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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION



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Continuous dopaminergic drug delivery in advancing Parkinson's disease: emerging evidence

Highlights of a satellite symposium held at the 9th International MDPD Congress, 18–21 April 2013, Seoul, South Korea, chaired by Heinz Reichmann and K Ray Chaudhuri

Key points

- Continuous dopaminergic drug delivery reduces motor fluctuations and non-motor symptoms in PD patients receiving conventional oral therapies
- Non-motor symptoms impair quality of life in PD even in the early stages of the disease
- Advanced therapies such as subcutaneous apomorphine infusion are effective for both motor and non-motor complications of PD
- Advanced treatments remain under-utilised and could be started earlier in the course of PD

Oral levodopa or dopamine agonists form the basis of treatment for Parkinson's disease (PD), a progressive disease characterised by both motor and non-motor symptoms. Chronic treatment with these oral therapies is associated, however, with the development of motor fluctuations. This presents a particular problem in the management of PD patients as their disease progresses. The addition of continuous dopaminergic drug delivery (CDD), for example using subcutaneous apomorphine infusion, can reduce motor and non-motor complications in PD patients receiving conventional oral therapies. The key question is when in the disease course CDD should be started.

At a recent international symposium examining management strategies for patients with advancing PD, Professor Ray Chaudhuri (London, UK) stressed that non-motor symptoms frequently occur quite early in the disease course. In his view, the staging of PD as early, moderate or advanced based simply on motor symptoms often misses the bigger holistic picture of the disease and the debilitating effects of non-motor symptoms with their negative impact on quality of life.

The traditional view is that the so-called advanced treatments – CDD with subcutaneous apomorphine infusion and intrajejunal levodopa/carbidopa infusion (LCIG), as well as the surgical procedure of deep brain stimulation (DBS) – should be retained for the advanced stages of PD, when fluctuating dopamine levels lead to increased dyskinesias.

However, Ray Chaudhuri's view is that CDD can in fact be used at any stage of PD. Management should be individualised to the patient, taking into account the balance of both motor and non-motor effects. He also adds that non-oral approaches are particularly useful for patients in the advanced stages of PD when gastric emptying is compromised and swallowing difficulties can occur (a surprisingly common symptom, even in early PD). Patients entering the NMS Quest study¹ had an average disease duration of 6.4 years yet 30% already suffered swallowing dysfunction (vs 4% controls), and in a large survey 59% of patients reported swallowing issues².

For Dr Simon Lewis (Sydney, Australia) there remain a number of unresolved issues regarding the advanced treatments, with a lack of directly comparable data between the infusion and surgical approaches. However the key issue, in his view, is that the advanced treatments remain underutilised. Frequently, patients are not given access to these therapies, in part because clinicians do not identify the appropriate patients. These strategies are not utilised early enough in the disease course, in Simon Lewis's view.

He went on to outline that PD patients have a diminishing therapeutic window as their disease progresses (Figure) and it becomes increasingly difficult to control patients' physical symptoms. Motor fluctuations occur as dopamine pulsatility reduces the threshold for

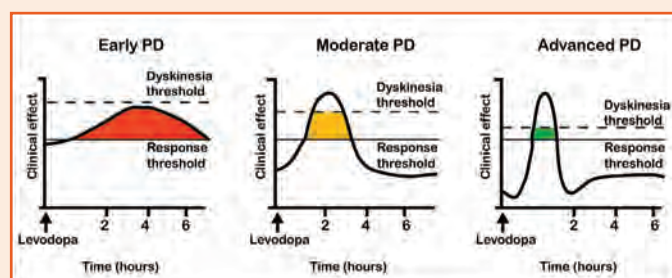


Figure. As Parkinson's disease progresses, the threshold for dyskinesias is reduced and the time when dopaminergic therapy is effective is also shorter, effectively narrowing the therapeutic window.

dyskinesias, while time 'off' increases. This vicious cycle of peaks and troughs can be broken using CDD.

Looking at advanced therapies, DBS involves invasive surgery within the brain and is a high-risk strategy in patients over the age of 70. Patients' cognition is often impaired following DBS and those with significant psychosis or cognitive impairment should not undergo this procedure. LCIG involves infusion directly into the bowel, with the inherent risk of infection. Apomorphine is infused subcutaneously (either intermittently by pen or continuously via a pump).

Irritation to the skin can occur at the apomorphine infusion site causing nodules, but according to Dr Tove Henriksen (Copenhagen, Denmark), who has extensive experience in treating patients with the apomorphine pump, these can be alleviated or even avoided altogether, for example by rotating the infusion site or using ultrasound treatment.



The Crono APO-go pump for continuous administration of apomorphine

In Simon Lewis's view there are clearly tiers of risk accompanying the different advanced therapies, and these need to be balanced against the evidence of their effectiveness when discussing treatment options with patients. For Tove Henriksen it is vital that the patient (and the care giver) have reasonable expectations regarding the efficacy, side effects, complications and practicalities of the treatment, as well as its long-term effects.

In terms of evidence, while there is observational data, randomised studies are lacking for all three advanced therapies. That evidence is needed to direct efforts in practice, and to decide the most appropriate option in the context of the individual patient. What PD patients themselves want from their treatment is also a major consideration, in Simon Lewis's view. Ray Chaudhuri agrees, noting that as evidence emerges for the benefits of earlier utilisation of these advanced therapies, it is important that patients are empowered with the choices that these therapies can provide.

References

1. Chaudhuri KR, Martinez-Martin P, Schapira AH et al. *Mov Disord* 2006; 21(7): 916-230.
2. Taylor H, Leitman R. *Health Care News* 2003; 3(15).

Prescribing information can be found overleaf

This article was commissioned by Britannia Pharmaceuticals Ltd and was written by Helen Lawn & Associates.

The debate was part of the Britannia sponsored satellite symposium held on Friday 19 April at the 9th International MDPD Congress, 18-21 April 2013, Seoul, South Korea

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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. Hospital admission under appropriate specialist supervision is necessary during patient selection and when establishing a patient's therapeutic regime. Please refer to the Summary of Product Characteristics for full details before initiating therapy. Treatment with domperidone (typical dosage 20mg three times a day) before and during apomorphine HCl therapy is essential. The optimal dosage of apomorphine HCl has to be determined on an individual patient bases; 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. Breast-feeding should be avoided during apomorphine HCl therapy.

Interactions Patients should be monitored for potential interactions during initial stages of apomorphine therapy. Particular caution should be given when apomorphine is used with other medications that have a narrow therapeutic window. It should be noted that there is potential for interaction with neuroleptic and antihypertensive agents. It is recommended to avoid the administration of apomorphine with other drugs known to prolong the QT interval. Apomorphine can increase the antihypertensive effects of domperidone.

Precautions Use with caution in patients with renal, pulmonary or cardiovascular disease, or who are prone to nausea or vomiting. Extra caution is recommended during initiation of therapy in elderly because of the risk of postural hypotension, and/or debilitated patients. Since apomorphine may produce hypotension, care should be exercised in patients with cardiac disease or who are taking vasoactive drugs, particularly when pre-existing postural hypotension is present. Neuropsychiatric disturbances are common in Parkinsonian patients. APO-go should be used with special caution in these patients. Apomorphine has been associated with somnolence and 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 bronchospasm.

Side Effects Local induration and nodules (usually asymptomatic) often develop at subcutaneous site of injection leading to areas of erythema, tenderness, induration and panniculitis. Irritation, itching, bruising and pain may also occur. Rarely Injection site necrosis and ulceration have been reported. Pruritus may occur at the site of injection. Drug-induced dyskinesias during "on" periods can be severe, and in a few patients may result in cessation of therapy. Postural hypotension is seen infrequently and is usually intransient. Transient sedation following each dose of apomorphine may occur at the start of therapy, but this usually resolves after a few weeks of treatment. Dizziness and lightheadedness have also been reported. Nausea and vomiting may occur, particularly when APO-go treatment is initiated, usually as a result of the omission of domperidone. Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine therapy and neuropsychiatric disturbances may be exacerbated by apomorphine. Positive 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

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Date of last revision: February 2013

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Mike Zandi, Editor.

In this issue we have for you a combination of articles on some of the latest scientific advances relevant to both higher cognitive functioning and peripheral nerve diseases, and some pragmatic clinical reviews.

Laura Gasparini and Andrea Contestabile from Genoa paint a clear picture of where we are now in the study of neurogenesis and how this knowledge may be harnessed to treat diseases such as Down Syndrome. The authors review some of their own animal model work using lithium in the Ts65Dn mouse model of Down Syndrome.

Florence Fricker and David Bennett from Oxford write an informative and up to date account of the molecular mechanisms underlying cross-talk between axons and Schwann cells, in particular after peripheral nerve injury. A clear problem, with some therapeutic hope in sight, is that of maintaining trophic support for Schwann cells distal to the point of nerve injury. Maybe we can piggy-back and gain therapeutic insights from recent knowledge of the mechanisms underlying leprosy.

We are pleased to have Anish Bahra from the National Hospital for Neurology and Neurosurgery, London, write the first of a series of articles she is editing for us on headache. In her article, entitled secondary headache, Dr Bahra provides an up to date and helpful survey of the published data on the imaging of patients with headaches, imaging healthy individuals and the nature of abnormalities picked up. Four reliable indicators of secondary headache are presented. We look forward to the development of this series.

In our epilepsy series, Mark Cook from St. Vincent's hospital in Melbourne tackles the question we are often asked in the clinic: how to predict the future (of seizure occurrence). He describes a study of an ambulatory intracranial EEG device and handset which allows real-time analysis of seizures and feature analysis of the EEG prior to seizures. This data may be used in future studies to develop short term therapeutic measures to pre-emptively abort seizures, and reduce the adverse effects of long-term anticonvulsant use.

In a Special Feature, clinical psychologist and neuropsychologist Daniel Friedland and academic neurosurgeon Peter Hutchinson help us classify traumatic brain injury in terms of severity, outcome and prognosis. The Mayo and Nakase-Richardson systems seem to be useful in this regard, the latter based on a recent study of post-traumatic amnesia in nearly 4000 individuals. Pitfalls in misclassification are discussed.

In our second Special Feature, Pam Enderby from Sheffield reviews augmentative and alternative communication methods for subjects with severe speech, voice or language impairments.

Finally, Kristian Aquilina from Great Ormond Street Hospital writes our neurosurgery article: an overview of diagnosis and management of posterior fossa tumours in children. This is a clear and detailed summary of the clinical features and molecular mechanisms underpinning these tumours and the evidence base for treatment.

As usual, we have our batch of conference, journal and book reviews and welcome contributions from our readers to add to these. Please visit our evolving website, where many future articles and conference and other reviews will start to appear on-line first.

*Mike Zandi, Editor.
Email: Rachael@acnr.co.uk*

Miratul Muqit receives Wellcome Senior Fellowship

Miratul Muqit has recently been awarded a prestigious Wellcome Senior Fellowship in Clinical Science to continue his ground-breaking research on the regulation and function of the Parkinson's disease associated PINK1 kinase.

Miratul is a Consultant Neurologist whose lab is based in the MRC Protein Phosphorylation and Ubiquitylation Unit at the University of Dundee. Over the next 5 years, Miratul plans to determine how disruption of PINK1 signalling leads to Parkinson's and exploit this knowledge to develop new ideas on diagnosis and treatment of Parkinson's.

The University of Dundee offers outstanding training to clinicians interested in basic science research through its Wellcome Trust Clinical PhD program (<http://www.dundee.ac.uk/wtclinicalphd/>) and Miratul would be happy to discuss potential projects with prospective applicants.

E: m.muqit@dundee.ac.uk.



ABN winners announced at Annual Conference

A number of winners were announced at the recent ABN conference held in Glasgow. Owen Pickerell was awarded £100 for best case presentation which was sponsored by ACNR.

Other award winners were, Shahrzad Hadavi for best poster; Patrick Collins for best Platform; quiz winners Ashvini Keshavan (registrar) and Ed Newman (student), as well as Julia Pakpoor who won the award for best student presentation.

Andrew Ross awarded an OBE

The former Chief Executive of The Children's Trust has been awarded an OBE for his services to children.

Andrew Ross, who retired in April from the national charity based in Tadworth, was recognised in the Queen's Birthday Honours list 2013 which was announced on June 15th.

He said: "I am absolutely delighted to have received this honour personally. However, I know that it also reflects the outstanding work of The Children's Trust and all the support I have had over a 20 year career. This includes the brilliant, professional staff and the huge number of volunteers, who have given such tremendous support to the children."

Commenting on the Award, Chair of Trustees, Duncan Ingram said: "All the trustees, staff and volunteers are thrilled. It is a testament to Andrew's success, making The Children's Trust the UK's leading children's charity in its field."

Andrew took on the role of Chief Executive for the Trust in 1992. He oversaw



developments in new services, which includes the UK's largest residential rehabilitation centre for children with an acquired brain injury, specialist care for some of the UK's most severely disabled children and a specialist school.

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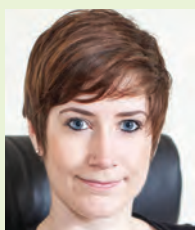
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Bookmark www.acnr.co.uk for exclusive online content – a report on the Primary Care Neurology Society meeting and the Alzheimer's research UK Conference

It takes two to tango: Bi-directional axoglial signalling is required for effective nerve repair



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Conflict of interest statement:

The authors declare that there are no financial or commercial conflicts of interest.

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Schwann cells are the glia of the peripheral nervous system, ensheathing and myelinating large axons and grouping smaller diameter axons within Remak bundles. Bi-directional signalling between axons and Schwann cells has long been known to be essential for the development of the peripheral nervous system. More recently, (and the focus of this review) it has been shown that axo-glial signalling in neural injury is essential for effective repair and is distinct from signalling events during development.

Injury to the peripheral nervous system can be caused by many insults, from metabolic diseases such as diabetes, inherited genetic disorders such as Charcot-Marie-Tooth disease (CMT), infectious and inflammatory disorders including Guillan-Barré syndrome and traumatic injury which alone affects up to 300,000 people in Europe per year.¹ Traumatic nerve injury in rodents is very commonly used as a model to study the process of peripheral nerve repair and functional recovery. Following an injury to the peripheral nervous system, axon and myelin fragments are broken down by a process termed Wallerian degeneration. Axons then regenerate, are remyelinated and eventually reinnervate target organs. How complete this process is and the extent to which target organs are innervated by the correct axons is related to the degree of functional recovery. Signalling between Schwann cells and axons is essential throughout the phases of this process and disruption of this signalling has severe consequences for nerve repair.

How do Schwann cells respond to nerve injury/support axons following nerve injury?

Schwann cells are essential for nerve repair. Following injury, they re-enter the cell cycle and activate Raf/MEK/ERK signalling.² This drives their differentiation into a phenotype which actively phagocytoses myelin and axonal fragments, promotes recruitment of macrophages, enhances axon growth and increases neuronal survival. The alignment of Schwann cells into bands of Büngner guides regenerating axons back to their synaptic targets (Figure 1).^{3,4} Schwann cells undergo this phenotypic transformation as a direct response to axon derived signals (the identity of which are not established), which trigger a transcriptional program driven by the transcription factor c-Jun. This results in a down regulation of genes that regulate myelination and an upregulation of genes

involved in macrophage recruitment, axon growth and survival. If this phenotypic switch is disrupted by inactivating c-Jun in Schwann cells, axon regeneration, functional recovery and neuronal survival is severely impaired following peripheral nerve injury.⁵ This phenotypic plasticity of Schwann cells may in rare instances be detrimental. *Mycobacterium leprae*, the causative agent of leprosy utilises this property of Schwann cells. Having infected Schwann cells the bacterium triggers reprogramming of these cells to aid bacterial dissemination.⁶

As axons regenerate through bands of Büngner, in addition to providing guidance towards their targets, Schwann cells must provide other supportive roles (Figure 1 C). Local translation in axons is likely to be necessary during growth cone formation and axon elongation, indeed, *in vitro* inhibition of local translation results in retraction of growth cones.⁷ Polyribosomes have been visualised to transfer from Schwann cells to regenerated axons, raising the possibility that Schwann cells may not only provide translational machinery to support axons but also mRNA and therefore could modify axonal translational products.⁸

The very long distances between axons and their cell bodies has long implicated a need for Schwann cells to provide a metabolic supportive role.⁹ In mutant mice in which Schwann cell mitochondria are dysfunctional, development occurs normally, but in adulthood mice develop a severe axonal neuropathy despite axonal mitochondria being unaffected.¹⁰ Schwann cell mitochondria function plays a role in repair, as although regeneration is unaffected in mutant mice remyelination fails.¹⁰ Furthermore mice with Schwann cells lacking functional peroxisomes, organelles housing oxidative metabolic reactions, present in non-compact myelin membranes, develop an adult-onset neuropathy.¹¹ Recently it has been demonstrated that myelinating Schwann cells contain glycogen granules which are likely to provide a source of glycogen derived lactate to axons in order to metabolically support axons particularly in hypoglycaemic conditions.¹² The long narrow channels of glial cytoplasm connecting to the periaxonal space including Cajal bands, Schmidt-Lanterman incisures and the lumina of paranodal loops are likely to provide a means for Schwann cells to transfer metabolites to axons in order to provide metabolic support necessary for maintenance and more than likely essential for the metabolically expensive process of repair of the peripheral nerve.

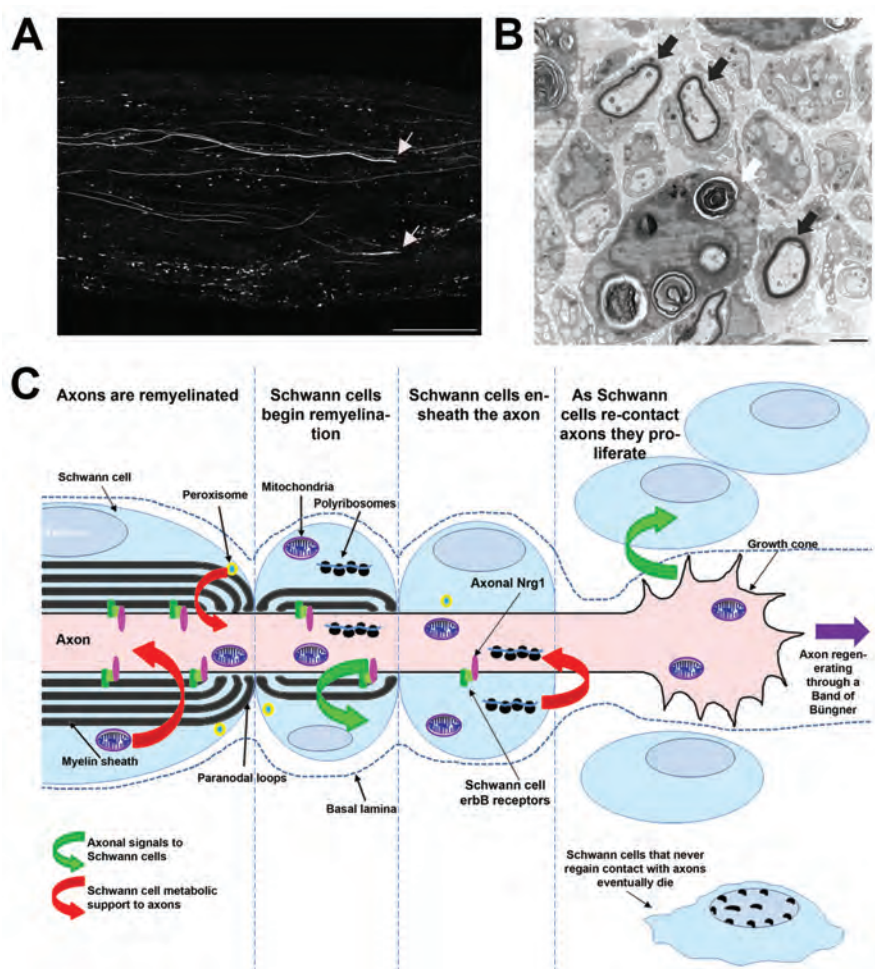


Figure 1: The bidirectional relationship between axons and Schwann cells during neural repair. A) A photomicrograph of YFP labelled axons regenerating in the tibial nerve following a Sciatic nerve crush. Arrows label leading growth cones. Scale bar 500µm. B) An electron micrograph of a transverse Sciatic nerve 10 days following a crush injury. Black arrows label axons with a diameter greater than 1µm where Schwann cells have begun the process of remyelination. Note that the myelin sheath at this stage is much thinner than in the uninjured state. White arrows label myelin debris still being degraded by macrophages. Scale bar 2µm. C) Schematic diagram showing an axon regenerating, the phases of repair and how bidirectional communication and metabolic support between Schwann cells and axons regulates this process.

How do axons regulate SC health and phenotype following nerve injury?

As axons re-contact Schwann cells after nerve injury, signals from the axolemma are critical in directing the differentiation of Schwann cells back into a mature state in which they ensheath and in the case of large diameter axons myelinate axons (Figure 1). There are a few receptor-ligand signalling pairs known to regulate axo-glial signalling, the most characterised of which is the protein Neuregulin-1 type III expressed on the surface of axons which signals through binding to erbB2/erbB3 heterodimer receptors expressed on the Schwann cell. Although essential for peripheral nerve development Neuregulin-1/erbB signalling is dispensable for peripheral nerve maintenance. In contrast, in the early phases following peripheral nerve injury Neuregulin-1/erbB axo-glial signalling drives a transcriptional programme which enhances the rate of remyelination, and regeneration of peripheral axons as well as functional recovery.

Interestingly at delayed time points after injury axons remyelinate and function is restored in the absence of axonal Neuregulin-1 implying the presence of alternative signalling systems instructive in determining myelination fate of axons following injury.^{13,14} It has recently been shown that Schwann cell-derived Neuregulin-1 can also promote remyelination.¹⁵ Other axoglial receptor-ligand signalling pairs which are known to regulate myelination during development and potentially mediate nerve repair include axonal adam22 signalling through Schwann cell Lgi4,¹⁶ Nect-1 on axons signalling through Schwann cell Nect-4¹⁷⁻¹⁹ and the as yet unidentified axonal ligand to Schwann cell G-protein-coupled receptor gpr126.²⁰

Ultimately, Schwann cells need axonal contact to survive, this is shown in chronically denervated nerve stumps where, as time progresses, in the absence of axonal contact survival of Schwann cells declines. Importantly the Schwann cells that survive

are much less able to support any axons that do eventually regenerate into such a stump.²¹ This is likely to be caused by transcriptional changes caused by a lack of axo-glial signalling. It is known that the expression of erbB receptors and of the growth factor glial cell-line derived neurotrophic factor (GDNF) is greatly reduced in such chronically denervated Schwann cells.^{21,22} This decline in Schwann cell capability and survival is clinically very important as the rate of axon regeneration is slow at 1-3mm per day resulting in Schwann cells distal to the injury being denervated for prolonged periods contributing to the poor functional outcomes particularly seen following proximal injuries for instance following brachial plexus avulsion.

