommunication technologies will enhance the quality and intensity of therapy delivered to the patient at home, and provides important clinical information to the health provider. To maximise cost-effectiveness, health care professionals and patients in various medical specialties should utilise a telemedicine service, rather than limiting its use to an exclusive few.

REFERENCES
A brain arteriovenous malformation is characterised by rapid blood flow from arteries to veins due to the absence of an intervening capillary bed. The venous components develop arterioised walls and often become dis tended. “Nidus” is the term used to describe the tangled mass of abnormal arteriovenous connections. The nidus should be distinguished from the feeding vessels and draining veins. AVMs occur anywhere in the neuraxis but are much more frequent in the brain. Whilst AVMs can be discovered incidentally (15%) they most commonly present with a spontaneous intracranial haemorrhage (85%) or seizures (20%). Occasionally other presenting symptoms occur (e.g. ischaemic deficits, headaches).

The incidence of brain AVMs is around 0.82 to 1.2/100,000 per annum, with a point prevalence of around 18/100,000.3 Many factors including the location, size, pattern of venous drainage, mode of presentation and angioarchitecture may influence the risk of haemorrhage. It is now clear that the natural history of an AVM can be stratified by the presence or absence of risk factors (see below). In population based studies the mortality from an initial AVM bleed was 12-18%.1,3,5 The risk of permanent or disabling neurological deficits after an AVM haemorrhage is substantial. A previous history of haemorrhage, exclusive deep venous drainage and deep location consistently increase the risk of a bleed (see Table 1). A natural history of AVMs Early studies suggested that the risk of an AVM bleeding over a 20 year period of follow-up was in the region of 28-40%.14 More recent studies have evaluated the natural history of AVMs in more detail (Table 1).11,12 Many factors including the location, size, pattern of venous drainage, mode of presentation and angioarchitecture may influence the risk of haemorrhage. It is now clear that the natural history of an AVM can be stratified by the presence or absence of risk factors (see below). In population based studies the mortality from an initial AVM bleed was 12-18%.1,3,5 The risk of permanent or disabling neurological deficits after an AVM haemorrhage is substantial. The Scottish Intracranial Vascular Malformation study reported a modified Rankin score of 2 or less (slight disability or better) in nearly 40% of cases aged <60 years. Around 25% of this age group sustained moderate disability and around 25% had severe deficits with a 12 month mortality of 12%.11 Data on the outcome of subsequent bleeds is not clearly enunciated in large numbers.

Are there any risk factors predictive of haemorrhage?

A previous history of haemorrhage, exclusive deep venous drainage and deep location consistently increase the risk of a bleed.
may be as high as 50%. Other authors dispute the interpretation of the radiological findings and caution against over interpretation of angiographic signs. Aneurysms have been classified as dysplastic, flow-related on proximal feeders, flow related on distal feeders, and intranidal. In patients presenting with a haemorrhage the possibility of a bleed from an associated aneurysm should be considered. Such a diagnosis is based upon correlating CT scan findings with angiographic information. If an aneurysmal bleed has been identified initial treatment should target occlusion of the aneurysm.

### Classification of AVMs

Spetzler and Martin developed a grading scale that has been widely used in describing the characteristics of an AVM. This is based upon scoring 3 parameters that influence the outcome of AVM surgery (see Table 2): size, location and pattern of venous drainage. Size was based upon angiographic measurements. Eloquent regions were described as sensorimotor, language and visual cortex; the hypothalamus and thalamus; the internal capsule; the brainstem; the cerebellar peduncles; and the deep cerebellar nuclei. Deep venous drainage included any lesion with a deep venous drainage component, even if most of the drainage was superficial. Summation of the scores leads to grading of the lesion on a Grade I to V range. Using this scale, Spetzler and Martin showed that the morbidity associated with surgery was very low for grade I and II AVMs, but increased progressively for grade III, IV and V lesions. Indeed, due to the high risks associated with surgery and the diminishing success with other treatment modalities, Spetzler's group advocate that the majority of patients with Grade IV and V AVMs are managed conservatively. Surprisingly, this group reported an annual risk of haemorrhage of only 1.5% per annum in their series of 73 cases. Overall, 25% of the 73 patients sustained a haemorrhage during follow-up. Pollock and Flickinger analysed 220 AVM patients treated with stereotactic radiosurgery and reported that the Spetzler-Martin grade did not correlate with patient outcome. They identified several factors that were predictive of complete obliteration and excellent clinical outcome for SRS treated AVM patients and modeled these into a grading system. Many institutions have validated this grading system. In 2008 the scale was simplified to facilitate clinical application and utility. The factors predicting treatment success comprised AVM volume, age, and location (deep location - basal ganglia / thalamus / brainstem, versus other location - hemispheric / corpus callosum / cerebellar).

### What treatment options exist?

The treatment options available when managing patients with AVMs comprise:

- No intervention
- Surgical excision
- Endovascular treatment
- Stereotactic radiosurgery

The primary aim of any management strategy is to balance the risks associated with conservative treatment against those associated with intervention. If intervention is pursued, total obliteration of the AVM with as few deleterious effects as possible is the prime objective. For large AVMs, combinations of different treatment modalities are frequently utilised to maximise the chances of obliteration, although many Grade IV and V lesions are managed conservatively if total obliteration is considered improbable. The American Stroke Association has issued guidelines for the management of intracranial AVMs.

### Surgical Treatment

Surgical treatment is commonly employed for Spetzler-Martin grade I and II AVMs that have...
presented with a haemorrhage. The translation of imaging information into 3D visualisation is imperative. Studying the architecture of the nidus from angiography helps determine whether the nidus is compact or diffuse. Functioning neural tissue within a diffuse nidus may increase surgical morbidity. A wider resection should be undertaken if the nidus is diffuse to avoid incomplete resection. It is also important to understand that the nidus of an AVM fed by both the anterior and posterior circulation may be underestimated when it is not visualised simultaneously in the selective carotid and vertebral injections. The venous drainage of an AVM must also be studied to help plan surgery.

Operative technique

The craniotomy should be large enough to achieve adequate exposure of the AVM, the surrounding cortex and draining veins. Image-guidance can be useful when planning the flap. An associated liquefied haematoma cavity can provide a useful corridor of access. Meticulous microsurgical “skeletonisation” of the vascular mass from superficial to deep is performed. Reference to the pre-operative imaging is essential when conducting surgery. A trans-sulcal approach is used for sub-cortical AVMs if possible. Premature injury to the venous drainage should be avoided, as outflow occlusion results invariably in catastrophic intra-operative haemorrhage.

