PostScript

LETTERS

Rhabdomyolysis during interferon-β 1a treatment

Interferon-β (IFN-β) is one of the most effective currently available treatments for multiple sclerosis. It has also been used in the therapy of viral diseases and certain malignancies, as has the other type I interferon IFN-α. Most frequent side effects are transient flu-like symptoms such as myalgia, chills, and headaches. We describe a patient with relapsing-remitting multiple sclerosis who developed acute rhabdomyolysis during IFN-β 1a treatment. After the medication was discontinued, the patient improved rapidly.

A 39 year old man with a history of first symptoms in April 2000 was diagnosed as having relapsing-remitting multiple sclerosis, supported by the demonstration of oligoclonal IgG bands in the CSF but not in the blood, and multiple white matter lesions in periventricular localisations on MRI. Treatment with 22 μg IFN-β 1a (Rebif®, Serono, Unterschleissheim, Germany) by subcutaneous injection three times weekly was initiated in October 2000 after three exacerbations with predominant sensory disturbances leading to an expanded disability status score (EDSS) of 1.5. To alleviate potential flu-like symptoms due to IFN-β therapy, the patient was recommended to take 400 mg ibuprofen at least 2 hours before and after the time point of injection. Because he did not recognise any adverse side effects, he first stopped omeprazole medication, which he had taken occasionally, and thereafter the ibuprofen medication. He reassured us that he did not use any other drugs not prescribed by his physicians. Thus, 3 months after initiation of IFN-β treatment the patient was only on this immunomodulatory therapy. One month later, he suddenly developed acute generalised myalgia as well as weakness 1 day after IFN-β application and was therefore referred to the hospital. He denied any antecedent signs of infection or any trauma, but reported going bowling in the evening before the symptoms started. However, there was no difference in the amount of physical exercise compared with other weekly bowling sessions.

At physical examination his heart, lungs, and abdomen seemed normal, whereas neurological examination disclosed a tetraparesis with emphasis on the proximal upper limbs (power 3/5). The muscles were tender to palpation with normal muscle tonus and no increased activity of tendon reflexes. A mild intention tremor at the left arm was preexisting.

Laboratory findings showed a marked increase in the concentrations of creatine kinase at 6632 U/l (normal range: 5–70 U/l) with normal concentrations of the isoform CK-MB, lactate dehydrogenase (LDH) at 670 U/l (normal range: 80–240 U/l), and moderately increased liver enzymes, which had been reported since the beginning of IFN-β treatment. Myoglobinuria was not determined and there were no pathological alterations in concentrations of creatinine, urea nitrogen, C reactive protein, blood cell counts, or glucose. No electrolyte abnormalities were detectable.

With the diagnosis of a rhabdomyolysis, IFN-β application was discontinued, the patient was subsequently monitored in the intensive care unit, and treated with intravenous fluids and bicarbonate to maintain an alkaline urine output. Under the treatment myalgia and the tetraparesis disappeared within 2 days. The patient returned to his baseline EDSS. With a delayed time course the creatine kinase declined steadily to normal values after 2 weeks. We now treat this patient with glatiramer acetate (copolymer-1) for the relapsing-remitting multiple sclerosis.

To our knowledge, this is the first reported case of rhabdomyolysis associated with IFN-β treatment. This adverse event has been previously associated with IFN-α, which also belongs to the type I interferons. This, however, exhibits only 30% of homology and differs in its immunological profile. Greenfield *et al* described a patient 10 weeks after initiation of IFN-α treatment starting with 5 MU three times a week for chronic active hepatitis C,[1] and Reinhold *et al* recorded acute rhabdomyolysis 4 days after high dose IFN-α therapy (20 MU/m^2 daily) in a patient with malignant melanoma.[2] Remarkably, the manifestation of muscle injury occurred when the dose of IFN-α was being increased in both patients described, suggesting that rhabdomyoloysis represents at least a dose dependent side effect of this type I interferon.

In the patient presented here the dosage of IFN-β1a was unaltered. Yet, the absence of any other medication, exclusion of infectious and metabolic causes usually related to a non-traumatic rhabdomyolysis, the lack of indications for an underlying metabolic muscle disorder as determined by the patients' history, the clinical presentation including laboratory investigation, and the temporal relation with IFN-β 1a application indicate that rhabdomyolysis is a possible adverse event of IFN-β therapy. Rhabdomyolysis can also be induced by unaccustomed muscular exercise in untrained people.[3] However, our patient often goes bowling and thus is used to this programme.

