

Conference Report

ENS 2003

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ACNR prize for the best gene at the ENS: CACNA1A

Michel Ferrari, from Leiden, gave an animated talk (including racy pictures of his family firm's products) on this gene on chromosome 19. It encodes the main alpha unit of the neuronal calcium channel, which is involved in the modulation of the release of neurotransmitters including monoamines, acetylcholine, glutamate and substance P. What could not be expected is the extraordinary diversity of diseases caused by mutations in CACNA1A. Most people will be aware of its association with familial hemiplegic migraine, spinocerebellar ataxia 6 and episodic ataxia type 2. But it seems that its dysfunction also causes generalised epilepsy and, most bizarre of all, a syndrome of delayed cerebral oedema after minor head injury. How can we possibly make sense of that? When the human genome project estimated that the number of genes was only 30,000, rather less than previous guesses, there was some disappointment that human genetics was not as complex as had been imagined. But if each of those genes is half as complex as CACNA1A, we are in for a long haul.

ACNR prize for the most provocative poster at the ENS: protective autoimmunity against MPTP toxicity

This is not an entirely novel story, but the context is interesting. Michal Schwarz and colleagues at the Weizmann Institute have shown before that autoreactive anti-myelin T cells improve the functional outcome of optic nerve crush injury and have postulated the concept of protective autoimmunity. In this poster, from Warsaw, EAE was induced in animals by myelin oligodendrocyte glycoprotein and then, 6 days later, MPTP was given. This toxin causes selective depletion of dopaminergic cells in the substantia nigra. In the MOG treated animals, MPTP caused less dopamine depletion, less glial reaction and reduced striatal inflammatory cellular infiltration. Extrapolating from this: perhaps idiopathic Parkinson's disease is less frequent amongst patients with multiple sclerosis (for which there is no evidence as far as I am aware)? Or can neurodegenerative diseases be treated by inducing autoimmunity?

ACNR prize for the best virus at the ENS: Epstein-Barr virus in multiple sclerosis

The nature of the oligoclonal bands in CSF has long been studied without clear conclusions. Hemmer's group, in Marburg, have taken the subject further by applying some technical wizardry to the CSF of 15 multiple sclerosis patients and 5 controls. They ran the CSF against a protein array, comprising 35,000 cDNA inserts from a human foetal brain library, and found four proteins that selectively bound CSF oligoclonal bands from MS patients. They demonstrated intrathecal synthesis of antibodies against these proteins and, by substitutional analysis, identified the binding epitopes in two of these proteins. These peptide sequences matched two motifs from the Epstein Barr virus, namely BRF2 and EBNA1. These are both located close to each other and use the same promoter. They went on to show higher CSF and serum BRF2 and EBNA1 peptide and protein immunoreactivity in 150 multiple sclerosis patients compared to 90 controls. What does this mean? Well the traditional interpretation is that Epstein-Barr might cross-react with a myelin peptide. However an alternative possibility is that the EBV acts as a B cell mitogen increasing B cell turnover in a non-antigen specific way and hence boosting antibody production, thus increasing the likeli-

hood of an anti-myelin antibody escaping tolerance and causing multiple sclerosis.

ACNR prize for the best prognosis at the ENS: cervical dissection

As we increasingly recognise cervical dissection as a cause of stroke, so we face the question more and more: how likely is it to happen again, Doc? This study, presented on behalf of the *Multicentre Survey on Natural History of Cervical Artery Dissection Group (!)* followed 459 patients with such a dissection for an average of 30 months. In that time, 0.9% (4 patients) had a recurrence, of whom 2 patients had an associated stroke, and only one had a recurrence in the same vessel. All very reassuring.

ACNR prize for the most exciting drug at the ENS: antisense therapy in myasthenia gravis

This really is a fabulous study, from a collaboration between Manchester and Jerusalem, into the treatment of that paradigmatic disease, myasthenia gravis. The teams treated 16 patients with EN101, an antisense oligodeoxynucleotide that binds selectively to AChE mRNA preventing its translation into protein. Or at least, that is what it does *in vitro*. As the drug was given orally in this trial, the sensible prediction would be that EN101 would be degraded long before it got anywhere near a neuromuscular junction. Regular anti-cholinesterase inhibitors were stopped 12-18 hours before instituting EN101 for three days. In 15/16 patients, this led to a clear deterioration in strength, followed by a marked improvement when EN101 was introduced. Of course, trial purists will immediately say this was a placebo effect, as there was no blinding and no control arm. Nonetheless, it is a really exciting approach. Antisense technology is taking off in all disease areas, particularly since 1998 when the FDA approved Vitravene® for HIV-induced cytomegalovirus eye infection.

ACNR prize for the most bizarre disease at the ENS: quail eater's disease

It seems that, from time to time, people from Mediterranean countries will eat quail and get rhabdomyolysis. Two such patients presented themselves to the University of Milan, with CKs of 33,981 and 10,500, normal EMG and normal muscle biopsy. The Italian myologists have carefully probed the mechanism of this curious illness. The usual molecular suspects of muscle disease were examined and found to be normal. But Western blot analysis of the muscle showed a reduced expression of calpain-3. Mutations in the gene encoding calpain-3 cause Limb-Girdle Muscular Dystrophy type 2A. The quail eaters had normal calpain-3 genes, so presumably something about the quails had interfered very specifically with calpain-3. The presenters were asked if quail muscle contained calpain-3. This stumped them. They had not looked. Tut tut.

This solves another mystery. You will remember the Israelites received all that manna from heaven. After a while they got fed up with it and wanted meat. God was annoyed with them. The story is told in Numbers, 11: "Now a wind went out from the LORD and drove quail in from the sea..... All that day and night and all the next day the people went out and gathered quail.... But while the meat was still between their teeth and before it could be consumed, the anger of the LORD burned against the people, and he struck them with a severe plague."

*Alasdair Coles
ACNR, Co-editor*

