

EDITOR'S CHOICE

EPILEPSY: The SANAD Study

I don't know if it is because it was sponsored by NHS R+D but this study has been subject to as many leaks as a confidential memo from Ruth Turner at No.10. It is however good to see the paper in print and its two arms between them merited 27 pages of the *Lancet*, which is a measure of their clinical importance; this study should alter clinical practice.

Study Design. Patients were divided into two groups. In the first group were those diagnosed by their clinicians as having focal epilepsy. This group was randomised to carbamazepine (standard drug), gabapentin, topiramate, lamotrigine or oxcarbazepine. There were 378 patients in each arm of this group, except oxcarbazepine, which was a late addition to the study and where there were only 210 patients. The second group of patients were those in whom either the clinician made a confident diagnosis of idiopathic generalised epilepsy (IGE) or they were not sure, for example, patients with tonic clonic seizures and no focal features clinically or on investigation. These patients were randomised to valproate (standard drug), lamotrigine or topiramate, with 239 patients in each group. There were two primary outcome measures; the time from randomisation to treatment failure, for whatever reason and the time from randomisation to the achievement of a one year seizure remission. Secondary outcome measures included the time to first seizure and the incidence of clinically important adverse events. In both arms of the study, early withdrawal was more commonly due to adverse effects and later withdrawal to lack of efficacy – it stands to reason that you don't know a drug isn't working until you have tried it for a while. Quality of life assessments were performed on a subset of patients and cost-effectiveness was also assessed, using the assumption that patients were treated with the cheapest available preparation, which presumably means generic preparations, where available.

Results for focal epilepsy. It was quite clear that treatment failures were most likely with gabapentin and topiramate. In the case of gabapentin, seizure control was 20% less likely than with carbamazepine and with topiramate 4-8%, depending on the time period; both these results were significant. Time to two year remission was also significantly worse with these two drugs. Gabapentin was however, better tolerated than carbamazepine and topiramate was roughly equally tolerated to carbamazepine. For lamotrigine total treatment failures were 12% less than carbamazepine in the first year, 8% in the second year and 6% in the third year. Treatment failures for adverse events were 10-11% less for lamotrigine in each of the six years of the study, which was significant throughout. Part of this was related to the very high rate of rash, which accounted for 37 out of 177 treatment failures for carbamazepine and 22 out of 155 treatment failures for lamotrigine. This begs the question of how large the differences are if the patient does not have an allergic rash to the drug. Since most allergic rashes are in the first year, it seems likely that the later adverse events, which are still significantly in favour of lamotrigine, reflect other events. Carbamazepine was the least likely to cause treatment failure as a result of lack of efficacy, although the difference from lamotrigine was not significant and was biggest in the first year, perhaps related to the slower dose titration of lamotrigine. The numbers of patients taking oxcarbazepine were smaller and so the results are less statistically robust, but they suggest that this drug may be roughly equivalent to carbamazepine, with slightly less efficacy and slightly fewer adverse effects. On the basis of efficacy data, therefore, lamotrigine emerges as first line treatment for most patients with focal epilepsy with carbamazepine and oxcarbazepine as reasonable alternatives, and topiramate and especially gabapentin as also-rans. Using the lowest available cost of drugs, lamotrigine gave cost-effective benefit.

Results for general epilepsy. Sixty-three percent could be diagnosed with a specific IGE syndrome. The others had unclassifiable epilepsy. Treatment failures for topiramate were 11-14% worse than for valproate for the first five years of the study, which was highly significant. Eight to ten percent of this was attributable to adverse events and 4-6% to inadequate seizure control. Lamotrigine withdrawals were 5-10% more than valproate throughout the