It is concluded that creatine kinase activity should be measured when a patient complains of severe myalgia differing from the often occurring myalgia under IFN-β treatment and, in particular when weakness is reported. This procedure might be effective in the prevention of irreversible rhabdomyolysis during IFN-β therapy. As a dose dependent effect of IFN-β 1a on both clinical and MRI outcomes in relapsing-remitting multiple sclerosis is known,[4 5] future observations will show whether increase in dosage of IFN-β predisposes to rhabdomyolysis as reported for IFN-α.

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References

1 **Greenfield SM**, Harvey RS, Thompson RPH. Rhabdomyolysis after treatment with interferon α. *BMJ* 1994;**309**:512.
2 **Reinhold U**, Hartl C, Hering R, *et al*. Fatal rhabdomyolysis and multiple organ failure associated with adjuvant high-dose interferon α in malignant melanoma. *Lancet* 1997;**349**:540–1.
3 **Vanholder R**, Sever MS, Erek E, *et al*. Rhabdomyolysis. *J Am Soc Nephrol* 2000;**11**:1553–61.
4 **Once weekly Interferon in MS Study Group (OWIMS)**. Evidence of interferon β-1a dose response in relapsing-remitting multiple sclerosis. *Neurology* 1999;**53**:679–86.
5 **The PRISMS Study Group and the University of British Columbia MS/MRI Analysis Group**. PRISMS-4: long-term efficacy of interferon-β-1a in relapsing MS. *Neurology* 2001;**56**:1628–36.

Superficial siderosis associated with anterior horn cell dysfunction

Superficial siderosis of the CNS is a rare syndrome of progressive cerebellar ataxia and sensorineuronal deafness associated with haemosiderin deposition from chronic subarachnoid bleeding.[1] We describe a patient with typical features of superficial siderosis and an anterior horn cell syndrome, a combination that to our knowledge has never been previously reported.

A 59 year old man presented with a 4 year progressive history of unsteadiness of gait, bilaterally impaired hearing, and weakness which had begun in the left hand, spreading to involve the left arm and leg, and right hand. He had a 2 year history of cerebellar dysarthria, bladder hesitancy with postmicturition dribbling, and impotence. Examination disclosed a broad based ataxic gait with left sided limb ataxia. Apart from bilateral sensorineuronal deafness the cranial nerves were normal. There were fasciculations in the arms and legs. In the upper limbs he had asymmetric wasting and weakness of the intrinsic hand muscles, biceps, and triceps bilaterally. In the left lower limb there was wasting and weakness of the hip flexors and quadriceps. Sensory examination was normal. The deep tendon reflexes were all present and symmetric. The abdominal reflexes were present and the plantar responses were flexor.

Magnetic resonance imaging of the brain and spinal cord demonstrated haemosiderin deposition around the cerebellar folia, outlining the whole spinal cord and sacral cul

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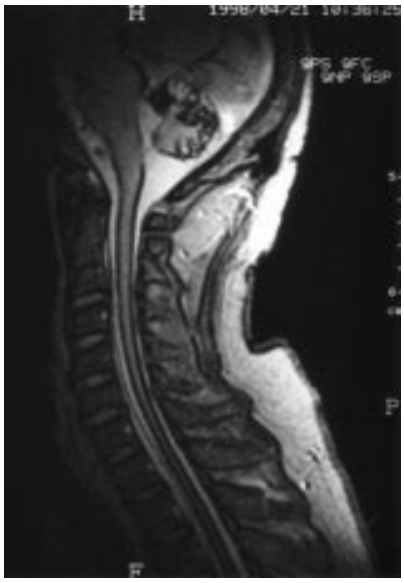

Figure 1 T2 weighted MRI demonstrating the characteristic rim of hypointensity around the posterior fossa and spinal cord seen in superficial siderosis.

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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References

1 **Fearnley JM**, Stevens JM, Rudge P. Superficial siderosis of the central nervous system. *Brain* 1995;**118**:1051–66.
2 **Bracchi M**, Savoiardo M, Triulzi F, *et al*. Superficial siderosis of the CNS: MR diagnosis and clinical findings. *Am J Neuroradiol* 1993;**14**:227–36.
3 **Koeppen AH**, Borke RC. Experimental superficial siderosis of the central nervous system. I. Morphological observations. *J Neuropathol Exp Neurol* 1991;**50**:579–94.
4 **Koeppen AH**, Dentinger MP. Brain hemosiderin and superficial siderosis of the central nervous system. *J Neuropathol Exp Neurol* 1988;**47**:249–70.

