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 1 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 severe exacerbations with predominant sensorineural deafness, optic neuritis, and bladder dysfunction. The patient reported an increased activity of tendon reflexes. A mild intention tremor at the left arm was present.

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 isofrom CK-MB, lactate dehydrogenase (LDH) at 670 U/l (normal range: 80–240 U/l), and markedly 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 the concentrations of creatine kinase and the creatine kinase isoenzyme M was increased. 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 400 mg ibuprofen at least 2 hours before and after the time point of injection. Because he did not recognize 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 ibuprofen medication. He suffered 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 5/5). 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 present.

To our knowledge, this is the first reported case of rhabdomyolysis associated with IFN-β 1a treatment. This adverse event has been previously associated with IFN-α, which also belongs to the type 1 interferons. However, this event seems to be less frequent because most reports were based on IFN-α treatment starting with 5 MU three times a week for chronic active hepatitis C.1,2,3 And, Reinhold et al recorded acute rhabdomyolysis 4 days after high dose IFN-α therapy (20 MU/m² daily) in a patient with malignant melanoma.4 Remarkably, the manifestation of muscle injury occurred when the dose of IFN-α was being increased in both patients described, suggesting that rhabdomyolysis represents at least a dose dependent side effect of this type 1 interferon.

In the patient presented here the dosage of IFN-β 1a 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.5 However, our patient often goes bowling and thus is used to this physical exercise. 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,6,7 future observations will show whether increase in dosage of IFN-β predicts rhabdomyolysis as reported for IFN-α.

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References

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 sub-archnoid 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 ataxia, 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 absent 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 col.
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."

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. 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 pigmentmentation may be found deep within the spinal cord and zona incerta. The authors have described. 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 intracranial 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. 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 the Schwann cell 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 periphery Schwann cell segments. Koeppen and Detinger have also suggested that the formation of haemosiderin is neuroprotective and it is once this protection has been lost hemorraghic damage occurs, thus it is not the haemosiderin which is toxic but the unbound iron. There are no other case reports of superficial siderosis causing an anterior horn cell syndrome, posing the question of why our patient developed this condition.

We think that our case of superficial siderosis was diagnosed and oral antispastic medication 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 at a rate 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 now 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 but the patient tolerated this in substantial discomfort. Thus a daily dose of 540 µg baclofen was maintained.

Due to bulbar involvement the patient was supplied with a nasoalveolar 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 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 progression of the disease resulted in rapid development of complete tetraplegia and respiratory insufficiency necessitating the use of non-invasive intermittent positive pressure 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 characterized by severe movement disorders. Although progressive paresis results 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' quality of life. As the aetiopathogenesis of amyotrophic lateral sclerosis remains unresolved and no cure thereof is available progression 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. 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. Intrathecal infusion simultaneously increases the effect of baclofen on spams and reduces the incidence of side effects.

Despite its widespread use and proved efficacy in the treatment 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. In a patient described here intrathecal baclofen need adequate palliative treatment more than anything else 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 interventions of patients of palliative treatment has proved to be a safe procedure without substantial risks.

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References

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 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 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), the updated pedigree of the Greek-American family H, and two Greek families. The families of Papapetropoulos et al are not included because the total number of persons at risk is not mentioned.

In these kindreds of 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 55.5:34:1 = 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. However, the segregation ratio for male α-sPD in the kindreds mentioned above equals 53/13 = 4:1, for female α-sPD 34/96 = 35%. These segregation ratios do not differ significantly (p = 0.21, χ² 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%). 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 these kindreds is significantly abnormal (p = 0.017; χ² 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, the difference from the α-synuclein kindreds is even more remarkable (p = 0.000; χ² test). If this male predominance 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 mutated α-synuclein, nervous α-synuclein innervomotor nuclei, Lewy body-type inclusions, and loss of dopaminergic nerve cells have been described, but there were no sex related abnormalities or differences in PD. However, sex differences of PD have 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
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, 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 statistical 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, 190 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 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), whereas of the 95 women at risk, 27 (28.4%) had α-synPD (male/female ratio 86/56=1.5). The male to female ratio of our Greek families at risk was 235/191=1.23 (p=0.002 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.