study and it was slightly better tolerated but withdrawal due to lack of efficacy was 7-15% more common throughout, which was highly significant. In an intention-to-treat analysis valproate was also the favoured drug in terms of achieving a one year remission, but this is an underestimate of the difference between the drugs. If you delve into the web tables of the study you will see that many patients switched to valproate after failing with lamotrigine or topiramate, so what patients were actually taking when they achieved a one year remission was valproate 196 patients, lamotrigine 135 patients and topiramate 111 patients, with a sprinkling of other drugs, and 19 on polytherapy. The authors found that the differences between valproate and the other drugs were greater when the analysis was restricted to those with an established diagnosis of IGE, suggesting that the others had a different diagnosis. Valproate was a clear winner over lamotrigine and topiramate in generalised epilepsy. So in male patients the decision is easy. What about in women of childbearing age? Results from the Belfast epilepsy and pregnancy register¹ suggests that high dose lamotrigine may cause problems with comparable frequency to valproate (*reviewed in ACNR vol 5, issue 6*). Will this swing practice back to valproate? What about those patients with unclassified epilepsy: valproate was better for those too. What was their diagnosis? Was it focal epilepsy? If so, should valproate have been in the focal epilepsy arm of the study? Only one study² comparing valproate and carbamazepine is sufficiently large to analyse alone and it showed that carbamazepine was better for time to first seizure but there was no difference in seizure-freedom at 12 months. So is it that valproate is good for generalised epilepsy and not for focal epilepsy or is it that it is so good at generalised epilepsy that we biased humans are relatively disappointed with it in focal epilepsy and actually it is as good as anything else? Marson et al undertook a meta-analysis of studies comparing valproate and carbamazepine³ and in their recommendations to the Cochrane database concluded: "We have found some evidence to support the policy of using carbamazepine as the first treatment of choice in partial epilepsies, but no evidence to support the choice of valproate in generalised epilepsies, but confidence intervals are too wide to confirm equivalence. Misclassification of people with epilepsy may have confounded our results, and has important implications for the design and conduct of future trials." Clearly the SANAD study throws into sharp relief the inadequacy of previous studies in giving basic answers and we need to question the assumptions on which our traditional treatment choices are based.

This study provides clinically useful answers, arguably for the first time in comparing different drugs in the treatment of epilepsy and it confirms some clinicians' impressions but also throws up some surprises and provokes questions. It should make us appreciate more clearly than ever that most AED drug studies are designed to get a drug to market (a good thing) but are not sufficiently robust to alter clinical practice. The standard pre-marketing study uses the test of getting half of a refractory group of epilepsy patients to be half seizure-free for a few months. Whilst this is a different group of patients from those above, the SANAD study clearly shows us that these short studies are really only useful for assessing adverse effects and as proof of principle for efficacy. Efficacy is a long term outcome and is the main determinant of quality of life for our patients – they may stop a drug because of adverse effects, but they won't be happy until they are taking one that works long-term. Comparisons between drugs had previously relied largely on number needed to treat comparisons of premarketing studies, with different designs. These had shown that gabapentin had a large NNT, consistent with its lack of efficacy in SANAD but that topiramate had a low NNT, different from SANAD. It is true that there have been studies comparing lamotrigine with carbamazepine, which roughly came out with the same answer as this one. So when the reps come and ask you what order you use drugs in and why you haven't changed, insist on a head-to-head study and that they put their money where their mouth is and fund SANAD 2.

For the mechanistic clinicians, there is the interesting conclusion that lamotrigine really is the drug of choice for focal epilepsy. This squares with its predominant mechanism of action as a sodium channel blocker alongside carbamazepine, oxcarbazepine and phenytoin. In the choice of polytherapies

Journal reviewers

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Ailie Turton, University of Bristol.

too, this will add force to the arguments that mechanism of action (where we know it) can predict logical therapy combinations. Certainly, along with those drugs it has a propensity to make myoclonus worse. However, I expect Glaxo-Smith-Kline will not be dissatisfied with the outcome of this study.