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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References

1 **Penn RD**. Intrathecal baclofen for spasticity of spinal origin: 7 years of experience. *J Neurosurg* 1992;**77**:236–40.
2 **Coffey JR**, Cahill D, Steers W, *et al*. Intrathecal baclofen for intractable spasticity of spinal origin: results of a long term multicenter study. *J Neurosurg* 1993;**78**:226–32.
3 **Albright AL**, Barry MJ, Painter MJ, *et al*. Infusion of intrathecal baclofen for generalized dystonia in cerebral palsy. *J Neurosurg* 1998;**88**:73–6.
4 **Borasio GD**, Voltz R. Palliative care in amyotrophic lateral sclerosis. *J Neurol* 1997;**244**:11–7.
5 **Marquardt G**, Lorenz R. Intrathecal baclofen for intractable spasticity in amyotrophic lateral sclerosis. *J Neurol* 1999;**246**:619–20.

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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References

1 **Papapetropoulos S**, Paschalis C, Athanassiadou A, *et al*. Clinical phenotype in patients with α-synuclein Parkinson's disease living in Greece in comparison with patients with sporadic Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2001;**70**:662–5.
2 **Golbe LI**, Di Iorio G, Sanges G, *et al*. Clinical genetic analysis of Parkinson's disease in the Contursi kindred. *Ann Neurol* 1996;**40**:767–75.
3 **Samii A**, Markopoulou K, Wszolek ZK, *et al*. PET studies of parkinsonism associated with mutation in the alpha-synuclein gene. *Neurology* 1999;**53**:2097–102.
4 **Papadimitriou A**, Veletza V, Hadjigeorgiou GM, *et al*. Mutated α-synuclein gene in two Greek kindreds with familial PD: incomplete penetrance? *Neurology* 1999;**52**:651–4.
5 **De Rijk MC**, Launer LJ, Berger K, *et al*. Prevalence of Parkinson's disease in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology* 2000;**54**(suppl 5):S21–3.
6 **Goedert M**. α-Synuclein and neurodegenerative diseases. *Nature Reviews* 2001:**2**:492–501.

Authors' reply:

As Horstink and Bloem suggest, the segregation ratio for men and women is indeed the most appropriate method to calculate the genetic risk for developing a disease. In our recent publication,[1] the sex ratio was calculated from the sample of 15 patients with α-synuclein Parkinson's disease (α-synPD) included in the study. We now provide additional unpublished data to calculate the segregation ratios and to compare them with the other published series of patients with α-synPD.

In the 10 families examined in our study,[1] 198 members were at risk of developing α-synPD. Of the 103 male members at risk, 27 (26.2%) developed Parkinson's disease (PD), whereas of the 95 women at risk, 27 (28.4%) developed PD (p=0.73). When our data were combined with the data computed by Horstink and Bloem, the segregation ratio of all patients with α-synPD was 82/235 (34.9%) for men and 61/191 (31.9%) for women (p=0.52; table 1).

Golbe *et al*[2] had first noted the tendency of the Contursi kindred to have fewer female members at risk for developing α-synPD (male/female ratio 86/56=1.5). The male to female ratio of our subjects at risk was 103/95=1.08 (p=0.31 for the difference from 1:1 ratio and p=0.02 for the difference from 1:1.3 ratio, which is the male to female ratio of the whole population found in the European Parkinson prevalence study[3]). After excluding the Contursi kindred, the male to female ratio of all subjects of Greek origin combined,[1 4 5] was 149/135=1.10 (p=0.22 for the difference from 1:1 ratio and p=0.002 for the difference from 1:1.3 ratio), whereas the male to female ratio of all known subjects at risk of developing α-synPD combined[1 2 4 5] was 235/191=1.23 (p=0.02 for the difference from a 1:1 ratio and p<0.0001 for the difference from a 1:1.3 ratio)

Our data confirm the finding of Horstink and Bloem that men and women are equally at risk of acquiring α-synPD. The Contursi kindred data are skewing the male to female ratios towards a male predominance. The male to female ratio of our Greek families at risk of developing α-synPD, as well as the ratio of all Greek origin families, did not differ significantly from the 1:1 ratio. However, when the male to female ratios were compared with the expected 1:1.3 male to female ratio in the general population, a statistical significant male predominance was found. Whether this is due to statistical bias, recall bias, or to genetic or environmental factors remains unclear. The identification of larger numbers of families at risk of developing α-synPD may help to resolve the question.