We have concentrated on traumatic neuropathy as an exemplar. The critical nature of axo-glial signalling to nerve injury and repair is virtually ubiquitous to all forms of neuropathy. An example is CMT1A which is due to an excessive gene dosage of PMP22 in Schwann cells, resulting in demyelination. However the level of disability in patients relates to the degree of secondary axonal loss and not the degree of conduction velocity slowing.²³

Axo-glial signalling may also be usurped by infective agents. Neuregulin-1 is normally presented to Schwann cells on the axolemma however high doses of exogenous soluble Neuregulin-1 have been reported to cause demyelination by triggering Schwann cell proliferation. The leprosy causing *Mycobacterium leprae* directly binds to and activates the erbB2 receptor activating the downstream MEK-ERK pathway and causing pathological demyelination.²⁴

Therapeutic opportunities

There is currently no pharmacological intervention to promote peripheral nerve repair. Greater understanding of how Schwann cells provide metabolic and trophic support to axons may provide means to provide axonal protection given that axonal loss is a major determinant of progressive disability. Manipulation of Neuregulin-1/erbB signalling may provide a means to promote remyelination. It is still not clear as to whether administration of exogenous soluble Neuregulin-1 *in vivo* can substitute for juxtacrine Neuregulin-1 which is presented on the axolemma. A more tractable means of manipulating this pathway may be to inhibit enzymes such as TACE (ADAM17) which process Neuregulin-1 into an inactive form.²⁵ In the problematic situation of chronic denervation substituting signals that Schwann cells would normally receive from axons could promote their survival so that when regenerating axons finally reach distal regions of nerve they enter a much more hospitable environment. Using these approaches we hope that greater knowledge of axo-glial communication can ultimately be used to choreograph effective nerve repair in patients. ♦

REFERENCES

1. Martyn CN, Hughes RA. *Epidemiology of peripheral neuropathy*. J Neurol Neurosurg Psychiatry. Apr 1997;62(4):310-318.
2. Napoli I, Noon LA, Ribeiro S, et al. *A central role for the ERK-signaling pathway in controlling Schwann cell plasticity and peripheral nerve regeneration in vivo*. Neuron. Feb 23 2012;73(4):729-742.
3. Chen ZL, Yu WM, Strickland S. *Peripheral regeneration*. AnnuRevNeurosci. 2007;30:209-233.
4. Vargas ME, Barres BA. *Why is Wallerian degeneration in the CNS so slow?* Annu Rev Neurosci. 2007;30:153-179.
5. Arthur-Farraj PJ, Latouche M, Wilton DK, et al. *c-Jun reprograms Schwann cells of injured nerves to generate a repair cell essential for regeneration*. Neuron. Aug 23 2012;75(4):633-647.
6. Masaki T, Qu J, Cholewa-Waclaw J, Burr K, Raaum R, Rambukkana A. *Reprogramming adult Schwann cells to stem cell-like cells by leprosy bacilli promotes dissemination of infection*. Cell. Jan 17 2013;152(1-2):51-67.
7. Zheng JQ, Kelly TK, Chang B, et al. *A functional role for intra-axonal protein synthesis during axonal regeneration from adult sensory neurons*. The Journal of neuroscience : the official journal of the Society for Neuroscience. Dec 1 2001;21(23):9291-9303.
8. Court FA, Midha R, Cisterna BA, et al. *Morphological evidence for a transport of ribosomes from Schwann cells to regenerating axons*. Glia. Oct 2011;59(10):1529-1539.
9. Nave KA. *Myelination and the trophic support of long axons*. Nature reviews Neuroscience. Apr 2010;11(4):275-283.
10. Viader A, Golden JP, Baloh RH, Schmidt RE, Hunter DA, Milbrandt J. *Schwann cell mitochondrial metabolism supports long-term axonal survival and peripheral nerve function*. The Journal of neuroscience : the official journal of the Society for Neuroscience. Jul 13 2011;31(28):10128-10140.
11. Kassmann CM, Quintes S, Rietdorf J, et al. *A role for myelin-associated peroxisomes in maintaining paranodal loops and axonal integrity*. FEBS letters. Jul 21 2011;585(14):2205-2211.
12. Brown AM, Evans RD, Black J, Ransom BR. *Schwann cell glycogen selectively supports myelinated axon function*. Annals of neurology. Sep 2012;72(3):406-418.
13. Fricker FR, A-MA, Galino J, Paramsothy R, La Russa F, Perkins J, Goldberg R, Brelstaff J, Zhu N, McMahon SB, Orenco C, Garratt AN, Birchmeier C, and Bennett DLH. *Axonal Neuregulin-1 is a rate limiting but not essential factor for nerve remyelination*. Brain : a journal of neurology. In Press 2013;In Press.
14. Fricker FR, Lago N, Balarajah S, et al. *Axonally derived neuregulin-1 is required for remyelination and regeneration after nerve injury in adulthood*. The Journal of neuroscience : the official journal of the Society for Neuroscience. Mar 2 2011;31(9):3225-3233.
15. Stassart RM, Fledrich R, Velanac V, et al. *A role for Schwann cell-derived neuregulin-1 in remyelination*. Nature neuroscience. Jan 2013;16(1):48-54.
16. Ozkaynak E, Abello G, Jaegle M, et al. *Adam22 is a major neuronal receptor for Lgi4-mediated Schwann cell signaling*. The Journal of neuroscience : the official journal of the Society for Neuroscience. Mar 10 2010;30(10):3857-3864.
17. Maurel P, Einheber S, Galinska J, et al. *Nectin-like proteins mediate axon Schwann cell interactions along the internode and are essential for myelination*. J Cell Biol. Aug 27 2007;178(5):861-874.
18. Spiegel I, Adamsky K, Eshed Y, et al. *A central role for Nectin-1 (SynCAM4) in Schwann cell-axon interaction and myelination*. Nature neuroscience. Jul 2007;10(7):861-869.
19. Zelano J, Plantman S, Hailer NP, Cullheim S. *Altered expression of nectin-like adhesion molecules in the peripheral nerve after sciatic nerve transection*. Neuroscience letters. Jan 2 2009;449(1):28-33.
20. Monk KR, Oshima K, Jors S, Heller S, Talbot WS. *Gpr126 is essential for peripheral nerve development and myelination in mammals*. Development. Jul 2011;138(13):2673-2680.
21. Li H, Terenghi G, Hall SM. *Effects of delayed re-innervation on the expression of c-erbB receptors by chronically denervated rat Schwann cells in vivo*. Glia. Aug 1997;20(4):333-347.
22. Hoke A, Gordon T, Zochodne DW, Sulaiman OA. *A decline in glial cell-line-derived neurotrophic factor expression is associated with impaired regeneration after long-term Schwann cell denervation*. Exp Neurol. Jan 2002;173(1):77-85.
23. Krajewski KM, Lewis RA, Fuerst DR, et al. *Neurological dysfunction and axonal degeneration in Charcot-Marie-Tooth disease type 1A*. Brain : a journal of neurology. Jul 2000;123 (Pt 7):1516-1527.
24. Tapinos N, Ohnishi M, Rambukkana A. *ErbB2 receptor tyrosine kinase signaling mediates early demyelination induced by leprosy bacilli*. Nat Med. Aug 2006;12(8):961-966.
25. La Marca R, Cerri F, Horiuchi K, et al. *TACE (ADAM17) inhibits Schwann cell myelination*. Nature neuroscience. Jun 12 2011;14(7):857-865.



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Targeting adult neurogenesis for therapy of intellectual disability



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Key Points

- 1 Hippocampal adult neurogenesis is reduced in mouse models of Down syndrome
- 2 The mood-stabiliser lithium carbonate rescued adult neurogenesis in trisomic mice
- 3 Restoring adult neurogenesis rescued both synaptic plasticity and memory in Down syndrome mice

Throughout life, the adult mammalian brain continuously generates new neurons that become integrated into pre-existing neuronal networks. Under physiological conditions adult neurogenesis is restricted to two neurogenic niches, i.e. the subventricular zone (SVZ), which generate interneurons that will integrate into the olfactory bulb, and the hippocampal dentate gyrus (DG), where new granule cells of the DG (DGCs) are continuously produced.

Newborn DGCs derive from neural progenitor cells (NPCs) of the DG subgranular zone through a process that lasts several weeks to reach maturity (Figure 1). During the first week of development, early neuroblasts undergo radial migration toward the inner granule cell layer. Axon and dendrite formation starts during the second week of development and coincides with afferent synaptogenesis with GABAergic neurons. Glutamatergic functional afferents begin to establish during the third week of maturation and increase their strength in the following week. Structural and functional maturation of new DGCs is completed after 6–8 weeks. During this maturation process, DG newborn neurons display enhanced synaptic plasticity properties (i.e. increased intrinsic excitability and reduced sensitivity to GABAergic inhibition) compared with that of preexisting mature DGCs. Remarkably, newborn neurons feature a specialised form of long term potentiation (LTP) that is distinguishable from that of mature DGCs for its reduced sensitivity to GABAergic inhibition¹. Such peculiar electrophysiological properties apparently confer to newborn neurons a key role in regulating hippocampal function and cognition. The DG plays a pivotal role in cognition. Experimental and computational studies indicate that newborn neurons in the DG are essential for hippocampal function. In fact, there is increasing evidence that maturing newborn neurons distinctively contribute to information processing in

the DG and participate in the expression of specific forms of hippocampal-dependent learning and memory in rodents, including contextual learning, cognitive flexibility and pattern separation.

The impairment of adult neurogenesis has been observed in a variety of models relevant to neuropsychiatric diseases, such as major depression, schizophrenia and Alzheimer's disease, and neurodevelopmental disorders, including Fragile X and Down syndrome (DS) (for reviews see ^{2,3}). Furthermore, recent data in epileptic patients undergoing en bloc hippocampus resection indicate that low proliferation and differentiation capacities of adult hippocampal stem cells correlate with memory dysfunction⁴. However, to date, the evidence supporting a role for adult neurogenesis in specific diseases is still sparse and inconclusive. Moreover, it is still unclear whether impairment of adult neurogenesis associated with neurodegenerative and neurodevelopmental diseases is a primary event or a neuroadaptive response to complex pathological mechanisms. Nevertheless, independently of the origin of its impairment, one fundamental question is whether adult neurogenesis could be boosted and exploited for therapeutic purposes. Indeed, adult neurogenesis is highly sensitive to environmental stimuli, including environmental enrichment and exogenous molecules⁵. Thus, adult neurogenesis represents an attractive, though unexplored, opportunity to develop therapies for disease-associated cognitive impairment and might be particularly relevant for neurodevelopmental diseases with complex genetic etiologies, such as DS.

DS results from the trisomy of chromosome 21 in humans and is the leading cause of genetically defined intellectual disability. In the DS brain, suboptimal network architecture and altered synaptic communication through neurodevelopmental impairment represent key determinants of intellectual disabilities, which involve several cognitive domains, such as language, verbal and spatial learning and memory (reviewed in ²). Both hippocampal and prefrontal-related functions appear defective in DS subjects, although these defects apparently manifest at different ages. Hippocampal dysfunction occurs in DS children and adolescents, with impairment of spatial associative memory and sparing of the prefrontal-mediated reference memory⁶.

Over the past decades, several trisomic DS mouse models have been generated, recapitulating essential genetic and cognitive deficits of human DS (reviewed in ^{2,7}). The results

of studies conducted in such models have suggested that cognitive dysfunction is not due to gross neuroanatomical abnormalities, but rather derives from both changes in synaptic connectivity (e.g. excitation/inhibition imbalance) and altered developmental neurogenesis during embryogenesis and the early postnatal period (reviewed in²).

The widely used Ts65Dn mouse is a relevant model of DS, reproducing several phenotypic abnormalities of the human disease⁸. Studies using this model have reported that adult neurogenesis is reduced in both the adult DG and SVZ, and its stimulation using drugs, such as fluoxetine⁹ or lithium^{10,11}, induces the proliferation of NPCs and the expression of discrete molecular markers of newborn neurons in both neurogenic niches. Specifically, it has been shown that treatment with fluoxetine for up to 24 days rescues the impaired hippocampal neurogenesis of young Ts65Dn mice, re-establishing levels of proliferating cells similar to euploid mice⁹. Beneficial effects on neurogenesis have also been obtained in the SVZ of 12 month-old Ts65Dn female mice fed with lithium-supplemented chow for 1 month¹⁰. Using the same model, we took one step further and we recently demonstrated that potentiation of dentate adult neurogenesis could translate into amelioration of hippocampal plasticity and behavioural performance in the multi-factorial context of DS¹¹. We found that the number of DG newborn neurons is reduced and neurogenesis-dependent LTP is deficient in the DG of Ts65Dn mice. Notably, the lack of this specialised form of synaptic plasticity in trisomic mice correlates with the impaired performance of Ts65Dn in hippocampal-dependent behavioural tasks, such as the contextual fear conditioning and object location tasks¹¹. To enhance neurogenesis, we treated 5-6 month old Ts65Dn mice with lithium, a mood-stabilising agent that specifically stimulates the proliferation of NPCs through the Wnt/Beta-catenin pathway. We found that DG adult neurogenesis could be restored to physiological levels after 4 weeks of lithium administration in the Ts65Dn trisomic mouse, resulting in the full recovery of DG synaptic plasticity and hippocampal-dependent cognitive functions. Lithium achieves these results by both enhancing NPC proliferation and favouring the integration of newborn neurons into the hippocampal circuit. Indeed, in trisomic mice, lithium stimulates NPC proliferation and increases the numbers of maturing DG newborn neurons without affecting fate determination and newborn neuron survival. Such neurons are functionally active, completely recover newborn neuron-dependent LTP, and are required to restore hippocampal-dependent learning and memory performance in lithium-treated trisomic mice.

Notably, we demonstrated that LTP was not rescued when lithium-treated trisomic and wild type mice were concomitantly administered the cytostatic drug temozolamide to inhibit NPCs proliferation, indicating that neurogenesis is required for LTP recovery. In this view line, short-term treatment (e.g. one week) with lithium fails to restore hippocampal synaptic plasticity in Ts65Dn mice. This rules out the involvement of other acute effects of lithium and further supports the notion that functional neurogenesis is specifically involved in reverting the hippocampal-dependent disease phenotype. Indeed, newborn neurons one-week old or younger do not show any spontaneous or evoked synaptic currents and are not integrated in the hippocampal circuits¹. In fact, their enhanced synaptic plasticity properties start to be expressed 3-4 weeks after their birth and last until 6 weeks¹.

Recovery of neurogenesis and newborn neuron-dependent LTP in Ts65Dn mice results in the specific rescue of behavioural performance in different hippocampal-dependent tasks, but not of working memory (i.e. T-maze). This is consistent with previous studies showing that only some forms of learning^{12,13}, rely on hippocampal adult neurogenesis, while working memory is independent of adult neurogenesis¹⁴. Although we acknowledge that lithium may exert diverse pleiotropic effects, such as for example, modulation of brain myo-inositol levels, our data consistently support the view that amelioration of adult neurogenesis underlies lithium effects on behavioural performance in Ts65Dn mice. This indicates that restoring adult neurogenesis to physiological levels can resolve some crucial hippocampal-dependent cognitive defects typical of DS. In DS, hippocampal dysfunction is characterised by impaired spatial associative memory as detected by the CANTAB Paired-associates Learning⁶ and is particularly evident in very demanding tasks. Although these and other results (reviewed in^{2,7}) suggest a potential impairment of

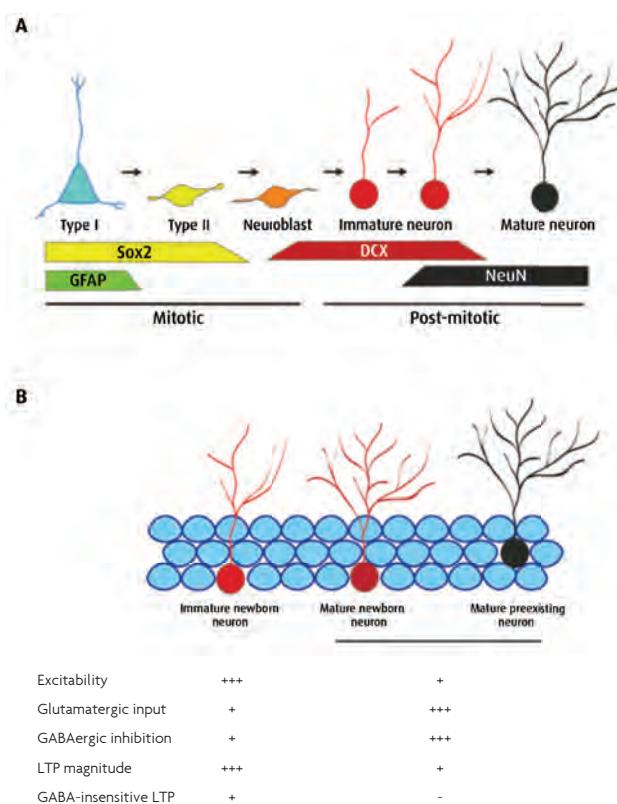


Figure 1 – Scheme of adult neurogenesis in the hippocampal DG. (A) During the mitotic phase, two types of progenitors proliferate in the subgranular zone (SGZ) of the DG: radial glia-like progenitors (type I cells, expressing Nestin, GFAP and Sox2) and amplifying progenitors (type II cells, expressing Sox2 only). Before becoming post-mitotic, the progenitors undergo a short intermediate stage (neuroblasts) during which they become committed to the neuronal fate and begin expressing doublecortin (DCX). In the post-mitotic phase, DCX-positive newborn neurons derived from neuroblasts undergo morphological and physiological maturation with the final expression of the mature neuron marker, NeuN. (B) Schematic representation of the most important electrophysiological differences between immature newborn neurons and mature DGCs (both preexisting and adult-generated).

cognitive functions typically regulated by adult neurogenesis, such as pattern separation¹⁵ and cognitive flexibility¹⁶, further studies are required to evaluate in depth these specific domains in DS patients and related mouse models.

From the molecular point of view, we found that the Wnt/Beta-catenin pathway mediates the neurogenesis-promoting effects of lithium, as functional signalling through this pathway is required for lithium-induced proliferation of trisomic and wild type adult dentate NPCs in vitro. However, at present, we cannot rule out that other neurogenic pathways may underlie adult neurogenesis impairment in DS and may also be exploited from a therapeutic perspective. Further studies are warranted to identify abnormal neurogenic pathways in DS and/or their potential exploitation for therapies.

In summary, our findings¹¹ strongly indicate that promoting adult neurogenesis may have profound impact on hippocampal synaptic plasticity and memory in DS. This is particularly relevant from the therapeutic perspective in view of the recent discovery that adult hippocampal neurogenesis persists throughout life in humans with only minor changes during ageing¹⁷. However, a note of caution should be raised in view of the fact that available animal models, in spite of recapitulating many disease features, do not replicate the entire genetics of DS. The effects of multiple genetic interactions on the treatment outcome cannot be fully controlled, hampering the translational predictivity of studies in animals⁷. Hence, proof-of-concept studies in DS subjects are warranted to investigate this approach. Lithium is a well-established, relatively well-tolerated mood stabiliser and is widely used in therapy of mood disorders. However, it has adverse effects that might be problematic in the DS population, prompting caution with its therapeutic application. Still, given its well-known therapeutic and safety profile, lithium might be useful for validating the neurogenesis target in DS subjects. Importantly, in the Ts65Dn mouse, the effects of lithium manifest at doses achieving

plasma concentrations consistent with the human therapeutic range (0.5-1.2 mEq/L). Nonetheless, one key factor shall be taken into account to design clinical trial of pro-neurogenic treatments. In DS, changes in neurogenesis are only part of a more complex and distributed pathology. In fact, DS patients often develop Alzheimer's disease (AD) at young age², which is accompanied by synaptic pathology and hippocampal deficits. Therefore, eligibility criteria shall be carefully set, limiting the study population to 30-40 year-old young adults to maximise the potential efficacy of the treatment and avoid confounding effects from neurodegenerative mechanisms. Notably, lithium has been also found to reduce Beta-amyloid pathology and alleviate memory deficits both in AD transgenic mouse models and patients with mild cognitive impairment^{18,19}. Thus, with cautious design, studies of chronic lithium administration to young DS subjects may also shed light on the potential preventive efficacy of the drug in reducing or delaying AD pathology.

In conclusion, lithium-based therapies may have important translational implications in the near future, in view of the increased prevalence of DS in EU²⁰ and USA²¹ over the past decades and the increased life expectancy of DS patients due to improved medical care. Moreover, from a long-term perspective, our findings point at adult neurogenesis as a potential target to design future therapies for the treatment of selected cognitive disabilities in DS patients and other neuropsychiatric disorders with flawed adult neurogenesis. ♦

REFERENCES

- Mongiat, L. A. & Schinder, A. F. Adult neurogenesis and the plasticity of the dentate gyrus network. *Eur J Neurosci* 33, 1055-1061 (2011).
- Contestabile, A., Benfenati, F. & Gasparini, L. Communication breaks Down: from neurodevelopment defects to cognitive disabilities in Down syndrome. *Prog Neurobiol* 91, 1-22 (2010).
- Winner, B., Kohl, Z. & Gage, F. H. Neurodegenerative disease and adult neurogenesis. *Eur J Neurosci* 33, 1139-1151 (2011).
- Coras, R. et al. Low proliferation and differentiation capacities of adult hippocampal stem cells correlate with memory dysfunction in humans. *Brain* 133, 3359-3372 (2010).
- Ming, G. L. & Song, H. Adult neurogenesis in the mammalian brain: significant answers and significant questions. *Neuron* 70, 687-702 (2011).
- Pennington, B. F., Moon, J., Edgin, J., Stedron, J. & Nadel, L. The neuropsychology of Down syndrome: evidence for hippocampal dysfunction. *Child Dev* 74, 75-93 (2003).
- Gardiner, K. J. Molecular basis of pharmacotherapies for cognition in Down syndrome. *Trends Pharmacol Sci* 31, 66-73 (2010).
- Reeves, R. H. et al. A mouse model for Down syndrome exhibits learning and behaviour deficits. *Nat Genet* 11, 177-184 (1995).
- Clark, S., Schwabe, J., Stasko, M. R., Yarowsky, P. J. & Costa, A. C. Fluoxetine rescues deficient neurogenesis in hippocampus of the Ts65Dn mouse model for Down syndrome. *Exp Neurol* 200, 256-261 (2006).
- Bianchi, P., Ciani, E., Contestabile, A., Guidi, S. & Bartsaghi, R. Lithium restores neurogenesis in the subventricular zone of the Ts65Dn mouse, a model for Down syndrome. *Brain Pathol* 20, 106-118 (2010).
- Contestabile, A. et al. Lithium rescues synaptic plasticity and memory in Down syndrome mice. *J Clin Invest* 123, 348-361 (2013).
- Saxe, M. D. et al. Ablation of hippocampal neurogenesis impairs contextual fear conditioning and synaptic plasticity in the dentate gyrus. *PNAS* 103, 17501-17506 (2006).
- Deng, W., Aimone, J. B. & Gage, F. H. New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? *Nature reviews. Neuroscience* 11, 339-350 (2010).
- Hernández-Rabaza, V. et al. Inhibition of adult hippocampal neurogenesis disrupts contextual learning but spares spatial working memory, long-term conditional rule retention and spatial reversal. *Neurosci* 159, 59-68 (2009).
- Clelland, C. D. et al. A Functional Role for Adult Hippocampal Neurogenesis in Spatial Pattern Separation. *Science* 325, 210-213 (2009).
- Garthe, A., Behr, J. & Kempermann, G. Adult-Generated Hippocampal Neurons Allow the Flexible Use of Spatially Precise Learning Strategies. *Plos One* 4, e5464 (2009).
- Spalding, K. L. et al. Dynamics of hippocampal neurogenesis in adult humans. *Cell* 153, 1219-1227 (2013).
- Zhang, X. et al. Long-term treatment with lithium alleviates memory deficits and reduces amyloid-beta production in an aged Alzheimer's disease transgenic mouse model. *J Alzheimers Dis* 24, 739-749, doi:10.3233/JAD-2011-101875 (2011).
- Forlenza, O. V. et al. Disease-modifying properties of long-term lithium treatment for amnesic mild cognitive impairment: randomised controlled trial. *Br J Psychiatry* 198, 351-356 (2011).
- Dolk, H. et al. Trends and geographic inequalities in the prevalence of Down syndrome in Europe, 1980-1999. *Rev Epidemiol Sante Publique*, 2587-95 (2005).
- Shin, M. et al. Prevalence of Down syndrome among children and adolescents in 10 regions of the United States. *Pediatrics* 124, 1565-1571 (2009).



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Classification of traumatic brain injury



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There are different systems for classifying traumatic brain injury (TBI). Systems include classifying traumatic brain injury by severity, which is generally based on clinical indexes at the time of presentation. TBI can be classified by pathoanatomic type i.e. type of injury such as diffuse axonal injury, haematoma and haemorrhages.¹ Further classification systems include classification of TBI by outcome and prognosis.^{1,2} This paper will focus on classification of traumatic brain injury by severity, outcome, and prognosis.

Classification by severity

In terms of the classification of severity, historically TBI was classified as mild, moderate or severe by using the Glasgow Coma Scale, a system used to assess coma and impaired consciousness. The Glasgow Coma Scale is divided into three components – eye opening, verbal response and motor responses. These are usually summed to produce a total score. A Glasgow Coma Scale score of 13-15 is defined as mild, 9-12 as moderate, 3-8 as severe.³ This is an example of classification of TBI severity during the acute phase of injury. However, clinically it is important to provide the individual scores (particularly the motor score) in addition to the total score.

Post-traumatic amnesia (PTA) is another important index of the severity of traumatic brain injury.⁴ PTA is the interval from injury until the patient is orientated, and can form and later recall new memories.⁴ A PTA of 1-24 hours used to be considered to indicate a TBI within the category of moderate severity.⁴ Current classifications of moderate TBI generally refer to PTA extending beyond 24 hours.^{4,5}

The diagnosis of mild traumatic brain injury (MTBI) is a good example of severity of TBI based on multiple acute injury indices. These include the Glasgow Coma Scale, length of post-traumatic amnesia, results of neuroimaging and focal signs. The American Congress of Rehabilitation Medicine, Centre for Disease Control, and the World Health Organisation include the criterion for a MTBI as: loss of consciousness less than 30 minutes following the injury and posttraumatic amnesia of less than 24 hours following the injury.^{5,6}

The Mayo Classification System for Traumatic Brain Injury Severity was developed to address the issue of the unreliability of some TBI severity indicators and the frequency of missing documentation in medical records. The Mayo Classification System has three main classifications including definite moderate-severe TBI, probable MTBI, and possible TBI.⁷ Multiple criteria are used in each diagnosis including loss of consciousness, post-traumatic amnesia, skull fracture, and evidence of neuroradiological abnormalities including subdural haematoma, cerebral contusion, and hemorrhagic contusion.

A TBI would be classified as definite moderate-severe in the Mayo system if one or more of the following criteria apply: death due to this TBI, loss of consciousness of 30 minutes or more, PTA of 24 hours or more, and worst GCS full score in first 24 hours is <13 providing this not invalidated by other factors such as intoxication or sedation. In addition if there is evidence of neurological injury such as haematoma, contusion, haemorrhage then the TBI would be in the definite moderate-severe category. A TBI would be classified as probable mild if there is loss of consciousness below 30 minutes, PTA is less than 24 hours, and there is a depressed, basilar, or linear skull fracture (dura intact). A possible TBI is diagnosed if there are one or more of the following symptoms: blurred vision, confusion, feeling dazed, dizziness, headache, or nausea.⁷

The authors compared the Mayo system i.e. multiple indicators versus single indicators such as PTA, GCS, and loss of consciousness. The Mayo system far outperformed any single indicator in classifying severity of TBI.⁷ Sensitivity and specificity for moderate-severe TBI was calculated to be 89% and 98% respectively.⁷

Classification by outcome

Outcome can be measured in many different ways including scales such as the Glasgow Outcome Scale, neuropsychological functioning, and mood. There are also scales measuring dimensions such as challenging behaviour, community participation, and neuropsychiatric difficulties.⁸

The Glasgow Outcome Scale originally had five categories – dead, vegetative state, severe disability, moderate disability and good recovery.⁹ An eight point scale was subsequently described as the extended eight point Glasgow Coma Outcome Scale which subdivides moderate and severe disability into upper and lower categories. A questionnaire has been developed to assist with classification. The Glasgow and extended Glasgow Outcome Scores have been extremely valuable adjuncts to the management of patients with TBI and in particular as endpoints in clinical trials.

Classification by prognosis

The recent paper by Nakase-Richardson et al (2011) looked at duration of PTA and outcome.⁴ This study included a large sample of approximately 4000 individuals who suffered a TBI, and who had been productive prior to the TBI. In this study a PTA of 0-14 days was classified as a moderate TBI, PTA of 15-28 days was classified as a moderately severe TBI, and a PTA of 29-70 days was classified as a severe TBI.

This prognostic classification system is a development on Russell and Smith's classification system where a PTA of 1-7 days was viewed as severe, and a PTA of 7+ days was viewed as very severe.⁴ It is difficult to see how a TBI may be clas-

sified as severe according to Russell and Smith's categorisation when Nakase-Richardson's study showed that 67% of individuals with a PTA of 0-14 days returned to productivity within one year.⁴ The one issue that is not clear is how many of the sample stayed in productive work beyond the one year mark as studies have shown that individuals with a TBI do not necessarily have a stable, uninterrupted return to productivity.¹⁰

Reasons for classifying TBI severity

Acute management

The Glasgow Coma Scale score is used to guide management of TBI from a neurosurgical perspective.¹¹ It is an essential part of the assessment of a patient with TBI. In terms of MTBI it is one of the criteria used to determine the need for CT scan as defined by the NICE guidelines.¹¹ Severe TBI (i.e. coma defined as GCS less than or equal to 8) is an indication for a definitive airway i.e. cuffed tube in the trachea. However, patients with moderate TBI particularly in association with agitation invariably also benefit from sedation and ventilation prior to a CT scan. Of critical importance is not to regard GCS as a static measure; repeating it by the process of regular (usually 30 minute observations) is a fundamental part of the management of patients with TBI.