The SANAD study showed cost-effectiveness of lamotrigine using the cheapest preparations available. What would the analysis have concluded if proprietary lamictal™ had been used? I suggest we have a duty to revisit the arguments of generic versus proprietary treatments; we can no longer think of ourselves exclusively as our patients' champions – our treatment choices impact on the health care available to others and we have a social responsibility to consider these. Decisions regarding the choice of proprietary versus generic drugs should be based on evidence. We all have anecdotal patients who have run into problems with generic AEDs but is this a reason always to prescribe branded medications? How about a study where we allocate patients to proprietary or generic drugs and for those on generics, plough the savings back into other aspects of epilepsy patient care? This is the true comparative study between generics and proprietary medication. Most likely it will remain a thought experiment but with the exception of phenytoin, I have little doubt where the QOLY's will lie. - **MRAM**

Marson AG for the SANAD study group.

The SANAD study for the effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial.

LANCET

2007;369:1016-26.

1. Morrow JJ, Russell A, Guthrie E et al. *Malformation risks of anti-epileptic drugs in pregnancy: a prospective study from the UK epilepsy and pregnancy register.* JNNP 2006;77:193-8.
2. Mattson RH, Cramer JA and Collins JF. *A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults: the Department of Veterans Affairs Epilepsy Cooperative Study No 264 group.* NEJM 1992;327:765-71.
3. Marson AG et al. *Carbamazepine versus valproate monotherapy for epilepsy: a meta-analysis.* Epilepsia 2002 May;43(5):505-13.

MULTIPLE SCLEROSIS: a new gene discovered for multiple sclerosis

The genetics of multiple sclerosis have been difficult to crack. For thirty years or so, we have known multiple sclerosis is associated with some HLA alleles, like many autoimmune diseases. In particular, in most populations, owning DRB1*1501, and perhaps DRB1*0301, increases your risk of getting multiple sclerosis. This is one variant of the genes which construct the 'class II' molecule which sits on the antigen-presenting cell, awaiting a passing T-cell. Since those landmark papers in the 1970s, there have been many thousands of DNA donations by patients, several genome screens, some key international collaborations and many millions of pounds spent to find the additional genetic cause of multiple sclerosis; but to no avail – until now. Finally, the increasing technological and analytical sophistication and vaster DNA banks have thrown up a novel gene underlying multiple sclerosis. This paper, presented by Stephen Sawcer in the Annals for the International Multiple Sclerosis Genetics Consortium, describes a filou pastry approach to HLA genetics... The starting database was DNA from 930 'trios' (people affected by multiple sclerosis and their parents), as well as from 721 other people with multiple sclerosis (presumably 'solos!'). But this was gradually whittled away as first people with DRB1*1501 and then with DRB1*0301 were excluded. With some SNPs here, some microsatellites there, and a lot of overheated PCR machines and computers... out emerged the result: people who have the HLA-C*05 allele are slightly protected against getting multiple sclerosis.

Now that is truly fascinating, because HLA-C produces proteins which act as ligands for immunoglobulin-like receptors on killer cells, a rather curious group of immune cells which are part of the innate immune response, which kicks in rapidly with infections based on recognising generic motifs on bacteria and viruses. 'Natural killer' and 'killer T cells' have yet to find an established role in the pathogenesis of multiple sclerosis. No doubt, someone is beavering away as I write this, working out exactly what is going on in the hope of harnessing the protective effect of HLA-C*05 for therapeutic gain. - **AJC**

Yeo TW, De Jager PL, Gregory SG, Barcellos LF, Walton A, Goris A, Fenoglio C, Ban M, Taylor CJ, Goodman RS, Walsh E, Wolfish CS, Horton R, Traherne J, Beck S, Trowsdale J, Caillier SJ, Ivinson AJ, Green T, Pobywajlo S, Lander ES, Pericak-Vance MA, Haines JL, Daly MJ, Oksenberg JR, Hauser SL, Compston A, Hafler DA, Rioux JD, Sawcer S.

A second major histocompatibility complex susceptibility locus for multiple sclerosis.

ANNALS OF NEUROLOGY

2007;61(3):228-36.

HUNTINGTON'S DISEASE: What is it the cause of Huntington's disease?

