

## EDITOR'S CHOICE

**A new prion disease with a terrible name**

Just when we were beginning to relax over variant CJD in the UK, a new prion disease has been described in the US: 'protease-sensitive prionopathy'. 11 cases (10 autopsy, 1 biopsy) were seen at the National Prion Disease Pathology Surveillance Centre. Clinically, these patients had a rather distinct phenotype: a mean age of 62 years, presenting with behavioural, cognitive and psychiatric abnormalities, then developing ataxia and parkinsonism and surviving only 20 months. 6/10 had a family history of 'dementia'. No tests proved helpful: EEG did not show periodic complexes and CSF 14-3-3 was nondiagnostic. MRI showed diffuse atrophy with no changes on diffusion weighting. Uniquely, protease-resistant PrP was not found in the neocortex; instead the abnormal prion protein found in the brain of these patients was sensitive to proteases and formed distinctive plaques in the cerebellum. All of the patients were homozygous for valine at codon 129 of the prion protein gene; this is the rarest genotype found in only 12% of healthy people, and in two forms of regular sporadic CJD (VV1 and VV2) that differ from these cases in other ways. None had a mutation in the PrP gene ORF that is characteristic of Gerstman-Straussler-Scheinker disease, although the family histories clearly suggest a genetic cause. This type of prion disease accounted for 3% of referrals to the US National Prion Disease Pathology Surveillance Centre, so it is not vanishingly rare. And it is possible that more exist, currently misdiagnosed as having Alzheimer's, fronto-temporal dementia or Lewy Body disease. But, as well as that practical point, there are some more intriguing questions. As with Gerstman-Straussler-Scheinker, we have to ask whether this new 'prion disease' is transmissible, a necessary characteristic of Pruisner's original 'prion hypothesis'. And why is this accumulate prion protein protease-sensitive? The relevant animal experiments are on-going.... – *AJC*

**Gambetti P, Dong Z, Yuan J, Xiao X, Zheng M, Alsheklee A, Castellani R, Cohen M, Barria MA, Gonzalez-Romero D, Belay ED, Schonberger LB, Marder K, Harris C, Burke JR, Montine T, Wisniewski T, Dickson DW, Soto C, Hulette CM, Mastrianni JA, Kong Q, Zou WQ.**

*A novel human disease with abnormal prion protein sensitive to protease.*

**ANNALS OF NEUROLOGY**

**2008 Jun;63(6):697-708.**

**EPILEPSY: injuries and Range Rovers**

The Canadian Health Study identified patients with epilepsy from a door-to-door survey of 130,882 individuals over the age of 12 years, across Canada and representative of 98% of the Canadian population. 835 people with epilepsy (PWE) were found and were asked if they had suffered an injury in the last 12 months. Injuries sufficient to limit activity had occurred in 13.3% of controls and 14.9% of PWE. There was no increase fractures or sprains but a trend towards more burns and scalds (6.9% v 3.9%) in PWE. Controls were a little more likely to have injuries whilst engaged in sports, perhaps reflecting a reluctance of patients with epilepsy to undertake sport. Even though many people were sampled, the number of injuries in PWE was only 121, which means that the power of the study to identify differences between groups was limited, especially when looking at subdivisions of injuries. The study did not look at Range Rover driver behaviour. This is otherwise known as risk compensation, where those who feel at risk (Trabant drivers, who perceive themselves as vulnerable) behave in a risk averse fashion, whereas those in black Range Rovers with dark tinted windows embrace risk, as they perceive themselves as safe. It seems likely that epilepsy patients will be more risk averse than controls. Most other studies point to a slight excess risk of injury amongst patients with epilepsy and I suspect this is closer to the truth. Of course Canada is so icy in Winter that perhaps everyone is falling and breaking something so that differences are hard to detect. – *MRAM*

