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Advances in Clinical Neuroscience & Rehabilitation

Conference and Society News • Journal Reviews • Diary of Events

Rustam Al-Shahi Saman, Henning Mast, Christian Stapf
Unruptured Arteriovenous Malformations of the Brain

David Baker, Samuel J Jackson
Models of Multiple Sclerosis

Oleh Hornykiewicz
Dopamine, Levodopa and Parkinson's Disease

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References: 1. Neupro Summary of Product Characteristics. **2.** Braun M *et al.* Poster presented at EFNS 2005. **3.** Watts RL *et al.* Poster presented at MDS 2004. Abstract P737.

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What you do on finding an incidental unruptured AVM on scanning is obviously something that causes great concern, both to clinician and patient alike. In the excellent article (and photo) by Rustam Al-Shahi Salman and colleagues, he discusses the evidence (or rather lack of it) for the best way to manage these patients, highlighting the fact that there is a new randomised trial on unruptured brain AVMs called ARUBA. This article explains the possible risks of not treating AVMs in terms of haemorrhage, and how this varies according to location and venous drainage. However, the bottom line seems to be that the behaviour and best treatment of these vascular abnormalities is far from clear - lets hope ARUBA gives us the answer.

That MS is an auto immune disease is not doubted, but how it comes about immunologically remains an area of great debate, as Claire Halliwell shows us in her excellent article on T cells. In this account we are introduced to Th17, a new type of T cell which appears to be regulated in part by Th1 and Th2 cells, and may be important in autoimmune disorders such as MS – a disease for which animal modeling has proven controversial. We are therefore fortunate to have David Baker and Samuel J Jackson (not Samuel L Jackson) to take us through these issues with respect to Experimental Allergic Encephalomyelitis (EAE). Both authors are professing 'EAEologists' and highlight the point that "EAE is not a single model but a number of models that have varying degrees of similarity to MS". A very helpful and informative read.

It is hard to believe that it was only 50 years ago that dopamine was fully recognised as a neurotransmitter in the CNS, and that in 1959/1960 it was discovered to be lacking in patients with Parkinson's disease, by Oleh Hornykiewicz and colleagues. It is therefore an enormous honour to have Professor Hornykiewicz write about this in our series on Living Legends. This vivid account conveys the excitement of the discovery and the reluctance of the established community of the day to fully accept these findings. As with all articles in this series, it is wonderful account that makes one feel very humble.

It is with great pleasure that I announce two new series of articles for the *ACNR* - one on Neurogenetics edited by Tom Warner and the other personal accounts of disease from patients. In the first of the Neurogenetics series, Tom sought to obtain a leading expert to write for us on Hereditary Spastic Paraplegia. After much searching and deliberating, he chose himself – and as a consequence his article, as one would expect, is a beautiful synthesis of a bewildering complex series of conditions. It combines simple clinical advice (e.g. spasticity is typically much greater than weakness in HSP) with up-to-date scientific advances (e.g. the interaction of spastin and atlastin in axonal maintenance)- a great start to what promises to be a terrific series.

In the first of our new series of articles on personal experiences of disease, I am enormously grateful to Claire Rytina (a patient of mine) who eloquently describes the consequences of the herpes simplex encephalitis that struck her back in 2004. This is a truly moving account of how a disease can change your sense of identity, worth and relationships – a theme which is discussed in the book review on Human Traces. The account that Claire relays to us is a remarkable and deeply moving account, which will impact heavily on all those involved in clinical practice.

The most recent ABN case report winner by Matthew Jones and colleagues deals with a unique cause of eosinophilic meningitis in the United Kingdom. The offending organism comes from eating infected snails, who in turn have eaten rat faeces. So beware the next time you see an unusual case of meningitis from one of the areas endemic for rat lungworm!

We also have all of our usual journal, book and conference reports. We hope that you continue to enjoy the *ACNR* and do let us know if there is an area of clinical neuroscience or rehabilitation that we should cover.

Finally on a sad note, many of you will already know that Professor Ian Mcdonald died suddenley on the 13th December 2006. Professor McDonald had been an inspiration to many neurologists worldwide and his loss is great.

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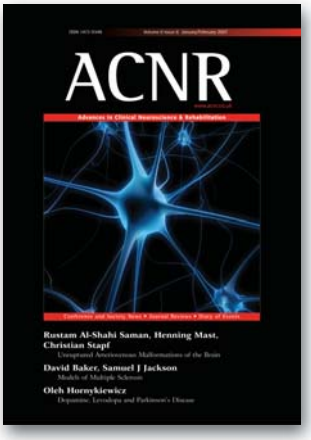

Cover picture of neuron courtesy of Stockxpert.

Contents

January/February 2007

4 Editorial

6 Review Article
Unruptured Arteriovenous Malformations of the Brain
Rustam Al-Shahi Saman, Henning Mast, Christian Stapf

8 Immunology Primer
Immunology News: a New Type of T Cell is Discovered
Claire Helliwell

10 Review Article
Models of Multiple Sclerosis
David Baker, Samuel J Jackson

14 Living Legends
Dopamine, Levodopa and Parkinson's Disease
Oleh Hornykiewicz

NEW

16 Neurogenetics Article
Hereditary Spastic Paraplegia
Tom Warner

NEW

18 Personal Experiences of Neurological Disorders
My Life Post HSA
Claire Rytina

20 Case Report - ABN Winner
Eosinophillic Meningitis Due to Angiostrongylus Cantonensis: First Reported Case
Matthew Jones, Rajiv Mohanraj, Sandip Shaunak

22 Conference News
7th International Congress of Neuroimmunology; 75th Anniversary Celebrations of the Association of British Neurologists; 17th Meeting of the European Neurological Society.

24 Events Diary

25 Courses & Conferences

28 Journal Reviews

30 Book Reviews
Stroke Treatment and Prevention: an Evidence-based Approach; Human Traces.

31 News

Letters to the Editor

Have your say about issues relating to your specialty, or in response to articles which appear in the magazine. Send your news and views to ACNR: Patriciamcdonnell@btinternet.com

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Unruptured Arteriovenous Malformations of the Brain

Unruptured, asymptomatic arteriovenous malformations (AVMs) lurk in the brains of approximately one person in every thousand; their prevalence, based on four studies of magnetic resonance imaging (MRI) of 7,359 people without brain disorders,[1-4] was 0.1 % (95% confidence interval [CI] 0% to 0.2%). Some of these brain AVMs may be discovered if and when they cause intracranial haemorrhage, epileptic seizure(s), headache, or a focal neurological deficit, but many brain AVMs may potentially lie dormant from the cradle to the grave.

The detection of this reservoir of unruptured brain AVMs is likely to depend on the differences in availability, uptake, and indications for brain MRI between countries. Indirect evidence for this comes from the two ongoing population-based studies of the clinical epidemiology of brain AVMs:[5,6] in Scotland 54% of all brain AVMs detected in an incidence study were unruptured at presentation,[5] whereas this proportion was 62% in New York (difference -8%, 95% CI -19% to 4%).[6] The detection rate of unruptured brain AVMs seems set to rise with the increasing appropriate use of brain MRI for investigating epilepsy and stroke, as well as more indiscriminate uses such as 'health check-ups' purchased from private health screening companies.[7]

What's the prognosis for an adult with an unruptured brain AVM?

Only a few published studies are of sufficient quality to provide reliable estimates of the prognosis for unruptured brain AVMs.[8-10] Most cohorts have been small, retrospective, hospital-based, with short incomplete follow-up from an unclear inception point, using unblinded assessment according to bespoke rather than generic outcome measures, without stratification by differences in treatment. Even in high quality studies, the outcome described for unruptured brain AVMs that are not treated is inevitably biased, since a conservative strategy may be adopted either because of the 'untreatability' of the AVM, or due to the patient's burden of disability or co-morbidity.

Nevertheless, some generalisations can be made about the crude first bleed rate from an unruptured brain AVM after diagnosis (Table). The most important elements of brain AVM vascular anatomy ('angioarchitecture') for risk stratification are deep venous drainage (Figure) and location deep within the brain (Table).

An old population-based study found 30-day case fatality after a bleed to be ~18%,[12] which is likely to be less nowadays, and certainly less than the case fatality following non-traumatic intracerebral haemorrhage or aneurysmal subarachnoid haemorrhage.[13] Few have estimated the morbidity due to haemorrhage, but it does seem to vary between studies: by the time of hospital discharge after a haemorrhage, 33% of patients had a modified Rankin score ≥3,[10] and others found this proportion to decrease to ~5% after ~1 year.[14] However, the Toronto AVM study group found that only 45% of adults made a recovery from a haemorrhage without a permanent deficit.[15] Although re-bleed rates do not concern us in this article, it is worth mentioning that they are higher than first bleed rates, and they seem to be particularly high in the first 6-12 months after a first bleed,[9,10] although the magnitude of the re-bleed rate varies between studies.[10,11,16]

Table: First bleed rates from unruptured brain AVMs

Subgroup	*Annual bleed rate*
Crude (overall) first bleed rate[9,11]	*~1%*
Exclusive deep venous drainage[9]	*~2%*
Deep brain location[9]	*~3%*
Exclusive deep venous drainage and deep location[9]	*~8%*
Neither deep location nor deep venous drainage[9]	*~1%*

Should an adult with an unruptured brain AVM be treated?

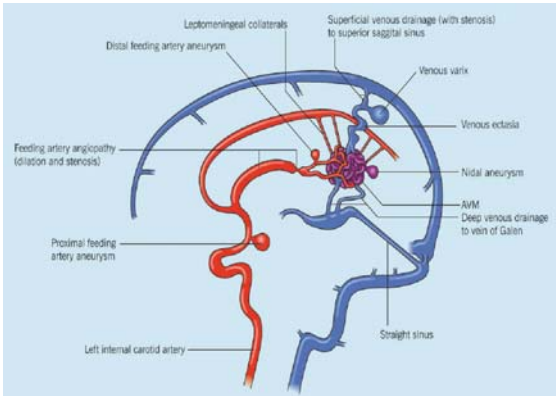
People with brain AVMs are likely to benefit from multidisciplinary management, although there is considerable value from a one-on-one meeting between doctor and patient. A neuroradiologist, neurosurgeon, radiotherapist, and clinical nurse specialist should ideally work with a neurologist with interest and expertise in the assessment and treatment of seizures, headaches and chronic disability. A neurologist also has an important independent role in counselling a patient about the risks and benefits of various management strategies.

In the absence of controlled studies, the decision to treat the brain AVM (with any combination of endovascular embolisation, microsurgical removal, and/or stereotactic radiation therapy) is based on the potential benefit of treatment reducing the future risk of haemorrhage, plus an indirect comparison of the possible risk of intervention against the presumed risk of future death/disability if the brain AVM is left untreated.[17] This decision involves the potentially flawed extrapolation of short-term outcome data to the rest of the patient's presumed life expectancy.[18,19] Recent research – albeit based on observational data at a single tertiary referral centre – leaves many physicians uncertain that treatment does more good than harm:[19,20] interventional treatment of unruptured brain AVMs was associated with a highly significant excess of subsequent haemorrhage and disability at five years in comparison to conservative management. If these findings and the paucity of controlled data aren't enough to support the case for randomisation, further justification is provided by the likely variation in treatment practice by personal conviction, local experience, centre, country, continent, available treatments, and health insurance policy.[13,18,19]

A Randomised trial of Unruptured Brain AVMs (ARUBA)

A potential solution to the clinical dilemma posed by an unruptured brain AVM is randomisation in ARUBA (www.arubastudy.org). ARUBA is investigating whether conservative management is superior to interventional

Figure: The vascular anatomy ('angioarchitecture') of brain AVMs



Rustam Al-Shahi Salman is an honorary consultant neurologist at the Western General Hospital in Edinburgh, where he has been researching the clinical epidemiology of intracranial vascular malformations since 1998, initially as an MRC clinical training fellow, and latterly as an MRC clinician scientist.

Henning Mast is a professor of stroke medicine and neurology at the Columbia University New York, the University of Nottingham, and the Charité in Berlin. His research interests focus on treatment and prevention of cerebrovascular diseases.

Christian Stapf is an Adjunct Assistant Professor of Neurology at Columbia University, New York (USA), a Privatdozent für Neurologie at the Charité in Berlin, and a tenured Consultant Neurologist at Hôpital Lariboisière in Paris (France). His main research interest is the neurology of brain arteriovenous malformations and other conditions predisposing to intracranial hemorrhage and stroke. He is the European Co-PI in the NIH-funded ARUBA trial and serves as a coordinator in the Columbia AVM Databank project and the New York Islands AVM Study.

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treatment for consenting adults aged ≥18 years, with an unruptured brain AVM that is potentially treatable, over a minimum follow-up period of five years, based on outcome assessments by a neurologist. Although enrolment in this trial may prove challenging because of the instinctive difficulties some patients (and doctors) may face in allowing randomisation to decide whether their 'time bomb' is treated or not, fully informed consent – involving a sanguine discussion of the risks of intervention – is crucial.

ARUBA is funded by the National Institutes of Health (ISRCTN 44013133), with per-patient reimbursement. The trial has ethical approval in the UK, and a decision about trial adoption by the UK Stroke Research Network is pending. Interested investigators should contact any of the authors, and may also consider participating in a similar trial randomising people with an unruptured intracranial aneurysm to endovascular or conservative management (www.teamstudy.org, ISRCTN 62758344).

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Immunology News: A New Type of T Cell Is Discovered

Immunology is a young, fast-moving, discipline. Today's dogma is often disproved tomorrow. But most people would have thought that the fundamental division of helper cells into 'Th1' and 'Th2' was conclusive. Not so, it turns out.

The Dogma

T helper (Th) cells are an important part of the adaptive immune system. They express T cell receptors (TCRs) that recognise a specific protein bound to class II MHC molecules and activation causes cytokine release. They are important in the defence against microbes but also induce inflammation in immune-mediated diseases. In the 1980s, Mosmann showed that CD4+ T lymphocytes could be divided into 'Th1' and 'Th2'.[1]

- The cytokine interleukin-12 (IL-12) promotes the development of Th1 cells, which secrete IFN-γ, IL-2 and TNF-β (lymphotoxin); these drive cell-mediated immunity to eliminate intracellular pathogens.
- In contrast, T cells stimulated in the presence of IL-4 turn into Th2 cells which secrete more IL-4, IL-5, IL-10 and IL-13, and up-regulate antibody-mediated responses for elimination of extracellular pathogens

Recently, regulatory T cells (Tregs) have been described which are thought to inhibit unwanted immune responses to self antigens. When this regulation fails, autoimmune disease results. Multiple sclerosis was thought to be a classic example of a disease driven by Th1 cells, whereas allergy was due to excessive Th2 cytokine production.

A major plank of evidence for all of this came from Experimental Autoimmune Encephalomyelitis (EAE). For instance, studies with IL-12 knock out mice (IL-12-/-),[2] or using IL-12p40 neutralising antibodies,[2,3] have shown that IL-12 is necessary for disease expression; hence Th1 cells and IFN-γ drive EAE. All very tidy.

The problem

According to all of this, mice which lack certain critical components of the Th1–IFN-γpathway (IFN-$^{-/-}$[4], IFN-R$^{-/-}$[5], IL-12Rβ2$^{-/-}$[6], and IL-12p35$^{-/-}$[7] mice) should not get EAE. Unfortunately however, they do.

The solution

The first step in sorting all this out was the finding that the subunit p40 is shared by both IL-12 and a newly-discovered cytokine called IL-23.[8] IL-23 is secreted by activated dendritic cells and stimulates IFN-γ production and proliferation of blast T cells and memory T cells.[8] Becher et al[7] showed conclusively that mice deficient in the specific p35 subunit of IL-12 (p35$^{-/-}$) develop severe EAE whereas those deficient to the common p40 subunit (p40$^{-/-}$) were resistant to EAE. So IL-12 is not responsible for EAE.

Daniel Cua, from Schering-Plough Biopharma, reasoned that all the p40 knock-out experiments were flawed and that deficits attributable to IL-12 deficiency may have actually been due to lack of IL-23. His team proved this by manipulating mice cells *in vitro* and seeing if they induced EAE on transfer to naïve mice. The result was clear: T cells cultured *in vitro* with IL-23, but not IL-12, caused severe clinical signs of EAE on transfer (Figure 1).[9] In IL-23 deficient mice, Th1 cells invaded the CNS, but did not cause disease. So IL-12 and Th1 cells do not drive EAE! This is a major paradigm shift….

What sort of T cells does IL-23 induce?

CD4+ T cells from IL-23p19$^{-/-}$ knockout mice are specifically unable to produce IL-17.[10] So the thinking is that IL-23 induces a new brand of helper T cells called 'Th17' cells characterised by their production of IL-17. IL-17 has not had much of a press until now. It induces the secretion of pro-inflammatory cytokines tumour necrosis factor (TNF), IL-1 and IL-6 from macrophages.[11] IL-17 also induces production of IL-6, IL-8, prostaglandin E_2 and granulocyte colony-stimulating factor (GCSF) from rheumatoid synovial fibroblasts and IL-6 from a variety of stromal cells.[12] Anti-IL-17 treatment of wild type mice immunised with myelin protein PLP are partially protected against EAE.[9]

How do Th17 cells develop?

