

EDITOR'S CHOICE

The first human PM study of the amyloid- β peptide vaccination cases

Regular readers of this section of ACNR will have seen our previous reports of the exciting animal studies that showed vaccination with amyloid- β peptide caused resorption of amyloid plaques in animals models of familial Alzheimer's; and then the disappointing –but intriguing – news that human trials of this approach were brought to a premature end by the unexpected development of meningo-encephalitis in some of the cases. This report, from Roy Weller's group in Southampton, is the first account of the pathology of one of these patients. She was a 72 year old woman with a five year history of Alzheimer's disease. She received five doses of the vaccine, AN-1792 (Elan), over 36 weeks with no clinical benefit. Six weeks after the last dose she became drowsy, feverish, ataxic and with worsening cognitive scores. 11 months later she died of a pulmonary embolus. Her brain makes for fascinating study. For the vaccine clearly worked at clearing the amyloid plaques and, just as in the animal models, probably through the scavenging of microglia in which A β immunoreactivity was found. However, as expected, the characteristic tangles, neuropil threads and amyloid angiopathy of Alzheimer's disease were all unaltered. Furthermore, and quite unlike the animal results, there was a CD4+ T cell meningitis and invasion of the cerebral white matter by macrophages. Quite what had got these cells excited is a mystery. But the conclusion is that perhaps, by going back to the drawing board and giving the vaccine a tweak or two, these cellular reactivities could be abolished whilst retaining the potential beneficial effects. Of course, the question then will be: does the vaccine do anything for the dementia? -AJC

Neuropathology of human Alzheimer [sic] disease after immunization with amyloid- β peptide: a case report.

Nicoll JAR, Wilkinson D, Holmes C, Steart P, Markham H, Weller R
NATURE MEDICINE
2003; 9: 448-52

PAIN

☆☆☆ RECOMMENDED

A poppy for your pain

It is gospel that opioids do not help in the treatment of neuropathic pain. John Scadding's article in this issue of ACNR mentions that this view may not be altogether correct. Here is the evidence, in a prominent article in the New England Journal of Medicine from the Pain Clinical Research Centre in San Francisco. 81 patients were randomised to low (0.15mg) or high dose (0.75mg) capsules of a μ -opioid, levorphanol. (The authors felt that a placebo-controlled trial for pain was inappropriate). Patients could taper the dose up themselves, up to a total of 21 capsules a day for four weeks, before weaning themselves off. The high dose ended up as three times the low dose (8.9 v. 2.7mg). Patients had peripheral neuropathy, focal nerve lesions, multiple sclerosis, incomplete spinal cord injury, postherpetic neuralgia and central pain from strokes or focal brain lesions. The primary outcome measure was a visual analogue scale of pain, which was reduced by both doses of levorphanol compared to baseline; but the high dose group reduced the pain significantly more (36 v. 21%). This level of pain reduction is equivalent to that achieved in trials by antidepressants and gabapentin. Levorphanol was least effective, and least well tolerated, for focal central lesions. It did rather better in patients with peripheral lesions, and best of all in those with multiple sclerosis. The most common adverse effects (which lead to withdrawal in 35% of those on the high dose) were a dry mouth, itchy skin, increased sweating and a feeling of drunkenness. So it may be reasonable to consider using an opiate in your patients with neuropathic pain, except perhaps those with pain caused by focal brain lesions, warning them that a third risk developing intolerable side-effects. -AJC

Oral opioid therapy for chronic peripheral and central neuropathic pain.
Rowbotham MC, Twilling L, Davies PS, Reisner L, Taylor K, Mohr D.
NEW ENGLAND JOURNAL OF MEDICINE
2003 348 (13) 1223-32

MULTIPLE SCLEROSIS

Multiple sclerosis: a forgetful disease

Christian Confavreux, Professor of Neurology in Lyons, has done one simple thing very effectively: since 1957, he has systematically recorded basic clinical data on patients in his multiple sclerosis clinic. And over the last five years or so, his diligence has been rewarded with a string of landmark studies. This is no exception. By April 1997, he could draw on information from 2021 patients, of whom 1562 had a relapsing-remitting course at onset. This exhaustive paper, only really suitable for a weighty journal like Brain, follows in the tradition of the London Ontario natural history studies of multiple sclerosis. It focuses on the prognostic value of events early in the clinical course of multiple sclerosis, which is important as treatment is advocated at increasingly earlier stages. The take home messages are:

