IN THE NEWS

Brain, heal thyself

Although treatments such as L-DOPA and fetal tissue grafts can alleviate some of the symptoms of Parkinson's disease, the ultimate goal is to reverse the degeneration of dopaminergic neurons, which lies at the root of the problem. According to recent newspaper reports, a team from the Frenchay Hospital in Bristol, UK, have made significant progress towards achieving this aim.

The researchers injected glial cell line-derived neurotrophic factor (GDNF) into the brains of five patients with Parkinson's. One of the patients, Stephen Waite, described the procedure: "They drilled two holes in the top of my skull into which they fed tiny tubes into the affected part of the brain. These were fed beneath the skin down the back of the neck behind my ears and through my body to connect up with two stainless steel pumps behind the abdominal muscles above the stomach" (*The Mirror* UK, 24 April).

All five patients reported considerable improvements in their condition. One patient, Roger Nelson, said: "I had the operation on the Friday and by Sunday lunchtime I could smell. Very shortly after I noticed that I could be a bit more articulate. My wife passed a slightly risqué comment just after I got home from hospital, and I burst out laughing, which I hadn't been able to do for several years" (*Independent* UK, 19 April).

Even the researchers were surprised by their success. Team leader Stephen Gill said: "We thought this drug would take some months or even years to be effective. We found that within a month or two patients were noting significant changes in their ability to do things" (*Guardian* UK, 19 April). However, they stress that it's still early days, and that it could be several years before the treatment can be used routinely.

Heather Wood

NEURODEGENERATIVE DISORDERS

Altering the course of disease

Although amyotrophic lateral sclerosis (ALS) is one of the most common neuromuscular diseases worldwide, we know relatively little about its causes. Most ALS cases are sporadic, but research has focused on familial ALS (FALS) in a search for the genetic defects that underlie the disease. One such defect — mutations in the superoxide dismutase gene, *SOD1* — occur in ~20% of FALS cases. But FALS onset and severity can vary remarkably in families with the same *SOD1* mutation. Now, Giess *et al.* report that additional mutations at *CNTF* — which encodes a potent motor-neuron survival factor — is probably one of several modifiers of ALS. Their findings indicate that, without the neuroprotective activity of CNTF, mutant SOD1 can trigger ALS earlier in both sporadic and familial patients, as well as in mice with mutant copies of both genes.

ALS is a rapidly progressive, invariably fatal neurological disease that attacks the neurons that control voluntary movement. It most commonly strikes between 40 and 60 years of age, but not always, as exemplified by the family studied by Giess *et al.* Three members of this family carry an exonic *SOD1* mutation believed to disrupt SOD1 function. The mother developed ALS at 54; however, the son developed the disease at 25 and died 11 months later, while his sister remains unaffected at 35. Giess *et al.* genotyped *CNTF* in this family because of its previous association with ALS, and found that the son was homozygous null for *CNTF*, his mother heterozygous and his sister wild type. They also genotyped eight sporadic cases, who had an early onset of ALS, and who also proved to be $CNTF^{-/-}$.

To check that this was not just a chance correlation, Giess *et al.* also studied motor-neuron survival in mice with mutations in both genes. As previous studies of ALS had indicated that mutant SOD1 acts as a dominant gain of function, the authors crossed transgenic mice (*hSOD-1G93A*) that overexpress a disease-associated, human mutant *SOD1* with *Cntf* null mice. They found that *hSOD-1G93A*/$Cntf^{-/-}$ mice lose more lumbar spinal-cord motor neurons and have an earlier onset of disease than *hSOD-1G93A*/$Cntf^{+/+}$ mice, but that disease duration is unchanged by *Cntf* loss. Linkage analysis showed that, although disease incidence is regulated by *SOD1* in this cross, disease onset, when analysed as a quantitative trait, is controlled by *Cntf*.

One study has reported that 2% of healthy individuals are homozygous for a null *CNTF* mutation — indeed, the unaffected father of the proband reported here was $CNTF^{+/-}$. Understanding how such mutations combine with other spontaneous, and perhaps epigenetic, events during life to give rise to sporadic neurodegenerative disease should fuel research for years to come.

Jane Alfred
Editor, Nature Reviews Genetics

References and links

ORIGINAL RESEARCH PAPER Giess, R. *et al.* Early onset of severe familial amyotrophic lateral sclerosis with a *SOD-1* mutation: potential impact of *CNTF* as a candidate modifier gene. *Am. J. Hum. Genet.* **70**, 1277–1286 (2002)
FURTHER READING Cleveland, D. W. & Rothstein, J. D. From Charcot to Lou Gehrig: deciphering selective motor neuron death in ALS. *Nature Rev. Neurosci.* **2**, 806–819 (2001)
WEB SITE
NINDS amyotrophic lateral sclerosis information page:
http://www.ninds.nih.gov/health_and_medical/pubs/als.htm