Figure 1 (A) HE: There is marked fibre size variation, and some fibres show ill defined inclusions. (B) ATPase, pH 9.4: section shows selective fibre type 2 atrophy. (C) Modified Gomori trichrome: there is marked variation in fibre diameter and multiple dark rod-like inclusions are seen in many fibres. (D) Ultrastructural examination shows these inclusions to be osmophilic and approximately rectangular, the classical appearance of nemaline rods.

and the presence of rod-like structures inside the muscle fibres. It is clinically and genetically heterogeneous. It usually presents in childhood; adult onset nemaline myopathy is very rare. Clinical symptoms vary and many patients are symptomatic long before diagnosis. Common complaints in adulthood include weakness, especially of proximal muscles, fatigability, and myalgia. Electromyography is characteristically myopathic. Histologically it is characterised by large numbers of rod containing myofibres, numerous rods per affected myofibre, and the absence of any other specific structural abnormalities. Some of the adult onset nemaline myopathy cases described were associated with underlying immunological disorders including monoclonal gammopathy, chronic hepatitis, HIV, and HTLV-2 infection, suggesting that an immune disturbance may play a role in the pathogenesis. Association with monoclonal gammopathy seems to bear an unfavourable prognosis.² HIV associated nemaline myopathy has distinctive pathological features on light microscopy and shows marked intrasarcoplasmic changes. Nemaline myopathy can also develop after radiation.

Our patient showed characteristic clinical and laboratory features of autoimmune hypothyroidism, and his muscle biopsy findings were characteristic of nemaline myopathy. This association has been described only once in humans, by Reyes *et al* in 1986. Their patient was a 50 year old black woman who presented with generalised weakness, progressive dyspnoea, and leg oedema. Examination and investigations revealed cardiac failure and hypothyroidism. Two months of thyroid replacement corrected her thyroid state but did not improve her muscle weakness. Muscle biopsy carried out that time

showed abundant nemaline rods consistent with nemaline myopathy.³

Though it is possible that the abnormal histology was caused by hypothyroidism or by the autoimmune process leading to its development, we think that it is more likely that subclinical nemaline myopathy emerged during the onset of severe hypothyroidism. A recent report described three patients from three separate families who were initially diagnosed as having hypothyroid myopathy but were later found to have proximal myotonic myopathy. None of these people were symptomatic before the onset of hypothyroidism.⁴ A prospective clinical and electrodiagnostic study of adult patients with newly diagnosed thyroid dysfunction showed that 13% of them had residual muscle weakness which could be confirmed on manual muscle testing after one year of treatment.⁵ It may be that in some patients the onset of hypothyroidism unmasks a pre-existing clinically silent or very mild myopathy.

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Parkinsonism in type 1 Gaucher's disease

Gaucher's disease (GD) is the most common hereditary lysosomal storage disorder, with a prevalence of 1:57 000 in the general population.¹ The disease results from mutations in the glucocerebrosidase (GBA) gene, localised in chromosome 1 (the most frequent mutation is N370S) and has an autosomal recessive pattern of transmission. As a result of such mutations, there is decreased activity of the enzyme and subsequent glucocerebroside accumulation in cells of the macrophage-monocyte system. This process may lead to hepatosplenomegaly, bone disease, and pancytopenia.

GD is classically divided into three types, according to the presence of neurological symptoms and the dynamics of the developing clinical picture.² Type 1 GD is the most common, affects mainly Ashkenazi Jews, and until recently was considered non-neuronopathic. It may present at any age and its course and presentation are variable. Many type 1 GD patients remain virtually asymptomatic, being diagnosed during evaluation for a non-related disorder or familial screening of a symptomatic relative.

In juvenile GD (type 3), movement disorders are frequently found, but there is growing evidence that neurological symptoms, particularly parkinsonism, may also occur as a late complication of type 1 GD.

The following case report illustrates such situation.

Case report

A 45 year old white man was referred to our movement disorders unit by his haematologist with the complaint of gait difficulty since 2002.

The patient had been diagnosed with type 1 GD at the age of 22, when routine blood tests showed anaemia. During investigation he was submitted to a bone marrow biopsy, which was suggestive of GD, and later to genetic studies, which showed N370S/L444P mutations in the GBA gene.

The patient is the second child of unrelated parents and had a normal delivery and development as a child. He has a non-Jewish ethnic background and his family history is negative for GD and Parkinson's disease.

The follow up evaluation by his haematologist revealed hepatosplenomegaly, and the patient complained of bone pain. In 1995 he underwent splenectomy (fig 1). In 1998, enzyme replacement therapy was started (imiglucerase 60 IU/kg every two weeks) and the patient reported improvement of symptoms. There was also reversal of the haematological abnormalities.

Figure 1 Histopathology of the patient's spleen showing Gaucher cells, which are macrophages enlarged by glucocerebroside accumulation, with their typical "wrinkled tissue paper" cytoplasmic appearance

By the age of 43 the patient noticed progressive gait disturbance—he mentioned diminished arm swing and trouble turning. At the same time, he developed bilateral asymmetrical action tremor (predominantly on the left side) and bradykinesia. He was prescribed levodopa/carbidopa and achieved partial improvement of the tremor and gait.

