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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

In this issue

DESITIN
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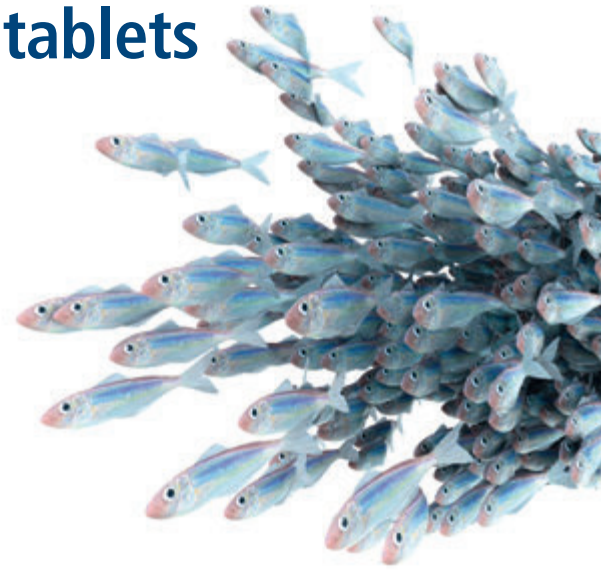

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Desitrend® (levetiracetam) Abbreviated Prescribing Information. Prescribers should consult the Summary of Product Characteristics before prescribing Desitrend®. Levetiracetam available as Desitrend® 250/500/1000 mg coated granules in sachet. Indications: Monotherapy of partial seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy. Adjunctive therapy of partial seizures with or without secondary generalisation in adults, adolescents, children and infants from 1 month of age with epilepsy. Adjunctive therapy of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy. Adjunctive therapy of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy. **Dosage and Administration:** *Monotherapy:* Adults and adolescents ≥16 years: Starting dose 250 mg twice daily increasing to 500 mg twice daily after two weeks. Dose can be further increased if required by 250 mg twice daily every two weeks to a maximum of 1500 mg twice daily. *Adjunctive therapy:* Adults and adolescents (12 to 17 years) weighing ≥50 kg: Initial dose 500 mg twice daily. Dose can be increased, if necessary, up to 1500 mg twice daily. Dose changes made in 500 mg twice daily increases or decreases every two to four weeks. Take orally, swallowed with a sufficient quantity of liquid, with or without food. Daily dose in two equally divided doses. Elderly: Adjust dose in renal impairment. Renal impairment: Adjust dose according to renal function. Hepatic impairment: severe impairment reduce daily maintenance dose by 50% when CLcr <60 ml/min. Children: Prescribe the most appropriate pharmaceutical form and strength according to age, weight and dose. Coated granules not adapted for use in children under 6 years. Available dose strengths not appropriate for initial treatment in children weighing less than 25 kg or for doses below 250 mg. Monotherapy: No data in children and adolescents below 16 years. Adjunctive therapy: Infants from 6 months, children and adolescents weighing less than 50 kg: Oral solution preferred formulation in children under 6 years. Initial dose 10 mg/kg daily. Dose can be increased if required up to 30 mg/kg twice daily. Dose changes should not exceed increases or decreases of 10 mg/kg twice daily every two weeks. Use lowest effective dose. Dose in children ≥50 kg same as adults. Infants from 1 month to <6 months: use oral solution. **Contraindications:** Hypersensitivity to levetiracetam, to other pyrrolidone derivatives or to any of the excipients. Infants and children under the age of 6 years (levetiracetam oral solution is the preferred formulation for use). **Special warnings and precautions for use:** Patients with renal or severe hepatic dysfunction may require dose adjustment. Discontinue gradually (see SmPC). Although available data in children do not suggest impact on growth and puberty, long term effects remain unknown. The safety and efficacy of levetiracetam has not been thoroughly assessed in infants with epilepsy aged less than 1 year. Suicide, suicide attempt, suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents (including levetiracetam). A meta-analysis of placebo-controlled trials of anti-epileptic medicinal products has shown a small increased risk of suicidal thoughts and behaviour. Patients should be monitored for respective signs and appropriate treatment should be considered. **Effects on ability to drive and use machines:** Reaction time may be impaired. **Pregnancy/lactation:** A teratogenic risk cannot be completely excluded. Use during pregnancy, lactation and in women of childbearing potential without contraception is not recommended unless clearly necessary. Levetiracetam plasma levels decrease during pregnancy, particularly in the third trimester. **Side effects:** *Very common:* Nasopharyngitis, somnolence, headache. *Common:* convulsion, dizziness, vertigo, lethargy, tremor, impaired balance, depression, hostility/aggression, anxiety, insomnia, nervousness/irritability, abdominal pain, diarrhoea, dyspepsia, nausea, vomiting, anorexia (increased risk when coadministered with topiramate), rash, cough, asthenia/fatigue. *Uncommon:* thrombocyto-/leucopenia, weight increase or decrease, suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusion, panic attack, emotional lability/mood swings, agitation, amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia, disturbance in attention, diplopia, blurred vision, abnormal liver function test, alopecia (in several cases recovery of hair loss was observed after discontinuation of levetiracetam), eczema, pruritus, muscular weakness, myalgia, injury. *Rare:* infection, completed suicide, personality disorder, thinking abnormal, choreoathetosis, dyskinesia, hyperkinesia, pancreatitis, hepatic failure, hepatitis, neutro-, pancytopenia (bone marrow suppression identified in some of the cases), agranulocytosis, DRESS, hyponatraemia, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme. Side effects occurring more frequently than in other age groups: children and adolescents between 4 and 16 years: *Very common:* vomiting. *Common:* agitation, emotional lability, mood swings, aggression, abnormal behaviour, lethargy. Infants and children between 1 month and 4 years of age: *Very common:* irritability. *Common:* coordination abnormal. **Pack sizes and NHS price:** Packs of 60, 250 mg sachets £22.41 [PL14040/0029]; Packs of 60, 500 mg sachets £39.46 [PL14040/0030]; Packs of 60, 1000 mg sachets £76.27 [PL14040/0032]. **Legal category:** POM. **Marketing Authorisation Holder:** Desitin Arzneimittel GmbH, Weg beim Jäger 214, 22335 Hamburg, Germany. **Prepared in:** June 2014. For further information on Desitrend® please contact Medical Information on MedInfo@desitin.co.uk.

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MAY/JUNE 2015

Cover image: As part of its 50th anniversary celebrations, the Economic and Social Research Council (ESRC) has run a photographic competition 'Changing World', asking children 14 - 18 to think about how the world has changed over the last 50 years, and how it may change in the future. Seventeen year old Stella Wharmby from Francis Holland School, London won a Judge's Choice award for her image '**Disappearing**', which explores how it feels to be around somebody suffering from dementia.

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Todd Hardy, Co-Editor.

Dear readers, do not adjust your set! Mike Zandi remains at ACNR and is in robust health. It is merely that from now on there will be a sharing of opening editorial responsibilities between myself, Mike and our fellow Co-Editor, Sian Alexander. So without further ado, let me introduce the latest articles.

In this issue Ruth Wood, from the Kent, Surrey and Sussex Deanery, and Dennis Chan, Cambridge, survey the role of the hippocampus and entorhinal cortex in spatial memory as it relates to the diagnosis of Alzheimer's disease, citing Nobel prize-winning contributions in the field.

Anke Hesiek, Cambridge, and Malcolm Taylor, Birmingham, write a clear account of the genetics of ataxia telangiectasia and highlight the clinical variability which can arise as a result of differences in ATM kinase activity. They stress the importance of screening for important co-morbidities and the value of a multidisciplinary approach to management.

In our neurosurgical article, Adam Williams, from the Severn Deanery, and Tim Nokes and Peter Whitfield from Plymouth, emphasise the critical importance of managing coagulopathy in neurosurgery and discuss the relevant decision-making difficulties pertaining to the use of thromboprophylaxis in the neurosurgical patient.

In our Rehabilitation article, Helen Currie, Helen Paterson and Stephen Block from London report on the range of assisted communication devices in patients with speech difficulties and present an interesting experience of what it is like to be reliant upon such a device for communication in the real world.

In a topic close to my own heart, Richard Davenport, Edinburgh, and Richard Butterworth, Milton-Keynes, write an enjoyable remembrance of their training year in Australia, and encourage applications for future Australasian Neurology Fellowships through the ABN.

The issue also contains Bianca Neumann May, Norfolk, on the inner workings of her Psychological Well-Being support group for stroke patients, and a thought-provoking article from Alex Massey of the Neurological Alliance on "invisible" neurological patients. In addition, there are reviews of the 2015 ABN conference in Cambridge and the 2014 Encephalitis Society Meeting in London and the usual helpful journal article and book reviews. We hope you enjoy.

Todd Hardy, Co-Editor
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The hippocampus, spatial memory and Alzheimer's disease

Ruth Wood
is an Academic Clinical Fellow in Neurology within Kent, Surrey and Sussex Deanery. She has been awarded a Clinical Research Training Fellowship to undertake a PhD under the supervision of Dr Dennis Chan and Professor John O'Keefe.

Dennis Chan
is University Lecturer and Honorary Consultant in Clinical Neurosciences, University of Cambridge. From 1988 to 1991 he undertook a PhD on the subject of hippocampal neurobiology under Professor O'Keefe at University College London. Dr Chan currently co-leads a project with Professor O'Keefe studying the effects of early Alzheimer's disease on the functions of the entorhinal cortex and hippocampus.

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Summary

- The entorhinal cortex and hippocampus are key components of the brain's spatial memory network and are affected from the initial stages of Alzheimer's disease (AD).
- Testing of spatial memory is a sensitive measure of early AD.
- Determination of disease effect on grid cell and place cell function, and of their behavioural correlates, will facilitate studies of disease mechanisms and development of future diagnostic tests.

Introduction

The hippocampal formation, comprising the entorhinal cortex and hippocampus proper (the dentate gyrus and Cornu Ammonis subfields), is the first brain region to exhibit neurodegeneration in Alzheimer's disease (AD) and determination of AD-related alterations in hippocampal structure and function is central to AD diagnosis. In addition to its role in episodic memory there is extensive evidence of hippocampal involvement in spatial memory, dating back to the discovery of spatially-related firing activity of hippocampal "place cells" in freely moving animals,[1] work recently acknowledged by the award of the 2014 Nobel Prize for Medicine or Physiology to Professor John O'Keefe of University College London.

Here we describe in brief the role of the hippocampal formation in spatial memory and the implications for AD. Episodic memory, and parietal contributions to "getting lost", will not be covered in this article.

The neural basis of spatial behaviour

Egocentric and allocentric spatial representations

The cortical processing of sensory information to generate representations of space is a prerequisite for spatial memory. Data are initially processed within single-modality primary and secondary cortices, and subsequently integrated within multimodal association cortices. The widely cited model of Ungerleider and Mishkin (1982)[2] posits that further information processing occurs along anatomically divergent pathways; information regarding objects is conveyed via an occipito-temporal pathway (the ventral "what" pathway) whereas information regarding space is mediated by an occipitoparietal pathway (the dorsal "where" pathway). At this stage spatial representation is egocentric, i.e. head-centred, in nature. A further stage of processing is required, possibly occurring within the retrosplenial cortex, to transform the representation of space from egocentric to allocentric, i.e. not centred on the person (or animal), with an attendant shift from a polar coordinate to a Cartesian coordinate system. Both forms of spatial representation may be used in navigational strategies, depending on the complexity of the route and environment; for instance, a direct navigation from A to B along a line of sight may be mediated by an egocentric ("follow your nose") approach whereas navigation within more complex environments may be more efficiently undertaken if those environments are mapped according to an allocentric framework.

Single cell studies

Accurate representations of space, and spatial memory, are fundamental to the survival of most mammalian species. Professor O'Keefe's discovery of "place cells" in the hippocampi of freely moving rodents during natural exploratory behaviour provided the first evidence of allocentric spatial representations within the mammalian brain.[1] "Place cells" fire in a particular location in any given environment thus encoding an animal's location;[3] the location in which a place cell fires is known as its place field (Figure 1).

Later experiments demonstrated further characteristics of place cell firing including a robust correlation between place cell activity and spatial memory[4] and the firing of individual place cells in different locations within different environments (place cell remapping).[5] Place cell firing is observed in preweanling rats prior to any significant exploration of the environment[6] supporting the Kantian notion of an innate spatial framework.[7] Finally, in a transgenic mouse model of AD (Tg2576), disruption of place cell firing was found to correlate with impairment of spatial memory and with amyloid burden.[8]

Following the discovery of place cells, O'Keefe and Nadel proposed that the hippocampal formation also contained information regarding direction and distance allowing construction of a cognitive map of the environment.[9] This postulated the existence of other spatially-tuned cells and, in line with this and other theoretical predictions, "grid cells" were identified in the entorhinal cortex in 2005 by May-Britt and Edvard Moser. Unlike place cells, which fire in a single location in any given environment, "grid cells" have periodic firing fields arranged with sixfold symmetry (Figure 1).[10] Other cells with spatially-related firing activity have also been identified; "head direction cells" fire when the animal is facing in a particular

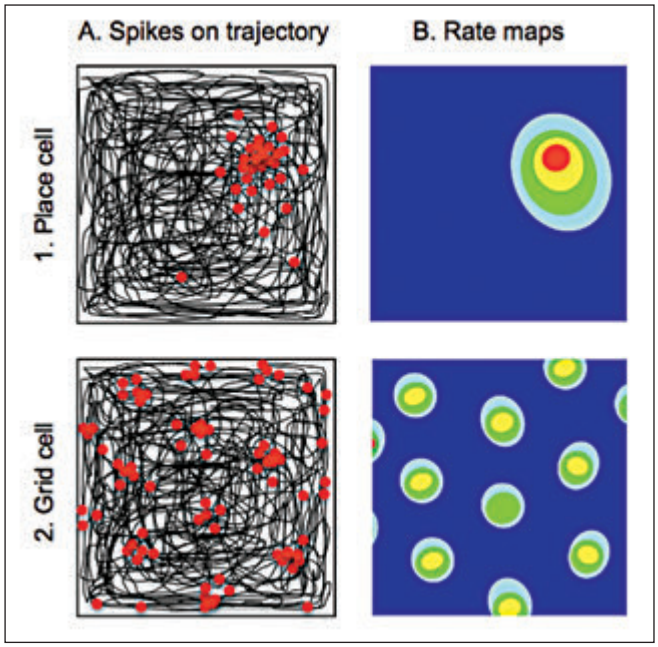

Figure 1. An illustrative schematic of place cell and grid cell firing.
Column A shows in black the path taken by a rat as it traverses a square arena. Electrodes implanted within the hippocampus and entorhinal cortex record from individual neurons. Place and grid cells show increased firing (each action potential represented by a red dot) at discrete locations in the environment. Whereas individual place cells (top) fire only in one location, grid cells (bottom) have multiple firing fields. The hexagonal symmetry of the spacing between these latter fields gives rise to the term "grid cells". The firing frequency of place and grid cells within the environment (rate maps) is shown in Column B, with lower wavelength colours (yellow and red) depicting higher rates of firing on a background of silent cell activity (dark blue).

direction whereas "boundary vector cells" fire in the proximity of a boundary, such as the edge of an environment. (For a comprehensive review of these different cell types and their respective functions, see reference 5).

Spatially-related single cell activity has been found in the hippocampal formation of humans and other mammals. Depth electrode recordings from epilepsy patients prior to temporal lobe surgery have revealed place cell and grid cell-like activity in the hippocampus and entorhinal cortex respectively[11] and three-dimensional place and grid cell activity have been recorded in flying bats.[12]

Brain regions

Different subdivisions within the hippocampal formation underpin separate components of spatial behaviour. Within the hippocampus proper animal and human studies support the notion of functional differentiation along an anteroposterior axis, with anterior regions encoding contextual information and spatial novelty and posterior regions implicated in the storage of spatial representations. The entorhinal cortex is the primary source of afferents to the hippocampus, with medial and lateral subdivisions conveying spatial and object-related information respectively.[13] The differing information content of these entorhinal inputs reflect the afferents to the medial and lateral entorhinal cortex from the parahippocampal cortex and perirhinal cortex, involved respectively in scene and object recognition.

A number of other brain regions subserve spatial processing. Mention has been made in passing of the role of parietal lobe regions, such as the retrosplenial cortex, which may additionally encode landmark information,[14] and the precuneus and posterior cingulate gyrus are of particular interest given the early manifestation of AD pathology in these regions. Finally there is evidence for a striatal system for landmark-related representations of space.[15]

Tests of spatial memory

Perhaps the best known test of allocentric spatial memory is the Morris water maze,[16] used extensively in preclinical phases of AD treatment trials. In this paradigm rodents have to remember the location of a hidden underwater platform within a pool of opacified (milky) water, on the basis of external sensory cues around the maze periphery. Other tests of spatial memory in animal models include continuous Y-maze alternation, forced-choice T-maze alternation, the radial arm water maze and the circular platform maze.