Avoiding misclassification

An obvious but important question is whether a patient has actually suffered a TBI. A clinician must ask whether they could be misclassifying a patient with a TBI who does not meet the criteria for such an injury.

Factors which may lead to misclassification include mistaking the patient's difficulty in recalling events post injury as post-traumatic amnesia when in fact the patient's memory has been affected by other factors such as intoxication with alcohol or drugs at the time of the injury. Medication administered at the scene of the accident for pain such as morphine can cause memory gaps which could be mistaken for PTA.¹² Kemp et al's (2010) study of orthopaedic patients who did not sustain a TBI but received opioids, underwent surgery, and were suffering clinical levels of anxiety at an early stage resulted in patients reporting PTA-like phenomenon at follow up.¹³ Acute stress disorder due to the traumatic nature of an event may also be mistaken for post-traumatic amnesia.¹⁴

Cognitive, physical, and emotional symptoms following MTBI are common. However, in reviewing the outcome studies Iverson and Lange (2011) conclude that following a mild traumatic brain injury neuropsychological deficits are not seen in athletes in 1-4 weeks following injury, and in trauma patients after 1-3 months.¹⁵ In contrast cognitive difficulties following moderate-severe traumatic brain injuries can persist.¹⁵ Thus, misclassifying a patient who has suffered a MTBI as having a moderate-severe TBI may lead a clinician to

explain that ongoing cognitive symptoms after three months is to be expected. There is a risk that this may then become a case of 'expectation as aetiology'. This may be even more of the case if a patient is told they suffered a TBI when in fact they did not.

The value of classification by severity in terms of guiding treatment and prognosis

Classification can help the clinician to predict outcomes in the longer term which may help to guide treatment decisions in the post-acute stages i.e. does the patient need intensive inpatient rehabilitation or can they be better managed by a rehabilitation team in the community. Secondly, it allows the clinician to be able to provide some information to the relatives/family of the patient with regards to prognosis in the long-term.

Conclusions

A useful starting point is to be explicit about the classification system used given the range of different classification systems. There is a general trend now to classify a MTBI as an injury in which the individual is not unconscious for more than thirty minutes, post-traumatic amnesia does not extend beyond 24 hours, and there are no abnormalities on neuroimaging.^{5,6,7,15} If any of these criteria are exceeded then the TBI is more likely to fall in the moderate to severe range. Classification of TBI is important in terms of differentiating a MTBI from a moderate-severe TBI given the difference in cognitive outcome.¹⁵

A system such as the Mayo system for classification of TBI has several advantages including using as much positive evidence as possible to classify TBI and does not rely on a single indicator.⁷ The Mayo system is structured in a conservative way to reflect severity of brain trauma based on the strength of available evidence i.e. by the use of distinctions such as definite, probable, and possible when classifying TBI, in addition to the use of multiple indicators.

The Mayo system is a useful classification system in the community rehabilitation setting, and has been used by the Hertfordshire Acquired Brain Injury Team. It provides a clear system for differentiating between mild versus moderate-severe TBI, which in turn guides rehabilitation. If a patient has suffered a probable MTBI, and they are reporting ongoing cognitive difficulties 3 months post-injury, this could guide clinicians to look at, and treat other factors such as pain, anxiety, depression, and disrupted sleep.

If a patient has suffered a moderate-severe TBI there is no guide as to long-term prognosis in the Mayo system. At this point, and if duration of PTA is known, it may be useful to then refer to Nakase-Richardson et al's prognostic classification system.⁴ This could help clinicians provide family members with a more accurate prognosis. It could also help guide intensity and type of neuro rehabilitation required. ♦

REFERENCES

1. Saatman K, Duhaime A, Bullock R, Maas A, Valadka A. *Classification of Traumatic Brain Injury for Targeted Therapies*. Journal of Neurotrauma. 2008;25(7):719-38.
2. Dikmen S and Levin H. *Methodological issues in the study of mild head injury*. Journal of Head Trauma Rehabilitation 1993;8(3):30-7.
3. Teasdale G. and Jennett B. *Assessment of coma and impaired consciousness. A practical scale*. Lancet 1974;2(7872):81-4.
4. Nakase-Richardson R, Sherer M, Seel RT, Hart T, Hanks R, Arango-Lasprilla JC, Yablon S, Sander A, Barnett S, Walker W, and Hammond F. *Utility of post-traumatic amnesia in predicting 1-year productivity following traumatic brain injury: comparison of the Russell and Mississippi PTA classification intervals*. Journal of Neurology Neurosurgery Psychiatry 2011;82:494-9.
5. Mild Traumatic Brain Injury Committee, A.C.O.R.M., Head Injury Interdisciplinary Special Interest Group. *Definition of mild traumatic brain injury*. Journal of Head Trauma Rehabilitation, 1993;8(3):86-7.
6. World Health Organization. (1992). *International statistical classification of diseases and related health problems (10th ed.)*. Geneva, Switzerland: World Health Organization.
7. Malec JF, Brown AW, Leibson CL, Flaada JT, Mandrekar JN, Diehl NN, Perkins PK. *The Mayo Classification System for Traumatic Brain Injury Severity*. Journal of Neurotrauma. 2007;24(9):1417-24.
8. Tate, R. (2010) *Compendium of Tests, Scales and Questionnaires. The Practitioners Guide to Measuring Outcome after Acquired Brain Impairment*. New York: Psychology Press.
9. Jennett B. and Bond M. *Assessment of outcome after severe brain damage: A practical scale*. Lancet 1975;1:480-4.
10. Olver JH, Ponsford J, and Curran C. *Outcome following traumatic brain injury: a comparison between 2 and 5 years after injury*. Brain Injury, 1996;10:841-8.
11. National Institute for Clinical Excellence. *Head Injury: triage, assessment, investigation and early management of head injury in infants, children and adults*. London: National Institute for Clinical Excellence, 2003.
12. Ruff R, Iverson G, Barth J, Bush S, and Broshek D. *Recommendations for diagnosing a mild traumatic brain injury: a National Academy of Neuropsychology education paper*. Archives of Clinical Neuropsychology, 2009;24:3-10.
13. Kemp S, Agostinis, House A and Coughlan A. *Analgesia and other causes of amnesia that mimic post-traumatic amnesia (PTA): A cohort study*. Journal of Neuropsychology. 2010;(4):231-6.
14. Bryant R. *Post-traumatic stress disorder vs traumatic brain injury*. Dialogues in Clinical Neuroscience 2011;13(3):251-62.
15. Iverson G and Lange R. (2011) *The Natural History of Mild Traumatic Brain Injury* In Zollman, S. (Ed) *Manual of Traumatic Brain Injury Management*. New York: Devos Medical Publishing.



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Secondary headache

Primary headache disorders are benign and the most commonly encountered headaches. Secondary headache is a headache syndrome which has been precipitated by a non-benign pathology. There is robust clinical data supporting the classification of primary headaches. However much of the classification of secondary headaches has yet to be adequately validated.

The International Classification of Headache Disorders (ICHD) divides the primary headaches into four sections: Migraine, Tension-Type Headache, the Trigeminal Autonomic Cephalalgias (cluster headache and related disorders), and a group of Other Primary Headaches consisting largely of a group of paroxysmal headache disorders. There is no readily available diagnostic marker for pain, let alone subtypes of pain. Structural imaging, computerized tomography (CT) and magnetic resonance imaging (MRI), have no diagnostic value in primary headache. Accurate diagnosis and treatment remains clinical. There is increasing evidence that individuals who experience headaches have a genetic predisposition and that headache is principally a disorder of central nervous system mechanisms.¹

What are the most reliable indicators of secondary headache? Which patients should be investigated and how? Imaging studies in headache are compounded by inconsistency. Not all have used the ICHD for primary headaches, thus categorisation of 'typical' and 'atypical' headache remains contentious. MRI studies reveal detail which cannot be visualised on CT. The question is whether the detail is pertinent to address if the headache is caused by the abnormality. Finally, there is the matter of uniform practice. What abnormality on imaging is considered to be benign? What should be kept under surveillance and what warrants intervention and when?

Imaging in "Normals"

It is first informative to look at imaging asymptomatic healthy individuals. A total of 2,536 healthy male German Air Force recruits underwent MRI. Abnormalities were found in 6.55% of scans; all were clinically silent. Of the total cohort 0.55% had significant lesions warranting surveillance or intervention (Table 1).² Examination of 1000 MRI brain scans on healthy paid volunteers revealed 1.8% benign findings of which the patients' clinicians were made aware.

Table 1. Imaging in Healthy Individuals								
Study	Patients N	Mean age	Type of Scan	Total % abnormal scans	Insignificant abnormalities		Significant* abnormalities	
					%	Nature	%	Nature
(2) Prospective German Airforce Recruits	2,536	20.5	MRI	6.55	6.0	Colloid cyst 3rd ventricle, pituitary adenoma, arachnoid and other cysts, vascular lesions, cortical atrophy, cerebellar dysplasia, hygroma, chiari I, cervical disc prolapse.	0.55	Arteriovenous malformations, cavernomas, primary brain tumours and demyelinating disease
(3) Retrospective Paid research volunteers	1000	30.6	MRI	18	15.1	Sinusitis, age related changes, T2 hyperintensities, mastoid/petrous fluid	1.1 (urgent referral) 1.8 (routine referral)	Arachnoid cyst, cavernous angioma, oligodendroglioma, pilocytic astrocytoma, aneurysm, low grade glioma, Benign cysts, prominent temporal horns, old traumatic changes, old lacunes, demyelinating lesion, scalp cystic lesions
(4) Population-based Rotterdam Study	2000	63.3	MRI	13.6	7.2	Asymptomatic brain infarcts	1.8	Aneurysm
					<0.1	Subdural haematoma	<0.1	Metastatic disease
					<0.1	Dermoid cyst Fibrous dysplasia	0.5	Major vessel stenosis
					0.4	Cavernous angioma	1.6	Primary benign tumours
					1.1	Arachnoid cyst		
					0.9	Chiari I		
* Significant = warranting surveillance or intervention								

Abnormalities warranting further attention were found in 1.1% of scans.³ A European population-based study of 2000 individuals found 3.5% significant abnormalities on imaging. The higher prevalence was attributed to the scanning protocols used.⁴ Aneurysms comprised the largest group of incidental abnormalities at 1.8%, consistent with autopsy and angiographic data. Only one primary malignant brain tumour and one metastatic disease was found. Imaging of 3,672 individuals over 65 years of age showed significant abnormalities in 1.74%.⁵

Imaging patients with headache

The most common headaches are tension-type headache (prevalence range 30-80%)

and migraine (prevalence 12%). Patients with headache make up 4% of primary care attendees, 4% of emergency complaints and 30% of neurology outpatients. The majority of patients have a primary headache disorder.⁶

The American Academy of Neurology Practice Parameters advised that patients presenting with migraine headache, with or without typical visual aura and a normal neurological examination, have a very low risk of abnormality on imaging.⁷ Of 897 individuals imaged with MRI or CT 0.45% had an abnormality requiring surveillance or intervention (Table 2).

Of 1876 consecutive patients attending a headache clinic imaged with MRI or high resolution CT (mean age 38 years) incidental find-

ings considered benign were found in 0.75% of scans.⁸ Abnormalities considered to be significant were found in 1.2% of scans; 0.9% had a normal neurological examination (Table 2). The study also addressed the type of headache and proportion of lesions requiring surveillance or intervention in each headache group. Significant abnormalities were found in 0.8% of patients with tension-type headache, 0.4% with migraine, 5% with cluster headache and 3.7% in those in whom the clinical syndrome could not be clearly defined by the ICHD. Patients who had not responded to appropriate treatment and who had had CT also underwent MRI. Of a total of 199 scans two MRI scans were abnormal in patients with normal CT. One revealed a small meningioma

Table 2. Imaging in Headache Patients.

Study	Patients N	Type of Scan	Type of Headache	Insignificant abnormalities		Significant* abnormalities		Comments
				%	Nature	%	Nature	
(7) Retrospective	897	CT & MRI	Migraine ffl visual aura. Normal neurological examination.	–	–	0.4	Glioblastoma, Papilloma of the choroid plexus, other tumour**, AVM**.	** Presented with seizures.
	1825		Unspecified headache (no information about examination).			2.4	AVM, tumour, aneurysm, hydrocephalus.	
(8) Prospective	1876	CT MRI	Migraine TTH Cluster Indeterminate.	–	–	1.2 (0.9% if neurological examination normal)	Pituitary adenoma, large arachnoid cyst, meningioma, hydrocephalus, Chiari type I, ischaemic stroke, cavernous angioma, AVM, low-grade astrocytoma, brain stem glioma, colloid cyst and posterior fossa papilloma.	119 patients had CT (normal) & MRI. MRI in 2 – acoustic neuroma and small meningioma. Abnormal neurological examination – predictor of significant abnormal imaging 3 patients with normal imaging diagnoses with Idiopathic intracranial hypertension from clinical examination.
	1432 580					0.8 0.4 5 3.7 (% of each headache type with significant imaging abnormalities)		
(26) Retrospective Normal neurological examination	373	CT (72.6% with contrast)	Migraine 76.1% TTH 23.1% Cluster 0.8% Referral criteria for headache: Increase severity, drug resistance, change in pattern, family history brain lesion.	3.5%	Old infarcts, atrophy, cavum vergae, hyperostosis frontalis, communicating hydrocephalus.	1	Low grade glioma, Osteoma, 5mm posterior communicating artery aneurysm.	In this paper - review of 6 studies of headache & CT – total 1,825 – 2% significant abnormalities.
(27) Prospective Normal neurological examination	306	MRI	Recurrent or chronic headache (>15 days/month).	44.1%	'Minor abnormalities.'	0.7	Pituitary macroadenoma and subdural hematoma.	Review of 12 studies of uncomplicated migraine and MRI in 771 patients – significant abnormality found in 0.58%. In 1036 'unspecified headache' significant abnormality in 2.1%.

AVM – Arteriovenous malformation

Table 3. Secondary Non-Traumatic Headache presenting to the Emergency Services							
Study	No. of patients	% of total Emergency visits	Secondary Headache %	Primary Headache			
				Migraine	Tension-Type	Non-Specific	Other
(10) Prospective	558	0.85	13.3	30	14.7	17.6	36.3
(28) Retrospective	100	-	8	42	-	42	8
(29) Prospective	277	1.7	5	60	8	25	2

Table 4. Presentation of Brain Tumours (30)		
Total Brain Tumours (N)	Primary	Secondary
Initial manifestation	%	%
Focal symptoms/signs	58.8	55.9
Seizures	8.2	10.5
Headache	9.3	7.0
Headache + Focal	15.5	16.2
Seizures + Focal	2.1	4.7
Headache + Focal + seizures	0	1.2
Asymptomatic	6	4.7
At diagnosis		
Headache	33	31
Headache as first symptom	9.3	7
Headache as first and sole symptom at diagnosis	0	17
Longest duration of headache as isolated symptom	Not applicable	77 days

Most reliable indicators of Secondary Headache
Sudden Onset Headache ('Thunderclap Headache')
Age > 50 years old
Additional neurological features
Additional systemic features

and the other an acoustic neuroma.

The only variable associated with a higher probability of a pertinent intracranial abnormality was neurological examination. None of the following had predictive value: sex, age, duration of headache, intensity or worsening of headache and type of headache. Notably three patients with normal imaging were diagnosed with idiopathic intracranial hypertension based upon the clinical examination.

Table 2 gives a summary of further cohorts of patients with headache imaged with CT or MRI and confirms that $\leq 1\%$ of patients presenting with typical migraine or tension-type headache will have an abnormality on imaging which warrants surveillance or intervention. Patients with headache which cannot clearly be classified or in whom neurological examination is abnormal have a higher probability of a significant abnormality on imaging at about 2-3%.

Secondary (non-traumatic) headache

Most secondary headache is identified through the emergency services. Only 0.1% presents through primary care⁹ (Table 3).

The most common reason for attendance to the emergency services with headache is for severity, recurrent headache and additional features.¹⁰ However neither severity nor response to drug treatment differentiate between primary and secondary headache. Headache associated with subarachnoid haemorrhage, venous sinus thrombosis,

carotid dissection and carbon-monoxide poisoning have all been reported to respond to sumatriptan.¹¹ Both recurrent headache and chronic headache do not seem to indicate a secondary pathology.^{8,10}

The most consistent indicators for secondary headache are sudden onset headache (thunderclap headache),^{10,12,13} age over 50 years^{11,14} and any neurological abnormality or additional systemic features.^{6,8,10} Clinically it is not possible to differentiate between primary and secondary thunderclap headache. Therefore all patients presenting with thunderclap headache should be investigated.

Headache and brain tumours

In a study of 183 patients with brain tumour, headache was the presenting complaint in 15%. Only in the metastatic group was headache the sole symptom at presentation. The longest duration of isolated headache before development of additional neurological symptoms was 11 weeks. The majority of patients with symptomatic brain tumour presented with focal neurology (Table 4).

Findings were similar in a prospective study of 206 patients diagnosed with brain tumour. Fifty-five percent complained of new onset headache or change in pattern of existing headache.¹⁵ Eighty-five percent became pain free or markedly improved post-operatively; in 15.3% of this group headache appeared to be the sole presenting manifestation. By the time

of diagnosis 96% had already presented with other neurological symptoms or signs.

'Intracranial tumour headache' is currently defined by the ICHD by severity of pain, morning occurrence and association with nausea or vomiting. Only 5.1% of patients fulfilled these criteria. In half of the patients the features were consistent with those of episodic tension-type headache or migraine without aura (Table 4). Nausea has an 80% specificity for a diagnosis of migraine¹⁶ and can occur in up to 90% of migraine sufferers.¹⁷ Moreover, migraine attacks have shown a morning preponderance of onset.¹⁸ In this study a longstanding history of a primary headache disorder was an independent risk factor for developing headache associated with brain tumour.

This data is similar to data for other types of precipitated headache, which show that the clinical syndrome of the precipitated headache can be exactly the same as a primary headache syndrome and respond to treatments effective for that headache phenotype, irrelevant of precipitating pathology.^{19,21} Removal of the precipitant may result in improvement of the headache but this is not invariable.²²⁻²⁴

Scanning for Reassurance

Proponents for imaging headache argue that the reassurance achieved by a normal scan has beneficial therapeutic value and is cost effective in reducing repeated attendance.⁸ One study has shown that the reassurance achieved by imaging was not maintained at one year. However, during this time patients scoring 11 or more on the Hospital Anxiety and Depression Scale had utilised health resources less.²⁵ Primary headache disorders can remain lifelong. Imaging may simply delay appropriate management of the headache disorder. Furthermore, the number of benign abnormalities on imaging is not insignificant. This can drive further unnecessary concern, or at worst unnecessary intervention.

Summary

Most patients who present with secondary headache do so through the emergency services. Isolated headache is a poor indicator of an underlying sinister brain pathology. The longer headache remains isolated the more likely it is to be benign. Patients with secondary headache are more likely to be aged 50 years and over, present with thunderclap onset headache or, have accompanying focal neurology or systemic ill-health. The multiple 'red-flags' for secondary headache

are covered within these four most consistent indicators.

The clinical syndrome of the headache, severity and response to treatment are not reliable indicators of secondary headache. The majority of patients presenting with secondary headache have features of migraine or tension-type headache. Patients with new onset isolated headache with another primary headache syndrome or 'atypical' characteristics may warrant further investigation, for example new onset cluster

headache. Such headache disorders are much less common. Evidence to guide whether isolated headache of other phenotypes are more likely to be associated with a secondary precipitant will take longer to establish.

The risk of imaging for reassurance brings with it a problematic 'incidentaloma' rate. In patients with normal imaging reassurance may detract from the main issue of managing the considerable morbidity associated with the primary headache disorder. ♦

REFERENCES

- Goadsby PJ, Charbit AR, Andreou AP, Akerman S, Holland PR. *Neurobiology of migraine*. Neuroscience. 2009;161(2):327-41.
- Weber F, Knopf H. *Incidental findings in magnetic resonance imaging of the brains of healthy young men*. Journal of the Neurological Sciences. 2006 Feb;240(1-2):81-4.
- Katzman GL, Dagher AP, Patronas NJ. *Incidental findings on brain magnetic resonance imaging from 1000 asymptomatic volunteers*. JAMA: The Journal of the American Medical Association. 1999 Jul 07;282(1):36-9.
- Vernooij MW, Ikram MA, Tanghe HL, Vincent AJPE, Hofman A, Krestin GP, et al. *Incidental findings on brain MRI in the general population*. The New England Journal of Medicine. 2007 Nov 01;357(18):1821-8.
- Chang Yue N, Longstreth WT, Elster AD, Jungreis CA, O'Leary DH, Poirier VC. *Clinically serious abnormalities found incidentally on MR imaging of the brain: Data from the cardiovascular health study*. Radiology. 1997 Feb 01(202):41-6.
- Hamilton W, Kernick D. *Clinical features of primary brain tumours: a case-control study using electronic primary care records*. The British Journal of General Practice: The Journal of the Royal College of General Practitioners. 2007 Sep;57(542):695-9.
- Alter M, Daube JR, Franklin G, Frisberg BM, Goldstein ML, Greenberg MK, et al. *Practice parameter: the utility of neuroimaging in the evaluation of headache in patients with normal neurologic examinations (summary statement)*. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 1994;44(7):1353-4.
- Sempere A, Porta-Etessam J, Medrano V, Garcia-Morales I, Concepcion L, Ramos A, et al. *Neuroimaging in the evaluation of patients with non-acute headache*. Cephalalgia. 2005 Feb;25(1):30-5.
- Kernick DP, Ahmed F, Bahra A, Dowson A, Elrington G, Fontebasso M, et al. *Imaging patients with suspected brain tumour: guidance for primary care*. The British Journal of General Practice: The Journal of the Royal College of General Practitioners. 2008 Dec;58(557):880-5.
- Locker TE, Thompson C, Rylance J, Mason SM. *The utility of clinical features in patients presenting with nontraumatic headache: an investigation of adult patients attending an emergency department*. Headache. 2006;46(6):954-61.
- Edlow JA, Panagos PD, Godwin SA, Thomas TL, Decker WW. *Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department With Acute Headache*. Annals of Emergency Medicine. 2008 Oct;52(4):407-36.
- Landtblom AM, Fridriksson S, Boivie J, Hillman J, Johansson G, Johansson I. *Sudden onset headache: a prospective study of features, incidence and causes*. Cephalalgia. 2002;22(5):354-60.
- Linn FHH, Rinkel GJE, Algra A, van Gijn J. *Headache characteristics in subarachnoid haemorrhage and benign thunderclap headache*. Journal of Neurology, Neurosurgery and Psychiatry. 1998;65(5):791-3.
- Ramirez-Lassepas M, Espinosa CE, Cicero JJ, Johnston KL, Cipolle RJ, Barber DL. *Predictors of intracranial pathologic findings in patients who seek emergency care because of headache*. Archives of Neurology. 1997;54(12):1506-9.
- Valentinis L, Tuniz F, Mucchiut M, Little D, Skrap M, et al. *Headache attributed to intracranial tumours: a prospective cohort study*. Cephalalgia. 2009;30(4):389-98.
- Lipton RB, Dodick D, Sadovsky R, Kolodner K, Endicott J, Hettiarachchi J, et al. *A self-administered screener for migraine in primary care: The ID Migraine validation study*. Neurology. 2003 Aug 12;61(3):375-82.
- Kelman L, Tanis D. *The relationship between migraine pain and other associated symptoms*. Cephalalgia. 2006 Jun;26(5):548-53.
- Fox AW, Davis RL. *Migraine chronobiology*. Headache. 1998 Jul;38(6):436-41.
- Slooter AJC, Ramos LMP, Kappelle LJ. *Migraine-like headache as the presenting symptom of cerebral venous sinus thrombosis*. Journal of Neurology. 2002 Jul 01;249(6):775-6.
- Rosenberg JH, Silberstein SD. *The headache of SAH responds to sumatriptan*. Headache. 2005;45(5):597-8.
- Lucas S, Hoffman JM, Bell KR, Walker W, Dikmen S. *Characterization of headache after traumatic brain injury*. Cephalalgia. 2012 Jul 18;32(8):600-6.
- Levy M, Matharu MS, Meeran K, Powell M, Goadsby PJ. *The clinical characteristics of headache in patients with pituitary tumours*. Brain. 2005;128(8):1921-30.
- Couch JR, Bearss C. *Chronic daily headache in the post-trauma syndrome: relation to extent of head injury*. Headache. 2001 Jul;41(6):559-64.
- Hoffman JM, Lucas S, Dikmen S, Braden CA, Brown AW, Brunner R, et al. *Natural History of Headache after Traumatic Brain Injury*. Journal of Neurotrauma. 2011 Sep;28(9):1719-25.
- Howard L. *Are investigations anxiolytic or anxiogenic? A randomised controlled trial of neuroimaging to provide reassurance in chronic daily headache*. Journal of Neurology, Neurosurgery and Psychiatry. 2005 Nov 01;76(11):1558-64.
- Dumas MDM, Pexman JHJ, Kreft JHJ. *Computed tomography evaluation of patients with chronic headache*. Canadian Medical Association Journal. 1994 Nov 15;151(10):1447-52.
- Tsushima Y, Endo K. *MR Imaging in the Evaluation of Chronic or Recurrent Headache*. Radiology. 2005 Jun 01;235(2):575-9.
- Sahai-Srivastava S, Desai P, Zheng L. *Analysis of Headache Management in a Busy Emergency Room in the United States*. Headache: The Journal of Head and Face Pain. 2008 Jul;48(6):931-8.
- Barton CW. *Evaluation and treatment of headache in the emergency department: a survey*. Headache. 1994;34(2):91-4.
- Vázquez-Barquero A, Ibáñez FJ, Herrera S, Izquierdo JM, Berciano J, Pascual J. *Isolated headache as the presenting clinical manifestation of intracranial tumors: a prospective study*. Cephalalgia. 1994 Aug;14(4):270-2.

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Seizure prediction



Professor Mark Cook

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Conflict of interest statement:

Mark Cook has received speakers honoraria from SciGen, Sanofi, UCB Pharmacy, and CSL New Zealand.