As well as IL-23, TGF-β1 is important in the development of Th17 cells. Mice over-expressing TGF-β1 had increased numbers of Th17 cells and worse autoimmune disease.[13] Th17 differentiation is inhibited by the products of Th1 and Th2 cells, IFN-γ and IL-4 respectively.[14] Development of Th17 cells is promoted by the combination of transforming growth factor (TGF-β1) and IL-6.[13,15] These cytokines are produced by many cells. TGF-β1 alone induces the differentiation certain subsets of Treg cells.[16] When TGF-β1 is combined with IL-6 it inhibits the expression of FoxP3, a gene transcription factor essential for Treg development, thus promoting Th17 and suppressing Treg cell development.[13,15] In the steady state TGF-β1 will induce FoxP3+ Tregs and maintain self-tolerance. When there is infection or inflammation, IL-6 produced by the innate immune system will suppress Tregs cells and induce pro-inflammatory response by Th17. So now, a scheme like this can be drawn (Figure 2).

Th17 cells drive autoimmunity and cancer

Serum IL-17 is raised in patients with MS,[17] SLE,[18] asthma[19] and in RA synovium.[20] It has been shown that there is increased IL-23 secretion from monocyte derived dendritic cells from MS patients compared to healthy controls and that there is increased IL-17 production by

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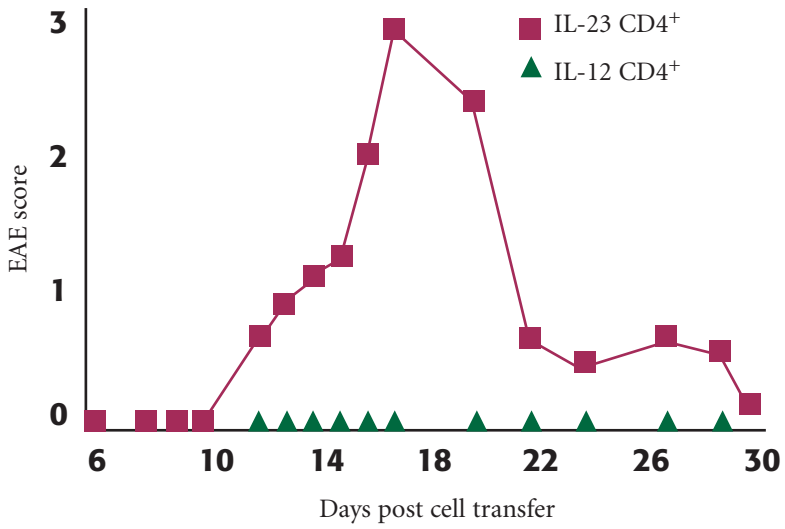
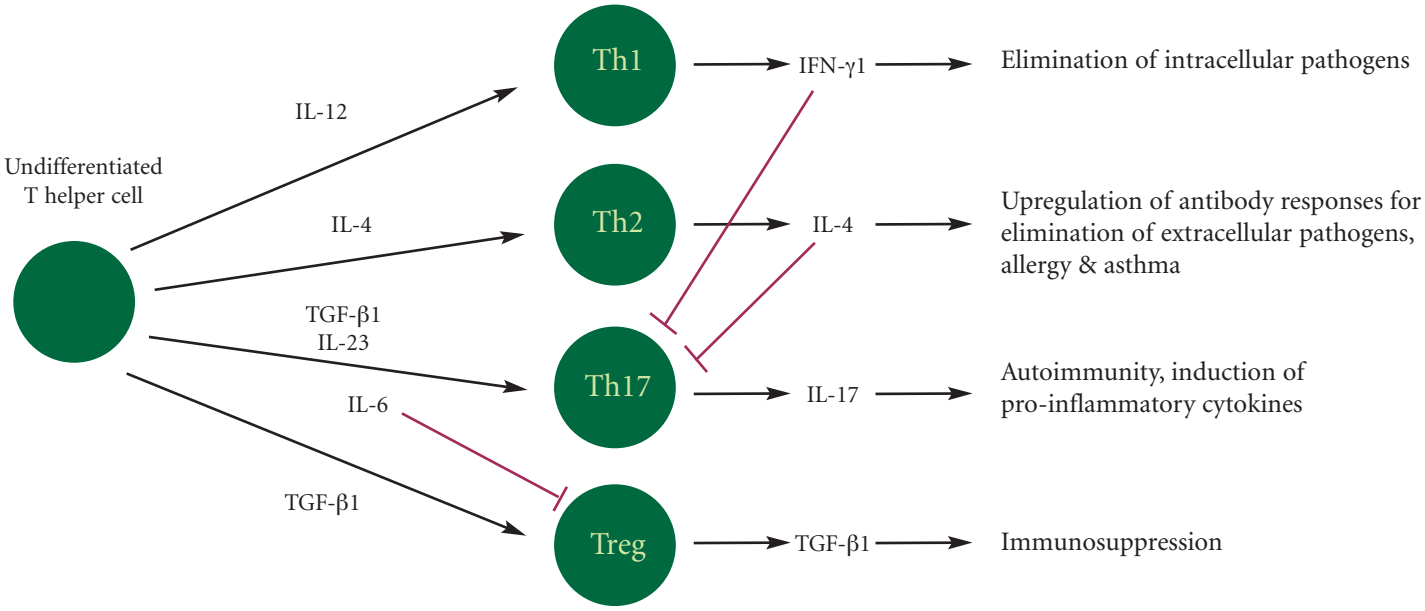


Figure 1 shows CD4+ T cells cultured *in vitro* with IL-23 (■), but not IL-12 (▲) induce EAE pathogenesis, Langrish et al.[9]



stimulated CD4+ T cells from MS patients.[2] IL23 may also play an important role in tumours as IL-23p19 mRNA expression has been shown to be increased in a variety of human tumours.[22] One mechanism for this may be that IL-23 reduces the ability of CD8+ T cells to infiltrate tumours as shown in mice.[22] At present a clear role for the IL-23/IL-17 pathway in response to infection has not been identified. IL-23 knock-out mice are less prone to some infections (tuberculosis and toxoplasmosis) than IL-12 knock-outs,[10,23] suggesting that it may not play an important role.

Summary

Newly described Th17 cells which produce IL-17 and are expanded in the presence of IL-23 are likely to have an important role in the pathogenesis of autoimmune diseases and possibly some cancers. Work done with mice has shown that EAE is prevented by the use of anti-IL23p19 antibodies[24] and that anti-IL 17 antibodies give partial protection.[9] In theory the selective neutralisation of the IL-23/IL-17 immune pathway (with an IL-23p19 or IL-17 antibody) might reduce autoimmunity, yet have little detriment on the immune response to infection.

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Models of Multiple Sclerosis

Multiple sclerosis (MS) is a major disabling disease of the central nervous system (CNS), which has been described for over two hundred years, yet it is still enigmatic and inadequately controlled.[1] As the CNS cannot easily be sampled, to gain ideas about disease mechanisms, a number of models have been developed. These include: myelin mutants, chemically-induced lesions, viral and autoimmune models, all of which show some evidence of demyelination, a pathological hallmark of MS.[2] Myelin mutants, such as the taiep rat, *Shiverer* (myelin basic protein (MBP) mutant), *Rumpshaker* and *Jimpy* (proteolipid protein (PLP) mutants) mice, as well as gene knockout animals such the myelin associated glycoprotein (MAG) knockout show dysmyelination, altered neurotransmission and in some instances clinical disease, and have been used to study myelination. The delivery of oligodendrocyte-selective toxins such as cuprizone, which causes focal demyelination notably to the cerebellar peduncle, or direct injection of ethidium bromide or lysolecithin into the CNS produces demyelination. These are usually effectively repaired once macrophages clear the myelin debris and glial precursor cells repopulate the lesion and remyelinate. These models have largely been used to study mechanisms of de/remyelination, notably after transplantation of myelinating glial cells and are currently seldom used as pre-clinical drug screening tools for MS.

Viral Models of MS

A number of viruses, including Semliki Forest Virus and Theiler's Murine Encephalomyelitis Virus, have been found to induce disease by neurotrophic infection of the CNS, specifically oligodendrocytes. Whilst some viral strains may be cytopathic to the oligodendrocyte, in many instances virally-infected cells are attacked by T cell and humoral responses, leading to demyelinating disease.[2,3] TMEV has notably been used to demonstrate mechanisms by which autoimmunity may develop following a viral infection. This paradigm is consistent with the aetiology of MS, where viral molecular mimicry and determinant spread, where damage from infection may stimulate subsequent autoimmunity, may contribute to the generation of an autoaggressive immune response.[3]

Autoimmune Models of MS

Experimental allergic encephalomyelitis (EAE) has received the most attention as a model of MS and is routinely used in testing therapeutic strategies for MS (Figure 1). This disease exhibits many clinical and histological features of MS and is caused by the induction of autoimmunity to antigens that are either naturally (typically myelin antigens) or artificially (such as implanted mycobacteria or ovalbumin that, following peripheral sensitisation to these antigens, allows local targeted lesions to be developed) expressed in the CNS.[2-4] Following sensitisation to myelin antigens animals develop disease, typified by limb paralysis. This is associated with blood:brain barrier dysfunction, mononuclear cell infiltration into the CNS and conduction block resulting in impaired neurotransmission. This can occur in the absence of demyelination and highlights a misconception by many that clinical EAE is due to demyelination. In some models disease is also associated with significant axonal loss, which is the underlying cause of persistent disability.[2] EAE is polygenic and susceptibility and the clinical course can vary depending on the immunising antigen (such as MBP and PLP) and the strain/species of animal being investigated.[2,4] For example, ABH and SJL mice develop relapsing EAE to disease induced by whole myelin, whereas C57BL/6 mice are resistant.[2] However, the discovery that MOG, a minor myelin protein, can induce chronic paralytic EAE in the C57BL/6 mice has allowed the numerous gene-knockout mice bred on that background to be used to investigate EAE.[2] Therefore EAE is not a single model, but a number of models that have varying degrees of similarity to MS.[2] As such, a similar clinical phenotype may be achieved via different routes of genetic control[2] and likewise suggests that there is likely to be some heterogeneity in the pathways leading to disease in MS.

Spontaneous CNS autoimmunity

Rodent EAE studies have demonstrated that disease develops once sufficient T cells escape the control mechanisms that keep autoimmunity in check. Furthermore, by transgenically introducing myelin (MBP, PLP or MOG)-specific T cell receptors (TCR) into all T cells, then even the slightest trigger can lead to spontaneous CNS disease.[2,4] These animals have proved to be important tools in understanding autoimmunity and both $CD4^+$ and $CD8^+$ TCR transgenic models of EAE have been generated,[4] thus accommodating thoughts that there may be a $CD8^+$ T cell bias in some MS lesions.[5] More recently, transgenic mice expressing MS-associated major histocompatibility class II haplotypes and human derived myelin (MBP)-specific TCR with or without human CD4 have been shown to spontaneously develop EAE.[7] These humanised models have been suggested to be significant improvements over standard models.[7] However, such animals are usually produced on the C57BL/6 mouse background, because of the availability of embryonic stem cells required for transgenesis, and this strain typically develops EAE that rapidly shows a chronic paralytic course, due to the nerve loss that this strain quickly accumulates.[2,4] As such, it is more difficult to manipulate EAE compared to other strains.[2] Furthermore, the incidence and phenotype can be so variable in such humanised-TCR mouse models[7] that they do not offer advantage over existing standard models for purposes of routine drug screening, unless there is an a priori reason for testing agents that are specific for these human components. Nevertheless, humanising models, such that they can accept MS-patient derived cells may lead to new tools for the future.[7]

Is EAE a misleading tool for MS research?

MS appears to be a uniquely human condition and no other animal spontaneously develops a disease identical to MS. Furthermore, it must be recognised that immunisation of mammals, including humans, with CNS proteins does not induce MS, but acute disseminated encephalomyelitis. This was recognised over a century ago when rabies vaccine containing residual CNS material was injected into humans or more recently when encephalomyelitis developed following amyloid beta protein vaccination in Alzheimer's disease.[8] As such, EAE will always be an imperfect model, but nevertheless it has shaped the therapeutic approaches applied to MS for decades.[5,6,9,10] However, because of the many failures to clinically translate experimental findings in EAE into MS, opinions have been voiced that animal models are of limited value in the search for treatments in MS.[5,9] This opinion is not entertained by all,[6,10] but in addition to arguments made by critics of EAE, such as differences in the cellular and cytokines responses between some EAE models and MS,[5,9] the failure of EAE studies to detect viable treatments[5,9] may also relate to how the results of the studies are interpreted by the scientific and clinical fraternity.

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Dr Samuel J Jackson is a neuroscientist (EAEologist) who has been working with *in vitro* and *in vivo* models of MS. Having trained at the Institute of Neurology, University College London, he moved to the University of Wisconsin, Madison, USA to help develop remyelination strategies. He is currently based at Queen Mary University of London, where he is part of a translation program aiming to treat progression in MS.

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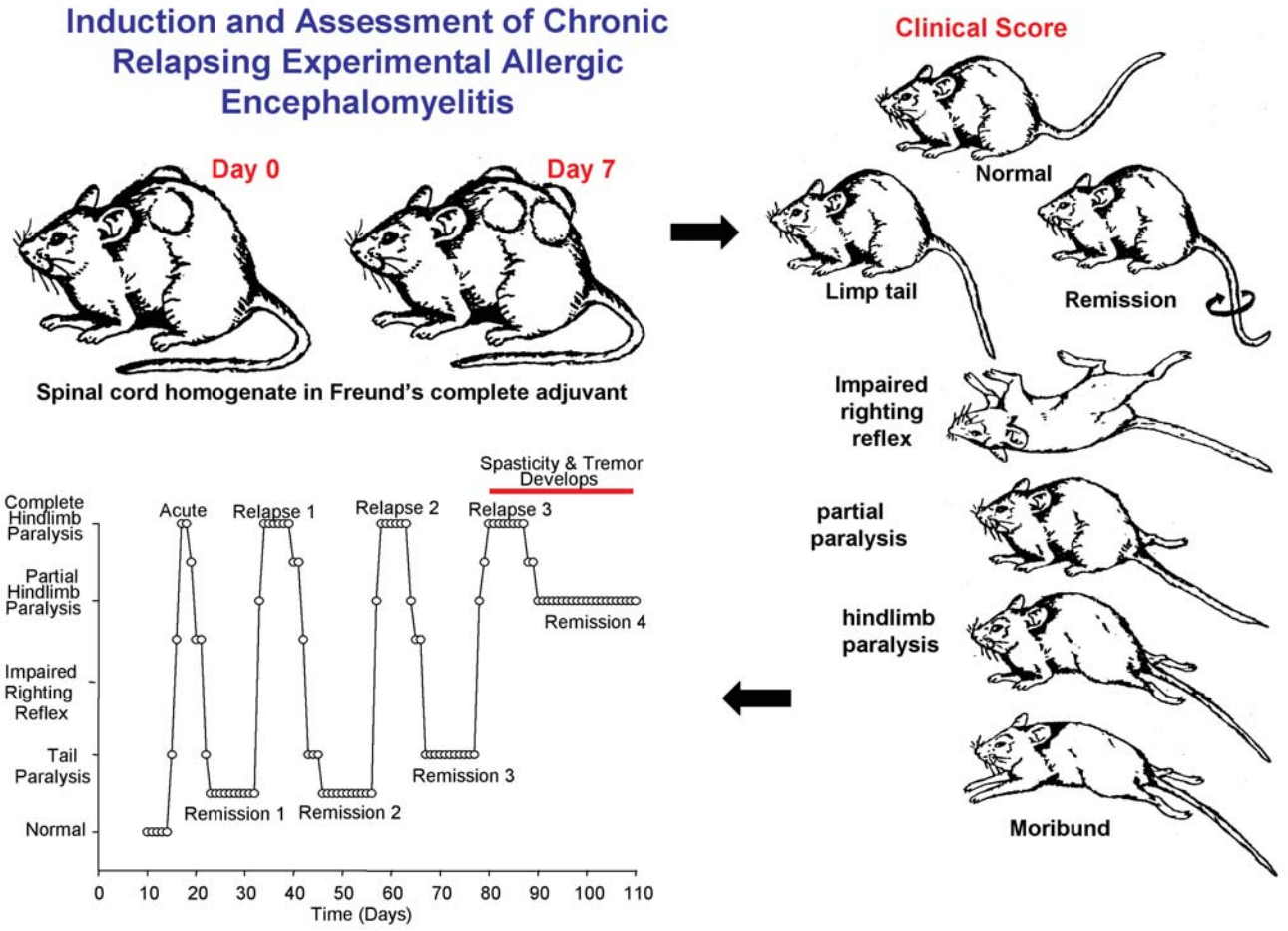

Figure 1: Induction and clinical course in an Experimental Allergic Encephalomyelitis Model.

EAE can be a leading tool for MS research

Disease in EAE is easy to detect and can relapse, unlike most other experimental autoimmune models, and is thus widely used. This is studied by many basic scientists who justify their research in terms of human disease, whilst they actually search for the unifying mechanism/theory for the development and control of autoimmunity. The EAEologist thus becomes preoccupied with the biology of a process and designs experiments as such, rather than concerning themselves with the biology of the disease, which by and large is complex. Therefore the experimental models and therapeutic agents may not have been used in a context where they are relevant to people with disease. It is relatively easy to stop an immune response from developing, but it is very much more difficult to switch off the immune response once it has been triggered.[11] This is because the immune response is designed to avoid the development of autoimmunity, but also to give us life-long protection from attack by infection, following previous activation. The vast majority of experiments in EAE are aimed at understanding the generation of the immune response. As such, prophylactic treatment, which probably has little relevance to treating the human condition, is the norm. Very few studies examine drug treatment once disease and demyelination is established in the CNS and the number of studies where treatment is initiated after only two attacks have occurred number very few. By contrast, many studies of immunological agents in MS have investigated their effect in late stage progressive disease, which may have thwarted them from showing any efficacy (see below). The successes of treatments of EAE, as a route to defining immune mechanisms, are published and lauded every month.[6] However, on closer inspection the results of some studies may show only a minor clinical improvement or a delay in disease course of just a few days. This is probably of marginal biological significance when viewed in terms of treating the heterogeneous human disease developing over years. Importantly, the doses of drugs given to animals may far exceed what one may be prepared to apply clinically to chronic disease in humans. Lower doses may be inactive but negative data seldom inspires editors to publish.

