

## 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 <sup>14</sup>C incorporated into DNA. This strategy relied on the facts that between 1955 and 1963 there was greatly increased levels of <sup>14</sup>CO<sub>2</sub> 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-

