

EDITOR'S CHOICE

MULTIPLE SCLEROSIS: A few bad lymphocytes spread all over the brain in multiple sclerosis

Open any neurology textbook and you will find multiple sclerosis described as a condition where CD4+ T lymphocytes invade the brain where they encounter a brain protein (perhaps "MBP", myelin basic protein) and so they set up pockets of inflammation ("plaques"). If it is an up-to-date textbook, it may go on to say that "antigen-specific therapy" is the holy grail of multiple sclerosis therapeutics; that is to say, those techniques which identify and eliminate, say, MBP-reactive CD4+ T cells are the answer. This German-Austria study has upset all that. It is a study of the lymphocytes found in 19 plaques and in normal appearing brain from the post-mortem brains of just four people with multiple sclerosis. In particular, the group analysed the T-cell receptor gene rearrangements, using "TCR spectratyping". This is a clever way of asking: what antigen do these lymphocytes recognise? (For the techno-nerds, 325 semi-nested PCR reactions were performed to sequence 800 Vbeta-NDN-Jbeta combinations at the single-cell level). There were four key findings:

1. In the brains of each patient, the lymphocyte population mainly consisted of just one or two clones which had considerably expanded. In other words, only a few antigens drive the abnormal immune response in each person with multiple sclerosis.
2. These distinct T-cell clones were present throughout the brain, both in plaques and in normal appearing white matter. So, the immune attack of multiple sclerosis is far less focal than we thought.
3. The lymphocyte clones from one patient's brain were completely different to those of another brain. So, the antigens driving multiple sclerosis are "private" and specific for each individual. (However, a little caveat here is that a study of just four brains is hardly epidemiology!)
4. At least some of the T cell clones are CD8+ cells. So we need to pay attention to this cell group as well in multiple sclerosis therapies.....

Unfortunately, Junker's technology does not actually tell us the identity of the antigens recognised by the T cell clones. Nonetheless, this is all seriously bad news for those academics and companies who are busy devising "antigen-specific therapies" on the assumption that one antigen (MBP, PLP and a host of other candidates) drives multiple sclerosis in all individuals. It turns out to be all rather more complicated..... Ah well.... – *AJC*

Junker A, Ivanidze J, Malotka J, Eiglmeier I, Lassmann H, Wekerle H, Meinel E, Hohlfeld R, Dornmair K.

Multiple sclerosis: T-cell receptor expression in distinct brain regions.

BRAIN

2007;130(Pt 11):2789-99. Epub 2007 Sep 21.

EPILEPSY: and osteoporosis

Anyone who has been to the Chalfont Centre for Epilepsy knows that it is a special place. A rural idyll fulfilling the 19th century dream of care for the severe epileptic. A cluster of houses and a workshop for simple work for the residents was a progressive development and the brainchild of the great neurologists of the late nineteenth century. That the residents are said to have built one nearby neurologist's house for nothing was simply part of their occupational therapy. Now with the addition of a 21st century assessment centre and the most up-to-date neuroimaging, it is a curious juxtaposition of cutting edge and faintly anachronistic – but a great place to work; all the clinical and support staff are devoted to the centre, its residents and its mission. I am not sure that the patients who end up there for a mixture of social and clinical reasons necessarily are representative of epilepsy sufferers in the community, but they nevertheless have some lessons to teach us. Of 208 patients, 31% were osteopaenic and 37% osteoporotic. All but one had started AED's before reaching maximum bone mass and the younger the patient at onset of epilepsy, the worse the problem. A small number of patients had never received enzyme-inducing drugs and these seemed to fare no better with regard to bone density. Interestingly, men were more affected than women. These patients tended to have low levels of physical activity; my recollection

is that sport does not figure largely on the timetable at Chalfont. By contrast, from memory, tobacco consumption is high and alcohol consumption is not and of course all these are confounding factors when assessing causation. The key lesson that bad epilepsy is likely to mean bad bones, reinforces recent research and we all need to take this more seriously. Did you know that NICE recommends densitometry every five years for patient on AED? Do you tell the GP this when you discharge the patient to their care? I feel an audit coming on, but I am going to bed and hopefully the feeling will have passed by the morning. Good night! – *MRM*

Swanton J, Simister R, Altmann D, Watts H, Keen R, Duncan JS, Koeppe MJ.
Bone mineral density in institutionalised patients with refractory epilepsy. SEIZURE

2007;16:538-41.

HUNTINGTON'S DISEASE: potential quantitative biomarker in peripheral blood or not?

