

## EDITOR'S CHOICE

**Multiple sclerosis**

For years, Maria Marrosu has been producing quality research on the Sardinian population of people with multiple sclerosis and has shown how unusual they are, for instance in their HLA genetic susceptibility and associations with other diseases. This intriguing study may be her finest yet and with more universal significance.

The basis of their work was a fairly standard question: do relatives of people affected by multiple sclerosis have abnormalities that look like multiple sclerosis on MRI brain scans? Technically, this is straightforward to answer. The main difficulty of this sort of research is dealing with the 'normal' participants who turn out to have 'abnormal' scans; so the consent process incorporated a question asking whether participants wished to know the result of their scan. Two hundred and ninety-six people were examined and scanned (56 of whom were unrelated to someone with multiple sclerosis). The result was unsurprising. If you are a first-degree relative of one person with multiple sclerosis, there is a 5% chance your brain MRI will show white-matter abnormalities consistent with multiple sclerosis using the Fazekas criteria.... And if two or more people are affected by multiple sclerosis in your family, this risk goes up to 11%. The magnetisation transfer ratio (MTr) of individual white matter lesions in such people's MRI scans was low, indicating loss of cellular structure, just as is seen in regular multiple sclerosis lesions. An interesting question, not addressed in this paper, is: what happens to those 'normal' people with abnormal scans? It is important for what follows that they never develop multiple sclerosis.

The excitement of this work lies in some negative results: MRI brain volumes and MTr of normal appearing white matter were identical between all groups and also between those who did or did not have white matter MRI abnormalities. Yet both of these measures are consistently reduced in people with multiple sclerosis, reflecting the widespread loss of axons and myelin outside of the focal plaques, even early on in the disease.

Perhaps then, there is a two-hit pathogenesis of multiple sclerosis. Firstly, there are focal areas of inflammation, producing focal axonal and myelin loss. But the disease is only manifest in those individuals who then go on to develop widespread axonal loss and cerebral atrophy. This is not an original idea, but Marrosu's research has put it on a more secure footing. And of course it has important implications, not the least being that focusing our efforts on reducing focal inflammation in multiple sclerosis may not be the wisest move.... And once again we are reminded that focal white matter lesions on a MRI scan do not necessarily cause any symptoms and do not mean that a person has multiple sclerosis. - *AJC*

*De Stefano N, Cocco E, Lai M, Battaglini M, Spissu A, Marchi P, Floris G, Mortilla M, Stromillo ML, Paolillo A, Federico A, Giovanna Marrosu M.*

**Imaging Brain Damage in First-Degree Relatives of Sporadic and Familial Multiple Sclerosis.**

*ANNALS OF NEUROLOGY*  
2006;59:634-9.

**EPILEPSY: A hairy tale**

## \*\*\* RECOMMENDED

Serum blood levels give a snapshot of antiepileptic drug ingestion but do not tell much about AED compliance over time. The drugs are deposited in hair shafts as the hairs grow, at a rate of about 1cm per month, and so 1cm lengths of hair can be analysed for their content of AED to give a picture of the variability of drug ingestion. The authors looked at hair removed from four groups of patients at post-mortem: 16 possible or definite SUDEP; nine non-SUDEP deaths; 31 patients with epilepsy living in their own homes and 31 residents of the Chalfont Centre for Epilepsy, who were expected to have very consistent drug dosing. They created a measure of the variability of AED levels in the hair, with an adjustment for the number of hairs sampled. They found that this coefficient of variance was 20.5% (S.E. 1.5%) in SUDEP patients, 15% (S.E. 3.9%) in non-SUDEP patients, 9.6% in outpatients and 6.2% in Chalfont residents. One SUDEP patient had no detectable level of his prescribed AED anywhere in his hair. Whilst previous data regarding the risk of SUDEP and compliance have been contradictory, it has been shown before

(not surprisingly) that patients with more frequent seizures are at increased risk of sudden death. This study does not control for seizure frequency but, with that caveat, it shows that compliance is an important factor in sudden unexpected death in epilepsy. So we need to explore the presence of, and reasons for, non-compliance more assiduously. - *MRAM*

*Williams J, Lawthom C, Dunstan FD, Dawson TP, Kerr MP, Smith PEM.*

**Variability of antiepileptic medication taking behaviour in sudden unexplained death in epilepsy: hair analysis at autopsy.**

*JOURNAL OF NEUROLOGY, NEUROSURGERY & PSYCHIATRY*  
2006;77:474-80.