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References

1 **Papapetropoulos S**, Paschalis C, Athanassiadou A, *et al*. Clinical phenotype in patients with α-synuclein Parkinson's disease living in Greece in comparison with patients with sporadic Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2001;**70**:662–5.
2 **Golbe LI**, Di Iorio G, Sanges G, *et al*. Clinical genetic analysis of Parkinson's disease in the Contursi kindred. *Ann Neurol* 1996;**40**:767–75.
3 **De Rijk MC**, Launer LJ, Berger K, *et al*. Prevalence of Parkinson's disease in Europe : a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology* 2000;**54**(suppl 5):S21–3.
4 **Papadimitriou A**, Veletza V, Hadjigeorgiou GM, *et al*. Mutated α-synuclein gene in two Greek kindreds with familial PD: incomplete penetrance? *Neurology* 1999;**52**:651–4.
5 **Samii A**, Markopoulou K, Wszolek ZK, *et al*. PET studies of parkinsonism associated with mutation in α-synuclein gene. *Neurology* 1999;**53**:2097–102.

Hashimoto's associated ataxia

Selim and Drachman described six patients with a progressive sporadic adult onset cerebellar degeneration.[1] Raised concentrations of antithyroid antibodies were found. Modest increases in antithyroid antibodies were considered to be the result of longstanding autoimmune thyroid disease. Analysis of CSF showed increased protein concentrations in one patient. Brain MRI disclosed atrophy of the vermis in four patients and showed a concomitant atrophy of the brain stem in two patients. Treatment with L-thyroxine did not improve cerebellar signs. The authors suggested that ataxia associated with Hashimoto's disease could be due to an autoimmune cerebellar degeneration.

This is a very interesting finding, which raises several issues for the diagnosis and management of sporadic adult onset cerebellar degeneration. I make three comments. Firstly, there is another clinical presentation of "Hashimoto's associated ataxia",[2] consisting of an acute cerebellar syndrome associated with abnormal behaviour. Protein concentrations are increased in CSF. Brain MRI shows a high intensity signal in T2 weighted images, restricted to the cerebellum. This other presentation should not be overlooked because steroids and thyroid hormonal therapy improve the cerebellar deficits markedly. This ataxic syndrome associated with Hashimoto's thyroiditis differs from the cases reported recently[1] by (1) the acute onset, (2) distinct MRI findings, and (3) the dramatic clinical/radiological response to treatment which is a strong argument in favour of an immune attack against the cerebellum.

The authors should consider multiple system atrophy (MSA) in the differential diagnosis of sporadic adult onset cerebellar degeneration.[3 4] Various combinations of extrapyramidal, pyramidal, cerebellar, and autonomic features occur in MSA. The disorder having an estimated prevalence ratio of 16.4/100 000[3]; raised concentrations of antithyroid antibodies might be a coincidence. Patient 6 exhibited cerebellar deficits associated with autonomic/urinary dysfunction, pyramidal signs (bilateral Babinski's signs), and parkinsonism (axial rigidity, hypertonia).[1] Multiple system atrophy is likely in this patient. Were sphincter EMG studies performed? Were dysautonomic signs specifically looked for in other patients?

In one of our patients exhibiting a chronic and sporadic cerebellar syndrome with atrophy, high concentrations of antinuclear antibodies and presence of a rheumatoid factor were initially considered as markers of an immune disease producing a cerebellar degeneration. However, a subsequent genetic testing disclosed a spinocerebellar ataxia type 6 (SCA-6). Genetic analysis for SCA-1 to 7 was performed in one of the patients reported by Selim and Drachman,[1] and was not available in the remaining five patients. Detailed genetic tests should be carried out, even when there is no family history of ataxia. Recent studies show that about 4% of patients with a sporadic ataxia harbour a mutation.[6] Negative genetic results would reinforce the appealing concept of "Hashimoto's associated ataxia".

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References

1 **Selim M**, Drachman DA. Ataxia associated with Hashimoto's disease: progressive non-familial adult onset cerebellar degeneration with autoimmune thyroiditis. *J Neurol Neurosurg Psychiatry* 2001;**71**:81–7.
2 **Manto M**, Goldman S, Bodur H. Cerebellar syndrome associated with Hashimoto's encephalopathy. *Rev Neurol (Paris)* 1996;**152**:202–4.
3 **Gilman S**, Quinn NP, Albanese A, *et al*. Consensus statement on the diagnosis of multiple system atrophy. *J Neurol Sci* 1999;**163**:94–8.
4 **Berciano J**. Olivopontocerebellar atrophy: a review of 117 cases. *J Neurol Sci* 1982;**53**:253–72.

