

EDITOR'S CHOICE

What's new in the treatment of Huntington's Disease?

Huntington's Disease (HD) is an autosomal dominant neurodegenerative disorder characterised by progressive cellular dysfunction and loss in many brain areas, but especially the striatum. As a result much attention has been focused on repairing this area of the brain with transplants of fetal striatal tissue and neurotrophic factors such as CNTF. Two recent papers using these approaches in different ways report some interesting findings. In the first of these Keene et al report the post-mortem findings of a young patient who was grafted with fetal striatal tissue into her affected basal ganglia, two years into the illness, who subsequently died 121 months later. Clinically the patient showed some initial improvement but then developed upper motorneuron signs and had a scan that showed space occupying cysts bilaterally in the putamen, which were examined histologically upon her death from advanced HD rather than any progressive mass effect from these cysts. This post-mortem examination worryingly revealed not only the cysts, but some mass lesions containing a range of neural structures including striatal elements, which is encouraging. The cysts seemed to be lined by GFAP-immunopositive ciliated ependymal cells- which were of donor (XY karyotype) origin in some instances. None of the lesions were mitotically active at the time of death, suggesting that they were not malignant cells but simply cells that had proliferated early on- perhaps in a developmentally normal fashion. Obviously this is a single case report, but it does emphasise that grafting cells into brains is not without risks, some of which are hard to quantify experimentally- making any translation to patients not straightforward.

In contrast, Lee et al report that using adipose stem cells can rescue the cells destined to misbehave and die in HD. This they show in vitro, using conditioned media from the cells, as well as in vivo using both the older excitotoxic striatal lesion model of HD as well as the R6/2 transgenic mouse. In all cases the grafted cells rescue the phenotype to a degree. The proposed mechanism, based on their in vitro data, is that this is mediated by the release of certain important factors from the cells that could reverse some of the known pathogenic mediators in HD cell death. Thus, they propose, as have many others, that stem cells could treat conditions such as HD not by cell replacement but by trophic support. Thus we have two transplant stories, both reporting some benefits but using different approaches with radically different pathological findings!

Whilst this is one approach to treating HD, an alternative strategy involves trying to block the effects of the mutant protein itself. This leads me onto two further papers on HD, the first of which strives to also better explain the pathology in a disorder in which the mutant protein is ubiquitously expressed in the CNS. In this new paper from the group of Lipton and Hayden, they postulate that it relates to the degree of glutamatergic stimulation- in particular the synaptic versus extrasynaptic NMDA receptor. In years gone by before the gene for HD was identified, the disease

was modelled through excitotoxic lesions to the striatum, on the grounds that such lesions selectively affected specific neuronal populations in a way that mimicked that seen pathologically in patients dying from this disease. In this recent article, it is shown using a variety of in vitro approaches as well as the YAC128 mouse model of HD, that the extent to which mutant htt aggregates is different depending on which type of NMDA receptor is activated- synaptic versus nonsynaptic- and involves different pathways. This was explored in the animal model using two different doses of memantine on the grounds that low dose only blocks extrasynaptic NMDA-R whilst high dose also blocks synaptic NMDA-Rs. This latter therapy encourages mutant htt disaggregation which exacerbates the pathological load to the cell and the animal, which was what was seen in this study both histologically and behaviourally. This is a new interesting angle in on the regional pathology of HD as well as highlighting the complexities of trying to treat it with disease modifying therapies, as it is not just what you use, but at what dose!

The final paper explores the use of siRNA to target the mutant htt and by so doing silence it and stop the pathological process. This is a technique that has often been shown to work well in vitro but is harder to use in vivo because of delivery problems and fear of silencing the non-mutant htt. In a recent paper by Drouet et al they have shown using a lentiviral system that mutant htt can be silenced with a beneficial effect, that is seen even after pathology has begun. Furthermore partially silencing the normal htt to a significant extent was not associated with a worsening of HD pathology or obvious changes in the striatum. This is all very encouraging, but does also throw up questions about what normal huntingtin does and the extent to which mutant htt interferes with normal htt function, as has been proposed by Elena Cattaneo et al with respect to BDNF. An effect that may also help explain the regional pathology of HD. All very interesting. – **RAB**

Keene CD et al.

A patient with Huntington's disease and long-surviving fetal neural transplants that developed mass lesions.

**ACTA NEUROPATHOLOGICA
2009;117:329-38.**

Lee ST et al.