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Seizure prediction is of obvious clinical relevance, as for many patients with epilepsy the largest part of their disability results from the unpredictable nature of the seizures. It is this component which has the greatest ramifications for driving, other dangerous activities, and work. As well the fear of having a seizure in public often restricts socialisation, with all the consequences of the isolation that results.^{1,2} Much of the stigma associated with the condition could be alleviated if people could anticipate their seizures and take necessary steps to make themselves safe, and modify their environment. Conceivably having accurate seizure prediction strategies could also permit administration of acutely acting anticonvulsant therapies. Seizure prediction systems may allow new insights into the natural history of the condition, and associated co-morbidities.

It has been recognised for many years that there are changes in cerebral activity that occur some time prior to seizures. To some extent the clinical evidence for this has been anecdotal, with reports of carers and patients who seem to be able to recognise changes in behaviour some time prior to the event, often surprisingly accurately.³ This is difficult to validate however, and it is possible they are often describing subtle seizure activity rather than a distinct prodrome.

Imaging studies have shown conclusively that there are changes in brain function that develop some time before seizures occur, and this has been demonstrated across a number of modalities.^{4,5} The changes reflect brain network activity distinct from typical electroencephalographic seizures, and the EEG correlates of these changes are often unclear.

Many attempts at predicting seizures have been undertaken over the years, with limited success until recently. Artifact and limited spatial resolution limit the utility of scalp EEG, and so intracranial EEG data is typically used. The majority of previous approaches have typically used mathematical algorithms estimating entropy, correlation dimension, and Lyapunov exponents.^{6,7} There has recently been interest in using EEG synchronisation analysis,^{8,10} as these measures are thought to be correlates of cortical activity. Unfortunately these algorithms have not delivered reproducible outcomes.^{11,12}

Recent interest in devices intended to abolish or modulate seizures through direct stimulation of cortical areas responsible for stimulation of deep cerebral structures^{13,14} has led to the development of implantable therapeutic devices for epilepsy, and the recent completions of two major trials. The first of these systems is a closed loop device, which detects and responds to individual events.¹⁵ The second is an open loop system that provides regular stimulation to the anterior thalamic nucleus to suppress seizures presumably by modulating cortical excitability.¹⁶ The results of the trials show sufficient promise

to warrant further exploration of such therapies. An attractive application of seizure prediction systems would be to link them to seizure suppression systems of this type, as it may allow more effective therapy, and as well have significant implications for the power requirements of these devices if utilisation could be better managed.

Therapeutic strategies are currently based around chronic administration of a medication to prevent often relatively infrequent but unpredictably occurring events. Accurate prediction may direct therapies toward short acting anticonvulsant agents, not a focus of drug development in this field to date, with a limited number of agents used in this manner. Similar approaches may ultimately allow safer driving and make occupational hazards less of an obstacle to employment.

We have recently completed a trial of an implanted device to predict seizures.¹⁷ This system was developed by the Neurovista Corporation, and consists of a set of intracranial electrodes, which are placed subdurally via a small craniotomy to lie on the surface of the brain and continuously record cerebral electrical activity. This is conducted via a lead to a subclavicular unit that transmits the data wirelessly to a hand-held device, which contains algorithms developed for each individual based on analysis of at least five seizures. The EEG is filtered and various features of interest extracted, these are then analysed with respect to later seizures, and the features that correlate best coded into the hand held unit. This then processes in real time the data being transmitted from the implanted unit, and recognises the features that allow accurate seizure prediction. The hand held unit has a series of lights to indicate the risk of seizure in the minutes or hours ahead, a red light indicates a high risk, white light a moderate risk, and blue light no risk. Various statistical criteria were established to test the predictive capabilities of the device.

The system also had other features, it allowed the patient to record audio to annotate the record, and as well would automatically record audio when a seizure was detected (rather than predicted). This feature was surprisingly useful, allowing the identification of events not reported by the patient.

Fifteen subjects were enrolled in the study; all had 2-12 disabling partial onset seizures/month; a lateralised epileptogenic zone; and no history of psychogenic seizures. After the surgery they entered a data collection phase to allow the training of an algorithm, and if the algorithm met satisfactory performance criteria the hand held unit was activated to give advice regarding seizure likelihood. The study was intended to provide advice on safety as well as accuracy and the utility of seizure prediction.

Eleven of the 15 subjects completed the data



collection period, and of these 10 met the criteria that had been set around algorithm performance, and went on to the advisory Phase.

The study demonstrated that ambulatory intracranial EEG monitoring is safe, with a complication rate similar to that of other implanted devices of this type, and that the majority of study subjects met criteria for enabling seizure advisories.

There were a number of unexpected findings in the study, most significantly that patients generally underestimated the number of seizures they had. It has long been known from inpatient telemetry studies that patients underestimate the number of events^{18,19} by a factor of 2-3 times, but in fact the variation was much greater than that with some patients underestimating by over 100 events per month. To complicate matters further, the misreporting varied within subjects month to month, preventing the application of any 'correcting factor'. Given seizure management is based chiefly on patient seizure estimates of frequency, this has significant clinical implications. As well the assessment of new anticonvulsant medications is also performed in this manner, and these findings place all this on much less certain ground. Some subjects had fewer seizures than they reported, and some turned out to be reporting other events as seizures, such as migraines. A few individuals took additional benzodiazepine therapy

when the light changed to red on their device, though anecdotally this seemed to be useful, the low numbers meant statistical analysis was not possible.

The practical utility of the system varied between patients. One early concern had been that anxiety would increase if patients were warned in advance of seizure, but this did not occur – patients are already anxious about unpredictable seizures and this was not magnified. Patients with very frequent seizures were often a little frustrated however to find the device was frequently warning them of an impending event. Though this information was accurate, it did not always benefit them greatly. For others though the information was life changing, allowing much greater independence, level of activity, and confidence. It allowed others to take appropriate action to avoid embarrassment in the work place, and others to discontinue planned potentially hazardous activities such as swimming.

This was a very preliminary study of what is the first device to allow successful seizure prediction, but the potential to improve quality of life for people with this devastating and unpredictable condition is obvious. As well we have seen unexpected outcomes with better understanding of the natural course of the illness, and this has significant implications for day-to-day management and future drug assessment. ♦

REFERENCES

1. Fisher RS, Vickrey BG, Gibson P, et al. *The impact of epilepsy from the patient's perspective I. Descriptions and subjective perceptions.* *Epilepsy Res* 2000;41:39–51.
2. Vickrey BG, Hays RD, Rausch R, Sutherling WW, Engel J, Brook RH. *Quality of life of epilepsy surgery patients as compared with outpatients with hypertension, diabetes, heart disease, and/or depressive symptoms.* *Epilepsia* 1994;35:597–607.
3. Haut SR, Hall CB, LeValley AJ, Lipton RB. *Can patients with epilepsy predict their seizures?* *Neurology* 2007;68:62–6.
4. Zhao M, Suh M, Ma H, Perry C, Geneslaw A, Schwartz TH. *Focal increases in perfusion and decreases in hemoglobin oxygenation precede seizure onset in spontaneous human epilepsy.* *Epilepsia* 2007;48:2059–67.
5. Badawy R, Macdonell R, Jackson G, Berkovic S. *The perictal state: cortical excitability changes within 24 h of a seizure.* *Brain* 2009;132:1013–21.
6. Babloyantz A, Destexhe A. *Low-dimensional chaos in an instance of epilepsy.* *Proc Natl Acad Sci USA* 1986;83:3513–7.
7. Pijn JP, Van Neerven J, Noest A, Lopes da Silva FH. *Chaos or noise in EEG signals: dependence on state and brain site.* *Electroencephalogr Clin Neurophysiol* 1991;79:371–81.
8. Lai Y-C, Harrison MAF, Frei MG, Osorio I. *Inability of Lyapunov exponents to predict epileptic seizures.* *Phys Rev Lett* 2003;91:068102.
9. McSharry PE, Smith LA, Tarasenko L. *Comparison of predictability of epileptic seizures by a linear and a nonlinear method.* *IEEE transactions on bio-medical engineering* 2003; 50: 628–33.
10. Freestone DR, Kuhlmann L, Grayden DB, et al. *Electrical probing of cortical excitability in patients with epilepsy.* *Epilepsy Behav* 2011;22 Suppl 1:S110–8.
11. Lehnertz K, Mormann F, Osterhage H, et al. *State-of-the-art of seizure prediction.* *Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society* 2007;24:147–53.
12. Mormann F, Andrzejak RG, Elger CE, Lehnertz K. *Seizure prediction: the long and winding road.* *Brain* 2007;130:314–33.
13. Boon P, Raedt R, De Herdt V, Wyckhuys T. *Electrical stimulation for the treatment of epilepsy.* *Neurotherapeutics* 2009.
14. Velasco A-L, Velasco F, Velasco M, Trejo D, Castro G, Carrillo-Ruiz JD. *Electrical stimulation of the hippocampal epileptic foci for seizure control: a double-blind, long-term follow-up study.* *Epilepsia* 2007;48:1895–903.
15. Skarpaas TL, Morrell MJ. *Intracranial stimulation therapy for epilepsy.* *Neurotherapeutics: the journal of the American Society for Experimental NeuroTherapeutics* 2009;6:238–43.
16. Fisher R, Salanova V, Witt T, et al. *Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy.* *Epilepsia* 2010;51:899–908.
17. Cook MJ, O'Brien TJ, Berkovic SF, et al. *Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study.* doi:10.1016/S1474-4422(13)70075-9.
18. Blum DE, Eskola J, Bortz JJ, Fisher RS. *Patient awareness of seizures.* *Neurology* 1996;47:260–4.
19. Stefan H, Kreiselmeier G, Kasper B, Graf W. *Objective quantification of seizure frequency and treatment success via long-term outpatient video-EEG monitoring: A feasibility study.* *Seizure* 2011.

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Examining the Need for and Provision of AAC Methods in the UK

People of all ages with severe speech, voice and language impairments use a range of Augmentative and Alternative Communication (AAC) methods to assist them communicate their views and needs. AAC includes non technological systems such as signing, use of symbols and picture charts as well as sophisticated technology including dedicated computerised systems and voice output communication aids. Without these systems people with communication difficulties are unable to realise their potential and face social isolation, dependency and a decreased quality of life which can lead to increased care costs.

The project summarised here was funded by the Big Lottery through Communication Matters a charity dedicated to supporting those who have difficulty in expressing themselves verbally and who require augmentative and alternative methods of communication (AAC).

Objectives of this research

- To investigate evidence of need for Augmentative and Alternative Communication (AAC) i.e. how many people would benefit?
- To map the provision of services in the UK for AAC. Identify the numbers and types of services in the UK, their funding arrangements and types of service provision.

Research Methods

In order to investigate the need for AAC several methods were used including:

- Identifying literature related to the prevalence of conditions which would benefit from AAC.
- Inspecting two National databases to determine information of relevance.
- Gathering data from AAC users (including dissatisfied users), carers, a range of health, social care and teaching professionals, charities

and suppliers. This data was gathered through focus groups, interviews (both face-to-face and by telephone), survey questionnaires (both paper and Internet-based).

Topic sheets and interview questions were informed by the literature and modified iteratively through the course of the study in order to elicit issues raised at different stages in the research.

A detailed research report is available at:

<http://www.communicationmatters.org.uk/shining-a-light-on-aac>
http://www.communicationmatters.org.uk/sites/default/files/downloads/projects/aac_evidence_base/2013_AAC_Evidence_Base_Beyond_the_Anecdote.pdf

Literature Review

All aspects of the study were informed by a broad ranging literature review (Baxter S, Enderby P, Evans P, Judge S 2012). A large number of databases (8) were reviewed and initially identified 2883 papers. Of these, 299 were accessed and scrutinised. One hundred and forty-one were found to be relevant to this study and included in the review. The key points from the literature are identified below.

Key Point 1: only three studies identified in the systematic review of AAC interventions included more than ten individuals.

Key Point 2: there are many references in the literature related to funding difficulties for the provision of high-tech equipment which is coming onto the market.

Key Point 3: the range of AAC for persons with language rather than motor speech disorders is increasing.

Table 1: Examples of types of AAC

Unaided	Aided	
	No power	Power
Eye Pointing	Symbol/Pictures/ Charts/ Books	Dedicated AAC systems (mostly computerised)
Facial expressions	Communication passport	Voice recognition software
Pointing	Etran frame	Software for non-dedicated computer systems
Gesture	Pointer	Voice Output Communication Aids
Signing	Paper and pencil	Assistive Technology Systems with voice

Key Point 4: whilst limited, the evidence of benefit for patients by providing AAC is clear.

Key Point 5: outcomes are not consistently reported making the pooling of data difficult.

Need and Impact of AAC

The population of individuals requiring and benefiting from AAC is heterogenous and changing. Medical successes have led to a larger proportion of children with severe disabilities and those with acquired injuries such as head injury surviving for longer. Furthermore, the population is becoming older with the associated increase in complex conditions and acquired neurological disease e.g. Parkinson's disease being represented.

Key point 6: the few papers reporting demographic information relating to AAC provide different figures suggesting variation in access to services.

Key point 7: devices can augment natural speech or writing, or can be utilised as an alternative to spoken utterances or writing which is required for supporting certain conditions.

Key point 8: the evidence of the impact of AAC from the literature is mostly limited to low-tech devices and provides little information which would facilitate generalisation to broader populations or knowledge of longer term maintenance and usage.

Key point 9: case and group studies indicate that AAC has been found to be useful in expanding the communication of many patients with broad range of underlying conditions affecting their communication potential. The complexity of the multifactorial impairments and frequently associated cognitive, sensory and environmental situations has an impact on study design and generalisability of the findings.

Key point 10: research, reported in the literature, comparing an individual's usage of different devices provides useful information regarding preferences and usage.

Key point 11: the majority of studies have indicated the importance of identifying the right AAC approach within the context of a service offering a programme of support and teaching for users and carers to maximise usage.

Epidemiology: Having an estimate of the numbers of individuals requiring services is necessary for the development of services and the commissioning of such. These numbers will also assist in identifying unmet need and benchmarking of provision. However, there are several reasons why it is difficult to make precise estimates of need.

Key point 12: the report of the Communication Champion (ref. 3) identified substantial variation in the provision of AAC services across the country which is confirmed by our research.

Key point 13: there is a highly dynamic policy and economic background to the data collection carried out in this project. This undoubtedly affected the data collection and nature of the data collected from participants. However, it also allowed for a direct and responsive link between the research and the policy and campaigning action.

Key point 14: Identifying the numbers of individuals requiring AAC services is important for planning but is challenging given changing demography and rapidly increasing sophisticated technology.

Data Sources

Existing data sources were identified as the General Practice Research Database (GPRD) and the English Health Survey. These sources were searched to provide information about statistics relevant to need for AAC. This data was put into the context of qualitative information gathered from users, professionals and others and subject to a validation exercise

Examples of aetiological conditions associated with AAC use for both adults and children as mentioned in the literature:

Child Group	Adult Group
Acquired neurological e.g.: <ul style="list-style-type: none"> • Stroke • Head Injury 	Acquired neurological e.g.: <ul style="list-style-type: none"> • Stroke • Head injury
Progressive neuromuscular e.g.: <ul style="list-style-type: none"> • Freidrich's Ataxia, Complex Syndromes, • Muscular dystrophy 	Progressive Neurological eg: <ul style="list-style-type: none"> • Multiple Sclerosis, • Motor Neurone Disease, • Parkinson's disease • Muscular Dystrophy • Dementia
Congenital conditions e.g.: <ul style="list-style-type: none"> • Cerebral Palsy • Multiple Complex Disabilities • Profound and Multiple Learning Difficulties (PMLD) • Physical Difficulties 	Changes to laryngeal and oral pathology e.g.: <ul style="list-style-type: none"> • Dysphonia • Head and Neck Cancer
Developmental disorders e.g.: <ul style="list-style-type: none"> • Learning Difficulties/Disabilities • Autistic Spectrum • Developmental delay • Speech and Language impairment 	Congenital conditions e.g.: <ul style="list-style-type: none"> • Cerebral Palsy • Cleft Palate & craniofacial malformations • Syndromic conditions • Profound and Multiple Learning Difficulties (PMLD) • Adults with Physical Disabilities • Adults with Learning Disabilities • Adults with Autism

with respondents generating and ranking most common aetiologies requiring AAC services. Questionnaire and survey methods were used to gather information from practitioners, suppliers and charities.

Key point 15: Estimating the need for AAC incorporated three methods: inspecting the GPRD database, examining the results of the Health Survey for England, deducting prevalence from the literature, and survey methods and validating information by questioning experts.

Key point 16: 0.5% of the population are estimated to require AAC. This equates to 529 people per hundred thousand population. The population of potential AAC users has a broad range of complex conditions with different underlying medical diagnoses.

Key Point 17: 97.5% of the total number of people who could benefit from AAC have the top 9 conditions. The 2 conditions that represent 45.9% of that population consist of Alzheimer's/Dementia and Parkinson's disease, conditions associated with an older population where amenable technologies are becoming more available but distribution and use are lagging behind.

Key Point 18: the validation exercise showed that there was some difference between the perception of AAC use and the estimated need calculated from conditions. Of particular note is the discrepancy relating to Alzheimer's disease and Parkinson's disease which is possibly related to the lack of knowledge relating to new technologies.

Key point 19: new technologies which can be accessed by individuals with more complex cognitive, physical, sensory and communication deficits are being developed and trialled in research but are not easily available to those with these needs.

Provision of AAC in the UK

Surveys, interviews and site visits investigated current provision, service models and views of practitioners. Surveys and interviews with AAC users and communication partners explored their experience of service provision.

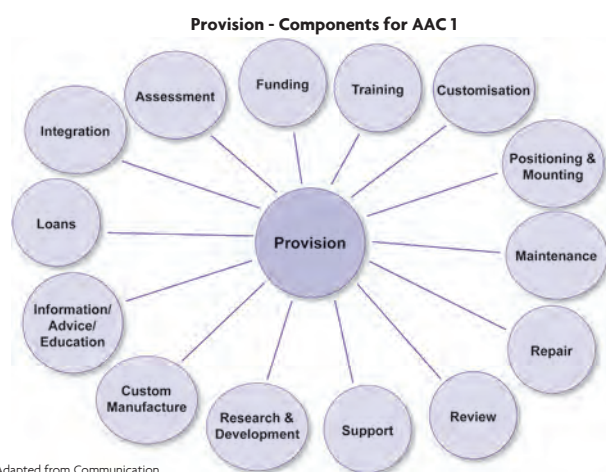
Key point 20: 38 AAC users responded to the survey. Most had heard about the research through the charity Communication Matters. The gender split was relatively even with only one of the responders being below the age of 18. The responders reported a broad range of communication strategies and experience of AAC device use.

Key point 21: 36 communication partners responded to the survey. Most were family members and all but one had English as their first language.

Key point 22: the qualitative data identified a number of components that were required for effective service provision of aided-AAC and the ongoing use of aided-AAC. The service components are: assessment, information and advice, loans, positioning and mounting, customisation, funding, maintenance, repair, review of needs, support, integration, research and development.

Service components were defined using a Delphi technique to assist with clarifying requirements of provision (see figure 2). Within each component there are different elements of activity e.g. **Assessment** incorporates: Identification of need, formal and informal assessment of physical and cognitive abilities, access requirements, needs and wishes of individual and their carers, environmental facilitators and barriers, identification of communication partners and their needs, training and support requirements, matching the device to the person etc. A full list of the components required for AAC provision is detailed in the final report.

Key point 23: there was consensus between professionals, AAC users and communication partners that the service components were all required to facilitate effective identification, provision and use of AAC.



Adapted from Communication Matters Research Matters: an AAC Evidence Base

Figure 2: components required for appropriate AAC service provision.

Key point 24: whilst most AAC users and partners expressed that they received sufficient support, timing and training in choosing a communication aid this was not the experience of all, with some expressing significant dissatisfaction.

Key point 25: there was consensus between professionals, AAC users and communication partners that all of the service components were required to facilitate effective identification and use of AAC.

Key point 26: Service providers emphasised that some aspects/components of their service were more important, more achievable, more available and reported different levels of satisfaction expressed by service users and their carers with different aspects of the provision.

Service Models

The provision of the services for aided-AAC rests with different providers including: the health service, local authority, educational authority, charitable organisations, and personal accounts. The study found a number of different models and types of provision of AAC in the way it was funded, skill mix, facilities and equipment.

Key point 27: the numbers of staff, skill mix and methods of working are unique to each team both locally and in specialist services.

Key point 28: there is no consistency in the elements/components of service provision of either local or specialist services in the UK.



Key point 29: many services have developed innovative methods to identify, assess and provide ongoing support to AAC users, communication partners and other relevant staff.

Key point 30: funding arrangements for services and equipment was the issue of concern most commonly raised by professionals, AAC users and communication partners. Lack of consistent arrangements for maintenance and replacement of AAC devices and a lack of clarity and consistency was the experience of most.

Key point 31: continuing support for developing communication skills through use of AAC varied by services and the age of the person. The lack of on-going support particularly for adults was raised by professionals, AAC users and communication partners.

Experience of services

AAC users, their family members and carers provided information through interview and survey regarding their experience of services. Frustration was expressed relating to time taken to identify that they would benefit, funding difficulties and lack of support. It was particularly disappointing that there were many more negative comments relating to speech and language therapy involvement than positive comments.

“Some speech and language therapists are shockingly ignorant of technology, have allocated no budget to technology, do not use technology themselves and are fearful of it”. (Adult communication aid user).

Key point 32: whilst many users and carers expressed satisfaction, more expressed frustration with all or some part of the service. Of particular note was the lack of technical skills and knowledge of speech and language therapists.

Service categorisation

The levels and types of services needed to be defined in order to reflect provision to this population.

A specialised service for AAC requires a set of resources and skills that can cater for the most complex needs of an individual requiring AAC and related services. The definition and components of specialist services has been built up taking information from the Draft Specification for Specialised AAC Services (currently under consultation) and using the data collected in the practitioners' survey in order to categorise and map service provision across the UK.

The definition determined that a specialised service provides:

- Assessment
- Loan for trial
- Provision of powered aid
- Maintenance
- Customisation of equipment (particularly hardware)
- Training for professionals

They are usually staffed with an interdisciplinary team with the following competencies:

- Electronic assistive technology (clinical scientists, clinical technologists, rehabilitation engineer, assistive technologists or equivalent);
- Speech and language therapist with specialism in AAC;
- Learning and educational development competence for those clients in education (teacher);
- Seating, positioning, mounting of equipment and access and control methods (physiotherapist or occupational therapist);

UK AAC services can be classified into five service types which are:

- A: Specialised service
- B1: Tertiary Specialist with custom manufacture
- B2: Tertiary Specialist without custom manufacture
- C: Local Specialist
- D: Local service

Key point 33: service provision was found to be distinctly different across the country with different levels of satisfaction expressed by service users and their carers with different aspects of the provision.

Key point 34: there is no consistency in the elements of service provision of either local or specialist services in the UK.

Key point 35: less than 5% of services responding to the survey reported joint funding arrangements for the provision of their service.

Key point 36: the majority of services cover an area equivalent to a local authority or NHS trust/board area with less than 20% of those surveyed covering a wider area.

Key point 37: a broad range of eligibility criteria are used by different services resulting in variable access to services.

Funding from the Big lottery through a charity for this research has given us opportunities to undertake work that otherwise would probably have not been undertaken.

This research required a multimethod approach and it is unlikely to have attracted funding from traditional research bodies. Collaboration with a broad number of partners (AAC users, communication partners, a broad range of health and education staff, and industry) was facilitated by working with Communication Matters. Being able to attend the conferences organised by this charity offered opportunities to facilitate the validation of findings, further exploration of issues and identify priorities. We are pleased that the research is assisting in identifying requirements in order for providers to consider their services and detail business plans for central commissioning which, we hope, will improve equity of access and reduce variation of services.

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REFERENCES

1. Baxter S, Enderby P, Evans P, Judge S. Interventions using high-technology communication devices: a state of the art review. *Folia Phoniatrica Logopaedia* 64(3):137-144 2012
2. The Bercow Report: *A Review of Services for Children and Young People (0-19) With Speech Language and Communication Needs*. 2008
3. *Specialised AAC provision, commissioning national services*. Office of the Communications Champion and Council, November 2011

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Posterior fossa tumours in children

– an overview of diagnosis and management



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The posterior fossa is the commonest site of primary intracranial tumours in children. The commonest neoplasms are pilocytic astrocytoma, medulloblastoma, ependymoma and brain stem glioma. In children over one year old, over two thirds of intracranial tumours arise from the cerebellum or brainstem, compared with 15% in adults. Survival rates of some of these lesions has improved markedly over the last twenty years, due to advances in surgical techniques, chemotherapy, delivery of radiotherapy and, more recently, an improved understanding of tumour biology. These tumours remain the focus of intense research aimed not just at prolonging survival, but also at minimising the impact of treatment on growth, cognitive development and long-term quality of life.

Clinical presentation

Posterior fossa tumours often present with clinical manifestations of hydrocephalus and raised intracranial pressure. More aggressive tumours present with a shorter history. The most prevalent symptoms include headache, nausea and vomiting. In young children headache is reflected in irritability and a desire not to be handled. Vomiting, usually an early morning phenomenon, may also be related to irritation of the lower fourth ventricular floor, at the area postrema, by the tumour. The hyperventilation associated with vomiting often transiently improves the headache.

Raised intracranial pressure may also cause drowsiness, neck stiffness, sixth nerve palsy and visual disturbances. Papilloedema is common in patients presenting with long-standing progressive symptoms. Aggressive brain stem tumours often present with pyramidal tract signs together with disorders of ocular motility and diplopia. A head tilt may be a reflection of tonsillar herniation or a fourth nerve palsy related to a diffuse brainstem tumour. Young children with progressive hydrocephalus demonstrate macrocephaly, with fullness of the fontanelles and increased separation of calvarial sutures. Ataxia arises from vermal and cerebellar hemisphere involvement, brainstem dysfunction and chronic hydrocephalus.

Headache is an uncommon complaint in early childhood; early referral and imaging is warranted. Similarly, early investigation of other symptoms allows rapid diagnosis and prompt initiation of treatment.

