**Vaccination for Alzheimer’s disease**

The death of neurones in Alzheimer’s disease is probably caused -at least in part- by aggregates of a peptide called amyloid β peptide that form the characteristic “amyloid plaques”. Perhaps the strongest evidence for this comes from work in experimental animals made transgenic for those mutations in the amyloid precursor protein that lead to the rare familial forms of Alzheimer’s disease. In 1999 and 2000, it was reported that vaccination of such animals with aggregated amyloid β peptide not only reduced the number of amyloid plaques, but also improved the animals’ cognitive deficits.

It seemed to be good to be true…. and in some ways it was. With great excitement the first patients were vaccinated with amyloid β peptide aggregates; only for disappointment to descend when the phase II trial was stopped early because of several cases of aseptic meningo-encephalitis. Now two papers in the latest issue of Nature Medicine restore some hope for the strategy.

Roger Nitsch’s group in Zurich studied 24 patients who had taken part in the trial, one of whom had developed the meningo-encephalitis. They showed that sera from these patients after vaccination bound selectively to amyloid plaques and diffused β-amyloid, both in brains from transgenic animals and Alzheimer’s disease postmortem brains. Three out of six patients tested also had antibodies in the CSF that bound to amyloid plaques. Importantly, neither the CSF nor sera bound to the normal full-length amyloid precursor protein or the soluble form of β-amyloid, Aβ40. So it seems that the vaccinations induced the response that was asked of them. The critical issue is, of course, whether this impacts on the course of their demen-
What is optic-spinal multiple sclerosis?

The optic-spinal form of multiple sclerosis (OSMS), otherwise known as Devic’s syndrome or neuromyelitis optica (NMO), is said to be particularly common in Japan. This retrospective study from a university hospital in Sendai in north-east Japan attempts to define the characteristics of “pure OSMS”.

From the case records of 118 MS patients seen between 1988-1999, 36 were found to have “clinical OSMS”, that is recurrent attacks of optic neuritis and myelitis as the only clinical features. Of these, only 10 (8.5% of the original sample) had persistently normal MRI brain scans (3-10 scans, over ≥ 5 year period), and hence “pure OSMS”.

There was a female preponderance in the pure OSMS cases (9:1), and all were CSF oligoclonal band negative. Despite this, clinical heterogeneity was apparent, in that 7 cases were mildly affected, with predominantly spinal sensory symptoms (as in so called “benign sensory” classical MS), whereas 3 with later onset disease were severely affected (as often noted in European and American cohorts of Devic/NMO patients). Spinal MR imaging in this latter group showed signal change and cavity-like structures extending longitudinally over several segments (not illustrated).

What does all this mean? Does “pure OSMS” represent a distinct demyelinating disorder, or is it simply one pattern of the protean manifestations of MS? The answer to these questions perhaps depends on whether the observer adopts the “splitting” or “lumping” point of view. From the data in this paper, there seems to be no prognostic (far less any therapeutic) implication from establishing a diagnosis of “pure OSMS”. - AJL

A drug for all diseases?

Simvastatin is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor. It was originally developed and licensed as a drug effective at reducing total body cholesterol and low density lipoprotein. Its main indications currently are the secondary prevention and treatment of coronary artery disease and more recently cerebral vascular disease. However, it was through its use in patients receiving cardiac transplants that it emerged that the drug has other perhaps more important effects in reducing inflammation and, in this situation episodes of rejection of the transplanted organ compared to transplanted recipients not treated with a statin. Its mechanism for reducing cardiovascular disease is now called into question and a wide variety of possible indications for the drug family is currently under investigation.

These papers focus on the drug’s possible use in multiple sclerosis. The first paper, by O. Neuhaus, et al, examines the in vitro effect of three HMG CoA reductase inhibitors simvastatin, lovastatin and mevastatin on T cell function, and compare this effect with that seen with Interferon beta. The second paper, published in Nature, assesses the effect of atorvastatin on experimental autoimmune encephalomyelitis (EAE) – an animal model of multiple sclerosis.

