

EDITOR'S CHOICE

Anti-epileptic drugs and pregnancy – the best data to date

Pick a common disease area with heavy pharmaceutical interest, something to do with children and long term outcomes for the emotional interest and something to do with sexuality to add a little zest and you have research money for life. The Belfast group need to be congratulated for their persistence. More importantly they have produced data which those of us at the coal face use every day to try and help our patients with tough decisions about their treatment. For nearly a decade this register has been collecting pregnancy outcomes of patients with epilepsy. The patients have to be reported to the study before any outcome is known, including before any antenatal scans and so is truly prospective and avoids selection bias towards abnormal outcomes that affects retrospective ascertainment. From the prevalence of epilepsy in the UK, the authors estimate that about half of all pregnancies in women with epilepsy are reported into the study. They measured major congenital malformations (MCM), requiring medical intervention, minor malformations and pregnancy loss. By March 2005, 4414 pregnancies were reported into the study and 2598 (72%) were on monotherapy, 21.3% on polytherapy and 6.7% on no treatment throughout pregnancy. 207 (5.7%) pregnancies were lost, 21 with a birth defect, 13 MCM. The rate of MCM was 3.5% for no AED, 3.7% for all monotherapy outcomes and 6.0% for polytherapy outcomes, which was significantly worse. Only 3 drugs had large enough numbers to compare monotherapy outcomes; carbamazepine 900, valproate 715 and lamotrigine 647. The next largest was phenytoin with 82 and the others were very much "also ran". MCM rate was 2.2% for carbamazepine, 6.2% for valproate ($P < .001$), 3.2% for lamotrigine and 3.7% for phenytoin. It is perhaps worth mentioning that 2 of 28 pregnancies on topiramate resulted in MCM. The spectrum of disorders was similar with the three main drugs. Valproate caused neural tube defects in 1% and facial clefts in 1.5%. Carbamazepine was associated more with cardiac abnormalities (0.7%) than NTD (0.2%) and the commonest abnormality seen with lamotrigine was hypospadias (0.9%). There was no significant difference in the dose of valproate or carbamazepine between those patients who had MCM and those who did not but there was a significant difference between those on lamotrigine with and without MCM. For all the drugs there was a fairly clear trend of a dose-response curve. Carbamazepine <400mg, 1.7% MCM and >1g, 3.3% MCM. Valproate <600mg, 4.1% and >1000mg, 9.1% MCM. For lamotrigine the dose effect was most marked (<100mg, 1.3%; 100-200mg, 1.9% and >200mg 5.4%). Polytherapy combinations containing valproate (9%) were significantly worse than those not containing valproate with an odds ratio 1.31-4.70. 141 pregnancies exposed to valproate and lamotrigine – a good combination for some IGE patients had a 9.6% risk of MCM. So what are the take home messages. Avoid polytherapy – nothing new there. As far as we know, carbamazepine is as good as it gets and especially with newer contraceptive methods there is no reason to change on account of 'women's issues'. Valproate is a real problem even without the recent considerations of possible mild cognitive problems in children without MCM. But it is not as simple as valproate bad, lamotrigine good. In doses over 200mg daily the risk from lamotrigine was comparable to valproate <1000mg daily. This is without taking into consideration the efficacy of the drug for the mother's epilepsy, which is the reason for stepping into this vipers' pit in the first place and that should never be forgotten. As for the new drugs, we await the next 10 years with interest. - **MRAM**

Morrow JJ, Russell A, Guthrie E, Parsons L, Robertson I, Waddell R, Irwin B, Morrison P, McGivern C, Craig J.

Malformation risks of anti-epileptic drugs in pregnancy: a prospective study from the UK epilepsy and Pregnancy register.

BMJ

<http://jnnp.bmjournals.com/cgi/rapidpdf/jnnp.2005.074203v1.pdf>

SPINAL CORD TRAUMA: New anti-Nogos get the nod

*** RECOMMENDED

Martin Schwab, in Zurich, has published on the molecular biology of neuronal growth since the mid 1970s. Perhaps his most important contribution has been the identification of Nogo-A, a membrane protein found especially in CNS myelin that inhibits neurite outgrowth. Key experiments from 1990 onwards showed that inhibition of Nogo-A with an antibody called IN-1 resulted in long-distance regeneration of lesioned fibres in the spinal cord of adult rats and improved functional recovery from animal models of stroke and traumatic spinal cord and brainstem lesions.