- The French love azathioprine! In 1997 (before the penetration of β FN into France) 49% of this group had received a disease-modifying agent; in 91% of cases this was azathioprine.
- It takes 11, 23 and 33 years, on average, for someone with relapsing-remitting multiple sclerosis to reach the disability points of first having difficulty with mobility (EDSS 4.0), requiring one stick to walk (6.0), and requiring a wheelchair (7.0). The equivalent figures for those with primary progressive multiple sclerosis are 0, 7 and 13 years.
- In those with relapsing-remitting course from onset, the time from onset to EDSS 4.0 was longer in women, those with a higher relapse frequency in the first five years, onset at an early age, optic neuritis as a first presentation, a complete recovery from the first episode and a longer interval between first and second episode of multiple sclerosis. None of these variables affected the time to EDSS 4.0 in those with primary progressive multiple sclerosis.
- Once patients had reached a fixed disability level of EDSS 4.0, their subsequent time to further levels of irreversible disability was completely unrelated to any of these variables.

"This indicates that when a detectable threshold of irreversible disability has been reached, the disease enters a final common pathway, where subsequent progression of disability becomes a seemingly self-perpetuating process amnesic to the clinical history of the disease." Understanding

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November 2003 A11-8103

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the different biologies of the initial phase of multiple sclerosis, so influenced by this or that clinical variable, and its forgetful later phase is critical. -AJC

Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process.

Confavreux C, Vukusik S, Adeleine P.

BRAIN

2003;126:770-82

REHABILITATION

Reduction of oro-facial hypersensitivity in brain injury

Increased hypersensitivity in and around the mouth is common following severe traumatic brain injury. It can be difficult to break the vicious circle consisting of negative reactions to attempts to maintain oral hygiene, decreased sensory stimulation and further reduced oral tolerance. Given the rather crucial role of the mouth in both eating and communication this is a problem that has received relatively little attention.

This single case study reported a successful controlled management programme in a 56 year old man whose oral intolerance, at 10 months post-injury, was leading to marked deterioration in oral hygiene. The stability of the patient's problems suggested that an ABA research design would potentially demonstrate any gain from focused intervention.

Measures included duration of tolerance to touch by different stimuli (e.g. oral sponge, toothbrush) in the four quadrants of the mouth and recording of associated negative reactions (e.g. facial grimacing, reflex biting). Treatment was carried out in 24 sessions of 15 minutes over 2 weeks. The programme used stimulation moving from distal structures (hands and shoulders) towards proximal structures, combined with passive mobilisation of facial muscles.

Touch tolerance increased to the designated ceiling level post-treatment. Negative reactions reduced after intervention, though a return of negative reactions was seen for the right teeth surfaces. Functionally, the reduction in hypersensitivity allowed for full maintenance of oral hygiene. No change in status was recorded on other functional measures, suggesting that experimental changes were not due to general spontaneous neurological improvement.

It is not clear from the article why such desensitisation measures could not be undertaken until 10 months after the injury, but this situation could conceivably arise in a variety of service settings. This small study demonstrates that improvements can be made at a relatively late stage and also encourages similar careful recording of interventions at a clinical level - RABody

Treatment of oro-facial hypersensitivity following brain injury.

Gilmore R, Aram J, Powell J, Greenwood R.

BRAIN INJURY

2003;17:347-354

Should post-polio patients exercise?

