

EDITOR'S CHOICE

MULTIPLE SCLEROSIS: Is BENEFIT of any benefit?

Is there any point to taking interferon-beta from the very first episode of demyelination, before a diagnosis of multiple sclerosis can be made? An important question but sadly, three trials later, the answer is... "maybe not, but not sure." An ideal group to test this question on are those people who present with a clinically isolated demyelinating syndrome and have three or more lesions on MRI: the Queen Square group has shown that, fourteen years later, nearly 90% of these will have developed MS, in contrast to less than 20% of those with normal scans (Brex PA. *NEJM* 2002;346:158). The BENEFIT trial, reported recently in *Neurology* has treated just that group with placebo or Betaferon, a 'me-too' study to follow that of Avonex (CHAMPS. *NEJM* 2000;34:898) and Rebif (Comi G. *Lancet* 2001;357:1576). The bottom line is that over two or three years, interferon reduces the proportion of people developing a second attack of demyelination, and thus converting to MS, by about one third (placebo arm conversion rates: CHAMPS 0.50, ETOMS 0.45, BENEFIT 0.45 versus treated arms: CHAMPS 0.35, ETOMS 0.34, BENEFIT 0.28). A similar effect size was seen in the BENEFIT trial on those diagnosed as having MS by the more sensitive 'McDonald criteria', in which new MRI lesions can substitute for a second clinical episode (0.85 versus 0.69). All very good. The key question, though, is does treatment with interferon-beta reduce the accumulation of disability? Extraordinarily, this data is deliberately omitted, despite having been collected, from the BENEFIT and the original CHAMPS papers. Forgive a cynical question, but would the data have gone unreported if it had been positive? In ETOMS, where the investigators were more open, interferon-beta had no significant effect on the accumulation of disability. And a similar lack of effect on disability was seen in the 5 year open-label extension study of the CHAMPS cohort (Kinkel RP. *Neurology* 2006; 66:678). (A similar 5-year extension study of the BENEFIT trial is planned.) This is not to say that interferon treatment of the clinically isolated syndrome is useless in the long-term. But it may be. And the current lack of rigour in editorial offices like *Neurology*, where trials like BENEFIT can be published with the most important data omitted, is not going to encourage sponsoring companies to bite the bullet and design big and long enough trials to answer the questions that patients ask. -AJC

Kappos L, Polman CH, Freedman MS, Edan G, Hartung HP, Miller DH, Montalban X, Barkhof F, Bauer L, Jakobs P, Pohl C, Sandbrink R. *Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes.*

NEUROLOGY
2006;10;67(7):1242-9.

ADULT NEUROGENESIS: Is my brain growing larger?

There is no doubt that neurogenesis takes place in the adult brain, including in humans, at least in the dentate gyrus of the hippocampus and the subventricular zone, although its significance and importance to normal behaviour is debated. Of late one area of great contention has been whether neurogenesis takes place at other sites in the adult human brain, including the cerebral cortex, with conflicting experimental data between rodents and non-human primates. In a recent paper in *PNAS*, this issue has been investigated in a cunning way using two different strategies in separate groups of individuals. One builds on an earlier BrdU study in patients with neck and head malignancies and the others relates to the testing of nuclear bombs 40+ years ago! In the first approach patients with certain types of non-CNS malignancy were given BrdU as part of their management. At death, four months to four years later, the number of BrdU positive cells which were labelled with NeuN (a neuronal marker) within the cortex were counted, in the same way as had been done previously for the hippocampus (Ericsson PS et al *Nature Med* 1998;4:1313-17). The result was clearcut - there were none. In the second approach, five individual brains were examined to ascertain the birth date of cortical neurones using ¹⁴C incorporated into DNA. This strategy relied on the facts that between 1955 and 1963 there was greatly increased levels of ¹⁴CO₂ in the atmosphere because of above-ground nuclear bomb testing, and that this would be incorporated into plants and then through the food chain into dividing cells. They then analysed post mortem cortical DNA through a process of accelerator mass spectrometry and compared its expression in