In vitro, statins were shown to reduce the capacity of T cells to proliferate when stimulated. The effect was equivalent to that seen with Interferon beta, and in combination the effect of these drugs was additive. The statins also reduced expression of chemokine receptors including ICAM-1 and matrix metalloproteinases, although not always to the extent achieved by the interferons. Youssef et al performed a series of experiments in which atorvastatin was given to mice both prior to and following induction of EAE. They demonstrated that oral atorvastatin prevented or reversed disease activity. This effect was maintained over six different models of EAE, including both chronic and relapsing remitting patterns, ruling out any disease pattern or species specific effect. A shift in cytokine secretion from a Th1 to a Th2 pattern was seen along with an increase in TGF beta production, a cytokine recently suspected of being involved in the regulation of autoimmunity. There was also a reduction in inflammatory infiltrate in the CNS of these mice.

The results published in these two papers taken together make a powerful argument for the further exploration of the use of HMG CoA reductase inhibitors in multiple sclerosis.

Clearly, although informative, in vitro studies sometimes poorly predict the effect of a drug in vivo, and similarly no animal model can truly predict the effect of a drug in humans. We wait with interest for the results of the ongoing phase II trial assessing the effect of statins on patients with multiple sclerosis. Given its many other proven and postulated indications this may be a tonic to add...
to the tap water! - ALC

Statins as immunomodulators: comparison with interferon-beta 1b in MS.

Neuhaus O, Strasser-Fuchs S, Fazekas F, Kieseier BC, Niederwieser G, Hartung HP, Archelas JJ. 

The HMG CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune disease.

NATURE 2002 Nov 7;420(6911):78-84

REHABILITATION


Most cases of mild head injury are completely recovered within 3 months. However there is a proportion of cases who experience persistent cognitive deficits. Memory and learning disturbances are frequently reported. Although these deficits are measurable by neuropsychological testing, explanation for the deficits remain questionable since images from CT and static MRI are often normal in this group of patients.

Dynamic imaging using PET and SPECT has been shown to have prognostic value in patients suffering from mild traumatic brain injury. Now a study in the USA has demonstrated its value towards explaining the persistent cognitive deficits that can develop in mild head injury patients.

20 patients who sought medical treatment for persistent cognitive and somatic complaints after a mild head injury were identified retrospectively from the register of an outpatient rehabilitation centre. All met the definition of mild traumatic brain injury proposed by the American Congress of Rehabilitation Medicine: that is they had a period of loss of consciousness or alteration of mental status lasting not greater than 30 minutes, memory loss for events immediately before or after injury and posttraumatic amnesia lasting not greater than 24 hours.

The patients' cognitive function was assessed by clinical neuropsychologists using recognised published tests. They were scanned with PET or SPECT depending on the terms of their insurance schemes. Experienced nuclear medicine physicians who did not have access to the findings of neuropsychological tests interpreted the scans.

Static scans taken during the acute post-injury period were normal in 15 of the 20 patients, but the later dynamic scans found abnormalities in 18. Nineteen of the 20 patients were found to have cognitive deficits and memory deficits were the most frequent, occurring in all 19. All in all, 17 of the 20 (85%) patients had positive findings on both dynamic imaging and clinical psychologists tests. Although there were a few cases where the abnormalities identified on the imaging did not match the cognitive impairment inferred from the test results, a large proportion of the abnormalities in scans were in the temporal lobe.

The authors of the study, Umile et al., considered that the prevalence of memory problems in the patients could be explained by damage to the temporal lobes in which the hippocampus and memory related structures are located. However they did not report the prevalence of attention disorders in the patients and it is possible that reduced cerebral blood flow in the temporal lobes was the result of disuse of the memory centres that was secondary to attention deficits sustained from damage in other brain areas.