Test of allocentric spatial memory in humans include the 4 Mountains Test (Figure 2), which uses computer-generated mountain landscapes and is sensitive to focal hippocampal damage,[17] and the Hidden Goal Task, which assesses memory for hidden locations within a three metre circular velvet arena.[18] Other tasks include The Heading Orientation Test, The Money Road Map Test and virtual reality tasks including a radial maze task.[19]

Impairment of spatial memory in early AD

Several studies have demonstrated impairment of spatial memory in AD, as assessed by route learning tasks and memory for scenes.[20-22] Both allocentric and egocentric spatial memory are impaired in AD[18,20] with one study finding that AD subjects were more impaired when using an allocentric, as opposed to an egocentric, wayfinding strategy.[23] Patients with AD also appear less able to translate between allocentric and egocentric representations, possibly reflecting damage to the retrosplenial cortex.[24] Performance on the 4 Mountains Test differentiates patients with AD from those with non-AD dementias[22,25] and more recently has been found to discriminate MCI patients with and without CSF biomarker evidence of underlying AD.[26] Other studies have also demonstrated impairment of allocentric and egocentric memory in Mild Cognitive Impairment (MCI).[18,21,27]

Structure-function studies have revealed an association between hippocampal volumes and spatial memory performance, with a positive correlation noted in MCI and AD patients.[26] In another MCI/AD patient study poor navigational performance and poor accuracy locating landmarks were associated respectively with a reduction in right hippocampal and posterior parietal volumes.[21]

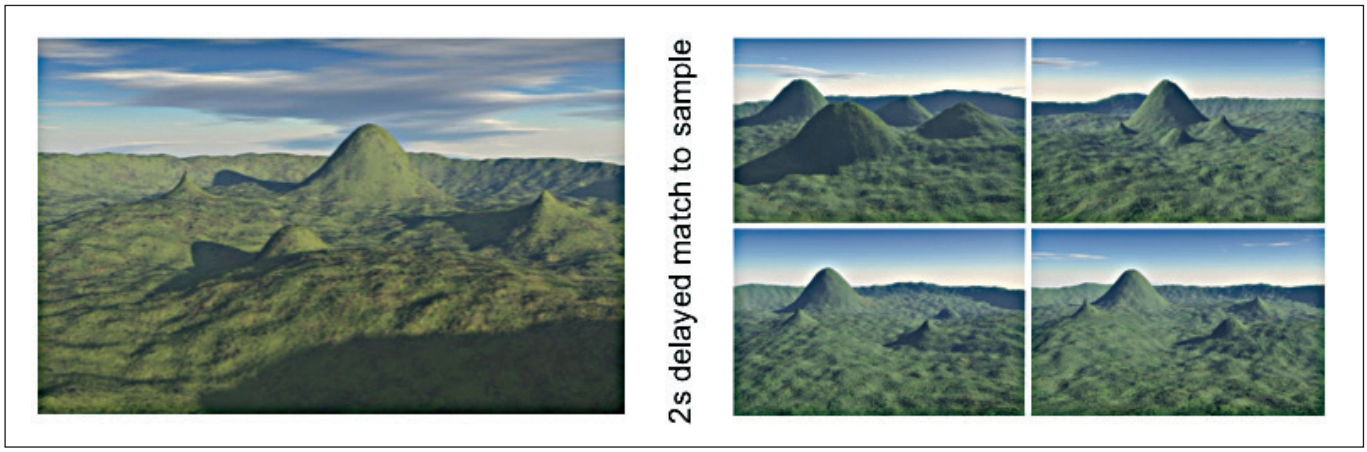

Figure 2. The 4 Mountains Test. "4 Mountains" landscape (left) is presented for 8 seconds and then removed. After a 2 second delay this landscape is presented again, but from a rotated viewpoint, with three additional "foil" landscapes (right), as part of a delayed match-to-sample paradigm. (Correct response: bottom right).

Conclusions and future direction

The 2014 Nobel Prize for Medicine or Physiology was awarded in recognition of the work undertaken in elucidating the role of the hippocampus and entorhinal cortex in the representation of space. Knowledge of the spatially-related firing properties of place cells and grid cells, and of the coupled behaviours in the form of spatial exploration and memory, provide new opportunities for studying the initial effects of AD on brain function. Such study will not only provide a platform for systems biology investigations of disease mechanisms but will also aid development of new behavioural tasks with increased sensitivity for the earliest stages of AD.

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British Indian Awards 2015

Pankaj Sharma, Professor of Neurology at Royal Holloway University of London and Consultant Neurologist at Imperial College London, was named the United Kingdom's top Asian medical doctor at the British Indian Awards 2015. The annual awards celebrate the achievements of leading British Asians in the UK. Prof Sharma's work on researching into the genetic causes of stroke in Asians across the UK, Middle East and India was particularly cited, as well as his charity work in the stroke sector. Prof Sharma is a frequent media commentator on neurology and stroke related issues. The award is seen here being presented by an Asian representative of the Royal Navy.

Addenbrooke's team wins innovation voucher for new device to treat Parkinson's Disease

A team at Cambridge University Hospitals (CUH) is celebrating winning funding worth £5,000 to help progress their idea for a new device for people suffering from Parkinson's Disease. It was created by Dr Andrew Michell, Consultant in Clinical Neurophysiology, together with team members Dr Philip Buttery, Consultant Neurologist, Dr Thomas Stone and Sonya Sireau, Medical Physics and Clinical Engineering (MPCE), all from Addenbrooke's, part of CUH. Dr Michell said: "In the work the team here at CUH Addenbrooke's and Cambridge University are doing, we hope to be able to reduce the debilitating impact that tremor can have in a Parkinson's patient's life in a simple and safe way. We are very grateful to Health Enterprise East for helping us to support this valuable work." Dr Stone added: "Our ability in Clinical Engineering to support the rapid research and development of new medical devices in this way is very exciting. Clinical scientists and engineers can work closely with medical staff and patients which really improves how quickly we can respond to unmet needs and improve the care of our patients in Addenbrooke's."

John Dystel Prize for MS Research

Alastair Compston has been awarded the 2015 John Dystel Prize for MS Research. The John Dystel Prize recognises a significant contribution to research in the understanding, treatment or prevention of multiple sclerosis (MS). The award was presented at the American Academy of Neurology's (AAN) 67th Annual Meeting in Washington, DC, in April. The Annual Meeting is the world's largest gathering of neurologists with more than 12,000 attendees and more than 2,500 scientific presentations on the latest research advancements in brain disease. Compston's research focuses on the evolution of ideas on the way multiple sclerosis develops. He said, "The advances in treatment of multiple sclerosis seen in the last 20 years have been remarkable and unmatched by therapies developed for any other neurological disease. I am conscious of the enormous contributions made by many clinicians, scientists and people with multiple sclerosis who enabled the successful outcome of this work."

The clinical variability of Ataxia Telangiectasia – an update

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Malcolm Taylor
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Summary

- Ataxia telangiectasia belongs to the group of DNA repair disorders and presents with a progressive neurodegenerative disorder
- Affected individuals can exhibit radiosensitivity, immunological abnormalities, respiratory problems and an increased malignancy risk
- The clinical phenotype of ataxia telangiectasia is variable and includes individuals with only mild neurological signs and late onset. In these patients, the condition is likely to be sometimes misdiagnosed or not recognised.
- It is important to be aware of this diagnosis, as patients require specific surveillance for malignancy and management by a multidisciplinary team.

Introduction

Ataxia Telangiectasia (AT) is an autosomal recessive hereditary multisystem disorder with an estimated prevalence of 1:400,000 in the UK.[1,2]

The disease is caused by mutations in the ataxia telangiectasia mutated gene (ATM, 11q22.3), which encodes a protein kinase that has an important role in DNA repair.[3] Affected individuals with classical AT typically present in childhood with a progressive neurodegenerative disorder that is associated with immune defects and a predisposition to malignancy. Life expectancy in classical AT is significantly reduced and affected individuals often die from respiratory complications or malignancy. It is increasingly recognized that a less severe form of the disease (variant AT) can be seen in adults, which is likely to be sometimes misdiagnosed.

In this review, we will provide a brief overview on clinical features, diagnosis and current management guidelines of classical and variant ataxia telangiectasia, as well as discussing genetics and pathophysiology of the condition.

Overview of subtypes and clinical features

Ataxia Telangiectasia shows significant genotype-phenotype correlation. Mutations in classical AT cause complete absence of ATM kinase activity, which relates to a severe phenotype with onset in early childhood. In contrast, individuals with variant ataxia telangiectasia have mutations that leave some residual ATM kinase activity. This corresponds to a much milder clinical phenotype, characterised by late onset and often predominantly neurological involvement, rather than associated systemic complications.[4,5]

Classical ataxia telangiectasia

Children with classical AT usually show no abnormalities in the first months and often sit and walk at the normal age. However, clumsiness, unsteadiness or abnormal eye-movements can already be apparent at that age and gradually progress during childhood. Most children with classical AT are wheelchair bound by the time they enter secondary school and present with a progressive cerebellar syndrome, that is frequently accompanied by extrapyramidal signs (dystonia, chorea), a peripheral neuropathy and myoclonus.

The eye movement disorder with prominent oculomotor dyspraxia is a distinguishing feature of the disease, particularly if accompanied by oculo-cutaneous telangiectasia which typically develop before the age of ten (Figure 1).

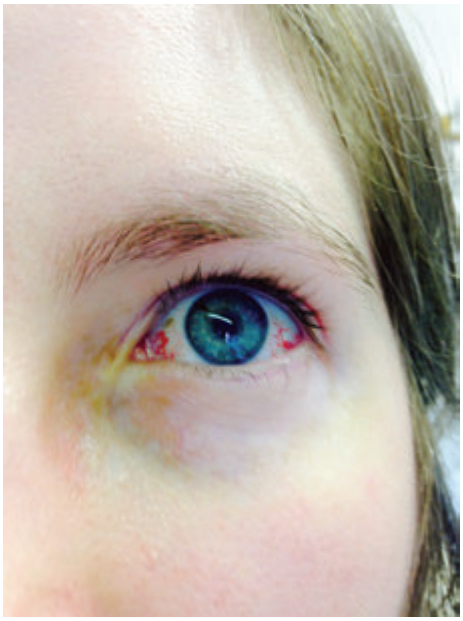

Figure 1. Ocular telangiectasia in a 21-year-old woman with classical ataxia telangiectasia.

Variable immunological abnormalities are common, including immunoglobulin deficiency, reduced numbers of lymphocyte subsets and poor vaccine response. Furthermore, many individuals with classical AT have a range of respiratory complications, caused by a combination of neurological problems (in particular poor swallow and respiratory muscle weakness), immune defects (leading to respiratory tract infections and risk of

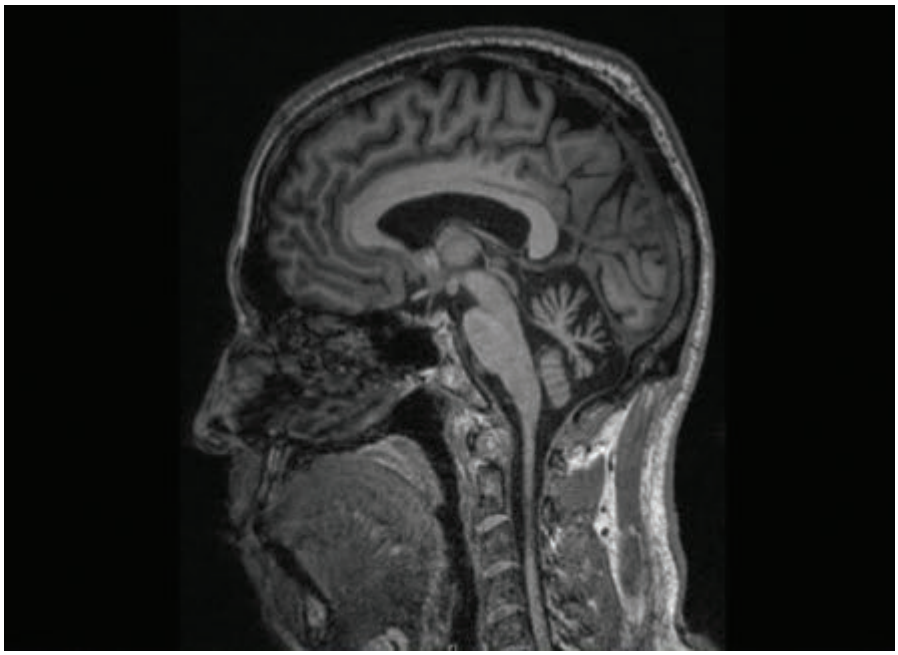

Figure 2a. Sagittal T1 weighted MRI (40 year-old man with variant ataxia telangiectasia), showing cerebellar atrophy.

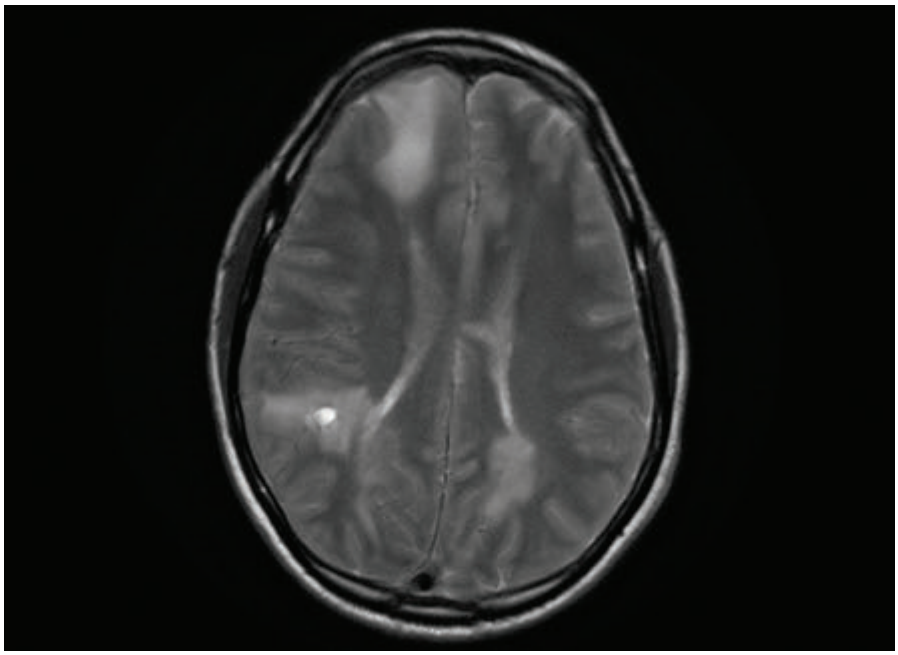

Figure 2b. Axial T2 weighted MRI (27 year-old man with classical ataxia telangiectasia), showing bi-bilateral areas of white matter high signal with a cyst-like lesion.

bronchiectasis) and other potential complications (i.e. pulmonary complications from chemotherapy, interstitial lung disease, etc). Classical AT is associated with a predisposition to cancer (in particular lymphoid and brain tumours) with an estimated malignancy risk of 25-30%. Together, the combination of systemic complications and progressive neurological decline lead to a severe phenotype and reduced life expectancy with a reported median survival age of 25 years.[6] The cause of death in classical AT is related to respiratory complications in the majority of individuals, but about a fifth die from malignancy.

Variant ataxia telangiectasia

The presence of some residual ATM kinase activity relates to a less severe phenotype with later onset, often only in adulthood. Individuals typically present with progressive neurological symptoms, most commonly extrapyramidal (dystonia, tremor, chorea) or cerebellar symptoms.[7] These symptoms relate to the abnormal brain regions that are also implicated in functional imaging and pathological studies.[8] Features of a peripheral neuropathy or amyotrophy are not invariably present; likewise, eye movements can be normal although some have slow saccades, nystagmus, broken pursuit or oculomotor apraxia. Conjunctival or peripheral telangiectasia can be absent and many individuals with variant AT have no evidence of immune defects or respiratory complications. Furthermore, the increased radio-sensitivity is not as large and the spectrum of malignancies that these patients are susceptible to is different to the classical form.[9]

The phenotype of variant AT can be very mild, for example some individuals only have a dystonic tremor or a mild ataxia neuropathy. It therefore seems likely that the condition is sometimes not recognised or misdiagnosed.

Whilst neurophysiology in variant AT can be normal, many patients have evidence of a sensory-motor neuropathy or amyotrophy and need to be managed accordingly. MRI brain scans in adults with variant AT often show cerebellar atrophy but white matter abnormalities, intracerebral telangiectasia and fluid collection (probably from 'leaky' capillaries) can also occur (Figure 2).[10] The frequency of these changes is unknown and we currently arrange baseline MRI scans in all adult patients with AT.

There are currently no epidemiological studies on life expectancy and clinical course of variant AT although there is likely to be significant variability within the group, possibly relating to specific mutations. However, several individuals over the age of 50 (some of whom are still relatively independent) have been reported in French, Dutch and American cohorts, which corresponds to our experience in the UK.

Genetics, pathophysiology, diagnosis (MT)

Patients with typical classical A-T all show biallelic mutation of the *ATM* gene that results in total loss of ATM kinase activity, irrespective of whether any ATM protein is expressed. In some classical patients mutant ATM protein without activity is expressed. The key is absence of ATM kinase activity. In contrast, milder forms of A-T are associated, in all cases, with expression of some ATM protein with some activity. In these circumstances the origin of protein is from ATM missense mutations, producing mutant protein but with residual activity, or leaky splice site mutations producing a low level of normal ATM with activity of course.[11]

Interestingly, therefore, different milder patients will express different ATM proteins. In the UK a significant proportion of milder A-T patients express normal ATM from the same leaky splice site mutation; these patients might be expected to have some uniformity of neurological presentation, and possibly different from other milder patients with mutant proteins. Indeed, there is some scope for several distinguishable neurological phenotypes in milder patients with different mutant proteins each with some residual activity. These different phenotypes may be dependent on the level of protein expressed, the range of targets of the different ATM proteins etc. These relationships are not

understood at present and there is interesting work to be done here.

The diagnosis of classical A-T usually occurs at the age of 2-4 years, because of early onset unequivocal signs. Approximately half of all A-T patients in the UK are adults and a good proportion of these have a milder phenotype. Significant numbers were diagnosed as adults although the age of onset is less clear and may be in either childhood or adulthood. The diagnosis of atypical and milder A-T may occur at any age, with the oldest patient diagnosed in the UK being 64y. With one exception so far, all milder A-T patients will express some ATM that has reduced activity compared with normal. Therefore any potential A-T patient of any age can have the diagnosis confirmed by analysing the activity of their ATM. This is done by carrying out the assay in a lymphoblastoid cell line made from the patient's blood. In those patients with reduced activity, the subsequent identification of *ATM* mutations will inevitably show the presence of sequence changes consistent with the expression of mutant protein. Interestingly, an increased level of serum AFP is a good marker for classical A-T and may also be associated with milder A-T although whether this is true for all milder A-T is not known and perhaps should not be relied on as an indicator for all A-T.

Finally, there is a milder and much rarer form of A-T (ATLD) caused by mutation, not of the ATM gene, but of *MRE11*.[12] The same ATM kinase assay described above, will also identify these patients, because they also have defective ATM kinase activity. The reason for this is because full ATM kinase activity is dependent on the Mre11 protein.