The T cell is instrumental to the development of EAE and thus most immunotherapies target the T cell in MS.[5] However, other factors besides T cell activity may contribute to pathology as already shown in EAE. B cell responses can shape the disease course once T cells have created the diseased environment, allowing entry of pathogenic/demyelinating or remyelination-inducing antibodies into the CNS.[12] In acute models, the first episode is often non-demyelinating and B cell responses may not have developed by the time this occurs. In contrast, marked demyelination occurs in EAE models, such as in strain 13 guinea pig and marmoset EAE, but this may take months to develop.[13,14] Likewise, macrophages/microglia have received relatively little attention as therapeutic targets in MS, yet they are probably instrumental in inflammatory pathogenic and repair mechanisms. Therefore some of the failures to translate findings from EAE into MS may not be simply the fault of the models, but the failure of the investigator to appreciate the very different scenarios in which the drugs were tested in animals and used in humans.

For many years drugs used in MS have had marginal efficacies on clinical course above placebo. Although it has to be accepted that a vast number of agents shown to ameliorate EAE have subsequently failed in the clinic,[5,9] the development of drugs such as Tysabri® have been critically dependent on biological studies in animals.[6] This and other drugs, such as CamPath®, can have a marked impact on the relapse rate but unfortunately this level of efficacy comes with the cost of increased adverse events. These can in some instances be fatal, such as the development of progressive multifocal leukoencephalopathy after treatment with Tysabri.[15] Whilst some people may berate the inability of animal studies to detect adverse events,[5,9] they in fact do so in the majority of cases for drugs that are destined to fail the Research and Development programme. Usually EAE studies aim to provide 'proof of concept' for therapeutic actions and are not designed to detect adverse events. Should risks of adverse events be in the range of 1:1000,[15] then it is unlikely that this would be detected as experimental group sizes used to test drug activity are considerably smaller. Furthermore, laboratory

animals are housed in environments free of animal pathogen, which removes the risk of infectious complications. However, when arresting the function of a significant portion of the immune system with potent immunomodulatory drugs, it is not surprising that development of infection and tumours become more probable.

EAE and MS are not just about autoimmunity

The concept that MS is just a problem of autoimmunity has been championed and directed by much EAE research, but immunotherapy has consistently failed in the clinic when progressive MS has been targeted.[1] Instead these studies suggest that while (auto)immunity may drive blood:brain barrier dysfunction and relapsing disease, this also appears to create a CNS microenvironment that is permissive to neurodegenerative processes that are no longer dependent on, or sensitive to inhibitors, of autoimmunity.[1] This has recently also been shown to be the case in long-established EAE,[11] which suggests that monotherapies solely targeting autoimmunity are insufficient to control EAE, let alone MS.[11] In addition, there is emerging evidence from studies employing chemical lesions or dysmyelinating genetic mutants that there is also 'slow burning' axonal loss in chronically demyelinated tissue. This indicates that the autoimmune paradigm is insufficient to describe both progressive EAE and MS and may go some way to explaining the clinical failures using anti-immunological therapies. Whilst aggressive immunotherapy early after diagnosis of MS may be desirable, once sufficient damage has accumulated, the additional use of neuroprotective agents will be needed to treat progressive MS. Whilst EAE may be able to detect agents that inhibit immunity, we have some way to go in determining which agents will inhibit (auto)immune-independent nerve loss and progression.

Conclusion

Experimental models of human disease, whether directly relevant to MS or not, help one to understand the underlying biology. Without these one would not have the base of knowledge to inform development of treatments towards the clinic. Importantly, they help provide the confidence to invest in the development of costly clinical trials that may ultimately lead to improvements in the lives of many people living with MS. It is important to realise that experimental models can only give sensible answers if we ask of them sensible and relevant questions!

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Our first report, from Vienna's University Institute of Pharmacology, about the brain dopamine (DA) deficit in Parkinson's Disease (PD) came out in print in December 1960.[1] Eleven months later, in November 1961, we published the results of our first clinical levodopa trials in PD patients.[2] Both articles were written in German; they were re-published in English translations, in 1974 in a book[3] and in 1998 in a neurological journal.[1,2]

How did all this come about? What was the status at that time of DA as a substance of biological importance? When in August 1957 Kathleen Mongatu, in England, reported the discovery that DA occurred in the mammalian brain,[4] DA was generally regarded as being merely a metabolic intermediate in the formation of the catecholamines noradrenaline and adrenaline in the body. However, already in the autumn of 1956, Hermann Blaschko of Oxford's pharmacology department, had proposed that DA, in addition to being a metabolic intermediate, may have "some regulatory functions of its own which are not yet known".[5] At that time, I was working as a visiting scientist in Blaschko's laboratory, trying to define the nature of DA's action on the guinea-pig blood pressure. The results of my study confirmed Blaschko's idea, indicating that DA had indeed its own biological activity; levodopa, DA's immediate precursor substance, had the same effects as DA.[6]

I finished my experiments shortly before the publication, between October 1957 and May 1958, of a cluster of animal studies related to levodopa's central effects, showing that, in chronological order, levodopa caused central excitation and abolished the 'hypnotic' effect of hexobarbital (Peter Holtz, Germany); abolished the 'tranquilising' effect of reserpine (Arvid Carlsson, Sweden); increased the brain catecholamine levels (Alfred Pletscher, Switzerland); and increased the brain DA levels reduced by reserpine (Arvid Carlsson, Sweden; Hans Weil-Malherbe, England). Interestingly, of the researchers involved in these studies, only Holtz came forward with the conclusion that the amine responsible for levodopa's central actions must be "the hydroxytyramine [DA] formed from dopa in the brain".[7]

For me, now back in Vienna, the idea of DA having central effects appeared quite exciting. I switched my research from the periphery to the brain, and in 1958 examined in the rat, together with Georg Holzer, the effect on brain DA of centrally acting drugs, among them chlorpromazine – the first drug to produce a reversible neurological syndrome in humans very much like PD. To do the study, I had to develop a chemical DA assay applicable to brain tissue. This proved very useful when, early in 1959, Bertler and Rosengren, in Sweden, and Sano, in Japan, discovered that DA was highly concentrated in the striatal/basal ganglia nuclei – in particular the caudate and putamen.[8,9] In a flash, I saw the connection between the striatal localisation of DA, its central stimulant effect, the DA depleting effect of reserpine (like chlorpromazine a parkinsonism-inducing agent) and human PD, a well-known disorder of striatal function. And rather than trying to use animal models of the disease, like many others did, I felt that the best way to test my idea was to go directly to the human brain and see whether in PD there was a DA deficit or not. After arriving at this conclusion, what remained to be done was simple: to arrange, together with my collaborator in training Herbert Ehringer, for the collection and dissection of freshly autopsied human brains; then process the tissue samples and analyse them for DA – with the chemical DA assay already in my hands.

We started the work in February/March 1959 and published the full paper in December 1960.[1] We included a total of 20 adult controls; six PD brains; six cases with extrapyramidal (basal ganglia) symptoms of unknown aetiology; and two Huntington's disease brains. Of the fourteen cases with basal ganglia symptomatology, only the six PD cases had a severe DA deficit in the caudate and putamen. The results of the study, remarkable for its completeness, were immediately accepted and never put in doubt. They have become common textbook knowledge. For the first time, a specific chemical abnormality was found in a specific brain region in a specific degenerative brain disorder – a model for all current research into the causes and treatments of neurodegenerative diseases.

The most important immediate consequence of the DA work was the step "from brain homogenate to DA replacement".[10] In November 1960, I proposed to the neurologist Walter Birkmayer a clinical trial with slow i.v. injections of levodopa. Being aware of the literature about levodopa, including my 1957 Oxford study, replacement of the missing DA with levodopa appeared to me the most rational thing to do. We started the first trials in July 1961 and published the results in November 1961. In most of the 20 patients studied, the antiparkinson effect of levodopa was spectacular. As stated in our report, "for short periods of time, the patients were able to perform motor activities which could not be prompted to any comparable degree by any other known drug".[2]

However, our observations were received with some reservations. Many neurologists suspected a placebo effect of the i.v. injections, ignoring the fact that we also had shown, using the same patients, the ineffectiveness of i.v. injected substances related to levodopa.[11] Finally, in 1967 George Cotzias, in New York, gave D,L-dopa orally in large, gradually increasing doses chronically and showed that the effect was not only dramatic but also sustained.[12] Nonetheless, some – among them rather prominent[10] – brain scientists were reluctant to admit that the 'miraculous' therapeutic effect of levodopa was actually due to the DA formed from it, thereby undermining the whole DA replacement concept as the rational basis on which our first levodopa trials had hinged. The doubts were eventually silenced in 1974 by Donald Calne, in England, who demonstrated that the direct DA receptor agonist bromocriptine had a clinical antiparkinson effect qualitatively identical with that of levodopa.[13] At present levodopa remains the single most potent drug for PD and the reference standard for any new approaches to the treatment of this common debilitating movement disorder.

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Hereditary Spastic Paraplegia

Hereditary spastic paraplegia (HSP) is a group of clinically and genetically heterogeneous conditions, with prevalence of 10 cases per 100,000 population. The key diagnostic clinical findings are of lower limb spasticity and pyramidal weakness, hyperreflexia and extensor plantar responses.[1] HSP can be divided into uncomplicated (pure) or complicated HSP depending on the presence of other neurological features in addition to spastic paraparesis. Even amongst individuals categorised as having uncomplicated HSP, mild sensory abnormalities of the lower limbs (e.g. reduced vibration sense), urinary symptoms, pes cavus, and mild to moderate cognitive decline are recognised.[2] However, cranial nerves are almost never involved in HSP.

Complicated HSP comprises a large number of conditions in which spasticity is accompanied by other features including muscle wasting (amyotrophy), optic atrophy, pigmentary retinopathy, mental retardation, extrapyramidal disease, ataxia, dementia, deafness, icthyosis, peripheral neuropathy and epilepsy. Perhaps unsurprisingly, this has led to overlap in classification schemes, leading to rather confusing dual classification: hereditary motor neuronopathy with spasticity (HMN type V) and SPG17 (HSP with distal amyotrophy) describe the same condition. Complicated forms of HSP are usually autosomal recessive and rare.

Clinical features

HSP has onset from early childhood onwards, with insidious development of leg stiffness and/or abnormal wear of the shoes. There often appears to be relative preservation of power despite dramatically increased tone in the legs. Important clues to the cause of spastic paraplegia are age and nature of onset, progression of symptoms, family history and presence of other clinical features. It is helpful to ask about athletic ability in childhood, as poor performance or lack of interest in sport may indicate a longstanding motor disability. There is a high incidence of urinary symptoms in HSP, reported in <40% of cases, but is rarely marked in early disease.[2]

The differential diagnoses according to age of onset are listed in Table 1. Spastic paraplegia developing over the age of 20 years is a relatively frequent clinical problem in neurological practice. It is likely that a significant proportion of cases of undiagnosed paraplegia are of genetic origin and detailed family investigations are critical, and sometimes leads to identification of an asymptomatic affected individual. The presence of a slowly progressive gait disorder with few sensory symptoms and signs favours HSP. Sudden onset of spasticity favours a vascular, inflammatory or mechanical cause, and in these cases there is frequently more marked weakness, sensory signs, and spinal or referred pain.

A family history compatible with autosomal dominant transmission in the context of adult onset spastic paraplegia, is almost always due to HSP. However, HSP can show autosomal dominant, recessive and X-linked inheritance.[1] For the apparently sporadic case of spastic paraplegia, HSP is a diagnosis of exclusion (see Table 1).

Investigations

The diagnosis of pure HSP in a family in which several members have typical clinical features presents few difficulties. For an isolated case with young adult onset, MRI scanning of brain, cervical and thoracic cord is important to exclude the main differential diagnoses. In HSP, the most common MRI abnormality is of thinning of the cervical and thoracic spinal cord. Studies in dominant HSP kindreds have also suggested that there is loss of volume of the corpus callosum and a higher incidence of cerebral white matter lesions. In most cases of pure HSP, nerve conduction studies and EMG are normal, but central motor conduction times can be delayed or unrecordable from the lower limbs, and lower limb somatosensory evoked potentials small. Blood investigations (vitamin B12, very long chain fatty acids, serology where appropriate) may be required. CSF analysis is usually normal in HSP. The mapping and cloning of HSP genes has led to specific molecular genetic tests which will allow more focused investigation of potential cases of HSP.

Genetic subtypes of HSP

HSP can be inherited as an autosomal dominant, recessive or X-linked recessive trait and currently 33 SPG loci have been mapped. Autosomal dominant HSP is the most prevalent form and represents around 70% of cases.[1] Most cases of pure HSP are autosomal dominant, whilst complicated forms tend to be autosomal recessive. The more common genetic forms are considered below:

Autosomal dominant HSP (AD-HSP)

SPG4 HSP:

The locus on chromosome 2p22-p23 (SPG4) is the most important and accounts for around 45% of AD-HSP kindreds. The gene encodes the protein spastin and has 17 exons spanning about 90kb.[3] Most pedigrees with spastin mutations have pure HSP, with onset from childhood to old age (typical age of onset 26-35 years). SPG4 HSP cannot be reliably differentiated from other forms of AD-HSP by clinical features alone. Cognitive impairment, dementia and epilepsy have been reported in some families.[4] The severity and age of onset can vary markedly, even within one family, suggesting the effect of modifying genes or environmental factors.

The function of spastin is unknown, but it is a member of a group of proteins known as the *A*TPases *A*ssociated with diverse cellular *A*ctivities (AAA). These AAA proteins act in various cellular functions, including cell cycle regulation, protein degradation, organelle biogenesis and vesicle mediated protein function. Mutations within the spastin gene that have been identified include missense, nonsense and

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Table 1: Differential diagnoses for childhood and adult onset spastic paraplegia

Childhood Onset:	***Adult Onset:***
Diplegic cerebral palsy	*Cervical spine degenerative disease*
Structural: Chiari malformation, atlanto-axial subluxation	*Multiple sclerosis*
Hereditary spastic paraplegia	*Motor neurone disease*
Leukodystrophy: e.g Krabbe's	*Neoplasm: primary/secondary tumour, parasagittal meningioma*
Metabolic: arginase deficiency, abetalipoproteinemia	*Dural arteriovenous malformation*
Dopa-responsive dystonia	*Chiari malformation*
Infection: myelitis	*Adrenoleukodystrophy*
	Hereditary spastic paraplegia
	Spinocerebellar ataxias
	Vitamin deficiency: B12 and E
	Lathyrism
	Dopa-responsive dystonia
	Infection: syphilis, HTLV1, HIV

splice site mutations in various exons which usually lead to major amino acid sequence changes in the AAA domain or truncation of the protein.[5] Deletions have become increasingly recognised. This implies that there is a loss of function and a threshold level of spastin required to maintain axonal integrity, although there is also evidence for a dominant negative effect.

Other forms of AD-HSP

The SPG3A gene on chromosome 14q11.2-q24.3 encodes the protein atlastin, in which a number of missense mutations have been identified.[6] The phenotype is of pure HSP with childhood onset (usually < 10 years of age) and a relatively benign course, such that most affected individuals remain ambulant. It has been estimated to cause 10% of AD-HSP. A small proportion of families with uncomplicated AD-HSP are caused by mutations in the SPG6 and SPG10 genes, which encode the proteins NIPA1[7] and neuronal kinesin heavy chain (KIF5A)[8] respectively.

Complicated forms of AD-HSP are all rare. SPG17 (Silver syndrome) describes HSP plus amyotrophy of the small muscles of the hands and feet with onset usually in the second to 4th decades. Mutations were identified in the BSCL2 gene on chromosome 11q12-q14 and can also cause HMN typeV.[9]

Autosomal recessive HSP (AR-HSP)

AR-HSP is rarer than AD-HSP, many of the genetic loci relate to single consanguineous families. The more common forms are:

- SPG5A: This locus on chromosome 8p12-q13 causes pure HSP with onset in first two decades.[10]
- SPG7: Mutations in SPG7 gene leads to a complicated form of AR-HSP with additional neurological features of ataxia, dysarthria, optic disc pallor, axonal neuropathy. Onset is between 20 and 40 years of age, leading to progressive disability. The gene encodes paraplegin, a mitochondrial ATPase protein.[11] Studies suggest that SPG7 HSP accounts for <10% of AR-HSP.[12]
- SPG11: Mapped to chromosome 15q13-q15, this locus cause a characteristic phenotype with onset in first two decades associated with mental retardation and agenesis of the corpus callosum.[13]
- SPG15: Another characteristic (Kjellin) syndrome maps to chromosome 14q22-q24 and the HSP is associated with a retinal degeneration and mental retardation.[14]

X-linked HSP

X-linked recessive HSP is very rare, although SPG1 and SPG2 were the first HSP genes cloned. SPG1 encodes the L1 cell adhesion molecule (L1CAM) and mutations cause a complicated form of HSP with mental retardation and absence of the extensor pollicis muscle.[15] SPG2 mutations are within the proteolipoprotein gene and can cause both pure and complicated forms of HSP. Mutations (usually duplications) of this gene also give rise to the dysmyelinating condition Pelizaeus-Merzbacher disease (PMD), which is characterised by congenital hypotonia, psychomotor deterioration and progressive pyramidal, dystonic and cerebellar signs.[16]

Pathophysiology

The main neuropathological finding in HSP is axonal degeneration of the terminal portions of the long descending (corticospinal tracts) and ascending (dorsal columns) pathways in the spinal cord. There have also been reports of degeneration of spinocerebellar tracts and loss of Betz cells in motor cortex layer V. Any pathophysiological mechanism must explain why the brunt of the disease falls upon the longest neurons in the spinal cord. The current hypothesis is that the different mutant proteins disrupt axonal transport of macromolecules and organelles, which selectively affects the distal axon.[17] This view has come from study of a number of genes, in particular SPG4. Spastin (SPG4) appears to play a key role in the dynamics of microtubule turnover, which make up the intracellular cytoskeleton, and along which axonal transport occurs.[18,19] Wild type spastin can sever microtubules, a property lost in mutant forms, and recent studies suggest this leads to excessive amounts of stabilised MTs occurring distally in terminal axons leading to altered distribution of organelles and other axonal cargoes.[20,21] A tantalising finding was that, in a Drosophila model of SPG4 HSP, the abnormal phenotype and pathological changes were ameliorated by vinblastine, a drug which destabilises microtubules.[21]

Atlastin (SPG3A) is a dynamin expressed in the Golgi, and may be involved in vesicular transport. Recent evidence suggests its pathogenic effect is mediated by an interaction with spastin.[22,23] Transgenic mouse models of other forms of HSP, including mutant paraplegin (SPG7)[24] and proteolipoprotein (SPG1)[25] also appear to disrupt axonal transport.

