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- 1 Powell TPS, Mountcastle VB. The cytoarchitecture of the postcentral gyrus of the monkey *Macaca mulatta*. *Bulletins of the Johns Hopkins Hospital* 1959;105:108-31.
- 2 Iwamura Y, Tanaka M, Sakamoto M, et al. Rostrocaudal gradients in the neuronal receptive field complexity in the finger region of the alert monkey's postcentral gyrus. *Exp Brain Res* 1993;92:360-8.
- 3 Delay JPL. *Les astérognosies: Pathologie du toucher*. Paris: Masson, 1935.
- 4 Iwamura Y, Tanaka M. Postcentral neurons in hand region of area 2: their possible role in the form discrimination of tactile objects. *Brain Res* 1978;150:662-6.
- 5 Vogt BA, Pandya DN. Corticocortical connections of somatic sensory cortex (area 3, 1, and 2) in the rhesus monkey. *J Comp Neurol* 1978;177:179-92.

Isolated spastic paraparesis leading to diagnosis of Friedreich's ataxia

Friedreich's ataxia is the most common hereditary ataxia. This neurological disorder was initially defined by the association of ataxia, cerebellar syndrome, and pyramidal signs. Atypical forms are increasingly recognised. The gene was mapped to 9q13-q21.1 in 1988 and identified in 1996. We report on a patient with a spastic paraparesis, of which molecular analysis confirmed the diagnosis of Friedreich's ataxia.

A 39 year old woman without any past condition presented with difficulty in walking since the age of 20. Neurological examination showed a spastic paraparesis, with tetrapyramidal signs, including generalised brisk reflexes, bilateral Babinski's signs, and clonus at the knees and ankles. Spasticity only concerned the lower limbs and spared the arms. Spastic paraparesis resulted in impaired walking at the time of the examination. No other neurological abnormalities were found; notably, proprioception and vibration sense, and cerebellar function were normal. No sensory symptoms were noted. No skeletal deformities were found. All hematological investigations (including lactate and pyruvate concentrations, cholesterol, apolipoproteinemia, Vitamin E, very long chain fat acid concentrations, arylsulphatase, and hexosaminidase activities) were normal. Electromyography, sensory and motor nerve conduction studies in the upper and lower limbs, including sural nerve action potentials (right sural nerve action potential 7 μ V, normal >6 μ V; left sural nerve action potential 8 μ V, normal >6 μ V) were normal. Cardiological tests (electrocardiography, transthoracic echocardiography) were normal. Cerebral and spinal resonance MRI were normal. No familial condition was found, except the sister who presented the same symptoms. No mutations involved in mitochondriopathies were found

(3243tRNA^{Leu}, 8344tRNA^{Lys}, nt 8993). The molecular analysis of the gene coding for Friedreich's ataxia was performed by Southern blotting from DNA extracted from peripheral blood and showed two abnormal expansions of 2.5 kb and 3.1 kb on the chromosome 9q13-q21.1 (Dr M Schmitt, CHRU de Strasbourg, France). These expansions correspond to 830 and 1030 repeats. Diagnosis of Friedreich's ataxia identified by an isolated paraparesis was definitely retained.

