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 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.

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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 tone and no 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 UI (normal range: 5–70 UI), with normal concentrations of the isofrom CK-MB, lactate dehydrogenase (LDH) at 670 UI (normal range: 80–240 UI), 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, uric acid, 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 1a treatment. This adverse event has been previously associated with IFN-α, which also belongs to the type 1 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 suffering from a myopathy associated with adjuvant high-dose IFN-α in malignant melanoma. Lancet 1997:349:540–1.


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-archaeal bleeding. 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 symmetrical. 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 cord.
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 pigmentation may be found deep within the spinal cord and around the Schwann cells have been 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. Koepen 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. 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. Koepen 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. 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

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

Baclofen, an agonist of γ-aminobutyric 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 dosage has shown its efficacy in numerous series of patients with spasticity of cerebral or spinal origin. Nevertheless, the use of intrathecal administration of baclofen in amyotrophic lateral sclerosis, representing the most common degenerative motor neuron disease in adult life, has been mentioned in only one short communication. 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; 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 treatments were 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 after 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, and the patient developed 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 had been followed up 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 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 attacks due to uncontrolled spasms and some 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 considerably as the patient was able to sleep the night through. Further progress of disease was halted for a prolonged period of time and the patient remained ambulatory for 6 months. Amyotrophic lateral sclerosis was diagnosed, and medical treatment consisting of riluzone and intrathecal baclofen was started. 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 characteristic 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’ quality of life. As the aetiopathogenesis of amyotrophic lateral sclerosis remains unresolved and no cure therapy is available, progress 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 antispasmodic agents. Several antispastic drugs such as baclofen, memantine, or benzo-diazepines 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 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 a large 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. However, intrathecal baclofen in patients with amyotrophic lateral sclerosis 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 intrathecal baclofen the last resort 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 compared 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 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. However, the segregation ratio for male α-sPD in the kindreds mentioned above equals 53/13 = 41%, for female α-sPD 34/26 = 35%. These segregation ratios do not differ significantly (p = 0.021, 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 (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 kindred is even more significant (p = 0.003; χ² 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 mutated α-synuclein, no sex effect on in vivo neurone immunoreactive nerve cells, Leavy body-type inclusions, and loss of dopaminergic nerve cells have been described, but there were no sex related abnormalities or differences in in vitro cultures. However, sex differences in α-synuclein expression has not been examined specifically, so the actual cause of the male preponderance in α-synuclein kindreds remains to be elucidated.

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Authors’ reply:

As Horstink and Bloom 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 reported 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 Bloom, 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 al2 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 study3). After excluding the Contursi kindred, the male to female ratio of all subjects of Greek origin combined,4,5 was 199/135=1.48 (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 combined4,5,6 was 235/191=1.23 (p=0.001 for the difference from a 1:1.3 ratio).

Our data confirm the finding of Horstink and Bloom 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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<th>Table 1 The segregation ratios of all α-synPD cases reported</th>
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<td>Family members at risk for α-synPD</td>
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<td>Family members with α-synPD</td>
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<td>Reported α-synPD cases</td>
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<td>Papapetroupolos et al5</td>
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<td>Pavlidou et al6</td>
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<td>Samii et al5</td>
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<td>Total</td>
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<td>α-synPD = α-synuclein Parkinson’s disease.</td>
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<th>Male (segregation ratio)</th>
<th>Female (segregation ratio)</th>
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<tr>
<td>Papapetroupolos et al5</td>
<td>27 (26.2%)</td>
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<tr>
<td>Pavlidou et al6</td>
<td>6 (42.8%)</td>
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<tr>
<td>Samii et al5</td>
<td>10 (31.3%)</td>
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<tr>
<td>Total</td>
<td>82 (34.9%)</td>
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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 CSE. 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 this 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.3 Various clinical features such as extrapyramidal signs, autonomic/urinary dysfunction, pyramidal signs (bilateral Babinski’s signs), parkinsonism, ataxia, rigidity, and hyperkina.s.a 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,3 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. Negative genetic results would reinforce the appealing concept of “Hashimoto’s associated ataxia”.

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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 imaging and evoked potential studies. These seem fairly consistent, noting the important association of the frontal and cingulate cortex to symptoms presentation, a somewhat serpentine 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 historical 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 patient continuum. It is perhaps that these should not be 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 he cannot without 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 “is he, 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 spoil 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 “inexcusable liars”. By the same token, hysterics should perhaps be seen as “genuine malingerers”” (Oakley).

Michael Trimble

Movement disorders in children


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 movement. 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 literature; and a discussion of the relevant treatment of the individual movement disorder. 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 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 neurophysiology should have access to this book and I suspect that most will want to own a personal copy. In addition, this book will be an excellent resource to help adult neurologists evaluating patients with a movement disorder the origins of which are in childhood or adolescence.

R Surtees

Advances in dementia research


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 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 collection 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, myotonic dystrophy, 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 or 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 that is not 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, they would use it probably well better than a book with JNPNP, 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 papers 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. 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 1998;97:174-176, would certainly 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


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 understanding of limbic 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 activation—long-term potentiation or depression. The surrounding properties of local 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 the 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 from limbic aspects of limbic seizures is 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


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 counselor.

The information in this book will assist predominately 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, occupational 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 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 several countries in improving 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 onto 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 more general theories of metabolic changes 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 practice. There are no 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 traumatic brain injured.

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