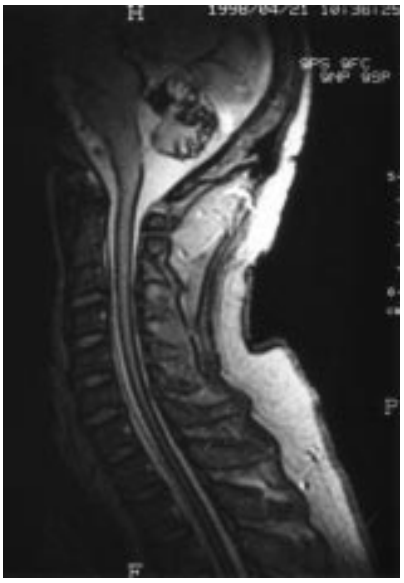

Figure 1 T2 weighted MRI demonstrating the characteristic rim of hypointensity around the posterior fossa and spinal cord seen in superficial siderosis.

de sac (fig 1). There were no other abnormalities on the MRI and a carotid and spinal angiogram failed to disclose a source of bleeding within the CNS. The patient declined a lumbar puncture to look for evidence of active haemorrhage. There was no history of CNS trauma or surgery.

Neurophysiological examination showed normal sensory nerve conduction. Motor conduction was essentially normal. Electromyography of the first dorsal interosseous and extensor digitorum communis muscles demonstrated fibrillations and fasciculations with high amplitude units. Somatosensory evoked potentials were normal from the arms but showed delayed latencies in the legs.

A diagnosis of superficial siderosis was made and he was given a trial of subcutaneous desferrioxamine fortnightly for 8 weeks with no benefit. The patient has continued to deteriorate.

Superficial siderosis of the CNS is a clinical syndrome characterised by progressive cerebellar ataxia and sensorineuronal deafness. Pyramidal signs develop in 76% and other features that may occur include dementia (24%), a neurogenic bladder (24%), anosmia (17%), aniscoria (10%), sensory signs (13%), and less frequent features are extraocular motor palsies, backache, sciatica, and lower motor neuron signs (all 5%–10%).[1] Interestingly, in superficial siderosis the vestibulocerebellum is spared and so despite the central nature of the cerebellar syndrome nystagmus is commonly absent. The pathology of superficial siderosis is of haemosiderin deposits along the subpial surfaces of the CNS and is a consequence of chronic or recurrent bleeding into the subarachnoid space. Superficial siderosis has been reported as a consequence of surgery, aneurysms, vascular malformations, spinal tumours, and traumatic root avulsions. Often the source of the haemorrhage cannot be identified, even at necropsy.

Magnetic resonance scanning has enabled the diagnosis to be made in vivo. The characteristic finding is a rim of marked hypointensity on T2 weighted images surrounding the brain stem, spinal cord, sylvian and interhemispheric fissures, and a few cortical sulci. Occasionally the second and seventh cranial nerves are also involved. In addition to the marginal hypointensity created by the paramagnetic ferric ions, high signal in the adjacent cerebellar tissue, due to secondary gliosis, may be seen on T2 weighted MRI.[2]

The most striking and unique feature of the patient described was the extensive limb wasting and fasciculations with asymmetric weakness but preserved reflexes and an absence of sensory signs. These clinical findings, along with the neurophysiology, suggest an anterior horn cell pathology. In the review of Fearnley *et al* of 63 patients four had lower motor neuron involvement with absent or diminished reflexes thought to be secondary to arachnoiditis or radiculopathy. One patient had muscle wasting with brisk reflexes thought to be due to concurrent lower motor neuron pathology and myelopathy.[1] In our patient the duration of the symptoms and the lack of bulbar and pyramidal features were against this being a classic amyotrophic lateral sclerosis. It is more likely that superficial siderosis was the cause of our patient's anterior horn cell dysfunction and it is recognised that iron pigmentation may be found deep within the spinal cord and intraneuronal deposits have been described.[1] The clinical picture of anterior horn cell damage in superficial siderosis is of particular interest as in the review of Fearnley *et al* they note that although heavy haemosiderin deposition is recognised in the anterior horns of the spinal cord there is little in the way of neuronal fall out.

The predominance of CNS involvement and the paucity of lower motor neuron features in superficial siderosis has been the subject of several novel studies. Koeppen and Borke have shown that an intracisternal injection of red cells produces increased synthesis of ferritin in microglia, especially Bergmann glia in the cerebellum, and this binds with iron to form haemosiderin.[3] It is postulated that the glia and astrocytes of the central nervous system respond to the presence of haemoglobin whereas this process does not occur in Schwann cells of the peripheral nervous system. This is supported by the pathological finding that there is a sharp demarcation of haemosiderin deposition in the cranial nerves and spinal roots at the junction of the central glial and peripheral Schwann cell segments. Koeppen and Detinger have also suggested that the formation of haemosiderin is neuroprotective and it is once this protection has been exhausted that tissue damage occurs, thus it is not the haemosiderin which is toxic but the unbound iron.[4] There are no other case reports of superficial siderosis causing an anterior horn cell syndrome, posing the question of why our patient developed this combination. Whether our patient's presentation was due to anomalous intracellular processing or an unusual source of haemorrhage impacting on the spinal cord remains speculative. It is also possible that in our case the motor root exit zone is a site of iron deposition with resultant lower motor neuron pathology.