Pilocytic astrocytoma

Cerebellar astrocytomas are the most frequent posterior fossa tumours in children, accounting for

up to 35% of these lesions.¹ Peak age is 5 to 13 years; approximately half arise in the midline and half from the cerebellar hemispheres. They are circumscribed, discrete, slow-growing lesions, often associated with cysts within and around the tumour.²

On computed tomography (CT), pilocytic astrocytomas are large cystic lesions arising from the cerebellar vermis or hemisphere. The solid components are hypodense and enhance avidly on contrast administration. On T1-weighted magnetic resonance imaging (MRI), the solid component tends to be iso- to hypo-intense on comparison with grey matter; heterogeneity is due to microcystic and necrotic areas. It is hyperintense on T2-weighted images (Figure 1A and B). The solid and mural components enhance prominently (Figure 1C). Enhancement of the cyst wall suggests tumour infiltration of the capsule.³

Histologically these tumours are characterised by a biphasic pattern. This consists of compacted bipolar cells with Rosenthal fibres, and loose multipolar cells with microcysts and eosinophilic granular bodies, which form globular aggregates within astrocytic processes.² Their slow growth permits development of regressive changes, such as hyalinised vessels, calcification, necrosis, lymphocytic infiltrates and cysts. In this context, necrosis carries no prognostic significance. Rarely, pilocytic astrocytomas seed the neuraxis, although this tends to occur with hypothalamic, rather than posterior fossa, primary tumours. In these cases the primary tumour may still demonstrate a low proliferation index; such tumours generally respond well to chemotherapy and radiotherapy, and long term survival is still possible.⁴

Pilocytic astrocytomas maintain their WHO grade I status for years; they only rarely show malignant transformation, and they should then be termed anaplastic pilocytic astrocytomas, rather than glioblastomas. Even then, their prognosis is not uniformly poor. Reported cases had undergone previous radiotherapy, and this was likely relevant to their transformation.²

A large percentage of pilocytic astrocytomas, particularly those arising within the cerebellar hemisphere, have demonstrated alterations in the BRAF gene, which is essential for growth signalling through mitogen-associated protein kinase (MAPK) pathways.⁵ These alterations have not been clearly associated with outcome. p16 deletions are commoner in midbrain, brainstem and spinal cord lesions.⁵

Resection is the treatment of choice for well-circumscribed lesions (Figure 1D) and the factor most strongly associated with outcome is the



Figure 1: Pilocytic astrocytoma. T2-weighted axial (A) and post-contrast sagittal (B) images of two posterior fossa pilocytic astrocytomas, demonstrating solid and cystic components; the close relationship of the tumour in (B) to the tectum (*) is evident on the axial post-contrast image in (C). Post-operative midline post-contrast MRI in (D) confirms gross total resection of the tumour in (B) and (C).

extent of surgical removal.^{6,7} Gross total resection leads to over 90% long-term survival.⁷ Cerebellar pilocytic astrocytomas are generally resectable and adjuvant therapy is not indicated. Those arising from the brainstem, however, are often not completely resectable and require adjuvant chemotherapy, usually including carboplatin and vincristine, and consideration of radiotherapy at progression. A clinical trial of BRAF and MAPK pathway inhibitors, such as AZD6244, is underway.⁸ Another trial, using the antiangiogenic agents bevacizumab and linalidomide, has already shown some promise in Phase I and II trials.⁹

A recent study has reported long-term follow up, to a mean of 18.4 years, for 101 children with benign posterior fossa astrocytomas.⁶ Complete resection, confirmed radiologically, was achieved in half the patients; only three of these recurred. 26 of 50 residual tumours progressed, at a mean of 30 months; the others demonstrated spontaneous regression or growth arrest. 60% of recurrences or progression occurred within two years, and only one beyond eight years of the original surgery. The interval to progression was shorter for subtotal resections, solid tumours and involvement of brainstem or cerebellar peduncle. The authors conclude that gross total resection should not be aggressively pursued when the tumour invades critical structures.

Medulloblastoma

Medulloblastoma is a primitive neuroectodermal tumour (PNET) occurring in the cerebellum. It is the most common malignant brain tumour in children and represents 30% of posterior fossa tumours. It is classified as WHO grade 4 and has a propensity to leptomeningeal dissemination. The annual incidence is 6.5 per million children.¹⁰ 10% of cases are diagnosed in infancy. 75% occur in the midline; cerebellar location is associated with older age and desmoplastic histology.¹¹

Medulloblastoma is typically a midline enhancing homogeneous posterior fossa mass on CT. The mass is hypointense on T1 and T2-weighted images; it enhances heterogeneously on gadolinium administration. Cystic components may be present (Figure 2A and B). The characteristic high cell density is reflected in

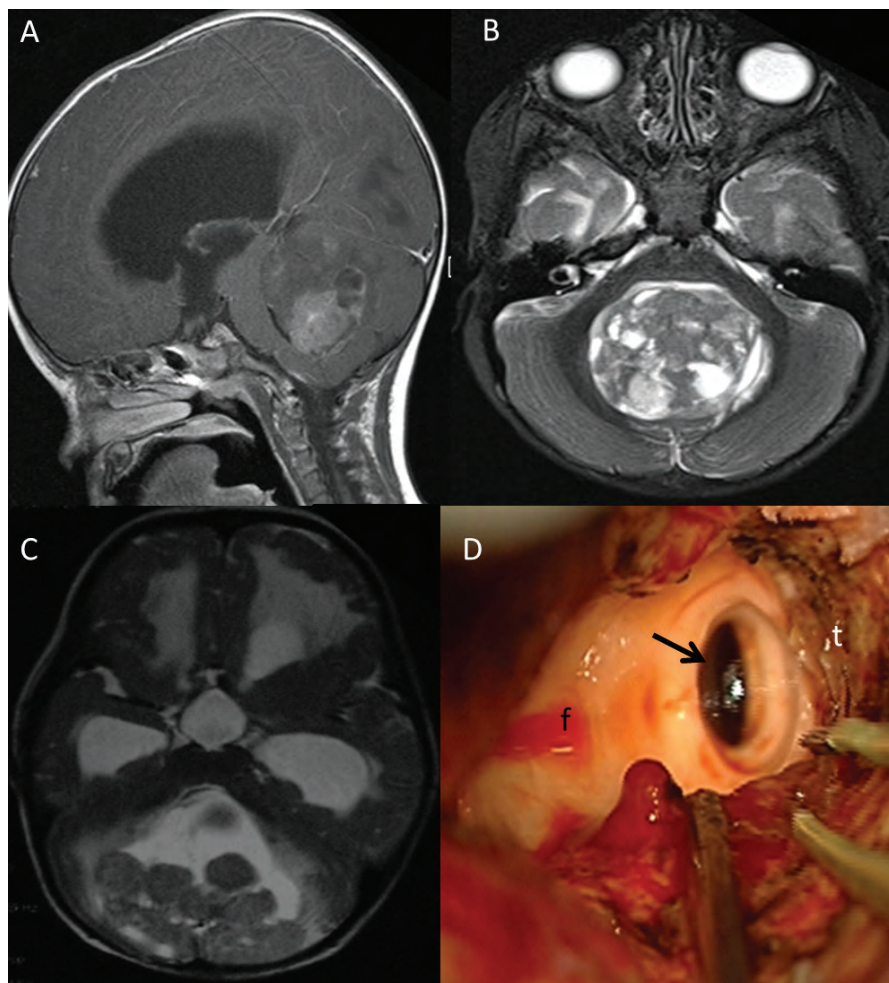


Figure 2: Medulloblastoma. Sagittal post-contrast (A), and axial T2 (B) images, showing typical posterior fossa medulloblastoma. Both demonstrate heterogeneous nature of the tumour. Obstruction of the aqueduct and secondary obstructive hydrocephalus is evident in (A); (C) demonstrates a nodular medulloblastoma in an infant with the typical 'bunch of grapes' appearance; (D) is an intra-operative photomicrograph obtained during resection of a posterior fossa medulloblastoma – 't' represents residual tumour around the cavity; the fourth ventricular floor 'f' is exposed and free of tumour; the arrow points to the dilated caudal end of the aqueduct after decompression.

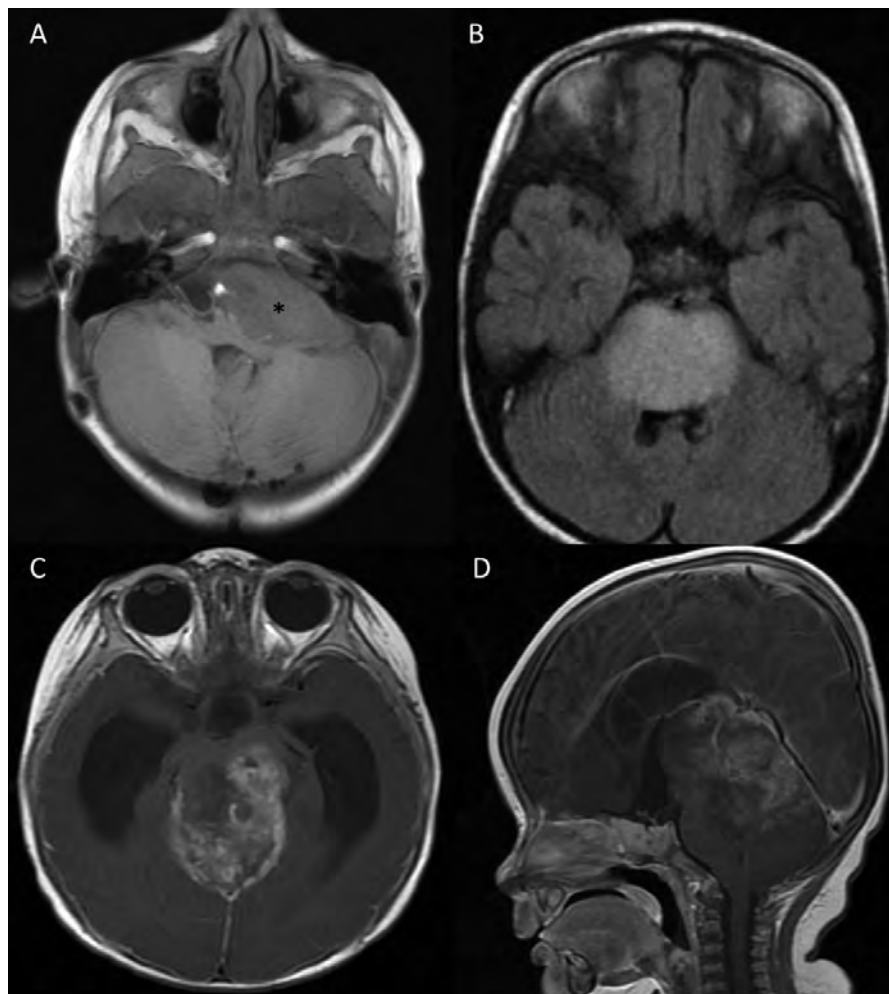


Figure 3: (A) post-contrast MR image demonstrating an ependymoma in the cerebellopontine angle (asterisk); the tumour is hypointense and does not enhance; the brainstem is distorted and rotated to the right; (B) FLAIR image demonstrating a diffuse hyper-intense lesion consistent with a pontine glioma. (C) and (D) post-contrast axial and sagittal MR images of posterior fossa ATRT; the tumour is large and diffuse, involving the cerebellum and brainstem and extends superiorly through the tentorial incisura.

diffusion restriction. Leptomeningeal disease is identified as enhancing nodules on the surface of the brain and spinal cord, often referred to as 'sugar coating'.

Histologically, medulloblastoma is composed of small blue round cells with a high nuclear to cytoplasmic ratio. The 2007 WHO classification of central nervous system tumours identified four distinct pathological subgroups: classical (65-80%), desmoplastic / nodular (15-25%), medulloblastoma with extensive nodularity (15-25%) (Figure 2C) and an anaplastic / large cell variant (4-5%).^{2,12} The desmoplastic variant is characterised by pale nodular areas within a reticulin network; this is commoner in older children and is associated with a better prognosis. The large cell and anaplastic variants demonstrate abundant mitoses and marked nuclear pleiomorphism; this subgroup is associated with a poor prognosis.

Extensive investigation into the genetic differences in medulloblastoma over the last ten years has led to further classification into distinct molecular variants. Current clinical medulloblastoma trials are still based on histological classification. Genetic typing

however is not far from clinical use and is likely to improve prognostication and risk stratification, as well as allow tailored therapeutic approaches.

Medulloblastomas arise from aberrant proliferation of granule neuron precursor cells that go on to constitute the external granular layer of the cerebellum. The different signalling pathways involved in this complex process have led to the identification of four molecular subgroups.¹³ Wnt signalling has an important role in neural stem cell proliferation in the normal cerebellum.¹⁴ This pathway, originally identified in mutant wingless fruit-flies, is fundamental to neural tube patterning. Tumours involving Wnt pathway anomalies are more likely to arise in younger children, demonstrate classic histology, tend to be located within the fourth ventricle and are associated with a very good prognosis; their nuclei stain positively for β catenin.^{13,15} The sonic hedgehog (Shh) signalling pathway regulates progenitor cell proliferation in the external granular layer; medulloblastomas associated with Shh signalling abnormalities tend to arise within the cerebellar hemisphere and are more likely to

occur in infants or older children; their prognosis is intermediate.¹⁶ Abnormalities in these pathways are not simply related to mutations in expressed genes, but also to epigenetic changes leading to abnormal expression of tumour suppressor genes, including promoter inactivation by DNA methylation, histone modification and gene silencing by nonprotein-coding micro RNAs.¹⁷ There are two additional non-Wnt, non-Shh subtypes; both tend to be either classic or large cell / anaplastic tumours, frequently with metastases at presentation and myc amplification. Group 3 have a poor and Group 4 an intermediate prognosis.¹³

Following resection, (Figure 2D) further adjuvant treatment of medulloblastoma depends on whether they are classified as standard or high risk. Staging requires MRI of the brain and spine, without and with contrast. CSF from the lumbar region is also required; this is obtained two weeks post-operatively to avoid false positive cytology early after resection, and is more sensitive than ventricular CSF.¹⁸ High risk patients include all children under three as well as those with positive CSF, macrometastases on MRI implying tumour dissemination and > 1.5cm² of residual tumour visible on post-contrast MRI within 24 to 72 hours of surgery. Children older than three with anaplastic histology or c-myc amplification are also considered high risk.

Children over three at standard risk undergo craniospinal irradiation (23.4 Gy), commenced within 40 days of surgery with a posterior fossa boost to a total dose of 54-55.8 Gy. This is combined with weekly concurrent chemotherapy. Hyperfractionation does not lead to an improvement in overall or progression free survival.¹⁹ Based on this regimen, five year event-free survival is up to 80%.¹⁰

Historically the five year progression-free survival for children with high risk disease is 40%.²⁰ Recent studies have focused on improving prognosis in this group using multimodality treatments.²¹ High risk patients are treated with 36 Gy to the craniospinal axis followed by a posterior fossa boost to 54 to 56 Gy. Studies have evaluated the use of hyperfractionated radiotherapy, including posterior fossa boosts to 60 Gy and myeloablative courses of chemotherapy followed by peripheral blood stem cell rescue, yielding five year progression free survival of up to 73%.^{15,22}

The neurocognitive sequelae of radiotherapy are more severe in young children. In infants and children under three, repeated cycles of chemotherapy have been used after surgery in an attempt to prevent progression until they become eligible for radiotherapy. Outcomes from early studies were poor, encouraging the introduction of high dose chemotherapy regimens.¹⁰ It is likely that such studies were affected by multiple tumour biological factors which directly affected survival; infants with desmoplastic variants, for example, consistently showed better outcomes than all the others.²³

Ependymoma

Ependymoma is the third most common paediatric brain tumour; over 50% of cases arise in children under five years of age.²⁴ Infratentorial ependymomas arise from the floor or roof of the fourth ventricle and grow into the ventricular lumen. They have a propensity to extend through the foramen of Luschka into the cerebellopontine cistern and around the brainstem (Figure 3A), as well as down through the foramen magnum. The extent of surgical resection is a major determinant of outcome. In historical series, five-year overall survival for ependymoma has ranged from 50 to 64%.²³ However institutions with gross total resection rates of up to 82% have reported five-year overall survival figures of 87.3% and 62.1% for ependymomas and malignant ependymomas respectively.²⁵

Infratentorial ependymomas in children are classified as WHO grade 2 or 3, grade 1 being reserved only for subependymoma and myxopapillary ependymoma.² They are well-delineated soft, heterogeneous tumours, often with cystic, necrotic and haemorrhagic elements. Histologically they are characterised by perivascular and, more rarely, ependymal rosettes. The latter consists of tumour cells concentrically organised around a lumen.² Ependymomas stain positively with GFAP, NCAM and EAM. Multiple chromosomal anomalies have been identified in ependymomas. Anomalies on chromosome 22q have been reported in 26 to 71% of ependymomas.²⁶ Chromosome 1q gain has been found in up to 22% of childhood ependymomas, and is associated with posterior fossa location, anaplastic features and a poor prognosis.²⁷ A recent study identified gains at chromosome 1q, high tumour cell density and high mitotic count as defining features of a high risk subgroup in infratentorial ependymoma.²⁷

On CT, ependymomas are iso- or hyperdense lesions. Punctate calcification is detectable in up to 50% of cases. They enhance heterogeneously on contrast administration.³ On MRI, they are iso- to hypo-intense on T1-weighted sequences and hypointense on T2. Calcification, cysts, areas of necrosis and micro-haemorrhages cause heterogeneity within the tumour mass on enhanced and non-enhanced sequences. Leptomeningeal dissemination at presentation is less common than in medulloblastoma; full spinal MRI at diagnosis is imperative as part of the staging process.²⁸

Despite several multi-institutional studies, mostly including platinum-based agents, no single chemotherapeutic regimen has demonstrated significant survival benefit for ependymoma.^{29,30} The role of chemotherapy alongside post-operative radiotherapy remains unclear. In a recent single-institution study, conformal radiotherapy, administered immediately after surgery, led to better overall survival rates, up to 85% at five years, compared to earlier studies with up to 73% at five years.²⁵ This may be partly attributable to the high rate of gross total resection in this study. Radiotherapy was

confined to the tumour bed and a 10mm margin, and was also administered, for the first time, to children under three years; children under 18 months received 54 Gy rather than the standard dose of 59.4 Gy. The seven-year local control rate was 87%. Among the patients with differentiated ependymoma treated with gross total resection and 59.4 Gy, there were very few local failures. The low frequency of side effects from limited volume irradiation has also encouraged this group to recommend repeated surgery and re-irradiation for children presenting with local recurrence.³¹

Brainstem tumours

Brainstem gliomas account for 10 to 20% of all CNS tumours in children.³² They are broadly classified into diffuse or focal. Focal brainstem tumours are well-circumscribed masses that may be intrinsic, exophytic or cervicomedullary.^{33,34} Diffuse intrinsic pontine gliomas are high grade fibrillary astrocytomas with median overall and progression-free survival of up to eleven and nine months respectively (Figure 3B).³⁵ They present with a short history, often characterised by cranial nerve palsies and ataxia. Hydrocephalus occurs late. They are diagnosed radiologically and when typical, do not require biopsy. They are hyperintense on T2- and hypointense on T1-weighted images, with ill-defined boundaries and diffuse enlargement of the brainstem. They generally do not enhance with contrast. Surgical resection has no role in these tumours. Despite several clinical trials over the last fifteen years, based on various chemotherapeutic agents and radiotherapy delivery techniques, there has been no improvement in clinical outcome.

Focal gliomas are discrete solid or cystic tumours, under 2cm in diameter, and are commonly low grade astrocytomas. In a recent large retrospective study of focal brainstem gliomas, following 52 children over a mean of ten years, the survival rate was 98% at five years and 90% at ten years; 36.5% underwent gross or near total resection. The authors recommend that surgery should be pursued if the tumour is considered accessible and the family understand the risks of new neurological deficit. In other situations, the authors recommend stereotactic biopsy, followed by radiation for clinical or image-based progression.³⁶

Atypical teratoid rhabdoid tumour (ATRT)

ATRT is a malignant WHO grade IV tumour with a poor prognosis, occurring typically in children under two years of age. Approximately 15% of children under 36 months with a malignant brain tumour have an ATRT.³⁷ First described in 1987, it is histologically difficult to differentiate from medulloblastoma or PNET. About half arise in the posterior fossa. Due to their high growth, presentation is often rapid, with macrocephaly and progressive neurological deficit. Up to 20% present with disseminated disease.³⁸

Radiologically, posterior fossa ATRTs often invade the cerebellopontine angle and enhance brightly on contrast administration. They are hyperdense on CT, with ill-defined wispy margins. On MRI, the tumour is heterogeneous due to areas of haemorrhage, necrosis and cyst formation (Figure 3C and D).

Histologically, ATRT consists of sheets of rhabdoid cells within a background of epithelial, mesenchymal or neuroectodermal cells.² Mitotic labelling typically shows indices of 50 to 100%. These tumours characteristically demonstrate mutation or inactivation of the INI1 gene on chromosome 22q 11.2. This is also abnormal in rhabdoid tumours outside the central nervous system, including the renal and extra-renal forms. Although the exact function of this gene is unknown, it is a component of an ATP-dependent chromatin remodelling complex and is involved in the regulation of transcription. The presence of an INI1 mutation in a tumour resembling PNET, even without sheets of rhabdoid cells, is still sufficient to secure the diagnosis of ATRT.³⁹

Treatment of ATRT consists of combinations of surgery, multi-agent chemotherapy and radiotherapy. Median overall survival for a large cohort was 17.3 months.⁴⁰ Patients with gross total resection had longer survival than subtotal resection or biopsy. Survival for children under three years old who also had radiotherapy was 15.8 months, compared to 7.9 months for those who did not. Variability in chemotherapy regimens, in conjunction with the small numbers of children, has made it difficult to establish the comparative efficacy of different agents. Intrathecal chemotherapy has been shown to be of benefit in some patients.⁴⁰ ♦

REFERENCES

1. Davis FG, McCarthy BJ. *Epidemiology of brain tumors*. Curr Opin Neurol 2000; 13:635-640.
2. Louis D.N. OH, Wiestler OD, Cerveree WK. *WHO classification of tumours of the central nervous system*. Lyon: International Agency for Research on Cancer (IARC), 2007.
3. Poretti A, Meoded A, Huisman TA. *Neuroimaging of pediatric posterior fossa tumors including review of the literature*. J Magn Reson Imaging 2012; 35:32-47.
4. Gajjar A, Bhargava R, Jenkins JJ, Heideman R, Sanford RA, Langston JW, et al. *Low-grade astrocytoma with neuraxis dissemination at diagnosis*. J Neurosurg 1995; 83:67-71.
5. Horbinski C, Hamilton RL, Nikiforov Y, Pollack IF. *Association of molecular alterations, including BRAF, with biology and outcome in pilocytic astrocytomas*. Acta Neuropathol 2010; 119:641-9.
6. Ogiwara H, Bowman RM, Tomita T. *Long-term follow-up of pediatric benign cerebellar astrocytomas*. Neurosurgery 70:40-47; discussion 47-48, 2012.
7. Wisoff JH, Sanford RA, Heier LA, Spoto R, Burger PC, Yates AJ, et al. *Primary neurosurgery for pediatric low-grade gliomas: a prospective multi-institutional study from the Children's Oncology Group*. Neurosurgery 68:1548-1554; discussion 1554-1545, 2011.
8. Pollack IF. *Multidisciplinary management of childhood brain tumors: a review of outcomes, recent advances, and challenges*. J Neurosurg Pediatr 2011; 8:135-48.
9. Warren KE, Goldman S, Pollack IF, Fangusaro J, Schaiquevich P, Stewart CF, et al. *Phase I trial of lenalidomide in pediatric patients with recurrent, refractory, or progressive primary CNS tumors: Pediatric Brain Tumor Consortium study PBTC-018*. J Clin Oncol 2011; 29:324-9.