Evidence of pathology in these patients should be useful in confirming that the problems they complain of are not just psychosocial. However the reduced activity or cerebral blood flow in particular brain areas may not always reflect the primary cause of the deficit. In addition PET and facilities are not widely available and both SPECT and PET use labelled markers and are therefore not usually used for repeated measures. Sensitive and safe physiological markers that can be used to determine the effectiveness of treatment for these patients are also needed. – AJT


Umile EM, Sandel E, Alavi A, Terry CM, Plotkin RC. 
ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION 2002: 83: 1506-1513

After stroke cortical space for hand recovery is pinched

Recovery of hand movement is often poorer than proximal arm movement after stroke. It has been hypothesised that this is because there is more redundancy in the motor pathways projecting to motoneurones of proximal musculature than there is in those projecting to the motor neurones of distal muscles. However a group of neuroscientists have tested and found support for another idea: that there is competition among body parts for territory in the sensorimotor cortex and that when the territory is reduced in size, due to stroke, even limited activity of the upper arm might prevent the hand from gaining more control.

Muellbacher and colleagues tested their idea in a rehabilitation experiment involving six patients who had hand weakness for over 12 months post stroke. After a single baseline measurement the six were given three intensive practice episodes in a metronome-paced pinch task. Maximum pinch force and acceleration of thumb flexion were measured after each practice episode. And as an indicator of change in cortical representation, the threshold level of transcranial magnetic stimulation intensity required to illicit EMG responses and amplitude of responses in flexor pollicis brevis were also measured at the beginning and end of the three practice episodes.

The patients improved over the first two practices but no further improvement occurred as a result of the third practice. There was no significant change in motor threshold or MEP amplitude in the flexor pollicis brevis muscle as a result of the practice. The researchers concluded that recovery with practice alone was saturated and that the practice had not resulted in measurable increase in the thumb representation in the motor cortex.

Next they selectively deafferented the patients' upper arms, but not the hands, with local anaesthetic. This was achieved by injection into the upper brachial plexus roots, using electrical stimulation for guidance. A further two practice episodes were completed. These resulted in additional improvement in pinch and acceleration performance and a significant increase in MEP amplitude.

Patients showed retention of the force gains two weeks later and reported benefits in some daily living tasks. So presumably the hand space was not reinvaded by the proximal arm representa-tion once the anaesthetic had worn off.

Deafferentation of the upper arm coupled with pinching practice appeared to reduce weakness by increasing the effectiveness of cortical connections influencing hand muscle activity. This is an interesting and novel therapeutic strategy that deserves further investigation. It will be particularly important to determine the acceptability to patients of the invasive brachial plexus injection weighed against its benefit in reducing disability. – AJT

Improving hand function in chronic stroke.

ARCHIVES OF NEUROLOGY 2002: 59: 1278-1282
PARKINSON’S DISEASE

RECOMMENDED

Tablets for fruit flies with Parkinson’s disease

Fruit flies do not get Parkinson’s disease, but they can be given it... They have dopaminergic neurones, 16-20 or so of them, in the dorsomedical cluster, which can be used as models of human dopaminergic nigral neurones. To investigate the mechanism of α-synuclein toxicity in dopaminergic cells, researchers from the University of Pennsylvania have directed expression of α-synuclein to Drosophila dopaminergic cells using the dihydroxyphenylalanine decarboxylase promoter. Using this model Pavan Auluck had previously shown that transgenic α-expression of the heat shock protein 70 (Hsp70) reduced dopaminergic cell death. In this paper, he and colleagues went one step further towards a human therapy. They fed the fruitflies a drug called geldanamycin, a naturally occurring benzoquinone ansamycyn that inactivates Hsp90, which in turn suppresses Hsp70. The experiment worked like a dream; geldanamycin protected the fruitfly dopaminergic neurones from α-synuclein toxicity. This short paper is an excellent example of how the experimental versatility of insect models can be exploited for insights into human neurodegenerative diseases. – RAB


Non-drug therapy in Parkinson’s disease – any evidence it does any good?