**TRIPLET REPEATS: New Treatments?**

There continues to be some controversy as to whether the formation of inclusions in cells in neurodegenerative disorders is a good or a bad thing for the neurons. A few years ago there was a great interest in developing drugs that have the potential to break down inclusions on the grounds that these may have some toxic function within the cells. Subsequently it appeared as though inclusion formation was an attempt by the cell to prevent cell death or at least was not causally related to its demise. As a result there has been a change in approach such that in a recent paper in the Proceedings of the National Academy of Sciences by Bodner et al they have used therapeutic approach which involves the promotion of inclusion formation. In this study the authors used alpha synuclein and huntingtin as their two mutant proteins in a number of cell lines and set about trying to use various agents to promote their aggregation into inclusions. They identified a number of compounds that could do this in their cellular models of both Huntington's disease and Parkinson's disease and comment that these compounds appear to reduce toxicity and thus may ultimately offer some benefit in the clinic. This is an interesting study, although is using a very artificial environment which limits its clinical significance. However it once more illustrates how in medical sciences subjects can be turned on their head in the space of a relatively short period of time. Of course we will now have to wait to see whether the trend reverses and inclusions become the perpetrator rather than the protector of cell death. - *RAB*

*Bodner RA, Outeiro TF, Altmann S, Maxwell MM, Cho SH, Hyman BT, McLean PJ, Young AB, Housman DE, Kazantsev AG.*

**Pharmacological promotion of inclusion formation: A therapeutic approach for Huntington's and Parkinson's diseases.**

*PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES*  
2006;103:4246-51.

**EPILEPSY: Worms, twiddly volumetrics & wires in the head**

About a quarter of all patients with epilepsy, close to 100,000 in the UK, will not respond to medication. Some of these can be treated surgically but most cannot. A key question is how to screen for those who will benefit. One potential strategy might be to scan patients and only put forward for surgery those patients whose scan shows a surgical target. However, according to this paper, that approach would miss some patients who would benefit from surgery. One hundred and thirty six patients had surgery, 105 of whom had implanted electrodes and 21 one of whom had normal neuroimaging. Three-quarters of patients, whether MRI positive or negative, were either seizure-free or nearly seizure-free at one year. The MRI studies were high resolution imaging with visual inspection but without volumetric measurements of the temporal lobes. Now every fisherman knows that what you catch depends on the bait. These authors argue that a 1.5 Tesla worm is all that you need but if you go a few miles across London you will find clinicians who think that if you use a 3 Tesla worm with twiddly volumetrics added, you will catch more fish. They will do many more clever scans and fewer electrode implantations. Are their patients comparable? Who knows! Perhaps they could challenge each other to a randomised trial of clever imaging versus wires in the head. So for the jobbing neurologist the debate moves on to who to refer from the group with normal routine MRI scans, even fewer of whom will benefit from surgery. The answer I believe comes down to good old clinical medicine. If the seizure type or the interictal or extracranial ictal EEG suggests a highly focal origin for seizures then your imaging has missed something. Either clever imaging will pick it up or you have to have wires in the head. Personally, I would go for clever imaging first and only have wires in the head later. - *MRAM*

*Alarcon G, Valentin A, Watts C, Selway RP, Lacruz ME, Elwes RDC, Jarosz JM, Honavar M, Brunhuber F, Mullatti, Salinas M, Binnie CD, Polkey CE.*

**Is it worth pursuing surgery for epilepsy in patients with normal neuroimaging?**

*JOURNAL OF NEUROLOGY, NEUROSURGERY & PSYCHIATRY*  
2006 Apr;77(4):474-80.