10. Massimino M, Giangaspero F, Garre ML, Gandola L, Poggi G, Bionessi V, et al. *Childhood medulloblastoma*. Crit Rev Oncol Hematol 2011;79:65-83.
11. Dhall G. *Medulloblastoma*. J Child Neurol 2009;24:1418-30.
12. Polkinghorne WR, Tarbell NJ. *Medulloblastoma: tumorigenesis, current clinical paradigm, and efforts to improve risk stratification*. Nat Clin Pract Oncol 2007;4:295-304.
13. Taylor MD, Northcott PA, Korshunov A, Remke M, Cho YJ, Clifford SC, et al. *Molecular subgroups of medulloblastoma: the current consensus*. Acta Neuropathol 2012;123:465-72.
14. Ciani L, Salinas PC. *WNTs in the vertebrate nervous system: from patterning to neuronal connectivity*. Nat Rev Neurosci 2005;6:351-62.
15. Gajjar A, Chintagumpala M, Ashley D, Kellie S, Kun LE, Merchant TE, et al. *Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial*. Lancet Oncol 2006;7:813-20.
16. Gibson P, Tong Y, Robinson G, Thompson MC, Currie DS, Eden C, et al. *Subtypes of medulloblastoma have distinct developmental origins*. Nature 2010;468:1095-9.
17. Faria CM, Rutka JT, Smith C, Kongkham P. *Epigenetic mechanisms regulating neural development and pediatric brain tumor formation*. J Neurosurg Pediatr 2011;8:119-32.
18. Gajjar A, Fouladi M, Walter AW, Thompson SJ, Reardon DA, Merchant TE, et al. *Comparison of lumbar and shunt cerebrospinal fluid specimens for cytologic detection of leptomeningeal disease in pediatric patients with brain tumors*. J Clin Oncol 1999;17:1825-8.
19. Lannering B, Rutkowski S, Doz F, Pizer B, Gustafsson G, Navajas A, et al. *Hyperfractionated versus conventional radiotherapy followed by chemotherapy in standard-risk medulloblastoma: results from the randomized multicenter HIT-SIOP PNET 4 trial*. J Clin Oncol 2012;30:3187-93.
20. Packer RJ, Rood BR, MacDonald TJ. *Medulloblastoma: present concepts of stratification into risk groups*. Pediatr Neurosurg 2003;39:60-7.
21. Bartlett F, Kortmann R, Saran F. *Medulloblastoma*. Clin Oncol (R Coll Radiol) 2013;25:36-45.
22. Gandola L, Massimino M, Cefalo G, Solero C, Spreafico F, Pecori E, et al. *Hyperfractionated accelerated radiotherapy in the Milan strategy for metastatic medulloblastoma*. J Clin Oncol 2009;27:566-71.
23. Rutkowski S, Gerber NU, von Hoff K, Gnekow A, Bode U, Graf N, et al. *Treatment of early childhood medulloblastoma by postoperative chemotherapy and deferred radiotherapy*. Neuro Oncol 2009;11:201-10.
24. Duffner PK, Krischer JP, Sanford RA, Horowitz ME, Burger PC, Cohen ME, et al. *Prognostic factors in infants and very young children with intracranial ependymomas*. Pediatr Neurosurg 1998;28:215-22.
25. Merchant TE, Li C, Xiong X, Kun LE, Boop FA, Sanford RA. *Conformal radiotherapy after surgery for paediatric ependymoma: a prospective study*. Lancet Oncol 2009;10:258-66.
26. Mack SC, Taylor MD. *The genetic and epigenetic basis of ependymoma*. Childs Nerv Syst 2009;25:1195-201.
27. Godfraind C, Kaczmarek JM, Kocak M, Dalton J, Wright KD, Sanford RA, et al. *Distinct disease-risk groups in pediatric supratentorial and posterior fossa ependymomas*. Acta Neuropathol 2012;124:247-57.
28. Yuh EL, Barkovich AJ, Gupta N. *Imaging of ependymomas: MRI and CT*. Childs Nerv Syst 2009;25:1203-13.
29. Brandes AA, Cavallo G, Reni M, Tosoni A, Nicolardi L, Scopeco L, et al. *A multicenter retrospective study of chemotherapy for recurrent intracranial ependymal tumors in adults by the Gruppo Italiano Cooperativo di Neuro-Oncologia*. Cancer 2005;104:143-8.
30. Geyer JR, Sposto R, Jennings M, Boyett JM, Axtell RA, Breiger D, et al. *Multiagent chemotherapy and deferred radiotherapy in infants with malignant brain tumors: a report from the Children's Cancer Group*. J Clin Oncol 2005;23:7621-31.
31. Merchant TE, Boop FA, Kun LE, Sanford RA. *A retrospective study of surgery and reirradiation for recurrent ependymoma*. Int J Radiat Oncol Biol Phys 2008;71:87-97.
32. Recinos PF, Sciubba DM, Jallo GI. *Brainstem tumors: where are we today?* Pediatr Neurosurg 2007;43:192-201.
33. Epstein F ME. *Intrinsic brainstem tumors of childhood: surgical indications*. J Neurosurg 1986;64:11-15.
34. Sandri A, Sardi N, Genitori L, Giordano F, Peretta P, Basso ME, et al. *Diffuse and focal brain stem tumors in childhood: prognostic factors and surgical outcome. Experience in a single institution*. Childs Nerv Syst 2006;22:1127-35.
35. Hargrave D, Bartels U, Bouffet E. *Diffuse brainstem glioma in children: critical review of clinical trials*. Lancet Oncol 2006;7:241-8.
36. Klimo P Jr, Pai Pandiker AS, Thompson CJ, Boop FA, Qaddoumi I, Gajjar A, et al. *Management and outcome of focal low-grade brainstem tumors in pediatric patients: the St. Jude experience*. J Neurosurg Pediatr. 2013.
37. Reddy AT. *Atypical teratoid/rhabdoid tumors of the central nervous system*. J Neurooncol 2005;75:309-13.
38. Hilden JM, Meerbaum S, Burger P, Finlay J, Janss A, Scheithauer BW, et al. *Central nervous system atypical teratoid/rhabdoid tumor: results of therapy in children enrolled in a registry*. J Clin Oncol 2004;22:2877-84.
39. Biegel JA, Kalpana G, Knudsen ES, Packer RJ, Roberts CW, Thiele CJ, et al. *The role of INI1 and the SWI/SNF complex in the development of rhabdoid tumors: meeting summary from the workshop on childhood atypical teratoid/rhabdoid tumors*. Cancer Res 2002;62:323-8.
40. Athale UH, Duckworth J, Odame I, Barr R. *Childhood atypical teratoid rhabdoid tumor of the central nervous system: a meta-analysis of observational studies*. J Pediatr Hematol Oncol 2009;31:651-63.

BOOK REVIEWS

Literary Medicine: Brain Disease and Doctors in Novels, Theater, and Film

(Frontiers of Neurology and Neuroscience volume 31)

If it is the case that "Medicine is fundamentally narrative", as suggested by Kathleen Montgomery Hunter in *Doctors' Stories. The narrative structure of medical knowledge* (Princeton University Press, 1991:5), then the kinship of medical practice with the verbal and visual narratives encountered respectively in literature and art is obvious. In focusing on brain disease as portrayed in novels, theatre, and film, the editors of this volume have at their disposal a potentially limitless resource for discussion (on occasion addressed in the pages of *ACNR*).

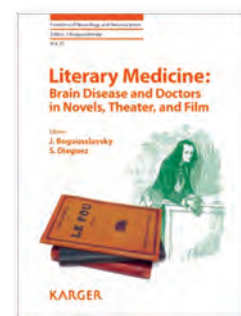
Many of the usual suspects are summoned to this banquet of literature/art and medicine: van Gogh (specifically his letters, replete with references to literature), Dostoevsky (accounts of epilepsy), Chekhov (doctors), Charcot (his interest in the theatre), Proust (diseases and doctors), and Balzac (doctors, and a possible early account of schizophrenia in the character of *Louis Lambert*), as well as less familiar names such as Blaise Cendrars and Joseph Gerard.

The two most substantial chapters, both authored by Sebastian Dieguez, undertake in-depth surveys of doubles and of amnesia. With respect to doubles, an extended review of literary contributions leads to the argument that cognitive mechanisms may underpin both clinical and scientific research and literary creations. With respect to

amnesia, criticisms of literary amnesiacs as too often of retrograde autobiographical type, rare in clinical practice, are rejected through citation of "stranger-than-fiction" type cases in the medical literature, and Dieguez contends that intuitive conceptions of memory may feed in to scientific understanding and vice versa, a notion which may be at odds with principles of neuropsychological research.

David Perkin gives examples of movement disorders he has encountered in his reading for pleasure, including some pretty convincing accounts of hemifacial spasm, tremor, and dystonia, but he reports (191) only one example which might fulfil the criteria of Tourette's syndrome. One hesitates to contradict so eminent a neurologist and so avid a reader, but I would recommend him to ponder some possible examples cited in *ACNR* 2003;3(5):26-27, and would be interested to hear his thoughts on the character of Pozdnyshv in Leo Tolstoy's 1889 novella *The Kreutzer Sonata*.

As with previous volumes in this series, the book's expense is made acceptable by the high production values, with only occasional errors (e.g p. 161, Primo Levi's If this is a man is given as published in 1942, when the writer had yet to be incarcerated, rather than 1947, the date of the first Italian edition). We may anticipate further volumes devoted to these kindred, narrative-based, subjects. ♦



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The 4th London-Innsbruck Colloquium on Status Epilepticus and acute seizures

Conference details: 4-6 April, 2013, Salzburg, Austria. **Reviewed by:** Dr Hannah Cock, Reader in Clinical Neurology, St George's University of London, Honorary Consultant Neurologist, Epilepsy Group, Akinson Morley Regional Neuroscience Centre, St George's NHS Trust, London UK.

Take home messages:

- A global audit on the treatment of refractory SE and super-refractory SE was launched at the colloquium. Please register at <https://www.status-epilepticus.net/>
- Clinical trials in status epilepticus are revitalising and improving practice. RAMPART has shown im midazolam to be superior to iv lorazepam as initial treatment, and a trial to compare Valproate, Levetiracetam and fosPhenytoin is planned.
- Basic science advances in microRNA technology and inflammation offer the promise of potential antiepileptogenic strategies in the future.

Status epilepticus: Impressive advances despite the challenges

Status epilepticus (SE), sometimes described as the maximal expression of epilepsy, together with acute seizures represents a significant proportion of acute medical presentations to emergency departments, as well as being a not infrequent complication of numerous neurosurgical, general medical and neurological conditions both in and out of hospital.¹ Progress in translating significant advances in scientific knowledge into clinical practice have perhaps been hampered in the past by the fact that the clinicians most interested in the condition, usually epileptologists/neurologists, are often not those most involved in the acute management (emergency physicians, general medical teams, neurosurgeons, anaesthetists, intensivists and paediatricians). Building on the success of three previous SE dedicated conferences (1962, 1980 and 1997) two of the world's leading authorities in SE, Simon Shorvon (London, UK) and Eugen Trinka (Previously from Innsbruck, now Salzburg, Austria) not only recognised the importance of facilitating true multidisciplinary debate and collaboration to drive progress, but did something about it. Thanks largely to their efforts, supported by the ILAE commission of European Affairs, 344 doctors and scientists from a broad range of backgrounds attended the fourth London-Innsbruck colloquium on SE and acute seizures held in Salzburg in April 2013.

Each of the meetings has been defined by a stated purpose to summarise current knowledge in key clinical and basic science areas, to define optimal clinical practice, to debate controversial issues, and to inform future clinical and scientific areas. Arguably, this is the purpose of any speciality conference, but by explicitly defining this at the outset and allowing considerable programme time dedicated to debate and discussion, together with taking advantage of the opportunity to have the best in the world from a broad range of disciplines focus on specific issues, this meeting has

become a "must attend" for anyone working in SE/acute seizures. It also has much to offer educationally for others with an interest. As well as a review of the achievements covered in the three prior colloquia since 2007, particular highlights of the most recent meeting are summarised below.

That the effectiveness of benzodiazepines in terminating SE decreases as SE progresses is now well established in a range of animal models, and also in clinical practice. The molecular mechanisms behind this are increasingly unravelling, including internalisation of GABAA receptors,² and enhanced AMPA mediated excitatory conductance, possibly due to post-synaptic changes in AMPA receptor expression.³ Whether this will translate into clinical benefits, e.g. a role for AMPA antagonists (at least one, perampanel is now licensed for adjunctive use in refractory epilepsy) in SE remains to be seen.

In a masterful presentation of quite complex science to a largely clinical audience, David Henshall from Dublin summarised work demonstrating changes in specific micro-RNAs (non-coding RNAs which function as post-transcriptional modulators of intracellular proteins) following SE.⁴ Proteins involved in neuronal structure and excitability, gliosis, inflammation and apoptosis are selectively affected, and of particular interest as a potential antiepileptogenic target (as opposed to anti-seizure as for current Anti-epileptic Drugs, AEDs). Using chemically modified antisense oligonucleotides, Antagomirs, in an animal model of SE, administration of a single dose one hour after SE was followed by a 90% reduction in subsequent spontaneous seizures (post-SE epilepsy) and substantially less structural damage, maintained even in animals studied up to two months later. Whilst there are undoubtedly still several hurdles to overcome before studies in man can be undertaken, this is certainly one of the most promising approaches in pre-clinical development in terms of neuroprotection and antiepileptogenesis in epilepsy.

A particular feature of these meetings has been a themed post-congress closed workshop, bringing together specific individuals to work towards a defined output. Clinical trial design was the focus of a 2009 workshop, informing a proposed Established Status Epileptics Treatment Trial (ESETT) proposal first outlined in 2011,⁵ with a funding application now in the final stages of refinement with USA and European collaborators. This hopes to learn from and build on the impressive success of the RAMPART study,⁶ lessons from which were

also reviewed at the meeting. RAMPART completed ahead of schedule, and despite being powered as a non-inferiority study, demonstrated the superiority of intramuscular midazolam over the previous gold standard intravenous lorazepam for the out of hospital initial treatment of SE. That this was named as Trial of the Year by the Society for Clinical Trials is not only a well deserved accolade, but also one hopes the start of a new era for clinical trials in this sometimes devastating condition.

A recurring theme throughout the meeting was the need for increased data sharing between centres, and the need for standardised data collection to facilitate this. This was also the topic of this year's post-congress workshop, with a global audit on the treatment of refractory SE and super-refractory SE launched at the colloquium, and now underway (<https://www.status-epilepticus.net/>). The methodological flaws inherent in non-randomised observational studies of this nature should at least be partly mitigated by that numbers (>1000 patients over 12 months is the target) should far exceed any achievable in the setting of a clinical trial.

Abstracts from the meeting are available from the congress website at http://www.status-epilepticus2013.eu/images/downloads/finalprogramme_2013.pdf, and will be published in full in *Epilepsia* later this year. Readers are encouraged to look out for advance notice of the anticipated 5th London-Innsbruck Status Epilepticus Colloquium to be held in April 2015. ♦

References

1. Shorvon, S. *The treatment of status epilepticus*. Current Opinion in Neurology, 2011;24(2):165-70.
2. Naylor, DE, Liu H, Wasterlain CG. *Trafficking of GABA(A) receptors, loss of inhibition, and a mechanism for pharmacoresistance in status epilepticus*. J Neurosci, 2005;25(34):7724-33.
3. Rajasekaran K, Joshi S, Kozhemyaykin M, Stodorovic M, Kowalski S, Balint C, Kapur J. *Receptor trafficking hypothesis revisited: Enhancement of AMPA receptor-mediated neurotransmission during established status epilepticus*. Epilepsia, 2013. In Press.
4. Henshall, DC. *Antagomirs and microRNA in status epilepticus*. Epilepsia, 2013. In press.
5. Cock HR, obotE group. *Established Status Epilepticus Treatment Trial (ESETT)*. Epilepsia, 2011;52:50-2.
6. Silbergleit, R, Durkalski V, Lowenstein D, Conwit R, Pancioli A, Palesch Y, Barsan W. *N Investigators. Intramuscular versus intravenous therapy for prehospital status epilepticus*. N Engl J Med, 2012;366(7):591-600.

Disclosure:

Dr Cock has been on the faculty for all of the Status Epilepticus Colloquium meetings since 2007. She has received honoraria or consultancy fees from the manufacturers of all currently licensed antiepileptic drugs, and unrestricted educational grants from UCB Pharma, Novartis and Sanofi-Synthelabo. The views expressed are her own.

Annual Meeting of the Association of British Neurologists

Conference details: 21–24 May, 2013, Glasgow, UK. **Reviewed by:** Sian Alexander, Addenbrooke's hospital, Cambridge, UK.

Those attending this year's ABN in Glasgow were treated to a warm and Scottish welcome. 615 delegates, including a significant number of medical students, junior doctors and non-physicians enjoyed a packed four-day schedule of Neurology. The conference contained a full programme of lectures, teaching/science sessions and specialist symposia, supplemented with lunchtime debates, Neuro-Ophthalmology "Breakfast with the Experts" and early morning fora. The social events in the evening introduced us to many elements of Scottish fare: bagpipes, Haggis, Cloutie pudding and whisky.

Outreach and specialist registrar (SpR) training components started the conference, with parallel sessions for medical students, GPs ('Need to Know' Neurology) and SpR trainees. SpR trainees were treated to a pair of interactive sessions on difficult consultations and managing peripheral nerve disease, followed by a brave variety of talks including the NMJ for neurologists (Arup Malik), Balancing Your

Neurology' reflects the growth in popularity of stem cells as models of many neurological diseases and as potential therapeutic agents. Siddharthan Chandran emphasised the potential for stem cells as models for identifying 'druggable targets'. We heard from Roger Barker on the history of stem cell transplantation in Parkinson's disease, the huge variability in outcomes in early studies, and current attempts to identify what factors determine a successful transplant in the 'Trans-euro' study. Finally, Keith Muir gave an update on the use of stem cells in stroke, just days ahead of his presentation at the European Stroke Conference with promising early results in five stroke patients treated with stem cells in a phase I trial. Concerns were voiced on the availability of clinical stem cell therapies advertised to patients who are willing to pay, despite the lack of evidence for benefit and potential for harm.

In the Dementia session, we were re-introduced to the cognitive history and examination by Chris Butler, and provided with some excel-

lations, but valproate, even at low doses (<600mg daily) was associated with greater risk of major congenital malformation than high dose lamotrigine (>400mg daily).

A fascinating adjunct to our study of human neurology was the talk by Jacques Penderis on veterinary neurology. This was a fascinating insight into some of the specific challenges of diagnosis in a multitude of species in the absence of our most-valued resource, the history. We were introduced to an intoxicating mix of video-genic cases, including infectious agents, complications of inbreeding (Chiari-like malformation as a complication of extreme bradycephaly) and founder effect (Episodic Falling in the Cavalier King Charles Spaniel, a microdeletion on canine chromosome 7). In addition, spontaneous diseases found in both animals and humans were presented, such as the neurometabolic disorder L-2-hydroxyglutaric aciduria, with a similar phenotype of learning disability, seizures and ataxia and with a shared genetic basis (L2HGDH).

Two lectures provided historical context to current modes of healthcare and physician training. David Chadwick considered the evolving process of providing healthcare to our patients in the ABN Medallist Lecture, and Geraint Fuller shared his journey into neurology. As a trainee, I was struck by two heartening features about a career in neurology: first, the inspiring effects of neurological friendships; second, the enduring rewards of seeking answers to neurological puzzles.

On the final day, a series of great case presentations competed for the ACNR-sponsored prize. This was awarded to Owen Pickrell for a case of West African sleeping sickness with an interesting context of 29-years latency and very elevated titres of VGKC and NMDA antibodies. Along similar lines of testing diagnostic prowess, John Paul Leach was in the CPC hot seat on the last afternoon, but I think all were tested with an unusual case of Vanishing White Matter Disease.

Well-organised, with an array of first-class presentations, interested delegates – and speakers – at all stages of training, this year's meeting was highly enjoyable and stimulating. Onto another Celtic nation in 2014, Wales. ♦

As a trainee, I was struck by two heartening features about a career in neurology: first, the inspiring effects of neurological friendships; second, the enduring rewards of seeking answers to neurological puzzles

Career with Family Life (Tracey Baird) and The Drug Discovery Pipeline. The quiz, organised by Jonathan Schott was entertaining and illuminating, not least for demonstrating the breadth of understanding of Cockney Rhyming Slang and 'txt-speak' in the neurological audience. Martin Rosser's public lecture, 'Supercomputer – the brain and what happens' when it crashes was an excellent demonstration of public engagement, conveying complex concepts with clarity and humour, including to those of us with more idea about what a brain might do rather than a supercomputer.

A range of excellent lectures and teaching/science sessions included Headache, Functional Disorders, Stem Cells in Neurology, Dementia and Specialist Updates. The 19th Gordon Holmes lecture was given by Mark Hallett on the pathophysiology of psychogenic movement disorders. Followed by further discussion of functional disorders by Mark Edwards, Jon Stone and Alan Carson, this session explored methods of making a positive diagnosis, the value of a video camera to fully capture the effect of distraction in functional movement disorders, and effective management of affected patients.

A dedicated session on 'Stem Cells in

Neurology' reflects the growth in popularity of stem cells as models of many neurological diseases and as potential therapeutic agents. Siddharthan Chandran emphasised the potential for stem cells as models for identifying 'druggable targets'. We heard from Roger Barker on the history of stem cell transplantation in Parkinson's disease, the huge variability in outcomes in early studies, and current attempts to identify what factors determine a successful transplant in the 'Trans-euro' study. Finally, Keith Muir gave an update on the use of stem cells in stroke, just days ahead of his presentation at the European Stroke Conference with promising early results in five stroke patients treated with stem cells in a phase I trial. Concerns were voiced on the availability of clinical stem cell therapies advertised to patients who are willing to pay, despite the lack of evidence for benefit and potential for harm.

Parallel symposia covered a variety of neurological topics: stroke; audit/training; Parkinson's disease; general neurology; multiple sclerosis; epilepsy and neuro-immunology. Of the numerous excellent presentations, one very practical presentation by Ellen Campbell and colleagues in Belfast provided data on the risk of major congenital malformations with different anti-epileptic medications over a fifteen-year period and 5510 cases. Similar levels of major congenital malformations were noted in 304 cases of levetiracetam monotherapy compared with carbamazepine and lamotrigine (n=1718 and 2198 respectively). Carbamazepine and valproate (n=1290) both demonstrated a dose-dependent effect of risk of major malfor-

Take home messages:

- Genetic panels (simultaneously-run, hundreds of genes) are nearly here; result interpretation remains unclear
- Stem cells are useful models of neurological disease; a role in clinical therapeutics is less clear

Debate: Does Progressive Multiple Sclerosis start on Day 1?

Report from a satellite symposium at the 2013 Annual Meeting of the Association of British Neurologists (ABN), Glasgow, 24th May 2013.



Chair:
Professor David Bates
Newcastle University,
Newcastle.



Debater: Dr James
Overell, Institute
of Neurological
Sciences, Glasgow.



Debater: Dr Belinda
Weller, Western
General Hospital,
Edinburgh.

The views expressed are those of the speakers in the context of a debate and are not necessarily those of the meeting sponsors.

Introduction

Multiple sclerosis (MS) is a chronic, clinically heterogeneous condition with an extended trajectory that can affect individual patients in many different ways depending on the location(s) of the lesions and the rate of progression. Clinically, most MS patients will present with a relapsing-remitting disease course that can last for decades followed by a 'subsequent' secondary-progressive phase, where relapses become less prominent and relentless neurological decline ensues.¹ In accordance with this model, the current treatment of MS has been mostly focused on the management of relapses and most MS drugs are aimed at reducing new inflammatory demyelinating lesions.

However, whereas MS was once considered to be the "prototype immune-mediated demyelinating disease",² we now also know that axonal degeneration is a major cause of irreversible neurological disability in MS patients.² The exact relationships between inflammation and neurodegeneration, and their relative contribution to disability remain controversial. A key question is whether there is an inevitable and continuing injury to the CNS that starts early on in the disease course?

Yes – Pathological progression starts at Day 1

Dr James Overell began the debate by reviewing the evidence that diffuse pathological changes are apparent in patients with very early MS. He challenged the dogma that inflammation is the cause of axonal and neuronal degeneration in multiple sclerosis, and instead argued that there is a close association between inflammation and neurodegeneration in all types of lesions (active, inactive) and at all MS disease stages. The evidence shows that both axonal damage and inflammation are present early on and that both progress over time.³ Dr Overell also reviewed the accumulating evidence that brain atrophy occurs early – it is present even in patients with clinically isolated syndrome (CIS) – and that atrophy correlates with progression of disability.⁴ Conversely, a recent review of natural history studies highlighted the apparent dissociation between relapses and disease progression.¹ In these studies, the progressive course was found to be independent of relapses either preceding the onset of relapse-free progression or subsequent to it.^{1,5} Moreover, the site of the original attack is not usually where progression begins.⁵ Dr Overell argued that such findings are important as they suggest that in addition to targeting relapses, it is also crucial to target the progression of the disease. Importantly, recent studies in patients with relapsing-remitting MS show that new treatments may impact atrophy and progression, but with less impact on relapses.^{6,7}

No – Clinical progression does not start at Day 1

Countering the debate, Dr Belinda Weller argued that when progression is defined clinically as "the onset of insidiously worsening and irreversible neurological function," it cannot be said to start at Day 1. A recent study of a population-based MS cohort showed that patients with RRMS do not inevitably develop a progressive disease course, indeed 38% of patients with RRMS did not develop progression by age 75.⁸ Dr Weller argued that, in her experience, significant numbers of patients have an attack and have abnormalities on MRI – but do not come back to the clinic as they continue to do well over many years. She argued that the patients who attend clinics and are enrolled in clinical trials represent more severely affected patients, and that there is a 'hidden' population of people with MS who do not need to come in for treatment.

Dr Weller discussed that while cognitive dysfunction is often used to support the idea that progression starts from day 1, cognitive dysfunction is common in MS, is related to the location of lesions and may already be seen in CIS, and in early-stage RRMS.⁹ Dr Weller noted that it is very difficult to disentangle the effects of aging from those of MS progression – but it does appear that pre-existing cognitive impairment represents the major risk for further cognitive deterioration.

Reaching consensus

The discussion following the two presentations noted that the debate came down to how progression was defined. When defined clinically, many patients can do well for decades and do not develop progressive MS. However, when defined radiologically or pathologically, it is clear that axonal damage and atrophy occurs early on. While the clinical course of MS differs widely between patients, it is likely that there will be some underlying disease progression – albeit at very different rates.

Both speakers agreed that both relapses and progression deserve consideration and treatment as appropriate to the individual patient. When MS is diagnosed early enough, effective treatment can lead to the reversal of disability.

References

1. Tremlett H, Zhao Y, Rieckmann P, Hutchinson M. New perspectives in the natural history of multiple sclerosis. *Neurology* 2010;74(24):2004-2015.
2. Trapp BD, Nave KA. Multiple sclerosis: an immune or neurodegenerative disorder? *Annu Rev Neurosci* 2008;31:247-269.
3. Frischer JM, Bramow S, Dal-Bianco A, et al. The relation between inflammation and neurodegeneration in multiple sclerosis brains. *Brain* 2009;132(Pt 5):1175-1189.
4. Popescu V, Agosta F, Hulst HE, et al. Brain atrophy and lesion load predict long term disability in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2013.
5. Kremenchutzky M, Rice GP, Baskerville J, Wingerchuk DM, Ebers GC. The natural history of multiple sclerosis: a geographically based study 9: observations on the progressive phase of the disease. *Brain* 2006;129(Pt 3):584-594.
6. Bruck W, Zamvil SS. Laquinimod, a once-daily oral drug in development for the treatment of relapsing-remitting multiple sclerosis. *Expert Rev Clin Pharmacol* 2012;5(3):245-256.
7. Barkhof F, Hulst HE, Drulovic J, et al. Ibudilast in relapsing-remitting multiple sclerosis: a neuroprotectant? *Neurology* 2010;74(13):1033-1040.
8. Tutuncu M, Tang J, Zeid NA, et al. Onset of progressive phase is an age-dependent clinical milestone in multiple sclerosis. *Mult Scler* 2013;19(2):188-198.
9. Guimaraes J, Sa MJ. Cognitive dysfunction in multiple sclerosis. *Front Neurol* 2012;3:74.

This satellite symposium and report are sponsored by Teva UK Limited.

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DEVELOPMENTS AND DEBATES IN NEUROLOGY: MRI DEVELOPMENTS, BRAIN ATROPHY IN MS, AND POTENTIAL IMPLICATIONS FOR MS TREATMENT

HIGHLIGHTS OF A SYMPOSIUM HELD AT THE ASSOCIATION OF BRITISH NEUROLOGISTS (ABN)
MEETING, 21–23 MAY 2013, GLASGOW, SCOTLAND



Key points

- Current disease-modifying therapies (DMTs) can shift the gradient of multiple sclerosis (MS) and therefore affect disease progression, rather than just managing symptoms
- Brain atrophy (BA) and loss of axon density occur early in MS and progress throughout the disease course
 - Neuronal dystrophy and BA occur mainly in the grey matter, which may explain observed disability and impairment
- Early MRI activity is indicative of poor disease prognosis and poor long-term patient outcomes (e.g. dementia, disability and early death)
 - However, current UK treatment guidelines (NICE, ABN) do not include prescribing based on MRI activity
- Neurologists and the ABN should initiate change in MS prescribing practices in the UK to allow patients to be treated earlier in the disease course

A current 'hot' topic among MS-ologists/neurologists is whether failure to treat a patient with active relapsing remitting multiple sclerosis (RRMS) is medically negligent. This issue formed the basis of a debate held at the ABN Novartis-sponsored satellite symposium, the scene for which was set by two preceding presentations.