Slowed progression in models of Huntington Disease by adipose stem cells transplantation.
**ANNALS OF NEUROLOGY
2009;66:671-81.**

Okamoto SJ et al.

Balance between synaptic and extrasynaptic NMDA receptor activity influences inclusions and neurotoxicity of mutant huntingtin.
**NATURE MEDICINE
2009;15:1407-13.**

Drouet V et al.

Sustained effects of nonallele-specific Huntingtin silencing.
**ANNALS OF NEUROLOGY
2009;65:276-85.**

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EPILEPSY: value of a tap on the head

Let's be honest, it is disappointing how little difference the great explosion of new antiepileptic drugs has proven in the search for the only truly useful outcome in epilepsy, that is seizure freedom. Sure, the new drugs are not enzyme inducers (mostly) but then who really cares, that is hardly an insurmountable problem. They have slightly less neuropsychiatric side effects than the old ones but they are hardly free of those problems. But then, virtually all our treatments do the same thing; they alter the relative balance of uppers and downers in the determination of cortical excitability. In truth they are not really anti-epileptic drugs at all, they are seizure control agents. It is perhaps not altogether surprising that whatever knife you use to skin a cat, you end up with a skinned cat (apologies to moggie-loving neurologists everywhere) and that nearly all the drugs (apart from the really awful ones) have very similar seizure control rates and pretty similar adverse event rates. So how can we find something better? One way of doing it is to look at models where we know there is a high risk of developing epilepsy and seeing if we can stop it happening. Of course this is only a minority of cases, but they may prove informative and several acute brain events have such high rates of later epilepsy that it is worth looking at them, such as haemorrhagic stroke, severe head injury and encephalitis. This study used an established model of traumatic brain injury, the fluid percussion model and looked at subtle clinical and electrographic changes in experimental rats. They found that very brief discharges, less than two seconds, which were only detectable on intracranial EEG, were associated with behavioural changes as seen on video, including an increased chance of behavioural arrest, when seen by blinded observers. This short duration of discharge would have been ignored as probably irrelevant in previous studies. The authors then went on to analyse intracranial EEG in 4 patients undergoing presurgical evaluation for their epilepsy and found similar short duration discharges, which were also associated with subtle behavioural changes when their videos were analysed. The argument goes that these brief discharges may be an early sign of epileptogenesis that has previously been ignored and that offers opportunities of a model to interfere with the process and develop drugs that are truly anti-epileptic, rather than anti-seizure. We are desperately in need of a fundamentally new approach to epilepsy control to keep up with the disease-modifying aspirations of our colleagues in Alzheimer's and MS. – **MRAM**

D'Ambrosio R et al.

Functional definition of seizure provides new insight into post-traumatic epileptogenesis.

BRAIN

2009;132:2805-21.

DEMENTIA: carving up behavioural variant FTD

The trouble with dementias is that they are difficult to classify. Like other conditions, they have clinical features, test results, imaging appearances, and histopathological findings. Unfortunately, you end up classifying patients in four completely different ways depending which of these you see as the most important. Behavioural-variant frontotemporal dementia (bvFTD) is a clinically-defined dementia syndrome, which may be more familiar by its colloquial name of 'frontal dementia'. Patients with this condition are 'frontal' - that is, they are apathetic or disinhibited in much the same way as patients with focal frontal lesions. Not surprisingly, then, if a group of bvFTD patients is compared with suitable controls, most atrophy is found in the frontal lobes. However, this group-wise analysis tends to lead to the belief that all bvFTD patients have predominantly frontal atrophy, which is not quite the same thing. Rather than assuming that all patients are the same, the authors of this paper examine the details of the data to see what classification they suggest.

The authors define the distribution of atrophy in each of a group of bvFTD patients, according to twenty-six pre-defined regions of interest,

and use the statistical method of hierarchical cluster analysis; the idea is that the most similar cases are categorised together first, then these groups gradually merge until they form one big group. The analysis doesn't tell you how many subgroups there might be, but it tells you the most meaningful way of dividing the patients into any particular number of groups. Having looked at the results, the authors choose to classify the patients into two groups, each dividing into two subgroups. These turn out to represent patients with frontal-dominant and temporal-dominant atrophy respectively, which in itself is an interesting result: a significant number of patients with 'frontal' dementia have atrophy predominantly in the temporal lobes. Of course, the behavioural features might still be caused by frontal atrophy, even if the temporal atrophy is more severe. Within the temporal-dominant group, there is a small subgroup who have fairly pure temporal atrophy, specific deficits in naming and verbal memory, and mutations in the gene for tau protein. In other respects though, the patient groups defined by the location of atrophy don't differ from each other significantly, in terms of the clinical features, neuropsychological deficits, or underlying pathology. Although the numbers are small, this result is just as important. The relationship between macroscopic atrophy and clinical features in dementia is a subtle one; a stroke destroys cells indiscriminately in the affected area, but degenerative disease affects certain groups of neurones while sparing others, and seems to proceed through functionally-connected distributed networks of cells. This paper's contribution to the classification debate is due as much to what it doesn't find as what it does. – **JK**

Whitwell JL et al.