**HEAD INJURY: Cage Fighting – athletes or assailants?**

Some of you may wonder what exactly is Cage Fighting – I did too when first contacted by a BBC journalist a few weeks ago about a big ‘cage fight’ event in Manchester. This paper describes its origins from 648BC when Pankration (Greek = All powerful) was featured in the 33rd Olympiad. It is also known as ‘no holds barred’ fighting, ‘mixed martial arts’ competition or extreme fighting. Basically, it involves two contestants, wearing minimal protective clothing, fighting (up to) three 5-minute rounds in a cage with a few limits such as no head-butting, biting or scratching/gouging etc. Apparently the cage is there to ‘protect’ participants from being thrown out of the fighting area. This paper is the first to systematically look at the health outcomes of this ‘sport’. The author reviewed publicly available video footage of 1284 men in 642 consecutive televised matches in the US and Japan from 1993–2003 to determine the reason for the contest finishing (note the study was by a single author and no funding was declared). The single greatest reason for match stoppage was head impact (28%), followed by expired match time (27%), musculoskeletal stress (17%), neck choke (14%), miscellaneous trauma (13%) and disqualification (1%). Comparative figures of match stoppage due to head injury in boxing of 8.8% and kickboxing of 7.7% are given. The paper discusses the rules, equipment, stoppage classification and implications of the injuries (especially head) sustained. Three questions come to mind: Who are the ‘expert doctors’ at ringside? When are gladiators and duelling returning? Who is going to shout stop? – *JMacF*

*Buse GJ.*

**No holds barred sport fighting: a 10 year review of mixed martial arts competition.**

BRITISH JOURNAL OF SPORTS MEDICINE

2006;40:169–72.

**HEADACHE: Neck-tongue syndrome**

★★★ RECOMMENDED

It is my hypothesis that every neurologist, even those especially interested in common disorders such as headache and epilepsy, has a (sometimes suppressed) passion for the obscure. This needs regular indulgence. Reading about neck-tongue syndrome fits the bill. This rare headache disorder consists of neck pain in the C2 distribution, coupled with ipsilateral tongue numbness, occurring during head rotation. The authors conducted a detailed headache survey and as part of this, looked for cases of neck-tongue syndrome. During a systematic epidemiological survey of 1838 parishioners of a community in Norway, four people with neck-tongue syndrome were identified. This gave a prevalence of 0.22% in this well-defined community group. None of the four had ever sought medical help for their condition. One subject had spasm of the tongue rather than numbness. Two also had ipsilateral cervicogenic headache at other times. Although the authors conclude that neck-tongue syndrome may be more frequent than previously thought, it is still pretty uncommon. Once encountered, it is hard to forget. Patients with it are likely to be pleased to have their syndrome recognised. Furthermore, it is a dramatic example of convergence of trigeminal and cervical sensory input, important in understanding mechanisms of headache. – *HAL*

*Sjaastad O, Bakkeig LS.*

**Neck-tongue syndrome and related (?) conditions.**

CEPHALALGIA

2006;26:233–40.

**MULTIPLE SCLEROSIS: and glandular fever**

Over the years, proposed infectious triggers for multiple sclerosis have included (in historical order) syphilis, canine distemper virus, measles, human herpes virus 6 and chlamydia pneumonia. There has been increasing scepticism about the relevance of these observations, especially as it has been shown that polyclonal expansion of B lymphocytes is part of the immune defect in multiple sclerosis (Derfuss Brain 2001;124:1325–35.) However Epstein-Barr virus may be an exception. The elegant work of Lars Fugger’s group (Nat Immunol 2002 Oct;3(10):940–3) has shown that there is sufficient sequence similarity between EBV and MBP to support molecular mimicry. And there has long been a clinical suspicion that EBV infection after childhood, to cause infectious mononucleosis or ‘glandular fever’, may predispose to multiple sclerosis. This has now been tested in a meta-analysis from this Boston team, which was so rigorous that 281 out of the 295 possible studies were discarded before the start! From the remaining 14 case-con-

trol and cohort studies, the relative risk of multiple sclerosis after glandular fever was calculated at 2.3 (95% confidence intervals 1.7–3.0). Under a model drawn up by the authors, individuals who had never been exposed to EBV (c.20% by serological tests in the UK), or those who had been exposed in childhood, had much lower risks of developing multiple sclerosis. The striking implication is that EBV vaccination might reduce multiple sclerosis frequency...