Up to now, no single therapy has been shown to delay disease onset or slow the progression of Huntington's disease, in part because it is hard to know how one can easily measure such an effect. One solution could be quantitative biomarkers in peripheral blood. In this recent study, Runne et al have measured mRNAs in peripheral blood cells and evaluated their utility as a potential transcriptomic biomarker. The authors have performed microarray gene expression profiling analysis on lymphocyte samples collected from 12 moderate stage HD patients and 10 controls using Affymetrix U133 Human Genome 1.0 Plus array for gene expression. Surprisingly, despite the authors initial hypothesis that neuroinflammation is an established and progressive facet of HD pathology and their expectation that related transcriptional change would be identified in HD blood, no HD-related statistical changes were detected on a single gene testing basis. This is in contrast to a previous study which had shown that transcriptomic changes in blood were a robust biomarker in tracking HD progression. The authors suggest that this difference may be due to varied subpopulations within HD. If this is the case, then there are real concerns as to whether any biomarkers may be useful in HD, until there is a better understanding of disease heterogeneity. – *CA*

Runne H, Kuhn A, Wild EJ, Pratyaksha W, Isaacs JD, Regulier E, Delorenzi M, Tabrizi SJ, Luthi-Carter R.

Analysis of potential transcriptomic biomarkers for Huntington's disease in peripheral blood.

PNAS

2007;104(36).

HEADACHE: Brainstem dysfunction in chronic migraine

The term "transformed migraine" used for chronic migraine accurately reflects the mystery surrounding its aetiology. In attempting to unravel central mechanisms in pathogenesis, this study investigated cortical excitability in chronic migraineurs and controls. Magnetic suppression of visual perceptual accuracy was measured. Positron emission tomography (PET) was used to see if there were correlated areas of excitation or inhibition. In patients with chronic migraine the study found reduced visual suppression and therefore a lack of inhibition in these patients. This correlated with PET studies in the same patients showing increased metabolism in the pons and right temporal cortex but reduced metabolism in the medial frontal cortex. The authors suggest that cortical excitability is raised in chronic migraine patients and point to evidence that patients with episodic migraine have similar but less marked changes. This correlates with the clinical observation of heightened sensitivity in migraine patients to external, particularly visual, stimuli. The findings must be treated with caution as the numbers studied are small, but they are intriguing. It seems likely that modulation of central excitatory and inhibitory pathways are one component of the intricate complex of peripheral and central changes in migraine. – *HAL*

Aurora SK, Barrodale PM, Tipton RL, Khodavirdi A

Brainstem dysfunction in chronic migraine as evidenced by neurophysiological and Positron Emission Tomography studies.

CEPHALALGIA

2007;47:996-1003.

NEURAL TRANSPLANTATION: Taking neural crest stem cells to new heights

Adult neurogenesis has been a hot topic for some time, but really in the context of the brain. A recent publication from a group in Spain led by Lopez-Barneo and colleagues has now taken the topic to the carotid body. In this structure they have shown:

- a. expansion or shrinkage of the carotid body as it experiences hypoxia and

normal oxygen tensions.

- that it contains BrdU positive cells that can be grown in vitro to produce neurospheres.
- that these cells can express tyrosine hydroxylase and release dopamine, and
- the source of these neuroprogenitors is a GFAP positive sustentacular cell derived from the neural crest.

Thus we have evidence for a neural crest derived precursor cell that is capable of dividing into dopaminergic releasing progeny and so could be considered for use in Parkinson's disease. Indeed this group have recently experimented with using carotid body transplants in patients with Parkinson's disease. There was variable clinical benefit with little evidence of dopamine cellular survival in the grafted striatum at least on PET scanning. Nevertheless these studies do suggest that more ethically neutral and practically accessible tissue sources may be available for patients with this common neurodegenerative disorder. – **RAB**

Pardal R, Ortega-Saenz P, Duran R, Lopez-Barneo J.

Glia-like stem cells sustain physiologic neurogenesis in the adult mammalian carotid body.

CELL

2007 131:364-377.

Mínguez-Castellanos A, Escamilla-Sevilla F, Hotton GR, Toledo-Aral JJ, Ortega-Moreno A, Méndez-Ferrer S, Martín-Linares JM, Katati MJ, Mir P, Villadiego J, Meersmans M, Pérez-García M, Brooks DJ, Arjona V, López-Barneo J.

Carotid body autotransplantation in Parkinson disease: a clinical and positron emission tomography study.

J NEUROL NEUROSURG PSYCHIATRY

2007;78(8):825-31. Epub 2007 Jan 12

PARKINSON'S DISEASE: smoking, coffee and NSAIDs

The effects of smoking, coffee drinking and use of nonsteroidal anti-inflammatory drugs (NSAIDs) on developing PD have been examined individually but their joint possibly synergistic effects have not. In this recent study, Payami et al have studied 1,186 Parkinson's patients and 928