After excluding the Contursi kindred, the male to female ratio of all subjects of Greek origin combined 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 was 235/191=1.23 (p=0.002 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 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.

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

<table>
<thead>
<tr>
<th>Family members at risk for α-synPD</th>
<th>Family members with α-synPD</th>
</tr>
</thead>
<tbody>
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<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Papapetropoulos et al</td>
<td>95</td>
</tr>
<tr>
<td>Papadimitriou et al</td>
<td>17</td>
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<tr>
<td>Golbe et al</td>
<td>56</td>
</tr>
<tr>
<td>Samii et al</td>
<td>23</td>
</tr>
<tr>
<td>Total</td>
<td>235</td>
</tr>
</tbody>
</table>

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’, 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 other presentation recently 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.

Various conditions such as Hashimoto’s encephalopathy, paraneoplastic cerebellar degeneration, and parkinsonism – axial rigidity, hypertonia. 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, and was not available in the remaining five patients. Detailed genetic tests should be carried out, even if there is no family history of ataxia. Recent studies show that such patients have 4% of patients with a sporadic ataxia harbour a mutation. Negative genetic results would reinforce the appealing concept of “Hashimoto’s associated ataxia”.

### Acknowledgements

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### References


10. Hashimoto’s associated ataxia

Selim and Drachman described six patients with a progressive sporadic adult onset cerebellar degeneration.1 Raised concentrations of antinuclear antibodies were found. Modest increases in antinuclear 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.
The similarity of this gradually progressive cerebellar disorder to that reported with antiglutamic acid decarboxylase (GAD) antibodies target Purkinje cells, or whether the mechanisms leading to the florid manifestations that may occur in patients galore, in different settings such as medicolegal practice. Yet the mechanisms leading to the florid manifestations of hysteria in these patients may be part of a neurological tendency available to a much wider range of progressive cerebellar impairment due to autoimmune disorders has yet to be elucidated; and multisystem atrophy may well overlap clinically, aetiologically, or both.

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 act 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 copy. In addition, this book will undoubtedly prove useful in our understanding of paediatric movement disorders and movement disorders covered include the hypokinetic-rigid syndromes, tremor, chorea, dystonia, myoclonus, tics, and complex. There are several important chapters on movement disorders and movement disorders in children. All child neurologists and paediatricians with an interest in neurology or neurosurgery need to have this book to hand. I suspect that most will want to own a personal copy of this book, which will be of particular help to adult neurologists evaluating patients with a movement disorder. The origins of which are in childhood or adolescence.

This is a comprehensive and up to date textbook about movement disorders in children. It is a good book to have, but encourages the reader to read the texts herein published. One quote will help to tempt: "In an attempt to encapsulate the self-deceptive view of hypotensioned patients, they have been labelled as 'habitual liars'". By the same token, hysteria should perhaps be seen as 'genuine malingerers' (Oakley).
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 would be 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, this approach might well be better doen 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 are based 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 would not surprise me at all. 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 Psychiatr Scandinav* 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 classical studies” of this proprietary compound. Things haven't changed much.

**Simon Lovestone**

**Limbic seizures in children**


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 inevitably, 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 perirhinal and perihippocampal cortex are distinguished by several features. Their cell properties are particularly determined by the level of activity—long-term potentiation or depression. Their surrounding properties coupling to subserve memory. Whereas the perirhinal cortex 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 particularly 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 years of age 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 automatism, impairment of consciousness, autonomic changes, and postural changes. The literature distinguishing frontal from mesial temporal lobe 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 research and this is not 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 Psychiatr Scandinav* 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 classical studies” of this proprietary compound. Things haven't changed much.


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, 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 systems of care for patients with spinal cord injury worldwide.

**Brian Gardner**

**Head trauma: basic, preclinical, and clinical directions**


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 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.

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**PETER J KIRKPATRICK**
Meeting the challenge of progressive multiple sclerosis


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 opportunity 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