Table 1 The segregation ratios of all α-synPD cases reported

	Family members at risk for α-synPD		Family members with α-synPD	
Reported α-synPD cases	Male	Female	Male (segregation ratio)	Female (segregation ratio)
Papapetropoulos *et al*[1]	103	95	27 (26.2%)	27 (28.4%)
Papadimitriou *et al*[4]	14	17	6 (42.8%)	6 (35.3%)
Golbe *et al*[2]	86	56	39 (45.3%)	21 (37.5%)
Samii *et al*[5]	32	23	10 (31.3%)	7 (30.4%)
Total	235	191	82 (34.9%)	61 (31.9%)

α-synPD = α-synuclein Parkinson's disease.

5 **Quinn N**. Multiple system atrophy. In: Marsden CD, Fahn S, eds. *Movement disorders 3*. London: Butterworths, 1994:262–81.
6 **Soong BW**, Lu YC, Choo KB, *et al*. Frequency analysis of autosomal dominant cerebellar ataxias in Taiwanese patients and clinical and molecular characterisation of spinocerebellar ataxia type 6. *Arch Neurol* 2001;**58**:1105–9.

Authors' reply

We thank Dr Manto for bringing to our attention this reported case of acute Hashimoto's encephalopathy with confusion, focal cerebellar signs, and MRI changes. Although the clinical manifestations, tempo, and imaging findings of the disease were clearly different, it is entirely plausible that this patient shared immunity as its underlying mechanism with the six patients we reported. It underlines the breadth of manifestations that may occur in autoimmune disorders of the CNS.

Precisely which structures are targeted to produce these varying clinical manifestations is unclear. Whether thyroperoxidase antibodies target Purkinje cells, or whether the increase in antithyroid antibodies reflects a broader autoimmune diathesis, is unknown. The similarity of this gradually progressive cerebellar disorder to that reported with antiglutamic acid decarboxylase (GAD) antibodies is also of interest.[1] The entire clinical range of progressive cerebellar impairment due to autoimmune disorders has yet to be elucidated; and multisystem atrophy may well overlap clinically, aetiologically, or both.

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Reference

1 **Honnorat J**, Saiz A, Giometto B, *et al*. Cerebellar ataxia with anti-glutamic acid decarboxylase antibodies: study of 14 patients. *Arch Neurol* 2001;**58**:225–30.

BOOK REVIEWS

Conversion hysteria: towards a neuropsychological account

Edited by Peter W Halligan and Anthony S David (Pp292, £24.95). Published by Psychology Press Ltd, Hove, 1999. IBSN 0-86377-651-5.

It probably would not have pleased Aubrey Lewis to know that one of his lasting legacies to psychiatry is his now often quoted words from his paper *The survival of hysteria* to the effect that hysteria will outlive its obituarists. It seems that in the past decade, almost in defiant opposition to the mighty DSM goliath, humble hysteria is not only once again a popular topic for investigation, but its very name lives on. In this book, the term hysteria is unashamedly used, even in the title, and it is not cloaked by its suit of new invisible clothes dressing up as somatoform disorders or one of their variants.

This small but very readable book is a collection of papers published as a special edition by the *Journal of Cognitive Neuropsychiatry*. The aim was to bring modern neurocognitive theory to the field, to balance the "traditional overreliance on psychodynamic accounts". However, it also embraces the paradigm, enunciated over a century ago by Charcot, that hysteria should be open to investigation as other conditions in medicine, using the same methods and observation techniques.

Thus, in the text, several of the chapters touch on the more recent neuroimaging and evoked potential studies. These seem fairly consistent, noting the important association of the frontal and cingulate cortex to symptom presentation, and, with a paretic limb, the failure of the appropriate parietal activation with effort to movement. Other chapters take a somewhat more traditional role, outlining the historical trends, discussing the Freudian and post-Freudian contributions, and linking in neuroanatomical and neurophysiological data with speculations on limbic and especially right hemisphere dysfunction in association with hysteria.