Regular readers of this section of ACNR will spot that this paper once again supports the ‘hygiene hypothesis’ of autoimmunity. It is clearly much better, at least as far as multiple sclerosis risk goes, to acquire EBV infection from a dirty childhood than from kissing at university! – *AJC*

*Thacker EL, Mirzaei F, Ascherio A.*

**Infectious mononucleosis and risk for multiple sclerosis: a meta-analysis.**

ANNALS OF NEUROLOGY

2006 Mar;59(3):499–503.

**HEADACHE: links with epilepsy**

This study looked at clinical evidence for a link between migraine and epilepsy in children and adolescents. Its impetus was the hypothesis of a shared mechanism due to underlying cortical hyperexcitability. In 137 children and adolescents seen consecutively in an Italian clinic with tension-type and migraine headaches, 14 (10.2%) had a positive history of febrile seizures, isolated seizures or epilepsy. The strongest association was with migraine with aura. ‘Specific’ electroencephalographic abnormalities were seen in 11.7% of the patients. In those with migraine with aura, ten of 23 (43%) had interictal EEG abnormalities. The authors suggest that these findings support the hypothesis of a possible clinical continuum between some types of migraine with aura and epileptic seizures. They propose that these conditions share an underlying pathophysiology, with resultant hyperexcitability. Ongoing research in the genetics of epilepsy and migraine, and particularly channelopathies, is providing details of potential mechanisms for this link. Despite potentially shared underlying mechanisms, the clinical implications of the two diagnoses, or having both diagnoses, are very different. The correct diagnosis or diagnoses relies on integrating the clinical findings and investigations. In this study, the significant incidence of EEG changes in the patients with migraine is important, as these could result in an erroneous label of epilepsy. These findings highlight the potential difficulty of distinguishing the conditions, particularly migraine with visual aura and occipital epilepsies. Given the established rate of misdiagnosis of epilepsy in both children and adults, it also demonstrates that investigations, in this case the EEG, have to be interpreted with great caution. – *HAL*

*Piccinelli P, Borgatti R, Nicoli F, Calcagno P, Bassi MT, Quadrelli M, Rossi G, Lanzi G, Balottin U.*

**Relationship between migraine and epilepsy in pediatric age.**

HEADACHE

2006;46:413–21.

**MULTIPLE SCLEROSIS: dodgy dendritic cells**

Just when I thought I had worked out the immunology of multiple sclerosis, it all gets turned upside down again. Forget the T lymphocyte! The real culprit is the dendritic cell, so Krzysztof Selmaj would have you believe. The job of dendritic cells is to recognise an infection is happening and to present antigen to T cells. To get enough dendritic cells to experiment on, this collaboration between Lodz and Wurzburg had to subject 35 multiple sclerosis patients and 30 controls to a formal leucapheresis procedure. Then the peripheral blood mononuclear cell cultures were exposed to rounds of IL-3 and CD40L stimulation, which would normally ‘mature’ dendritic cells; but in the multiple sclerosis patients, this maturation was impaired. The functional effect of this was seen when dendritic cells were added to peripheral blood mononuclear cell cultures. The key finding, though, was that dendritic cells from multiple sclerosis patients completely failed to promote the regulatory (FoxP3+) T cell. So, the story now is that multiple sclerosis is due to hopeless dendritic cells failing to promote the generation of regulatory T cells and so allowing pre-existing enthusiastic anti-myelin T cells to rip up myelin unchecked. All very well. But (as in what came before the Big Bang?) this study just pushes us one level back: why do the dendritic cells fail in multiple sclerosis? – *AJC*

*Stasiolek M, Bayas A, Kruse N, Wiczarkowicz A, Toyka KV, Gold R, Selmaj K.*

**Impaired maturation and altered regulatory function of plasmacytoid dendritic cells in multiple sclerosis.**

BRAIN

2006;129:1293–305.