Huntington's disease is a disorder that is currently attracting a great deal of attention. Whilst the genetic defect of Huntington's disease is well known to be mutant huntingtin, exactly how this interferes with cellular function is currently poorly understood. Joel Perlmutter and colleagues in this recent paper in PNAS has looked at this in vivo, building on the previous post mortem data suggesting that there are oxidative phosphorylation abnormalities in this condition. In this study they took patients with genetically proven HD and age matched controls and used positron emission tomography to look at changes in cerebral oxygen and glucose metabolism. They reported that there was a significant abnormality in the striatum, characteristic of defects in mitochondrial oxidative phosphorylation. This is not that surprising perhaps, except that the abnormalities in the mitochondrial electron transport system may be mediated by astrocytes; thus implying that the neuronal pathology of HD may be secondary to a primary defect in astrocytes! This is an interesting study and obviously raises questions as to how neurons and astrocytes interact in normal brain behaviour and disease. A second paper on Huntington's disease raises interesting questions about what triplet repeat size mediates disease pathogenesis. In this case report in 'Movement disorders', Joseph Jankovic and team report on a patient who developed pathologically proven Huntington's disease with a CAG repeat of only 29. This patient, had clinical manifestations of the disease, and went on to have an autopsy that confirmed the pathology of this condition. Whilst this is only a single case report it does raise interesting issues as to what other factors drive the pathology in HD as only 70% of the variance can be explained by the CAG repeat length. Certainly in this case the patient had clinical and pathological evidence of the disease whilst having what appeared to be a normal CAG repeat length. Exactly what is going on in this case is far from clear but obviously raises many questions about what interacts with the polyglutamine region of the huntingtin protein and how this causes cellular dysfunction and neuronal death and clinical manifestations of the condition. - **RAB**

Powers WJ, Videen TO, Markham J, McGee-Minnich L, Antenor-Dorsey JV, Hershey T, Perlmutter JS.

Selective defect of in vivo glycolysis in early Huntington's disease striatum.

PROC NATL ACAD SCI U S A

2007;104:2945-9.

Kenney C, Powell S, Jankovic J.

Autopsy-proven Huntington's disease with 29 trinucleotide repeats.

MOVEMENT DISORDERS

2007; 22;127-130.

EPILEPSY: Sudden unexplained death

Like all meta-analyses this paper is only as good as its sources and, in this area, quality is very variable, with the definition of SUDEP and case ascertainment being particular difficulties. Papers were included if they met the author's criteria for quality: of 120 papers relating to SUDEP, only 27 fulfilled the authors' criteria for analysis. Those factors previously suspected of conferring a risk of SUDEP were analysed with respect to these papers, including demography, seizure type, associated psychiatric morbidity, treatment and circumstances at time of death. Those which conveyed the greatest risk of SUDEP were: young age (15-30), male sex, the presence of generalised tonic clonic seizures and being in bed. Seizure frequency was not a high risk factor which is surprising but it may be that some patients with low risk seizure types, such as simple partial seizures, had high seizure frequencies. Weak risk factors included prone position, subtherapeutic drug levels, being in the bedroom and sleeping. Why being in bed should carry a high risk but being asleep a low risk is not clear – what were those patients doing? - **MRAM**

Monté CPJA, Arends JBAM, Tan IY, Aldenkramp AP, Limburg M, de Krom. Sudden unexplained death in epilepsy patients: risk factors. A systematic review.

SEIZURE

2007;16:1-7.