The most interesting contributions, however, are the newer cognitive neuropsychological approaches to the subject. For, and here Lewis was surely right, hysteria lingers on in clinical practice, as seen in patients galore, in different guises, especially in the neurology clinic and in settings such as medicolegal practice. Yet the mechanisms leading to the florid manifestations of hysteria in these patients may be part of a psychological tendency available to a much wider community, and to this extent perhaps should not be even regarded as pathological. The main thrust of the book, and the most relevant for those engaged with such patients, reflects on this theme. The wider patient social construct is emphasised, the relevance of the concept of the Will is debated (another famous quote, from Paget, repeated here: "The patient says he cannot, it looks like he will not, but the truth is that the patient cannot will"), and the role of consciousness re-examined. For sure, one of the most tedious yet well intentioned questions that doctors are asked when discussing such patients is "well, is it conscious, or unconscious?".

The text provides elegant ways of resolving this dilemma, in themes in keeping with modern cognitive psychology. Like a good book reviewer, I will not give the game away, but encourage the interested to read the texts herein published. One quote will help the temptation: "In an attempt to encapsulate the self-deceptive view of hypnotised subjects, they have been labelled as "honest liars". By the same token, hysterics should perhaps be seen as "genuine malingerers"" (Oakley).

Michael Trimble

Movement disorders in children

Edited by E Fernandez-Alvarez and J Aicardi (Pp 263, £50.00). Cambridge University Press, London, 2001. ISBN 1 898 683239

This is a truly marvellous book. The authors combine their vast clinical experience with an up to date review of literature scattered throughout neurological and paediatric publications to produce the first text book on movement disorders in children. A clinical approach to movement disorders in childhood is taken with chapters devoted to the predominant movement disorder. Clinical descriptions and illustrations are given for all of the important conditions producing that movement disorder; comprehensive lists of the rarer causes of movement disorders are also provided.

The authors start by reviewing general concepts relevant to the diagnosis of movement disorders in childhood. The current model of basal ganglia functioning is discussed and this is followed by a description of the main types of movement abnormality. This is followed by a brief, but important, guide to specific areas of clinical history taking and examination in the evaluation of movement disorders in children. Subsequent chapters are based on the predominant movement disorder. Each is organised with an initial introduction and classification followed by a discussion of the major disorders producing the abnormal movements. Important features of each chapter are a discussion of conditions that may simulate the movement disorder; the discussion of difficult cases according to the authors' own experience and from the search of the literature; and the symptomatic treatment of the individual movement disorders. Relevant investigations are also presented within the context of each individual movement disorder. A chapter is also devoted to those complex movement disorders where one type does not predominate. The movement disorders covered include the hypokinetic-rigid syndromes, tremor, chorea, dystonia, myoclonus, tics, and complex. There are also important chapters on drug induced movement disorders and movement disorders in cerebral palsy. Last is a chapter about ancillary investigations that either have, or may well in the future, prove useful in our understanding of paediatric movement disorders. Throughout the book, additional authors have contributed their own expertise.

This is a comprehensive and up to date textbook about movement disorders in children. All child neurologists and paediatricians with an interest in neurology or neurodisability should have access to this book and I suspect that most will want to own a personal copy. In addition, this book will be of tremendous help to adult neurologists evaluating patients with a movement disorder the origins of which are in childhood or adolescence.

R Surtees

Advances in dementia research

Edited by Kurt A Jellinger, Reinhold Schmidt, and Manfred Windisch (Pp 336, US$99.00). Published by Springer, Wien, 2000. ISBN 3-211-83513-X

This book is a collection of presentations from a symposium "Ageing and Dementia" held at the end of 1999 in Graz. As always with such collections, the book is as good as the presentations were and some of these are excellent and useful, others are worth reading. One or two could just have provided an opportunity to go and have a look around Graz. What the book is not is a systematic review of advances in dementia research and probably books are not good places to turn to for such reviews, as this material is generally best accessed directly from the journals themselves. The book starts well enough with an interesting series of papers on the relation between vascular damage to the brain and dementia. Some of the articles are non-systematic and short reviews, others are more thoughtful discussions of an interesting but difficult area of research, and others are straightforward data presentations. I was left with more questions than answers, which is probably healthy. The papers in the book then go on to discuss other important issues in dementia research including neuroinflammation, apoptosis, mytochondrial dysfunction, and genetics. Some of the most important advances came just a little bit after this book was published. The discussion of transgenic models of Alzheimer's disease for

example includes no discussion of transgenic models of the frontal lobe dementias even though that is clearly related and the various papers on immunological approaches do not include any of the amyloid vaccine data.