Distinct anatomical subtypes of the behavioural variant of frontotemporal dementia: a cluster analysis study.

BRAIN

2009;132(11):2932-2946

HEADACHE: allodynia, migraine and mood

This study examined and highlighted the link between migraine, other pain syndromes, cutaneous allodynia, and mood disorders. Cutaneous allodynia is a recognised manifestation of migraine and has been studied clinically and experimentally. It is a manifestation of central sensitisation, and reflects convergence of nociceptive pathways at many levels of the nervous system, including spinal cord, brain stem, thalamus and cortex. The authors found that 60% of migraineurs reported cutaneous allodynia, and this was associated with mood disorders (depression and anxiety), and other pain conditions (irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome). The worse the allodynia, the more likely the co-morbidity. This is a tangled web, and it is likely that there is a mixture of causality and consequence. Chronic pain, and in particular migraine, is associated and worsens depression, and depression is likely to be worse if the pain is more severe. Central up-regulation of nociceptive pathways and central receptor and transmitter modulation may exacerbate or cause mood disorders. Central changes are documented in cerebral reactivity, metabolism and function, and are becoming more clearly understood, and will be important in clarifying these clinical observations. Clinically this is really important. We all need to be aware of the link between mood disturbance and migraine, and that often both may need treatment in migraineurs. This is crucial in making therapeutic choices and in monitoring response, for example in ensuring that treatment with beta-blockers is not worsening depression. Further, in patients with daunting multiple symptomatology of fatigue, pain and low mood, untargeting and treating the migraine may bring great benefit. – **HAL**

Tietjen G et al.

Allodynia in Migraine: Association with Comorbid Pain Conditions.

HEADACHE

2009;49:1333-44.

CONSCIOUSNESS: as night follows day

The recently reported case of a Belgian man with a locked in syndrome who was “missed” for 23 years, suffering in apparent silence while the world moved on around him has been this year’s cause-célèbre in the world of vegetative and minimally aware states. The application of ever more sophisticated scanning techniques in the assessment of those with severe brain injury has changed the way that we conceptualise the disorders of consciousness. Whether you consider that changes in activity within certain parts of the brain in response to stimulation really equate to “consciousness”, the role of the clinician in the proper assessment of these patients at various stages in their recovery should not be understated. The value of a good history, examination and the assimilation of evidence from imaging and neurophysiological modalities underpin proper clinical assessment. Part of this assessment is the longitudinal observation of patients in minimally aware states over time. This small study (5 patients) looked specifically at circadian rhythms in patients in low awareness states. The presence of a sleep-wake cycle is felt to represent the threshold at which the comatose state becomes the vegetative state, which may be an important herald of change. Surface skin temperatures were recorded continuously for three consecutive days. Surface skin temperatures are known to change in a circadian pattern in accordance with environmental and light intensity changes. The degree of cerebral atrophy was also determined for this patient group. Of the 5 patients, only 2 demonstrated circadian patterns of temperature variation. These patients had sustained traumatic brain injuries and demonstrated significantly less cerebral atrophy than the 3 who did not display circadian rhythms (who had all sustained anoxic brain damage). Although the authors freely acknowledge that the study is too small to allow definite conclusions to be drawn, the difference in pattern of circadian rhythms between the traumatic and anoxic brain injury group demonstrates that this may form a valuable addition to the assessment battery in low awareness states. – **LB**

Bekinschtein T et al.

Circadian Rhythms in the Vegetative State.

BRAIN INJURY

2009; 23(11):915-19.

HEADACHE: a measure between auras?