The appearance of the vascular nidus is usually unmistakable. Circumferential dissection with meticulous coagulation and division of all feeding arteries must be performed. If these vessels tear, they tend to retract into the surrounding white matter and may be responsible for deep parenchymal haematomas. In eloquent areas the dissection should not stray into the surrounding tissues. In periventricular locations control of the subependymal feeding vessels is important to avoid significant intraventricular haemorrhage. Some of the feeding arteries may supply the AVM en passant. Preservation of such blood supply is important to minimise morbidity. Once the anatomy is clearly established the main feeders can be occluded near the nidus with clips or coagulation and divided.

It is common towards the end of the AVM resection, even after division of the main feeders, that the nidus and draining veins appear increasingly tense. In these situations an arterial feeder is often encountered in close proximity to the vein’s adventitia, especially if it is a deep draining vein. Once this is occluded, the nidus and in particular the draining vein collapses completely and turns dark blue due to the loss of arterialisated blood. This enables complete AVM removal.

Pitfalls, difficulties and their management

The most common mishap is the occurrence of haemorrhage resulting from intra-nidal dissection. If significant haemorrhage occurs, packing the area with haemostatic Surgicel™ and cottonoids plus applying gentle pressure by a fixed retractor on the nidus itself usually controls the situation. This region should be left undisturbed for some minutes whilst dissection proceeds in a different area. Frantic attempts at coagulation in these situations may aggravate the bleeding.

If significant haemorrhage is emanating from the peripheral feeders, attempts to control this by coagulation are usually futile due to retraction of the feeders into the parenchyma. It is advisable to undertake a wider resection margin to regain control of such a situation.

If there is continuous “ooze” from the resected AVM bed, controlled hypotension may be an option. The rationale being that the surrounding vascular bed lacks autoregulation and lowering the blood pressure therefore will decrease the bleeding.

Management of Intracerebral Haematomas Secondary to AVMs

Most neurovascular surgeons favour an initial conservative approach when managing AVM patients presenting with an intracranial haematoma. This permits full angiographic characterisation of the AVM (including after haematoma resolution) and allows brain conditions to be optimised for any subsequent treatments. In addition, neurological deficits often improve significantly in the weeks and months after the initial presentation. Occasionally, an intracranial haematoma requires emergency evacuation due to the effects of raised ICP. In such cases, if the AVM is small and amenable to resection, the haematoma is evacuated and the AVM removed. In cases with underlying complex AVMs, every attempt is made to evacuate the haematoma without disturbing the AVM. If bleeding occurs, suboptimal resection of the AVM may ensue. A decompressive craniectomy with a duretomy alone may be the most prudent option if the AVM is large and deep. Once recovery permits, an angiogram should be obtained and any residual AVM treated to avoid recurrent haemorrhage. Other modalities such as stereotactic radiosurgery may be used in these circumstances if an elective resection appears high risk. In AVM patients with an associated aneurysm that appears to be the culprit for the bleed, urgent aneurysm occlusion by endovascular techniques or surgical clipping is appropriate.

Endovascular Treatment

Endovascular AVM therapy is frequently used as an adjunct to surgical or radiosurgical treatment. Embolisation can achieve volume reduction making large AVMs suitable for surgical or radiosurgical treatments. Focal obliteration of part of the AVM is preferable to diffuse, patchy obliteration in achieving volume reduction. Endovascular treatments aid surgery if they occlude deep feeding vessels. Pre-operative embolisation may also decrease the risk of breakthrough phenomena resulting from disordered autoregulation in the parenchyma surrounding large high flow AVMs.
Endovascular therapy may be used as the sole treatment modality when treating some small AVMs with few feeding arterial pedicles. Endovascular coiling may also be used in the treatment of flow aneurysms. Finally, embolisation can be used as a palliative intervention in patients suffering from venous hypertension secondary to a large incurable AVM.

Endovascular treatment is usually performed using compounds (e.g. N-butyl cyano-acrylate, Onyx, polyvinyl alcohol) that are injected in a controlled fashion into feeding vessels. Technical complications may occur (up to 10% of procedures). AVM rupture is a rare but feared complication from inadvertent occlusion of significant venous drainage channels. The durability of endovascular treatment is not always robust due to re-canalisation of occluded vessels in some cases.

### Stereotactic Radiosurgery (SRS)

SRS was developed by Lars Leksell and has been used as a primary modality for the treatment of AVMs for several decades. SRS causes endothelial cell proliferation and progressive vessel wall thickening leading to AVM obliteration. The timing of obliteration is usually two years or more after the treatment. This delay in effect is influential in determining the optimal treatment modality for any given patient. Pre-treatment MRI and CT images (including CT angiography) can be fused with day-of-treatment stereotactic angiographic imaging to maximise definition of the radiosurgical target (see Figure 1). Radiation is then delivered by a gamma knife source (eg Perfection Gamma Knife, BrainLab, Cyberknife, Accuray). The prime objective of SRS is to eradicate the AVM with high dose radiation effecting obliteration and causing minimal collateral damage to surrounding structures. There are many studies in the literature testifying to the efficacy of SRS treatments. A large pooled series reported complications in 8% of cases, including a death rate of 0.16%. Complications included neurological deficits, seizures and radiocerebral cyst formation. Many of the patients improved with steroid therapy.

The Pittsburgh group has published dose-response curves showing obliteration rates and tissue tolerance according to AVM location. They advise a maximum marginal dose of 25 Gy (with an obliteration rate of 86%) and a minimal marginal dose of 35 Gy.

For patients with very large AVMs, volume staged SRS may be employed. Treatments are delivered to different parts of the nidal several months apart. An alternative approach using hypofractionated stereotactic radiotherapy to the entire AVM has also reported some success in managing these challenging lesions. Such a strategy involves low dose treatment in seven fractions.

### Summary

The management of a patient with an AVM is an individualised pathway that requires the multidisciplinary input of a neurovascular surgeon, a radiation oncologist and a stereotactic radiologist. A neurologist can be a useful addition to the team approach having strengths in dealing with epilepsy and neuro-rehabilitation. In guiding patients, an understanding of the natural history of an AVM is required by all team members who may be advising the patient on treatment options. However, data on the probability of a subsequent bleed, whatever the initial mode of presentation, is difficult to predict with any degree of accuracy. Treatment morbidity and success rates also require accurate prediction to fully inform patients during the pre-treatment assessment phase.