A more general question arises, to my mind, however, reading this book, as to quite who else is likely to read it. If read by somebody coming new to the dementia field they would have a very unbalanced picture of the field and this book could not be recommended to novices to dementia research. On the other hand, those familiar with dementia research are unlikely to treat this book as other than a collection of primary papers and if browsing, then browsing time might well be better spent with *JNNP*, for example. The participants of the meeting are almost certainly going to flick through the book if only to recall what they said. Other readers of course will include reviewers. However, and this is a very personal review, I am not a huge fan of collection of papers from meetings. I suspect they largely go unread and I cannot really recommend this book to anybody. Interestingly the final six or so articles are all on a proprietary compound which is being developed for treating Alzheimer's disease. According to one article, this compound is widely used to relieve symptoms in various neurological disorders, which was certainly news to me. A previous meeting held in 1997 also resulted in a book very similar to this one and is advertised in the back. A review of the 1997 meeting book, published in *Acta Psychiatria Scandinavica* and used as a promotional blurb mentions that "The book will be of interest to those following the development of neurotrophic factors for treatment of dementia who need an extensive introduction to the preclinical studies" of this proprietary compound. Things haven't changed much.

Simon Lovestone

Limbic seizures in children

Edited by G Avanzini, A Beaumanoir, and L Mira (Pp 258, £39.00). Published by John Libbey and Co Ltd, Eastleigh, 2001. ISBN 0 86196 595 7

Limbic seizures in childhood differ from those in adults. They are more likely to be caused by cortical dysplasias, related malformations, and tumours. They are more easily, but not invariably, controlled by drugs. Have new imaging and EEG techniques advanced the cause and effect debate about febrile seizures and mesial temporal sclerosis (MTS)? Such considerations make this monograph timely.

Initial chapters on the history of the subject, the evolving definition of what constitutes limbic structures, their functional organisation and the relevance of MTS are clear, instructive, and thought provoking. "Limbus" is a border, in this case the border between the midbrain and the rest of the cerebral hemisphere. In non-primates, primarily concerned with smell, it has decreased in size relative to the elaborating neocortex, but in so doing has acquired multiple connections with association cortices. The hippocampus and perihippocampal cortex are distinguished by several features. Their cell properties are particularly determined by the level of activity—long term potentiation or depression. These enduring properties could subserve memory. Whereas the perihippocampus may code memories by semantic association, the hippocampus assigns them a personal context in time and space. The number of possible associations and ways of filing past events is almost infinite. The original roots in olfactory function may linger as the powerful evocation of memories by smell (Madeleine cakes served Proust for his life's work). It is possible that the flexibility and enhanced activity of certain hippocampal circuits on which its function is contingent make it peculiarly liable to epileptogenesis.

Many patients with catastrophic epilepsy do not have MTS. Seizures themselves do not cause MTS. Fifteen per cent of patients with MTS have dual pathology, 15% have increased neuronal heterotopias, and 15% have bilateral involvement. Degree of cell loss is not related to duration of epilepsy. Mossy fibre sprouting is not seen in children younger than 10, suggesting that this is a secondary progressive lesion. From facts such as these Spencer *et al* conclude that mesial temporal lobe epilepsy has a probable developmental aetiology. Hippocampal abnormalities pre-exist (and can be demonstrated in unaffected members of familial temporal lobe pedigrees) but convey vulnerability to febrile convulsions and subsequent MTS.

Subsequent chapters treat different aspects of limbic seizures—language disturbances, motor automatisms, impairment of consciousness, autonomic changes, and postural changes. The literature distinguishing frontal lobe from temporal lobe complex partial seizures is summarised. There are chapters on structural and functional imaging.

This book arose out of a colloquium. Of the 26 contributions all but four are from French or Italian centres. The two from America are particularly good and perhaps the standard of the rest might have been higher if the net had been spread wider. Some authors speak from very limited experience. The chapters on treatment are particularly disappointing. That systematic errors in English abound and much information is repeated throughout implies lack of adequately firm editorial grip.

This book will be useful to paediatric epileptologists, but the patchy quality overall precludes a warm recommendation to a wider audience.

Richard Robinson

Spinal cord injury desk reference. Guidelines for life care planning and case management

By Terry L Blackwell, James S Krause, Terry Winkler, and Steven A Stiens (Pp 282, US$59.95). Published by Demos Medical Publishing, New York, 2001. ISBN 1-888799-49-8

This book is a reference text. It contains information that will be of considerable assistance to those who are involved in the planning of the long term care of those with spinal cord injury in the United States. The authors, all United States based, include two spinal cord injury physicians, a behavioural scientist, and a rehabilitation counsellor.