Management

All individuals with a diagnosis of classical or variant AT should be managed by a multidisciplinary team with experience in the condition. The team should include a respiratory physician, immunologist, geneticist, neurologist and various therapists who will co-ordinate care with local services. In the UK, patients are assessed annually or bi-annually in the National ataxia telangiectasia clinics for children (Nottingham) or adults (Papworth Hospital) (Figure 3). Guidelines for the management of children with AT have recently been published by the ataxia telangiectasia society together with the Nottingham team.[2]

It is recommended that adults with variant AT also undergo a multidisciplinary assessment, as some will have immune defects or respiratory complications. Furthermore, all adults with AT should receive genetic counselling including guidance on the increased risk of cancers. Women with AT should have annual breast MRI from age 25, heterozygote carriers (whose malignancy risk is also increased[13]) should be offered 18-monthly mammograms from the age of 40 years until the age of 50, after which they receive three-yearly mammograms as part of the National Breast Screening programme. Individuals with AT often have increased radiosensitivity and it is important to limit X-ray exposure and be aware of increased toxicity from chemotherapeutic agents.

Unfortunately, disease-modifying agents for ataxia telangiectasia have as yet not been identified and neurological management of adults is therefore is symptomatic. Drug treatments including levodopa, amantadine, trihexiphenydil, baclofen or clonazepam are useful in some patients, particularly those with predominant extrapyramidal presentations. Furthermore selected patients may be suitable for deep brain stimulation.

Figure 3

Contact Details for National Ataxia Telangiectasia Clinics in the UK.

Nottingham Children's AT Centre
Dr Mohnish Suri, Consultant Clinical Geneticist,
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Papworth Adult A-T Centre
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Managing coagulopathy and thromboprophylaxis in the neurosurgical patient

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He has lectured frequently on hospital acquired thrombosis and VTE outcomes at national and international meetings. Tim has experience with novel anticoagulants and has presented a number of them to NICE technology appraisals. He has published a number of articles on thrombosis and haemostasis.

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Abstract
Our understanding of the mechanisms underlying coagulation have advanced rapidly in recent years. In addition, there are new methods to assess coagulation and new agents in the treatments of thromboembolic diseases such as atrial fibrillation, myocardial infarction and venous thromboembolism. It is particularly important for the neurosurgeon to be familiar with this topic in order to balance risks between bleeding and thrombosis in association with surgery. This review provides an overview of the 'cell-based' theory of coagulation and the technique of rotational thromboelastograpy to measure whole-blood coagulation. We discuss current management strategies related to haemorrhage control, haemostasis in polytrauma, and the elective and emergency peri-operative management of aspirin, thienopyridines, warfarin and the novel oral anticoagulants (rivaroxaban, dabigatran, apixaban). Finally, the current evidence regarding neurosurgical thromboprophylaxis is reviewed.

Introduction
Coagulation will always be pivotal to the neurosurgeon. The finite space of the cranium mandates an acute concern to minimise the risk of haemorrhage, no matter how small. Much work has been undertaken recently that has improved our understanding of coagulation and this review article covers some of these critical advances. The modern 'cell-based' theory of haemostasis is discussed, along with new near-patient techniques to assess whole-blood coagulation. Beyond theory, we review changes to the acute management of haemostasis in the polytrauma patient, and the neurosurgical management of common antiplatelet agents (aspirin, clopidogrel, prasugrel and ticagrelol) warfarin and the novel oral anticoagulants (NOACs). Finally, the current evidence around thromboprophylaxis is reviewed.

Modern theory of coagulation
The classical model of clotting has been a 'cascade' of clotting factors associated with platelets in which there is a tissue-factor (TF) -initiated 'extrinsic pathway' and a contact-activated 'intrinsic pathway.' Undoubtedly, this has proven an accurate model to explain laboratory clotting assays such as prothrombin time (PT) and activated partial thromboplastin time (aPTT), however, a more modern theory has evolved that includes cellular and molecular components that better explains in-vivo haemostasis. Coagulation is theorised to be a process regulated by the properties of particular cell surfaces and occurs in three overlapping processes: initiation, amplification and propagation[22] (Figure 1).

A breach in the wall of a blood vessel allows plasma to contact TF-bearing extra-vascular cells such as the fibroblast. TF is an integral membrane protein and structurally unrelated to other coagulation proteins.[27] It remains localised to membrane of the cell in which it was synthesised and is neither expressed nor contained on normal circulating unactivated platelets. If this procoagulant stimulus is of sufficient strength, initiation commences on the surface of these TF-bearing cells. Factor VII is key, combining with TF to form a FVIIa/TF complex that activates factors X (itself activating factor V) and factor XI. Activated factor X (Xa) in combination with factor V, phospholipid and calcium (so-called prothrombinase) produce small volumes of thrombin (factor IIa) from the activation of Prothrombin (factor II).

In the amplification phase, platelets that previously adhered to extravascular collagen (by polymerised von Willebrand factor (vWF) released from endothelium), become partially activated. Factors Xa, IXa and thrombin induce further activation by adhering to platelet surface glycoproteins and other receptors. Platelets accumulate activated cofactors (Va, VIIIa, XIa and vWF) on their surface,[29] amplifying the process. Activated platelets, with surface-bound Va and VIIIa, provide the surface for production of thrombin on a larger scale.

In the propagation phase, factor IXa diffuses from TF-bearing cells to the activated platelet surface, enabling the formation of active protease tenase (FVIIIa/IXa). Thrombin is the one of the primary activating factors from the small amount released during the initiation phase, causing back-activation of several clotting factors and platelets. Tenase activates factor X on the platelet surface, forming a complex with its co-factor to produce more prothrombinase (FXa/FVa). The activated platelet-surface FXa/Va promotes the development of haemostatic volumes of thrombin (so called thrombin 'burst') and the subsequent fibrin polymerisation necessary for coagulation. As well as activation of several clotting factors and platelets, thrombin is also involved in regulation of the haemostatic pathways by its activation of thrombomodulin and plasminogen.

New technology for coagulation assessment: Rotational Thromboelastometry
As our understanding of coagulation has evolved, so have newer methods of monitoring dysfunctional coagulation. Standard laboratory tests of coagulation are performed on citrated plasma

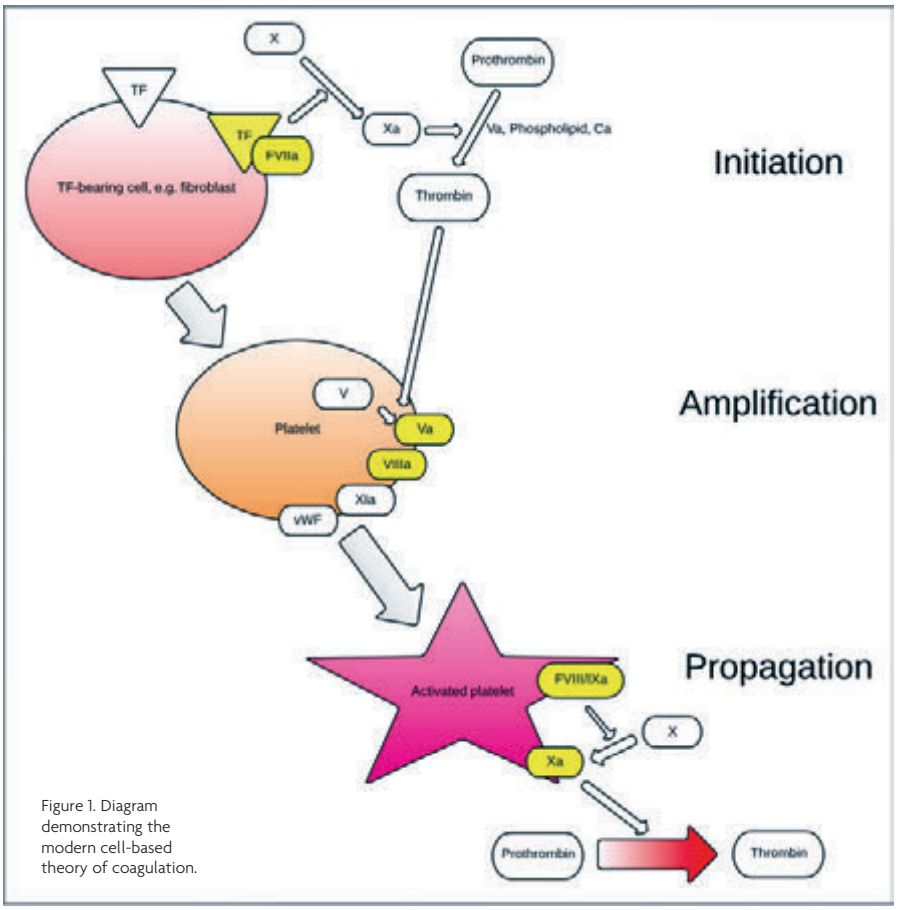

Figure 1. Diagram demonstrating the modern cell-based theory of coagulation.

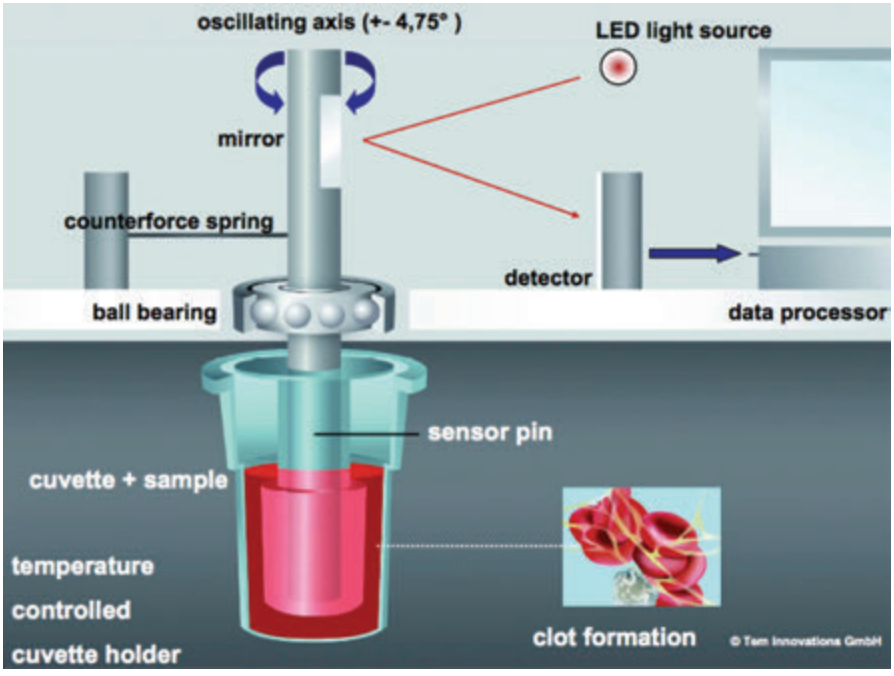

Figure 2. Schematic diagram to demonstrate the principles of action of ROTEM®.

samples and include aPTT and PT. These tests are not affected either by platelet function or the surface properties of the whole haemostatic constitution as discussed previously. Since the advent of the cell-based model of coagulation there has been some concern over the appropriateness of the standard laboratory tests in the assessment of clotting due to the absence of the effect of any cell surface or platelet effects. Moreover, coagulation assays are performed using an excess of calcium and TF to stimulate clotting and thus are designed only to detect hypocoagulation that is due to factor or fibrin defects or deficiency. In many clinical situations it is not possible to determine the cause of abnormal haemostasis using these routine tests. These limitations have led to a growing interest into assays of coagulation that test haemostasis in whole blood, and the development of near-patient testing techniques.

Thromboelastography (TE) was first described in 1948 by Hartert[21] as a means to monitor clot development by measuring its visco-elastic properties. It is now well established in the assessment of whole blood coagulation and in routine use across a range of surgical and anaesthetic specialties.[5,25,34,36,37] TE has been refined by two companies into TEG® (Haemoscope Corporation, Niles, IL, USA) and rotational thromboelastography (ROTEM®, by © Tem International GmbH, Munich, Germany). Using the latter as an example, the technology employs a rotating shaft, connected to a spring that allows a computer to calculate changes in elasticity by detecting shifts in reflected light via an optical sensor. A disposable pin is connected to the tip of the shaft, this is inserted into a blood filled disposable cuvette. The exact position of the rotating shaft is used to calculate the change in elasticity of the blood being tested. Figure 2 illustrates this arrangement and a sample trace is seen in Figure 3. The definitions of the parameters reported in ROTEM® analysis are also given in Figure 3. It is beyond the scope of this article to provide detailed guidelines for the interpretation of such traces, but in essence the analysis is carried out along the time axis (left to right). Comparison between the measurements obtained and normal values can aid the clinician in diagnosing the underlying cause for haemorrhage. For example, abnormal clot formation prolongs the clot formation time (CFT) and often reduces the maximum clot firmness (MCF). If the CFT is affected more than MCF this implies a polymerisation disorder whereas if MCF is reduced with a normal CFT there is likely to be a deficiency in a clottable substrate (fibrinogen and/or platelets). Pathologic fibrinolysis is detected by shortening of the clotting time (CT) or a rise in the maximum lysis (ML). Different ROTEM® assays can also detect heparin effects.

As an ex-vivo test, ROTEM® provides information on the rate and quality of the interaction between the solid components of blood that result in fibrin polymerisation and thus the kinetics of clot formation and strength, and also subsequent fibrinolysis. As such, ROTEM® is considered to be a more sensitive test of haemostasis than standard laboratory clotting tests.

One of the greatest clinical benefits of this technology is in the definition of the coagulopathy to factor, platelet or fibrinogen deficiencies. The benefit of this rapid near-patient test has been clearly documented in a variety of fields including major trauma,[19] neurosurgery[17,25] and intensive care.[2] It is likely that, as greater awareness of the cell-based theory of coagulation occurs, there will be greater surgical interest in TE as a better means of assessing whole blood coagulation and the optimum means by which correction can be rapidly achieved.

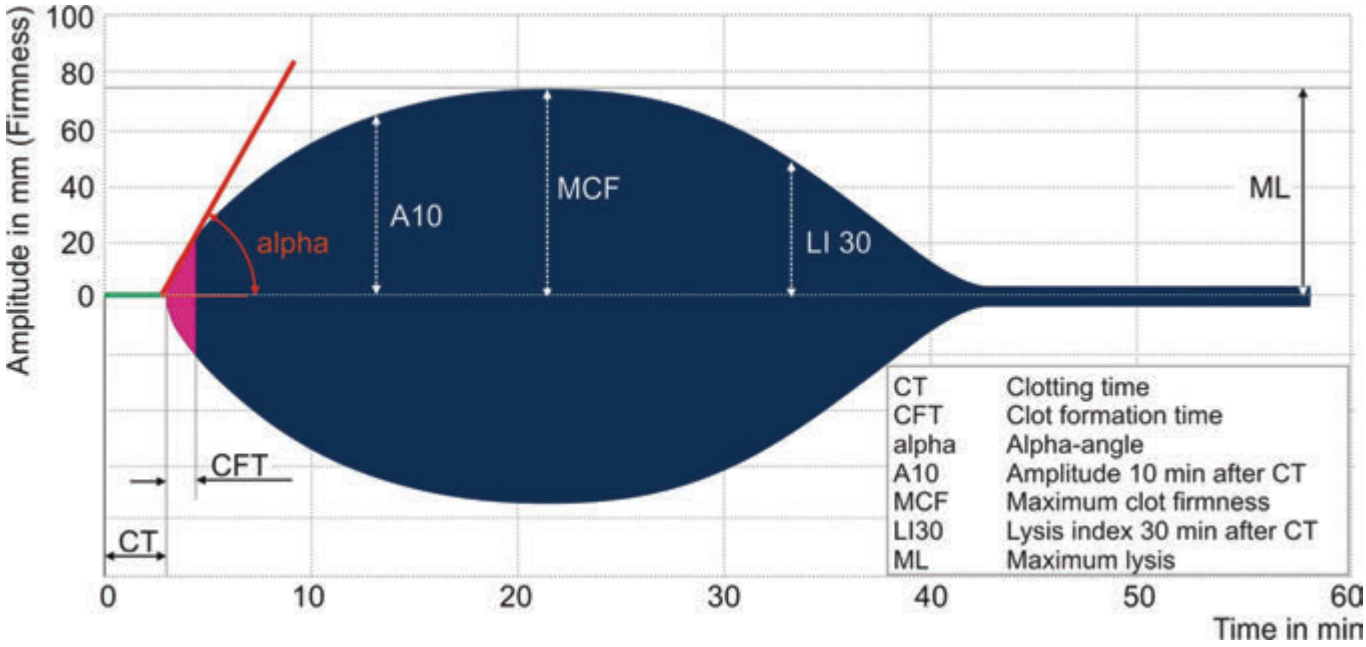

Figure 3. Graphical output produced by ROTEM®. Known as a TEMogram, this provides critical information including the clotting time, rate, maximum clot strength and rate of lysis.

Coagulopathy in major trauma and haemorrhagic shock

Thromboelastography technologies have been integrated into the management of the patient with exsanguinating trauma. The treatment of such patients has rapidly evolved over the last twenty years. Prior strategies had incorporated aggressive and definitive surgical control of bleeding, aggressive crystalloid fluid resuscitation, without particular focus on either coagulopathy or management of the inflammatory response. Much has changed.[18] Current strategies employ early 'damage control' surgery (including topical haemostatic agents and endovascular techniques) with definitive surgery after completion of resuscitation, early empiric (or TE guided) administration of clotting factors to address coagulopathy, blood component resuscitation with permissive hypotension until control of haemorrhage and minimal use of fluids that exacerbate inflammation during resuscitation. These changes have been driven by research into areas including microcirculatory and inflammatory changes in shock that are outside the remit of this article, but progress in the understanding of coagulation has also been critical.