A recent study by Chan *et al*, illustrates a growing trend in neurophysiology towards monitoring and guiding rehabilitation strategies. Post-polio patients are reliant on their surviving motor units to perform daily activities, and whilst intact motor neurons have a remarkable ability to reinnervate and compensate for deficits, through axonal sprouting, there is a limit to this rehabilitative mechanism. Of particular concern is the question that strength training may overwork the surviving neurons leading to a further decline in their precious numbers. This Canadian team performed a randomised control trial, in which, post-polio patients (10) either underwent a moderate strength-training program or were followed up as controls. A small group of healthy elderly subjects were also randomised and trained in a similar manner. Baselines neurophysiological measurements were applied to the thumb muscles and included maximum voluntary contraction (MVC), voluntary activation index (VAI, based on supra-maximal electrical stimulation of hand nerves during MVC, which will generate an additional twitch if voluntary activation is deficient), and motor unit number estimates (MUNE) utilising surface EMG. Patients with very low MUNE were excluded from the study. Exercise involved a 12 week graded resistance training regime with safeguards against the risk of overuse. The above parameters were measured 4 weekly and a significant increase in strength (MVC) was seen in both healthy elderly controls and even more so in the post-polio patients ($P < 0.05$). Reassuringly MUNE did not appear to change, whilst modest increases in VAI suggest that the increase in strength may have a central

component. The conclusion has to be that moderate exercise is good for post-polio patients that do not have a severely depleted motor neuron pool. Ideally, this research needs to be followed up in more patients over a longer period of time, to see if the benefits are retained and whether adaptive mechanisms differ depending on the particular muscles exercised. -JLR

Randomised control trial of strength training in post-polio patients.

Chan K, Amirjani N, Sumrain M, Clarke A, Strohschein F.

MUSCLE AND NERVE

2003;27:332-338

☆☆☆ RECOMMENDED

A randomised controlled trial of splinting the hand in brain damaged patients

Frustrated by the development of contractures affecting the hand in hemiparetic patients, many occupational and physiotherapists encourage patients to wear splints at night. The hope is that splints that keep the hand in the 'functional' position over a long period of time will prevent further contracture or even reverse it and result in muscle and tendon lengths that will allow the hand to be functional should recovery after the brain damage occur. The 'functional' position most often used holds the wrist in between 10° and 30° of extension, the fingers slightly flexed and the thumb abducted and in opposition. There has been little in the literature to support this treatment. Splints are expensive and are intrusive to wear in bed. We need to know whether wearing a splint is beneficial and the cost in money and sleep is justified? At last, a good randomised control trial from Australia has been reported, but it may not resolve the question for therapists in many British hospitals.

28 patients admitted to a rehabilitation unit after stroke or brain injury were recruited to the trial. All were given daily upper limb training and stretches as part of their routine therapy. 17 were randomly allocated to the experimental group and wore a static palmar resting splint for up to 12 hours a night for a period of four weeks. The length of wrist and finger flexors were assessed by measuring with a standard force the range of wrist extension with fingers extended. Motor assessment and pain evaluation using an analogue scale were also carried out. The assessments were performed before random allocation, at the end of the 4 weeks of treatment and at a follow up one week later. Assessors were blinded to allocation.

Compliance with wearing the splint was high, but the effects of splinting were found to be non significant and clinically unimportant in this study. However before throwing out the treatment as a waste of time and money it is important to realise the therapy routinely practiced in the rehabilitation in Townsville Hospital, Queensland may have been effective on their own in maintaining muscle length. All of the patients were given training for the upper limb for approximately 30 minutes a day, 5 days a week. In addition they were given two 30-minute stretches, five days a week which placed the wrist and fingers into extension. Prolonged stretching is not routinely practiced in the UK and 30 minutes daily for motor training of the upper limb is very rare. All too often upper limb training is neglected.

It could be that splinting may prevent contractures in hands of patients who are not given such an intensive training and stretching regime. Or perhaps we are putting our resources into the wrong kind of treatment. -AJT

Splinting the hand in the functional position after brain impairment: a randomised, controlled trial.

Lannin NA, Horsley SA, Herbert R, McCluskey A, Cusick A.

ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION

2003;84:297-302

TINNITUS

Brain stimulation for tinnitus

Is tinnitus one of those conditions that, like stroke, punches below its epidemiological weight when it comes to publications? Certainly the neurological journals do not seem to be awash with articles, despite the frequency and morbidity of the condition. This may be a little surprising in view of the growing evidence, for example from functional imaging, that higher order processing is important in tinnitus perception, so called "auditory phantom perception".