Management and testing

There is no disease modifying therapy currently available for HSP. Physiotherapy is important to maximise function and prevent complications such as contractures. Anti-spasticity drugs such as baclofen, tizanidine, and to a lesser extent diazepam and dantrolene, can be helpful, as can botulinum toxin injections into specific muscles. Footdrop can be helped by orthoses. Occasionally surgery is required to release contractures or tendons. Early referral to continence advisory clinics is helpful to deal with urinary problems.

In appropriate circumstances, and with adequate counseling, molecular genetic testing can be performed and prevent extensive investigations. Testing is available for SPG4 (spastin), SPG3A (atlastin) and SPG6 (NIPA1) for families with pure AD-HSP. Other testing (e.g SPG7 and SPG17) may be available on a research basis. Testing for mutations in spastin (SPG4) should also be considered in cases of sporadic progressive spastic paraplegia where no cause has been identified, as mutations have been detected in <10% of apparently sporadic cases of pure HSP.

Summary

The HSPs are a heterogeneous group of degenerative disorders with a common pathogenetic theme of abnormalities of axonal transport leading to axonal dying back of long spinal neurons. Greater understanding their aetiology will shed light on the function of these long spinal neurons in both health and disease.

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Below is the first in a new series of articles on personal experiences of disease. In this issue, I am enormously grateful to Claire Rytina (a patient of mine) who eloquently describes the consequences of the herpes simplex encephalitis that struck her back in 2004. Claire was admitted to our hospital in May 2004 with a three day history of nausea, vomiting, headache and increasing confusion with difficulty recognising her children. On admission she was able to follow commands with a GCS of 14 and no focal neurology. Her CT scan that showed some swelling of the right temporal lobe, with an MRI scan that confirmed this with involvement of the adjacent insula and basal ganglia and subtle changes in the left temporal lobe. A presumptive diagnosis of HSE was made and she was started on acyclovir. Her CSF showed 32 white cells, a raised protein, normal glucose and subsequently PCR confirmed HSV. She improved, but from the outset had major problems with facial recognition. She remained in hospital for almost three months and subsequently has been involved with an active rehabilitation programme through the Oliver Zangwill Centre in Ely. This is her account of this illness and how it has affected her.

Roger Barker, Editor.

My Life Post Hse

Claire Rytina

The first I knew of my illness with herpes simplex encephalitis was being told I had been in hospital for six and a half weeks. I am told that I had a gastro-intestinal upset, was off work, felt depressed and had unusual dreams for a few days. Apparently I then became confused and was taken to hospital. My daughter tells me I called my husband Stephanie. The MRI scan reported a high signal intensity in the right mesial temporal lobe extending into the adjacent basal ganglia, insular and inferior frontal lobe. There was limited high signal change in the left temporal lobe.

I awoke, very lost, confused and disorientated in my surroundings. I know it was a while later before I realised that I was not recognising people, or being able to place their identity. I am told that the first time I recognised someone was at five and a half weeks, when my son spoke to me from behind the bed where I was unable to see him, but I must have recognised his voice and said his name. They must all have been so delighted and relieved. And so special that it was him that I recognised. I still find now that some people's voices are very familiar and I can make correct guesses at who they might be. The weeks between then and my discharge home, at eleven weeks, are mostly unrecorded in my memory. I am told about all the kind people who came to visit me, having no memory of this I find very saddening. I still have cards and presents, now two and a half years later, that I cannot bring myself to look at as I feel so upset that "I" was not there to thank them for caring so much about me. I feel absent from such an important time in my life.

The illness has affected me in many ways: I have lost a bank of factual information, semantic memory, and consequently confidence. I have prosopagnosia, have had a seizure and have lost the ability to recognise both taste and smell. I have verbal communication misunderstandings leading to low self-confidence and emotional anxiety.

These difficulties leave me with a huge loss of identity and feelings of low self-worth. I don't trust myself to live life and react to the world around me appropriately. My continuous state of anxiety gives me headaches, back, shoulder and neck ache a great deal of the time and I am nervy and jump at the slightest noise. I am constantly anxious about times gone and times to come so that I have sleep difficulties leading to overtiredness and less ability to feel any confidence to manage.

I was discharged home and had to believe that my husband was the right person, but I had no sense of certainty about him. Although I could not recognise our children I did have the belief that they were mine. I have memories of that time which are very frightening and upsetting. I had no sense of belonging to this family who I was told was mine. I remember feeling very frightened about the identity of my husband in particular and very separate from a unit of individuals who seemed so intense and confident together. I remember coming home to a house I could not find my way around and being helped to go to the right rooms. I am told that I struggled to believe that it was the home that I lived in, even that some of my clothing belonged to me. I do remember not wanting to wear any of it, denying that it had anything to do with me. I know I bagged some items up to hide them away from myself and many things have never been found. My husband thinks I disposed of most of the items which were previously my favourites, ones I suppose which identified more with the person I had lost. For some time I was unable to stop crying and continued to be confused.

In my life prior to illness I had a good education, nurse training and twenty-seven years experience working for the NHS. I found myself unable even to name plants and animals, also panicking not knowing where to go just two doors from home. I had had access to a huge bank of knowledge, most of which like anybody I just took for granted, and find myself at a loss to grasp most of it. It has left me feeling very anxious and confused and unable to trust myself to manage everyday situations.

Deep in my heart I have a huge need to be caring for others and I now feel a dismal failure. I misunderstand the needs of my children and frequently make them upset by behaving in a way they can't possibly understand and this has led to tensions within our relationships. Our family set-up has had to change with roles which worked before my illness being adjusted. I have been so confused within my "self " and how and where I fit in, that these changes have given me much grief in so many ways. How difficult to readjust my lack of self-worth when told "we managed perfectly well when you were in hospital." This of course was meant to make me feel better and that I shouldn't worry.

After two and a half years, I am now able to recognise my own family at home if they are the only ones there. I struggle to pick them out when they are in their friendship groups. I regularly rely on clothing to help me identify people once I know who they are, which helps me mind out for my children or keep with a friend while we are out.

People are told that I am home now but suffering a loss of facial recognition. That makes them feel that I will know who they are and all about them when they give me their name. They are so pleased to be telling me they are "Linda!" and I then feel so desperate to snatch at something to jog my memory of who on earth this person can be – just something so I can react appropriately, understand them, know them. But they don't realise I don't know them and start talking to me as if they have met me before, telling me about this person, that person, events that I would have known about which they expect me to know about. They are so pleased to see me and have no idea that they feel like a complete stranger to me. They are someone who knows so much more about the person that was me, than "I" do. As if the meeting isn't bad enough, then comes that terrible question: "How are you?" Do I just lie and say: "Okay thanks" or "Fine" and hope that's the end of it or do I set about telling them that I am struggling to adjust myself to a new life, a life where all the parameters have changed, leading to confusion, disappointment, low self-esteem and huge anxiety? Just "I'm not me" is probably the answer. I have come to a point now that I have felt so much at a loss when meeting people and so guilty about not being able to care for them in any meaningful way, that I feel I have become very unsociable. I choose not to join in with sociable occasions,

keep in a back seat if I do and make sure I never make eye contact with anyone in case they start to speak to me. Expecting I'll fail again.

I feel very oddly separated from the idea of 'myself' so that I can't feel I properly belong to any group anymore. I don't feel like I am the wife, the mum, the nurse, the friend that I believe I was before. I am fearful that I will never fit into these roles again.

I struggle to understand what people are telling me and feel very anxious about misunderstanding what is happening, what is expected of me and how I will manage. I can't concentrate for very long on things which need me to think and work things through in a logical meaningful way. I get very tired just trying to manage simple everyday things. I am my own worst enemy for helping myself relax. I don't do stop. I've led a busy working and home life in which relaxing had very little part, and nor did I want it to. I struggle to make the new myself do it, and can't wind down because I'm anxious about all the things I'm not doing.

I feel very sad most of the time, and even when I'm not tired, anxious or stressed and I should relax and have some enjoyment, I just can't. My family are fun-loving in a full-on way and I can't relax enough to have much enjoyment even with them. They do tease me to try and make me laugh, and sometimes I don't recognise this, so it upsets me. More and more now I am able to recognise the repeated teasing for what it is, just fun, and react more normally. I don't manage to relax and have fun very much, especially when out with special friends as their expectations of me to be the 'me' they made friends with feel threatening to the mixed up feelings I have about myself. I find it a lot easier to talk to people and be 'myself?' if I have never met them before and they have no expectations of who I am, they just take me for the person that I appear to be. In that situation I can relax and almost feel okay about the person that I am now. I can still be sociable, polite, helpful, even enjoy a bit of a joke. I can relax and not feel threatened by the muddle of who I was. It's like I'm starting again, as the new me, and it feels okay. This has made it a lot easier for me to take friendship and support from the other people with brain difficulties, and the therapists whom I have met along the way. It has been easier for me to spend time with them and feel like a person accepted for who I am.

I feel completely separate from the world I think I used to live in, I suppose I just carried on with life; wife, mother to four children, nurse, close friend, a person known, loved and valued by so many people. I feel now that I am no more the person I was and I have a huge difficulty feeling any sense of belonging in this new world.

I know I am not the same person that I was before my illness and that my life has changed completely. I have to take ten deep breaths before I venture out into the village in case someone speaks to me, I avoid meeting up with my close friends and keep a low profile when I do, and I struggle hugely emotionally with my family. Since having my illness I have found social contact much easier to manage by emails. I don't need any facial recognition and I have time to think about what to say, and reply, without any body language or facial nuances to try to understand. I am able to re-read post messages to jog my memory and then write and say as much or as little as I like at that time. I can even change my mind about what I have said which is easy to do and doesn't involve a whole lot of shock and guilt, laughing or teasing. I can take those three deep breaths, and choose a moment when I am calm and able to manage the communication positively and properly. None of these are possible at the village post office or when answering the phone. I never answer the phone unless I have to.

I have been encouraged by my rehabilitation therapists to use relaxation methods: specific CD to listen quietly to, using breathing techniques and taking proper rest time.

I have had support to help me face the difficulty of asking people who they are; polite and practical methods of trying to know who they are and ways of explaining my difficulties to them. It feels so rude and un-caring to have to ask. Many people now just come straight up to my face and announce their name with great pleasure and I do get lots of hugs.

I have always said, "I was born a nurse" and have worked my heart out for the NHS for 27 years, so recently having my contract terminated on ill-health grounds has broken my heart. I know I can't do the job I did because of my memory and confidence problems but the one thing that has kept me going was the Occupational Health Consultant saying to me "I'm not saying that you can't do anything".

My poor family have had to live with me throughout my illness, struggling hugely with my sense of negativity and my loss of any feelings of belonging, even to them. All our interactions are complicated both practically and emotionally and as much as they have tried to help me, I have misunderstood and felt rejected, pushed out by losing my own sense of any worth. I feel my husband organises the family and that the children refer to him for everything, quite fairly as I feel I can't be trusted to give the correct answer – even down to the basic question "When's tea?"

I am feeling almost like I am one of the children at times. I have been unable to drive for the last year, following a tonic-clonic seizure, and don't do any of the household shopping, but I can do household jobs and cooking – now even without a timing list, so I am improving. I can even do a roast dinner now, let alone dippy eggs using a timer. I have even coped recently with my husband teasing me, and calling me "a housewife" which I not only recognised as fun, but I managed to tell myself should feel positive, not negative.

I do need to remember that, although my life has turned upside down, it has also been a huge emotional upset for my family. The sooner I accept that going backwards isn't going to help, the more positive I will feel about going forwards. My family have always been there to help me, even when it hasn't quite felt like it, and I am a very privileged and thankful person. I want to relax and enjoy life again, enjoy being with them and I have been very lucky to have the support of specialist people to help not just me, but all the family to support us managing. I know that I have to face what has happened and try to move forwards and not dwell on my difficulties. I need to do this for myself and all my family and friends.

I have recently accepted the idea that rehabilitation is not synonymous with recovery – and that I can't expect to get back to be the person I was before the illness. I will do my best to use the strategies I have been given to continue to help myself to become a new happy, meaningful, belonging, valued and loving person, caring and sharing. A year ago I had never heard of a strategy application, let alone cognitive thinking! I know there are things which may never mend – like the part of my brain which tells me the truth about taste and smell and that I may never taste chocolate again or be able to smell roses. But I do know that brains are good at learning and I am busy teaching mine about who I know and how I know them, what paths in our lives have crossed. I get great pleasure from writing a friendship book where I write information down to re-read. I use face-on photographs with names. I make photo-scrapbooks and watch old home videos with my family to help me improve my sense of belonging. My husband and children enjoyed these and I became able to relax and laugh at their pleasure shouting out "There's you Mum!!" "We had a storm that night!!" Many bits of memory were happily jogged so that I coped with the bits missing without too much heartache.

My brain has been taught to use a Filofax and not to scribble on millions of scraps of old paper and then lose them. And I have learnt not to hide any more official letters or documents so they can never be found – and I keep my clothing.

Right from coming home from hospital I have used a pack of cards to gain some relaxation and feel like I am getting my head together. I have recently read about Clive Wearing and was amazed that I am playing patience almost addictively, rather like he did. I pester others to play card games with me and have played on many train journeys to pass the time and reduce agitation and worry about the journey and what the day may have in store. I have been lucky to travel with other clients to our centre for rehabilitation but strangers on the train have often joined in a card game very happily. It's an easy type of social communication which I cope well with and feel enjoyment and sharing out of.

Over a long period of wonderful rehabilitation I have realised that we only have one life, and that I should live it. They have helped me to form strategies to do this. They can't do it for me. No-one can. I have to do it for myself. No-one can mend my brain.

How lucky I am to be able to say that my heart is in the right place, even if my head isn't.

I give huge thanks to the heads and hearts of my family, my friends and all the caring therapists who have helped me so much throughout my illness and who still give me understanding, caring and a more positive outlook for my future.

Claire Rytina,
December 2006.

Eosinophillic Meningitis due to Angiostrongylus Cantonensis: First Reported Case in the UK

Angiostrongylus cantonensis, the rat lungworm, is the commonest cause of eosinophilic meningitis worldwide.[1] The organism is endemic in Southeast Asia and the Caribbean, although an increase in world travel has seen cases occurring outside of these areas. Cases have been documented in the USA,[2] Switzerland,[3] Australia,[4] and New Zealand.[5] There are no previous reported cases of angiostrongyliasis in the UK. Eosinophilic meningitis is rare in the UK and awareness of parasitosis as an emergent cause of infectious disease remains relatively low. We report a case of A. cantonensis infection in a female patient returning to the UK from Thailand.

Case report

A thirty-year-old Thai woman, living in the UK, attended her local district general hospital with five days of worsening headache and meningism. The patient had been a resident of the UK for two years but had visited Thailand recently, returning ten days prior to her presentation to hospital. On her admission she was pyrexial with a temperature of 38°C. She had nuchal rigidity and photophobia, but no focal neurological deficits. A CT brain scan was reported as normal and lumbar puncture revealed slightly turbid CSF with 626 WBC per mm^3 (90% lymphocytes, 10% polymorphs). CSF protein was 0.55g/L (normal 0.15-0.45). No organisms were seen on Gram stain and there was no growth on bacterial culture. The patient was treated symptomatically with a presumptive diagnosis of viral meningitis and discharged after seven days. At home, the patient's headache worsened and she developed diplopia and hyperaesthesia of the right lower limb. She was readmitted to her district general hospital nine days later and underwent further lumbar puncture. This revealed slightly turbid CSF with 483 WBC per mm^3 (70% lymphocytes, 30% polymorphs). CSF protein was 0.75g/L. She was commenced on intravenous Aciclovir and an MRI of the brain ordered. MR scanning revealed multiple hyperintense white matter lesions and the patient was then transferred to the regional neurology centre.