Friedreich's ataxia, an autosomal recessive disorder, is one of the most common hereditary ataxias. The frequency of the gene is close to 1/90 in the general population and the prevalence of the disease is estimated to be 1/50 000. Diagnosis is classically based on the association of recessive inheritance, onset before the age of 25, progressive ataxia of the four limbs, loss of deep tendon reflexes, pyramidal signs, cerebellar dysarthria, distal loss of position and vibration sense, and electrophysiological evidence of axonal neuropathy.¹ Association of pes cavus, scoliosis, cardiomyopathy, hearing loss, diabetes, and retinal disease are inconstantly seen. By contrast, atypical clinical symptoms are increasingly encountered—for example, late onset, brisk reflexes, spasticity, and slow progression of the disease,² and idiopathic ataxia.³ Friedreich's ataxia is a genetically homogeneous condition. The frataxin gene was mapped to 9q13-q21.1 in 1988,⁴ and identified in 1996.⁵ The mutations are most often GAA expansions located in the first intron.⁵⁻⁷ Normal alleles range from 6 to 36 GAA repeats, whereas pathological alleles range from 90 to 1300 repeats. Ninety six per cent of patients are homozygous for GAA trinucleotide repeat expansions in the first intron of the frataxin gene. The remaining patients are compound heterozygotes for a GAA expansion and point mutations (missense, nonsense, and splice site mutations).^{5,7} Frataxin, the protein encoded by the gene, is a protein associated with the inner mitochondrial membrane.⁸ It is thought to regulate the flux of iron in or out the mitochondria. Identification of the mutated gene allowed the correlation of certain phenotypes with genotypes. Larger expansions of the GAA repeats are correlated with an earlier age of onset, a faster progression of the disease, and additional clinical manifestations such as cardiomyopathy, pes cavus, scoliosis, and extensor plantar responses.⁶ The length of the expansion explains 50% of the variability of age at onset only. Other factors are certainly involved in the phenotype variability. We note that the correlations were established from expansions measured in lymphocytic DNA. We cannot exclude the possibility of somatic mutations. Thus, the length of expansion in affected tissues would be different from the length found in lymphocytes. Some punctual mutations (D122Y, G130V) are correlated with a mild phenotype.⁷ Previous reports have noted that patients with Friedreich's ataxia could present with spasticity, usually associated with other neurological signs.⁹ Our report of isolated paraparesis confirmed again that the phenotypic range of Friedreich's ataxia is much broader than previously considered.^{3,6} In addition, the spastic paraparesis presented by our patient could be related to the cases of mitochondriopathies presenting with spastic paraplegia. Similar clinical symptoms in these two diseases can be an additional argu-

ment for the implication of frataxin in mitochondrial function.

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- 1 Harding AE. Friedreich's ataxia: a clinical and genetic study of 90 families with an analysis of early diagnosis criteria and intrafamilial clustering of clinical features. *Brain* 1981;104:589-620.
- 2 Richter A, Morgan K, Poirier J, et al. Friedreich's ataxia in Acadian families from eastern Canada: clinical diversity with conserved haplotypes. *Am J Med Genet* 1996;64:594-601.
- 3 Schöls L, Amoiridis G, Przuntek H, et al. Friedreich's ataxia. Revision of the phenotype according to molecular genetics. *Brain* 1997;120:2131-40.
- 4 Chamberlain S, Shaw J, Wallis J, et al. Mapping of mutation causing Friedreich's ataxia to human chromosome 9. *Nature* 1988;334:248-50.
- 5 Campuzano V, Montermini L, Molloy MD, et al. Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. *Science* 1996;271:1423-7.
- 6 Dürr A, Cossee M, Agid Y, et al. Clinical and genetic abnormalities in patients with Friedreich's ataxia. *N Engl J Med* 1996;335:1169-75.
- 7 Cossee M, Dürr A, Schmitt M, et al. Friedreich's ataxia: point mutations and clinical presentation of compound heterozygotes. *Ann Neurol* 1999;45:200-6.
- 8 Campuzano V, Montermini L, Lutzky, et al. Frataxin is reduced in Friedreich's ataxia patients and is associated with mitochondrial membranes. *Hum Mol Genet* 1997;6:1771-80.
- 9 Gates PC, Paris D, Forrest SM, et al. Friedreich's ataxia presenting as adult-onset spastic paraparesis. *Neurogenetics* 1998;1:297-9.

Marked increase of interleukin-6 in injured human nerves and dorsal root ganglia

Nerve injury, particularly of the brachial plexus, may result in lifelong disability and chronic pain, despite technically excellent reconstructive surgery. Studies of molecular changes in injured nerves may identify new treatments to enhance the success of nerve repair, such as with recombinant human neurotrophic factors. Interleukin-6 (IL-6) is a member of the neurotrophic cytokine family that includes ciliary neurotrophic factor (CNTF), leukaemia inhibitory factor (LIF), and oncostatin M. As there is increasing evidence of a neurotrophic role for IL-6 in animal models of nerve injury and inflammation,^{1,2} we have studied, for the first time in humans, IL-6 protein in injured and control peripheral nerve and dorsal root ganglia, using specific immunoassay, immunocytochemistry, and western blotting. We report a most remarkable increase of IL-6 concentrations in acutely avulsed dorsal root ganglia and injured nerves.