Coagulopathy in severe trauma is common, occurring in as many as one in four patients,[6] and is initiated by the maladaptive response to the combination of severe shock and tissue trauma. This combination initiates multiple poorly-understood pathological mechanisms resulting in systemic anticoagulation and fibrinolysis.[18] Previous theories have included hypothermia, acidaemia and consumption of coagulation factors as the underlying causes, although it is now clear that these, although important, are not central to the pathologic mechanisms, particularly in the acute phase. It is more likely that the dilution of clotting factors either consequent to auto-resuscitation or iatrogenic (with packed red cell or crystalloid resuscitation) is contributory,[35] compounded by both the inflammatory response[18] and platelet dysfunction.[46]

Better understanding of the detrimental effects of red cell and crystalloid resuscitation have driven the development of institutional 'massive transfusion protocols,' that include plasma, platelet and cryoprecipitate components. Difficulties in the provision of thawed fresh frozen plasma in the acute setting can be circumvented by the use of freeze-dried plasma,[28] allowing for rapid and high volume plasma transfusion, although this is not currently readily available. However, whilst massive transfusion protocols are likely only to alleviate further iatrogenic exacerbation of traumatic coagulopathy, other products are intended to actively reverse the coagulopathy. Recent areas of interest have included fibrinogen concentrate (readily available in other parts of Europe), recombinant factor VIIa prothrombin complex concentrate (PCC) and tranexamic acid. The last of these has demonstrated a significant reduction in mortality in general trauma patients in the CRASH-2 trial[9] and work is ongoing on the CRASH-3 trial into isolated traumatic brain injury.[11]

Antiplatelet and anticoagulation agents:

1) Antiplatelet agents:

Oral anticoagulant and/or antiplatelet agents are commonly prescribed for primary or secondary prevention of stroke, myocardial infarction, peripheral vascular disease and VTE. However, with their significant reduction in thromboembolic events, comes an increased risk of intracerebral haemorrhage (7-10 fold for oral anticoagulation), which is often larger at initial presentation and has a greater risk of extension.[14]

Aspirin is a very commonly prescribed antiplatelet, which irreversibly binds to cyclooxygenase-1 and inhibits the production of thromboxane A2 (TXA2), adversely affecting platelet function throughout its life (7-10 days). It is metabolised rapidly to an ineffective metabolite, and thus all new platelets produced thereafter have normal function. Therefore, discontinuing aspirin 10 days prior to elective neurosurgery is sufficient to ensure normal platelet function. Emergency correction is achieved by a single unit of platelets, the adult therapeutic dose (ATD).

The thienopyridine drugs clopidogrel and prasugrel are newer antiplatelet agents with greater efficacy than aspirin, which probably leads to a higher degree of morbidity and mortality in the neurosurgical patient.[7] They are prodrugs and undergo hepatic metabolism (by cytochrome P450) to their functional metabolite. They irreversibly bind to P2Y12 subtype of the platelet ADP receptor, inhibiting the GPIIb/IIIa complexes, fibrinogen binding and P-selectin expression.[23] Another different P2Y12 inhibitor (ticagrelor) is also being increasingly used in modern arterial dysfunction management. In the elective setting, normal platelet function can be expected 10 days after discontinuation.[45] As platelet dysfunction is more severe than that of aspirin, in neurosurgical emergencies the prescription of 2 units of platelets has been suggested.[4] Other groups have suggested platelet transfusions do not achieve correction in all patients on clopidgrel[40]. Although there is an absence of high quality evidence it is reasonable to undertake emergency surgery with caution subsequent to a 2 unit platelet transfusion.

2) Classical anticoagulants:

Warfarin, a commonly prescribed anticoagu-

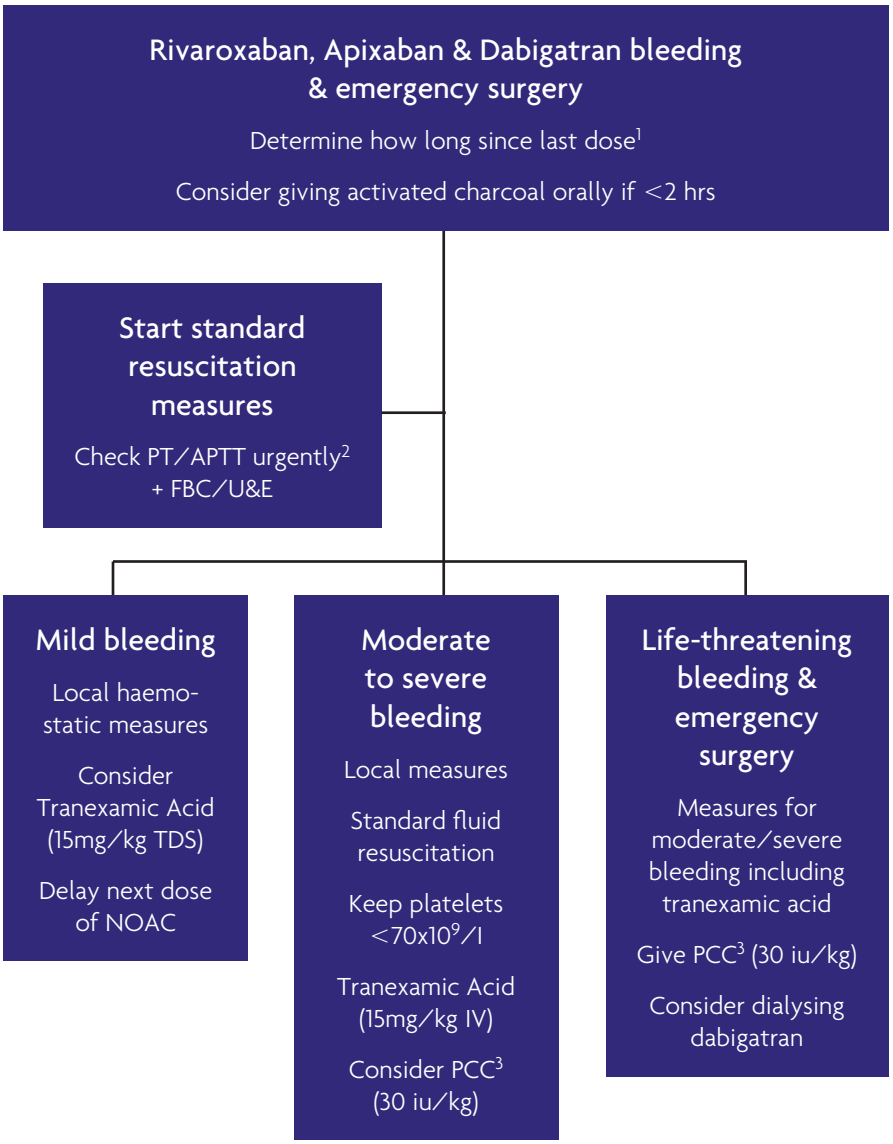

Figure 4. Correction of NOACs in Derriford Hospital, Plymouth, UK, TJ Nokes November 2014. Further information provided in the local guidelines are that: vitamin K and protamine sulphate do not reverse the activity of rivaroxaban. The numeric references in the flowchart refer to: 1) Half-life of Rivaroxaban and Apixaban is 6-12 hours / Dabigatran 12-17 hours (will be prolonged in renal failure – GFR <30ml/min), 2) If PT/APTT normal, there is no need to reverse Rivaroxaban and Apixaban / Dabigatran respectively and 3) Consider PCC after discussion with Haematologist (off license use for PCC, and thus a need to exercise caution). It is advised not to use rfVIIa (Novo7) and to keep careful record of bleeding associated with all agents.

lant, inhibits vitamin K epoxide reductase and thus antagonises vitamin K dependent factors (FII, FVII, FIX, FX, protein C and S). The reversal strategies are twofold: improved regeneration by vitamin K supplementation and direct replacement of the depleted coagulation factors. The former is slow, with intravenous administration only beginning to reduce the INR from two hours, and has an unpredictable response. It is appropriate for 'elective' correction as a normal INR can be achieved in most cases within 24 hours. Intravenous doses of 5-10mg of vitamin K are normally advocated.[3] Having said that, hospital protocols will often suggest merely stopping the warfarin approximately five days before the planned procedure, with monitoring of the INR. Consideration should be made in such cases as to the need for bridging therapy. This usually takes the form of either low molecular weight heparin or unfractionated heparin, and the decision to prescribe bridging therapy is dictated by stratifying the thromboembolic risk to the patient.

In emergency situations, it is necessary to replace the depleted coagulation factors more rapidly. Fresh frozen plasma (FFP) can be effective but has several limitations: very variable levels of vitamin K dependent factors, thawing takes time causing inevitable delays and large volumes required can cause overload and congestive cardiac failure, particularly in elderly patients. FFP is now actively discouraged for emergency reversal of vitamin K antagonist drugs such as warfarin. Consequently, four factor prothrombin complex concentrate (PCC) is now recommended by haematology guidelines (BCSH). These have predictable, higher levels of vitamin K dependent factors and thus allow almost immediate correction of associated coagulopathy and smaller transfusion volume. The elimination half-life of some factors in PCC is short, and therefore it is recommended that vitamin K (5-10mg IV) is concurrently prescribed to avoid the rebound to an anticoagulated state.[4] Post PCC INR should be monitored to detect this potential rebound effect.

3) Direct New Oral Anticoagulants (NOACs)

The NOACs are either direct thrombin (dabigatran) or direct factor Xa (rivaroxaban and apixaban) inhibitors, and are used largely in the prevention of systemic embolisation in non-valvular atrial fibrillation or the treatment of venous thromboembolic (VTE) disease. They benefit from predicable pharmacokinetic and pharmacodynamic profiles compared with alternatives such as warfarin,[13] do not require laboratory monitoring and are equivalent or have significantly improved efficacy to warfarin in preventing stroke or embolic disease.[8,32] Significantly however, there are no current specific reversal agents and thus these agents are problematic for neurosurgeons![15]

Apixaban and rivaroxaban have a half-life of 7-14 hours[33,42] and are predominantly liver excreted (65-75%). Dabigatran has a half-life of 12-17 hours[39] and is 80% excreted in the urine.

Whilst there is no requirement to monitor these agents in routine practice, in the emergency situation, assessment of the aPTT and PT can be useful only to check if any active drug is not present, when in the normal range. The aPTT is increased by dabigatran, rivaroxaban and apixaban, however the relationships are not straightforward. The PT and INR are poorly sensitive to dabigatran and not suitable for monitoring.[39] Conversely, PT correlates better with rivaroxaban and apixaban plasma concentration, but is dependent on PT reagents used and is not very linear.

If elective neurosurgery is required whilst the patient is taking NOACs, then one should discontinue the medications prior to surgery. Fawole et al.[13] have suggested the following guideline for termination of the NOAC prior to elective surgery (Table 1) based on a number of studies.

The optimal time to re-start NOACs after neurosurgery is not defined. Consensus guidelines suggest it can be re-started once the surgical bleeding risk is under control in the early post-operative period.[41] It has been suggested that re-commencement at 24-48 hours post-operatively is reasonable and some have suggested that clinicians might consider a re-introduction at half the patients' normal dose for the first day.[38] However, where some thromboprophylaxis is required, the use of low dose low molecular weight heparin is probably sensible and licenced.

If patients suffer significant intra-cerebral haemorrhage whilst prescribed a NOAC, they should be considered for intensive care treat-

Table 1. Common NOACs with creatinine clearance rates and the number of days prior to neurosurgery or spinal surgery that they should be stopped.

Anticoagulant drug	Creatinine clearance (mL/min)	High-risk surgery (e.g. Neurosurgery or Spinal surgery)
Dabigatran	>50	2 days
	31-50	4 days
	≤30	6 days
Rivaroxaban	>30	2 days
	≤30	4 days
Apixaban	>30	2 days
	≤30	4 days

ment and an accurate drug history must be obtained including the time of last NOAC dose. If within two hours, charcoal administration may be helpful. There are no specific reversal agents beyond studies in rat models,[24] although clinicians might consider supportive therapies such as fluid resuscitation or packed red-cell transfusions.[43] In addition, recombinant factor VII (rVIIa, novoseven) and three or four factor PCCs and Factor VIII inhibitor bypassing activity (FEIBA or activated four-factor prothrombinase complex concentrate) have also been suggested, however the evidence is not strong.[10,12,26] Haemodialysis can be considered to accelerate the removal of dabigatran in life-threatening cases. Rivaroxaban and apixaban are more highly plasma protein bound and haemodialysis is not useful in these cases. Our current protocol for the reversal of NOACs is demonstrated in figure 4. We do not advocate the use of rVIIa as there has been a number of adverse arterial events in previous off licence trials. We do suggest using tranexamic acid for moderate to life-threatening bleeds, but not FFP as the factor concentrations are so unpredictable.

Peri-operative venous thromboprophylaxis (TP)

All surgical patients mandate a decision regarding the timing of peri-operative deep venous thromboprophylaxis. Neurosurgical patients are particularly complex in that even a small, induced haemorrhage secondary to thromboprophylaxis can be fatal or cause severe morbidity. However, given the long surgical times and often poor mobility post-operatively, the patients are at significant risk of VTE. Decision-making about when to commence TP is challenging. Options available to the surgeon broadly include unfractionated heparin (UFH) or low molecular weight heparin (LMWH) for chemical prophylaxis, and intermittent pneumatic compression, venous foot-pumps and anti-embolism stockings as mechanical options.

NICE guidance (2010) on TP has suggested neurosurgical patients who are at increased risk of VTE should commence mechanical prophylaxis at admission and this should continue for the duration of any impaired mobility.[30] Pharmacological prophylaxis (UFH or LMWH) should be added for any patient without risk of major bleeding, but this should be considered at an individual patient level. There is specific advice that pharmacological TP is not prescribed to patients with unsecured, ruptured cranial or spinal vascular malformations or haemorrhage in the unstable patient.

UFH has a short half-life (45-90 mins) and thus requires continuous intravenous infusion to achieve therapeutic anticoagulation, although it can also be prescribed as a twice or thrice daily subcutaneous injection for prophylaxis. With intravenous prescriptions of UFH it is necessary to monitor the therapeutic activity with regular aPTT measurement as the response can be highly variable. Owing to its short half-life, correction can be rapidly achieved by the termination of the infusion. It is therefore useful for short-term therapeutic anticoagulation in the patient with a high risk of both thromboembolism and haemorrhagic complications. In situations requiring emergency correction, protamine sulphate is very effective.[4] LMWH has a longer half-life (6-12 hours) and is therefore more convenient for the patient. It is not necessary to monitor its therapeutic activity in routine clinical situations, although this is possible with anti-Xa assays, and should be considered in those with renal impairment (GFR <30ml/min), the morbidly obese patient and pregnancy. It is, however, not totally reversible. Protamine can reverse 40-60% of the anti-FXa activity, at the recommended dose of 1mg per 1mg of LMWH administered in the previous four hours.[1,44]

Significant recent work into TP in neurosurgical patients has been undertaken by Hamilton et al.,[20] publishing a systematic review and meta-analysis of eight randomised controlled trials. Six studies compared either UFH or LMWH (low molecular weight heparin) with or without mechanical prophylaxis, with placebo or mechanical prophylaxis. Two studies compared UFH plus mechanical prophylaxis with LWMH plus mechanical prophylaxis. They found that heparin prophylaxis reduced the risk of symptomatic and asymptomatic VTE by 42%, but with an insignificant increase in the rate of intracerebral haemorrhage (ICH), and a statistically significant doubling of minor haemorrhages (e.g. extracranial haemorrhage). These corresponded to a number needed to treat (NNT) to prevent a VTE of 11, and a number needed to harm (NNH) of 143 for ICH and 36 for other minor bleeding. Clinicians should be cogent to the impact of the events however, most would consider a screened finding of a distal lower limb deep venous thrombosis (DVT) less of a burden to the patient than a proximal or symptomatic DVT, or a pulmonary embolus. The ratio of screen-detected events to symptomatic events is in the region of 10-20%.[16] This is important as only two RCTs in the aforementioned meta-analysis distinguished such clinically significant VTEs from screen-detected DVTs. However, with all such trials of anticoagulants, which report asymptomatic DVT, it cannot be predicted who will go on to develop significant VTE events. Ultimately, Hamilton et al. state that for every 1000 elective cranial neurosurgical patients, 56 clinically asymptomatic distal DVTs will be prevented, 35 proximal DVTs/PEs would be prevented (of which 9-18 would be symptomatic). Conversely, seven patients could suffer an ICH. Therefore, the decision in these cases ultimately rests on the risk of a statistically significant reduction in the risk of symptomatic VTE versus the clinical significance of an intracerebral haemorrhage.

Conclusions

The modern neurosurgeon has witnessed the emergence of new challenges in coagulation. These include: polytrauma patients, the significant increase of elderly neurosurgical patients who take antiplatelet agents, increased numbers of patients anticoagulated with warfarin, and the increasing numbers of patients taking NOACs. In addition whilst NOACs have reliable pharmacokinetics, they lack an accurate method to measure their effects and clear options for timely reversal of their effects. However, the stroke prevention trials of NOACs have shown significant reductions in intracranial bleeding over warfarin; trials of reversal agents are ongoing. Fortunately, advances in both our understanding of the theory behind coagulation, and better methods for its assessment with rapid near-patient testing provide us with an armamentarium with which we can address some of these challenges.

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Focusing on the invisible patients

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The controversial 2012 Health and Social Care Act introduced major changes to key structures and processes in health and social care. For neurology in particular – a historically neglected grouping of conditions, which consumes an ever-expanding portion of the NHS budget – the reforms represented both a challenge and an opportunity. Would the creation of a new cohort of clinical commissioning groups (CCGs) lead to disruption of existing services? Or could the new commissioners lead the development of new and better pathways of care for the 10 million people living with a neurological condition in England?

Reform of this magnitude will always carry both risks and benefits. Clinical commissioners have faced the difficult task of taking on a swathe of new commissioning responsibilities at a time when funding is stretched and the NHS is grappling with the challenges of an ageing population. There is little doubt that the transition to clinical commissioning has led to disruption which has, in some cases, impeded the NHS's efforts to develop more effective, better-integrated services with a stronger preventative focus.

At the same time, clinical commissioners find themselves faced with a huge opportunity to transform care and outcomes for the people living in their area. With a stronger local presence than their Primary Care Trust predecessors, CCGs are well-placed to take a strategic approach to service improvement, based on a better understand of local needs and priorities. Unfortunately, the available evidence suggests that many CCGs are failing to engage with the challenge of improving neurological services.