On arrival, the patient was pyrexial (38°C) with signs of nuchal rigidity and photophobia. She had a right sixth cranial nerve palsy and a patch of altered sensation over the lateral border of her right lower limb. No other abnormalities were evident on neurological examination. Review of her MRI scans revealed multiple white matter hyperintense lesions in the deep cerebral white matter, periventricular regions and in the corpus callosum, which did not enhance with gadolinium contrast (Figures 1 and 2). There was no enhancement of the pachymeninges. Lumbar puncture was repeated and revealed an opening pressure of 28cm of water, 361 WBC per mm^3 (70% lymphocytes), protein of 0.73g/L, glucose of 2.61mmol/L (serum glucose 5.3mmol/L) and was negative for AAFB.

Further questioning revealed that whilst recently in Thailand she had visited Bangkok and the Northern region of Isaan. She had eaten snails, which she believed to be cooked, as part of a salad in the village from where she originally came. She had no specific risk factors for HIV infection and said she had tested negative six months prior to this illness. Review of her blood results from the original hospital admission revealed an eosinophilia of 1.35*10^9/L (total white cell count 10.1*10^9/L), which had persisted into her second admission. This prompted re-examination of the original CSF samples for eosinophils. Cytological analysis revealed a significant eosinophilia (Figure 3). In light of this, a parasitic infection was considered likely, in particular 'rat lungworm' meningitis caused by Angiostrongylus cantonensis.

While further microbiological investigations were being performed, the patient was treated with isoniazid, rifampacin, pyrazinamide and ethambutol with dexamethasone to cover the possibility of tuberculous meningitis. We discussed the case with the Department of Parasitology at the Hospital for tropical diseases in London, who arranged to send the patients serum and CSF samples to Bangkok to test for *Angiostrongylus cantonensis* and *Gnathostomia spinigerum* antibodies.

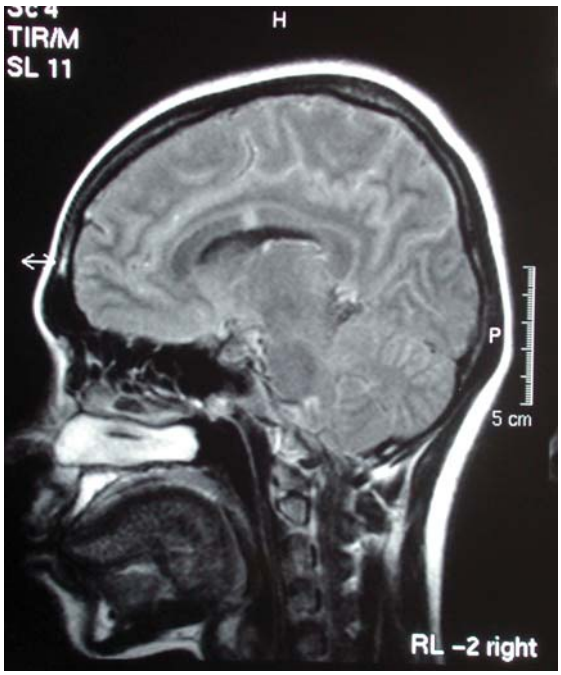

Figure 1: MR scan of the brain showing high signal lesion on the corpus callosum on T1 weighted images.

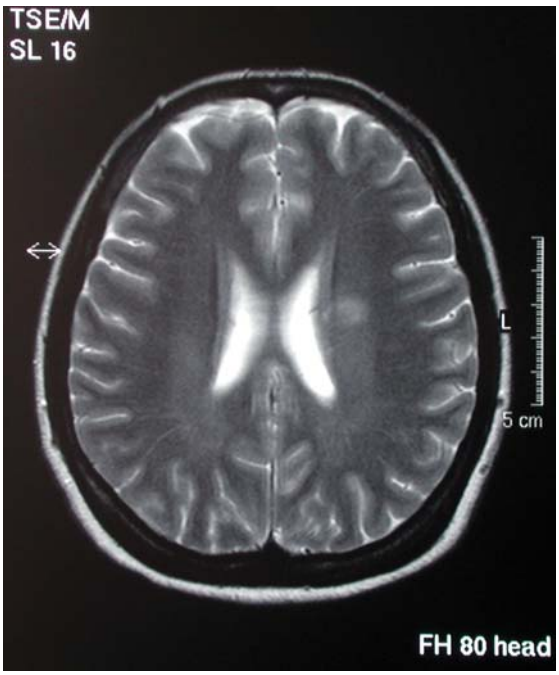

Figure 2: High signal lesion in the deep white matter on T2 weighted images.

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This is the ABN Case Report Winner and we congratulate the authors on this achievement.

If you would like to report similar interesting case reports then do contact us at: patriciamcdonnell@btinternet.com

Polymerase Chain Reaction (PCR) for herpes simplex virus, varicella zoster virus, enterovirus and parechovirus nucleic acids were negative in the CSF. PCR for Mycobacterium tuberculosis was also negative. Serum HIV test was negative and cryptococcal antigen was not detected in the CSF. Stool and urine were negative for ova, cysts and parasites. As she was originally from an endemic area for Strongyloides stercoralis and was receiving steroids as part of the antituberculosis treatment, she was treated with Ivermectin to prevent strongyloides hyperinfestation. ELISA testing for Strongyloides was positive. Her symptoms however, were not thought to be attributable to Strongyloides infection.

The patient's symptoms improved with reduction in severity of headache, resolution of meningism and improvement in diplopia. Repeat MRI scan of the brain showed almost complete resolution of the white matter lesions seen on the initial scan. Thirteen days after admission she was discharged home. Upon review seventeen days later her headache had considerably improved and she had no diplopia. Neurological examination was normal. Repeat lumbar puncture showed 170 WBC, predominantly lymphocytes.

Serum and CSF results confirmed infection with Angiostrongylus cantonensis. Anti tuberculosis chemotherapy was stopped and the dexamethasone tapered at a rate of 1mg per week until stopped. One month later she returned complaining of increasing headache and neck stiffness. Repeat LP revealed 506 WBC per mm^3 (80% eosinophils). She was then treated with a further reducing course of dexamethasone. The patient's symptoms improved and her CSF WBC returned to normal.

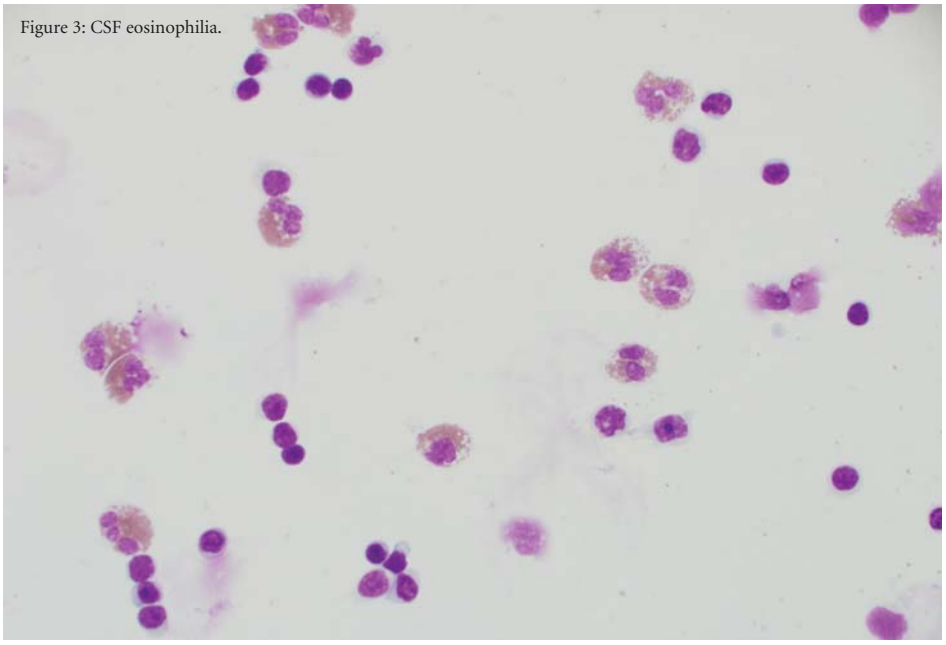

Figure 3: CSF eosinophilia.

Discussion

Angiostrongylus cantonensis is the most common cause of eosinophilic meningitis worldwide. This helminth is endemic in Southeast Asia and the Caribbean, and the disease is well recognised in these areas. The rat is the primary host of A. cantonensis. First stage larvae hatch in the lungs of rats and migrate into rat faeces via the trachea and gut. Molluscs that feed on rat excrement become intermediate hosts and within these organisms the first stage larvae moult twice to become the infective third stage larvae. Humans who eat the snails may then become infected. Vegetables contaminated with mollusc slime can also be a source of infection, as can transport hosts such as freshwater prawns, fish or crabs. In humans, larvae migrate via the bloodstream to the CNS where they cause an inflammatory response. Man is an accidental end stage host in which the larvae are unable to complete their life cycle and eventually die.[1,6]

Symptoms occur 4-23 days after infection.[7] The illness is characterised by headache and meningism.[2] Hyperaesthesia and paraesthesia are well described.[1] Other symptoms may include visual disturbance, fever, fatigue and cognitive impairment.[7,8] On examination there may be photophobia, nuchal rigidity, sensory disturbance, encephalopathy, and cranial nerve, including abducens and facial nerve, palsy.[2,7]

In this case, finding a peripheral eosinophilia prompted the search for parasitic causes and necessitated re-examination of the CSF for eosinophils. If parasitosis is clinically suspected the CSF should be specifically examined for eosinophils. It may be possible to visualise the worms on direct microscopy. The diagnosis can be confirmed by serological tests on serum and CSF.

The MRI scan in the patient described above demonstrated high signal lesions in deep white matter and corpus callosum, reminiscent of demyelination. A wide variety of MRI abnormalities have been reported in Angiostrongyliasis. High T2 signal intensity lesions, contrast enhancing lesions, meningeal enhancement and high signal intensity in the globus pallidus have all been reported.[9,10,11]

We gave our patient no specific treatment for A. cantonensis infection. Treatment is primarily supportive, with repeated lumbar puncture thought to relieve symptoms of persistent headache due to raised intracranial pressure. Anthelmintics can theoretically worsen symptoms due to an inflammatory reaction to dying worms. One randomised, double blind, placebo controlled trial has assessed the use of corticosteroids in eosinophilic meningitis.[12] This trial concluded that a two week course of prednisolone, 60mg per day, significantly reduced headache and the need for repeat lumbar puncture. No adverse effects were reported. In our patient, we believe that the initial improvement in symptoms and CSF findings was due to dexamethasone which she received as part of antituberculous treatment. Her symptoms recurred and CSF eosninophilia worsened after discontinuing the steroids, but a further, more prolonged, course of steroids had a beneficial effect.

In cases of meningitis in travellers returning from endemic areas, it is vital to specifically look for eosinophils in the CSF. A. cantonensis is the commonest cause of eosinophilic meningitis worldwide, and subacute meningitis with associated hyperaesthesia and paraesthesia should alert the clinician to this organism. MRI scan appearances in this condition can be normal or widely variable. The hyperintense T2 signal lesions can appear demyelinating in character and location. This is, to our knowledge, the first reported case of A. cantonensis meningitis in the UK. With increasing international travel, it is likely that cases will be encountered more frequently in the future.

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The 7th International Congress of Neuroimmunology

Nagoya, Japan, 15-19 October 2006.

For five days, on alternate years, the International Society of Neuroimmunology (ISNI) brings together research groups from all over the globe that are dedicated to understanding the relationship between the central and peripheral nervous system and the immune system in both health and disease. This year the conference was held in Nagoya - Japan's fourth largest city located on the Pacific coast; one of Japan's major ports. The newly opened conference centre housed some 2000 delegates attending distinguished review talks, plenary sessions, workshops, seminars, poster sessions and satellite symposia. There were many highlights; a handful of which are described below. I cannot however fail to applaud the traditional Japanese folk music 'minyo', to which the delegates were treated on the penultimate evening (compelling most to learn some new moves on the dance floor). Singers were accompanied by the 3 stringed lute known as the shamisen, taiko drums and a 13 stringed zither known as the koto.

IL17/23 cells

The breaking story of T cell immunology over the last two years has been the discovery of a new type of helper T cell, called the Th17 cell. (It is called this not because Th1 through to Th16 have already been defined, but because these secrete interleukin-17). In fact, like Helicobacter, these cells were always there, but their presence has been misunderstood. All the exciting news about this cell are summarised in Claire Helliwell's immunology primer in this issue of *ACNR* (page 8).

Now this scheme has to be redrawn. It turns out that a key experiment was flawed. The IL-12 receptor subunit knock-out in these animals also forms part of the IL-23 receptor. So, both IL-12 and IL-23 function was being neutralised. IL-23 stimulates a new kind of cell which secretes high levels of IL-17 and low levels of IFN-γ or IL-4. It is these cells, called 'Th17 cells', which drive EAE, not IFN-γ secreting Th1 cells. Animals that truly lack IL-12, but retain IL-23 and Il-17, still get EAE. Daniel Cua from Shering-Plough Biopharma, USA - also showed that the transcription factor that drives naïve cells to become IL-17 cells is called retinoid orphan receptor (ROR). This, is in turn promoted by a cytokine milieu in which there is IL-6 and IGF-β.

Burkhard Becher (Zurich) showed that Th17 cells secrete IL-22 as well as Il-17; but IL-22 knock-outs are not resistant to EAE and EAE brains do not contain IL-22 when examined histologically. However, VJ Kuchroo has shown that IL-22 is expressed in the EAE model of neuromyelitis optica developed by Wekerle and himself.

A new treatment for Guillain-Barré

Huw Willison's group in Glasgow have studied the neuromuscular effect of the anti-ganglioside antibody, anti-GD1a, that is normally produced in the motor axonal form of Guillain-Barré. They showed this antibody destroys the motor nerve endplate, by a process that is dependent upon the presence of complement.

Very happily, there is now a drug that can block complement in humans. A monoclonal antibody against complement, C5, (*ecluzimab*) has been used effectively as a treatment for paroxysmal nocturnal haemoglobinuria. Willison and colleagues are attempting to secure funding for a trial of *ecluzimab* in Guilllain-Barre.

Predicting who needs treatment in MS

The factors that determine the localisation of multiple sclerosis lesions are far from understood. It was interesting, therefore, to hear Michael Pender present data suggesting that proteolipid protein (PLP) reactivity drives the development of brainstem and cerebellar lesions.

His group performed HLA-DR and HLA-DQ typing and examined T cell reactivity (proliferation assays) to myelin proteins in 121 patients with MS, 71 healthy controls and 47 patients with other neurological disorders. Patients were assessed clinically by a blinded assessor and gadolinium enhanced MRI scans were performed. They found that nearly 50% of patients with brainstem and or cerebellar disease had increased T cell responses to the immuno-dominant region of myelin $PLP_{184-209}$, but not to other myelin proteins, compared to 10% of MS subjects without brainstem or cerebellar lesions, 11% of healthy controls and 19% of patient with other CNS disease.

They also found that 79% of patients with brainstem and or cerebellar lesions carried the HLA-DR4, DR7 or DR13 alleles compared to 29% of patients with disease elsewhere. In addition, the majority of patients with HLA-DR4, DR7 or DR13 alleles had increased T cell reactivity to $PLP_{184-209}$ compared to only 12% of patients not carrying these alleles.

They concluded that reactivity to $PLP_{184-209}$ drives the development of brainstem and cerebellar lesions and suggested that patients carrying the susceptibility alleles HLA-DR4, DR7 or DR13 may benefit from therapy with altered peptide ligands based on $PLP_{184-209}$.

How the immune system protects against autoimmunity - a step closer.

The demands on our immune system are great: the system must defend against incoming pathogens, repair damaged tissue, recognise and remove abnormal cells, all without causing disease (autoimmunity). Naturally occurring regulatory T cells (Tregs) play an essential role in the maintenance of peripheral self-tolerance. Tregs express elevated levels of the high affinity interleukin-2 (IL-2) receptor alpha subunit (CD25); neutralisation of IL-2 reduces the size of the CD4+CD25+ compartment inducing autoimmune disease in mice. Tregs also express FoxP3, a transcription factor which is critical in the development and function of Tregs. Transduction of FoxP3 into effector T cells results in these cells differentiating into Tregs, however, the mechanism by which FoxP3 prevents the emergence of autoimmune diseases have remained unsolved until now.

Shimon Sakaguchi has shown that FoxP3 interacts with acute myeloid leukaemia 1 (AML1 also known as Runx1). AML1 regulates the expression of a variety of haematopoietic genes and is a critical regulator of haematopoietic development, including T cell development. A variety of post-translational modifications can modulate AML1 activity and these determine whether AML1 acts as a transcriptional repressor or activator of gene expression.

AML1 binds to the IL-2 promoter upon T cell receptor (TCR) stimulation. Sakaguchi showed that FoxP3 binds to AML1 and suppresses AML1 enhanced IL-2 production. T cells that do not express AML1 fail to bind wild type FoxP3, do not suppress IL-2 production and fail to up-regulate CD25, CTLA-4 and GITR, markers of Tregs; these cells were also shown to be less suppressive than those that could bind AML1 in a functional assay. Sakaguchi also demonstrated that single nucleotide polymorphisms (SNPs) affecting the AML1/FoxP3 interaction resulted in susceptibility to rheumatoid arthritis, systemic lupus erythematosus, psoriasis and other autoimmune diseases.

This work is crucial in our understanding of the regulation of self-tolerance and the mechanisms that control the critical balance that our immune system has to strike between defense, repair and autoimmunity. Importantly, it offers a possible target for future treatments that can hope to prevent autoimmunity without causing immunosuppression.

The enhancement of neurogenesis post stroke - a new role for rosiglitazone?