Proximal and distal injured nerve segments were obtained from six adult patients with traction brachial plexus injury, ranging from 2 weeks to 10 weeks after trauma. Injured dorsal root ganglia were collected from seven adult patients with brachial spinal root avulsion injuries (central axotomy), ranging from 3 days to 15 months after trauma. Tissue removal was a necessary part of the surgical repair procedure; in all cases

informed consent was obtained for tissue collection, and the study had ethics committee approval. Control dorsal root ganglia were obtained from four subjects and segments of normal nerve from five subjects at postmortem, with a mean delay of 36 hours after death; all died from myocardial causes. Tissue extracts prepared as previously described^{3,4} were analysed for IL-6 using an enzyme immunoassay (Peline CompactTM, Eurogenetics, UK Ltd, Middlesex, UK) with recombinant human IL-6 standard calibrated against the World Health Organisation (WHO) First International Standard 89/548. For immunohistochemistry, frozen sections (8 µm) were fixed in 4% paraformaldehyde in phosphate buffered saline for 30 minutes. Sections were incubated with monoclonal antibodies to IL-6 (CLB.IL-6/7 20 µg/ml, diluted 1:400; gift from K Nordlind, Sweden, or ref No 1618-01, Genzyme, USA) and immunoreactivity to IL-6 visualised using a standard immunoperoxidase method (ABC; Vector Labs, UK) with nickel enhancement as described elsewhere.^{3,4} Specific immunoreactivity was extinguished by a concentration of rhIL-6 (ImmunoKontakt, Frankfurt, ref 111-40-136) in the range 0.01–0.1 µg/ml. For western blotting, tissue extracts were separated by gel electrophoresis on 15% acrylamide gels and then electrophoretically transferred to nitrocellulose membranes (Hybond Super, Amersham) using a semidry transblotter. Strips were blocked in a solution of 5% non-fat milk in phosphate buffered saline (PBS) containing 0.05% Tween-20 for 1 hour and then probed with CLB.IL-6/7 (with or without IL-6 peptide, 20 µl) at a final titre of 1:1000, for 2 hours. The strips were then incubated with anti-rabbit HRP (Sigma) at 1:10,000 dilution for a further 30 minutes. Bands were then visualised on x ray film after treatment with ECL reagents (Amersham).

Concentrations of IL-6 were increased in injured nerves (figure). The increase was greater in nerve segments distal to injury, but IL-6 concentrations in both proximal and distal segments were both significantly increased compared with controls ($p < 0.01$, Mann-Whitney test). Concentrations of IL-6 were greatly raised in two avulsed dorsal root ganglia obtained 3 and 4 days after injury (354 pg/mg and 128 pg/mg). At longer operative delays after injury, IL-6 concentrations in avulsed dorsal root ganglia approached the range of values obtained for postmortem controls (4.9 (SD 2.9) pg/mg for operative delays from 1 week to 15 months, and 0.2 (SD 0.06) pg/mg for controls). Western blotting showed the presence of an expected strong 29 kDa band in detergent extracts of injured nerve, which was abolished in the presence of excess synthetic IL-6. Immunohistochemical studies with both antibodies demonstrated IL-6 staining within the soma of avulsed dorsal root ganglion neurons of all sizes, particularly of small size. Immunostaining of postmortem ganglia seemed similar in pattern, but was generally weaker. Interleukin-6 immunoreactivity was also seen in nerve-like structures within the dorsal root ganglia and distal injured nerve segments.

The pattern of changes of IL-6 in injured nerves and dorsal root ganglia differs from that seen for other neurotrophic factors, such as nerve growth factor (NGF) and glial-derived neurotrophic factor (GDNF).^{3,4} Concentrations of IL-6 were usually higher in distal nerve segments when compared with those proximal to the site of injury: this seems

IL-6 immunoreactivity in human nerve tissues. Assay concentrations of IL-6 in extracts of human nerve, comparing segments proximal and distal to injury with control postmortem nerve.

to result from IL-6 synthesis in Schwann cells in Wallerian degeneration, as shown by immunostaining, and previous animal model studies.² Interleukin-6 and its receptor have been shown to be required for normal nerve regeneration in animal models, which may be enhanced with exogenous IL-6.¹ The injured nerves presumably take up IL-6 synthesised in the Schwann cells, and transport it proximally, which accounts for the higher IL-6 concentrations in proximal segments of injured nerves in comparison with controls. Anterogradely transported IL-6, if released in the spinal cord, may play a part in pain processing, for which there is some evidence from animal models. In this study, the most remarkable finding was the very high concentration of IL-6 in extracts of the acutely avulsed dorsal root ganglia, with much smaller increases at later times after injury. The acute increase of IL-6 could originate from sensory cell bodies themselves, as has been shown with IL-6 mRNA in situ hybridisation studies in rat sensory ganglia after peripheral nerve injury,⁵ or from inflammatory cells. This increase may have autocrine/paracrine effects, which may aid cell survival, or have a role in sensory or sympathetic sprouting.