Professor Siddharthan Chandran (University of Edinburgh, Scotland), the session Chair, presented 'The consequence of not identifying and controlling disease activity in MS'. He suggested that MS was a pathologically interesting condition – the 'pathfinder disease' of chronic diseases – because, unlike other chronic neurological diseases, MS treatments can affect the actual disease, rather than just manage symptoms. In general, MS pathology involves inflammation, an effect on myelin, and neuronal injury. Although neuronal injury/degeneration and inflammation are apparent, the relationship between the two remains to be fully established. The typical view of MS, largely driven by immunomodulatory therapies, is that there is an initial manifestation of inflammation followed by neurodegeneration. Professor Chandran concluded that the progressive burden of MS presented an unmet need and, despite available treatments, questions remained, such as: how early to treat? What is an effective treatment? How can success versus failure be measured?

Professor Paul Matthews (Imperial College London, England) presented 'Emerging evidence on brain atrophy as a measure of disease progression and treatment effect'. He said the aim in MS was to stop processes leading to neurodegeneration, and that BA may be used as an index of neurodegeneration. Professor Matthews showed MRI evidence of reduced N-acetylaspartate (NAA) concentration, a neuronal biomarker, in both the lesion and normal appearing white matter (NAWM) of an MS brain compared with a healthy brain. He demonstrated progressive, linear

loss of NAA from the early disease stages, and loss of brain axonal mass. A primary inflammatory trigger, e.g. acute inflammation, contributes to axonal loss. BA is more severe in later stages of MS, occurring mainly in grey matter. Professor Matthews showed how BA proceeds throughout the course of the disease at a similar rate across the different disease stages, and suggested that BA/brain volume measures (as related to disability change) may provide an index to monitor the efficacy of various treatments. He suggested that radiologists should move from qualitative assessment of MRI images to a quantitative base methodology. He concluded by showing that in RRMS, treatment effect on BA could predict the effect on disability progression.

Dr Bob Brenner (Royal Free London Hospital, England) and Professor Gavin Giovannoni (Blizard Institute, Barts and the London School of Medicine and Dentistry, England) then debated 'for' (Dr Brenner) or 'against' (Professor Giovannoni) the motion 'Failure to treat a patient with active RRMS is medically negligent'.

Dr Brenner supported the motion by demonstrating the low uptake of MS treatments in the UK versus other European countries, suggesting this to be owing to the 'conservative' nature of the UK, due partly to the need for long-term data and outcome measures. He showed that treatment in patients with early disease prevents relapse, and that MS drugs help patients retain cognition and improve memory. Evidence from long-term analysis of patients treated with interferon β -1b (IFN β -1b) showed a lower incidence of outcomes, such as inability to walk or wheelchair confinement, compared with patients not receiving treatment. Further, there was a significant survival advantage in patients receiving early IFN β -1b treatment versus placebo. Dr Brenner concluded that delaying treatment leads to patient relapses, BA, earlier onset of disease progression, subsequent disability, dementia and eventual early death.

In his ‘against’ argument, Professor Giovannoni presented a case study of a patient on current guideline-recommended treatment who relapsed and was found to have active disease, evident from an MRI protocol for a clinical study and not part of the routine review for the patient’s treatment, thus the patient did not receive early DMTs. Professor Giovannoni argued that based on current practice guidelines and available evidence, the prescribing neurologist was not considered medically negligent by not offering treatment to this patient. The case demonstrates the dilemma whereby clinicians know a patient has subclinical or MRI disease activity, or ‘smouldering MS’, and a

poor prognosis for disease progression, but under current prescribing guidelines, there is no option to elevate therapy. Professor Giovannoni suggested that where disease activity is present, patients be escalated beyond first line therapy rather than administered other first line therapies, to reduce the likelihood of disease progression. He described the potential for a patient to receive non-NHS funded therapy through private prescribing. However, this could create a two-tiered healthcare system of patients who can afford treatment and those who cannot. Professor Giovannoni ended by asking whether this type of healthcare system was desirable.

Following the debate the audience discussion raised the following actions and concerns:

- Drive change in prescribing practices in the UK to early treatment initiation
 - Are current treatments good enough and cost effective?
 - Who should pay for the treatments?
- Encourage the ABN to lead the change with additional support from NICE
 - Are there sufficient MS specialists/neurologists interested in MS to rally for change?
 - Is there sufficient continuity of follow-up by neurologists treating specific patients?
- Obtain long-term data to show that currently available DMTs improve disability when prescribed early
 - Do we need to wait for these data before changing treatment in clinical practice?
 - Will waiting for long-term data be at the expense of improving patient outcomes now?
- Develop an updated, simple ‘bar code’ type of classification of MS that could describe patients more accurately

Abbreviated Prescribing Information:

GILENYA® (fingolimod) ▼

Important note: Before prescribing, consult Summary of Product Characteristics (SmPC).

Presentation: Hard capsule containing 0.5 mg fingolimod (as hydrochloride).

Indications: Gilenya is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups:

- Patients with high disease activity despite treatment with a beta-interferon. These patients may be defined as: those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gadolinium-enhancing lesion. A “non-responder” could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

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

Dosage: Adults: Treatment should be initiated and supervised by a physician experienced in multiple sclerosis. One 0.5 mg capsule to be taken orally once daily. Patients can switch directly from beta interferon or glatiramer acetate to Gilenya provided there are no signs of relevant treatment-related abnormalities, e.g. neutropenia. Use with caution in patients aged 65 years and over. No dose adjustments required in patients with mild to severe renal impairment or mild to moderate hepatic impairment. Exercise caution in patients with mild to moderate hepatic impairment. Do not use in patients with severe hepatic impairment (Child-Pugh class C). Use with caution in patients with diabetes mellitus due to an increased risk of macular oedema.

Contraindications: Known immunodeficiency syndrome, patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies), severe active infections, active chronic infections (hepatitis, tuberculosis), known active malignancies, except for patients with cutaneous basal cell carcinoma, severe liver impairment (Child-Pugh class C), hypersensitivity to the active substance or to any of the excipients.

Warnings/Precautions: *Bradycardia:* Initiation of treatment results in a transient decrease in heart rate (HR), which may be associated with atrioventricular block. Patients should have an ECG pre-dose, 6 hours post dose and observed for 6 hours with hourly HR and BP. Continuous ECG monitoring is recommended for 6 hours. In the event of bradycardia-related symptoms, initiate appropriate clinical management and monitor overnight. Also monitor overnight if at 6 hrs: HR < 45 bpm, new onset 2nd degree heart block or higher, QTc>500 msec, or 3rd degree heart block at any time. If HR is lowest at 6 hrs monitor for > 2 hrs until HR increases. The same precautions apply if treatment is interrupted for one day or more during the first 2 weeks of treatment, if treatment is interrupted for more than 7 days during weeks 3 and 4 of treatment, or if Gilenya is discontinued for more than 2 weeks. Do not use Gilenya in patients with Mobitz type II or higher AV

block, sick-sinus syndrome, sino-atrial block, symptomatic bradycardia, recurrent syncope, QTc>450 msec significant cardiovascular disease, or severe sleep apnoea unless in consultation with a cardiologist and monitored overnight. Gilenya should not be given to patients taking beta blockers, HR lowering calcium channel blockers or other HR lowering substances (eg digoxin, diltiazem, ivabradine) unless in consultation with a cardiologist. *Infections:* Reduction of the lymphocyte count to 20-30% of baseline values occurs with Gilenya. Perform a complete blood count (CBC) at baseline and periodically during treatment, and in case of signs of infection, stop Gilenya until recovery if absolute lymphocyte count < 0.2x10⁹/L is confirmed. Consider VZV vaccination of patients without a history of chickenpox or VZV antibody negative patients prior to commencing Gilenya. Gilenya may increase the risk of infections. Employ effective diagnostic and therapeutic strategies in patients with symptoms of infection while on Gilenya and for 2 months after discontinuation. *Macular oedema:* Macular oedema with or without visual symptoms has been reported in patients taking Gilenya. Perform an ophthalmological evaluation 3-4 months after Gilenya initiation. Evaluate the fundus, including the macula in patients reporting visual disturbances. Perform ophthalmological evaluation prior to initiating therapy and periodically thereafter in patients with diabetes mellitus or a history of uveitis. Discontinue Gilenya if a patient develops macular oedema. *Liver function:* Do not use Gilenya in patients with severe pre-existing hepatic injury (Child-Pugh class C). Delay Gilenya initiation in patients with active viral hepatitis until resolution. Recent transaminase and bilirubin levels should be available before initiation of Gilenya. Monitor liver transaminases at months 1, 3, 6, 9 and 12 and periodically thereafter. Institute more frequent monitoring if transaminases rise above 5 times the ULN, including serum bilirubin and alkaline phosphatase (ALP) measurement. Stop Gilenya treatment with repeated confirmation of liver transaminases above 5 times the ULN and only re-commence once liver transaminase values have normalised. Patients with symptoms of hepatic dysfunction should have liver enzymes checked and discontinue Gilenya if significant liver injury is confirmed. Resume Gilenya only if another cause of liver injury is determined and if the benefits of therapy outweigh the risks. Exercise caution with Gilenya use in patients with a history of significant liver disease. *Serological testing:* Peripheral blood lymphocyte counts cannot be utilised to evaluate the lymphocyte subset status of a patient treated with Gilenya. Laboratory tests involving the use of circulating mononuclear cells require larger blood volumes due to reduction in the number of circulating lymphocytes. *Blood pressure effects:* Gilenya can cause a mild increase in blood pressure. Monitor blood pressure regularly during Gilenya treatment. *Respiratory effects:* Use Gilenya with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease due to minor reductions in values for forced expiratory volume (FEV₁) and diffusion capacity for carbon monoxide (DLCO). *Prior immunosuppressant treatment:* No washout is necessary when switching patients from interferon or glatiramer acetate to Gilenya assuming any immune effects (e.g. neutropenia) have resolved. Exercise caution when switching patients from natalizumab to Gilenya owing to the long half life of natalizumab and concomitant immune effects. *Stopping therapy:* Gilenya is cleared from the circulation in 6 weeks. Caution is indicated with the use of immunosuppressants soon after the

discontinuation of Gilenya due to possible additive effects on the immune system.

Interactions: Anti-neoplastic, immunosuppressive or immune-modulating therapies should not be co-administered due to the risk of additive immune system effects. Exercise caution when switching patients from long-acting therapies with immune effects, e.g. natalizumab or mitoxantrone. No increased rate of infection was seen with concomitant treatment of relapses with a short course of corticosteroids. Vaccination may be less effective during and for up to 2 months after Gilenya treatment. Avoid use of live attenuated vaccines due to infection risk. Due to additive effects on heart rate, Gilenya should not be given to patients receiving beta blockers, or class Ia and III antiarrhythmics, calcium channel blockers, digoxin, anticholinesteratic agents, pilocarpine or other HR lowering substances. Caution is indicated with substances that may inhibit CYP3A4. Co-administration of fingolimod with ketoconazole increases fingolimod exposure. No interaction has been observed with oral contraceptives when co-administered with fingolimod.

Fertility, pregnancy and lactation: There is potential for serious risk to the fetus with Gilenya. A negative pregnancy test is required before initiation of Gilenya. Female patients must use effective contraception during treatment with Gilenya and for 2 months after discontinuation. Discontinue Gilenya if a patient becomes pregnant. Fingolimod is excreted into breast milk. Women receiving Gilenya should not breast feed. Fingolimod is not associated with a risk of reduced fertility.

Undesirable effects: *Very common* (≥ 1/10): Influenza viral infections, headache, cough, diarrhoea, increased alanine transaminase (ALT), back pain. *Common* (≥ 1/100 to < 1/10): herpes viral infections, bronchitis, sinusitis, gastroenteritis, tinea infections, lymphopenia, leucopenia, depression, dizziness, paraesthesia, migraine, blurred vision, eye pain, bradycardia, atrioventricular block, hypertension, dyspnoea, eczema, alopecia, pruritus, asthenia, increased gamma-glutamyltransferase (GGT), increased hepatic enzymes, abnormal liver function test, increased blood triglycerides, decreased weight. *Uncommon* (≥ 1/1,000 to < 1/100): pneumonia, macular oedema, decreased neutrophil count. Rarely, reports of lymphoma, posterior reversible encephalopathy syndrome, peripheral arterial occlusive disease.

Packs and price: Perforated unit dose blister packs containing 7 x 0.5 mg hard capsules: £367.50. Blister packs containing 28 x 0.5 mg hard capsules: £1470.

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Marketing Authorisation Holder: Novartis Europharm Ltd, Wimblehurst Rd, Horsham, W Sussex, RH12 5AB, UK.

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Adverse events should also be reported to
Novartis (01276) 698370 medinfo.uk@novartis.com

Magstim Neuroenhancement Conference and Workshop 2013

Conference details: 4-5 May 2013. Oxford, UK. **Reviewed by:** Dr Nick Davis. Postdoctoral Research Officer, School of Psychology, Bangor University.



The seventh annual meeting of this series of conferences on brain stimulation was held in Oxford's imposing Examination Schools. The meeting place is only a short walk from the home of Thomas Willis, who in the mid seventeenth century coined the term 'neurology' and produced the first functional anatomical atlas of the brain. Willis' house should be a site of pilgrimage for delegates at this meeting.

The organising committee for this meeting was the same as that for the previous meeting (see ACNR vol. 12 issue 3, p28): Prof. Vincent Walsh (UCL), Dr Charlotte Stagg (Oxford) and Dr Sven Bestmann (UCL). As before the meeting was sponsored by Magstim, manufacturers of devices for non-invasive brain stimulation (<http://magstim.com/>), but the scientific committee was given complete independence in organising the topics and the speakers. The two main techniques of brain stimulation were represented: transcranial magnetic and current stimulation (TMS, tCS). In addition a series of workshops gave participants hands-on experience with the equipment and techniques.

Day 1

The meeting opened with a session on "Integrating methods in cognition". Antonio Strafella (Toronto) demonstrated the promise of combining TMS with positron emission tomography (PET) to understand dopamine transmission in cognitive circuits. His and others' work shows how PET can be used to study stimulation-related dopamine dynamics in the striatum in healthy cognition and in Parkinson's disease. The second talk, from Marom Bikson (City University of New York),

addressed an important topic in brain stimulation: how to understand the effect of stimulation on the brain. Bikson uses finite element modelling to estimate the electric field on the brain surface during tCS. With this technique he and others have designed new electrode montages for focusing tCS, and have studied individual differences in brain anatomy and response to stimulation; with these advances there is hope for individualised targeting and dosing of tCS.

Simone Rossi (Siena) touched on a recent debate in the brain imaging community: how can fMRI and related techniques inform cognitive neuroscience? One solution is to use brain stimulation to explore the causal role of brain areas that appear to be active during scanning. Rossi and colleagues have done this in studying different models of human memory. Alex Sack (Maastricht) continued the theme of combining brain stimulation with imaging techniques, this time in the study of visual perception and cognition.

The second session dealt with "Clinical applications and depression", a topic of particular relevance since at present the only disorder for which brain stimulation is approved as a treatment in the USA is depres-



To list your event in this diary, email brief details to Rachael Hansford at Rachael@acnr.co.uk by 6th Aug, 2013

July

Human Brain Anatomy
15-17 July, 2013; London, UK
Book online at www.neurocourses.com

August

EPFL SV- Life Science Symposium: Motor control
– from neural circuits and diseases to neuroprosthetics
28-30, August 2013; Lausanne, Switzerland
T. +41 21 693 96 95,
E. egizia.carbone@epfl.ch
<http://lss2013.epfl.ch/index.php>

September

NSpine 2013: The UK's Most Comprehensive Spine Course
5-7 September 2013; Nottingham, UK
T. 0800 0 43 20 60, E. info@nspine.co.uk
www.nspine.co.uk

BioDynamics 2013
– Where Biology, Medicine and Mathematics meet
11-13 September, 2013; Bristol, UK
T. +44 (0)20 8977 7997, E. biodynamics@conferencecollective.co.uk

35th Edinburgh Clinical Neurology Course
16-17 September, 2013; Edinburgh, UK
Further information from:
www.dcn.ed.ac.uk/dcn/research/training.asp
or E. Judi.Clarke@ed.ac.uk

Ion Channels in Health and Disease:
To celebrate the 50th anniversary of the award of the Nobel Prize to Alan Hodgkin and Andrew Huxley
16-17 September, 2013; Cambridge, UK
E. dg248@cam.ac.uk
www.neuroscience.cam.ac.uk

The Children's Trust's Open Day for Professionals
19 September, 2013; Tadworth, UK
Book free online at www.thechildrenstrust.org.uk/opendays
T. 01737 365890, E. opendays@thechildrenstrust.org.uk

Specialist Rehabilitation Medicine Course
19th and 20th September, 2013; Derby, UK
Karen Kirkland, Course Administrator,
T. 01332 724842, E. karen.kirkland@nottingham.ac.uk

XXI World Congress of Neurology
21-26 September, 2012; Vienna, Austria
T. +41 22 9080488, E. Dnuriel@kenes.com www2.kenes.com/wcn

October

3rd World Parkinson Congress
1-4 October, 2013; Montreal, Canada
T. (+001) 800.457.6676, E. info@worldpdcongress.org
www.worldpdcongress.org

November

Nurses' Training Day: Chiari Malformation and Syringomyelia
7 November, 2013; Sheffield, UK
T. 01964 535 448 or 07976 400 881,
E. info@britishsyringomyelia-chiarisociety.org

The United Kingdom Acquired Brain Injury Forum 5th Annual Conference
21 November, 2013; London, UK
T. 0845 6080788, E. info@ukabif.org.uk
www.ukabif.org.uk

West of England Seminars in Advanced Neurology (WESAN)
21-22 November, 2013; Exeter, UK
Programme and booking online at
<http://www.aquaconferencemanagement.co.uk/wesan/>
2013-programme
E. barbara@aquavenuesolutions.com

RAaE 2013
25 November, 2013; Coventry, UK
www.raate.org.uk

December

24th International Symposium on ALS/MND
6-8 December, Atahotel Quark Milan, Italy
E. symposium@mndassociation.org
T. 01604 250505

The Encephalitis Society Professional Seminar
2 December, 2013; London, UK
Free entry for our Professional Members,
for more information E. admin@encephalitis.info
T. 01653 692585.

BNPA December Teaching weekend
13-15 December, 2013; Oxford, UK
T. 020 8878 0573,
E. admin@bnpa.org.uk or jashmenall@yahoo.com

sion. The first speaker, Richard Carson (Trinity College Dublin), addressed the seeming heterogeneity in individual responses to brain stimulation. While differences in brain anatomy are known to affect efficacy (as Marom Bikson had discussed earlier), Carson focused on genotypic differences, in particular different forms of the gene for the precursor protein for brain-derived neurotrophic factor (pro-BDNF), which is known to be involved in short- and long-term plasticity in brain function. This will have important implications for determining who will respond most favourably to brain stimulation as an intervention. The next two speakers, Linda Carpenter (Brown) and Klaus Ebmeier (Oxford), both dealt with TMS as a treatment for depression. Two major trials in the USA, NeuroStar and OPTTMS, are generating important knowledge about dose and efficacy for TMS treatment of depression, and are showing promising results.

The day concluded with a poster session, in which exciting new results were presented by the large number of junior researchers who attended the meeting. Later that evening a dinner was held in the beautiful old hall of Wadham College, at tables formerly frequented by generations of scientific pioneers.

Day 2

The second day started with a session entitled "Cognition and enhancements", which promised much excitement. Nor were we disappointed: the first speaker, Roi Cohen Kadosh (Oxford) presented work on improving mathematical abilities

through the use of transcranial random noise stimulation (tRNS). Although Cohen Kadosh acknowledges that his studies are based on small numbers of participants, nevertheless these early results show highly promising improvements in numerical reasoning with seemingly no side-effects. These improvements were particularly evident in people with lower abilities at the start of the trial, which implies the possibility of negating any disadvantages experienced by people entering education at a lower level of attainment.

Lorella Batelli (Harvard) then discussed enhancing perceptual functions in people with damaged brain tissue. Improving perception also helps us to understand healthy perceptual processing. In particular Batelli highlighted the so-called "when" pathway in the brain, that supports temporal judgements. The third speaker of this session was Marinella Cappeletti (UCL) who talked about the effect of ageing on efficacy of brain stimulation. Since many clinical applications of brain stimulation involve disorders associated with older age, such as stroke or Parkinson's disease, it is important to know how the older brain responds to stimulation. Using a simple numerosity judgement task, Cappeletti showed that people improved when given tRNS. However when the participants were tested on an untrained but related task, such as temporal judgement, younger participants in the tRNS group improved in these tasks but older participants showed worse performance. This is an important consideration in

using brain stimulation as a treatment.

The final session of the meeting was a chance to recognise outstanding achievements. The Magstim Senior Investigator Prize was awarded to Salvatore Aglioti (Rome) for his study of corticospinal excitability during action observation in experts and non-experts. The Magstim Young Investigator Prize was won by Matteo Fuerra (Siena) for studying transcranial alternating current stimulation (tACS). Finally James Dowsett (Oldenburg) won the Magstim Poster Prize with work on the instantaneous effects of tACS on cortical excitability.

Conclusion

Once again the Magstim conference has shown itself to be the premiere annual meeting for brain stimulation research. The organisers balanced the most exciting developments in technical, scientific and clinical domains to produce a programme that was exciting, educational and, to risk a pun, stimulating. ♦

To register your interest in next year's event
Email: joseph.durrant@magstim.com

Take home messages:

- The promise of TMS for treating neurological disorders is being tested in two major clinical trials.
- Early studies have hinted at the possibility of tRNS to substantially enhance cognition, especially in people who start at a lower level of ability.
- Combining brain stimulation with brain imaging has led to exciting new perspectives in cognitive neuroscience.

European Stroke Conference (ESC) 2013

Conference details: 29-31 May, 2013, London, UK. **Reviewed by:** Josef Alawneh, Specialist Registrar in Neurology, Addenbrooke's Hospital, Cambridge.

The European Stroke Conference was held this year in the ExCel Exhibition centre in London on the 29-31 of May. It was attended by more than 4000 participants, and included more than 1000 posters in addition to the multiple symposia, oral sessions and lectures. The venue was excellent and the atmosphere relaxing, friendly and very educational.

During the first day the JJ Wepfer award was presented to both W Hacke and H-C Diener, and both gave informative lectures not only about their well-known achievements but also the mistakes they made and lessons learned over the years (particularly Dr Diener).

Results of several trials were presented during those three days, and there were several learning points. We learned, first, that intensive blood pressure reduction in acute cerebral haemorrhage was safe, but this did not significantly improve functional outcome (INTERACT II). On the same topic, surgery for lobar haemorrhage did not improve overall functional outcome; but some subgroup analyses were promising and I suspect the question of who would benefit from surgery remains open

(STICH II). In acute ischaemic stroke, Chinese traditional medicine could not stand the test of RCTs and Neuroaid failed to show any benefit (CHIMES); albumin failed as well despite previous promises (ALIAS), while rtPA continued to show long term benefit at 18 months in the IST3 trial.

In lacunar strokes, aggressive blood pressure treatment (Systolic pressure (sys) <130) compared to standard blood pressure treatment (Sys <149) did not significantly reduce stroke recurrence (SPS3). Percutaneous PFO closure after a stroke, at one moment, did not reduce recurrent events (PC Trial) but later it did (RESPECT) and thus who benefits from PFO closure after stroke is still uncertain. The Germans did new things again; they showed us that you can provide thrombolysis in an ambulance, with a neurologist on board and a CT scanner, if you lived in Berlin; and onset to rtPA time can come down from 77min to 52 min.

Disability and maintaining vessel patency after stenting symptomatic carotid stenosis is similar to carotid endarterectomy on long term follow up beyond the peri-operative stage

(ICSS, EVA3S). Treat unruptured asymptomatic AVMs conservatively; ARUBA was prematurely stopped as intervention of any kind was associated with significantly higher stroke and death rates. Another study which was stopped prematurely but for different reasons was the NEST 3 trial investigating transcranial laser therapy in acute stroke; this was stopped due to fatality and we learned how funding suddenly disappeared and investigators were left alone to close the study. Another important finding was that intermittent pneumatic compression is useful in reducing proximal DVT after stroke (CLOTS 3).

There is always a controversial topic; this time we learned that hemispherectomy significantly reduces death and severe disability in malignant MCA infarct also in patients above 60 years old (DESTINY II); this certainly will take us to uncharted territories. A final learning point, relevant to UK clinicians, is that alteplase is safe in patients on warfarin with INR <1.7.

At the closing ceremony the ESO flag was handed to the French organisers from Nice and they promised it will be very nice. See you there... ♦

4th UK-Dutch Rehabilitation Meeting

Conference details: 18-19 April 2013, Harrogate, UK. *Reviewed by:* Dr Lenyalo King, Rehabilitation Registrar, Poole Hospital.

The 4th joint British Society of Rehabilitation Medicine (BSRM) and the Dutch equivalent the Nederland's Vereniging Van Revalidatieartsen (VRA) Meeting was held in the pretty Spa Town of Harrogate in North Yorkshire, UK on 18th & 19th April, 2013 and attracted 252 delegates, with our Dutch colleagues making up just over half of the total. Thirteen posters were on exhibition.

The first day began with a pre conference BSRM/VRA amputee rehabilitation special interest group meeting in the morning. The meeting opened with a plenary session on pain, chaired by Professor Rob Smeets. Pain is prevalent in the neuro-rehabilitation patient population with reports ranging from 50% to 75% in those with Multiple Sclerosis, 32% following severe traumatic brain injury and up to 75% following mild traumatic brain injury. I certainly have found that there are challenges in formulating a pain diagnosis in individuals with traumatic brain injury as well as in those with complex neurological conditions.

Pain in adolescence was considered in a presentation by Dr Jeanine Verbunt. She outlined that although a broad array of medical diagnoses are involved in adolescent pain conditions, a specific medical disease is identified in only 10-30%. Unexplained musculoskeletal pain is not always as self limiting as assumed: persistent rates of pain up to 30-64% after 4 years have been reported. In about 40 % the pain would have a disabling impact on daily functioning. As rehabilitation practitioners we need to consider the current available evidence – which remains much less than that which addresses adult pain – on the underlying mechanisms for disability in adolescent pain.