### References


20th International Symposium on ALS/MND
Berlin, Germany, 8-10 December 2009

The International Symposium on ALS/MND is a unique annual event which brings together leading international researchers and health and social care professionals to present and debate key innovations in their respective fields. Taking place over three days, the Symposium features a scientific meeting and a clinical meeting.

Proposed biomedical sessions include:
- Proteinopathies
- Protein regulation and degradation
- Motor neuron biology
- Stem cell biology
- Genetics
- Cell biology and pathology
- Axonal transport and maintenance
- Emerging disease models
- Neuro inflammation

Proposed clinical sessions include:
- Palliative care
- Translating evidence into practice
- Spiritual care
- Multidisciplinary care management
- Cognitive change
- Quality of life/decision making
- Exercise and metabolism
- Respiratory management
- Caregiver support
- Clinical electrophysiology and imaging

For more information and to register, contact the Conference Team by email: symposium@mndassociation.org, or register online at: www.mndassociation.org/symposium.

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The meeting of the American Academy of Neurology


A tale of four treatments
Time was when neurologists were accused of being interested only in diagnosis and not treatment. At best we might disdainfully prescribe steroids, but usually we were content to watch the natural history of the disorder we had so cleverly delineated. That stereotype has been whittled away by anticonvulsants and stroke treatments, of course. But never before have I felt so resoundingly among therapists, rather than diagnosticians, than at this year’s AAN. Four treatments caught my attention particularly.

Rapamycin and tuberose sclerosis
David Franz, of the University of Cincinnati, presented breath-taking data to show that tuberose sclerosis, that nasty genetic disorder causing astrocytomas, seizures, developmental delay, behavioural problems and skin abnormalities, may be treatable! This story has emerged from understanding the molecular pathogenesis of TS. The two causative genes, TSC1 and TSC2, which encode for the proteins hamartin and tuberin respectively, both normally act to inhibit mTOR. mTOR is also the target of rapamycin and its derivatives, so the obvious question is: can inhibition of mTOR compensate for the lack of hamartin or tuberin in TS? Franz’s group had previously shown that it does: in 2006 reporting that it shrinks astrocytomas in TS. Now he reported on a trial of RAD001, a variant of rapamycin, in 28 patients. On MRI, the size of the subependymal nodules reduced. And MRI spectroscopy suggested that the astrocytomas in these patients seemed to change towards a chemical profile more like subependymal nodules. Clinically, patients’ EEGs and seizures vastly improved. And there was even evidence of a reversal of cognitive impairment.

Deep brain stimulation and depression
Helen Mayberg, from Emory University, Atlanta, Georgia, is a neurologist who has stepped over the abyss to psychiatry and taken with her functional imaging and DBS. She has been championing DBS for depression for some years. Her thinking arose from the demonstration –through functional imaging– of overactivity of the subcallosal cingulate gyrus in depression; and that successful treatments of depression (drugs and ECT) reduce this overactivity. So she has performed two uncontrolled studies of DBS stimulation of the subcallosal cingulate gyrus in depression. In the larger, of 20 patients followed for one year, reported in Biological Psychiatry, she reports a 55% response. Given that these patients were regarded as treatment-resistant and chronically disabled, that seems pretty good to me. More rigorous trials are planned. What most struck me was her report of the effect of the treatment. It seems that DBS of the subcallosal cingulate gyrus specifically reduces the negative aspects of depression. And it does so very rapidly. As Mayberg has said in an interview: “In general, patients described a sudden disappearance of some negative, which was more often than not a change in a visceral state: a sudden sense of intense calm and relief, clearing of mental heaviness, lifting of a black cloud, the disappearance of a void, fading of a brooding dread in the pit of the stomach, are some examples. Of interest, the turning off of these negative sensations was followed almost immediately by a change in attention and interest with objective evidence of increased spontaneous speech and motor speed.”

Pills to treat multiple sclerosis
The results of two phase 3 trials of oral treatment of multiple sclerosis were reported. Both trials were large, involving over one thousand people with relapsing-remitting multiple sclerosis, who had little disability, tested with two different doses of the new drug. We can expect to see both drugs emerging into the clinic in the next 2-3 years.

Gavin Giovannoni, from London, presented the final results of the CLARITY study of cladribine (n=1326). Cladribine is taken in quite a unique way: 1 or 2 tablets for 4-5 days in the month, for 2 to 4 months in the year! In other words, a patient takes literally a handful of tablets a month. In this trial, it was compared with placebo over 96 weeks. Cladribine reduced the relapse rate by 55-58% and reduced the chance of getting disabled by 31-33%. 2% got a reactivation of shingles and there were four cancers in those taking cladribine (n=884), with none in the placebo arm.

Jeff Cohen, from Cleveland, reported the final results of the TRANFORMS study of fingolomid (n=1292). Fingolomid (which is sometimes called FTY720) is taken as a pill once a day and was compared over one year with beta-interferon. Fingolomid was more efficacious at reducing the relapse rate (on fingolomid there were 49-50% fewer attacks) but disappointingly it did not reduce the rate at which people acquired fixed disability. There were some slightly worrying side-effects: there were two fatal viral infections (transmural varicella zoster and herpes encephalitis), 1-2% incidence of cardiac AV block and 8 skin cancers (compared to 2 on interferon).

These new drugs potentially fit into the category of being convenient, reasonably effective with real, but low-level side-effect concerns. It is likely that they will steal a sizeable share of the interferon market, leaving that drug for those with mild disease or people who want the almost risk-free interferon.
Non-Motor Symptoms in Parkinson’s Disease: What’s New? Fourth Meeting of the UK PD Non Motor Group

The fourth annual meeting of the UK Parkinson’s Disease Non-Motor Group (PDNMG) was the largest yet, with over 200 delegates attending the Royal Society of Medicine, London. This in part reflects the continued and increased recognition of Parkinson’s Disease (PD) as a non-motor disease as much as a motor one.

After a brief introduction by PDNMG Chairman and Meeting Organiser, Prof KR Chaudhuri (UK), all delegates attended lectures on Olfaction and Sleep in PD (Prof H Reichmann, Germany) and Imaging of NMS in PD (Prof D Brooks, UK).

Bilateral and invariable impaired olfaction is now a recognised early NMS, and occurs in 70-100% of all PD patients independent of medication. Earlier diagnosis based on olfactory symptoms, may be pivotal to treatment choice and prognosis.