During and after migraine with aura there is cerebral hyperperfusion and hypoperfusion. The situation between attacks has been unclear, with transcranial Doppler giving inconsistent results. This study used semi-automated transcranial Doppler measures to visually evoked responses. In 70 patients with migraine with aura and 40 controls (with migraine without aura or with no migraine), the visual evoked flow rate, a robust measure of functional vasomotor reactivity, was measured. There was a significant difference in vasomotor reactivity interictally, with higher visually evoked flow rate in migraine with aura patients than controls. This change must be considerable as it has been demonstrated in quite small numbers. Of course this is likely to be quantitative, as migraine is so common and migraineurs are not separate from the rest of the population but at one end of a continuum. This work provides a potential tool to monitor and understand therapeutics. – **HAL**

Wolf ME et al.

Changes in functional vasomotor reactivity in migraine with aura.

CEPHALALGIA

2009;29:1156-64.

ENCEPHALITIS: status quo vadis

The latest discovery from Josep Dalmau, of antibodies to GABA receptors, will surprise no-one who has been following the story of neuropil-encephalitis. And the prominent seizures seem to make sense. In a throw-away line in the methods, we see the pecking order of these antigens start to emerge from the fog. Seemingly, a growing bank of 410 sera, from

patients suspected to have a paraneoplastic or autoimmune encephalitis, has been extensively studied for antigen specificities. 357 samples found an antigen – nearly 90%. Of note, 275 were specific for NMDA receptors – that’s a whopping two-thirds of the total collection. 27 were specific to potassium channels, 19 to glutamic acid decarboxylase, 15 to AMPA receptors. The remainder were subjected to a well trodden path of antigen identification, through staining of brain sections, cultured neurons, and decorated human embryonic kidney cells. The focus here is on the clinical features of 15 patients with antibodies that recognise the B1 subunit of the GABA receptor. There are no surprises. The patients were relatively old (range 24 – 75). 7 of the 15 had a tumour, 5 of which had small cell lung cancer. Clinical response to tumour removal or immunotherapy was good in 9 of the 10 treated cases. But where are we going? There is a clear need to fully demonstrate the pathogenicity and origins of these antibodies, and to further develop novel methods of antigen identification – **MZ**

Lancaster E et al.

Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen.

LANCET NEUROLOGY

2010;9:67-76. Published Online December 3, 2009.

NEUROGENESIS: new for old

Adult neurogenesis occurs in two constitutive areas of the adult mammalian brain- the subventricular zone from where the cells migrate out to the olfactory bulb, and the subgranular zone of the hippocampus where they migrate out to form neurons that contribute to the normal circuitry of this structure. The function of these new neurons is not fully resolved, we have postulated that they contribute to pattern separation (Clelland C et al, Science 2009), whilst others have postulated that they mediate other cognitive or affective processes. In this last respect Kitamura et al have recently shown using a combination of approaches “that decreased hippocampal neurogenesis is accompanied by a prolonged hippocampal dependent period of associative fear memory”, whilst enhancing this process with voluntary exercise “sped up the decay rate of HPC dependency of memory, without loss of memory”. They therefore conclude that “the level of hippocampal neurogenesis plays a role in the determination of the HPC-dependent period of memory in adult rodents”. This is of interest, but one of the critical questions that obviously arises is the extent to which this is also true for man, and what this means therapeutically in patients with neurological diseases. In this respect there are two papers that explore this- one looking at the cognitive deficits of cranial irradiation and the other Alzheimer’s disease. In the first study Acharya et al depleted the stem cell/precursor cell pools in the adult brain (especially the hippocampus) using irradiation and then grafted them 2 days later with human embryonic stem cells (hESCs) into the hippocampal complex. These transplanted cells survived and differentiated and appeared to ameliorate some of the cognitive deficits- presumably by replacing the adult neurons that were lost to the irradiation process. In the second study Biscaro et al showed that ABeta immunotherapy not only removed amyloid plaques but promoted the survival and maturation of neurons generated through the normal hippocampal neurogenic pathway. The exact mechanism by which this is achieved is not clear nor is its relationship to the increased angiogenesis that they also report, but it does once more highlight that innate repair processes may be useful in disease recovery, if they can be helped by combining strategies that also involve removing the pathological proteins themselves. – **RAB**

Kitamura T et al.

Adult neurogenesis modulates the hippocampus-dependent period of associative fear memory.

Cell – 2009;139:814-27.

Acharya MM et al.

Rescue of radiation-induced cognitive impairment through cranial transplantation of human embryonic stem cells.

PNAS – 2009;106:19150-5.

Biscaro B et al.

ABeta immunotherapy protects the morphology and survival of adult-born neurons in doubly transgenic APP/PS1 mice.

THE JOURNAL OF NEUROSCIENCE – 2009;29:14108-19.