STROKE: Hereditary multi-infarct dementia of Swedish type

When CADASIL was first described as such (Tournier-Lasserre et al., Nature Genetics 1993;3:256-9.), it was noted that prior descriptions of familial disorders characterised by multiple brain infarcts and dementia might also be cases of CADASIL, specifically a Swedish pedigree described under the rubric of 'Hereditary multi-infarct dementia' (Sourander & Wälinder, Acta

Neuropathol 1977;39:247-54.) and a British pedigree described as ‘chronic familial vascular encephalopathy’ (Stevens et al., Lancet 1977;i:1364-5.). In this paper, these families have been subjected to further clinical, neuroradiological, neuropathological and neurogenetic analysis to establish their precise diagnoses. However, beyond the bald statement that patients had “moderate to severe cognitive impairment” no neuropsychological assessment was reported. The British family was found to have a mutation (R141C) in the NOTCH3 gene, confirming the diagnosis of CADASIL. In the Swedish family however, sequencing of the entire 8091 base pair exonic sequence of NOTCH3 identified no pathogenic mutations; nor were there any mutations in the APP gene. Moreover limited haplotype analysis showed no linkage to NOTCH3. Histological analysis of skin biopsy showed no granular osmiophilic material in association with muscle cells, nor was it seen in the brain. Absence of NOTCH3 N-terminal fragment accumulation in the walls of the brain microvasculature was noted on immunocytochemistry of Swedish brain. Hence Swedish MID is not CADASIL, but a novel small vessel disease. -*AJL*
Low WC, Junna M, Borjesson-Hanson A, Morris CM, Moss TH, Stevens DL, St Clair D, Mizuno T, Zhang WW, Mykkanen K, Wahlstrom J, Andersen O, Kalimo H, Viitanen M, Kalaria RN.

Hereditary multi-infarct dementia of the Swedish type is a novel disorder different from NOTCH3 causing CADASIL.

BRAIN

2007;130(2):357-67.

NEUROGENESIS: a happy event or not?

Of late there has been a great deal of interest in the possibility that anti depressants work by increasing neurogenesis in the dentate gyrus of the hippocampus. In a recent paper in PNAS Jennifer Warner-Schmidt and Ronald Duman advance further our understanding of this by suggesting that vascular endothelial growth factor (VEGF) is important in mediating the effects of anti depressants on cell proliferation. Using a number of different strategies they demonstrate that anti depressants can increase hippocampal VEGF expression. They then go on to show that this is responsible for the cell proliferation and mediates the behavioural responses to chronic anti depressant treatment. This is important as anti depressants have traditionally been thought to work by upregulating noradrenaline and serotonin neurotransmission at the synapse. Perhaps changes at the serotonin and noradrenaline synapses mediate changes in VEGF. How this produces an anti depressant effect is still to be worked out but clearly this provides interesting new data on the mechanism of action of anti depressant drugs. In a second paper in the same issue of PNAS, Michael Saxe and colleagues have also attempted to look at hippocampal neurogenesis but this time looking at its effects on behaviour. What they demonstrate is that hippocampal neurogenesis can have different effects on different cognitive tasks depending on the exact paradigm used. The early work by Shors et al suggested that hippocampal neurogenesis was critical for contextual fear conditioning, whereas others have felt it has more to do with spatial learning. In this study the group show young neurons generated through the neurogenic process can have a negative influence on specific forms of working memory. They therefore conclude that a “strategy ... aimed at stimulating hippocampal neurogenesis to elicit antidepressant or pro-cognitive effects will need to strike a fine balance between restoring function and avoiding the potential or negative consequences of an excess in neurogenesis”. It is clear that fine tuning hippocampal neurogenesis is not straightforward and there is the potential that negative outcomes could arise if the system is not properly regulated or manipulated. - *RAB*

Warner-Schmidt JL, Duman RS.

VEGF is an essential mediator of the neurogenic and behavioral actions of antidepressants.

PROC NATL ACAD SCI U S A

2007;104:4647-52.

Saxe MD, Malleret G, Vronskaya S, Mendez I, Garcia AD, Sofroniew MV, Kandel ER, Hen R.

Paradoxical influence of hippocampal neurogenesis of working memory.

PROC NATL ACAD SCI U S A

2007;104:4642-6.