NeuN (neuronal and non NeuN populations of cells) and found that essentially all cortical neurons were born by birth and did not arise during adulthood. Thus these two approaches show that no new neurons are generated in adulthood in the normal human neocortex, although it should be stressed that new cells were seen but they were not neurons. Furthermore, it is unclear whether this is also true for the damaged and degenerating cortex. Thus whilst these elegant experiments seem to have laid to rest one bone of contention in the field of adult neurogenesis it does not mean that adult neurogenesis is not possible in the cortex under some circumstances which could be of reparative significance. - RAB

Bhardwaj RD, Curtis MA, Spalding KL et al.

Neocortical neurogenesis in humans is restricted to development.
PROCEEDINGS OF THE NATURAL ACADEMY OF SCIENCES
2006;103(33):12564-8.

HEADACHE: Cluster headache presentation

Cluster headache remains underdiagnosed and undertreated. This paper examined clinical features of cluster headache, as defined by International Headache Society criteria, between April 2002 to March 2004. 257 patients were recruited prospectively from the Headache Clinic at the University Hospital in Essen in Germany, as well as nation-wide from self-help groups, and internet advertising on a clinic webpage. This design was both the strength and weakness of the study. It allowed a pragmatic study of the differences between patients seen in a super-specialised setting and those in a general population. The weakness of course was failure to define the overall population, negating any estimation of prevalence; and the introduction of a selection bias in those self-referred. The study confirmed the typical features of cluster headache, but there were features usually associated with migraine in many (nausea and vomiting in 27.8%, photophobia and phonophobia in 61.2%), sometimes confusing the diagnosis. A considerable number of patients (17.8-59.8%) had used acute and prophylactic medications, such as opioids, with no proven efficacy in cluster headache. Neurologists in the United Kingdom face a huge challenge to work to improve triaging and management of common neurological conditions in primary care (hopefully allowing us to focus more at the acute end of neurology where our impact is potentially greatest). This study highlights one area where there is scope for improved education, diagnosis and management of headache patients by all treating doctors. - HAL

Schurks M, Kurth T, de Jesus J, Jonjic M, Roskopf D, Diener H-C.

Cluster headache: clinical presentation, lifestyle features, and medical treatment.

HEADACHE
2006;46:1246-54.

HEAD INJURY: holds out in the long-term

When Charles Warlow received his Gold Medal from the ABN, he gave a lecture which emphasised the value of long-term studies of neurological conditions. A title in a recent *JNNP* paper would have pleased him: a 16 year follow-up of head injury from Swansea. The basic issue was: do people with head injury have accelerated decline in cognition as they get older? And the headline result was: no. There was no real difference between psychometric scores at 16 (10-32) years compared to 1 year (1 week to 5 years) after a head injury. So far so good. The small print throws up some wobbles though. Firstly, from a pool of 351 cases with an initial assessment, only 133 replied to the letter inviting them to take part in the research, of whom only 74 (24%) were eventually studied. It is very likely that those omitted from this small cohort would be over-represented by people whose cognition had deteriorated in the long-term. And secondly, only 15/74 patients had their initial assessment at least two years from the injury. For the others, it remains possible that their cognition improved in the medium term, and then declined. - AJC

Wood RL, Rutterford NA.

Long-term effect of head trauma on intellectual abilities: a 16-year outcome study.

J NEUROL NEUROSURG PSYCHIATRY
2006;77(10):1180-4.