In this study from Tubingen, patients (n = 14; all right-handed) with

chronic subjective tinnitus of ≥ 1 year duration underwent repetitive transcranial magnetic stimulation (rTMS) at twelve scalp positions (five randomised trials at each position). Stimulus intensity was 120% of individual resting motor threshold (for thumb twitch), delivered at 10 Hz for 3 sec. After each train, the relative change in tinnitus was evaluated with a 5-point self-rating scale. Patients were blinded to the hypothesis of the experiment; controls for the noise and discomfort of rTMS were undertaken. 8/14 patients noted reduced tinnitus ratings immediately after rTMS, and at the group level (ANOVA) there was a significant effect for stimulus location in the left temporal and temporoparietal positions.

These data suggest that a "virtual" temporary lesion to the left temporoparietal region, "jamming" neuronal circuitry, may reduce tinnitus perception. Excess activation of temporoparietal cortex, as suggested by functional imaging, perhaps reflecting maladaptive cortical reorganisation (possibly in Brodmann areas 42, 22, and 21), may be critical to tinnitus perception. Whether a therapeutic role for rTMS may be feasible awaits further studies: one patient in this trial did experience exacerbation of tinnitus for two months. -AJL

Transient suppression of tinnitus by transcranial magnetic stimulation.

Plewnia C, Barthels M, Gerloff C.

ANNALS OF NEUROLOGY

2003;53(2):263-266

EPILEPSY

When is a drug not a drug? When it's a herb

In this study the authors reviewed the literature relating to the use of herbal remedies in the treatment of epilepsy. A resource called napralert was particularly useful in obtaining information about herbs. They found a whole spectrum of effects. At one end of the scale Zhenxianling was used as add-on therapy to anti-epileptic drugs (AED) in an open label study of 239 patients and gave >75% reduction in seizures in 66% of patients. This is better than any trial of new AED's that I know of in refractory epilepsy. Zhenxianling is thought to contain peach buds and human placenta amongst its ingredients. Also from China, Qingyangsen roots controlled seizures over 2-9 months in 9 patients for whom standard AED had been unsuccessful and who suffered 4 seizures per month. If ingesting human placenta gives you the heeby-jeebies, even washed down with Chianti, how about cow's urine concoction, a traditional anti-epileptic preparation used widely in Africa? It is the leading cause of drug poisoning in childhood in Western Nigeria resulting in cardiovascular collapse, respiratory depression and CNS depression – not recommended.

At the other end of the spectrum are herbs that may cause seizures. One boy was admitted with status epilepticus after ingesting roots of water hemlock. The authors went on to test the root in animal studies and found it triggered convulsive EEG patterns within 60 seconds of IV injection of the alcoholic extract. Among the things you are more likely to meet for which there is evidence of proconvulsive activity are Ginkgo biloba, borage, marine wormwood oil and oil of evening primrose - surely not, it's so good for you!

Herbal remedies may also interact with AED, for example eucalyptus oil lowers pentobarbitone levels and one to remember: grapefruit juice increases carbamazepine bioavailability and may trigger toxicity.

So, there you have it: drugs are good, bad or toxic and may interact but herbs are natural and they are good for you. Hmmm – I'm off for an invigorating cup of rosehip tea, I don't touch caffeine. -MRAM

Herbal remedies, dietary supplements and seizures.

A Tyagi and N Delanty

EPILEPSIA

2003;44:228-235

People who go bump in the night

My teachers always told me never say never in medicine. Despite this wise counsel I still cling to some beliefs in the hope of certainty in an uncertain world. With this paper, another of my emotional struts crumbles to dust. One of the most difficult diagnostic conundrums is the differentiation of epileptic from non-epileptic seizures. There are few clear rules as epileptic and non-epileptic seizures may have very similar manifestations. One useful one has been that if a patient is truly asleep (EEG verified sleep) at the onset of an attack, then the attack is organic, whether a parasomnia or epilepsy, but alas no longer according to this paper. In 5 patients of 76 with a clinical diagnosis from video-telemetry, the seizures