EPILEPSY: in intellectually disabled patients

It is easy to become demoralised when faced with patients with severe disability and awful epilepsy. So here is a study you can view as a ray of hope or a justification of therapeutic nihilism. It is a retrospective, observational study of 550 patients so the usual caveats of this design apply. Seventy-two percent had mild to moderate learning disability and patients were divided into categories according to seizure frequency: seizure-free; >1/year; >1/month; >1/week and >1/day. Moving up to the next best category over the 10 year period of observation was

described as improved and moving up by two categories as strongly improved. In this cohort, 156 patients were seizure-free at the outset and 84% remained seizure-free at ten years. Of those in whom seizures returned, fifteen had >1/year, nine >1/month and one >1/day. Fifty-five percent of patients with seizures were improved (15% strongly improved). This was similar, whether or not patients had a medication change. The greatest improvement was seen in those with the most frequent seizures, perhaps suggesting a natural regression to the mean. There was no relationship between either epilepsy type or degree of intellectual disability and the improvement in epilepsy. Since case ascertainment was retrospective, it is possible that a particular group may have suffered a higher mortality and been selected out of the study – that it’s impossible to determine. The authors go on to discuss different therapeutic regimens. They identified 78 different drug combinations but clearly any conclusions about relative merits – which actually occupies over half the results and discussion – is deeply suspect. So the bottom line is that on balance patients will improve over time, but it is usually nothing to do with anything done by their physician. - *MRAM*

Huber B, Hauser I, Horstmann V, Jokeit G, Liem S, May T, Meinert T, Robertson E, Schorlemmer H, Wagner, W, Seidel M.

Long term course of epilepsy in a large cohort of intellectually disabled patients.

SEIZURE

2007;16:35-42.

REHABILITATION: Robot better than physio...

It is accepted nowadays that task specific repetitive training is beneficial for improving recovery of function after stroke. This is largely based on the results of a high quality meta-analysis of the intensity of treatment that concluded that at least a 16-hour difference in treatment time between experimental and control groups provided in the first six months after stroke is needed to obtain small but significant differences in independence in activities of daily living (ADL) (Kwakkel et al. Stroke 2004;35:2529-36.) This is a lot of extra practice to provide within the constraints of the resources for rehabilitation in the UK. And even if time for extra face-to-face therapy was available therapists often display a low boredom threshold when supervising practice so that the number of repetitions of single tasks would likely remain low. One way to increase repetitive practice is to use assisted technology. This has been demonstrated very successfully in a single blind multicentre RCT of walking training using a mechanical gait-trainer and harness to support the patient. Early treadmill systems with body weight support required lots of effort from one or more therapists to assist in limb positioning during the exercise. Patients using the new mechanical gait trainer were able to practice alone or with a little assistance at first so it has the potential for greater intensity of practice.

Pohl et al have shown the potential in their trial in which 155 stroke patients who needed help to walk, were randomly allocated either to physiotherapy and the gait trainer, or to physiotherapy only. The experimental group received 20 minutes practice in the gait trainer in addition to 25 minutes of physiotherapy that concentrated on standing and walking. The control group received 45 minutes of the standing and walking physiotherapy intervention. The treatments were given five days a week for four weeks. The results were very impressive: At the end of the treatment period 41 of 77 patients in the gait trainer augmented therapy group were walking independently compared with only 17 of the 78 physiotherapy only group. These large differences between groups were also evident in the Barthel (ADL) scores. What’s more the effects were long lasting: at the six month follow up there were 30% more independent walkers in the gait trainer group (54/77) than in the physiotherapy only group (28/78).

The investigators did not count the number of steps made in the physiotherapy only group, but based on the therapists’ estimates of the distances covered, it is thought that patients in the control group rarely exceeded 150-200 steps during their 45 minute sessions. The patients in the gait trainer group practiced between 800 and 1200 steps at each session in addition to the steps taken in their 25 minutes of physiotherapy. It seems likely that the superior outcomes of the experimental group were due to the intensity of practice. It is scandalous that patients are not able to fulfill their potential in our rehabilitation services. Every rehabilitation unit should invest in an electromechanical gait trainer. - *AJT*

Pohl M, Werner C, Holzgraefe M, Kroczeck G, Mehrholz J, Wingendorf I, Hölig G, Koch R, Hesse S.