We think that our case of superficial siderosis with anterior horn cell dysfunction is unique, and raises interesting questions about pathological mechanisms in this rare disorder.

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Use of intrathecal baclofen for treatment of spasticity in amyotrophic lateral sclerosis

Baclofen, an agonist of γ-amino butyric acid, is one of the most effective drugs in the treatment of spastic movement disorders. However, higher oral dosages required for sufficient spasticity control are related to intolerable central side effects. In this situation, continuous intrathecal application of baclofen in microgram dosages has proved its efficacy in numerous series of patients with spasticity of cerebral or spinal origin.[1–3] Nevertheless, the use of intrathecally administered baclofen in amyotrophic lateral sclerosis, representing the most common degenerative motor neuron disease in adult life,[4] has been mentioned in only one short communication.[5] In this context our experience with intrathecal baclofen therapy is worth presenting. These two patients are the only ones we have treated in this manner and both experienced a marked improvement in their quality of life.

Patient 1, a 25 year old man, was previously reported in brief [5]; he is still alive and benefiting from intrathecal baclofen therapy. Five years ago he noticed progressive gait disturbance, weakness of his right foot, and painful nocturnal cramps in his legs. At that time he exhibited neurologically mild pareses of his right hand and foot, generalised fasciculations, and spasticity. Amyotrophic lateral sclerosis was diagnosed and oral antispastic treatment with baclofen and memantine was started. The patient remained ambulatory but an increase in spasticity due to the underlying disease required subsequent increases in dosage of baclofen. After 1 year a daily dose of 80 mg baclofen was reached but spasticity was no longer ameliorated. The patient was still able to walk a few steps with help but had to use a wheelchair otherwise. Furthermore, he complained of central side effects, such as weakness, daytime fatigue, and sleepiness. Intrathecal baclofen therapy was started, and at a daily dose of 160 μg the patient showed only minimal clinical signs of spasticity. He was able to walk at large without help and could even climb stairs. Spasticity increased during the next 21 months; however, by adjustment of the daily dosage up to 540 μg the patient remained able to walk without additional devices and was capable of caring for himself. Then increasing pareses due to progression of amyotrophic lateral sclerosis came into prominence, and the patient is tetraparetic to a high degree depending on special care. Attempts to reduce baclofen dosage led to a significant increase in spasticity and painful muscle cramps, resulting in substantial discomfort. Thus a daily dose of 540 μg baclofen was maintained.

Due to bulbar involvement the patient was supplied with a nasofacial mask for non-invasive intermittent ventilation to alleviate

symptoms of nocturnal hypoventilation. He has been followed up now for 49 months, and no complications related to intrathecal baclofen therapy have been seen.

Patient 2, a 39 year old man, experienced progressive stiffness and weakness of his legs 2 years ago. Amyotrophic lateral sclerosis was diagnosed, and medical treatment consisting of riluzole and baclofen was started. Initially the patient remained ambulatory for 6 months but then he rapidly developed a severe spastic tetraparesis. He was able to stand with help, but confined to a wheelchair otherwise and completely in need of care. The major sources of discomfort were frequent nocturnal pain attacks due to uncontrolled spasms and central side effects related to oral baclofen medication. Intrathecal baclofen therapy was initiated, and at a daily dose of 80 μg painful spasms stopped despite preservation of some spasticity on purpose for support and improvement in general ease of care.

None the less, quality of life was improved considerably as the patient was able to sleep the night through. Further progress of disease resulted in rapid development of complete tetraplegia and respiratory insufficiency necessitated the use of non-invasive intermittent ventilation. Recently the patient died after 25 months of follow up. No complications related to intrathecal baclofen therapy had occurred.