Early idiopathic olfactory dysfunction has also been shown to coincide with abnormalities on parenchymal sonography of the substantia nigra (SN) and Beta-CIT SPECT imaging. People identified as suffering from olfactory dysfunction are five times as likely to subsequently develop PD within four years, compared to normosmic individuals. Olfaction may thus have utility as a screening tool to detect those at high risk of developing PD or ‘preclinical’ PD.

Although it appears that dopamine modulates executive function and sleep, there is no correlation between striatal dopamine and fatigue symptoms. Instead, decreased dopamine in the right insular and ventral thalamic connections are correlated with fatigue. Dementia is associated with decreased parieto-temporal metabolism, as well as decreased frontal lobe dopamine storage and cortical cholinergic function. Although decreased serotonin is seen in PD with depression, Prof Brooks suggested that this symptom relates more to noradrenaline and limbic dopamine concentrations.

Cardiac MIBG scans, imaging the sympathetic nervous system, have shown a post-ganglionic deficiency in patients with PD. Recent evidence suggests that cardiac MIBG scans of patients with REM Sleep Behaviour Disorder (RBD) show the same pattern of autonomic dysfunction, further substantiating RBD as a pre-motor NMS in PD. This is reflected by reduced uptake seen on DAT and PET imaging in RBD patients, in the same pattern as with patients with PD alone.

The next lectures, given by Prof P Jenner (UK) and Prof A Schapira (UK), looked at non-dopaminergic therapies in PD, and the question of when to start treatment in PD, respectively.

Use of non-dopaminergic treatments to treat PD is widespread. The wide range of transmitter and brain areas altered in PD in addition to nigrostriatal, dopaminergic systems, emphasises the importance of taking a global approach to management. Prof Jenner pointed to the relative success of toxin-based models such as the 6-OHDA lesioned rat and the MPTP treated primate for the introduction of new therapeutic strategies for the motor symptoms of PD. However, the development of treatment for NMS has been slow, e.g. Sarizotan (a 5HT1A agonist), and the effects of non-dopaminergic drugs in models do not translate into clinical efficacy. Perampanel, an AMPA-type glutamate receptor antagonist, has also failed in recent trials. Similarly, there has been little real progress in treating NMS in PD as a group, with clinicians still having to address each symptom individually.

Prof Jenner outlined how none of the currently used models reproduce all the key features of pathogenesis specific to PD. Rather than waiting for models based on gene-gene/toxin interactions in familial PD, he discussed methods to mimic Lewy Body formation including using injection of lipopolysaccharide into the SN to initiate inflammation, peroxynitrite formation and cytokine release, and using proteasomal inhibitors such as PSI and epoxymycin. However the ultimate goal is modifying disease progression and identifying at risk populations to target with neuroprotective strategies.

‘When’ to treat is as perplexing a question as ‘how’. Due to the heterogeneity of PD, pre-symptomatic time is variable, and clues to diagnosis, whether clinical, pathological, imaging-based or genetic, are crude estimates. The long ‘pre-symptomatic’ period, where there is evidence of dopaminergic and nigrostriatal cell degeneration without motor symptoms, must be exploited. To explain this, Professor Schapira supported a ‘theory of compensation’ – other parts of the brain compensate and therefore correct early basal ganglia dysfunction.

Treatment of PD appears to have short-term side effects and long-term complications. However, evidence based reappraisal appears to recommend early symptomatic relief and improved quality of life, despite the inevitable undesirable effects of treatment, such as wearing off. Treatment-naïve patients have lower quality of life scores than those receiving treatment, and early intervention should become common practice. More so, recent evidence from DATATOP, ELLDOPA, ADAGIO, and TEMPO studies even suggest better outcomes, perhaps due to a neuroprotective mechanism, for PD patients started on early treatment.

The morning’s second session focused on the issue of sleepiness and parasomnias in PD. Excessive daytime sleepiness (EDS) is a frequent and disabling symptom of PD. It can result from lesions in arousal systems causing abnormal night time sleep, or as a side effect of dopaminergic treatment. Patients taking dopamine agonists are three times as likely to suffer from EDS than those on Levodopa alone. Dopamine related sleepiness occurs most often at the peak of dopamine serum concentration. However, there is only weak evidence that prolonged-release dopaminergic treatment is less sedative.
Dr I Arnulf (France) reviewed promising data on sodium oxybutynate, an anticholinergic. Small trials have shown significant decreases in Epworth Sleepiness Scale scores in patients with PD and EDS. Phase II studies have also recently shown histamine-3 receptor antagonists to reduce EDS and motor symptoms.

Prof C Trenkwalder (Germany) demonstrated the difficulty of diagnosing RBD. Although caregiver history is essential, objective evidence from polysomnography is the gold-standard device for confirming this parasomnia. RBD can change the motor pattern during sleep, compared to daytime movements. It is also typical for vocalisation to be combined with motor acting, often in the extremities.

An individual with idiopathic RBD has a higher risk of developing Lewy Body Dementia (LBD) or PD. Prof Trenkwalder suggested that a flip-flop switch, which normally controls the onset of REM-Sleep, is dysregulated in PD. Lesions in the mesopontine tegmen-tum may be responsible.

Despite its debilitating effects on the quality of life of patient and carer, there is a deficiency of clinical trials looking at the treatment of RBD. Prof Trenkwalder echoed widespread recommendations of clonazepam or melatonin, and called for controlled trials comparing these treatments and strategies.

The final speaker of the session, Prof CJ Fowler (UK), discussed bladder dysfunction in PD. These problems are notoriously difficult to treat, and often associated with advanced PD. It is essential that any treatable urological cause of bladder dysfunction is first excluded. Prof Fowler stressed the importance of selecting anticholinergic drugs that do not affect central M1 receptors and do not cross the blood-brain barrier. Botulinum injection directly into the bladder wall is an exciting, albeit challenging, new treatment that can prevent hyperreflexia, urgency and overactivity.

In a series of ‘snapshot reviews’ Prof Chaudhuri highlighted first the need for more research into visual dysfunction in PD. A range of visual problems may be seen in patients, ranging from retinal defects leading to contrast sensitivity or diminished blue-green colour vision, to motor defects presenting as diplopia, hypometria or dyskinasias. These NMS may be again part of a pre-motor complex, and may be best recognised using the Farnsworth-Munsell 100 Hue Test. There is a paucity of evidence that suggests that colour discrimination in PD patients is improved after ingesting levodopa.