The trouble with the antibody, IN-1, is that it is an IgM and is administered by the cumbersome technique of actually grafting the hybridoma cells onto the animals. Cesar Milstein would have despaired! So their study in October's Annals examined the utility of two IgG anti-Nogo-A monoclonals (7B12 and 11C7) that could be administered by infusion through catheters placed in the subdural space over the spinal cord. The spinal cord was cut and antibody was dripped over the lesion for two weeks. . . . and the outcome tested. When the Schwab machine moves into action, it is impressive. Histology of the cord demonstrated that there was long-distance tract regeneration and sprouting in the corticospinal tract with the anti-Nogo-A monoclonals. Fibres actually formed bridges over the lesioned areas, unlike in the control antibody animals. And there were functional improvements in the ability of the antibody animals to run, swim, walk along narrow beams and ladders. Their footprints were better! And then the poor things were put through a fMRI protocol, which showed increased cortical activation following forepaw activation in the antibody animals. All in all, very impressive. But it is ever so slightly unrealistic that we will be able to get epidural catheters into people immediately after their spinal cord trauma! Much more pragmatic was their study in December's Annals, which showed the effect of intra-ventricular infusion of the 7B12 anti-Nogo-A monoclonal in aged adult rats one week after a MCA occlusion stroke. The 7B12 animals were no better off to begin with. But, by 8 weeks after the stroke, their performance on behavioural tasks exceeded controls and continued to improve faster than controls until the end of the study at 14 weeks post-stroke. Rather unexpectedly this improvement seemed to arise, using fMRI pictures, from plasticity within the thalamus – an area not involved in the original stroke. Intriguing. . . So, perhaps the future management of stroke will be thrombolysis in the community, followed by admission to the neuro-surgical theatre for intraventricular catheter placement for infusion of anti-Nogo-A antibody, CNTF, BDNF and whatever else is good for neuronal regeneration. . . - **AJC Markus TM, Tsai SY, Bollnow MR, Farrer RG, O'Brien TE, Kindler-Baumann DR, Rausch M, Rudin M, Wiessner C, Mir AK, Schwab ME, Kartje GL.**

Recovery and brain reorganization after stroke in adult and aged rats.

ANNALS OF NEUROLOGY

2005 Dec;58(6):950-3.

Liebscher T, Schnell L, Schnell D, Scholl J, Schneider R, Gullo M, Fouad K, Mir A, Rausch M, Kindler D, Hamers FP, Schwab ME.

Nogo-A antibody improves regeneration and locomotion of spinal cord-injured rats.

ANNALS OF NEUROLOGY

2005 Nov;58(5):706-19.

EPILEPSY: Antigial cell autoantibodies and childhood epilepsy

The role of autoimmunity in epilepsy is currently a focus of interest. The identification of syndromes which may present with seizures such as limbic encephalitis associated with voltage-gated potassium channel antibodies has increased interest in this group of disorders. However, these patients are usually unwell in other ways and do not usually just have seizures. The authors describe a child of 2 who developed refractory right focal motor epilepsy, suffering up to 100 seizures per day, associated with a right hemiparesis. An MRI showed an area of cortical abnormality in the left pericentral region and a presumptive diagnosis of Rasmussen's encephalitis was made, leading to treatment with immunosuppression. Epilepsy continued to be severe but neither the hemiparesis nor the MRI features progressed over the next 8 years. He underwent a biopsy of the abnormal region, which showed Taylor type cortical dysplasia with balloon cells but no evidence of an active inflammatory process. In recent years there has been a question of a relationship between antibodies to GluR3 to Rasmussen encephalitis and serum was taken from this child at 6, 11 and 20 months after diagnosis. Control sera were taken from other patients with RE, five patients with West Syndrome and two with Lennox Gastaut syndrome. The patient's serum appeared to increase calcium in glia in an in vitro model and the effect was not affected by Glu-R3, suggesting no major influence of this receptor on ion fluxes. In neurons, the effect of patient's serum was reduced by GluR3B suggesting competitive binding with patient's antibody and the changes in calcium were mediated via the Glu R3 receptor. The antibodies were present only in the early, very active phase of the disease. This patient had a developmental abnormality but early in the course of their illness expressed functioning antibodies – the first time this has been demonstrated. The relationship of these antibodies to pathogenesis is uncertain, and the same antibodies were not found in controls. It remains to be proven that the antibodies are not an epiphenomenon but their functional effect suggests a potentially more complex relationship between histopathology and immunology in the genesis of some epilepsy. Unfortunately the child's condition was not helped by steroid or IVIg early in the course of the disease. We await more evidence of immunological epilepsy with interest. - **MRAM Rouberti A, Boukhaddaoui H, Sieso V, de Saint-Martin A, Lellouch-Tubiana A, Hirsch E, Echenne, B and Valmier J.**

Antigial cell autoantibodies and childhood epilepsy: a case report.