We conclude that IL-6 is a significant factor in the events after nerve injury in humans, particularly in sensory neurons. The potential therapeutic role in nerve repair for recombinant human IL-6, and agents that modulate its action, deserves further investigation.

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1 Hirota H, Kiyama H, Kishimoto T, *et al*. Accelerated nerve regeneration in mice by upregulated expression of interleukin-6 and IL-6 receptor after trauma. *J Exp Med* 1996; **183**:2627–34.

2 Bolin LM, Verity AN, Silver JE, *et al*. Interleukin-6 production by Schwann cells and induction in sciatic nerve injury. *J Neurochem* 1995; **64**:850–8.

3 Bar KJ, Saldanha GJ, Kennedy AJ, *et al*. GDNF and its receptor component Ret in injured human nerves and dorsal root ganglia. *Neuroreport* 1998; **9**:43–7.

4 Anand P, Terenghi G, Birch R, *et al*. Endogenous NGF and CNTF levels in human peripheral nerve injury. *Neuroreport* 1997; **8**:1935–8.

5 Murphy PG, Grondin J, Altares M, *et al*. Induction of interleukin-6 in axotomized sensory neurons. *J Neurosci* 1995; **15**:5130–8.

Crossed face apraxia

Apraxia refers to the disorder of movement planning and execution that cannot be accounted for by motor or sensory deficits nor by other cognitive impairments. The term apraxia encompasses several different deficits, including "face apraxia", which defines the impairment of movements performed within the district of the cranial nerves. Group studies have shown that face apraxia results from lesions of the left hemisphere.¹ However, a few cases can be gleaned from the literature of patients whose face apraxia followed lesions in their right hemisphere and was mentioned in fleeting comments.^{2–4}

Face apraxia has generally been equated to oral apraxia and tests aimed at assessing it only comprise items exploring skilled movements of the lips, cheeks, and tongue. However, several early authors reported on patients with face apraxia also showing movement deficits of the eyes and eyebrows.⁵ Some anecdotal evidence of upper face apraxia is also reported in more recent investigations.⁶ We report on a patient, who, 2 years after a right hemispheric lesion, showed severe face apraxia for movements of both the lower and the upper parts of the face. A 55 year old artist with 17 years of education had an ischaemic stroke in August 1997. A series of CT and MR scans showed a right frontoparietal insular hypodensity also encroaching on the anterior region of the right internal capsule and of the right deep nuclei, sparing the mesial and the anterior part of the parietal lobe. He had always been right handed, scored 100% right handed on both the Edinburgh handedness questionnaire⁷ and the 12 question handedness inventory.⁸ He also denied familiarity for left handedness. We examined the patient in October 1999, 5 months after the end of his rehabilitation therapy and more than 2 years after his stroke. He still showed a severe left paresis, hemianopia, and a deficit of the lower facial nerve. No further deficits of the cranial nerves were seen. In particular, spontaneous movements of the oculomotor nerves were normal. The patient did not show general cognitive impairment: his scores on intelligence tests were well within the normal range. At the time of our assessment he did not show clear evidence of visuospatial neglect which was mentioned in the clinical notes at onset. He performed flawlessly tasks assessing the ability to search for particular targets, in reading, or in line bisecting, although he omitted a few left details in copying complex geometrical drawings. During neurological examination the patient proved unable to close his eyes on verbal command. He failed even when the examiner showed him how to do it. He was therefore submitted to a battery of tests assessing apraxia including the upper and lower face apraxia test.⁹ The nine upper and 29 lower items of the test were performed first on imitation and then, considering the possibility that the patient could have some difficulty in perception, on verbal command. On imitation, the patient scored 2/45 and 320.25/435 (adjusted scores) on the upper and lower face