In the management of Parkinson’s disease one often refers patients for occupational therapy, physiotherapy or speech and language therapy (SALT) with gratifying results. However one is never entirely certain what is the evidence that it works and when patients should be referred, and thus one is left basing one clinical practice on anecdote and personal experience. Now Deane et al have attempted to answer this question by synthesising six Cochrane systematic reviews, and found that there is no evidence that any of these therapies work in PD – not because there is evidence to show this but because there is no proper evidence one way or the other. In their review they found 16 randomised controlled trials for physiotherapy, 2 for occupational therapy and 5 for SALT and dysarthria. However all the trials used unique methods of assessment and outcome, with problems of bias and so could not be subject to a meta-analysis. Thus no conclusions about these therapies could be made.

This is perhaps not surprising but it is a sobering thought to know that we refer many patients for this therapy based on no clinical evidence of efficacy. It therefore seems critical that we know that we refer many patients for this therapy based on no evidence to show this but because there is no proper evidence one way or the other. In their review they found 16 randomised controlled trials for physiotherapy, 2 for occupational therapy and 5 for SALT and dysarthria. However all the trials used unique methods of assessment and outcome, with problems of bias and so could not be subject to a meta-analysis. Thus no conclusions about these therapies could be made.

Deane KH, Ellis-Hill C, Jones D, Whurr R, Ben-Shlomo Y, Playford ED, Clarke CE. MOVEMENT DISORDERS 2002 17:984-991

RECOMMENDED

Novel sites to target therapy in Parkinson’s disease – the pedunculopontine nucleus

The pedunculopontine nucleus or PPN is a small structure found in the rostral tegmental area of the brainstem that has long been thought to be important in some of the features of Parkinson’s disease. It is known to receive from the outflow nuclei of the basal ganglia and to project both rostrally to the thalamus and caudally to the spinal cord, and has long been known experimentally to have something to do with locomotion. In this recent paper from the Oxford group, they now explore the role of this nucleus in the akinesia of parkinsonian syndromes. The hypothesis being that in PD there is excessive activity in the basal ganglia outflow nuclei, which thus produces increased inhibition in the PPN resulting in akinesia and that blocking this may relieve this feature of the illness.

In this study 2 macaque monkeys were used and the parkinsonian state induced using MPTP – a toxin known to induce parkinsonism in people, although in a fashion that is distinct from PD both clinically and pathologically. Nevertheless this is a toxin that is of use and does selectively target central catecholaminergic pathways when given systemically. These monkeys were studied using a range of clinical measures, as well as the response to micro-injections of GABA antagonists and agonists studied.

In the non-parkinsonian state injection of the GABA agonist muscimol reduced their activity, whilst in the MPTP treated monkeys the injection of the GABA antagonist reversed their akinesia in an equivalent fashion. It does any good?

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PRION DISEASE

RECOMMENDED

Treating prion disease: a set back

Prusiner and colleagues reported in 2001 that lsoysosomotropic acridine derivatives, including the anti-malarial drug quinacrine, could rapidly eradicate the production of disease-associated (prion-mediated) isoforms of the prion protein (PrPSc) in stably infected murine neuroblastoma (N2A) cell cultures. Since quinacrine is known to cross the blood-brain barrier and has a reasonable safety profile, these observations have prompted its use in human prion disease (initially on compassionate grounds, although a trial is now underway). However, no animal model data to support its use have been reported.

Collins and colleagues inoculated Balb/c mice intracerebrally with pooled brain homogenate from mice confirmed as dying from a spongiform encephalopathy. Three groups of animals (n = 8 each) received no treatment, early treatment (5 days post-inoculation), or late treatment (65 days post-inoculation), with quinacrine hydrochloride (20 mg/kg loading dose on day 1, followed by 10 mg/kg/day, by gavage feeding). The mean survival was identical in all three groups of animals. Neuropathological examination and Western immunoblots for protease-resistant PrP showed no intergroup differences.