EPILEPSIA

2005; 46:1308-1312.

MIGRAINE: cortical hyperexcitability between episodes

It is known that visual processing between migraine attacks is abnormal, and we see this in some migraineurs who are constantly sensitive to light and certain patterns. (One of my colleagues owns a diagnostic patterned tie which migraineurs object to, and others simply tolerate). Whether this phenomenon is due to cortical hyper- or hypoexcitability was the subject of this interesting study. Twenty migraineurs and twenty controls were compared in their motion perception thresholds in two settings: responses to coherent moving dots presented in an incoherent and then a coherent environment. The results were that migraineurs performed better than controls in the coherent environment (with high signal to noise ratio) and worse in the incoherent environment. It is suggested that several neuronal encoding patterns in a defined cortical area in migraineurs may be activated during a noisy task, while a distraction free task allows a small focused area of activation. Excessive excitation due to abnormal release of excitatory neurotransmitters may be a factor in this and is supported by the finding of higher plasma levels of glutamate in migraineurs. It has also been suggested that repeated episodes of cortical spreading depression may result in suppression or damage to GABAergic inhibitory function. Alternatively it has been suggested that cortical hyperexcitability may cause migraineurs to be vulnerable to cortical spreading depression. It seems clear that the central factors in migraine are complex and as yet poorly understood. – *HA-L*

Antal A, Temme J, Nitsche MA, Varga ET, Lang N, Paulus W.

Altered motion perception in migraineurs: evidence for interictal cortical hyperexcitability.

CEPHALALGIA
2005;25:788-94.

STROKE: A helping hand to help a hand

Can you pat your head and rub your tummy at the same time? Many people find this difficult and end up doing the same action with both hands. This is because the motor system has a strong tendency towards synchrony. There has been interest in exploiting this tendency in retraining arm movements in stroke patients. But the question is: Would the affected arm improve its movement in line with the non-paretic side or would its performance deteriorate? There have been a number of small n kinematic studies looking at stroke patients' movements using one arm or both at the same time. Results have been conflicting; some have found improved performance of the affected limb in bilateral movements while others have found its movement quality is degraded. Using a larger group of thirty-two chronic stroke patients with moderate hemiparesis, Harris-Love et al have analysed the kinematics of arm movements in bilateral and unilateral reaching movement conditions. They also investigated the effect of loading the non-paretic arm to see if the increased effort needed to move the non-paretic arm would trigger increased activation of the paretic arm. The patients were asked to reach forward across a table towards a box as fast as possible. The non-paretic limb was loaded with weights ranging from 5-20% of the maximum strength of the shoulder flexors. Kinematic data was captured using a magnetic tracking system and peak velocity, peak acceleration and total movement times were calculated. The paretic arm achieved higher peak velocity and acceleration in the bilateral condition, although movement time was not significantly different from when the reach was performed unilaterally. No further improvement was gained by weighting the non-paretic arm. It seems that performing the movement bilaterally at least improves activation of the ballistic phase of reaching. This makes sense since it is known from anatomical studies and from transcranial magnetic stimulation studies that the proximal muscles are strongly influenced by bilateral projections. Encouraging bilateral movements could be a useful strategy to facilitate early recovery of arm movements. There have been some encouraging results so far. It will be interesting to see if, when tested using a randomised controlled trial, these effects translate to long lasting improvements in function. – *AJT*

Harris-love ML, McCombe Waller S, Whittall J.

Exploiting interlimb coupling to improve paretic arm reaching performance in people with chronic stroke.

ARCHIVES PHYSICAL MEDICINE AND REHABILITATION
2005; 86: 2131-7.

EPILEPSY: What difference does a neurologist make?