For its report *The Invisible Patients: Revealing the state of neurology services*, the Neurological Alliance carried out a Freedom of Information audit of all CCGs in July 2014. 91% of CCGs responded, but the replies showed that far too many are not carrying out the key processes that enable a strategic approach to service improvement in neurology. For example, as few as 20% of CCGs have ever carried out an assessment of the number of people using neurological services in their area, while fewer than 15% have assessed the costs relating to the provision of neurological services locally. Only a third of CCGs have mechanisms in place to obtain feedback from people living with neurological conditions locally regarding their experiences of the services they receive.

This represents a major missed opportunity. NHS spending on neurological conditions has soared by 200% over the past ten years, which also saw a dramatic rise in emergency hospital admissions for neurological conditions, reaching 700,000 in 2012/13. A recent Neurological Alliance survey of just under 7,000 neurological patients found that almost 40% of people diagnosed with a neurological condition waited at least a year for that diagnosis, while over 30% saw their GP five or more times before finally accessing a specialist Neurologist. Care coordination is often very poor, and over 70% of people with neurological conditions do not receive a care plan, even though the majority of neurological conditions are long-term. There is clear scope to improve outcomes and alleviate pressure on budgets through better designed pathways of care, but only a minority of CCGs appear to be engaging with this challenge.

This is partly the result of neurology's lack of representation in the quality and improvement architecture of the NHS. In its 2012 review of service for people with neurological conditions, the Public Accounts Committee identified a profound lack of accountability for neurology services at all levels of the health and care system, to the detriment of patient outcomes, quality of care and value for money. Unfortunately, little progress has been made in this area since 2012. For example, both the NHS Outcomes Framework and the Clinical Commissioning Group Outcomes Indicator Set make reference to only three neurological conditions (dementia, stroke, and epilepsy in children), and neither make any reference to neurology as a whole. Consequently, CCGs have little incentive to devote appropriate attention to local neurological services.

Neurology is also disadvantaged by the shortage of available data that would guide local commissioning decisions. Despite the creation in 2014 of the first minimum dataset for neurological conditions and the establishment of the Neurology Intelligence Network, neurology continues to lag behind other condition areas in the accuracy and consistency of data and intelligence collected. The shortage of reliable local data covering (for example) prevalence, costs and outcomes relating to neurological services inhibits CCG understanding of neurology and impedes service improvement. Given the spiralling costs of treating neurological conditions, there is a clear need for accurate and comparable local data, in order to improve understanding of local needs and identify areas requiring improvement.

It is now time for these issues to be addressed. At a time when NHS England is planning to expand CCGs' commissioning responsibilities for neurology to include involvement in specialised commissioning, it has never been more important for local commissioners to actively improve their engagement with and understanding of neurological conditions. It can no longer be acceptable for people living with these conditions to be 'invisible patients,' overlooked by the key decision-makers and budget holders within today's NHS. It is vital that both CCGs and central organisations such as NHS England and the Department of Health recognise the need for service improvement in neurology, and work together to deliver it across the country. Only then will the millions of people with neurological conditions receive the care they need and deserve.

The creation of a 'Psychological Wellbeing after Stroke' group

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The Psychological Wellbeing Group takes place weekly at the multidisciplinary team led, 24-bed Stroke Rehabilitation Unit, Beech Ward at Norwich Community Hospital.

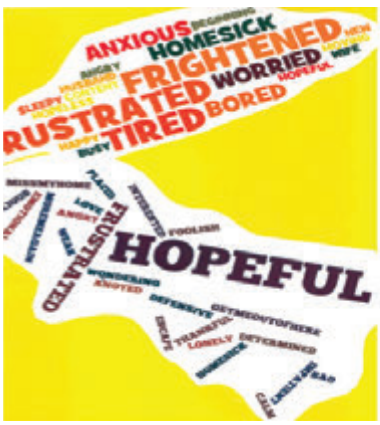
The group was created to support and educate stroke survivors about adjustment, offering opportunities to share experiences of their journeys and to help normalise feelings related to adjustment to their illness and resulting disability, also providing patients with space to acknowledge and express their feelings.

NICE guidelines recommend setting up psychosocial education groups; based on findings from Croydon's national stroke project, NICE further suggest that 'people with stroke may want to access support in the form of meeting other people with stroke, or receiving information and advice'. This may include groups developed for people and their families; stroke education, psychological wellbeing, information giving or 'telling your story'. Recommendations state 'the role of such a group is to provide basic important stroke education (causes, physical and psychological effects and treatment approaches), describing local care pathways and what to expect. They suggest 'resources and educational materials should be accessible for people with communication, visual and cognitive impairments, backed up with information people can take away from the group' and 'always ask for feedback from those who attend and act on it'.

The group steps include:

- Introduction of group members, the facilitators and the psychology service for the stroke pathway, group session overview.
- Ground rules – confidentiality, right to leave group and choice of participation.
- Mindfulness exercise 1 – 'feelings are like clouds'. Participants to engage and tune into feelings in the here and now. Patients to name three feelings and to record on a post-it note on a worksheet – facilitators support participants with this. They are encouraged to share with the group, following which discussion is encouraged and under guidance of the psychologist, feelings in the room are being explored.
- Group members are asked if they have ever watched clouds or observed changing shapes and asked the question 'what do clouds do?' Answers include 'change shape', 'rain on you' and 'have a silver lining'. These are set in context with feelings and participants are encouraged to view their feelings mindfully, i.e. to see them in their current shape and form, intensity and acuteness and then watch them drift away, change and disappear or turn into something else, just like clouds.
- The psychologist guides them through the adjustment process graph, highlighting that patients in the room have coped with and mastered similar challenges.
- Similarities and differences are reflected by the psychologist highlighting the shared experience aspect and encouraging the participants not to view themselves as isolated with the aftermath of this potentially traumatic life event.
- Adjustment and rehabilitation process is compared to a rollercoaster ride.
- If the group allows time and appears appropriate for this exercise, they are asked to describe 'if you were a piece of fruit what would you be and why?', allowing dialogue and participants to open up about themselves, supports laughter and light heartedness and gives the group a lighter, more uplifting moment.
- The facilitators answer questions and deal with other issues.
- Three-minute mindfulness exercise recorded by Dr Melanie Fennell.
- Filling in feedback forms with co-facilitators.

The group content has been adapted slightly over the



Below: Wordle cloud containing feelings patients have reported. The bigger the word, the more often it has been reported.

past 12 months due to patient feedback, which influences content and delivery frequently in order to mirror the patient's voice. Quality is assessed constantly and is at the heart of the project. It also gives the MDT an indication of the participant's needs and psychological mindset and is part of the psychology pathway and intervention for patients. Detailed results and analysis of the feedback from patients on their experience can be found in the full-length article.

PATIENT COMMENTS

Useful
I can now understand more about my stroke and emotions
Helped to cope with the stroke
I enjoyed the group discussions
You share something so you don't feel alone
I don't think it was very enjoyable, it was quite painful, but cathartic
Small group helped me feeling comfortable to share my feelings & thoughts
Facilitator was very understanding of our feelings and journey
Coming to this group has done me very good
Nice to talk
It is useful to talk to others with similar experiences
We are all in the same boat
I have been to the group 4 times and it is always helpful
It is beneficial to the share experience
It is very nice to meet other people who have been affected by stroke
It has been very helpful
Meeting and sharing with others means you are not the only one
It helps to discuss with people in the same situation
Very beneficial to hear what happened to others
I hope I helped others by telling my story

Participants will have a copy of the 'Feelings are like Clouds' sheet, aiming to support patients to not feel trapped with certain feelings but instead see and notice them for what they are and then letting them go.

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Guillain Barré Syndrome

Reviewer: Dr Simon Rinaldi, Academic Clinical Lecturer, University of Oxford, Oxford, UK.

My review includes one paper, two clinical trials, and a multicentre observational study, united under the common theme of the year in Guillain Barré syndrome – international collaboration.

Ever since the 1976 "swine flu" vaccine was suspected of inducing GBS there have been anxieties that subsequent vaccines might also have this adverse effect. This was especially the case during the contemporary outbreak of a similar influenza strain (H1N1). In a study published earlier this year, the Global H1N1 GBS Consortium demonstrate the feasibility of international collaboration in assessing vaccine safety.[1] An impressive 479 GBS cases were contributed by 15 countries, providing unprecedented power to assess this rare adverse event. Using a self controlled case series methodology not reliant on accurate knowledge of underlying background incidence rates, the consortium report a relative increased incidence of 2 to 3 for GBS in the 42 days following H1N1 vaccination, translating to 1-2 excess cases per million vaccines administered. They were also able to show the time of peak GBS risk is 8-21 days post vaccination, as might be expected for a pathological mechanism likely to be driven by an IgG based humoral immune response. The at risk period chosen and the influence of seasonal infections, including influenza itself, can confound these estimates. Nevertheless, the study addresses these concerns using a number of different statistical approaches, and gives a consistent estimate of the risk of vaccination with respect to GBS. This has immediate utility in counselling patients who might receive vaccination, and in informing vaccination policies.

The bottom line is that this high quality evidence shows that the risk of GBS is low, and almost certainly outweighed by the protective benefits of vaccination.

Likewise, patients with GBS are often understandably anxious to know how long they will take to recover. Until recently, meaningful prognostication proved difficult. Another highly impressive ongoing international study aims to identify easily obtainable factors which predict disease course at an early stage, building upon earlier excellent work from the Dutch GBS study group. The International GBS Outcome Study (IGOS) aims to collect detailed clinical data, along with serum samples and DNA, from 1000 patients with GBS.[2] In the last year 100 centres over 13 countries have joined the study and approaching 220 patients have been included at the time of writing.[3] This unprecedented international collaboration has great promise in improving prognostication, but also will provide an extremely valuable bio-bank for study of immunopathological mechanisms and genetic susceptibility. Moreover, IGOS will integrate with international multi-centre treatment trials, as has already begun with the International Second-dose IVIg trial, and will underpin future studies of novel agents such as complement inhibitors.

The benefit of international collaboration for addressing key questions in GBS has already been well demonstrated, and as such the results from IGOS and related studies are eagerly anticipated.

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An overview of current augmentative and alternative communication trends, services and experiences

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Current issues in AAC

AAC describes methods of communication used by individuals with communication difficulties that add to or replace spoken communication. These include communication boards and books (low technology) as well as electronic devices such as voice output communication aids (high technology).[1]

The proliferation of inexpensive mobile technologies has dramatically changed the landscape for individuals with communication difficulties, with the use of touch screen phones and tablet devices being readily adopted by these individuals, partly as they are cheaper and more universally available than traditional dedicated communication aids.[2] These also enable digital, as opposed to face-to-face, communication e.g. e-mail, Skype and social networking. iPads are an example of a mainstream device now commonly used as a communication aid by children and adults, with many communication apps being developed and sold for minimal cost. The development of mainstream technologies is largely driven by the needs and preferences of the wider population, which rarely match the needs and skills of individuals with complex physical and communication needs.[3] It is important to ensure that provision for individuals who require adaptations and specialist soft and hardware does not diminish.

Another field of development has been voice banking for individuals who are likely to lose their speech as a result of a progressive condition, which enables a person's own voice to be stored for use later with their communication aid.[4] The computer generated voices of high technology aids have been cited as critical factors in the acceptance and use of communication aids.[5]

Eye-gaze technology has been used by small numbers of severely disabled people to control bespoke communication aids for some time, but is now being developed as a more consumer friendly tool for mainstream devices, such as a laptop or Windows tablet. Recent developments have seen lower cost eye-gaze cameras, originally intended for gaming, being developed to work with lower cost tablets including iPads.

There has also been a growth in Brain-Computer Interface (BCI) research over the past 15 years, with one development being its use as a communication aid. BCI systems measure brain activity recorded from the scalp or cortical neurons which enable individuals to communicate through computers by controlling cursor movements or selecting letters.[6] BCI does offer a new potentially life-changing method of communication for those with limited or no muscular movement, particularly with poor vision. However, technological development and larger-scale research is needed before it can be used reliably as a communication aid with any vulnerable client group. There are a number of practical issues that need to be explored before it is released to the larger population of individuals with communication difficulties e.g. technical support, training, ease of use of set up and reliability of response rates. Alongside technological changes, financial and political factors are influencing AAC provision. Historically, funding for and access to AAC provision and assessment has been problematic in the UK, with a history of poor provision and a postcode lottery for individuals with communication needs.[7] However, from April 1st 2013, AAC was assigned under NHS Specialised Commissioning, commissioned directly by NHS England, with specialist AAC assessment, equipment, training and support having a dedicated, albeit finite funding budget, ensuring a more equitable service.[8] A 'hub and spoke' service model was proposed with specialist centres ('hubs') providing assessment and provision for the 10% of individuals who require a specialised service, and local services ('spokes') to provide the remaining 90% requiring non-specialised AAC. Services are currently awaiting confirmation of hub designation status.

If specialised AAC services are to meet the NHS Outcomes Framework Domains, required by the new NHS specialised commissioning contract, of enhancing quality of life, ensuring individuals have a positive experience of care and protecting individuals from avoidable harm,[9] we need to ensure that the services and AAC devices provided are evidence-based and person-centred.

Experiences of communication and interaction using a tablet to communicate

In June 2014 students from University College London underwent various 'communication challenges' as part of the Royal College of Speech and Language Therapist's Giving Voice Campaign to raise awareness of services essential to people who have communication or swallowing difficulties. One student, Helen Currie, spent a week using a text-to-speech application on her tablet. This was her sole means of communication aside from typical non-vocal communication strategies such as facial expression, gesture, basic signing and body language. In what follows, Helen recounts her experience of a week with no speech.

Why I did it

As a Student Speech and Language Therapist (SLT) I had been learning about the implementation of assistive devices to support communication. Before

starting my course I had worked as an assistant with many people with communication difficulties. Some used devices with great success but some abandoned them altogether. I wished to gain further insight into the use of such devices and discover why people may accept and/or abandon them.

What I found

My reactions to using the device surprised me and several key interactional issues became apparent:

- I was a slow communicator

I found it difficult to get noticed, to initiate my turn in a conversation and to fight for my space to talk. The social environment in which I was interacting did not allow for minutes to go by without a response. People would often jump in to help out and guess what I wanted to say, or simply take the floor for them, as what I had to say was not worth the wait. This led to a sense of loss of control. Not only control of my end of the conversation, but with it, my ability to express my beliefs and negotiate my personhood within my social networks. I was now in the hands of those I interacted with, as maintenance of my interactional space was largely up to their patience.

- My tablet stole my identity

The focus of my communication was the device, not me. People were looking at what I was typing, not at my face or body: much information about how I felt about something was therefore lost or not conveyed simultaneously with the message but at a delayed point. Similarly, as I was looking where I was typing, I was not able to see people's faces and pick up on how they felt or their needs in the conversation and so could not react as I would have liked to. The subtleties of meaning conveyed through intonation, stress and pitch and idiosyncratic features such as my accent were lost to an electronic voice, its only similarity to mine was that it was female.

- Communication became a chore

Communication breakdown was very common due to difficulty with the volume of the voice or the lack of intonation. I was constantly typing, repeating, and clarifying. It was exhausting. Therefore communication became frustrating and bothersome and I found myself avoiding circumstances in which I would bump into people to avoid the trouble of taking out my device. Further to this, I felt a certain stigma in taking out my device and drawing attention to my different way of communicating. Someone even told me they deliberately avoided me when I was using it.

Conclusion

My experience was not that of somebody who has genuine communication difficulties, which may warrant the introduction of an assistive device. However, the challenges I faced raised certain issues around interaction with assistive devices. These experiences resonate with published work by people with disabilities.[10,11] Mainly, that the interaction is not about the equipment, it's about the people. Provision of assistive technology is vital but is not a miracle solution to communication difficulties. This highlights the fact that simply supplying a device for communication does not solve 'the problem'. Interactional advice could help people who use devices and their significant others to develop conversational patterns which are satisfactory to them. The full blog of the communication challenges can be found at: uclugivingvoiceblog.wordpress.com

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TBK1 mutations in sporadic ALS

Reviewer: Jemeen Sreedharan, The Babraham Institute, Cambridge, UK.

Exome sequencing has revolutionised gene mutation discovery, focusing the hunt on disease-causing variants. A recent study in familial ALS (fALS) patients identified mutations in Tuba4A (a tubulin, thus implicating axon dysfunction) as a needle in the haystack (Smith et al 2014,). They looked at 363 fALS cases, with a replication cohort of 272 cases. But no other mutations were immediately obvious. This suggests that the identification of other coding mutations in novel genes in fALS is going to be challenging.

So, given the paucity of clearly pathogenic novel exonic variants in fALS, what are the chances that new mutations could be found in a cohort of sporadic ALS patients (sALS), who by definition have no family history of ALS? The chances ought to be slim, but the sheer size of the latest exome study published in Science was key to identifying a number of novel variants. Cirulli et al looked at a cohort of 2874 sALS and a replication cohort of 1318 ALS cases, some of which were familial. The most significant finding was an over representation of missense and loss of function variants in TANK-binding kinase 1 (TBK1). TBK1 phosphorylates many targets, perhaps most interestingly proteins involved in autophagy, such as OPTN and SQSTM1, both of which are also mutated in some ALS cases. Autophagy is a major mechanism of rubbish disposal that may go awry in neurodegenerative diseases leading to aggregates of TDP-43 in ALS, Lewy bodies in PD and amyloid plaques in AD, and is currently an area of intense research. TBK1, OPTN and SQSTM1 are also all implicated in a second pathway, NFkB, which is involved in inflammation, which is also broadly implicated in ALS.

The authors do not go into more detailed functional studies regarding TBK1 (figure 2 summarises mutations they found in well-known ALS genes, while figure 3 is a pathways/interactions diagram). They do, however, show that another less significant hit from their study, NEK1, interacts in vitro with known ALS genes (VAPB and ALS2).

Clearly a lot more functional work is needed to identify how these TBK1 variants contribute to disease, and TBK1 inhibitors, which are already in existence, may be useful tools to begin this process. Furthermore, the huge amount of data generated by Cirulli et al will serve as an important resource for current researchers and for future, larger studies of ALS, which will identify the missing genes in the interaction networks that underlie motor neuron degeneration.