The formation and maintenance of central nervous system circuit integrity has been a focus of Theo Palmer's work for over ten years. Now as assistant professor in Neurosurgery at Stanford University, he presented recent data examining the roles of inflammation on neurogenesis. He showed that in a post-stroke rat model, neurogenesis is enhanced, and microglial activation is suppressed, by non-steroidal drugs such as indomethacin. However, these results were overshadowed by the superior results seen with rosiglitazone. This peroxisome proliferator-activated receptor gamma agonist, used clinically in diabetics to enhance glycaemic control, is emerging as a new neuroprotective agent. How it does this remains to be defined, but is sure to involve modulation of pro-inflammatory cytokines and attenuation of an otherwise activated immune system.

Amanda Cox, Alasdair Coles
Dr Jo Jones,
Dr Vicki Robertson and
Dr Ben Wright.

PREVIEW: 75th Anniversary Celebrations of the Association of British Neurologists

Cambridge, UK, 11 – 13 April, 2007.

Homerton College, Cambridge.

The Association of British Neurologists will visit Cambridge on April 11-13th 2007 and this will form part of the 75th anniversary celebrations of the Association.

The main symposium on the Thursday will outline the history of Neurology in the United Kingdom during the 20th century, focusing on activities of the Association. The programme for Thursday also includes a guest lecture on spinal cord injury and repair by Professor James Fawcett. One of the meeting highlights will be the unveiling of the ABN Coat of Arms on the Thursday evening.

The Conference Dinner is at Kings College with music from members of the College Choir. Our principal guest is Baroness Onora O'Neill – Reith lecturer in 2002, and an authority on bioethics.

We shall be building upon the previous success of the case presentation competition and again putting greater focus upon poster presentations. The scientific events close with a debate with the motion 'Modernising Medical Careers for patients, trainees and the practice of neurology,' proposed by Chris Clough, and opposed by Professor Compston.

We are looking forward to seeing everyone in Cambridge and hope to make this an enjoyable, memorable and instructive meeting of the Association, fit for our 75th anniversary.

Association of British Neurologists.

PREVIEW: 17th Meeting of the European Neurological Society

Rhodes, Greece, 16 – 20 June, 2007.

Neurology: Learning, knowledge, progress and the future

Key lectures:
- Axonal protection in chronic inflammatory neurological disorders
- Mitochondrial disorders
- Repair of brain and spinal cord injuries
- Stroke prevention

The ENS 2007 scientific programme includes 4 symposia featuring lectures by experts discussing new advances in neurology and clinical neurosciences. The first symposium on Monday is the presidential symposium on axonal protection in chronic inflammatory neurologic disorders, chaired by G Comi. This symposium will include lectures on mechanisms between inflammation and axonal degeneration, the implication of stem-cells for regeneration as well as new therapeutical avenues.

On Tuesday, two symposia will run in parallel. The first symposium deals with mitochondrial diseases and will be chaired by P Chinnery and includes lectures on the clinical investigation of mitochondrial disorders, the discovery of novel nuclear genes, the management of mitochondrial disorders and the implication of mitochondrial dysfunction in common neurological disorders.

The other symposium - chaired by V Dietz - is devoted to the contribution of repair of brain and spinal cord injuries and includes lectures on neuronal plasticity of the spinal cord injury, achievements in basic research on regeneration and advances in experimental spinal cord injury.

On Wednesday, the symposium focussing on stroke prevention will be chaired D Leys and includes lectures on preventing early recurrences after cerebral ischaemic event, new development in antiplatelet therapy, stroke prevention in women and stroke prevention in young adults.

This will be followed by the best of free communications 2007 which will give a summary of the best papers presented during the meeting.

In addition to the symposia, the scientific programme includes 5 poster sessions and 16 oral sessions of free communication. There will be an integrated programme on the management of MS patients, on the treatment of acute stroke and of motoneuron disease. After the successful introduction of poster walks last year, we will once again have these to display the posters in a more lively and interesting format. Experts will lead a review of selected posters promoting discussion with the authors.

Prof A Steck, Executive Committee.

Visit the ENS 2007 website www.ensinfo.com featuring:
- Continuously updated scientific programme
- Online abstract submission (deadline February 7, 2007)
- Online registration as well as hotel & tour registration
- Information about Rhodes

To list your event in this diary, email brief details to Patricia McDonnell at patriciamcdonnell@btinternet.com by January 22nd, 2007

2007

January

NEW
Understanding and treating cognitive problems after brain injury.
12-13 January, 2007; London, UK
W. www.braintreetraining.co.uk
E. enquiries@braintreetraining.co.uk

NEW
Encephalitis Society Professional Seminar
16 January, 2007; Liverpool; UK
T. 01653 692 583 F. 01653 604 369
E. mail@encephalitis.info
W. www.encephalitis.info

BISWG South Wales and the West Country Regional Meeting
18 January, 2007; Cardiff
Kate Coles
T. 02920 224871
E. kate.coles@hughjames.com

35th National Conference Indian Association of PMR Specialists
19-21 January 2007; Patna, India
E. pmrenquiry@yahoo.com
ajitvarma592@yahoo.com

NEW
Multiple Sclerosis Trust Masterclass in Postural Management
30 January, 2007; London, UK
W. www.mstrust.org.uk
T. 01462 476704 E.
Education@mstrust.org.uk

February

Think Ahead Think Success - OT Support Workers 2nd Biennial National Conference
6 February, 2007; York, UK
Julie Hawkins
T. 020 7450 2337
F. 020 7450 2349
E. julie.hawkins@cot.co.uk

NEW
RSM Schizophrenia
7 February, 2007; Cardiff, UK
T. 020 7290 2965
E. primrose.ante-bennett@rsm.ac.uk

35th Annual INS Meeting
7-10 February, 2007; Portland, Oregon, USA
International Neuropsychological Society
T. + (614) 263-4200
F. + (614) 263-4366
E. ins@osu.edu

NEW
Multiple Sclerosis Trust General Study Day in MS
8 February, 2007; Stoke, UK
W. www.mstrust.org.uk
T. 01462 476704
E. Education@mstrust.org.uk

The Society for Research in Rehabilitation Winter Meeting
8 February, 2007; Sheffield, UK
W. www.srr.org.uk
E. m.marshall@sheffield.ac.uk

Global Conference on Neuroprotection & Neuroregeneration
14-16 February, 2007; Garmisch-Partenkirchen, Germany
W. www.gcnpnr.org

NEW
RCSE Intracranial and Spinal Anatomy for Neurosurgeons
19-23 February, 2007; London, UK
T. 020 7869 6332
F. 020 7869 6329
E. neurosurgery@rcseng.ac.uk

3rd Annual Update Symposium on Clinical Neurology and Neurophysiology
19-21 February; 2007, Tel Aviv, Israel
W. www.neurophysiology-symposium.com

1st East Mediterran Epilepsy Congress
21-24 February, 2007; Luxor, Egypt
T. +353 1 205 6720
F. +353 1 205 6156
E. info@epilepsycongress.org

British Neuropsychiatry Association 2007 Meeting - Parkinson's Disease, Epilepsy, Mind and Brain: The next 20 years
22-23 February 2007; London, UK
T/F. 01621 843334
E. gwen.cutmore@lineone.net
W. www.bnpa.org.uk

March

NEW
Myelination, Demyelination and Multiple Sclerosis 2007
2 March, 2007; London, UK
W. www.abcam.com/myelin2007

1st Congress on Epilepsy, Mind & Brain
2-4 March, 2007; Prague, Czech Republic
W. www.kenes.com/epilepsy

NEW
Multiple Sclerosis Trust Annual Meeting for Specialist Nurses
6-7 March, 2007; York, UK
W. www.mstrust.org.uk
T. 01462 476704, E. Education@mstrust.org.uk

International Congress on Neurology and Rehabilitation (ICNR)
9-11 March, 2007; New Delhi, India
E. icnr2007@gmail.com
W. www.iamst.com

23rd Annual Pacific Rim Conference on Disabilities
12-13 March, 2007; Waikiki, Hawaii
E. prinfo@hawaii.edu
W. www.pacrim.hawaii.edu

NEW
First London Colloquium on Status Epilepticus
12-15 April, 2007; London, UK
E. denise@conference2k.com
T. 01323 740 612 / 01691 650 290

4th Annual Meeting of the Global College of Neuroprotection & Neuroregeneration
14-16 March, 2007; Garmisch-Partenkirchen, Germany
W. www.gcnpnr.org
E. info@gcnpnr.org
T. +44 115 969 2016, F. +44 115 969 2017

8th International Conference AD/PD 2007
14-18 March, 2007; Salzburg, Austria
W. www.kenes.com/adpd/

NEW
RSM "Growth factors and psychiatric disorders"
23 March, 2007; London, UK
T 0207 290 2965
E. primrose.ante-bennett@rsm.ac.uk

1st International Congress on Epilepsy, Mind & Brain
29-31 March, 2007; Prague, Czech Republic
T. +41 22 908 0488
F. +41 22 732 2850
E. epilepsy@kenes.com

April

NEW
International Symposium on 'Brain Ageing and Dementia in Developing Countries'
10-13 April, 2007; Nairobi, Kenya
Samantha Tannahill, c/o Prof RN Kalaria
T. +44 191 256 3206
F. +44 191 256 3011
E. advascular@ncl.ac.uk
W. http://advascular.ncl.ac.uk

Certificate Course in Neurological Rehabilitation
10-27 April, 2007; Newcastle upon Tyne, UK
E: traceymole@wfnr.co.uk

ABN Spring Scientific Meeting
11-13 April, 2007; Cambridge, UK
Info: info@theabn.org

NEW
1st London Colloquium on Status Epilepticus
12-15 April, 2007; London, UK
T. 01323 740 612 / 01691 650 290
F. 01691 670 302.

Alzheimer's Disease: Update on Research, Treatment, and Care
12-13 April, 2007; San Diego, California, USA
W. htttp://cme.ucsd.edu

NEW
Understanding and treating insight problems after brain injury
20-21 April, 2007; London, UK
W. www.braintreetraining.co.uk
E. enquiries@braintreetraining.co.uk

The Challenges of Commissioning for Brain Injury Services-A National Conference
25 April, 2007; London, UK
Patti Simonson
T. 0208 780 4530
F. 0208 780 4530
E. psimonson@rhn.org.uk

NEW
Synaptic Plasticity in Pain
27 April, 2007; London, UK
W. http://www.abcam.com/pain07

NEW
5th Staffordshire Conference On Clinical Biomechanics
27 - 28 April, 2007; Stoke-on-Trent, UK
Cheryl Blewitt
E. c.l.blewitt@staffs.ac.uk
T. 01782 294341

59th Annual Meeting of the American Academy of Neurology
28 April-5 May, 2007; Boston, USA
W. www.aan.com

American Academy of Neuroscience Nursing (AANN) Annual Meeting
29 April – 2 May, 2007; Orlando, USA
E. info@aann.org

May

NEW
Management of Parkinson's disease - Joint conference of the Royal College of Physicians and the Parkinson's Disease Society
3 May, 2007; London, UK
RCP Conference Dept
T. 0207 935 1174 ext 252/300/436
E. conferences@rcplondon.ac.uk

NEW
Visual Perceptual Dysfunction and brain injury, Part 2
9 - 11May, 2007; London, UK
W. www.braintreetraining.co.uk
E. enquiries@braintreetraining.co.uk

NEW
Brain Development 2007
10 May, 2007; London, UK
W. www.abcam.com/brain2007

EFNS Academy for Young Neurologists 8th Course
10-13 May, 2007; Staré Splavy, Czech Republic
E. efns@fnkv.cz or pragueoffice@efns.org
T/F. +420 2 6716 35 63

NEW
Primary Care Neurology Society 2007 Conference
17 May, 2007; Birmingham, UK
W. www.p-cns.org.uk

NEW
Multiple Sclerosis Trust Masterclass for MS Specialist Nurses
22 May, 2007; London, UK
W. www.mstrust.org.uk
T. 01462 476704
E. Education@mstrust.org.uk

2nd Biennial Vocational Outcomes in Traumatic Brain Injury Conference
24-26 May, 2007; Vancouver, BC Canada
E. sljproductions@telus.net
W. www.tbicvancouver.com

8th European Neuro-Ophthalmology Society Meeting
26-29 May, 2007; Istanbul
Pinar Aydin O'dwyer
E. Aydinp@Eunos2007.Org
W. www.Eunos2007.Org

XVI European Stroke Congress
29 May – 1 June, 2007; Glasgow, UK
E. info@stroke.org.uk

Consortium of Multiple Sclerosis Centers (CMSC)
30 May – 3 June, 2007; Washington DC, USA
E. info@mscare.org

June

39th International Danube Symposium for Neurological Sciences and Continuing Education in conjunction with the 1st International Congress on ADHD
2-5 June, 2007; Wurzburg, Germany
W. www.danube-wuerzburg.de or
www.adhd-wuerzburg.de

1st International Congress on ADHD: From Childhood to Adult Disease
3-7 June, 2007; Wuerzburg, Germany
E. peter.riederer@mail.uni-wuerzburg.de

11th International Congress of Parkinson's Disease and Movement Disorders
3-7 June, 2007; Istanbul, Turkey
W. www.movementdisorders.org/meetings/index.shtml

NEW
Multiple Sclerosis Trust Study Day in MS – Focus on Health Professionals in the Residential Environment
5 June, 2007; UK
W. www.mstrust.org.uk
T. 01462 476704
E. Education@mstrust.org.uk

Kuopio Stroke Symposium
6-8 June, 2007; Kuopio, Finland
E. jukka.jolkkonen@uku.fi
W. www.uku.fi/stroke2007

2nd International Congress on Neuropathic Pain
7-10 June 2007; Berlin, Germany
T. +41 22 908 0488
F. +41 22 732 2850
E. neuropain@kenes.com
W. www.kenes.com/neuropain

4th World Congress of the International Society of Physical Medicine and Rehabilitation
10-14 June, 2007; Seoul, Korea
E. isprm2007@intercom.co.kr
W. www.isprm2007.org

NEW
MS Frontiers - MS Society flagship research event presenting key themes in international MS research
14-15 June 2007; London, UK
T. 020 8438 0809
F. 020 8438 0877
E. pcrossman@mssociety.org.uk

Workshop: Prediction of Outcome
15-16 June, 2007; Erlangen, Germany
Prof. Dr. Hermann Stefan
E. Hermann.stefan@neuro.imed.uni-erlangen.de

17th Meeting of the European Neurological Society
16-20 June, 2007; Rhodes, Greece
W. www.ensinfo.com
T. +41 61 686 77 11
F. +41 61 686 77 88
E. info@akm.ch

Advances in Neurorehabilitation
Part of The Festival of International Conferences on Caregiving, Disability, Aging and Technology (FICCDAT)
16-19 June, 2007; Toronto, Canada
E. catherine@smartmove.ca
W. www.ficdat.ca

International Society for Stem Cell Research Meeting
17 –22 June, 2007; Cairns
Info: International Society for Stem Cell Research
T. +847-509-1944
F. +847-480-9282
E. isscr@isscr.org

2nd Neurorehabilitation Panamerican Congress
18-20 June, 2007; Buenos Aires, Argentina
E. dfelder@ineba.net
W. www.ineba.net

Canadian Neurological Sciences Federation (CNSF) 42nd Annual Scientific Meeting
19-22 June, 2007; Alberta, Canada
W. www.ccns.org

Seventeenth Meeting of the
European Neurological Society

June 16-20, 2007 – Rhodes/Greece

Neurologists in training offer
Deadline January 18, 2007

Young neurologists programme 2007

Following the great demand in 2006, ENS is pleased to offer once again a limited number of grants providing free accommodation from Saturday to Wednesday, including registration and admission to teaching courses at the ENS 2007 meeting in Rhodes to European Neurologists in training, born on or after January 1, 1972. This programme is **not** dependent on submitting an abstract.

Applications should provide a letter from chairman of their department to certify that they are in training as well as a copy of their passport.

The applicants must also select the 3 courses they want to attend. Application is only available **online** at www.akm.ch/ens2007.

Attendance to courses is compulsory and no-shows will be excluded from this offer in the future and will be charged for their attendance.

Deadline for applications: **18 January 2007**. Applications without passport copy or arriving after this date will not be considered.

Good qualitiy accommodation has been reserved this year and will be on a double room occupancy basis. We invite applicants to mention on their registration form the name of another young neurologist they would wish to share the room with.

For further information please check our regularly updated website: **www.ensinfo.com**

Please apply online on **www.ensinfo.com** – ENS 2007 the online application will be available from October onwards.

Separately to this offer, young colleagues who have an abstract accepted for presentation at the ENS meeting may also apply for a travel grant. Please see further details on the congress website.

Visit the ENS 2007 website featuring:

- Continuously updated scientific programme
- **Online abstract submission (deadline February 7, 2007)**
- Online registration as well as hotel & tour reservations
- Option to compose your personal congress programme
- Details about the industrial exhibition
- Information on the congress venue and the island of Rhodes

www.ensinfo.com

For further information please contact:

Administrative Secretariat: 17th ENS 2007, c/o AKM Congress Service
P.O. Box, CH-4005 Basel / Switzerland
Phone +41 61 686 77 11 Fax +41 61 686 77 88 E-mail info@akm.ch

A Day in the Life...

...is a simple and fun way for European neuroscientists to get involved in communicating what you do to the public. Using a disposable camera to document your day, we want to show the public and young people in particular what the everyday lives of neuroscientists entail: highlighting the important research work as well as showing the human side to a career in neuroscience.

The project is run by The Manchester Science Group **www.manchesterscience.blogspot.com** and sponsored by the European Dana Alliance for the Brain.

To take part, email your postal address to: **mansci@googlemail.com** with **A DAY IN THE LIFE** in the subject line and you will receive a disposable camera pack and instructions.