The authors contacted all patients with possible or definite epilepsy in the Wrexham catchment area, identifying them from GP records of diagnosis or anti-epileptic drug intake. In a population of 200,000, they excluded 183 children under 16 and 123 over 80. They also excluded 357 adults already attending an epilepsy clinic, leaving 275 patients. Only 53 (19%) had previously been seen by a neurologist. Each patient was seen and classified as definite or

doubtful epilepsy. Prevalence of epilepsy was 0.69% - very similar to other studies. Overall remission rate was around 60%, similar for neurologists and non-specialists (Perhaps we should all go home). Misdiagnosis rate was 16%, similar to the one fifth of patients misdiagnosed in many hospital based studies in the last 20 years. For patients seen by neurologists, the misdiagnosis rate was 5.6% compared to 19.3% for patients diagnosed by non-specialists. For 87 patients (one third) they felt there were sufficient grounds to recommend specialist follow-up. In 17 patients a long-term remission was achieved by adjusting the dose of medication or changing the treatment. Ten of these were focal and 6 idiopathic generalised epilepsies, with one symptomatic generalised epilepsy. In this cohort, few of whom had previously seen a neurologist, a full clinical assessment led to a major change in diagnosis or treatment in about 20% of patients. So neurologists do seem to do better than non-neurologists and the study shows the size of the unmet need of patients in the community who suffer continuing seizures, and could either be re-diagnosed or treated better if they were seen by specialists. The challenge is to find ways of developing services to deal with this when neurologists are still quite thin on the ground. – *MRAM*

Leach JP, Lauder R, Nicolson A, Smith DF.

Epilepsy in the UK: Misdiagnosis, mistreatment and undertreatment? The Wrexham area epilepsy project.

SEIZURE
2005;14:514-20.

NEUROGENESIS: Forget Atkins, try CNTF

*** RECOMMENDED

Neurogenesis, as ACNR readers are probably now aware, occurs constitutively in the adult mammalian CNS in the subventricular zone (SVZ) and the dentate gyrus (DG) of the hippocampus. Constitutive neurogenesis may occur elsewhere in the brain but this is difficult to detect using current methods of labelling of newborn cells. Newborn cells are labelled using bromodeoxyuridine (BrdU), a thymidine analogue which binds to cells undergoing division. Kokoeva, Yin and Flier have infused BrdU continuously for 7 days into the ventricles of adult mice, and this labels more dividing cells than the normal, less frequent administration protocols. As a consequence, BrdU-positive cells were found in the hypothalamus, particularly in the arcuate nucleus, and the cells were unlikely to have migrated from the SVZ. Thus, neurogenesis may play a role in hypothalamic function. Ciliary neurotrophic factor (CNTF) is known to induce weight loss that is, unlike most other agents, sustained in the long term. An infusion of CNTF was found to increase the number of BrdU-positive cells in the hypothalamus, particularly in areas pertaining to feeding control. Newborn cells expressed CNTF receptors; around 50% expressed neuronal markers and around 20% oligodendrocyte markers. The newborn cells, after CNTF infusion, were also leptin responsive, as would be appropriate for such neurons. Mouse models of obesity, deficient in leptin or its receptor, also displayed a neurogenic response following CNTF but not sustained weight loss suggesting that the latter requires leptin signalling. CNTF-induced neurogenesis and sustained weight loss was abolished after anti-mitotic administration suggesting the two are causally related. This study shows that neurogenesis occurs in the hypothalamus, and this can be manipulated to produce weight changes. Thus, neurogenesis seems to be involved in other processes other than olfaction (SVZ neurogenesis) and memory (DG neurogenesis), with wide-ranging therapeutic implications. – *WP*

Kokoeva MV, Yin H, Flier JS.

Neurogenesis in the Hypothalamus of Adult Mice: Potential Role in Energy Balance.

SCIENCE
2005;310(5748);679-83.