arose within seconds of arousal or in sleep. In one case the patient interacted immediately with the nurse upon her arrival, terminating the non-epileptic seizure. The attacks were all with prominent motor activity, including opisthotonic posturing, shaking movements of either hand or asynchronous jerking. A niggling doubt remains in my mind whether some of these could have been frontal lobe epileptic attacks, which are often characterised by bizarre motor activity and may have no ictal EEG changes. The more perceptive of you will no doubt attribute this to a feeble mind clinging to preconceptions in the face of evidence to the contrary. I take consolation from the fact that it was only 5 patients in a large series so the rule can be demoted to a clinical pointer, rather than having to be abandoned altogether. -MRAM

Psychogenic, nonepileptic seizures associated with EEG-verified sleep.

Orbach D, Ritaccio A and Devinsky O

EPILEPSIA

2003;44:64-68

Look into their eyes

It is 5pm and you are called to see a patient on the medical ward. She is drowsy and confused. The general physicians have done all the usual tests; there is no intracranial lesion, meningitis, encephalitis, metabolic disturbance or infection and no suggestion of drug overdose. Is she in non-convulsive status epilepticus (NCSE)? Are you going to transfer her that night to the regional centre for an urgent EEG? Current opinion is that delay in managing status may lead to neuronal damage. In this paper the authors sought clinical predictors of NCSE. They asked residents requesting an urgent EEG to fill out a questionnaire for the presence of recent or remote risk factors for seizures, tonic-clonic activity in the current episode, history of epilepsy, mental state/Glasgow coma score, ocular movement abnormalities or subtle motor activity. Ocular movements considered were hippus, nystagmoid jerks, repeated blinking and eye deviation, but not roving eye movements. Forty-eight patients were enrolled, 12 turned out to have NCSE and 36 did not. The proportion of women was greater (2:1) in NCSE compared to 16:20 in non-NCSE. Mean age was 55-60 in both groups. GCS scores in NCSE was 4.5 v 9.2 in other cases, $P < 0.001$ but no single factor predicted the presence of status epilepticus. The presence of both abnormal eye movements and a remote cause of seizures had a sensitivity of 100% with much lower specificity. It is sensitivity that is crucial in a screening test of this kind, you don't want to miss the diagnosis. The number of patients in this study was small and one feels that exceptions are likely to emerge in larger series. Nevertheless, I for one shall look more carefully at the eyes in future. -MRAM

Non-convulsive status epilepticus: usefulness of clinical features in selecting patients for urgent EEG.

AM Husain, GJ Horn, MP Jacobson

JNNP

2003;74:1289-91

COGNITION

☆☆☆ RECOMMENDED

Anticipating a switch. Brain control processes

Humans switch between activities as necessary. This capacity is achieved via "executive control processes". On behavioural paradigms, performance improves as preparation for switching is maximised. Nevertheless there is a performance "cost" on switch trials compared to repeat trials. Switch trials tend to be performed more slowly and less accurately. It seems that however much preparation for switching there is prior to the switch stimulus being presented, some control aspects necessary for switching occur only after the presentation.

Non-clinical, different-gender subjects performed a task switching-"Go/NoGo" behavioural paradigm. High-density event related potentials recorded the brain's activity allowing cognitive processes to be examined with defined timing. An early potential over posterior visual cortex differentiates Go and NoGo trials and occurs about 140-150ms after stimulus presentation. Here, this "Discrimination potential" was used as a readiness measure, presumed to indicate recognition processes drawing on an existing cognitive set. The potential is thought to reflect preparation for a task occurring some time before the relevant stimulus is presented. During repeat trials, the Discrimination potential was robust and the authors concluded that the correct cognitive set had been accessed.

However, during switch trials, the potential was absent. This is proposed to reflect prior processing, different from processing occurring on repeat trials, and evidenced by behavioural measures indicating only partial success. The paper suggests that preparation for switching may not be a separate process but rather the start of competing stimulus-response associations where competition is "resolved during the switch trial".