HEADACHE: Three cases of nummular headache

This article describes three patients with a distinct primary headache, previously proposed in 2002 by Pajera as a separate entity. The headache is mild to moderate, chronic with exacerbations, and crucially, in a circumscribed rounded or elliptical area of 2-6cm. The area of pain is not tender and sensation is normal. One patient had a minor head injury three months prior, one patient had some migrainous features with the headache, none had struc-

tural lesions. The headache was chronic, often present for decades. The authors propose that these headaches do not fit in with any other headache category and that the term nummular headache is useful. None of the treatments tried were successful. It is always helpful to provide patients with an accurate diagnostic label, and the curious headache distribution is very distinctive. This report is likely to increase awareness of this headache type, and having seen people who have described this curious shape, I will be on the lookout. If SUNCT is anything to go by, it is likely that over time, successful treatments will be reported. - *HAL*

Dach F, Speciali J, Eckeli A, Rodrigues GG, Bordini CA.

Nummular headache: three new cases.

CEPHALALGIA

2006;26:1234-7.

STROKE: Living with mental slowness

Stroke has many physical and cognitive effects and as clinicians we can predict fairly well how poor mobility or hand function will affect a person's independence in self care or social participation. Similarly we can guess how cognitive impairments such as memory, language or unilateral inattention will impinge on function. However we are inclined to compartmentalise the effects and this leads to a rather narrow forecast of how people will cope in daily life. There is a tendency to forget that difficulties in one area of function can impinge on other functions, for example if a task is slightly difficult adding the load of another simultaneous task requiring more attention can lead to impoverished performance of both. Some studies have measured reduced performance in dual task scenarios such as walking and doing simple calculations, others have picked up on a general mental slowness evident from prolonged reaction times; however studies exploring the real world consequences of mental slowness have been rare. Now a group in the Netherlands have reported the results of a study in which patients with stroke who suffer from mental slowness were interviewed about its effect on their lives. The patients were interviewed serially until saturation of the data was reached. In total thirteen patients were interviewed and the group comprised of a mixture of hemispheres affected, types of stroke, ages, genders, times since stroke and education. Most of the sample complained that they weren't able to process information quickly enough or adequately. For example they found it difficult to follow conversation on the phone or in meetings or even when listening to the radio. They complained of problems in decision making. Storing and retrieving information from memory required more time and effort than before their stroke. All the participants reported problems in dividing attention and many were easily distracted and could no longer perform tasks automatically. These problems all increase difficulty in everyday life and many of the patients reported psychological or somatic complaints as a result. For example, they reported feeling agitated, tired, dizzy or having headaches. The study also shed light on the strategies that the patients use to compensate for their mental slowness. They either avoided or withdrew from difficult situations or they tried to control their activities, for example by doing things in a quiet environment or preparing for events ahead of time. Of course some of these complaints may have been due to depression or more introspection following stroke, but this study paves the way for the development of new tools for measuring mental slowness after stroke and highlights the need for continuing rehabilitation to try to improve people's mental acuity after stroke. Brain speed training exercises are available on games players and PC now. Perhaps these might be useful for continuing rehabilitation at home. - *AT*

Winkens I, van Heugten CM, Fasotti L, Duits A, Wade DT.

Manifestations of mental slowness in the daily life of patients with stroke: a qualitative study.

CLINICAL REHABILITATION

2006;20:827-34.

MULTIPLE SCLEROSIS: Nose and IL-10 required

David Wraith, an immunologist in Bristol, spends a great deal of time thinking about antigen-specific therapies for autoimmune and allergic disease. He has shown that it is possible to re-educate the immune system not to attack the brain in an animal model of cerebral autoimmunity, Experimental Allergic Encephalomyelitis (EAE). He does this by administering a key peptide from the CNS myelin molecule, myelin oligodendrocyte protein, intranasally. For good reasons, but by unclear mechanisms, the immune system becomes tolerant to peptides administered to a mucosal surface, either nasally or orally. This observation led to a North American trial of eating bovine myelin basic protein (thankfully not sourced from UK cattle!) as a treatment of multiple sclerosis. It did not work. But there is still some hope that the nasal route will be more effective. In this study Wraith's group attempted to

induce tolerance to EAE with nasal peptide in mice knocked out for the IL-10 cytokine. They could not. The fact that nasal tolerance requires IL-10 is provocative for it is this cytokine that is key to a group of regulatory T cells, called Tr1 cells, which are found in humans as well as mice. The nose may well be the answer to multiple sclerosis. First, the nose could be inoculated to induce nasal tolerance and suppress disease activity... And then nose-derived ensheathing cells could be used to repair areas of demyelination (Barnett S. Brain 2000; 123: 1581)! - *AJC*

O'Neill EJ, Day MJ, Wraith DC.