BRAIN AWARENESS WEEK

BRAIN AWARENESS WEEK
Get Connected
EUROPEAN DANA ALLIANCE FOR THE BRAIN

12-18 MARCH 2007

A global celebration of the latest brain science

Brain Awareness Week is an annual celebration dedicated to raising public awareness of brain research. Coordinated by the European Dana Alliance for the Brain, and the Dana Alliance for Brain Initiatives in the US, Brain Awareness Week has become a major international collaboration.

You can become involved in Brain Awareness Week by organising an activity. By registering as a partner, and then posting your event, your organisation will be listed on our worldwide Brain Awareness Week calendar of events, and you will receive information on running and publicising your programmes.

Please join us in this major international campaign

To organise an event or get involved:
Contact EDAB on 020 7019 4914 or by email at enquiries@edab.net

www.edab.net

Great Ormond Street Hospital for Children NHS Trust

UCL

UCL Institute of Child Health and
Great Ormond Street Hospital for Children NHS Trust

Practical Neurology Study Days 2007

19th – 23rd March 2007

Leolin Price Lecture Theatre, Institute of Child Health

Organisers:

Vijeya Ganesan, Sarah Aylett, Carlos de Sousa, Catherine DeVile, and Robert Surtees.

These study days are to help clinicians update their knowledge regarding common paediatric neurology problems, develop practical skills in dealing with common acute neurology problems and consider management of neurological illness in different settings.

The course uses a combination of lectures, interactive sessions, case presentations, slides and videos. All the lecturers are currently practising paediatric neurologists.

Monday	Overview of Paediatric Neurology & Epilepsy
Tuesday	Headaches, Hydrocephalus, Brain Tumours & Spinal Cord
Wednesday	Neuromuscular Disorders
Thursday	Acute Neurology
Friday	Neurogenetic & Neurometabolic Disorders

The course is intended for:

Consultant hospital and Community Paediatricians, Trainees in Paediatrics, Neurology and Neurodisability

There are limited places available so book now to avoid disappointment!

Fees: £645 or £149 daily rate

For further information, please contact:
Courses and Conferences Office, Institute of Child Health,
30 Guilford Street, London WC1N 1EH, UK
Telephone: +44 (0)20 7829 8692, +44 (0)20 7905 2135;
Fax: +44 (0)20 7831 6902; e-mail: courses@ich.ucl.ac.uk;
Website: www.ichevents.com

The child first and always

Royal College of Physicians
Setting higher medical standards

Parkinson's Disease Society

MANAGEMENT OF PARKINSON'S DISEASE

Thursday 3 May 2007

at the Royal College of Physicians, 11 St Andrews Place, Regent's Park, London NW1

With the ageing of the population, the prevalence of Parkinson's disease is set to increase dramatically in the next 20 years. Research in this important condition has led to many significant developments in the last few years. This conference, organised by the Royal College of Physicians and the Parkinson's Disease Society will summarise recent developments in relation to the recently introduced NICE guidelines for the diagnosis and management of Parkinson's disease.

The programme and booking forms are available on-line: **www.rcplondon.ac.uk/conferences** or from:
Conference Department,
Royal College of Physicians
Tel: 020 7935 1174 Ext. 436/252/300
Fax: 020 7224 0719
Email: conferences@rcplondon.ac.uk

EUROPEAN FEDERATION OF NEUROLOGICAL SOCIETIES

11th CONGRESS OF THE EUROPEAN FEDERATION OF NEUROLOGICAL SOCIETIES

BRUSSELS, BELGIUM, AUGUST 25-28, 2007

President of EFNS Management Committee: **Jacques L. De Reuck**, Belgium
Chairperson of the Congress Programme Committee: **Gian Luigi Lenzi**, Italy
Chairperson of the Local Arrangements Committee: **Jean Schoenen**, Belgium

DEADLINE FOR SUBMISSION OF ABSTRACTS: FEBRUARY 15, 2007

The Congress Programme includes Teaching Courses, Focused Workshops, Special Sessions, Short Communications as well as the following Main Topics:

- RTMS and neuroplasticity
- Scientific basis of headache
- Frontiers in movement disorders
- The “more-than-6-hours” stroke
- Neuromuscular diseases
- Multiple sclerosis (MS) treatment: how and when?
- New disease modifying treatment approaches in Alzheimer’s disease
- Status epilepticus: toward European treatment guidelines

www.efns.org/efns2007

EDITOR'S CHOICE

HUNTINGTON'S DISEASE: new cells for old

The role of neural stem cells in neurodegenerative disorders has been something of a passion of mine for many years, as abnormalities in this process may have important implications for therapy both in terms of innate repair and exogenous cell transplants in disorders of the CNS. Furthermore, understanding the processes of neurogenesis in diseased brains may also provide us with a better understanding of abnormal signalling pathways involved in disease pathogenesis. This new paper from the van der Kooy group raises some very interesting questions on how disease processes may influence stem cell behaviour in one of the neurogenic regions of the adult brain (the subventricular zone [SVZ]) in the R6/2 transgenic mouse model of Huntington's disease. They report that in this mouse, which contains the expanded exon 1 CAG repeat of human Huntington's disease gene:

1. There is an increase in neural precursor cell/neurospheres generated from the SVZ in R6/2 mice compared to wild type with increasing age and the development of symptoms.
2. There is an increase in BrdU in the SVZ 30 days after injection in the R6/2 mice compared to the wild type, implying there is an increase in stem cells at this site which is confirmed using EM and the demonstration of more precursor 'B' cells in the SVZ in the R6/2 mice.
3. There is an increase in proliferation with age which occurs *in vitro* with cloning but only at a time when such abnormalities in proliferation have been seen in the R6/2 mouse *in vivo*.
4. The increase which is seen *in vitro* is clearly primed *in vivo* and cannot be mimicked by growing early stage neurospheres for longer periods of time *in vitro*.
5. There is no change in the fate potential of the precursor cells *in vivo* or *in vitro*.
6. There is a decrease in olfactory bulb BrdU positive cells with an increase the BrdU positive cells in the striatum, suggesting a switch in migration of the stem cells to sites of more pathology.

These series of observations suggest that, with disease progression in this mouse model of Huntington's disease, there is a steady increase in the number of stem cells in the SVZ which, once primed and induced *in vivo,* is maintained *in vitro*. This suggests that the stem cell changes its properties with the evolving disease process in the brain. This would therefore imply that, in neurodegenerative disorders of the CNS, there are signals that cause a fundamental switch in the properties of proliferating neural stem cells which attempts to compensate for the pathology. Obviously if this process can be properly harnessed, then it will have important implications for CNS repair, but the key question remains as to what that signal is and how can we manipulate it to effect better repair in conditions such as Huntington's disease. - ***RAB***

Batista CM, Kippin TE, Willaime-Morawek S, Shimabukuro MK, Akamatsu W, van der Kooy D.

A progressive and cell non-autonomous increase in striatal neural stem cells in the Huntington's disease R6/2 mouse.

JOURNAL OF NEUROSCIENCE

2006;26:10452-60.

HUNTINGTON'S DISEASE: up and down or side to side?

Huntington's chorea is characterised by cognitive decline and chorea, but patients often display other deficits, including abnormalities of eye movement. Blekher et al have carried out a detailed and sensitive series of oculomotor tests in a group of patients with HD. Clinical evaluation was carried out using the standardised clinical rating scale UHDRS (Unified Huntington's Disease Rating Scale). The study included 215 individuals grouped into four classes depending on the presence or absence of motor abnormalities representative of HD. All the individuals in this study had a parent affected with HD and followed one of two patterns: they were either at risk of HD but not yet diagnosed or they had been diagnosed with HD within the past two years. Both vertical and horizontal saccadic readings were recorded using a video eye tracking system. Eye movement measures included visually-guided, anti-saccade, predictable, memory-guided (two versions) and fixation tasks. None of the participants reported significant eye problems and all had normal or corrected visual acuity. The authors showed that HD gene carriers – but not nongene carriers - had impaired saccades and were particularly poor in anti-saccade and memory-guided tasks, and this when standard clinical assessments currently used in HD were normal. The improved sensitivity provided by these quantitative saccadic measures may open a new chapter in the diagnosis of disease onset and also may enable researchers to ascertain whether disease modifying therapies are just that. - ***CA***

Blekher T, Johnson SA, Marshall J, White K, Hui S, Weaver M, Gray J, Yee R, Stout JC, Beristain X, Wojcieszek J, Foroud T.

Saccades in presymptomatic and early stages of Huntington disease.

NEUROLOGY

2006;67:394-9.

STROKE: a pit of vipers

If you get bitten by a Malaysian pit viper, you may bleed to death. A key component of the venom is Ancrod which splits fibrinopeptide A from fibrinogen. Ancod has been used in several trials as a treatment for ischaemic stroke. The previous North American Stroke Treatment with Ancrod Trial (STAT) showed that Ancrod outperformed placebo if given within three hours of a stroke. This study looks at its ability to improve stroke outcome if given later, within six hours. The result, perhaps unsurprisingly given what we know of TPA, is that later treatment is not beneficial. Normally such a pedestrian study would not make it onto the review pages of *ACNR*, but it is the vipers in the last paragraph of the report that merit attention:

"Preliminary data from this trial were first presented at the World Federation of Neurology Congress in London in 2001. Soon thereafter, the sponsor company, which was always supportive of the scientific outcomes of this trial, was sold. In the meantime, data from the study were not fully available to the investigators, and further analysis was difficult. Only with the support of many dedicated investigators and after careful reassessment of the material finally provided, could the members of the executive and safety committees prepare this report on behalf of the investigators. This situation illustrates the understandable but often regrettable divergences between sponsor and investigators' interests, leading to scientific losses and unethical waste of patients' and investigators' efforts. The bias towards easier publication of successful trials, sometimes at too early a stage, is another important issue to consider: the publication of this report is therefore an important recognition of the scientific and medical value of all clinical trials."

The moral is that it is critical that investigators have free access to data accumulated in their trial. It has always amazed me that some investigators are prepared to work in any other way. - AJC

Hennerici MG, Kay R, Bogousslavsky J, Lenzi GL, Verstraete M, Orgogozo JM; ESTAT investigators.

Intravenous ancrod for acute ischaemic stroke in the European Stroke Treatment with Ancrod Trial: a randomised controlled trial.

LANCET

2006 Nov 25;368(9550):1871-8.

PARKINSON'S DISEASE: First gene therapy trial

This very short abstract buried at the back of an issue of Movement Disorders is one that was presented at the 20th Annual Symposium on the Aetiology, Pathogenesis and Treatment of Parkinson's Disease and Other Movement Disorders. This gives a very brief account (as one would expect) on 12 patients who have received open label unilateral subthalamic viral vector (AAV-GAD) injection as a treatment for their Parkinson's disease. This open label study involves 12 patients with an average age of 58.2 years and in this abstract the authors report on their FDG PET studies using this approach. The strategy involves trying to convert the excitatory subthalamic nucleus to an inhibitory one by changing the phenotype of the projection neurons from this structure and builds on earlier experimental work reported in Science in 2002 (see *ACNR* 2.5). Five patients appeared to respond to this virally delivered therapy and seven did not. In those that responded, there were clearly changes in FDG metabolism as one would anticipate, namely a decline in the internal globus pallidum and ventral lateral thalamus ipsilateral to the delivery of the viral vector and increased metabolism in the premotor and supplementary motor regions. These changes appear to correlate with improvements in their UPDRS scores. Whilst this is an abstract, it is important because this is the first ever gene therapy trial in Parkinson's disease and clearly gives us hope that this approach may have a future. - ***RAB***

Feigin A, Tang C, During M et al.

Gene therapy for Parkinson's disease with subthalamic nucleus AAV-GAD: FDG PET results.

MOVEMENT DISORDERS

2006;21:1543-4.

PARKINSON'S DISEASE: Get the rhythm

The role of dopamine in the control of movement is well known (*see for example the historical article in this issue of the ACNR by Oleh Hornykiewicz*), but how exactly dopamine achieves this is not altogether clear. The classical model of basal ganglia function has nigral dopamine stimulating the direct and indirect pathways through the striatum by activation of the D1 and D2 receptors on the projection neurons respectively. This then changes the outflow of the basal ganglia (the internal part of the globus pallidum and the substantia nigra pars reticulata) to the thalamus and so cortex, especially motor areas and by so doing contributes to the initiation of movement. As a result, in diseases such as Parkinson's disease (PD) there is a loss of the nigrostriatal dopaminergic projection with a decrease in activation of cortical areas, causing akinesia amongst other symptoms, presumably through a failure of motor cortical activation. However, a recent paper suggests that it may not be as simple as this and that dopamine may be more important in coordinating activity between the striatum and motor cortex, so that in PD the problem is more a loss of this synchronous activity. The work leading to this suggestion uses a dopamine transporter (DAT) knock out mouse in which dopamine levels can be easily manipulated such that:

a) a hyperdopaminergic state with hyperactivity can be achieved by placing the DAT knock out mouse in a novel environment;
b) a hypodopaminergic state with akinesia can be achieved by blocking dopamine synthesis using alpha methyl-p-tyrosine (AMPT) [as there are no dopamine stores to compensate for this synthetic block];
c) restoration of dopamine in the hypodopaminergic state can be achieved using L-dopa.

Using this system the authors show that there are differences in firing frequency (both at the single level and local field potential level) in the striatum and motor cortex with differing levels of dopaminergic tone. More importantly though, they show that with dopamine depletion the degree of synchrony between striatum and cortex is enhanced whilst the hyperdopaminergic state is characterised by asynchronous activity in corticostriatal networks. This is an interesting study given the recent work on the mechanisms underlying the beneficial effects of deep brain stimulation in PD and its postulated functions on changing corticostriatal rhythmicity and synchrony. However, this paper more importantly raises fundamental questions about how diffusely projecting neurotransmitters may work in the normal brain and how they fail in disease across networks and as such this work has implications on how best to treat conditions such as PD. - ***RAB***

Costa RM, Lin SC, Sotnikova TD, Cyr M, Gainetdinov RR, Caron MG, Nicolelis MA.
Rapid alterations in corticostriatal ensemble coordination during acute dopamine-dependent motor dysfunction.
NEURON
2006;52:359-69.

nvCJD: Its in the blood

★★★★ RECOMMENDED

Almost anything, however trivial, about variant CJD gets straight into the media, but this report probably deserves to, because it is very worrying. It describes the case of a 22-year-old man who, after several years of symptoms of inflammatory bowel disease, had an ileostomy. Complications of its reversal some time later were so severe that he required 22 units of blood transfusion. Unfortunately one of the donors of this blood died 20 months afterwards of variant CJD. The recipients were all informed there was a slight risk of developing CJD, which cannot have been an easy message to relay or receive. All was well for six years, and then the patient developed progressive limb pain, balance and cognitive deficits. He died nearly nine years after the vCJD implicated transfusion (age 32 years). Prior to death, a MRI had shown the pulvinar sign, which had not been seen on a scan done at the onset of symptoms. Deposition of type 4 PrP, the hallmark of vCJD, was seen post mortem throughout the cortex and cerebellum, and likewise in the tonsils. There are two other such cases in the literature, which does not amount to a whole lot of beans until you consider that the long incubation period of vCJD, and lack of reliable blood test, means that much of the transfusion stock may be contaminated. As Collinge told listeners of Radio 4's Today programme, we really need to know the results of the National Anonymous Tonsil Archive's screening of 100 000 tonsils for disease-associated PrP. It is still not clear whether vCJD is going to be a ghastly pandemic or a fascinating rarity. - ***AJC***

Wroe SJ, Pal S, Siddique D, Hyare H, Macfarlane R, Joiner S, Linehan JM, Brandner S, Wadsworth JD, Hewitt P, Collinge J.
Clinical presentation and pre-mortem diagnosis of variant Creutzfeldt-Jakob disease associated with blood transfusion: a case report.
LANCET
2006 Dec 9;368(9552):2061-7.

EPILEPSY: The cost of misdiagnosis

You all know that in everybody else's clinic, not your own of course, the chronic misdiagnosis of epilepsy is 20-25%. You all want to help those other neurologists resolve their diagnostic problems and the only way to do so is to have video-EEG-telemetry. You go to your friendly, local health care commissioner and tell them that epilepsy misdiagnosis causes misery, psychosocial deterioration, inappropriate treatment, lack of appropriate treatment and all those clinical things that medical practice is supposed to help. The response is: "That is all very interesting but how will you save money?" So here is the answer. Using standard prevalence and misdiagnosis rates, these authors calculate a misdiagnosis rate of 1,769 cases per million population. The cost of medical resources allocated to these patients was taken from another paper, including inappropriate admissions (45%), AEDs (26%), outpatient attendances (16%) and GP care (8%). The total they came to is £316 per patient. This is similar to the NICE guidelines calculation of £263 and works out as £559,076 per million population per year. I reckon it is still an underestimate, considering that a new AED for a year costs about £1,000. What we don't know from this calculation, is how much it will cost to treat the patient's true diagnosis, but so far my managers have not thought of this and I am not going to tell them. So now you have the data you can help all those other guys who can't diagnose fits. Good luck. Any other tips on managerial bamboozling, please email to mark.manford@addenbrookes.nhs.uk. - ***MRAM***

Juarez-Garcia A, Stokes T, Shaw B, Camosso-Stefinovic, Baker R.
The costs of epilepsy misdiagnosis in England and Wales.
SEIZURE
2006;15:598-605.