Smith BN, Ticozzi N, Fallini C, et al. Exome-wide rare variant analysis identifies TUBA4A mutations associated with familial ALS. Neuron. 2014 Oct 22;84(2):324-31

Elizabeth T. Cirulli[1],* Brittany N. Lasseigne[2],* Slavé Petrovski[3] et al Exome sequencing in amyotrophic lateral sclerosis identifies risk genes and pathways. Science. Published online Feb 19th 2015.

Diet and Nutrition in Dementia and Cognitive Decline

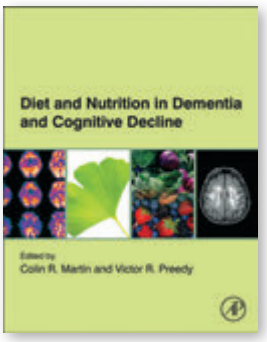
This is a comprehensive publication which has dual aims of looking at the role of nutrition in the development of various forms of dementia, and how nutrition is affected as dementia progresses. It also includes practical strategies to manage the various challenges.

Before addressing the question of nutrition, a detailed introduction describes the range of dementing disorders, including conditions not always placed under the dementia 'umbrella', such as Motor Neurone Disease and Normal Pressure Hydrocephalus. The diagnosis and management of these conditions may be a useful reference, particularly for non-Neurologists, and especially for the rarer conditions such as Pick's Disease.

The literature base is fully sourced and referenced consistently in every section, and authored by experts in that field. This reassures the reader that a balanced argument is given for the data presented. There is the additional advantage that this book is extremely up to date and therefore includes the most recent and topical of trends or innovations in diet, such as the 'Paleo' diet and the use of the over the counter nutritional supplement 'Souvenaid®'.

This is a reference book which is likely to be helpful to 'dip in and out of' according to your clinical speciality, and the patients you see. For clinicians specialising in Neurology and Palliative Medicine it can provide a useful guide to provide objective answers to questions patients may bring to clinic. Such questions may seem trivial, such as 'I have heard I should take a Magnesium supplement/eat oranges etc. etc. to slow the rate of my dementia progressing – what do you think Doctor/Nurse/Dietitian?', but will be important to the patient and should be addressed. This book allows, at a moment's glance over the wide-ranging content and index, a review of the literature and the practical advice required.

Over the last few decades, there has been intense focus on primary prevention of cardiovascular disease. Many of the elements of a cardio-protective diet may also be protective in cognitive conditions, especially vascular dementia. However, as we look to prevent cognitive disorders, this book serves to also remind clinicians of the role of diet, as well as other risk factors. Its wider readership might include those working in Health Promotion and Public Health. And it is probably accessible enough that relatives of those affected by the conditions described might use it to pick up information about lifestyle adjustments that they might consider.



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Reviewed by:
Rebecca McManamon, Consultant Freelance Dietitian, London, UK.

Pharmacology and Aphasia

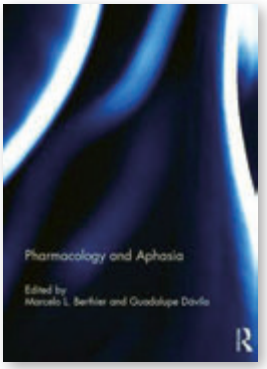
This short collection of essays, originally published as a special volume of the journal Aphasiology, is a surprisingly optimistic read. Notwithstanding the fact that my favourite sentence in its 138 pages (on Page 1, as it happens) refers to the addition of 'complimentary interventions' (c.f. complementary) to traditional forms of rehabilitation for syndromes of language impairment, the volume as a whole is serious-minded and measured in its handling of content which is somewhat outside the mainstream of Clinical Neurology. Of course, there are no definitive answers, let alone any offer of a magic potion to restore speech. However, there are several pointers to potential drug treatments that might complement current approaches, and perhaps mollify the turn of phrase of the most uncomplimentary therapist.

There are seven chapters in all, including a general introduction. It will hardly come as a surprise that the drugs reviewed are the usual suspects of current practice in the neurodegenerative disease. Thus we have the dopaminergic drugs, as well as those acting on the cholinergic system, and memantine. It is a little disconcerting for those who have learnt to avoid ergot derivatives because of their fibrotic side-effects to see bromocriptine commended for its potential to improve the success of speech therapy after stroke. I must also admit to becoming a little uneasy as I read at the very idea of chemically enhancing the processes of cognition! Might clinical evidence of efficacy form part of an argument to justify the use of similar approaches in the healthy? How soon would this become the norm, and not the exception? How long would it be before its wisdom could truly be determined? But such concerns are probably an indulgence – certainly, any patient with aphasia, struggling to make progress with speech therapy, could be forgiven for thinking so.

The first of my points of optimism is best encapsulated in the extensive tabulation of published research on pharmacotherapy in aphasia in the second chapter: this extends over eight whole pages. And this despite the fact that aphasia, as a focal cortical syndrome, must be a less promising object of chemical amelioration than syndromes affecting the function of distributed brain systems (e.g. impaired memory) whose ascending and descending cortical- subcortical projections, make use of particular neurotransmitters.

The second point of optimism was to see the important role for the study of very small numbers of patients in the development of novel treatments, when this is done with appropriate rigour and transparency. Of course, there is no doubt that randomised controlled trials are at the epicentre of evaluating medical intervention, but it seems to me that an uncritical acceptance of the RCT approach is unhelpful in numerous neurological conditions. Even in diseases that are quite common, such that suitable numbers may accrue for an RCT, the variety in the manifestations of brain diseases, from one patient to the next, seriously undermines analysis of any but the crudest of outcome measures. The result is the appearance of RCTs, impressive for the sheer amount of work involved, but facile in their conclusions. While collaborative approaches across centres and across borders must form part of the response to the challenge of evaluating treatment in rare presentations, and in rare forms pathology, I think that painstaking study of prototypical cases (such as the chapter by Galling and colleagues in this book) ought not to be discounted.

Might we find a 21st-century therapeutic equivalent of Paul Broca's Tan, whose misfortune taught us so much about the neurological basis of speech? I am prepared to indulge my sense of optimism that there could be a patient with the good fortune to be an early recipient of a drug that substantially reduced the symptoms of aphasia, whose doctor documents the process sufficiently well to provide guidance for the rest of us.



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The ABN Australasian Fellowships

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Introduction

For many years, Australasian trainee Neurologists have come to the UK for training – this has proved very profitable for UK neurology, and helped forge strong links between the countries. It has been less common for UK trainees to make the reverse journey, but both authors of this article have done so – to Perth, Western Australia. Based on our overwhelmingly positive experiences, one of us (RB) decided it was time to encourage UK trainees to travel "down under", and thus in 2012 the ABN Australasian Fellowships were conceived with the first cohort of trainees starting their fellowships in February 2013. In this article we explain how the system works, and why it represents an ideal opportunity to experience a different (and fabulous) part of the world, see how a different healthcare system functions (for better or worse compared to the NHS), and make new, and lifelong friends.

How does it work?

The Fellowships are advertised (via the ABN and ABNT websites) in the early part of each year, with interviews taking place in April/May. This allows several months for successful applicants to obtain the required visas and other paperwork for starting in the following January/February. It is important for applicants to liaise with their Training Programme Directors early (i.e. at the application stage) to allow TPDs to make suitable cover arrangements for the out-of-program period. Applicants are asked to submit their CV along with a short statement as to why they wish to go, and how best they would represent the ABN.

What's on offer?

Three 12-month Fellowships are offered each year. The Fellowships are primarily clinical, and begin in February (this being the antipodean equivalent of August in the UK as far as medical jobs are concerned). They form part of ST3+ training and the successful applicants are given 12 months' accreditation. The venues for each Fellowship change each year, and are carefully selected by ANZAN, the Australasian ABN equivalent. Thus far venues have included Melbourne, Sydney, Perth, Adelaide, and Auckland. The ABN does not provide travel expenses or other financial support, and applicants bear responsibility for ensuring they have the appropriate documentation.

Why should I apply?

They say travel broadens the mind, and whether one considers the professional or social aspects, Australia and New Zealand tick all the boxes. Both are extraordinary countries to explore – but they are a long way away, and, in Australia's case, vast. Thus spending a whole year there is an ideal way to enjoy all they have to offer. Whilst very different in so many ways from the UK, they speak English (sort of), and the way of life is familiar and thus easy to adapt to. Professionally, the Fellowships offer numerous advantages – not least the prestige of an ABN Fellowship, which will sparkle brightly on your CV, and lift you above the masses.

As laid back as Australasians are, expect to work hard; this is not a year off! Both of us went with the idea that we would enjoy some sunshine, and in between barbecues and eating out wander into hospital occasionally and show our cousins how neurology is done properly. It took less than a week for these foolish notions to be rudely wrenched from us – neurology trainees work hard, and we discovered the pleasure of spending long weekends and nights in the emergency department – no general medical registrar or primary care cushions, many people use the ED as their primary care contact in Australasia, and (curiously), they have the idea that people with neurological symptoms should see a neurologist – first - a quaint idea that should perhaps catch on in the UK. Furthermore, some patients may have literally been flown 1500 miles via the Royal Flying Doctors Service in order for you to give a neurological opinion.

We also quickly learnt that Neurologists down there are pretty good, and most have trained overseas, often in modest units such as the Mayo or Queen Square. We knuckled under, cancelled the barbie plans, and learnt a lot. There is time for play, but don't be fooled that a Fellowship is one long extended holiday. We enjoyed Carswell's account of his time, which very much mirrored our own – his stark recounting of unexpected nights in the ED rang very familiar bells (Prac Neurology, in press), and he elegantly provides all the reasons why you should go.

Even now with many years' experience as Consultants, we still acknowledge that cases seen in Perth, examination tricks witnessed and the experience of seeing 'front door' acute neurology influences the way we practice neurology today.

How do I apply?

The Fellowships for 2016 have been already awarded, (this time round to Melbourne and Perth), but 2017 is not that far away, so, watch the ABN website (http://www.theabn.org/what-we-do/awards,-fellowships-and-bursaries/australasian-fellowship.html). You will never regret it.

In Parkinson's disease, patients may suffer from delayed ON as well as wearing OFF – which is more important?

Highlights of a debate held at the 9th World Congress on Controversies in Neurology (CONy) as part of the Britannia-sponsored symposium, 28th March 2015, Budapest, Hungary

Key points

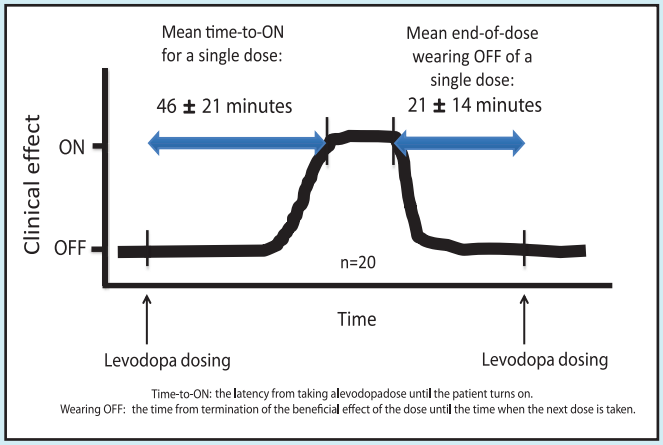
- **A progressive reduction in the consistency of effect of oral medication is a common phenomenon in PD patients resulting in increasingly frequent, and often unpredictable, OFF periods which negatively impact their quality of life and ability to undertake daily activities**
- **OFF periods can result from 'wearing OFF' of the effect of an oral medication dose and a return of symptoms, or a delay in the onset of benefit of a levodopa dose ('delayed ON'), often due to gastrointestinal (GI) dysfunction (delayed gastric emptying and/or impaired intestinal absorption)**
- **OFF periods can be effectively managed by improving time-to-ON with non-oral medications that avoid GI effects on oral therapies, such as subcutaneous apomorphine intermittent injection (APO-go penject) which has a rapid and reliable time-to-ON in patients with morning akinesia and delayed-ON**

In patients with Parkinson's disease (PD), OFF periods that occur despite optimised oral PD medication are a common problem as the disease progresses. Not only do frequent OFF periods present a management challenge to the physician, but importantly they have a significant impact on the patient's daily routine and their quality of life (QoL) [1]. They arise due the fact that with prolonged levodopa treatment, the duration of response, which is initially rapid, reliable and sustained, becomes progressively shorter and so OFF periods occur with increasing frequency. These OFF periods include not only end-of-dose wearing OFF but also delayed time-to-ON (TTO) which contributes as much as two-thirds to total OFF time [2] (Figure 1). At the 9th CONy Congress in Budapest, an international faculty chaired by Professor Amos Korczyn (*Tel Aviv, Israel*) met to debate whether delayed ON or wearing OFF is more important in terms of patient management and outcomes, and also looked at effective options for returning patients to the ON state quickly.

Professor Ubaldo Bonuccelli (*Pisa, Italy*) discussed the importance of wearing OFF and highlighted that it occurred in around 60% of PD patients within 5 years of starting therapy [3]. Wearing off can be observed in early PD and is often underestimated by routine neurological clinical evaluation [4]. The number of OFF periods increases with disease duration and these have a negative impact on patients' QoL [4, 5]. A range of therapeutic options has been investigated in an attempt to alleviate the problem of wearing off, including fractionating levodopa doses, extended-release levodopa, oral dopamine agonists and enzyme inhibitors, but with limited success. However, subcutaneous apomorphine injection has been proven in a range of randomised, double-blind trials to provide rapid (effects seen within 10 minutes) and reliable resolution of OFF periods in PD patients, as measured by a decrease in UPDRS motor scores [6-8] and is well tolerated [9].

Professor Stuart Isaacson (*Miami, USA*) considered that delayed ON was the critical aspect of OFF time and a major unmet need in PD management. GI dysfunction is a common feature of PD and delayed gastric emptying is likely to be a causative factor in delayed ON of a levodopa dose [10, 11] since it will prolong transit to the small intestine where it is absorbed [12, 13]. Dietary protein can also impair levodopa response due to competitive inhibition of

Figure 1: Contribution of delayed time-to-ON and end-of-dose wearing OFF to total OFF time. *Reproduced with permission from Clinical Neuropharmacology.*



absorption by large neutral amino acids in food [14]. Early morning OFF periods are common throughout the course of PD being reported in around 60% of patients [15]. For effective resolution of delayed ON he recommended a non-oral therapy that bypasses the GI route and referred to pivotal clinical studies in PD patients with motor fluctuations which showed that subcutaneous apomorphine injection produced a therapeutic response equivalent to levodopa but more rapidly [6, 7]. Results of AM-IMPAKT (Apokyn for Motor IMProvement of morning AKinesia Trial) support these findings showing a more rapid and more reliable TTO with apomorphine injection compared with the usual oral morning levodopa dose – 95% of patients achieving at least a 20-minute reduction in TTO with an average reduction of ~37 minutes [16]. Dose failures were common with oral levodopa but not after apomorphine injection. Therefore delayed ON and dose failure related to impaired GI delivery and/or intestinal absorption of oral levodopa can be significantly improved with apomorphine penject.

Following the presentations, the audience voted on whether wearing OFF or delayed ON was more important. Many audience members recognised that both are important and each requires effective management. While adjunctive oral medication can improve end-of-dose wearing OFF, delayed ON can be rapidly and reliably treated with subcutaneous apomorphine injection.

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Prescribing information can be found on the adjacent page

This article was commissioned by Britannia Pharmaceuticals Ltd and was written by Helen Lawn & Associates.
The debate was part of the Britannia-sponsored plenary session on Parkinson's disease treatment held on 28th March 2015 during the recent 9th CONy Congress in Budapest, Hungary.