**Tellez-Zenteno JE, Hunter, G, Wiebe S.**

*Injuries in people with self-reported epilepsy: A population-based study.*

**EPILEPSIA**

**2008;49:954-61.**

**CHRONIC FATIGUE SYNDROME: shrinking brains**

This Dutch group have previously shown that people with chronic fatigue syndrome (CFS) have reduced grey matter volume in the lateral prefrontal cortex. They now go on to ask whether this is cause or consequence of the illness. They first showed that grey matter volume was most reduced in those CFS patients with lower physical activity and slower cognition (perhaps supporting that rather annoying dictum 'if you don't use it, you lose it'). They then followed 22 women with CFS as they had 16 sessions of cognitive behavioural therapy and graded exercise programs over 6-9 months. The expected improvements in health status, physical activity and cognitive performance followed. This correlated with an increase in lateral prefrontal cortex grey matter volume, ('pain and gain?') less marked in older patients. This increase amounted to only 12% of the difference between CFS patients and controls, raising the possibility that some of the deficit of CFS is irreversible. But much more interesting is the mechanism of the increase in grey volume.... for which the authors offer speculations only. They argue that, as neocortical neurogenesis is rare or absent from adult brains, that an increase in volume is likely to arise from increased dendritic growth or synaptogenesis.

**de Lange FP, Koers A, Kalkman JS, Bleijenberg G, Hagoort P, van der Meer JW, Toni I.**

*Increase in prefrontal cortical volume following cognitive behavioural therapy in patients with chronic fatigue syndrome.*

**BRAIN**

**2008 Aug;131(Pt 8):2172-80.**

**NEURODEGENERATION: emerging new treatments**

To complement the conference review by Tom Foltynie I perused the abstracts (all 1200 of them!!) of the recent Movement Disorder meeting in Chicago to find those of particular interest for restorative treatments of movement disorders. So here goes!

- Marks et al (A96) report on the 24 month efficacy of the safety and efficacy of AAV2 virus - neurturin in 12 patients with Parkinson's disease. The result is very encouraging with 8 out of the 12 having a major response of greater than 50% in the UPDRS off score without any significant adverse effects being reported.
- In contrast Frank et al (A568) show that there is no long term survival and efficacy of porcine striatal xenotransplants for Huntington's disease. Only 2 patients are still alive out of the original 12 and none showed any significant benefit with two patients having no surviving cells of porcine origin at post mortem.
- Watts et al (A598) provide an update on the Spheramine trial in patients with moderately advanced Parkinson's disease. Spheramine consists of human retinal pigmentary epithelial cells, attached to a microcarrier support of matrix cells, which are capable of synthesising dopamine. Six patients receiving transplants of these cells and matrix have shown no major adverse events but there again at 60 months there have been no major improvements either.

So at the moment gene therapy with neurotrophic factor delivery is winning over novel cell therapies for neurodegenerative disorders but the full publication of these studies will ultimately help us decide on the merits or otherwise of these studies. – *RAB*

**All abstracts from MOVEMENT DISORDERS (2008) 23: Supplement 1**

**EPILEPSY: More than two syndromes**

Some neurologists, and we all know who they are, are funny diseases doctors. They can remember all the weird and wonderful eponymous syndromes. I was never one of those and as middle age slips its tentacles ever deeper between my synapses, the chances of my ever remembering the clinical characteristics of 28 types of spinocerebellar ataxia is – well you can guess. So adult epilepsy is a great specialty for me; just two conditions to remember, focal epilepsy and generalised epilepsy. But I always knew it was too easy. It has never been realistic to think that all forms of focal epilepsy are the same, that the mechanism of the epilepsy is the same whatever the aetiology and this is one of a really small number of studies that has looked systematically at the differences. The authors studied 119 consecutive patients with refractory focal epilepsy, defined as failing two AED's. Where the cause remained cryptogenic after detailed MRI, the chances of a one year remission was 40%. Those with pathologies usually considered for surgical treatment, such as hippocampal sclerosis or dysplasia, achieved a remission of 11% and 27% of those with other forms of focal epilepsy achieved remission. Numbers were too small to analyse individual pathologies, but previously it has been demonstrated that hippocampal sclerosis carries a poor prognosis, especially if there is dual pathology. We know that dysplasia exhibits spontaneous EEG spikes and electrographically appears different from other causes and per-

haps this reflects a different mechanism and drug sensitivity. This area is crying out for some studies to try and tease out these differences, even if it means I have to remember more than two syndromes. – *MRAM*

Liimatainen S, Raitanen J, Ylinen A, Peltola M, Peltola J.

*The benefit of active drug trials is dependent on aetiology in refractory epilepsy.*

JOURNAL OF NEUROLOGY NEUROSURGERY PSYCHIATRY

2008;79:808-12.