Hence, disappointingly, there was no concordance between the animal model findings and the earlier cell culture studies. These results do not entirely close the door on quinacrine as an antiprion therapy: it might perhaps have been more effective in animals inoculated peripherally, or receiving other prion strains. However, it does point up the considerable difficulties in extrapolating from...
Sporadic CJD: anatomical substrate of myoclonus and periodic sharp wave complexes

Myoclonus and electroencephalographic periodic sharp wave complexes (PSWC) are characteristic findings in sporadic Creutzfeldt-Jakob disease (sCJD) but their pathogenesis is ill understood; there is even disagreement as to whether the two are pathophysiologically linked. The laborious, retrospective, pathological study reported in this paper from Germany attempts to correlate these features with thalamic pathology, specifically the loss of parvalbumin immunoreactive neurones. Parvalbumin (PV) is a cytosolic Ca2+ binding protein, implicated in the buffering and transport of Ca2+, predominantly expressed in inhibitory GABAergic interneurones, and for which neuroprotective roles have been suggested.

Counting PV+ neurones in various thalamic nuclei (cases n = 21; controls n = 5), the investigators found reductions in most nuclei in sCJD brains, most marked (40% vs. controls) in the reticular nucleus. sCJD patients with PSWC on EEG had a greater reduction in reticular nucleus PV+ neurones than those without PSWC, but this did not reach statistical significance; whereas patients with myoclonus and PSWC did have a statistically significant reduction in reticular nucleus PV+ neurones compared to those with myoclonus without PSWC.

The reticular nucleus is believed to serve as a pacemaker, generating and maintaining highly synchronous electrical activity. Loss of reticular nucleus PV+ immunoreactivity, reflecting loss of GABAergic interneurones, may therefore lead to loss of thalamic inhibition, and hence increased synchronicity and the appearance of PSWC. This hypothesis might be tested by looking at thalamic PV immunoreactivity in other neurodegenerative diseases in which PSWC occasionally occur, such as dementia with Lewy bodies. -AJL

Clinical findings in sporadic Creutzfeldt-Jakob disease correlate with thalamic pathology.
BRAIN 2002;125(11):2558-2566

NEURO-ONCOLOGY

Can we stomach nerve injury?

Following nerve transection, the chances of recovery depend on the ability of the proximal stump to sprout, and then correctly link up with distal motor endplates or sensory receptors. Axons have the potential to regenerate over short distances, usually less than 5 mm, divisions greater than this are problematic. Even when anatomical reconnection is achieved, functional recovery is not guaranteed since individual axons can lose their way and head towards the wrong target. Scar formation can also impede this rewiring mechanism and if the axons fail to cross this barrier, a neuroma can develop. Autologous nerve graft is considered as conventional surgical treatment if end-to-end repair is not possible, complications of this method include painful neumroma formation and loss of function at the donor site. Therefore the impetus to use natural or synthetic materials has driven experimental studies, including the insertion of conduit tubes with growth factors being added to the recipe. An important ingredient for success is ample vascular supply.

A novel approach has recently been adopted by Castaneda and Kinne, whereby omental grafts were used to bridge transected sciatic nerves in the rat. The omentum has a number of advantages as a natural framework to aid axon regeneration, including a large vascularisation capacity, harvesting is relatively easy and can be performed laparoscopically, and no significant injury at the donor site. Additionally the omentum can synthesise growth factors. The study compared functional recovery in three groups of rats, all groups underwent 25-30mm transections, one group had a conventional end to end repair whilst the other had an omentum graft and the third group had no further intervention following transection. Functional recovery, measured at 2 weekly intervals, was quickest in the omentum graft group based on an objective measure of hind leg walking. Histology was also favourable at eight weeks. These are encouraging results and perhaps the next step is to compare repair rates in autologous nerve grafts and include neurophysiological assessment. -JR

Omental graft improves functional recovery of transected peripheral nerve.
Castaneda F and Kinne R.
MUSCLE AND NERVE 2002;26(4):527-532