APO2-0415-6309 Date of preparation: April 2015

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PHARMACEUTICALS LTD

RAPID RELIABLE 'ON' FOR PARKINSON'S DISEASE

APO-go® Apomorphine hydrochloride
PRESCRIBING INFORMATION

Consult Summary of Product Characteristics before prescribing. **Uses** Treatment of motor fluctuations ("on-off" phenomena) in patients with Parkinson's disease which are not sufficiently controlled by oral anti-Parkinson medication **Dosage and Administration** Apomorphine hydrochloride is administered subcutaneously either as an intermittent bolus injection or by continuous subcutaneous infusion. Its rapid onset (5-10 mins) and duration of action (about 1 hour) may prevent an "off" episode which is refractory to other treatments. Apomorphine should be initiated in the controlled environment of a specialist clinic. The patient should be supervised by a physician experienced in the treatment of Parkinson's disease (e.g. neurologist). Please refer to the Summary of Product Characteristics for full details before initiating therapy. Treatment with domperidone (typical dosage 20mg three times a day) before and during apomorphine HCl therapy is essential. The optimal dosage of apomorphine HCl has to be determined on an individual patient basis; individual bolus injections should not exceed 10mg and the total daily dose should not exceed 100mg. Do not use if the solution has turned green. The solution should be inspected visually prior to use. Only clear, colourless and particle free solution should be used. **Contraindications** Children and adolescents (up to 18 years of age). Known sensitivity to apomorphine or any other ingredients of the product. Respiratory depression, dementia, psychotic disease or hepatic insufficiency. Intermittent apomorphine HCl treatment is not suitable for patients who have an "on" response to levodopa which is marred by severe dyskinesia or dystonia. **Pregnancy and lactation** Apomorphine should not be used in pregnancy unless clearly necessary. 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Since apomorphine may produce hypotension, care should be exercised in patients with cardiac disease or who are taking vasoactive drugs, particularly when pre-existing postural hypotension is present. Neuropsychiatric disturbances are common in Parkinsonian patients. APO-go should be used with special caution in these patients. Apomorphine has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution whilst driving or operating machines during treatment with apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa with given concomitantly with apomorphine. Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including apomorphine. Dose reduction/tapered discontinuation should be considered if such symptoms develop. Since apomorphine, especially at high dose, may have the potential for QT prolongation, caution should be exercised when treating patients at risk for torsades de pointes arrhythmia. Apomorphine has been associated with local subcutaneous effects that can be reduced by rotation of injection sites or use of ultrasound on areas of nodularity and induration. Contains sodium metabisulphite which rarely causes severe allergic reactions and broncospasm. **Side Effects** Local induration and nodules (usually asymptomatic) often develop at subcutaneous site of injection leading to areas of erythema, tenderness, induration and panniculitus. Irritation, itching, bruising and pain may also occur. Rarely injection site necrosis and ulceration have been reported. Pruritus may occur at the site of injection. Drug-induced dyskinesias during "on" periods can be severe, and in a few patients may result in cessation of therapy. Postural hypotension is seen infrequently and is usually intransient. Transient sedation following each dose of apomorphine may occur at the start of therapy, but this usually resolves after a few weeks of treatment. Dizziness and light-headedness have also been reported. Nausea and vomiting may occur, particularly when APO-go treatment is initiated, usually as a result of the omission of domperidone. Neuropyschiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine therapy and neuropsychiatric disturbances may be exacerbated by apomorphine. Positive Coombs' tests and haemolytic anaemia and thrombocytopenia have been reported in patients receiving apomorphine and levodopa. Local and generalised rashes have been reported. Eosinophilia has occurred in only a few patients during treatment with apomorphine HCl. Patients treated with dopamine agonists, including apomorphine, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality (especially at high doses). Apomorphine is associated with somnolence. Yawning and breathing difficulties have been reported as has peripheral oedema. *Prescribers should consult the Summary of Product Characteristics in relation to other side effects* **Presentation and Basic NHS Cost** APO-go ampoules contain apomorphine hydrochloride 10mg/ml, as follows: 20mg in 2ml – basic NHS cost £37.96 per carton of 5 ampoules. 50mg in 5ml – basic NHS cost £73.11 per carton of 5 ampoules. APO-go pens (disposable multiple dosage injector system) contain apomorphine hydrochloride 10mg/ml, as follows: 30mg in 3ml – basic NHS cost £123.91 per carton of 5 pens. APO-go Pre-filled syringes contain apomorphine hydrochloride 5mg/ml, as follows: 50mg in 10ml – basic NHS cost £73.11 per carton of 5 syringes. **Marketing Authorisation Numbers:** APO-go Ampoules: PL 06831/0245 APO-go Pens: PL 06831/0246 APO-go Pre filled syringes: PL 06831/0247 **Legal Category** POM **Date of last revision:** December 2014 For further information please contact: Britannia Pharmaceuticals, Park View House, 65 London Road, Newbury, Berkshire, RG14 1JN, UK

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The Encephalitis Society Annual Seminar

Conference details: December 2014, London, UK. ***Report by:*** James Pamment, Oliver Zangwill Centre for Neuropsychological Rehabilitation, and edited by Dr Ava Easton, The Encephalitis Society

When the opportunity arose to come to this year's Encephalitis Society Professional Seminar I was delighted to attend and brought along high expectations of increasing my knowledge base in an area of research and clinical practice that I am admittedly fairly new to. A day of highly stimulating talks, packed with innovative research from across the globe highlighted the day's theme of a wider community, endeavouring to share information relevant to best practice.

The seminar had a wide ranging audience allowing multi-disciplinary, service user and family perspectives to fuel lively post talk debates and questions. This diverse range of perspectives added to the quality of the day by offering what felt like extremely comprehensive discussions on thoroughly engaging topics.

The afternoon started with a very warm welcome from Dr Ava Easton CEO and Professor Tom Solomon, Chair of the Encephalitis Society Professional Panel. We were given an exciting sneak preview of the events the Society had planned for its 21st birthday celebrations next year; including a 21 day road-show visiting a different location in the country each day, raising awareness of Encephalitis and the work of The Society.

It was then time to kick off the talks, with Dr Arun Venkatesan from the John Hopkins University, presenting 'Acute encephalitis: prognostic factors and novel therapies'. Dr Venkatesan highlighted factors that through his work in acute settings have shown to contribute to poor outcomes and how this might inform patient care during hospitalisation. The audience was given an overview of Encephalitis hospitalisation rates of 250,000 patients from the US dating between 2000-2010. Predictors of mortality within this data set suggest that there is a need to focus on the very young and old. Dr Venkatesan then honed in on factors identified through his work on patients admitted to the Johns Hopkins Hospital. Research showed that patients that had thrombocytopenia, cerebral oedema or status epilepticus were at a greater risk of death. The focus of the talk then went on to the question; what can we do as clinicians to further reduce these risk factors? Dr Venkatesan then put forward persuasive evidence to suggest that a ketogenic diet can be effectively used to treat status epilepticus in patients with encephalitis, and may also have a protective anti-inflammatory effect.

Next, Dr Jennifer Lemon, University of Liverpool presented a talk looking at how qualitative, semi-structured interviews with parents might be a useful tool in deciding which outcomes are important to measure in children. Dr Lemon highlighted the need for a core set of outcomes that help understand a condition that is complex and varied. The parent's perspective of how outcomes change over time were shown to be a key theme. Transcripts with parents documented how the focus of concern shifts through the different stages of the illness. Initially they have concerns about mortality and impairments whilst their child is in acute care, then the focus moves to the impact of problems back in their child's normal setting and anxieties about the future. Dr Lemon ended the talk by stating that there is currently a lack of standardisation of outcomes and previous encephalitis trials have focused more on impairments rather than the impact of problems on the child's day to day life.

Professors Solomon and Venkatesan

Professor Solomon and Professor Kennedy CBE

Dr Defres, also based at the University of Liverpool then followed with a talk titled 'Understanding and improving the outcome of encephalitis'. Dr Defres explained that the aim of The EncephUK study was to determine the clinical predictors of encephalitis for a diagnostic tool for the junior doctor on the frontline. However, this is quite an undertaking given the knowledge of how tricky it can be to diagnose Encephalitis. But poor outcomes resulting from delays in recognising symptoms and starting treatment, dictate the need for this important research to be carried out and completed.

Dr Thomas Miller, University of Oxford, continued the afternoon seminar with a talk showing the research directions on patient related outcomes in VGKC limbic encephalitis. Describing memory as a 'broad church', Dr Miller introduced his work on creating 'PROMS' (Patient related outcome measures) as part of a multi-pronged approach that can drill down to patient problems. Dr Miller found using a questionnaire in combination with semi-structured interviews a useful way of picking up the social narrative that can be lost in a questionnaire alone. Dr Miller stated that PROMS are useful in explaining the 'how & what' people experience. Dr Miller's talk was insightful in his opinion that a more holistic model of measuring patient experience can be used to better guide research and drug treatment targeting a more patient driven agenda.

After a short break it was then time for Professor Peter Kennedy CBE, Head of the Neurology department at Glasgow University, to deliver his highly anticipated keynote address on 'Human African Trypanosomiasis (sleeping sickness) in sub-Saharan Africa'. One of only a handful of medical doctors working on the disease, he is the world's leading expert on nervous system infection in sleeping sickness, and has spent much of his career devoted to raising awareness of sleeping sickness in Africa and beyond. His acclaimed popular science book on the topic 'The Fatal Sleep' has also been highly commended by the BMA and generates money for charities in Africa. Professor Kennedy introduced the audience to the historical context of a disease that currently puts 70 million people at risk of developing it in Africa. During the period 1894-99, the bite of the tsetse fly was discovered by Sir David Bruce to be the mode of transmission of the causative trypanosome parasites in animal Trypanosomiasis. Over the following decade different forms of trypanosomes, also transmitted by the tsetse fly, were shown to be the cause of Human African Trypanosomiasis (HAT), both forms occurring in sub-Saharan Africa. Professor Kennedy pointed out that recurrences and the periodic re-emergence of HAT have been due to several factors, in particular wars and socio-economic instability which lead to inadequate patient surveillance and vector control. Professor Kennedy then provided an overview of the current highly toxic drug treatment and promising drugs that are in the pipeline, whilst clearly pointing out the major challenges involved in treating an at-risk population living in some of the poorest rural areas of Africa. The talk was summed up

by looking at how a better understanding of HAT pathogenesis, better disease staging and more effective drug therapy could improve both the control of the disease and the outlook of patients suffering from sleeping sickness.

In keeping with the global theme of the day, Dr Jay Selman then joined us via satellite from Blythedale Children's Hospital, Valhalla, New York (USA). Dr Selman's talk, 'Outcome: Cohort of 15 children with anti-NMDA Receptor Encephalitis,' presented the results of his research, the characterisation of anti-NMDA Receptor Encephalitis and a preliminary evaluation of the economic burden of the condition in the acute and rehabilitation settings. The research presented the clinical pathways of a cohort of consecutively-admitted patients from acute inpatient to inpatient rehabilitation to outpatient settings. Both tracheostomies and gastrostomy-tube were indicators of severity and more prolonged hospital stays. Although most of the patients did make some improvement, 25 – 40% were left with moderate to severe global deficits. Two thirds had moderately delayed language function and 71% had a change in mood. Having summarised the interventions and deficits in detail, Dr Selman's closing point was that intensive rehabilitation is essential in many children with this disorder. Early and aggressive initial treatment improves the outcome. Dr. Selman is continuing to follow the outcome of this cohort. Dr. Selman closed the presentation with preliminary data on the estimated charges for the acute and rehabilitation hospitalisations in the cohort of 17 children; this totalled almost $4,000,000 or €4,900,000.

Dr Mike Griffiths & Dr Rachel Kneen, both Consultant Neurologists from Alder Hey Children's hospital and researchers at the University of Liverpool, co-presented a talk on their work in Nepal. The joint talk outlined the work that they had been involved with in Nepal via the Institute of Infection and Global Health and with partners from Kanti Children's hospital in Kathmandu. Dr Griffiths explained the type of viral encephalitis most common to the region, Japanese Encephalitis Virus (JEV). The virus is normally hosted by animals but due to the humid, rural and agricultural land, humans become accidental hosts. It is a condition that needs to be treated seriously as there are over 20k deaths annually resulting from JEV, leaving 20-50% with neurological impairments, epilepsy, behaviour, language and motor problems. He talked about the economic burden that encephalitis had on families there, which has one of the poorest countries in the world. Dr Kneen then expanded on one particular impairment; epilepsy. She talked about an exciting new project to provide paediatric epilepsy training courses in Nepal. Dr Kneen highlighted how epilepsy was a global health concern that warranted investigation in countries such as Nepal, where it is stigmatised and mortality rates are higher. From the findings of an initiative to start paediatric epilepsy training courses in Nepal, Dr Kneen showed that better awareness and good management can have a positive effect on outcomes.

Dr Sarosh Irani, a Consultant Neurologist from Oxford, spoke about the links between infectious and autoimmune forms of encephalitis and how it is important to understand the mechanisms of encephalitis and the optimal treatments for various forms of encephalitis. Sarosh described the role of autoantibodies in Japanese encephalitis (JE). There are clinical similarities between JE and autoantibody-mediated forms of encephalitis, especially NMDA Receptor -antibody encephalitis, given the prominent hypokinetic movement disorder, coma and few seizures. Sarosh and colleagues from Oxford found that from a cohort of patients with JE, around 70% had antibodies which target the surface of neurons. Following the time course of these antibodies in individual patients, suggested that they appear a few weeks after the clinical onset of JE and may be responsible for modifying the disease course. This study suggests the potential importance of immunomodulatory therapies in patients with JE, as has been suggested by several recent studies examining herpes simplex virus encephalitis.

The penultimate talk of the day came from last year's essay winner Dr Katarzyna Bera with her short talk 'Could pathogenic autoantibodies in autoimmune encephalitis cross-link neurology and psychiatry.' Dr Bera described the body of evidence that suggested early intervention has shown to produce better outcomes, however we can only treat somebody once we know what the disease is. A better understanding of the autoantibodies that are present in anti-NMDA-receptor encephalitis can help spur early interventions. Patients with these autoantibody presentations are often initially seen by psychiatrists. The aim would be to have a joint understanding that would join expertise between psychiatry and neurology, finishing her talk with the quote 'The mind is the living brain in action.'

The last scheduled talk of the afternoon came from last year's essay prize runner-up Dr Satyasheel Ramful. His talk focused on predisposing genetic factors that make some patients more susceptible to developing Herpes Simplex virus-1. An understanding of newly identified toll-like receptor pathway deficits might ultimately result in more effective and targeted therapeutic agents for Herpes Simplex Encephalitis.

The conference concluded with a book signing of The Fatal Sleep by Professor Peter Kennedy, CBE and a cheese and wine reception.

Photos and videos of the 2014 presentations can be viewed here
www.encephalitis.info/index.php?cID=420

If you are interested in attending the 2015 seminar, please register to become an Encephalitis Society Professional member (free of charge) and you will automatically be notified of the details.

www.encephalitis.info/get-involved/membership-online/professional-membership

To list your event in this diary, email brief details to Rachael Hansford at Rachael@acnr.co.uk by 6th June, 2015

2015

May

Pain Therapeutics
18-19 May 2015; London, UK
www.smi-online.co.uk/pharmaceuticals/uk/pain-therapeutics

ABN Annual Meeting
19-22 May, 2015; Harrogate, UK
E. info@theabn.org

11th European Paediatric Neurology Society Congress 2015
27-30 May, 2015; Vienna, Austria
www.epns2015.org

June

Registrar PD Masterclass –
16/17th September, 2015; Sheffield, UK
www.parkinsonsacademy.co.uk for further details.

Consultant PD Masterclass – Sheffield, UK
Module 1 - 2, 3rd & 4th June 2015
Module 2 - 26th November 2015
(Both modules must be attended)
www.parkinsonsacademy.co.uk for further details.

1st Congress of the European Academy of Neurology
20-23 June, 2015; Berlin, Germany
E. headoffice@eaneurology.org

Dizziness : A Multidisciplinary Approach – Dilemmas, diagnosis and developments
23-26th June, 2015; London, UK
E.thedizzinesscourse@uclh.nhs.uk
www.thedizzinesscourse.co.uk
T. 020 3448 3275
Online registration and payment
www.uclhcharitycourses.com/courses/neurology/dizziness-dilemmas-diagnosis-and-developments

Psychological and Neuropsychological Impact of Paediatric and TYA Cancer on Patients and their Families
29 June, 2015; London, UK
www.royalmarsden.nhs.uk/psychologicalimpact
T. 020 7808 291/2924,
E. conferenceteam@rmh.nhs.uk

July

14th Annual Kings Neuromuscular Disease Symposium
3rd July, 2015; King's College, London, UK
E. samantha.smith@kcl.ac.uk

September

Paediatric Oncology Solid Tumours Study Day
14 September, 2015; London, UK
www.royalmarsden.nhs.uk/paedsolidtumours
T. 020 7808 291/2924,
E. conferenceteam@rmh.nhs.uk

November

Consultant PD Masterclass – Sheffield
Module 1 - 2, 3rd & 4th June 2015
Module 2 - 26th November 2015
(Both modules must be attended)
www.parkinsonsacademy.co.uk for further details.

ABN MD SIG Conference

Conference details: 15-16 January 2015, Cambridge, UK. ***Report by:*** Dr Sathiji Nageshwaran (Imperial College) & Dr Benjamin Tsang (NHNN).

The inaugural ABN Movement Disorders Special Interest Group (ABN MD SIG) meeting took place on the 15th and 16th of January 2015 at Downing College, Cambridge. The programme was organised by Professor David Burn (Newcastle) and Dr Paul Worth (Cambridge) and included several internationally renowned speakers.

The ABN MD SIG is the new name for the British and Irish Neurologists Group for Movement Disorders (BRING-MD). The ABN MD SIG is affiliated with the ABN.

The meeting opened with the keynote lecture by Professor Andrew Lees of Queen Square, titled 'Hanging out with the molecules', in which he discussed his early career, in particular his research and successes with dopaminergic therapy in Parkinson's disease and his fundamental role in the institution of apomorphine treatment in patients with frequent 'off' periods.

To inspire delegates before we embarked on an intensive day of talks, Chris Moon MBE delivered a motivational speech. He is a distinguished ex-soldier, whom amongst his many noteworthy experiences was captured by the Khmer Rouge (and negotiated his own release), cleared landmines in Africa (during which time he was unfortunately significantly injured) and now with a prosthetic leg and arm runs ultra marathons.

The morning session aimed to summarise current topics that have furthered our understanding in the pathophysiology of movement disorders.

Professor Tony Schapira enlightened us on how GBA1 gene mutations (encoding a ubiquitous lysosomal enzyme glucocerebrosidase,GBA) have provided further insights into the pathogenesis of Parkinson's disease (PD). Around 7 to 10% of PD patients have GBA1 mutations and studies of GBA1 mutation cohorts which found higher RBDQ and UPDRS motor scores have stimulated closer inspection at the connection between the GCA and alpha-synuclein. Robust mice models have shown a reciprocal relationship between GCA enzyme activity and alpha-synuclein levels. Professor Schapira proposed that future research should investigate if this association can be replicated in vivo and thereby slow neurodegeneration in PD.

Professor Maria Grazia Spillantini summarised the role of alpha-synuclein in the pathogenesis of PD as well as other synucleinopathies. We were impressed by her discussion of how alpha-synuclein overexpression, post-translational modification and mutation leads to pre-synapatic aggregation with consequent redistribution of SNARE (Soluble NSF Attachment Protein Receptor) proteins and abnormal neurotransmitter release.

Most are aware that conventional MRI signs are often absent or late in various parkinsonian conditions. Dr James Rowe introduced us to the growth in understanding of novel MRI techniques such as Diffusion Tensor Imaging (DTI) as biomarkers in the diagnosis and differentiation of parkinsonian disorders. He left us with an interesting hubs and spokes connectivity analogy for understanding corticostriatal networks that are vulnerable to degeneration in parkinsonian disorders.

Professor Henry Houlden gave a riveting historical account of how the field of neurogenetics have expanded upon Sanger sequencing and gene panels with the advent of exome and genome sequencing. He finished off most appropriately by reminding us that clinical acumen is still vital despite these advances and inspired us to be involved in the movement disorder subdomain group for Genomics England whereby many patients with rare inherited neurological diseases will have their whole genome sequenced. Professor Houlden is overseeing the Genomics England Clinical Interpretation Partnership (GeCIP) for Neurology.