EPILEPSY: Sliced resistance to carbamazepine

★★★ RECOMMENDED

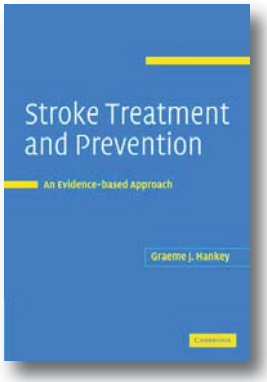
Antiepileptic drugs often don't work and epilepsy associated with hippocampal sclerosis is particularly resistant to medical treatment. Hypotheses for the mechanism of this resistance include failure of drugs to cross the blood brain barrier, but perhaps the varying effect of different drugs in different types of epilepsy make an alteration intrinsic to the tissue more likely. This study explored that possibility by applying carbamazepine directly to the mesial temporal lobe slices from 28 patients with mesial temporal lobe epilepsy and from 6 patients with extrahippocampal tumours. The resected tissue was sliced and stimulated until spontaneous discharges occurred. Then carbamazepine was applied and finally washed off. Different types of epileptic activity were induced in different slices. The slices from patients with mesial temporal lobe epilepsy showed little change in spike activity when carbamazepine was applied but tissue from those with extrahipocampal tumours showed a reduction of abnormal activity by about 90%. Tissue showing lower drug resistance generally came from patients with a shorter duration of epilepsy and clinically less resistant epilepsy, suggesting that this model is clinically relevant. Seven per cent of patients who were carbamazepine-sensitive in the model, where the drug could gain access to tissue, had been resistant *in vivo*, suggesting that this subgroup may have had a different mechanism of resistance, perhaps at the blood brain barrier. The authors speculated on the mechanism of resistance. They found from voltage clamp experiments that there was reduced sensitivity of voltage dependent sodium channels to the effects of carbamazepine in resistant slices. The authors argue that, since carbamazepine acts on the sodium channel on the outer surface of the cell, cellular transporters which increase efflux of the drug are unlikely to have any impact on resistance. They speculated on the possibility that synaptic reorganisation in the hippocampus may be a factor in drug resistance but had no direct evidence for this hypothesis. This new finding moves a step closer to understanding why the drugs we use act so differently in different patients, but clearly this kind of work is limited by the availability of human experimental tissue. - ***MRAM***

Jandova K, Pasler D, Antonio LL, Raue C, Ji S, Njunting M, Kann O, Kovacs R, Meencke HJ, Cavalheiro EA, Heinemann U, Gabriel S, Lehmann TN.
Carbamazepine resistance in the dentate gyrus of human hippocampal slices.
BRAIN
2006;129:3290-306.

For a list of Journal reviewers please turn to page 03

If you would like to review books for ACNR, please contact Andrew Larner, Book Review Editor, c/o patriciamcdonnell@btinternet.com

Stroke Treatment and Prevention: An Evidence-based Approach



Author: Graeme J Hankey
Published by: Cambridge University Press, 2005
ISBN: 0521827191
Price: £80.00

This book represents a typically thorough and conscientious approach by Graeme Hankey to gather together the best of the evidence, where it exists, to help the clinician manage patients with cerebrovascular disease. It is a book of just over 500 pages and 18 chapters, all following a similar structure. The first two chapters briefly discuss, firstly 'the size of the problem of stroke' and, secondly, understanding the evidence. The latter is a particularly useful chapter, leading one through the currently standardised levels of evidence, helping the reader to understand and evaluate critically randomised trials, and also, and more pertinent to this book, meta-analyses and systematic reviews.

Then the book proper begins. Each chapter, looking at different clinical questions or dilemmas (e.g. acute thrombolysis, neuroprotection, anticoagulation, blood pressure lowering, carotid artery revascularisation, etc), follows a similar theme. The first part of each chapter is entitled 'rationale' and describes the arguments believing that a certain treatment might work. Different treatments are then described, the evidence for or against in relation to placebo or other existing therapies, with accompanying forest plots of all included trials. Then, most importantly there is a comment regarding interpretation of the evidence and implications for practice. The latter is largely a comment based upon analysis of the previous evidence, but where such evidence is lacking or controversial, Graeme Hankey provides the reader with potential options to take. Finally, each chapter finishes with a section titled 'implications for research' which brings the reader completely up to date with where a given field was heading at the time of writing and where it might go in the future. There is a final summary for each chapter which is an excellent means of getting to grips with the data in a very convenient way.

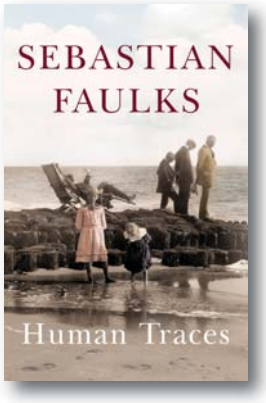
Each chapter is of course fully referenced, as are all the studies included in each meta-analysis, and as a rapid source of reference to any clinician dealing with stroke it is the sort of book that really should be on the office shelf.

I would very much hope that in five years time Graeme Hankey will have the energy to update the book as it is an excellent format and he deserves enormous credit for his commitment to gathering such a wealth of trial evidence.

Although much of the data is available through the Cochrane Library (which Graeme Hankey is the first to acknowledge in his preface) his interpretation of the evidence, and his ability to highlight where the data are lacking, incomplete, or need further work, is what makes this work a very worthy addition to the cerebrovascular literature.

Peter Martin,
Addenbrooke's Hospital, Cambridge, UK.

Human Traces



Author: Sebastian Faulks
Published by: Hutchinson, London. 2005.
ISBN: 0091794552
Price: £17.99

"I am suffering from the limits of my mind," he said. "There is a simple enough problem that I have set out to solve. How our minds work….."

"Yes, I suppose for simplicity's sake, you might say that his guiding light is Charcot and mine is Darwin."

" So a man may first have deduced the existence of his own consciousness by imagining it in others"

".... perhaps for quite simple reasons connected to the limits of their ability to reason, human beings could live out their whole long lives without ever knowing what sort of creatures they really were. Perhaps it did not matter; perhaps what was important was to find serenity in not knowing."

Many writers have grappled with the fundamentals of what constitutes the human mind, consciousness and the soul of a person. Sebastian Faulks in his latest novel explores such issues in the context of the late 19th century running from 1870 to just after the First World War – a time of great change in many differing spheres of life and science. In Human Traces, Faulks uses two fictional characters to unwrap the arguments that formed the kernel of the debate in neurological-psychiatric circles in Europe at the turn of the last century, and grapples in particular with the question of whether mental illness can best be understood through a psychological approach fashioned through experiences or a more deterministic one in nature with a basis in genes and evolutionary pressures. These two stand points are adopted by the two main characters- a French psychiatrist Jacques Rebière trained in the ways of Charcot at the Salpetrière in Paris and Thomas Midwinter, an English physician influenced by his experiences in a London lunatic asylum. These two doctors enter their respective practices with the ambition that they can begin to understand the basis of mental illness, and through this offer cures as well as providing insights into consciousness and what it is to be human. These ambitions are driven by different influences and guiding philosophies- Jacques is possessed by a desire to cure his schizophrenic brother, Olivier, within whom the only memories of his mother are trapped whilst Thomas is encouraged by his desire to understand the creative genius of great artists. After spending formative years in Paris and London respectively, the two aspiring doctors unite and combine their efforts in a sanatorium they set up in the Austrian mountains, and the relationship thickens as Jacques marries the influential older sister of Thomas, Sonia, whilst Thomas marries a patient of Jacques, Kitty. This, however, is no ordinary patient, as she comes to define the difference between the two men and contributes to the unravelling of their friendship and their ultimate destinies. Initially Kitty is seen by Jacques, who explains her problems through some tortuous psychological reasoning, which he regards as being so seminal that he wishes to present her case to a scientific meeting and asks Thomas to read the case history he has written on her. His reading of it, far from confirming the validity and insight of Jacques approach, alerts him to the real problem of her condition and the physical, organic cause of her complaints. The failure of Jacques to recognise his error in this case, coupled to his introspective outlook and philosophy on mental illness, leads him to become more isolated and distant from the kindly, more physically minded and egregious Thomas. Their relationship founders and survives in no small part because of their spouses and their over-arching but crumbling ambitions.

This tension remains despite the sanatorium moving location, and is heightened by the loss of Olivier (and later Daniel, the only son of Jacques and Sonia). In contrast, Thomas and Kitty have two thriving twin girls and seem destined to live out their days happily despite Thomas nearly dying in Africa during a 3-month sabbatical. However, the arrival of the 1st World War causes them to return to their respective countries and, after time apart, the final act is played out. The two become reconciled as Thomas enters

a new final phase of his life, and Jacques accepts the losses and false hopes of his work and family.

Throughout this whole novel the scientific theories that dominated the neurological world and formed the foundation of psychiatry at this time are laid out, often in great detail. Whilst of interest, especially to those wishing to understand these formative years of psychiatry, they can arrest the flow of the story and impede the unfolding of the narrative. Indeed some reviewers have criticised the book as being more concerned with describing research than being a novel. Whilst this is true in parts, and there are many diversions which seem to be not wholly necessary – for example the trips to America and Africa by Jacques and Thomas respectively- there is nevertheless an underlying rhythm to the work which drives the reader on to find out how these different philosophies will work themselves out in the lives of the main characters. En route the reader is invited to engage with a range of interesting questions, not least of which is why mental illness is so common given its destructive nature on patients and families and what it can tell us about consciousness and the human mind and soul. Whilst Jacques and Thomas try to answer this question from different perspectives, Kitty and Sonia seek to understand such things using less rigorous approaches and in many ways seem to have a greater, more profound understanding of what it is to be human. This they would argue is through relationships and love with their attendant memories and a sense of tomorrow and looking beyond oneself. Thus the true human traces are those left by our effect on and interactions with others, physically, mentally and spiritually. This is no better encapsulated than in the moving speech by Thomas at the end of the book, where, guided by his wife Kitty at the final family reunion, Thomas describes his own evaluation of his life: as a doctor he feels he has achieved nothing (although others disagree) but in love he has been rich.

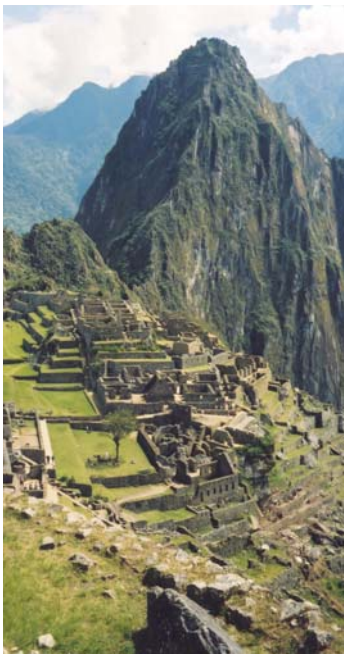
Roger A Barker,
Honorary Consultant,
The Cambridge Centre for Brain Repair,
Cambridge, UK.

A 2007 Challenge...

Are you or someone you know interested in taking part in a once in a lifetime trek or cycle ride whilst at the same time raising money for Headway – the brain injury association?

In 2007 Headway are offering the following trips:

15-25 Feb	-	Cuba Cycle Ride
17-25 Mar	-	Sahara Trek
27 Apr-6 May	-	China Trek
13-17 Jun	-	London to Paris Cycle Ride
18-26 Aug	-	Iceland Trek
14-23 Sep	-	Peru Trek
27 Oct - 8 Nov	-	Vietnam Cycle Ride



We will take care of all event organisation and administration, leaving you to concentrate on raising sponsorship and preparing for the trip.

For further details please contact:
Rachel Broughton,
Events and Conferences Officer,
Tel: +44 (0)115 924 0800 or
Email: eventsandconferences@headway.org.uk

Primary Care Neurology Society Conference

The Primary Care Neurology Society will be holding one annual conference in England and one conference in Scotland in 2007. The first conference will be on the 17th of May at the Birmingham Hippodrome. The date and venue for the Scotland conference is still to be finalised. Over 180 people attended their conferences in 2006 with 93% rating it good or excellent. "Brilliant conference – I've learnt a lot and will approach my neurological patients with more confidence" and "Excellent lecturers and content – thank-you" were just two of the many positive comments received. The Society is keen to develop a 2007 programme that reflects the interests of their members and is offering a 40% discount on the conference delegate fee on completion of the pre-conference questionnaire which you can access from www.p-cns.org.uk.

Trigeminal Neuralgia Association UK – first 2-day conference

Trigeminal Neuralgia Association UK will hold its first two day conference at Keele University on 30 June-1 July 2007. The programme will include eminent speakers from the USA and the UK and this event will include a Continuing Education Programme for healthcare practitioners. All interested professionals and non-professionals are welcome to attend the conference as it will be an opportunity to meet Trigeminal Neuralgia patients and encourage two-way communication about the difficulties faced by patients. From previous conference evaluations, patients and professionals have valued the interaction that this type of conference encourages.

The proposed healthcare professionals' conference is aimed at dentists, local GPs, neurologists and neurosurgeons. The fee for the conference will include full refreshments, and accommodation is available if required. Full details will be published in future editions of ANCR, but please make a note of the date.

The aim of the programme is to increase healthcare professionals' awareness of trigeminal neuralgia, especially its diagnosis and up-to-date management. From recent data produced by Hall et al (Pain, 2006) on the epidemiology of neuropathic pain in the UK, it would appear that trigeminal neuralgia is more common than previously thought in UK medical practices. Its incidence has been put at 26.8 per 100,000, whereas this was thought to be 4-6 in 100,000. Carbamazepine is the drug of choice but this is only prescribed to 58% of patients.

For further information contact:
Trigeminal Neuralgia Association UK,
Tel: 020 8462 9122,
Web: www.tna-uk.org.uk

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ARICEPT® (donepezil hydrochloride) Please refer to the SmPC before prescribing ARICEPT 5 mg or ARICEPT 10 mg. **Indication:** Symptomatic treatment of mild to moderately severe Alzheimer's dementia. **Dose and administration:** ***Adults/elderly;*** 5 mg daily which may be increased to 10 mg once daily after at least one month. Treatment should be initiated and supervised by a physician with experience of Alzheimer's dementia. A caregiver should be available to monitor compliance. Monitor regularly to ensure continued therapeutic benefit, consider discontinuation when evidence of a therapeutic effect ceases. No dose adjustment necessary for patients with renal impairment. Dose escalation, according to tolerability, should be performed in patients with mild to moderate hepatic impairment. ***Children;*** Not recommended. **Contra-Indications:** Hypersensitivity to donepezil, piperidine derivatives or any excipients used in ARICEPT. **Pregnancy:** Aricept should not be used unless clearly necessary. **Lactation:** Excretion into human breast milk unknown. Women on donepezil should not breast feed. **Warnings and Precautions:** Exaggeration of succinylcholine-type muscle relaxation. Avoid concurrent use of anticholinesterases, cholinergic agonists, cholinergic antagonists. Possibility of vagotonic effect on the heart which may be particularly important with "sick sinus syndrome", and supraventricular conduction conditions. There have been reports of syncope and seizures - in such patients the possibility of heart block or long sinusal pauses should be considered. Careful monitoring of patients at risk of ulcer disease including those receiving NSAIDs. Cholinomimetics may cause bladder outflow obstruction. Seizures occur in Alzheimer's disease and cholinomimetics have the potential to cause seizures and they may also have the potential to exacerbate or induce extrapyramidal symptoms. Care in patients suffering from asthma and obstructive pulmonary disease. No data available for patients with severe hepatic impairment. Should not be used in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. Donepezil has minor or moderate influence on ability to drive/use machines so this should be routinely evaluated. **Drug Interactions:** Experience of use with concomitant medications is limited, consider possibility of as yet unknown interactions. Interaction possible with inhibitors or inducers of cytochrome P450; use such combinations with care. May interfere with anticholinergic agents. Possible synergistic activity with succinylcholine-type muscle relaxants, beta-blockers, cholinergic agents. **Side effects:** Most commonly diarrhoea, muscle cramps, fatigue, nausea, vomiting, and insomnia. Common effects (>1/100, <1/10): common cold, anorexia, hallucinations, agitation, aggressive behaviour, syncope, dizziness, insomnia, diarrhoea, vomiting, nausea, abdominal disturbance, rash, pruritis, muscle cramps, urinary incontinence, headache, fatigue, pain, accident. Uncommon effects (>1/1,000, <1/100): seizure, bradycardia, gastrointestinal haemorrhage, gastric & duodenal ulcers, minor increases in serum creatine kinase. Rare (>1/10,000, <1/1,000): extrapyramidal symptoms, sino-atrial block, atrioventricular block, liver dysfunction including hepatitis. **Presentation and basic NHS cost:** Blister packed in strips of 14. ARICEPT 5 mg; white, film coated tablets marked 5 and Aricept, packs of 28 £63.54 ARICEPT 10 mg; yellow, film coated tablets marked 10 and Aricept, packs of 28 £89.06 **Marketing authorisation numbers:** ARICEPT 5 mg; PL 10555/0006. ARICEPT 10 mg; PL 10555/0007. **Marketing authorisation holder:** Eisai Ltd. **Further Information from/Marketed by:** Eisai Ltd, Hammersmith International Centre, 3 Shortlands, London, W6 8EE and Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS. **Legal category:** POM **Date of preparation:** July 2006

Information about adverse event reporting can be found at www.yellowcard.gov.uk Adverse events should also be reported to Eisai Ltd on 0208 600 1400 or Lmedinfo@eisai.net

References: 1. Aricept SmPC. **2.** Aricept Evess SmPC **3.** Rivastigmine SmPC **4.** Galantamine SmPC **5.** Galantamine XL SmPC **6.** Memantine SmPC

Date of preparation: November 2006
A968-ARI955-10-06

Eisai Pfizer NEUROLOGY