When evaluated at our movement disorders unit, patient was taking levodopa/carbidopa 200/50 mg, half a tablet five times a day. From the beginning he presented with dyskinesias. His Hoehn-Yahr stage was 2, his UPDRS score was 18, and the Schwab and England Activities of Daily Living was 90%. General physical examination was unremarkable. On neurological examination there was moderate bilateral weakness of ankle dorsiflexion (he had an electroneuromyography in 2002 which revealed bilateral L4–S1 radiculopathy and left fibular nerve neuropathy; lumbosacral spine computed tomography showed spinal stenosis at L3–L4; such abnormalities had been attributed to GD), cogwheel rigidity of both upper and lower limbs, mild bilateral kinetic tremor, lower limb dyskinesias, and loss of ankle reflexes.

The patient was prescribed pramipexole 0.25 mg three times daily and obtained mild symptomatic improvement.

Comment

Recent reports have emphasised the association between GD and parkinsonism.

In 1985 McKeran *et al* described a 55 year old patient with type 1 GD diagnosed at the age of 17, who developed a parkinsonian syndrome, only initially responsive to levodopa.² Neudorfer *et al* reported six patients with GD and parkinsonism.³ Four patients were followed up and a poor response to levodopa was observed. In 1999, Machaczka *et al* reported another patient with parkinsonism preceding the clinical manifestations of GD by 12 years.⁴

More recently, Bembi *et al* described four patients with GD and parkinsonism.¹ The age of onset was younger than in classical Parkinson's disease, but the clinical picture was indistinguishable. Two patients had been diagnosed with type 1 GD at an early age and developed parkinsonism several years afterwards. Enzyme replacement was effective for systemic symptoms, but had no effect on the parkinsonism.

The patient we report here developed parkinsonism at a young age (43), like most cases described in published reports. This seems to be a consistent feature of patients

with type 1 GD who develop parkinsonism. Another interesting point is that the patient presented with parkinsonian symptoms while receiving enzyme replacement therapy, confirming previous published data about the ineffectiveness of this specific GD treatment for correcting neurological manifestations of the disease. He had bilateral signs from the start and so far a suboptimal response to levodopa therapy, which would not be expected in classical Parkinson's disease.

The nature of the association between GD and Parkinson's disease remains to be elucidated. The mechanism involved in the development of parkinsonism in carriers of GBA mutations may be related to protein misfolding. Studies indicate that glucocerebroside accumulation induces apoptosis in cultured neurones and that neurones with high levels of glucocerebroside have a higher sensitivity to agents that lead to cellular death.⁵

In spite of the association described, most patients with GD never develop parkinsonism, suggesting the involvement of other factors, genetic or environmental, in the disease process.

It has been increasingly recognised that parkinsonism may be a clinical feature of type 1 GD and may even precede this diagnosis, so GD must be considered in the differential diagnosis of parkinsonism in subjects with early onset and poor response to levodopa. The basis for this association remains unknown. The treatment of parkinsonism in these cases is similar to classical Parkinson's disease. However, it is usually less effective. Enzyme replacement therapy is an important advance in controlling the systemic manifestations of GD, but its impact on neurological symptoms is limited.

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BOOK REVIEW

Head injury, pathophysiology and management, second edition

Edited by Peter L Reilly, Ross Bullock. Published by Hodder Arnold, London, 2005. £145.00 (hard cover), pp 501. ISBN 0-34080-724-5

Traumatic brain injury is one of the most difficult and challenging management problems facing clinicians. The last 20 years have seen major advances in the prevention and treatment of head injury, resulting in a substantial decrease in associated mortality. In the 1970s, 50% of patients with severe head injuries died as a result. In the 21st century mortality rates of around 25–30% are commonly reported. There has been a concomitant increase in the number of good to moderately disabled survivors as opposed to those left severely disabled or vegetative. This improvement is due to several factors, including better patient retrieval and resuscitation, enhanced emergency facilities and early surgery. However, head injury remains a major health and social problem both for developed and developing nations. Research is increasingly clarifying the underlying physiological mechanisms involved in neuronal damage, offering the chance of better methods of diagnosis and treatment. There has been particular interest in the development of neuroprotective agents.

This is a comprehensive and extensively updated guide to the management of severe head injury. It provides a complete management framework for traumatic brain injury and is divided into three sections covering mechanisms of injury, quantification and monitoring, and treatment of the injury. There is detailed coverage of the relevant basic sciences, which then leads on to more clinical aspects with particular emphasis on the rapidly evolving areas of neuromonitoring and neuroprotection.

It is extensively referenced and well-illustrated. The contributors come from a wide range of clinical and scientific disciplines with an international perspective, resulting in a balanced contemporary review of our current knowledge and understanding of head injury. Some of the illustrations suffer from being outdated in style but this is compensated for by a section of colour-plates.

It would be a useful reference addition to the library of neurosurgeons, trauma surgeons and intensivists responsible for the care of head injured patients.

J Grieve

CORRECTION

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A F J E Vrancken, S Kalmijn, E Buskens, *et al*. Feasibility and cost efficiency of a diagnostic guideline for chronic polyneuropathy: a prospective implementation study (*J Neurol Neurosurg Psychiatry* 2006;**77**:397–401). In the legend to figure 1 of this paper the abbreviation CIAP is erroneously stated as "chronic inflammatory axonal polyradiculoneuropathy". It should be "chronic idiopathic axonal polyneuropathy".