Repetitive locomotor training and physiotherapy improve walking and basic activities of daily living after stroke: a single blind, randomized multicentre trial (Deutsche GangtrainerStudie, DEGAS).

CLINICAL REHABILITATION

2007;21:17-27.

PARKINSONIAN SYNDROMES: Can the accuracy of diagnosis be improved?

The importance of saccadic eye movements in neurological conditions such as Parkinson's disease has been repeatedly illustrated by various groups over the past decade. PD patients typically present with difficulties in initiating movements which are then executed slowly, especially when these movements are sequential, repetitive or simultaneous. Rivaud-Pechaux et al investigated prosaccades (saccades towards a visual target) and antisaccades (saccades away from a visual target) in three groups of patients with parkinsonian syndromes; Parkinson's disease, corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) as well as in a control group. The authors' primary goal was to demonstrate that in patients with different patterns of neurodegeneration, performances in pro and antisaccades could significantly differ according to the task design. The groups consisted of 12 PSP patients (8 male and 4 female), 8 CBD patients (4 male and 4 female) and 15 PD patients. The control group was made up of 10 individuals with no history of neurological or psychiatric disorders and on no medication. Eye movement recordings were made using a horizontal electro-oculography with red and green LEDs subtending a visual angle of 0.18° and luminance of 5 cd/m². Each recording session did not exceed 40 minutes. The authors used single tasks and mixed tasks of both pro- and antisaccades. CBD patients exhibited the greatest deficits; pro and antisaccade latencies were markedly increased in both single and mixed tasks. When the single tasks were compared with the control group, an increased prosaccade latency was observed in the CBD group only and antisaccade latency was significantly longer in CBD patients than in PSP. For the mixed trials, an increased prosaccade latency was found in the CBD group only and increased antisaccades in both CBD and PSP groups. When compared with the control group, a higher prosaccade error rate was observed in the CBD group and the PD group which was not the case in the PSP group. The authors were not able to define precisely the neural structures involved in oculomotor mixing tasks. However, it pinpointed the profound deficits present in CBD and the different patterns in PSP and PD patients. Thus, such studies may help not only in diagnosing PD and PD plus conditions but may also provide unique insights into decision making processes especially those involved in the control of movement. - CA

Rivaud-Pechoux S, Vidailhet M, Brandel JP, Gaymard B.

Mixing pro and antisaccades in patients with parkinsonian syndromes.

BRAIN

2007;130(Pt 1):256-64.

EPILEPSY: Move over Hughlings Jackson

Like most British neurologists I think of John Hughlings Jackson as the father of modern epileptology; the pictures with a long white beard invest him with the appropriate gravitas to be patriarch of the specialty. But this article suggests that he may have to move over or at least share his pedestal with a relative unknown; a whipper-snapper who worked at Guy's Hospital and in a few short years, from 1869-1874, wrote his ideas on epilepsy before he suddenly dropped dead at the age of 33 in a carriage with his wife at his side. At least he had the decency to have a double-barrelled surname so as not to further debase the history books. Dickson said: "there is ample reason to believe that the seat of intellectual impressions is the surface of the brain" and went on to describe the subtle cognitive phenomena of partial seizures. Taking these two statements together he clearly suggested that focal epilepsy arose from the cerebral cortex and seems to have been the first to move away from the idea of the brainstem as their source. He believed that an alteration in cortical activity produced a release of the striatum, producing the motor activity of grand mal and thus was the first to consider the possibility of a release phenomenon as part of epileptic seizures, a concept later borrowed by Hughlings Jackson. It is clear that the two men knew each other as they had consulted over patients. He also believed in cerebral localisation of function. In 1870 Thompson gave a clear description of Jacksonian (Thompsonian?) seizure progression and in 1872 he wrote: "if the spot on the surface which becomes the seat of the affection should be a centre presiding over a ganglion controlling muscular movement, convulsion or movement in the muscles so deprived of control will occur; but if, on the other hand the spot on the surface not be associated with ganglia controlling muscles, muscular manifestations cannot occur". Perhaps on reflection, the term Jacksonian should be kept, as the poor man not only described the seizures more or less contemporaneously with Dickson but also had the misfortune to see his beloved wife suffer from them before her death in 1876. - MRAM

Eadie M.