### **MULTIPLE SCLEROSIS: CD8 cells again... and Epstein-Barr virus... again**

There have been many false dawns in the search for the 'viral trigger' of multiple sclerosis. But one particular bug keeps cropping up as a risk factor in epidemiological studies of multiple sclerosis: Epstein-Barr virus infection, particularly of adolescents. And recently, the exciting discovery has been made of EBV-laden lymphoid follicles in the meninges of people with multiple sclerosis. A great deal of time and money has been spent measuring serum antibodies to EBV in this or that patient group, which is not helped by the fact that in a country like the UK, some 90% of all people will have IgG antibodies to EBV by adulthood. Far less research has been done on the cellular response to EBV in people with multiple sclerosis, probably because that is rather more difficult to do. Nonetheless, Du Pasquier's group in Lausanne have systematically studied the response of peripheral T cells in response to various EBV and CMV antigens in sub-types of multiple sclerosis (nearly 100 in total) and healthy controls. The headline result is that CD8+, but not CD4+, T cells show increased reactivity to EBV, but not CMV, in patients with clinically isolated syndromes compared to controls. But this was not seen in patients with established multiple sclerosis, of whatever type. It would be reasonable to conclude that EBV does trigger early multiple sclerosis, but does not induce relapses... Back-to-back with the Du Pasquier paper is one from Howard Weiner's lab in Boston. His group have undertaken the enormous, tedious and ultimately rewarding task of non-prejudicial screening of a vast array of surface markers on peripheral lymphocytes of people with multiple sclerosis. The bottom line is that his trawler caught one fish: people with early, but not established, multiple sclerosis have a reduced number of cells with this signature: CD4neg CD8low CD56pos. This is not a well-known cell type. But it has been proposed to be a Natural Killer Regulatory cell. Do you feel any the wiser? Well, perhaps what this means is that people

with early multiple sclerosis have a reduced ability to appropriately restrain a CD8+ immune response. So, when EBV infection comes along, the immune system over-reacts and spills over, targeting anything else that looks like EBV... and certain stretches of the myelin basic protein molecule look exactly like EBV (Lang Nat Immunol. 2002 Oct;3(10):940-3)... so myelin is destroyed. Or perhaps it is the other way round: EBV infection impairs the function of the CD8low regulatory NK cells... Which somehow leads to anti-myelin T cell activity... What I think we can say is that the sharks have tasted blood and are circling... around EBV and the CD8+ T cells as important to the pathogenesis of multiple sclerosis. – *AJC*

De Jager PL, Rossin E, Pyne S, Tamayo P, Ottoboni L, Viglietta V, Weiner M, Soler D, Izmailova E, Faron-Yowe L, O'Brien C, Freeman S, Granados S, Parker A, Roubenoff R, Mesirov JP, Khoury SJ, Hafler DA, Weiner HL.

*Cytometric profiling in multiple sclerosis uncovers patient population structure and a reduction of CD8low cells.*

BRAIN

2008 Jul;131(Pt 7):1701-11.

Jilek S, Schlupe M, Meylan P, Vingerhoets F, Guignard L, Monney A, Kleeberg J, Le Goff G, Pantaleo G, Du Pasquier RA.

*Strong EBV-specific CD8+ T-cell response in patients with early multiple sclerosis.*

BRAIN

2008 Jul;131(Pt 7):1712-21.

### **Journal reviewers**

Heather Angus-Leppan, Royal Free & Barnet Hospitals;

Chrystalina Antoniadou, Cambridge Centre for Brain Repair;

Roger Barker, Cambridge Centre for Brain Repair;

Lloyd Bradley, Colman Centre for Specialist Neurological Rehabilitation Services in Norwich;

Alasdair Coles, Cambridge University;

Andrew Larner, Walton Centre, Liverpool;

Mark Manford, Addenbrooke's Hospital, Cambridge and Bedford Hospitals;

Wendy Phillips, Addenbrooke's Hospital, Cambridge;

Robert Redfern, Morrilton Hospital, Swansea;

Ailie Turton, University of Bristol.

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**Abstract Submission Deadline: February 11, 2009**

**Early Registration Deadline: April 22, 2009**

**[www.ensinfo.org](http://www.ensinfo.org)**

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