Prof T Renton (UK) briefly evaluated trigeminal pain in PD. Pain appears to be both profound and prognostic. Oculofacial pain (OFP) is extremely debilitating, and is associated with headaches, burning mouth syndrome, temporo- mandibular joint pain, and compromised trigeminal reflexes. Research currently being conducted by Prof Renton hopes to better identify the aetiology of OFP in PD.

The afternoon’s lectures took on a new format once more, with delegates splitting into three symposia addressing therapy in advanced disease, psychiatric issues and dopamine agonists, and comorbidities and quality of life in PD.

Duodopa can have a powerful effect on motor function, with patients seeing a 70%-90% reduction in off-time, and reduced dyskinesia. More so, unpublished data suggests that pump therapies reduce NMS by 55%, particularly improving perception, and alleviating urinary dysfunction and depression. This needs to be offset against device-related problems and cost.

Deep brain stimulation (DBS) also improves motor symptoms and quality of life, although its effects on NMS and neurocognitive side-effects are less well-defined.

Psychiatric issues, particularly depression and compulsive behaviour, dominated discussion in the second symposium. Regarding the treatment of depression in PD, tricyclic antidepressants (TCAs) may be more effective than SSRIs, whilst pramipexole has significant anti-depressive properties. The third and final symposium reviewed new developments in determining comorbidities of PD and their effects on health-related quality of life (HRQoL). Trials currently underway may provide a solution to constipation using botulinum toxin. The importance of checking the mouth for signs of oral infection, to prevent aspiration pneumonia, was emphasised for patients with drooling oral infection, to prevent aspiration pneumonia. Memantine, a non-competitive NMDA receptor antagonist, may be more effective than standard memantine in patients. The Mini Mental State Examination is not sensitive to the Addenbrooke’s Cognitive Examination (ACE-R), the Montreal Cognitive Assessment, and the Neuropsychiatric Inventories (including NPI) were recommended as screening tools.

The wide range of transmitters and brain areas altered in PD, in addition to nigrostriatal, dopaminergic systems, emphasises the importance of taking a global approach to management
The 17th meeting of the International Society for Magnetic Resonance in Medicine (ISMRM) again provided an excellent mix of cutting edge technological advance in imaging coupled with their application to all specialities of medicine. Stationed in the glamorous location of Honolulu, the North American organisers laid on a huge event with over 850 oral presentations, 2242 traditional posters and 1601 multimedia e-posters. It appears the organisers have (perhaps not surprisingly!) an affinity for this location as it was the second time the conference was held in Hawaii in seven years.

Preceding the main meeting itself were two days of educational courses which give a thorough rundown of the various imaging techniques starting (very usefully) at a basic level and becoming ever more complex. The meeting itself has a fine line to tread to maintain a balance in trying to provide enough clinically based presentations to keep the clinician happy in addition to papers reporting, for example, how a minute echo time change coupled with a different gradient spoiler can help improve a new echo planar imaging sequence (very much more for the benefit of the physicists, I suppose). To a large degree this balancing act is achieved and there was much for a neurologist (not just one with an imaging research background like myself) to find of interest. It was also noticeable that there were a large number of presentations on a number of conditions in addition to the usual large body of work on multiple sclerosis (MS).

Now for the presentations I found of most interest. Well it is amazing how this technology is moving on, and faster and more refined magnetic resonance imaging (MRI) sequences are becoming a reality allowing increased brain coverage with greater resolution in shorter times. This increases measured signal and reduces artefact and with suitable adjustments to various parameters tissue types can be differentially viewed to look for specific pathology. This was elegantly shown in a presentation by SCL Deoni describing a new sequence mcDESPOT (acronyms were very popular at the meeting!) which uses multiple radio frequency pulses and is easy to implement and allows effective suppression of fat, including that of lesions, in multiple sclerosis. The apparent disparity between lesion loads as viewed on MRI with a patient's actual disability has long been a frustration for both neurologist and clinical trial designer alike. The suggestion here and from other previous publications is that although not all brain lesions are predictive of clinical state, some might be and therefore with appropriate modelling MRI may yet give useful information for treatment selection for example, how a minute echo time change coupled with a different gradient spoiler can help improve a new echo planar imaging sequence (very much more for the benefit of the physicists, I suppose). To a large degree this balancing act is achieved and there was much for a neurologist (not just one with an imaging research background like myself) to find of interest. It was also noticeable that there were a large number of presentations on a number of conditions in addition to the usual large body of work on multiple sclerosis (MS).

There were also some excellent presentations on neurodegenerative disease and movement disorders also. A number of presentations looked at the application of tractography and functional MRI in these conditions, suggesting metabolic abnormalities in areas of the brain specific to these disorders. In addition, Zhang et al demonstrated different MR perfusion and diffusion characteristics of Alzheimer's disease and frontotemporal dementia, potentially aiding specificity of diagnosis of these disorders.1

The poster section contained a vast amount of information and selectivity was the order of the day to prevent an overload of information. It was interesting to note how widespread research is now in implementing imaging to study virtually any neurological disorder one can think of.

Another major part of the conference is the study group meetings in which further selected papers are presented to specific interested delegates. One particularly enlightening session was the white matter study group which had presentations of what would be the ‘ideal’ group of sequences to visualise white matter disease (in other words MS for the purpose of the meeting) in under an hour. The apparent discrepancy between new and clever sequences and everyday clinical practice was clear, and of particular interest to me. In all the years that quantitative imaging has been with us it is disappointing how infrequently it is used in clinical neurological practice, not just in the United Kingdom. Newer and better sequences have been devised but how implementable are they or will they be in day to day practice? The appeal in the study group meeting for more involvement from clinicians was relevant. There is a danger that in amongst all the advance made in MRI technology by physicists (i.e. non-clinicians) we lose sight of what a lot of this is for (i.e. clinical benefit of patients).

Hence, it is important for clinicians, not least neurologists, to participate in the development of MR techniques so that clinically meaningful questions can be answered. This is not said to undermine the excellent research that has been and is being carried out. Using imaging models the understanding of disease pathogenesis and diagnosis and monitoring of conditions such as MS and others has undeniably improved. However, there is still, I feel, a gap that needs to be bridged in order for such techniques to be more widely used in patient management. Next year’s meeting is in a less tropical but more accessible destination (Stockholm), and so long as one applies a degree of selectivity to concentrate on clinical presentations the ISMRM meeting is well worth attending.