Amyotrophic lateral sclerosis is a degenerative motor neuron disease characterised by severe movement disorders. Although progressive pareses result in increasing debilitation of the patient and finally death due to respiratory insufficiency, spasticity and painful muscle cramps are disabling symptoms markedly reducing the patients's quality of life. As the aetiopathogenesis of amyotrophic lateral sclerosis remains unresolved and no causative therapy is available prognosis is poor, demanding optimal palliative treatment. As with all other palliative measures, the primary goal is improvement of quality of life rather than life prolongation. [4] Thus, symptomatic treatment comprises a diverse range of medical and physical measures aiming at relieving the specific symptoms of the patient at any point in the continuous progression of the disease. This includes the administration of antispastic agents. Several antispastic drugs such as baclofen, memantine, or benzodiazepines can effectively relieve spasticity but their use is restricted when the maximum daily dose is reached and side effects occur. Due to the drug's limited ability to penetrate the blood-brain barrier and to reach its site of action this is generally the situation with baclofen when an oral daily dose of 80 mg is exceeded. Continuous intrathecal administration of baclofen produces CSF concentrations that are 10 times higher than those achieved with oral administration even though the amounts infused are 100 times less than those taken orally. Thus intrathecal infusion simultaneously increases the effect of baclofen on spasms and reduces the incidence of side effects.

Despite its widespread use and proved efficacy in numerous series of patients with spasticity of cerebral or spinal origin, this form of treatment has not been mentioned in regard to amyotrophic lateral sclerosis apart from one short communication. [5] However, as patients with amyotrophic lateral sclerosis need adequate palliative treatment more than anything else [4] the intrathecal application of baclofen offers the maintenance of a functional status for a prolonged period of time and an appreciable improvement in quality of life. It is a marked reduction of disabling spasticity that helps to achieve these goals and not the influence on prevalent muscle weakness. Our clinical findings show that even in the terminal phase of the disease the patients still benefit by relief of painful spasms, making immobility more tolerable. This form of palliative treatment has proved to be a safe procedure without substantial risks.

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CORRESPONDENCE

No male predominance in α-synuclein Parkinson's disease but the affected female fetus might be less viable

In their recent article on the clinical phenotype in Greek patients with α-synuclein Parkinson's disease (α-sPD) Papapetropoulos *et al*[1] reported male predominance (60%) in their patients. The authors concluded that the sex ratio in their families does not differ significantly from patients with sporadic idiopathic Parkinson's disease (3:2) or with autosomal dominant α-sPD in the Contursi kindred (3.7: 2) and in the Greek-American family H (2.7: 2). The sex ratio as computed by Papapetropoulos *et al*[1] is somewhat misleading. These results suggest that men are more susceptible to PD, or women less. It would be better to compute the segregation ratio for men and women. The segregation ratio is the percentage of persons at risk who are affected. At risk is defined as having an affected parent or sibling. We computed the segregation ratios for the combined numbers of persons at risk in the Contursi kindred (data from Golbe et al),[2] the updated pedigree of the Greek-American family H,[3] and two Greek families.[4] The families of Papapetropoulos et al[1] are not included because the total number of persons at risk is not mentioned.

In these kindreds with α-sPD we counted 228 persons at risk: 132 men and 96 women. The total number of patients with α-sPD is 89, comprising 55 men with α-sPD and 34 women. These numbers yield a simple male/female patient ratio of 55/34=1.6, which is about the same as the ratio 60%/40%=1.5 in the patients with α-sPD reported by Papapetropoulos *et al*.[1] However, the segregation ratio for male α-sPD in the kindreds mentioned above equals 55/13 =41%, for female α-sPD 34/96=35%. These segregation ratios do not differ significantly (p=0.21, χ^2 test) suggesting that men and women are equally at risk of acquiring α-sPD, despite the greater number of male patients. There are just more men than women in these families! Furthermore, as far as the sex ratio in sporadic idiopathic PD is concerned, the largest epidemiological analysis we know—comprising 18 506 subjects of seven community surveys in Europe—found no difference in prevalence between the sexes either (men 1.74%; women 1.79%).[5] This seems to confirm the conclusion about absence of sex difference in patients with α-sPD.

The only question that remains is why there are more men (n=132) than women (n=96) in these α-synuclein kindreds? If the number of men and women are equal in the general population, the male/female ratio 132/96=1.37 in the α-synuclein kindred is significantly abnormal (p=0.017; χ^2 test). However, normally there are fewer men than women in the older age groups. If we take the ratio male/female=0.77 as computed for the whole population (patients plus controls) from the European Parkinson prevalence study mentioned above, which considers a very large similar age group in western and southern Europe,[5] the difference from the α-synuclein kindred is even more remarkable (p=0.000; χ^2 test). If this male preponderance is related to the abnormal α-synuclein gene, it could be speculated that the affected female fetus is less viable and more prone to fetal death. However, as it stands we are inclined to think that this notion is prompted by statistics rather than biological evidence. In transgenic mice and flies expressing mutant α-synuclein, numerous α-synuclein immunoreactive nerve cells, Lewy body-type inclusions, and loss of dopaminergic nerve cells have been described,[6] but there were no sex related abnormalities or differences in sex. However, sex differences have probably not been examined specifically, so the actual cause of the male preponderance in α-synuclein kindreds remains to be elucidated.

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