The epileptology of John Thompson Dickson (1841-1874).

EPILEPSIA

2007;48:23-30.

MULTIPLE SCLEROSIS: Intravenous stem cells, the new immunotherapy

The great hope of stem cells as therapy is that their capacity for self-renewal and differentiation could be used to repair damaged tissues and restore function. It turns out, though, that this is not how they work in animals with experimental autoimmune encephalomyelitis, an inflammatory disorder of the CNS that poorly models multiple sclerosis in humans. Stefano Pluchino and colleagues in Milan have led the way in this story. Now two other groups have arrived at the same conclusion. Tamir Ben-Hur's team from Hadassah-Hebrew University and Antonio Uccelli's group from Genoa have each studied different stem cells in different situations. Ben-Hur showed that intravenous injection of neural progenitor cells reduced the severity of EAE (the MOG35-55 peptide C57BL/6 mice version) nicely. Uccelli took a slightly different approach: injecting iv bone marrow-derived stem cells into animals with (the SJL/J mice /PLP139-151 version of) EAE. In each case, clinical and pathological disease severity was reduced. The key finding was that both investigators labelled their stem cells with green fluorescent protein and found that... no stem cells were to be found in the brain or spinal cord. Instead, it turns out that these stem cells were treating EAE by downregulating the immune response in the peripheral lymph nodes. The mechanism is not yet worked out fully. But the message is clear: the honeymoon is over and stem cells now have to line up against beta-interferon, Tysabri and the rest as immunotherapies rather than magic healers. I wonder if they will make the cut? - AJC

Gerdoni E, Gallo B, Casazza S, Musio S, Bonanni I, Pedemonte E, Mantegazza R, Frassoni F, Mancardi G, Pedotti R, Uccelli A.

Mesenchymal stem cells effectively modulate pathogenic immune response in experimental autoimmune encephalomyelitis.

ANNALS OF NEUROLOGY

2007 Mar;61(3):219-27.

Einstein O, Fainstein N, Vaknin I, Mizrahi-Kol R, Reihartz E, Grigoriadis N, Lavon I, Baniyash M, Lassmann H, Ben-Hur T.

Neural precursors attenuate autoimmune encephalomyelitis by peripheral immunosuppression.

ANNALS OF NEUROLOGY

2007 Mar;61(3):209-18.

HEADACHE: occipital nerve stimulation

Cluster headache can be horrible. And the chronic form, where over 12 months there is no break of more than a month, is terrible. A proportion of these patients do not respond to medications. In the past, options for them have included just about every sort of lesion of the trigeminal nerve, nervus intermedius or sphenopalatine ganglion. Here, Peter Goadsby's team at Queen Square report their experience of using bilateral occipital nerve stimulation as a treatment over a median of 20 months. Under local, the stimulating wires were placed around the occipital nerves, using induced parasthesiae to confirm correct location; then, under general, the pulse generator was put into an abdominal or subclavicular pocket. The bottom line is that six of eight said their headache was improved and that they would recommend an occipital nerve stimulator to other patients with chronic cluster headache. But there were problems. For instance, a total of eight operations had to be performed after the initial procedure, for electrode migration or the like. And this was an open-label, uncontrolled study..... Nonetheless, this is such a painful condition, any prospect of a useful treatment is worth pursuing.

Burns B, Watkins L, Goadsby PJ.

Treatment of medically intractable cluster headache by occipital nerve stimulation: long-term follow-up of eight patients.

LANCET

2007;369(9567):1099-106.

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