REFERENCES
Valproate: bad news for the foetus

This multicentre UK and USA study recruited over 300 pregnant women taking monotherapy with common antiepileptic drugs, phenytoin, carbamazepine, lamotrigine and valproate. They evaluated these women at baseline and found them to be similar for maternal IQ, epilepsy severity, folate use and gestational age at birth. For children exposed in utero to phenytoin, carbamazepine or lamotrigine, the main determinant of IQ at 3 years of age was maternal IQ. However this relationship was broken in the women taking valproate whose children suffered a dose-related reduction in IQ. On average, children exposed to valproate had an IQ score 9 points lower than those exposed to lamotrigine, 7 points lower than those exposed to phenytoin and 6 points lower than those exposed to carbamazepine. These results were statistically significant but there was no significant difference between the other drugs. A further analysis will be made when the children are six. The authors point out that these drugs are used frequently for indications other than epilepsy and, although this study was only in women with epilepsy, they would expect the results to be similar for other groups. This study provides convincing evidence of the dangers of valproate to the foetus over and above obvious major malformations.

They will cause increasing headaches to those of us who find ourselves with a limited choice of medication in patients with generalised epilepsy, especially juvenile myoclonic epilepsy. When do these problems arise? Is it safe to start valproate in the 2nd-3rd trimester for patients where no other drug will do? I guess we shall never know. Do you undertreat the mother to save harm to the foetus? It must be remembered that in one confidential enquiry into maternal mortality the risk of maternal death in women with epilepsy was ten times expected. Treating mothers remains the first priority and sometimes the risks may be unavoidable. What about other drugs? Can one justify giving levetiracetam? The balance of the hope of the future against the devil you know. A balanced decision needs to be made with each mother prior to conception. This new knowledge is crucial but the decisions just get harder.

LEARNING: Adult hippocampal neurogenesis — a phenomena looking for a function?

The role of adult neurogenesis in the dentate gyrus of the hippocampus is an area of intense debate. The fact that new neurons are born in this area of the mature CNS is not in doubt, but the question is what do these cells do once they have matured and been incorporated into new circuits? A couple of papers have added to the literature in this area.

The first by Kim et al investigated the consequences of preventing the death of these cells using a BaxKO mouse. Bax is pro-apoptotic and its absence prevents programmed cell death in newly born neurons. Using this model (which of course assumes that most new neurons born in the dentate gyrus are lost through apoptosis), they found that there was a readjustment of synaptic connections with impairments in both electrophysiological and behavioural hippocampal function. In other words, if a population of newborn neurons in the hippocampus is an area of intense debate. The fact that new neurons are born in this area of the mature CNS is not in doubt, but the question is what do these cells do once they have matured and been incorporated into new circuits? A couple of papers have added to the literature in this area.

This is consistent with the study of Trouche et al who followed the fate of newly dividing (BrDU-positive) neurons in terms of their integration and functional abilities. In this study the authors used the activity-dependent protein Zif268 in combination with high resolution confocal imaging and co-labelling with BrDU and the neuronal marker NeuN, to follow the fate of cells in the context of controlled behaviours involving the water maze. They found that these newly born neurons are recruited into neuronal networks involved with spatial memory and that once incorporated are involved in the updating and strengthening of that memory and thus contribute in part to its durability. Thus these cells are recruited under experience-specific conditions and store those conditions as part of their contribution to the spatial memory of the hippocampus.

Quite how this information is then used, updated and modified in the long term is not clear, but this and the other study of Kim et al does highlight that these new neurons do make a significant contribution to some aspects of hippocampal memory.


SPINAL CORD INJURY: Too much of a good thing

It seems obvious: if physiotherapy improves the outcome after spinal cord injury and so does a drug, then combining the physio and the drug should be better still, shouldn’t it? Well, no...

The drug in question is the antibody to Nogo-A, the neurite growth inhibitor, which is in human trials. In this paper, the discoverer of Nogo-A, Martin Schwab and colleagues, investigated the efficacy of step training or intrathecal delivery of an anti-Nogo-A antibody on the recovery of rats from a surgical cord lesion at T8. The outcome measure was stunningly simple and beautifully illustrated: the animals’ gait was analysed by 3-D video recording using four cameras monitoring 5 reflective markers on each hindlimb. After a spinal cord injury, the animals’ steps are irregular and disordered. This is restored to near-normal by the antibody to Nogo-A. Locomotor training has a less dramatic, but nonetheless clear effect in regularising the gait. But the combination of antibody and training leads to more dragging and more irregularity of gait than with the antibody alone. In other words: the training has interfered with the effect of the antibody. By far the best group were those animals who had received the antibody and been left to ‘self-Healin’ in their cages.

As you might expect from these careful scientists, the paper is brimming with data and careful analysis. But the bottom line is that they cannot work out why these two treatments of spinal cord injury should interfere with one another. So the obvious is not always right and we need to be careful about combining treatments of spinal cord injury... and the prospects of anti-NogoA antibody being efficacious seem to increase with each study. Roll on the clinical trials. – AJC


BRAIN INJURY: Rise and shine

The recent short lived excitement surrounding the potential for zolpidem to “waketh” patients in a minimally conscious state demonstrated the power that this concept exerts on the public imagination. Faced with the seemingly hopeless situation of a patient with a severe brain injury who will not wake up, there is often an overwhelming need to “try something” to facilitate a return to consciousness. Because patients and their brains are frustratingly heterogeneous, no single approach or treatment has yet been shown to reliably offer itself as a therapeutic option with a consistent evidence base.