MIGRAINE: Size really matters

*** RECOMMENDED

The significance of patent foramen ovale (PFO) in migraine remains a troubled area. Studies show an increased incidence of PFO in migraineurs compared to controls. But a significant number of normals have a PFO, and as clinicians we have trouble knowing what PFOs mean in migraine and what to do about them. This is the first study examining the anatomy and size of these right-to-left shunts. 93 consecutive patients with migraine with aura and 93 healthy controls were studied with transoesophageal echo. A PFO was found in 47% of the migraine with aura group, significantly more than the 17% of controls. This is not a new finding. What is novel is the finding of a moderate to large shunt in 38% of the migraine group compared to only 8% in controls. In this study, the presence of a moderate to large shunt increased

the odds of having migraine with aura almost 8-fold. The echo findings in the two groups were otherwise identical. Unfortunately the study found no distinguishing clinical features of migraineurs with a shunt compared to those without, which could potentially help us to know who to focus our investigations on. It is good to have a study which details characteristics of shunts in migraineurs and this offers promise of untangling "benign" incidental PFOs from those which matter and require further action. – *HA-L*

Schwarzmann M, Nedeltchev K, Lagger F, Mattle HP, Windecker S, Meier B, Seiler C.

Prevalence and size of directly detected patent foramen ovale in migraine with aura.

NEUROLOGY

2005;65:1415-8.

PARKINSON'S DISEASE: Deep brain stimulation – is it really that good?

★★★ RECOMMENDED

In 1987 Alim-Louis Benabid developed a new therapeutic approach of using deep brain stimulation as a way of managing the more advanced motor complications of patients with advanced Parkinson's disease. It stemmed from the chance observation that thalamic high frequency stimulation in a patient with tremor alleviated their symptoms. As a result of this a large number of groups around the world slowly adopted this procedure and it is now one of the treatments of choice in patients entering this phase of the disease. Whilst there is no doubt that it is extremely effective the questions have always been what is the best site, how effective is the treatment and are there any significant side effects. Over the years the papers have rolled out reporting on various aspects of the procedure but of late there have been a flurry of papers looking at the long term efficacy of this treatment. The first major study of this sort was two years ago by Krack et al reporting in the *New England Journal of Medicine*. However in a recent issue of *Brain*, Rodriguez-Oroz and colleagues publish on a world wide multicentre study where 69 patients were assessed 3 – 4 years post operatively. The majority had subthalamic stimulation although about a third of the patients had pallidal stimulation. Overall the two sites seemed to be of equal efficacy with the main benefit being in reducing the off periods and dyskinesias, the axial symptoms responding less well and indeed complications of speech not being uncommon. Furthermore in terms of the underlying Parkinson's disease itself, the major benefits seem to be in tremor followed by rigidity, bradykinesia and gait. This study is very much corroborated by the study of Schupbach et al reported in the *JNNP* in which they follow up for five years 37 patients who had bilateral subthalamic stimulation. The conclusion from this study was again that dyskinesias were greatly improved as were other features of the disease but they also report on cognitive decline and a series of other side effects all of which have been described before including disturbances of mood, dysarthria and weight gain. Thus overall deep brain stimulation clearly seems to offer advantages in the management of patients with relatively advanced Parkinson's disease. However the procedure is not without side effects which to some extent reflects pathology outside of the basal ganglia circuitry which is obviously not targeted by such interventions. The emerging publication of these long term series is clearly important and I suspect may impact upon recruitment of patients to such studies such that as the years go by the procedure will be reserved for more selected patients. Whatever the essential role of this treatment in the management of Parkinson's disease it is clear that the use of deep brain stimulation is here to stay (assuming that the economics of it in the UK can be resolved) and that when targeted to the right site, in the right patient has dramatic benefits at a stage of disease when medical therapies are often extremely difficult to use successfully. – *RAB*

Rodriguez-Oroz MC, Obeso JA, Lang AE, Houeto JL, Pollak P, Rehnrona S, Kulisevsky J, Albanese A, Volkmann J, Hariz MI, Quinn NP, Speelman JD, Guridi J, Zamarbide I, Gironell A, Molet J, Pascual-Sedano B, Pidoux B, Bonnet AM, Agid Y, Xie J, Benabid AL, Lozano AM, Saint-Cyr J, Romito L, Contarino ME, Scerrati M, Fraix V, Van Blercom N.

Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up.

BRAIN

2005;128:2240-9.

Schupbach WM, Chastan N, Welter ML, Houeto JL, Mesnage V, Bonnet AM, Czernecki V, Maltete D, Hartmann A, Mallet L, Pidoux B, Dormont D, Navarro S, Cornu P, Mallet A, Agid Y.

Stimulation of the subthalamic nucleus in Parkinson's disease: a 5 year follow up.

JOURNAL OF NEUROLOGY NEUROSURGERY & PSYCHIATRY.

2005;76(12):1640-4.

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