After morning tea, Professor Oliver Bandmann explored why neuroprotection studies in PD to date have mostly been negative. Current approaches are to test drug libraries using fibroblast lines from patients with monogenic causes of PD only such as patients with parkin and LRRK2 mutations. The economic climate has seen promising candidate drugs mainly sourced via natural compounds and licensed drugs used in other areas of medicine such as ursodeoxycholic acid (for primary biliary cirrhosis) and exenatide (for diabetes mellitus). Professor Bandmann advocates the need to develop good tools to monitor PD progression, such as the bradykinesia-akinesia incoordination (BRAIN) keyboard test (developed by Dr Alastair Noyce) which has shown good correlation with UPDRS motor scores. The well-coordinated trio of Drs Mike Samuel, Tom Foltynie, and Monty Silverdale provided us with a concise update on recent advances and how techniques in deep brain stimulation (DBS) have influenced motor and non-motor symptoms of PD. The parallel improvements in surgical outcomes and hardware such as battery life and size, have been a very welcomed development in advanced PD management. We are increasingly recognising that DBS patients can have non-motor psychiatric symptoms post-insertion and therefore the need for personalised DBS care.

After lunch the CPC discussion was undertaken by Prof Huw Morris who discussed two cases of atypical parkinsonism and complex cognitive dysfunction. Both cases were discussed alongside the available literature with the final diagnosis being one of dual pathology (PSP and MSA with Dementia), a significant and frequently overlooked diagnostic category.

The final session concerned the psychiatry of movement disorders and included talks by Dr Valerie Voon on our current understanding of the pathophysiology of ICDs in PD, Dr Jeremy Stern who discussed the management of Tics and Tourette's Syndrome.

The meeting ended with a pleasant and informative debate between Dr Graham Lennox and Dr Mark Edwards discussing the controversial title 'Functional Movement Disorders: it's really not our business'. Although Dr Lennox proposed engaging arguments, it was evident that the realm of functional movement disorders is one of the Neurologist, requiring special training in the management of this sub-speciality in its own right.

We feel the inaugural ABN MD SIG to have been a resounding success, bringing together a small and focused group of people to discuss the most up-to-date issues within the Movement Disorders field, in an idyllic Cambridge setting. There was ample opportunity to network and discuss ideas and it has set the benchmark high for subsequent meetings.

Trigeminal Neuralgia 4th Study Day

The Trigeminal Neuralgia Association UK are holding a CPD-accredited Study Day and combined patients' conference on Saturday 6th June, designed so that during break times and for the later sessions, both groups will join together to improve communication and understanding of TN from all points of view. This year, the event is being held at the Grange Holborn Hotel, London and the £75 includes all refreshments including a buffet lunch. From previous conferences, feedback has always been positive from both professionals and patients & carers.

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BNA Festival of Neuroscience

Conference details: 12-15 April 2015; Edinburgh, UK. ***Report by:*** Dr Tarek Gaber, Consultant in Rehabilitation Medicine, Leigh Infirmary, Leigh, UK.

With more than 250 international speakers including two Nobel laureates the festival of neuroscience promised a lot. I am delighted to report that it did not disappoint. As a clinician I was hoping not only to learn about the current trends in neuroscience research but also to be able to construct a mental picture of what neuroscience is and how its main domains interact with each other and eventually translated to techniques and agents I can use in my every day practice.

It was clear that understanding how the brain works is mainly dependent on two techniques. In the cellular level; neurophysiological examination of a single neurone activity using a micro-electrode had been developed more than 50 years ago. The Nobel laureate John O'Keefe took us through this fascinating journey in his plenary lecture. I felt that his prize was not only recognition for his discovery of the hippocampal cognitive map but also recognition of the role neurophysiology played in the recent advances in neuroscience. Two recent developments revolutionised this field. The first is the extraordinary ability to insert tens of thousands of micro electrodes into a corresponding number of neurones enabling researchers to gather data about the neuronal activities of whole networks instead of a single neurone. Computational neuroscience then developed to help analyse these data, providing deeper insight into how such small networks function. We learned about mirror neurones firing when we perform tasks or observe someone else doing it (as presented by Giacomo Rizzolatti in the plenary lecture) and about the grid neurones mapping the enviroment in our hippocampus.

The second innovation is our ability to apply the same technique to humans. The ethical issues were resolved by recruiting patients with refractory epilepsy needing neurophysiological studies (surgical insertion of micro electrodes in their hippocampus) to determine which area needs ablating. The patient would then be asked to have cognitive tests and the data

could be collected. This technique gives us a fascinating glimpse of how we store pictures of families or celebrities.

Examination of the macrostructures of the brain is still dependent on imaging especially functional MRI (fMRI). In my opinion, Diffusion Tensor Imaging (DTI) with its impressive ability to analyse white matter will be the quickest to translate into standard clinical practice. It demonstrated very good sensitivity in MND patients (Peter Bede, Trinity College Dublin) and for traumatic axonal damage (Adrian Own, plenary lecture).

There were two dedicated symposia discussing sleep. The main work focused on the role sleep plays in memory consolidation. This may be another area with potential to impact clinical practice especially in areas such as Post Traumatic Stress Disorder and dementia.

Stem cell research for neurological disorders was highlighted well during the meeting. Pluripotent stem cells or iPS cells are stem cells that can be produced directly from adult cells. Clive Svendsen's (Cedars Sinai, L.A) lecture explored the therapeutic potential of these cells. Dr Svendsen challenged common opinion by suggesting we should focus on glial cells rather than neurones: the brain is composed of 10% neurones and 90% glial cells. He suggests that manipulating glial cells appropriately could help processes such as myelination or slowing down degeneration.

'Do drug addicts have free well?' This was an alluring and equally enthralling talk. It was fascinating not in the way I expected but in the way the excellent panel interacted. The speakers were neuroscientists, psychiatrists and an ethicist. This particular session highlighted the only weakness in pure neuroscience and what it can learn from clinical practice. Having a cocaine-taking rat as a model of a human drug addict seemed rather tagential from a clinician's perspective.Similarly, the notion that radiological findings in the prefrontal cortex can tell us anything about free will is a difficult concept to accept. Nevertheless, everybody benefited from the discussion between the different disciplines especially the warning about neuro-reductionism: we need more humility when dealing with human nature as its representation by radiological findings, biochemical changes or neuronal activities is only part of the whole story.

Professor Nutts was part of this panel. On the previous night he gave an excellent lecture presenting overwhelming and convincing evidence against the current drug laws. I felt that Professor Nutts was asking too much of human nature. Like using rats to understand complex human behaviour, using evidence from the literature to inform public discourse about such as sensitive and complex area is extremely difficult in a liberal democracy. Failing to appreciate how irrational humans are is what gave us the credit crunch, PPI and Libor.

Even the most committed delegate will fail to manage navigating such a wonderful event. I did my best and had a great time in Edinburgh the heart and soul of the Scottish enlightenment. The old city dotted with the statues of Smith, Hume and other giants of the enlightenment was a perfect back drop for the festival.

Dementia Conference calls for "earlier and more accurate diagnosis" of growing disease

Medical charity Cobalt held its inaugural annual Dementia Conference in conjunction with Siemens Healthcare, attracting over 100 healthcare professionals including radiologists, neurologists, psychiatrists, and nursing staff. "Dementia is now being recognised for what it is – a sizeable concern that places a significant drain on resources, stated Professor Iain Lyburn, Medical Director and research lead at Cobalt Health. "While there continues to be no cure, heightening awareness is essential to early diagnosis."

The annual Dementia Conference follows Cobalt's recent unveiling of a new Biograph mCT Flow EdgeTM PET/CT system from Siemens Healthcare, installed at Cobalt Imaging Centre in Cheltenham. Anna Cartwright, UK Molecular Imaging Product Specialist at Siemens Healthcare said, "With the evolution of our PET/CT technology paving the way for enhanced dementia diagnosis through the elimination of stop-and-go imaging, Siemens is proud to have been able to support this inaugural event."

For more information E. laura.bennett@siemens.com, www.siemens.co.uk

Professor Iain Lyburn, Medical Director and research lead at Cobalt Health, speaks to delegates at Cobalt's inaugural annual Dementia Conference held in conjunction with Siemens Healthcare.

The British Neuropsychiatry Association 28th AGM

Joint meeting with the British Psychological Society's Division of Neuropsychology, the UK Functional Symptoms Research Group in collaboration with the ABN Cognitive Special Interest Group

Conference details: 4-6 February, Royal College of Surgeons, London, UK. ***Report by:*** George Pengas, Consultant Neurologist, University Hospital, Southampton, UK.

This was my first time at the BNPA AGM, and I was attracted this year by their collaboration with the recently formed ABN Cognitive SIG. Getting to the heart of London was not as easy as I thought, especially on the second day when there was a bus strike in the capital! However, my efforts negotiating the jammed London transport system were rewarded by the sessions and lectures.

As one might expect for such a meeting, there was a lot of material on functional neurology, an area with much crossover and interdisciplinary collaboration between psychiatrists, neurologists and neuropsychologists. The sessions were kicked off by Jon Stone, one of the few Neurologists who has taken on functional neurology as a bona fide and worthwhile subject for Neurologists, given how prevalent and disabling it is, and how little Neurologists have been interested in this area until recently. He spoke on functional cognitive symptoms and how to approach them.

Continuing on the theme, we heard Tony David give a very honest tour of recent fMRI experiments in functional conditions, which suffer the same limitations as most imaging correlations in neuroscience. I found one of his conclusions quite elegant: for a patient with functional loss - I say "I cannot", it looks like "I will not", it is "I cannot will".

I thoroughly enjoyed the video sessions illustrating both functional disorders and not: dissociative seizure, fixed dystonia, Latah; but also paroxysmal kinesogenic dystonia and Pantothenate kinase 2 mutation.

Another towering figure in the neurology of functional (movement) disorders is Mark Edwards and he spoke on a Bayesian approach to describe how these phenomena can arise in the brain, i.e. how (false) expectations can drive and distort predictions and therefore perceptions, whilst inward attention would affect the sense of agency.

Marina de Koning-Tijsen gave an excellent talk on movement disorders and how to differentiate tics, myoclonus and functional jerks.

I thought the best session in the theme of functional disorders was by Glenn Nielsen on physiotherapy of such patients, which involved a lot of (re-)education, both cognitive and physical, resulting in astonishing results. It was both elating (because we can effectively treat even the most difficult cases) and depressing at the same time, because his sort of expertise is not widely available in all neurophysiotherapy departments in the country.

Another important theme, as would be expected, was memory. Here we heard from Adam Zeman on new theories of memory, and the zeitgeist shift from centres of memory (or any higher cortical domain) to networks. This immediately makes dementias into network disorders. In particular, for too long has early Alzheimer's disease been studied as a pure hippocampal lesion study, while we are finally coming round to the realisation of it being better described by damage across selective networks e.g. the circuit of Papez and the default network.

Markus Reuber spoke on intrusive memories, such as flashbacks, deja vu and deja vecu, while Torsten Bartsch spoke on Transient Global Amnesia (TGA), which was first described by Charles Miller Fisher and Raymond Adams but later on by John Hodges. John Hodges was also an honoured speaker on the day, giving a tour de force on another condition which has consumed the latter part of his research career - Frontotemporal dementia (FTD) - where he spoke on the imperfect match between pathology, clinical phenotype and genetics of FTD. He focused on his recent work on behavioural variant FTD and FTD-MND, but also spoke on the language variants of semantic dementia and progressive non fluent aphasia.

The next big theme was on body image. Michael Trimble lectured on a conceptual history of the body image and the self, starting from the Discobolos and Narcissus in Ancient Greece, to Penfields's homonculus, Macdonald Critchley's corporeal awareness and the modern "selfie" as evidence of the dominance of narcissism in the modern world. Through this thesis, conditions such as schizophrenia, anorexia, hallucinations, heautoscopy, phantom limb phenomena, anosognosia, body image distortions in epilepsy and migraine and hysteria with regard to agency and body image can all be better conceptualised.

Peter Brugger spoke as an expert phantomologist, on phantom limb phenomena in amputees but also on a rare condition called xenophilia or apotemnophilia where people wish for a limb to be amputated.

James Rowe spoke on the pathognomonic and rare alien limb phenomenon in corticobasal degeneration, suggesting it arises, at least in part, by disinhibition, but also with loss of intention, to move the limb.

Giuseppe Valar spoke on neglect and its various manifestations, in particular of a form called somatoparaphrenia, where patients, usually with a right parietal lesion, develop a belief that their limb is not their own, but belongs to someone else.

The most inspired lecture of the conference, in my opinion, was by Katerina Fotopoulou, who spoke on her studies on disorders of body image and especially on successful therapeutic approaches of anosognosia and somatoparaphrenia using videos, mirrors and the "rubber hand illusion" with very encouraging results.

Finally, I must say I really enjoyed the "diagnostic masterclass" session where interesting cases were shared and discussed. I found the mixed audience discussions, where Neurologists and Psychiatrists came to different diagnostic conclusions after seeing videos of patients being assessed with various neurological conditions, most illuminating. The whole conference seemed dedicated to expounding the common substrate of both Neurologists and Psychiatrists and hence making a case for the two specialties to work in a more integrated way. Both sides increasingly see patients that would benefit from the specialist input of the other: Greater knowledge and communication between the two specialities provides our patients with the best chance of getting the correct diagnosis and optimal treatment.

PREVIEW 1st Congress of the European Academy of Neurology

Conference details: June 20-23, 2015, Berlin, Germany.

The European Academy of Neurology (EAN) is the organisation that unites and supports neurologists across the whole of Europe. Currently, 45 European national neurological societies as well as 800 individuals are registered members of the EAN. Thus, the EAN represents more than 21,000 European neurologists.

We are pleased to invite you to this great event on behalf of the EAN and the German Society of Neurology. Today, Berlin is one of the world's most vibrant capitals, with an impressive cultural, scientific and economic scene. The city is also emerging as the centre of German healthcare, last but not least due to the Charité Hospital, the largest clinic in Europe, counting 3200 beds and 7000 medical and healthcare students and many medical research institutes.

Berlin has a long neurological history. It was here that Moritz Heinrich Romberg wrote the 'Lehrbuch der Nervenkrankheiten des Menschen', a frontier breaking mid-19th century textbook which is seen as the foundation of modern neurology. Almost 25 years after the fall of the wall, the once divided city of Berlin today symbolises peaceful revolution, the overthrow of outworn systems and the venture into a new political era. A series of neurological history in

Germany can be found in our newsletter here. The 1st Congress of the EAN will also write European neurological history. EAN is the joint subsequent organisation of the EFNS (European Federation of Neurological Societies) and ENS (European Neurological Society), and thereby the first united voice of European Neurology. This founding act was celebrated on June 3rd, 2014 at the Joint Congress of European Neurology in Istanbul. The first congress of this new society will be celebrated in the united Berlin.

The EAN Congress in Berlin will provide the ideal platform for continuing education in all fields of neurology, covering a broad spectrum of topics with state-of-the-art lectures by renowned experts. The EAN is dedicated to providing the highest quality of continuing medical education and to opening professional education opportunities.

The following Symposia will be presented at the EAN Congress in Berlin:

- EAN-ESO Symposium: Spontaneous intracerebral haemorrhage
- Epilepsy and the injured brain: causes and consequences
- Modern molecular genetics in clinical myology
- Plenary Symposium: Hot topics in neurological sciences
- Preclinical Alzheimer's disease
- Expanding fields in neurology
- Present and future treatment in movement disorders
- Multiple sclerosis therapy moving forward/ where is the truth? Hopes and hazards
- Infections of the central nervous system: recent advances

Apart from that, there will be a wide range of lectures in the fields of stroke, ALS, epilepsy, Alzheimer's and Parkinson's disease, multiple sclerosis, neuroimaging and many more. Find out about all the sessions you should not miss at our Berlin Congress in our newsletter Neuropenews.

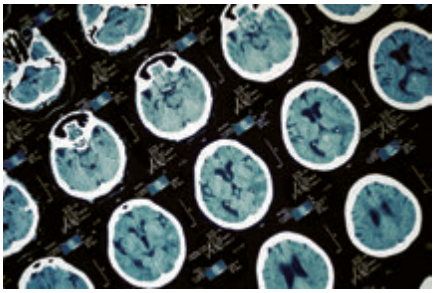
PREVIEW The Neurological Rehabilitation Therapy & Technology Expo 2015

Conference details: June 10-11, 2015, London, UK.

The Neurological Rehabilitation Therapy & Technology Expo 2015 is the UK's leading innovative event committed to medical professionals working in the rehabilitation of neurological conditions. Here, professionals from the world of neuro rehab will highlight the importance of research into neurological conditions, the application of assistive technology, and what the future holds for the neurological rehabilitation profession.

Understanding the advancements in technology in terms of how people who have suffered a major neurological event recover, is crucial to the enhancement of their function and mobility. This is the aim of the Neurological Rehabilitation Therapy & Technology Expo highlighted by the array of industry thought leaders who will be presenting in the keynote seminar theatre over the two days.

Amongst the speakers is Clare Hartigan, program manager at the Shepherd Center in Atlanta, Georgia, which specialises in medical treatment, research, and rehabilitation for people with spinal cord and brain injury. Clare has twenty six years of clinical experience and plays a critical role in the final stage of trials for robotics-assisted walking devices that could



improve the lives of the population suffering from limited mobility and function.

Clare will make the trip over to the UK to discuss her research into locomotor training, an activity-based rehabilitation treatment device included in the center's Shepherd Step Program.

How does locomotor training work?

Body-weight supported locomotor training uses unique body-weight-supported treadmill systems. The participant is suspended in a harness over a treadmill whilst the participant's legs are moved to simulate walking, either through a trained therapist or the robotic system. As the individual's function strengthens, they move from the treadmill to walking over ground.

The idea behind this innovative device stems from research carried out by Clare and the Shepherd Center team into neural plasticity and the role the spinal cord plays in the function of stepping and standing. Clare will provide thorough details into the research behind the device and its impact on improving over ground walking for individuals with movement in their legs.

The Neurological Rehabilitation Therapy & Technology Expo is an annual event. In March, the exhibition debuted in the USA and was a huge success bringing together neuro rehab professionals from around the world.

This June's event will have a total of 1,500 researchers, medical practitioners, and technological innovators taking part, which is being held at ExCeL London on the 10th and 11th of June. If you are involved in the field of neurological rehabilitation and research, this event is the perfect opportunity for you to hear from renowned keynote speakers, compare ideas, and gain first-hand experience of assistive technologies.

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