IL-10 is essential for disease protection following intranasal peptide administration in the C57BL/6 model of EAE.

J NEUROIMMUNOL

2006;178(1-2):1-8.

EPILEPSY: How bad is epilepsy?

From 1981-2001, 890 patients were seen at the Western General Hospital in Edinburgh with newly diagnosed epilepsy. Over the same period 2,689 patients were referred with uncontrolled epilepsy from elsewhere. Mortality was calculated in relation to actuarial risk as defined by UK government data for each individual and the predicted and actual survivals were plotted on Kaplan-Meier curves. Causes of death including post-mortem confirmed SUDEP and unconfirmed (probable SUDEP) were analysed. In the newly diagnosed cohort, about half achieved seizure-freedom for at least one year and about a third were refractory. The mortality rate in this group was 10.4%, significantly higher than the expected 7.4%, giving an SMR of 1.42. In the refractory group the SMR was 2.54. There was no increase in mortality amongst those patients who entered remission. Amongst those patients with chronic epilepsy the crude death rate was 11.7% with an expected mortality of 5.7%. Symptomatic epilepsy did worse than other groups but idiopathic epilepsy was no worse than expected for an age-matched population. In the newly diagnosed group the SMR was higher than expected for self-harm, respiratory disorders and accidents. In the chronic group, deaths due to SUDEP, status epilepticus, accidents, suicide and cerebrovascular disease were also increased. Probable SUDEP affected seven patients (1.08 per 1000 patient years) and six of these were in patients who did not respond to treatment. In the chronic cohort there were 55 probable SUDEP deaths (2.46 per 1000 patient years). This study supports data that has been published previously. It has the usual flaws of not being population-based or prospective but is valuable nevertheless. It relates to the patients we all see in our clinics (except mine eat fewer deep-fried Mars bars) and enables us to give them information on their prognosis. Some of this is moderately reassuring; SUDEP rates were about half the figure of 0.5% annually, which is widely quoted for a refractory group and even better for a newly diagnosed group. Some we can try to prevent, by identifying and treating depression early and by being more fastidious in dispensing advice about avoiding accidents. The data are also very reassuring for those young patients with idiopathic generalised epilepsy. - *MRAM*

Mohanraj R, Norrie J, Stephen LJ, Hitiris N, Brodie MJ.

Mortality in adults with newly diagnosed and chronic epilepsy: a retrospective comparative study.

LANCET NEUROL

2006;5:481-7.

HEADACHE: Does acupuncture work?

Acupuncture has a number of potential advantages as a treatment of migraine and other headaches, including the perception that it is 'natural', acceptability to many patients who do not like to take tablets, and no interactions with medications. This small study examined the response of 28 patients randomised to actual or sham acupuncture, and treated with 16 sessions in 12 weeks. There was no difference in the response rate between the two groups in terms of headache reduction and associated symptoms. This is a well designed study, but it is unfortunate that the numbers are small. A larger study along the same lines could resolve the doubts left after the Cochrane review of acupuncture for idiopathic headache (last updated in 2001). This concluded that existing evidence supports the value of acupuncture for idiopathic headache, but that the quality and amount of evidence was not fully convincing. Unfortunately the need for a large-scale study to assess the effectiveness of acupuncture for migraine and other headache remains. - *HAL*

Alecrim-Andrade J, Maciel-Junior JA, Cladellas XC, Correa-Filho HR, Machado HC.

Acupuncture in migraine prophylaxis: a randomized, sham-controlled trial.

CEPHALALGIA

2006;26:520-9.