Showing the benefit of converging methodologies, maybe another experiment would uncover gender differences in task switching. In certain clinical populations switching is excessive and maladaptive to productive behaviour, while in others, maladaptive behaviours perseverate as switching is impaired. Perhaps this model could help explore the brain basis of these dysfunctions and help gauge outcome of rehabilitation interventions. -LAJ

Cognitive control processes during an anticipated switch of task.

Wylie G.R, Javitt D.C and Foxe J.J

EUROPEAN JOURNAL OF NEUROSCIENCE

2003; 17: 667-672

PARKINSON'S DISEASE

☆☆☆ RECOMMENDED

Agonies over agonists...The role of dopamine agonists in early Parkinson's disease

There has always been enormous controversy as to how to best treat the early stages of Parkinson's disease (PD). There were those who have advocated that starting with the most effective drug, namely L-dopa, is the best strategy whilst others have emphasised the use of dopamine agonists, given that they delay the motor complications of drug therapy. Then there was selegiline and its role as a neuroprotective agent. So it is that we now embark on a whole new debate about whether dopamine agonists are neuroprotective - giving more weight to their early use.

This debate has been sparked by the recent claims that the use of both pramipexole and ropinirole reduce the progression of disease as measured using imaging ligands - a way of trying to get around the problems of using rating scales with drug therapies and unknown wash-out periods. These studies have suggested that the rate of loss of dopaminergic striatal signal using either SPECT or PET scanning is less with agonist therapy compared to L-dopa over several years.

These claims are exciting and have massive implications if true and such is their significance that the studies have generated a whole series of articles in Neurology. These articles take various stand-points with respect to the trials, one of which has only been reported in abstract form to date (showing how heated the debate is becoming!). These articles question the validity of these functional imaging paradigms to measure what they claim to be doing, which if true also has far-reaching implications given how much they have become the gold-standard in trials of therapy in PD.

So what should we conclude from all this? Well as with all things to do with first line therapy in PD, I would suggest that we do not rush to conclusions. The results with dopamine agonists are exciting, but further analysis of the data is required, and once the ropinirole study is published

in full then a clearer picture may emerge. Till then I would suggest you continue doing whatever you do with your patients and wait until a consensus appears - assuming of course that one will be reached!!
-RABarker

Wooten GF

Agonists vs Levodopa in PD. The thrill of witha

NEUROLOGY

2003 60: 360-362

Ahlskog JE

Slowing Parkinson's disease progression. Recent dopamine agonist trials.

NEUROLOGY

2003 60: 381-389

Albin RL, Frey KA

Initial agonist treatment of Parkinson disease. A critique.

NEUROLOGY

2003 60: 390-394.

☆☆☆ RECOMMENDED

Dopamine pathways in Parkinson's disease - do they all do the same thing?

The loss of dopamine in the nigrostriatal pathway is the biochemical hallmark of Parkinson's disease and lies at the core of the symptoms and therapy...but what about the other dopaminergic pathways in the brain, what happens to them? Recently there has been interest in the cortical dopaminergic networks, which seem overactive in early PD, although this is lost with disease progression. The reason for this is not known, but it may be that the initial overactivation of the mesocortical dopaminergic pathway represents some global upregulation of all dopaminergic pathways to compensate for the failing nigrostriatal system. However the functional consequences of having such an overactive pathway may be significant, and may explain some of the deficits seen in early PD with cognitive tasks using prefrontal cortical networks (e.g. working memory and probabilistic reversal learning).

In this latest study Brooks and colleagues have extended these observations on central dopaminergic pathways by studying the less well-known dopaminergic nigropallidal pathway. In this study using PET, they showed that in early PD there is increased dopaminergic activity in the nigral projection to the internal (but not external) part of the globus pallidum, an effect that is lost with advancing disease.

The significance of this early compensatory increase is not known, but it may be important in the development of drug induced dyskinesias. Namely the loss of compensation in this pathway leads to the development of these movements, which if true would have far-reaching consequences not only to our understanding of their aetiology but to their treatment especially with novel neurosurgical procedures -RABarker
Plasticity of the nigropallidal pathway in Parkinson's disease.

Whone AL, Moore RY, Piccini PP, Brooks DJ (2003)

ANN.NEUROL.

53:206-213

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