This case report describes a young man in a minimally conscious state following a brain injury sustained in a road traffic accident. The authors describe an initial 100 day period during which he received trials of methylphenidate followed by bromocriptine without evidence of increased wakefulness. Both agents have been previously reported as having an effect on consciousness. Methylphenidate promotes wakefulness and alertness in the face of the need to present and purposeful attention. The higher efficacy of methylphenidate compared to bromocriptine, despite both agents having similar efficacy scores in animal studies, suggests that methylphenidate is more efficacious in the face of increased wakefulness. Methylphenidate has been shown to exacerbate the symptoms of a patient with a brain injury. The authors therefore conclude that methylphenidate is not appropriate for this patient. Methylphenidate has been shown to potentiate the effects of other drugs, such as anti-depressants. However, the recent study by the group of Mark Tuszynski (who brought us a trial of NGF for AD) has investigated the extent to which NGF delivered to the entorhinal cortex can restore hippocampal function in aging, diseased and lesioned animals. The entorhinal cortex (ECx) provides the major input to the hippocampus via the perforant pathway and the integrity of this system is needed for some aspects of normal learning and memory. BDNP is anterogradely transported along this pathway and as AD pathology involves this part of the brain early on in the disease course, it would be logical to see if manipulating BDNP levels affects the functional capabilities of the system. The team therefore explored this to show that:

• LentiBend (LV-BDNP) delivery to the ECx of the APP transgenic mouse models of AD ameliorated some hippocampal dependent behavioural deficits with anatomical and microarray profile correlates of cell rescue without there being any effect on pathology.
• Bilateral infusion of recombinant BDNP into the medial ECx had similar effects on aged rats through restoring age related deficiencies in synaptic integrity mainly through an action on the Erk signalling pathway.
• BDNP did not only rescue neuronal atrophy and synaptic loss but also has the capacity to rescue cells “lesioned” in vitro by beta-amyloid and in vivo following perforant pathway transections and LV-BDNP delivery into the ECx.
• The same was then done in non-human primates. Here the perforant pathway was again lesioned and LV-BDNP injected into the ECx with the rescue of cells.
• Finally, the same viral vector delivery system was used to rescue the aged ECx in non-human primates at both the anatomical and functional level.

These series of experiments therefore suggest that BDNP may help in rescuing aspects of hippocampal function which in turn has implications for the treatment of disorders such as AD. The translation of this work to the clinic is though not straightforward given (i) the extensive pathology seen in all neurodegenerative disorders including AD, (ii) the problems of long term targeted delivery of growth factors and (iii) the risk of the patient developing neutralising antibodies to the growth factor. Nevertheless, studies such as this rekindle the hope that growth factors could be useful in treatment of neurodegenerative disorders of the CNS. – RAB


BRAIN REPAIR: Repairing the brain in Alzheimer’s disease: a role for BDNP?

BDNF was the second neurotrophic factor to be discovered after NGF and has long been known to be involved in CNS plasticity especially in the hippocampal complex. As a result it has been a favoured therapeutic target as it may improve memory and cognition in disorders such as Alzheimer’s Disease (AD). This ability to use BDNF for therapeutic benefit is not just restricted to exogenous delivery (see below) but it could also be endogenously upregulated by environmental enrichment and some drugs, such as anti-depressants. However, the recent study by the group of Mark Tuszynski (who brought us a trial of NGF for AD) has investigated the extent to which BDNF delivered to the entorhinal cortex can restore hippocampal function in aging, diseased and lesioned animals. The entorhinal cortex (ECx) provides the major input to the hippocampus via the perforant pathway and the integrity of this system is needed for some aspects of normal learning and memory. BDNP is anterogradely transported along this pathway and as AD pathology involves this part of the brain early on in the disease course, it would be logical to see if manipulating BDNP levels affects the functional capabilities of this system. The team therefore explored this to show that:

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[1] Happy Birthday to Rita LeviMontalcini, one of the discoverers of NGF who was 100 years old this April.
Involving patients in decisions about prescribed medicines and supporting adherence – NICE clinical guideline 76 - Jan 2009

In a new guideline NICE have stated that between a third and a half of all medicines prescribed for long term conditions are not taken as recommended and this may represent a loss to patients, the healthcare system and society. Adherence presumes an agreement between prescriber and patient about the prescriber’s recommendations. Non adherence may limit the benefits of medicines, resulting in lack of improvement, or deterioration, in health. Non adherence should not be seen as the patient’s problem. It represents a fundamental limitation in the delivery of healthcare. A no blame approach is required to encourage patients to discuss non adherence and any doubts or concerns they have about treatment. A patient centred approach encourages informed adherence. The treatment and care should take into account patients’ needs and preferences.

In epilepsy the consequences of non-adherence can be significant. Part of the answer may be to use patient friendly options that allow a simple once daily nighttime dose with an AED that is easy to swallow.

Further information on the use of Episenta (controlled release sodium valproate) may be obtained from Tel: 01892-506958. www.nice.org.uk/Guidance/CG76

Zeiss LSM 700 Confocal Microscope sets New Standard

Carl Zeiss has introduced the LSM 700 Laser Scanning Microscope, which uses proven modules from the world’s largest range of fluorescence and laser scanning microscope systems to offer radical flexibility in both application and system structure. The LSM 700 may be combined with a large number of microscope stands to deliver innovative image analysis solutions with exceptional sensitivity and quality tailored to the personal requirements of each user.

The LSM 700 guarantees high efficiency in the detection even of weak fluorescence signals. Key elements of the optical system include the beam path design with its maximum optical precision and the uncompromising concentration on the essentials, the beam combiner system for extremely accurate beam coupling and superimposition, the beam splitter with continuous and loss-free splitting of the light spectrum, and an extremely stable pinhole.

The LSM 700 is ideally suited to both individual workstations and user groups. In addition, the system’s small footprint makes it suitable for small rooms. Operation is simple and easy and the intuitive design allows even first-time users to image successfully unaided. The ZEN 2009 software allows users to set-up complex methodologies quickly and displays a clear overview of the experiment at all times.

For more information E.micro@zeiss.co.uk

Elekta chosen to deliver sophisticated Brain Mapping Technology to The Mind Research Network

The Mind Research Network (MRN) will bring world-leading technology to Albuquerque, with the acquisition of an Elekta Neuromag® a device for non-invasive measurement of brain activity using Magnetoencephalography (MEG) technology.

MRN has been utilising MEG technology to study brain function and disorders for approximately the last five years; however, the organisation will upgrade to the Elekta Neuromag MEG system in early 2009, allowing researchers to record human brain activity better and more accurately than before.

“When looking to replace our current MEG system, we chose Elekta because we felt that their data collection software and analysis and archiving of records would meet all of our research and clinical needs,” says Michael Weisend, Ph.D., director of MEG/EEG Core at MRN, and expert in investigating and specifically defining the location of epileptic seizures.

“We are funded to study a variety of neuroscience areas that will exploit the Elekta Neuromag’s capability,” says Weisend. “Currently, we investigate the fundamental mechanisms of learning and memory in healthy individuals, as well as those with brain-based disorders such as traumatic brain injury, epilepsy, drug addiction, and schizophrenia."