The information in this book will assist predominantly those healthcare professionals who are closely involved in the case management of spinal cord injury. It will also be of interest to all who are involved with spinal cord injury including patients, their families, and all the many groups who work in the area including doctors, nurses, therapists, healthcare planners, lawyers, and many others. For those who already have wide knowledge of spinal cord injury care the chapter on resources and legislation may be of particular value as it contains numerous addresses and telephone contacts.

Even though the specific information in this book is largely relevant to the United States, many outside that country will find the book of interest, perhaps encouraging them to seek the comparable data relevant to their own countries. The information contained in texts such as this is a prerequisite for ensuring that there is adequate appropriate long term provision for people with spinal cord injury, especially as they age.

Inevitably in a wide ranging book there are weaknesses. For example, the debilitating orthostatic hypotension induced fatigue and coat hanger pain experienced by many persons with higher level spinal cord injury is not mentioned and the 1993 rather than the more complete 1998 United Kingdom life expectancy data are used. These omissions do not detract from the importance of this book's attempt to fill an important niche that has not been adequately addressed before.

It would be of great interest if similar texts were produced in other countries. Not only would this help improve long term care in these countries but it would also enable comparisons of costs and approaches to care to be made that would assist the evolution of ever improving systems of care for patients with spinal cord injury worldwide.

Brian Gardner

Head trauma: basic, preclinical, and clinical directions

Edited by Leonard P Miller and Ronald L Hayes (Pp 494, £107.00). Published by Wiley-Liss, New York, 2001. ISBN 0471 360 155

Miller and Hayes have assembled chapters from 42 expert contributors renowned for their work in investigation of traumatic brain injury. They have divided the text into three main sections, basic science: overview; preclinical studies, and clinical directions.

Organising the text in this way the authors have struck a theme which passes from experimental concepts through to preclinical feasibility studies and eventually on to clinical trials. They acknowledge from the outset that the wealth of basic scientific information gathered over the past 3 decades has not led to substantial clinical gain. The reasons for this are debated in a latter chapter.

The work represents a comprehensive review of the information available on traumatic brain injury. The basic science overview I found to be particularly well written and concise, introducing concepts and experimental data in a highly readable way. The main theories of cytotoxicity, inflammatory response, apoptosis, traumatic axonal injury, and mitochondrial dysfunction have separate attention, as do the important vascular aspects of severe head injury.

The final section refers to the clinical efforts of attempting to translate scientific knowledge into clinical work. The major clinical trials organised in the United States, Europe, and Asia are discussed and potential reasons for their failure debated.

In summary the work of Miller and Hayes is a valuable addition to the reading of those involved in traumatic brain injury. This is particularly so for those who engage in the experimental and clinical design of novel therapies for the traumatised brain.

Peter J Kirkpatrick

Meeting the challenge of progressive multiple sclerosis

By Patrick K Coyle and June Halper (Pp 124, US$19.95). Published by Demos Medical Publishing, New York, 2001. ISBN 1 888799 46 3

Having been diagnosed in 1982 I have lived for 19 years with a slowly progressive form of multiple sclerosis. I was therefore glad of the opportuntity to catch up on recent developments in the understanding of the disease and discussion of some of the latest options for treatment. Although the book states in the opening paragraph that it is written for people with this form of multiple sclerosis, it is also obvious from the first page that it is going to be very hard work for anyone without a scientific or medical background to make sense of the information it contains. I constantly found myself having to reread and struggle to understand the technical language used throughout the book. Such a pity when there is much potentially useful information there.

I was interested to see what the writers would have to say in the section on management and self help since this is an area the medical profession has often overlooked. There is discussion under various headings such as coping with fatigue, bladder dysfunction, tremor, and cognitive dysfunction, followed in each case by a series of bullet points on the management of symptoms. Once again the language defeats the object of the book as these read more like checklists for doctors and multiple sclerosis nurses than clear, accessible summaries that people with multiple sclerosis can make use of.

It is heartening to see that in these days of disability legislation (the Disabilities Act in the United States and the Disability Discrimination Act in the United Kingdom) questions of access to buildings and equipment and discussions of legal rights and financial entitlements are seen as having a place in a book on multiple sclerosis. The past 19 years have taught me that factors such as attitudes towards disabled people, the design of buildings, and the way in which services are delivered may impact on the lives of people with multiple sclerosis and their families just as much as the effects of the disease.

Michele Wates