Dr Frances Cole presented a range of approaches and tool options for individuals living with pain. These ranged from engaging patients in self assessment of their own health outcomes to changing unhelpful pain related behaviours. Such tools help in developing a participative partnership with health and social care practitioners and enhancing patient self efficacy.

There were three parallel sessions in the late afternoon, one which showcased free paper abstracts, another that looked at falls after stroke – underlying mechanisms and novel options for intervention, and a third session on hereditary spastic paraparesis.

Both the Dutch and UK rehabilitation trainees held a trainee meeting at the end of the first day. Much of the meeting was an exchange of experiences with our Dutch colleagues, with a trainee from each country giving an outline as to what training in rehabilitation involves. Dr Margaret Phillips gave a short talk on rehabilitation research in the UK. There appears to be

regional variation in both opportunities and support for trainees to be involved in research, but it was encouraging to see the enthusiasm from trainees for getting involved in research. We were encouraged to do the European board examination by Prof Anthony Ward. The UK trainees historically have a very high success rate in passing this exam, so no pressure for current trainees then!

The last day of the meeting opened with a plenary session on Stroke with Professor Lynne Turner-Stokes chairing. Some exciting developments in understanding upper limb recovery at an early stage post stroke were presented by Professor Gert Kwakkel, from the department of rehabilitation medicine in the Netherlands, VU University Medical Centre in Amsterdam. There is growing evidence that the natural pattern of functional recovery can be modified and improved upon by intensive task oriented practice, preferably initiated within 6 months following a stroke. The impact of practice on the intrinsic and spontaneous learning mechanisms of neurological recovery remains poorly understood. A hypothetical phenomenological model for understanding skill reacquisition post stroke was presented.

It is well known that balance and gait capacities may considerably improve after supratentorial stroke and that this recovery may be facilitated by intensive task oriented practice. Studies that have sought to improve our understanding of the underlying mechanisms of functional recovery post stroke have focused mainly on kinematic, kinetic and electromyographic changes during the sub acute phase post stroke. Kinetics is studying the motion of objects (particles/rigid bodies etc.) and the forces that cause those motions. Kinematics is studying the motion of objects (particles/rigid bodies etc.) but not considering the forces, just examining the motion itself.

These studies have consistently highlighted the role of compensatory mechanisms and relatively little evidence for true restoration of original motor function. Rehabilitation efforts should therefore focus on optimal use of compensatory mechanisms to promote functional independence. Soft tissue surgery such as percutaneous Achilles tendon lengthening is one such intervention that aims to optimise compensatory motor function. As rehabilitation clinicians, we should fully assess our patients and consider all possible interventions which could help their rehabilitation process.

Professor Helen Rodgers outlined the structure of the UK National Institute for Health Research, and shared experiences from the Stroke Research Network in particular. The website on the NIHR was shown and it was encouraging how easy it was to navigate and

locate information.

The BSRM National Training Programme was launched; there are 51 talks to be used at regional training events with the aim to have consistent teaching among trainees across different deaneries. This is currently being piloted in Newcastle, London and Wessex deaneries. The national training programme is to be reviewed every 2-3 years.

There were parallel symposia that ran concurrently in the late afternoon, making for difficult choices on which to attend.

The provision of early and specialist rehabilitation following major trauma is a relatively new concept in the UK. During the setup of trauma networks in England, the National Director for trauma recognised that earlier access to rehabilitation after trauma was necessary to improve the poor outcomes after major complex trauma, reported in the UK. To try and achieve better outcomes, the concept of a rehabilitation prescription was introduced in November 2011 by the Department of Health. Several forms of the prescription were created by various groups across the country, following on some work that was subsequently done, some more recent formats for rehabilitation prescriptions were described and the opportunities as well as challenges to their use were discussed. We had the opportunity to hear the Netherlands experience, from Dr Bea Hemmen, of Maastricht University Medical Centre, Maastricht. She discussed innovative rehabilitation for multi-trauma patients called the 'supported fast track rehabilitation service' - a scheme which ensured the timely delivery of rehabilitation measures with the demonstrated subsequent improvement of clinical measures.

In their transition to adulthood, young people with childhood onset disabilities such as cerebral palsy, spina bifida and neuromuscular diseases may experience problems in regulating their own life and taking responsibility for their health. At adult age they experience restrictions in participation. At present in both the UK and the Netherlands, networks of healthcare professionals and researchers are aiming to innovate transitional care for emerging adults with childhood onset disabilities (16-25 years of age). Professor Allan Colver, Donald Court Chair of community health gave an exciting presentation on the changes that occur in the adolescent brain. These include neurotransmitters (adolescence is an age where the brain shows peak sensitivity to dopamine) and differing rates of development of different areas of the brain. He concluded that pubertal hormones and brain development are still not fully understood. Many challenges to transition were discussed and ongoing current research at Newcastle

University was outlined, which concentrated on the young person and what is important to them for successful transition. Dr Jetty van Meeteren and Dr Marij Roebroek gave a presentation on the approaches to transitional care from the Dutch transition network. They looked at the age-appropriate interventions focusing on autonomy in life areas.

The day concluded with a lively and exciting debate chaired by Dr Vera Neumann. It appro-

priately debated the issue: 'This house proposes that, in people with long-term neurological conditions, we should promote independence and therefore avoid routine review by rehabilitation medicine services'. Dr Kate Sansam and Dr Imelda argued for the case, and were well balanced by Dr Ruth Kent and Dr Jetty van Meeteren against. I am reliably informed that a show of hands indicated a 50:50 split for the debate, which reflects my feelings on the topic.

This was a very successful and informative meeting with some very lively debate. It will result in several changes to my practice, and has enhanced my enthusiasm for what I consider to be an exciting and challenging speciality. I will be looking forward to the next meeting which is planned for December 2013, in London, the day after the Royal College of Physicians conference on vegetative and minimally conscious states. ♦

Annual Clinical Neurosciences President's Prize Meeting

Conference details: 7 February, 2013, Royal Society of Medicine, London, UK. **Reviewed by:** Dr Andrew Nanapragasam, Foundation Trainee, St. Peter's Hospital, Surrey, UK.

The annual Clinical Neurosciences President's Prize Meeting provides a forum for trainees to discuss their shared interest in neurology, neurosurgery, or neuroradiology. The evening comprised a series of five lectures given by trainee doctors either on their research or on interesting neurological cases. A wide range of subject matter was covered, with topics ranging from research into intra-operative nerve conduction monitoring to case presentations on post-stroke psychosis. Whatever your medical background, whether accomplished neurologist or junior trainee, there was something to pique your interest.

The session began with a brief, light-hearted introduction from Mr Michael Powell, consultant neurosurgeon and the president of the RSM's Clinical Neurosciences Section. He enthusiastically praised the five selected speakers, and offered only one piece of advice: to keep to time!

The evening's highlight was the lecture given by Dr Michael Devine of Imperial College London. He began by outlining the symptoms experienced by three different patients following a stroke. The patients had a variety of the expected neurological deficits, from hemiparesis to tangential speech. However, they all had one unusual symptom in common: psychiatric disturbance. The psychiatric disturbance manifested itself as persecutory delusions, hallucinations, or Fregoli syndrome (delusional misidentification of people). Analysis of the CT imaging for these patients showed that the right inferior frontal gyrus was involved in all patients. However, many patients with a stroke of the right inferior frontal gyrus do not experience psychiatric disturbance, suggesting that there may be an element of behavioural susceptibility. Dr Devine was a well-informed and amicable speaker, and a deserved recipient of the 2013 Clinical Neurosciences President's Prize.

Some of the speakers were caught out by their enthusiasm for their selected topics. Their desire to be comprehensive clashed with the chair's desire for accurate time-keeping! Despite this, all five speakers were an excellent advertisement for UK neurology/neurosurgery trainees, and an inspiration for those seeking a career in these exciting fields. To close the event, Sir Graham Teasdale, the renowned professor of neurosurgery and inventor of the Glasgow Coma Scale (GCS), gave a charming presentation on life in research.

In previous years, this event has failed to attract large audiences, and that continues to be the case. The 2013 annual meeting was attended by a mere 30 doctors, almost all of whom had some professional or personal connection to one of the five speakers. This thoroughly enjoyable and thought-provoking event deserves a larger audience. Hopefully, in years to come more trainee physicians will attend. ♦

PREVIEW: The Practical Cognition Course

Conference details: 10-11 November, 2013, Newcastle, UK.

The practical cognition course, now in its sixth year will take place at the Research Beehive, Newcastle University on Thursday and Friday 10-11th October 2013. This small but popular course is organised by Tim Griffiths, professor of cognitive neurology at Newcastle University and Chris Butler, clinical lecturer in medical neurology at the University of Oxford.

The course is designed for consultants and trainees in neurology, psychiatry, neuropsychology and rehabilitation medicine who want to develop their practical expertise in cognitive assessment and relate this to clinically relevant neuroscience. Day one starts with a practical introductory session to cognitive assessment followed by four sessions of case presentations discussing the assessment, diagnosis and management of common cognitive syndromes.

The course begins and ends with the patient. Case presentations will feature video material illustrating disorders that clinicians may encounter in daily practice. Each session will also include a talk from an invited expert, who will provide a framework for understanding the clinically relevant neuroscience.

In order to make it as relevant and useful as possible the programme changes each year and this time will include frontal lobe disorders, traumatic brain injury, functional cognitive disorders and speech disorders. This year's speakers include Chris Kipps (University Hospital Southampton), Stuart Anderson (Brighton and Sussex University Hospitals), Tom Kelly (Newcastle General Hospital), Andrew Larner (Walton Centre Liverpool), Jon Stone (University of Edinburgh) and Jason Warren (University College London Hospitals).

The course is sponsored by the Guarantors of Brain, and accredited for CME points with the Royal College of Physicians. An early bird rate of \$200 is available until the 6th September, where after it will rise to \$250. Included in this are lunch and refreshments on both days and the course meal on Thursday evening at Six restaurant which sits on the top floor of the Baltic centre for contemporary art. Delegates can take this opportunity to enjoy views of the beautiful river Tyne and Newcastle skyline – weather permitting and discuss topics in a relaxed atmosphere. ♦

To register please visit:
<http://webstore.ncl.ac.uk>.
For any enquiries please contact
Ann Fitchett on +44 (0)191 222 8320 or by
email: ann.fitchett@ncl.ac.uk. We look forward to
welcoming you to the North East!

Parkin Puzzles

Parkin mutations should be considered in early-onset parkinsonism. They are the most common cause of autosomal recessive familial PD cases, and also account for 15% of sporadic cases in the under-45 age group. The parkin gene plays an important role in mitochondrial quality control and the ubiquitin proteasome system.

Doherty and colleagues describe the clinicopathological features of 5 unrelated patients with parkin disease and compared them with 5 pathologically confirmed PD cases and 4 control subjects. The parkin and PD patients were matched for both disease duration and age of death.

Consistent with previous reports, the presenting features of the parkin disease patients were hand or leg tremor, often associated with dystonia and gait abnormalities. The patients' disease followed a slowly progressive course and responded well to levodopa, but all developed motor fluctuations. Perhaps reassuringly for patients with this mutation, there was a dearth of cognitive and neuropsychiatric features in these cases, despite the long disease duration (range 27-50 years). The authors speculate that this may be explained by the sparing of the nucleus basalis of Meynert and the cortex.

As well as being phenotypically distinct from the PD cases, parkin cases were pathologically defined by relative preservation of the dorsal tier of the substantia nigra with sparse or no Lewy bodies. This is in contrast with the brain bank studies of typical clinical PD which invariably predicts Lewy pathology. As larger pathological studies of genetic PD patients are done in future, they may be expected to yield further insights into the complex cellular mechanisms of genetic Parkinson's disease, with the hope that this will eventually translate into therapeutic advancements. - **GC**

Doherty KM, Silveira-Moriyama L, Parkkinen L et al.

Parkin disease: a clinicopathologic entity?
JAMA Neurol. 2013 May 1;70(5):571-9
doi: 10.1001/jamaneurol.2013.172

Riding the CREST of the ALS genetic wave

The Gitler lab have just identified 25 new genes potentially linked with ALS. The technique of exome sequencing was at the heart of their approach - a high throughput technology focusing on the exons alone, looking for mutations that effectively alter the amino acid sequence of genes. By looking at apparently sporadic cases in which both parents were still alive and from whom DNA was also available they looked specifically for genetic variations that were present in the affected individuals, but not in the parents i.e. de novo mutations. The discovery of 25 mutations in 47 cases is striking, all the more

so because of the concentration of genes involved in chromatin regulation. One gene, SS18L1 (or CREST), is of particular note as the team did indeed find a further mutation on screening a cohort of 62 familial ALS index cases. Determining the wider significance of this and other variations requires large scale screening in ALS cohorts. It is also important to note that the cases in the trios studied were all remarkably young (mean age less than 40y), which is somewhat atypical, but might suggest that strong genetic factors may underlie their disease. CREST is implicated in neurite outgrowth and in vitro studies suggested that the mutant forms of CREST impaired activity dependent dendritic outgrowth. However, the functional data the team present leaves out some details, including the reasoning for their use of a mouse construct rather than a human construct for the truncation mutation, and the apparent use of a human construct to model the missense mutation. Furthermore, their dendritic images may suggest dendritic degeneration rather than aberrant branching (which is still, nevertheless, interesting). More interesting is the interaction they seem to find between CREST and FUS, a major ALS gene that causes a predominantly lower motor neuron phenotype. We hope to hear further developments on this front soon. - **JS**

Chesi et al.

Exome sequencing to identify de novo mutations in sporadic ALS trios.

NATURE NEUROSCIENCE

16, 851-855 (2013)

doi:10.1038/nn.3412

A nose solution?

For many years injectable therapies were the main stay for the treatment of relapsing remitting multiple sclerosis (MS). More recently novel oral and intravenous therapies have become available. This animal study by Duchi et al. investigated the efficacy of nasal drug administration as a new, non-invasive treatment delivery strategy in MS. Mice with experimental autoimmune encephalomyelitis (EAE) were administered Glatiramer acetate (GA), Cannabidiol (CBD) or prednisolone by different routes. Specifically, subcutaneous and nasal administration, with and without the nasal delivery system (NDS), were compared. Differences between groups were measured using clinical scores and levels of inflammatory cytokine expression. Clinical scoring was carried out twice daily for 26 days following EAE immunisation by two different observers. Prednisolone was administered on the same day as disease inoculation (preventative) while the other treatments were introduced on the day the first clinical sign appeared (acute). After 26 days, there was a significant reduction (39%) in clinical disease signs following nasal administration of GA via the NDS, as compared to the subcutaneous injection (6.5%) of the same drug and dose (6.7mg/kg/day). This suggested high efficacy of the NDS in the mouse model.

There was also suppressed expression of both cytokines tested (IL-6 and TNF-alpha) in the cerebellar tissue of the GA NDS group. Nasal GA via the NDS significantly suppressed the histopathological outcome of disease compared to untreated (control) EAE mice.

The same dose of GA given nasally as an aqueous solution was ineffective in reducing clinical disease signs or suppressing cytokine expression in EAE mice and caused more inflammation of the nasal mucosa than GA administered via the NDS. The combination of GA and CBD via the NDS showed increased suppression of clinical signs when compared to either drug alone, indicating that the addition of an anti-inflammatory drug, such as CBD, could improve treatment. This combination also augmented neuronal proliferation in the hippocampus compared to untreated EAE mice. Prednisolone administered via the NDS showed a significant reduction (79.6%) in clinical scores while the same dose given subcutaneously had no effect (0% reduction). Prednisolone via the NDS also appeared to delay the development of disease, as the first clinical signs in this group appeared on day 15 compared to day 10 in the untreated mice. Lower inflammatory cytokine mRNA expression and improved histological disease manifestations were also noted in this group.

While this is a preliminary study, it offers support for the efficacy of the nasal delivery system in the administration of Glatiramer acetate, Cannabidiol and prednisolone, which may in the future translate to use in humans for the treatment of MS. There are many possible benefits of nasal drug administration including; improved compliance, non-invasiveness, and use in needle-phobic or dysphagic patients. The use of appropriate intranasal administration techniques (mice in the study were lightly anaesthetised to avoid sneezing!) and the effect of repetitive/long-term dosing on the nasal mucosa are areas requiring additional consideration in the future. Further research is warranted to continue to explore this alternative treatment strategy. - **HB**

Duchi S, Ovadia H and Touitou E.

Nasal administration of drugs as a new non-invasive strategy for efficient treatment of multiple sclerosis.

J NEUROIMMUNOL 2013; 258:32-40.

doi: 10.1016/j.jneuroim.2013.02.013.

Panel of reviewers

GC – Gemma Cummins

Van Geest Centre for Brain Repair,
Cambridge University.

JS – Jemeen Sreedharan

Dept of Neurobiology/
Neurology, University of Massachusetts
Medical School, Worcester, US.

HB - Heidi Beadnall

Royal Prince Alfred Hospital/
Brain Mind and Research Institute,
Sydney, Australia

Fujifilm introduce Synapse Mobility

Fujifilm is now providing Radiologists and referring physicians with on-the-go access to images and reports stored in Synapse PACS.

Synapse Mobility is a zero footprint application that enables access to

Fujifilm's Synapse PACS from hand-held mobile devices, as well as Macintosh or Windows-based PCs. Using the web browser or mobile device of their choice, radiologists and referring physicians can now review patient images and reports, increasing accessibility to patient information to optimise workflow.

Synapse Mobility also includes a collaboration feature designed to foster greater communication between professionals by allowing clinicians to consult in real-time. The collaboration feature enables physicians to bring information to their patients and ultimately aide in consultation during clinical situations such as the communication between physicians, referring clinicians and patients, using the web browser or mobile device of their choice.

A differentiator of Synapse Mobility is its ability to display high quality, interactive 3D images in any platform accessed, including iPads®, iPhones® and Android™ Smartphones. This interactive feature enables images to be manipulated using the zoom, window and level, and MIP/MPR within the application, just as the physician would do at a clinical workstation.

Synapse Mobility is browser independent and scalable, providing facilities with virtually an unlimited number of users.

For more information see <http://www.fujifilm.eu/uk/products/medical-systems/>



First licenced oral liquid suspension of clobazam

Martindale Pharma has launched Tapclob 5mg/5ml and Tapclob 10mg/5ml Oral Suspension, the first licensed oral liquid suspension version of clobazam. Supplies of this widely used and much needed oral liquid version of clobazam are now available to fulfill prescriptions.

Tapclob will be distributed exclusively by Alliance Healthcare Distribution Limited.



Tapclob 5mg/5ml and 10mg/5ml Oral Suspension (clobazam oral suspension) will be used principally as an adjunctive therapy for epilepsy, with the majority of use believed to be in children. It is an off-white oral solution presented in a 150ml glass bottle in two strengths 5mg/5ml and 10mg/5ml to maximise flexibility of dosing. Tapclob has the same indications as clobazam tablets. This new licensed oral liquid version of clobazam not only allows for better ease of use, especially for paediatrics, but also provides healthcare professionals with a much needed replacement to prescribing expensive, unlicensed 'special' versions of clobazam oral liquid products.

For further information on Tapclob 5mg/5ml and 10mg/5ml Oral Suspension please contact Martindale Pharma on 0800 0287933 or our Medical Information Team on 01708 382145 or via medinfo@martindalepharma.co.uk.

Professor Nick Alderman leads on the expansion of care pathways for patients with acquired brain injury in PiC Brain Injury Services in Essex

The new care pathways for patients with an acquired brain injury will enable patients to step down from a low secure setting to locked rehabilitation and community rehabilitation, whilst being supported by the same clinical team, providing stability and consistency on treatment. The provision of a low secure service will enable the treatment of patients with challenging behaviour to benefit from an intensive rehabilitation programme in a safe and structured environment.

Brain Injury Services were established in 1985 at Grafton Manor, Northampton as the first brain injury rehabilitation hospital in the UK. Brain Injury provision expanded with a 17 bedded unit in Essex, in 1995, building on the expertise at Grafton Manor.

The new care pathways for patients with an acquired brain injury, often accompanied by challenging behaviour and a forensic history are led by leading expert Professor Nick Alderman, and a highly experienced and established full multi-disciplinary team including Psychology, Psychiatry, Occupational Therapy, Speech and Language Therapy, Physiotherapy, Nursing and Rehabilitation Workers

The discharge care pathway now offers an 8 bed low secure unit Rowan Ward with a step down locked rehab unit (8 beds) on site known as Redwood.

With time-lined goals and objectives, patients are supported



to move quickly through the pathway to locked rehabilitation and finally community rehabilitation where they will develop the skills and experience they need to move back home to their families or to an alternative long term placement. BIS has an extensive and proven track record in treating and stabilising patients with challenging behaviour enabling them to fully participate and successfully complete a rehabilitation programme to their optimum potential.

A patient currently placed in BIS Essex said "That's the main thing I get out of it, the incentive to keep going".

The launch of the low secure services and extended pathway comes shortly after the nomination for BIS Essex at the Laing and Buisson awards for their innovation in services following the development of their time-lined patient focused treatment tool.

The provision of a full discharge pathway has been launched by Professor Nick Alderman, Director of Clinical Services who joined BIS in May 2013. Professor Alderman says "The service model is Neurobehavioural Rehabilitation, a specialist approach with proven clinical outcomes using recognised outcome measures such as SASNOS. BIS clinically demonstrates a successful, intensive and specialist rehabilitation programme with a proven discharge pathway to community rehabilitation and successful and sustainable discharge".

Clinical Pocket Reference Neurosciences

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

Selected pages from Clinical Pocket Reference Neurosciences - *third instalment*.

Reviewer's comments:

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

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

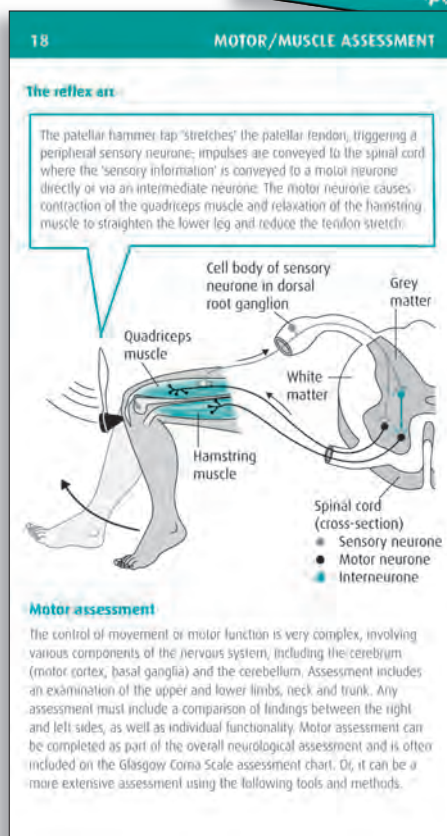
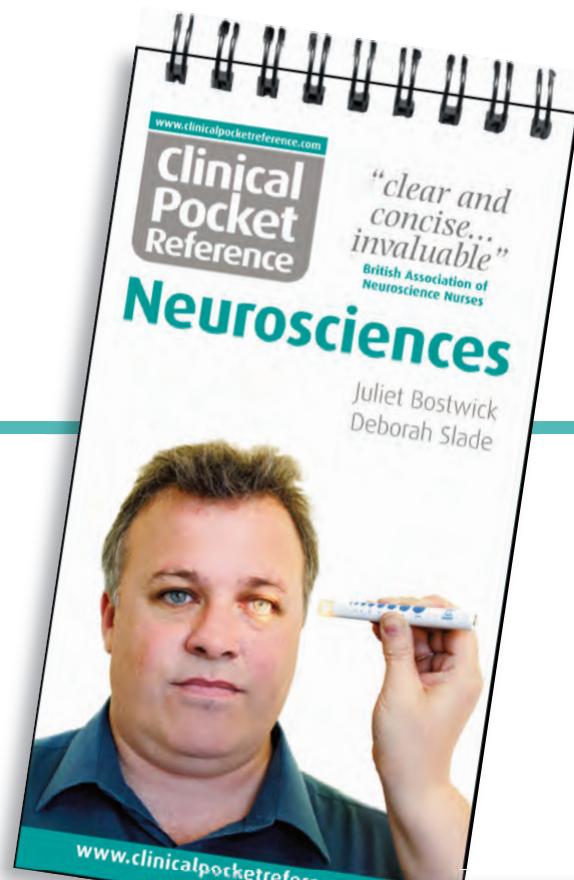
ACNR

This book will be an invaluable resource for nurses and allied healthcare professionals of all backgrounds and levels of experience...

It is clear and concise, pitched at the right level, with good use of images.

British Association of Neuroscience Nurses

ACNR are publishing selected content from **Clinical Pocket Reference: Neurosciences** over current issues... neuroscience nurses will find this a useful aide memoire. Ideal for keeping on the ward or in the pocket as a teaching and reference tool.



Muscle group assessment (agonist and antagonist)	
Component to be assessed	Tool/technique
Size	Observe specific muscles; can measure to compare right and left sides Look for muscle wasting
Tone	Modified Ashworth Scale (see below)
Strength	MRC Scale (see below)
Involuntary movement or tremor	Observe for trembling movements at rest
Gait	Observe position of body parts, posture and steps taken when walking

Modified Ashworth Scale - assessment of muscle tone	
Scale	Description of muscle tone
0	No increase in tone
1	Slight increase in muscle tone. There may be a catch and release when performing passive movement or slight resistance at the end of the normal range of movement for the joint when flexed or extended
2	There is a more noticeable increase in muscle tone during the whole range of motion. Passive movement is still easy
3	Muscle tone is very strong and passive movement difficult
4	The joint is rigid and cannot be moved passively

Medical Research Council (MRC) muscle strength grading scale	
Score	Description
0	There is no visible or palpable movement
1	Minimal movement when the patient moves the muscle on request
2	There is movement in the muscle but the patient cannot overcome gravity (e.g. can move a limb but not lift it off a surface)
3	There is movement against gravity, but not against resistance from the examiner (e.g. can lift limb off surface but not against pressure from examiner)
4	There is movement against gravity and against resistance (can raise limb with moderate pressure from examiner)
5	Full strength (can overcome the force of gravity and resistance applied by examiner)

Sources/bibliography: Bohannon RW, Smith MB (1987) Interrater reliability of a Modified Ashworth Scale of muscle spasticity. *Physical Therapy* 67: 206-7; Medical Research Council (1981) *Aids to the examination of the peripheral nervous system*. Memorandum No 45. London: Her Majesty's Stationery Office; James MA (2007) Use of the Medical Research Council muscle strength grading system in the upper extremity. *Journal of Hand Surgery* 32(2): 154-6.



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