controls to quantify any associations of these factors in different combinations. Standardised questionnaires were used throughout the study where detailed questions on smoking, drinking and over the counter (OTC) and prescription (Rx) NSAIDs habits were recorded. Results show that smoking at any time was associated with 23% reduction in risk of Parkinson's disease and current smoking with a 55% reduction in risk. Risk seemed to decrease with increasing smoking pack-years ($P < 0.001$), where the lowest risk (56%) was reported for patients with a > 40 pack-year history, regardless of age, sex or family history. High coffee consumption was associated with a 25% risk reduction with a significant dose-response gradient ($P < 0.001$). The coffee effect was more pronounced in men than in women with the coffee dose response relationship being highly significant in men but not in women. For NSAIDs the results revealed a 19% reduction but no obvious dose-response effect. When family history was taken into account, it revealed that the risk reduction for PD was only evident in nonfamilial PD cases. The effects of smoking, amount of coffee intake and use of NSAIDs appeared to be independent and cumulative. This collection of data on such a large number of patients is clearly a major achievement and represents a powerful data set though the fact that individuals were asked to reflect on their habits covering a lifetime of customs such as smoking, coffee drinking and consumption of NSAIDs is problematic. Nevertheless when interactions are further probed, it can be seen that the combined risks of any two factors is lower than the risks associated with the individual factors with the combination of all three factors giving the lowest risk profile. The additive effects of all three factors give a highly significant reduction of developing PD by as much as 87% although whether they are due to direct protective effects remains to be explored by further studies. Till then we might want to start consuming more coffee! – **CA**

Powers KM, Kay DM, Factor SA, Zabetian CP, Higgins DS, Samii A, Nutt JG, Griffith A, Leis B, Roberts JW, Martinez ED, Montimurro JS, Checkoway H, Payami H.

Combined effects of smoking, coffee and NSAIDs on Parkinson's disease risk.

MOVEMENT DISORDERS

E Pub6 Nov 2007

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Episenta: Controlled release sodium valproate that's easy to swallow

The issue of compliance of AEDs has been raised by a number of studies indicating that poor compliance in patients with epilepsy can relate to increased seizure frequency. However, some tablets, particularly controlled release ones, can be rather large and many patients experience swallowing difficulties. The use of syrup presentations may help, but they are not very palatable and are more expensive.

Whereas some formulations may be difficult to swallow, Episenta capsules or sachets can be opened and the minitables sprinkled onto soft foods such as yoghurt or taken with drinks. Episenta aims to be the patient friendly option. The capsules and sachets contain many minitables each of which is a prolonged delivery unit to reliably deliver sodium valproate as a once-a-day treatment to help



enhance acceptability to patients and improve compliance.

Episenta can be taken either before, during or after meals without any affect on absorption as the minitables pass through the pylorus independent of food and do not get retained in the stomach to cause gastric irritation. This makes it easier for the patient to fit the medication to their lifestyle.

There are good pharmaceutical reasons why Episenta should be the presentation of choice when requiring a prolonged release sodium valproate, but there are also sound financial reasons. Episenta is bioequivalent to Epilim Chrono and yet the NHS price is about 25% less. Episenta even costs less than standard Epilim tablets. Using Episenta ensures significant savings to the drug budget.

For more information T. 01892-600930.

EPISENTA (Prolonged-Release Sodium Valproate) - ABBREVIATED PRESCRIBING INFORMATION See Full SmPC For Details. Episenta 150 mg & 300mg capsules and Episenta 500 mg & 1000mg sachets contain prolonged release sodium valproate minitables. Indication: The treatment of all forms of epilepsy. Dose: Give in 1 - 2 single doses. Monotherapy: Adults: Start at 600mg daily increasing by 150-300mg at three day intervals to a max of 2500mg/day until control is achieved. Children over 20kg: Initial dosage - 300mg/day increasing to max. of 35 mg/kg bw/day until control is achieved. Children under 20kg: 20mg/kg bw/day; max. 40mg/kg/day. Patients with renal insufficiency: May require decreased dose. Combined Therapy: It may be necessary to raise dose when used in combination with liver enzyme inducing drugs. The dose of concomitant barbiturate should be reduced. Administration: Oral. Swallow capsule or sachet contents without chewing the prolonged-release minitables. Contraindications: Liver disease. Hypersensitivity to valproate. Precautions: The onset of an acute illness e.g. vomiting, lethargy, anorexia, jaundice or loss of seizure control is an indication of the early stages of hepatic failure and requires immediate with-

drawal of the drug. Routinely measure liver function in those at risk before and during the first six months of therapy. Discontinue if signs of liver damage occur or if serum amylase levels are elevated or if spontaneous bruising or bleeding occurs. Withdrawal of sodium valproate should be gradual to avoid increased in seizure frequency. Interactions & Pregnancy and Lactation: See full SPC. Undesirable Effects: See full SPC but most frequently, gastrointestinal disturbances. Less commonly, increased appetite and weight gain, tremor, drowsiness, ataxia, confusion, headache, reversible prolongation of bleeding time, thrombocytopenia, leucopenia, bone marrow depression and congenital malformations have been reported. Further information & MA Holder: Beacon Pharmaceuticals Ltd. 85 High St., TN1 1YG UK. Tel: 01892-600930. Presentations & Price: POM. Episenta 150 mg capsule x 100 PL 18157/0021, Episenta 300 mg capsule x 100 PL 18157/0022, Episenta 500 mg sachet x 100 PL 18157/0023 and Episenta 1000 mg sachet x 100 PL 18157/0024 have the following NHS prices: £5.70, £10.90, £18.00 & £35.50 respectively. Date of text: March 2007.