For further information
E. Michael.enwall@elekta.com

Invitrogen develops new technology to promote safer stem cell therapies

Invitrogen, a division of Life Technologies, has announced a new technology to enable the development of safer stem cell therapies. Dynabeads® SSEA-4 addresses a key challenge in translational research, by separating undifferentiated stem cells from those that are differentiated. Scientists from Invitrogen and the Buck Institute for Age Research, located in Novato, California, collaborated in developing this solution that depletes greater than 99% of undifferentiated human embryonic stem cells from differentiated populations.

“Human embryonic stem cell research is one of the fastest growing areas in cell biology. A key issue for translational stem cell researchers is the ability to reliably identify and isolate undifferentiated hESCs, which are not considered as suitable for transplantation as those which are differentiated, because of the potential of unregulated cell growth. Their objective is to obtain pure and homogenous cell populations, which will help to ensure the safe development and manufacturing of therapeutics. Dynabeads® SSEA-4 achieves this by utilising magnetic beads that latch onto a common marker on embryonic and induced pluripotent stem cells, removing them from a culture in less than 45 minutes. These leaves behind highly pure and differentiated cells that are unaffected by the Process. This is a significant advancement over typical protocols, which leave a considerable amount of contaminating cells behind.”

For more information see www.invitrogen.com
Carl Zeiss introduces Dual Camera Module to capture Fast Intracellular Processes

Carl Zeiss has launched a Dual Camera Module for its AxioVision image analysis software to improve the imaging of fast intracellular processes. The new software is aimed at life scientists, such as cell biologists, virologists and physiologists, and allows the simultaneous acquisition of images from two cameras and their synchronisation within nanoseconds.

Combined with two identical cameras, the Dual Camera Module will control all aspects of their operation and enable camera parameters, such as exposure time or contrast, to be set independently. Due to the simultaneous capture of two separate images, the software allows users to capture more images in any given timeframe. Furthermore, artifacts that can occur in the sequential capture of double-stained structures using a single camera are prevented, as are errors in ratiometric measurements of two emission channels.

The capture of two different wavelengths in two channels will be especially valuable in the measurement of emission ratio imaging (Indo-1), fast FRET examinations, and the imaging of cellular transport processes in cell cultures, tissues or organisms. It will also be an important asset in the simultaneous imaging of tissue and cell structures using infrared transmitted-light techniques, such as IR-DIC and fluorescence excitation. The latter is a key requirement for electrophysiological work in neurobiology.

For more information E. micro@zeiss.co.uk

Streamlining microbiology workflows with PREVI™ Isola

The PREVI Isola automated specimen and agar plate management system from bioMérieux offers clinical microbiology laboratories new flexibility for routine processing of samples, allowing resources and expertise to be concentrated where they are needed most.

The PREVI Isola features revolutionary streaking technology which maximises colony isolation through pressure-controlled contact with the agar surface during inoculation, and uses the same quantity of inoculate every time to standardise results.

The PREVI Isola can process different sample and container types at a rate of up to 180 plates per hour, saving time and increasing throughput and integrating effortlessly into your laboratory’s workflow. The PREVI Isola also assists with clinical pathology accreditation by eliminating cross-contamination between samples, and provides traceability through automated barcode labelling.

It is particularly suited to high throughput applications where negative results are prevalent, such as MRSA or urine specimen screening. Automation of these essential, yet tedious, front-end processes will change your laboratory workflow, offering the flexibility to improve patient care while containing costs.

For more information see www.biomerieux.com

Real-time Measurement of Physiological Parameters in Living Cells

A new software module from Carl Zeiss enables real-time image capture and measurement of physiological parameters in living cells both during microscopic observation (online) and afterwards (offline). The AxioVision Physiology software captures the images and measurement data together with any changes in experimental parameters.

The AxioVision Physiology Module is ideal for cell biologists, neurobiologists, physiologists and electrophysiologists. Applications include the determination of calcium concentrations or pH values through ratiometric calculation of fluorescence images after the addition of indicators, such as Fura-2 or Indo-1. The software also offers users an easy and reliable way to measure the change in fluorescence intensity over time of fluorescent proteins and for FRET analysis of protein interaction.

The Physiology Module integrates totally with Zeiss microscopes, enabling users to plan highly flexible experiments. In addition to the monochrome AxioCam cameras from Carl Zeiss, cameras from other manufacturers such as Hamamatsu or Roper are supported. Two synchronously controlled AxioCam cameras are also supported when combined with the Carl Zeiss Dual Camera Module.

For more information E. micro@zeiss.co.uk

Elektta And Nucletron combine forces to market leading software

Elekta and Nucletron have reached an agreement to market and license Elekta’s software system MOSAiQ®. Nucletron’s existing Oncentra® Visir and Oncentra® Information Management product lines. Nucletron will focus efforts on innovations in brachytherapy and treatment planning for external beam.

MOSAiQ is an Oncology Information Management system that features an image-enabled electronic medical record fully integrated with comprehensive administrative management functionality that provides workflow automation designed specifically for the oncology specialty. Supporting multi-vendor, multi-disciplinary, and multi-site organisations, it unites diverse systems and ensures that all information about a cancer treatment is easily accessible throughout the entire treatment process.

For further information E. Danielle Davis, ddavis@rosecomm.com

If you would your news to feature in ACNR, please contact Rachael Hansford, T. 01753 860168; E. rachael@acnr.co.uk
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. Data suggests safety and efficacy in adults. Children (<12 years) Not recommended. Elderly No specific data. 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 urticarial reactions. 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. Adverse events should also be reported to Teva Pharmaceuticals Ltd on telephone number: 01296 719748.

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. >1%: Nausea, anxiety, rash, back pain, chills, face oedema, vomiting, skin disorders, lymphadenopathy, tremor, eye disorder, vaginal candidiasis, weight increased. Rarely: Anaphylactoid reactions. Please refer to the SPC for a full list of adverse effects.

Pregnancy and lactation – Not to be used in pregnancy. Consider contraceptive cover. No data on excretion in human milk.

Overdose – Monitor, treat symptomatically.

Pharmaceutical Precautions – Store Copaxone in refrigerator (2ºC to 8ºC). If the pre-filled syringes cannot be stored in a refrigerator, they can be stored at room temperature (15ºC to 25ºC) once for up to one month. Do not freeze.

Legal Category – POM.

Package Quantity and Basic NHS Cost – 28 pre-filled syringes of Copaxone: £524.31.

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: March 2009

Date of Preparation: March 2009 C0309/566a

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk.