

## EDITOR'S CHOICE

**Transplants, Lewy bodies and Parkinson's disease – a new link?**

The use of fetal ventral mesencephalic dopaminergic cell therapies for Parkinson's disease has been a contentious treatment since its first use in the late 1980s. Its proponents point to the success of individual patients who have remained on low doses of medication for many years after their transplant. Their opponents refer to the two double-blind placebo controlled trials, published in 2001 and 2003, which showed no significant clinical benefit over sham surgery. Thus the field is in a state of indecision. A series of articles in a recent issue of *Nature Medicine* further complicates the situation as these papers report alpha synuclein pathology in these transplants.

The rationale for using ventral mesencephalic transplants in Parkinson's disease is to replace the dopaminergic cell loss that characterises this disease. By using the developing dopaminergic cells of the fetal midbrain, derived from elective terminations of pregnancies (abortions), the expectation is that they survive and mature into fully functional adult dopaminergic neurons and replace the function of the patient's own nigral dopamine cells that have been lost in the disease process. To date this approach has been seen to work, inasmuch as dopamine cells so transplanted have survived long term and some individuals have shown marked improvement with evidence for dopamine release from the transplants and restoration of normal cortical motor activation. However the results are inconsistent. These new papers now also highlight that the pathology of PD may occur in the transplants. In two of these, the authors report on alpha synuclein positive elements within the transplant despite the fact that these dopamine cells are only 10-15 years old. Whether this pathology affects the functional efficacy of the transplant is unknown, as the patients reported in these papers did not derive a huge benefit from the transplant. Thus, it is not known whether these pathological abnormalities have implications for the cell

transplant approach to Parkinson's disease, especially given that the remaining paper reports that the graft is free of PD pathology. So these papers certainly do not spell an end to fetal ventral mesencephalic allografting for PD. Perhaps of greater interest is what this says about the pathogenesis of Parkinson's disease, as it would imply that the diseased brain can induce pathology in normal dopaminergic cells. In other words, either the glia in the PD brain or some trans-synaptic communication from diseased neurons to grafted neurons, can induce alpha synuclein aggregation in 'non-PD' dopaminergic nigral neurons. Thus, the disease may be self propagated within the CNS once some critical pathological event has occurred. It is this which is the most important message of these papers, rather than anything to do with cell transplants and their future use in patients with Parkinson's disease. – **RAB**

**Li JY, Englund E, Holton JL, Soulet D, Hagell P, Lees AJ, Lashley T, Quinn NP, Rehncrona S, Björklund A, Widner H, Revesz T, Lindvall O, Brundin P.**

*Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to graft disease propagation.*

NATURE MEDICINE

2008; 14: 501-503.

**Kordower JH, Chu Y, Hauser RA, Freeman TB, Olanow CW.**

*Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease.*

NATURE MEDICINE

2008; 14: 504-507.

**Mendez I, Viñuela A, Astradsson A, Mukhida K, Hallett P, Robertson H, Tierney T, Holness R, Dagher A, Trojanowski JQ, Isacson O.**

*Dopamine neurons implanted into people with Parkinson's disease survive without pathology for 14 years.*

NATURE MEDICINE

2008; 14: 507-509.

**EPILEPSY: Should patients with bad brains be considered for epilepsy surgery**

Bad brains as evidenced by low IQ mean a poor prognosis for epilepsy surgery, or so the received wisdom goes. In the Swedish National Epilepsy Surgery Register, 448 patients were operated from 1990 to the date of publication and of these 18 had IQ < 50 and 54 had IQ 50-69. When low IQ groups were compared to higher IQ groups it was clear that the median seizure frequency correlated inversely with IQ; patients with IQ < 50 had a median seizure frequency of more than 100 per month compared with 10/month in the temporal lobe cohort and 30/month in the cohort with IQ > 70. The ratio of temporal lobe versus extratemporal resections was similar in all the groups. Seizure-freedom at two years was achieved in 80% of those with IQ > 70, 36% of those with IQ 50-70 and 22% of those with IQ < 50, another 22% achieving > 75% seizure reduction and a further 35% > 50% seizure reduction. The likelihood of seizure freedom was predicted by histopathological lesion type in all groups, with lesions doing better than cortical malformations or gliosis. IQ was an independent predictor of seizure outcome. Three of five patients in the lowest IQ group who had a lesion underlying their epilepsy became seizure-free. This means that only one of the remaining 13 became seizure free. So in the lowest IQ group, unless there is a clear lesion underlying the epilepsy, it is hard to give an unreserved recommendation for surgery. We clearly need more data on quality of life benefits of lesser degrees of seizure reduction in this cohort, as well as longer term follow-up, as lesser levels of seizure reduction may (or may not) be useful. This is clearly a retrospective study in which only the best candidates were offered surgery and it does not give enormous ground for optimism. – **MRAM**

**Malmgren K, Olsson I, Engman E, Flink R, Rydenhag B.**

*Seizure outcome after respective surgery in patients with low IQ.*

BRAIN

2008; 131:535-42.

**GUILLAIN BARRE: a new treatment?**

Despite all our cleverness with ITUs and IVIG, people still die from Guillain-Barre and its variants. One such is the Miller Fisher syndrome:

ophthalmoplegia, ataxia and areflexia. We could do with a better treatment. And Hugh Willison and colleagues from Glasgow and the Netherlands may have come up with just that. The key step in their study was getting hold of a monoclonal antibody against the ganglioside GQ1b. This mimics the antibody produced in vivo during the disease. Using this antibody both in vivo and in an in vitro model (mouse hemi-diaphragm), they had shown that this antibody disrupts pre-synaptic neuromuscular junction signalling. Crucially, this only occurs through activation of complement and formation of the membrane attack complex. Enter eculizumab. This humanised monoclonal antibody prevents formation of the C5 components and thus disables the complement pathway. Very happily, it is already a licensed therapy: for that curious illness paroxysmal nocturnal haemoglobinuria, in which there is complement-mediated haemolysis. Does it work to suppress experimental Miller Fisher? In short, yes. An impressive array of data, from histology, immuno-histochemistry, electrophysiology and electron microscopy, confirms that pre-treatment with eculizumab successfully prevents the damage done by anti-GQ1b antibodies. Unfortunately, the experimental monoclonal caused damage so rapidly, it was not possible to test the more real-life situation of treating with eculizumab after the disease has started. Against all the odds, it seems there is a real prospect of a new agent for the treatment of Guillain-Barre syndrome... provided the relevant drug company (for your stockbroker: Alexion Pharmaceuticals) can be persuaded to invest in the necessary trials. – **AJC**

**Halstead SK, Zitman FM, Humphreys PD, Greenshields K, Verschuuren JJ, Jacobs BC, Rother RP, Plomp JJ, Willison HJ.**

*Eculizumab prevents anti-ganglioside antibody-mediated neuropathy in a murine model.*

BRAIN

2008 May; 131(Pt 5):1197-208.

**STROKE: Robots can help recovery of hand function**

It is recognised that task specific training with lots of repetition is important for optimising motor recovery following stroke. The problem in many stroke services with resources is how to deliver intensive practice. The provision of robots to assist therapy may provide a solution in the future. A

number of groups have developed robotic based systems for helping people to practice goal directed arm movements, concentrating mainly on the elbow. Early phase studies have produced promising improvements in performance, however without a functioning hand there is little point in moving the arm. Perhaps because of its greater complexity the hand has been neglected in rehabilitation robotics. Now in a paper by Takahashi et al. it appears advances have been made to address this omission. In Brain they report a behavioural evaluation with investigation of the specificity of the robot assisted therapy effects on brain reorganisation. The actuated device developed and evaluated by Takahashi et al. helps the hand in grasp and release movements by assisting flexion and extension of the fingers, thumb and wrist. Patients use the device in conjunction with some virtual reality games or with real objects to perform grasp and release actions. The robot-assisted therapy programme emphasises movement repetition as well as attention, speed, force, precision and timing. Task difficulty is also adjustable to avoid ceiling and floor performances. Thirteen patients with chronic stroke resulting in moderate weakness in the right hand were recruited for evaluation using the robotic system and programme. After two baseline assessments (over two weeks) the participants followed the therapy programme for 15 days. However seven of the participants were given assistance from the robot for all 15 days while the remaining six, although strapped into the apparatus, were only given assistance from the robot after the first 7.5 days of treatment. The groups were allocated by a pseudo random method. Outcome was measured after the first 7.5 days, after 15 days and at a follow up one month later. fMRI scans were carried out during the baseline period and after the completion of the 15 day course of treatment. During the scans the participants performed a target grasp and release action and a control (unpractised) task involving pronation and supination of the forearm. Of course the sample was a small select group, but nevertheless the results were impressive: significant gains on both a hand function and an impairment level assessment were found at the end of treatment and these benefits were still present at follow up. The participants who received robotic assistance in all sessions made greater gains than those who received robotic assistance in only half of sessions. The grasp task performed during fMRI showed increased sensorimotor cortex activation across the period of therapy, while the non-practiced task, supination/pronation did not. Takahashi et al have shown that their robotic system and therapy program based on motor learning theories can improve hand function and that the assistance of the robot to perform the practice is helpful in achieving this. Given the equity of the intensity of practice this finding may be considered surprising. Shouldn't those who had to do the tasks more independently have done better than those who received assistance everyday? The authors suggest that by providing assistance the movements produced are wider in range of motion, more normally coordinated, and thus provide a larger and more organised afferent signal to brain sensorimotor areas, which could be important for recovery. While this may be the case, the fMRI results emphasise another principle that can be applied to rehabilitation in general and not just to robot assisted therapy: task specific practice is important for the recovery. – *AJT*

Takahashi CD, Der-Yeghiaian L, Le V, Motiwala RR Cramer SC.

*Robot-based hand motor therapy after stroke.*

BRAIN

2008;131:425-37.

### MULTIPLE SCLEROSIS: Pathologists awry

Since people have been studying the plaques of multiple sclerosis for over one hundred years, you would have thought their basic histology would be sorted by now. But, if anything, we are more in disarray today than we ever were. For the recent literature contains apparently irreconcilable results. In 2000 Hans Lassman, Claudia Lucchinetti and others published an oft-quoted study, in which they classified plaques into four types... and, importantly, insisted that only one type appeared in each patient. So multiple sclerosis is heterogeneous between patients, but homogenous within an individual. Now Esther Breij, Lars Bo and colleagues from Amsterdam have completely contradicted this work. They studied 131 lesions from 39 patients with definite multiple sclerosis, from the Dutch Brain Bank. They showed homogenous pathology of active demyelination amongst all patients, with deposition of complement and macrophage-associated immunoglobulin in all cases. There may be a simple explanation for the controversy. Breij studied post-mortem material from patients with established multiple sclerosis, present for a median of 22 years. In contrast, Claudia Lucchinetti had examined 81 cases of acute multiple sclerosis, 49 from biopsy samples. As all clinicians know, the need for a brain biopsy suggests the patients had very atypical multiple sclerosis, at least at presentation. So perhaps there is

no real debate and the described differences are just those between early, fulminant disease and established multiple sclerosis. – *AJC*

Breij EC, Brink BP, Veerhuis R, van den Berg C, Vloet R, Yan R, Dijkstra CD, van der Valk P, Bö L.

*Homogeneity of active demyelinating lesions in established multiple sclerosis.*

ANNALS OF NEUROLOGY

2008 Jan;63(1):16-25.

### BRAIN REPAIR: how stress alters fate

What happens to neural precursor cells (NPCs) when they are exposed to oxidative stress or at least manipulation of local redox states - a state that is probably altered in most neurological conditions? The answers, from this Nature Cell Biology paper, from a series of in vitro and in vivo studies are:

1. that E17.5 mouse cortical NPC have reduced proliferation as measured by Ki67 or BrdU.
2. astroglial differentiation is promoted at the expense of neurons, with the opposite occurring in reducing conditions. There is no change in oligodendrocyte differentiation nor in the proportion of monopotent or bipotent NPCs, suggesting there is a switch in the differentiation process rather than a selective growth of different types of NPCs.
3. there is increased expression of Sirt1 - a class III NAD dependent histone deacetylase - without there being any change in neural transcription factors. This mediates the shift in differentiation as blocking it using siRNA, or increasing its activation using resveratrol, has the anticipated effects on the differentiation profile in oxidatively stressed NPCs.
4. The downstream mechanism by which Sirt1 exerts this effect involves a co-operative action with the transcription factor hes1. They then act together on the promoter region of Mash1, which is an important transcription factor in normal neuronal differentiation. This effect on Mash1 also involves the TLE1 containing co-repressor complex.
5. To look at the in vivo relevance of this work, the authors then go to show that Sirt1 and Mash1 are expressed in one of the major sites of neurogenesis in the adult brain - namely the subventricular zone. They also demonstrate that their expression are altered by the oxidative state in these P2 mouse brains with a change in the differentiation profile as predicted from the in vitro studies.
6. Finally the expression of Sirt1 in Experimental Allergic Encephalomyelitis (EAE) was investigated. EAE is an animal model of autoimmune demyelination often used to model MS. In this model it was shown that areas of inflammation with astroglia had marked Sirt1 upregulation in GFAP positive cells, which could be further increased with the Sirt1 activator resveratrol.

Therefore this group has revealed a clear pathway by which the differentiation fate of NPCs can be changed by the local redox state, although how this plays out in disease is unknown - outside of their interesting observations in EAE. Whatever its exact significance, it does show that relatively subtle local changes in the brain may impact on its innate ability to repair itself. – *RAB*

Prozorovski T, Schulze-Toppoff U, Glumm R, Baumgart J, Schröter F, Ninnemann O, Siegert E, Bendix I, Brüstle O, Nitsch R, Zipp F, Aktas O.

*Sirt1 contributes critically to the redox-dependent fate of neural progenitors.*

NATURE CELL BIOLOGY

2008;10:385-94.

### Journal reviewers

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