Figure 1 Chest 16-slice computed tomography, showing the thrombosis of a pulmonary arteriovenous fistula (C) and efferent (A) and afferent (B) vessels.

Comment

ROW disease, also called hereditary haemorrhagic telangiectasia, is an inherited autosomal dominant vascular dysplasia.¹ Currently, it remains a clinical diagnosis based on two or more of the following manifestations: epistaxis, telangiectasia, a family disorder, or documented visceral involvement such as PAVF.¹ PAVFs are found in approximately 15–20% of patients with ROW disease. They progressively enlarge and usually become symptomatic in adult life.² PAVFs can be suspected on contrast transoesophageal echocardiography.³ However, as in our case, when a patent foramen ovale coexists with PAVF the early passage of contrast bubbles through the foramen ovale may prevent the contrast echocardiography from identifying the concomitant PAVF.

PAVFs are the most frequent cause of cerebral ischaemic events and brain abscesses in patients with ROW disease. Maher *et al*⁴ showed that stroke or transient ischaemic attacks occur in 30% of such patients with PAVF. The risk of stroke may be increased in patients with multiple PAVFs.⁵ However, the pathophysiology of these events remains unclear. A role of polycythaemia (resulting from chronic hypoxaemia) or air embolism has been suggested but never well documented.² In fact, paradoxical embolisation through a right to left shunt caused by PAVF is probably the main mechanism for cerebral ischaemic events in ROW patients⁵; however, the source of embolism is rarely found. Indeed, conventional diagnostic techniques may fail to detect a small thrombus, particularly when located in some areas such as the pelvis or because thrombus has totally migrated when the stroke occurs.⁶ Although, we cannot completely exclude the possibility that PAVF thrombus resulted from peripheral embolism, our case suggests that PAVF may constitute a site of thrombosis. A slowing of blood flow through the fistula and a thrombotic state after abortion are two conditions that may have favoured in situ thrombosis in our case. To our knowledge, such a complication had never been documented before.

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Hypothyroidism and nemaline myopathy in an adult

A significant proportion of patients with myopathy attributed to hypothyroidism remain symptomatic after long term thyroxine treatment, but muscle biopsies are rarely undertaken. Systemic review of published reports revealed only one case of typical nemaline myopathy associated with the condition. We hypothesise that hypothyroidism may not directly cause nemaline changes in muscles but it may unmask asymptomatic muscle disorders.

Case report

A 65 year old white man presented with bilateral lower limb oedema extending to the abdomen, and shortness of breath on exertion. The oedema improved on diuretics but he was noted to have muscle tenderness and weakness. He was unable to stand up from sitting. Physical examination showed proximal muscle weakness of grade 3/5. There was no previous history of an autoimmune disease and no relevant family history of muscle disease or weakness. There was no consanguinity in his family. His creatine kinase was found to be raised at 912 U/l (normal range 24 to 195 U/l) and he was referred for muscle biopsy with suspected polymyositis.

Section of muscle biopsy showed scattered atrophic fibres and occasional necrotic and regenerating fibres but no inflammation (fig 1A). Staining with ATPase showed selective fibre type 2 atrophy (fig 1B). Many fibres contained eosinophilic inclusions of varying shapes and sizes that stained dark red on a Gomori trichrome stain (fig 1C). Electron microscopy showed these bodies to either have a periodicity of 8 nm with filaments protruding from the end as from a Z disc, or to show a tetragonal filamentous array to a Z disc (fig 1D). The features were those of nemaline rod myopathy.

Following the biopsy his weight increased and he noted increasing swelling of his legs, abdomen, and chest. Settled facial features of myxoedema were noted and direct questioning revealed cold intolerance, constipation, and voice change. Thyroid function tests confirmed severe hypothyroidism. Thyroid microsomal (TPO) antibodies were strongly positive. Serum immunoelectrophoresis did not show monoclonal gammopathy and his HIV test was negative. He slowly improved on thyroid replacement but residual weakness of proximal muscle groups (grade 4/5) was still detectable by manual testing after three years of meticulous thyroid replacement. He declined a repeat muscle biopsy.

Comment

A myopathic syndrome is a common association of hypothyroidism and can be its only manifestation. Thus thyroid function tests should be always checked in people with muscle weakness. In our patient they had not been checked until after the muscle biopsy. In hypothyroidism, muscle biopsies may be normal or show non-specific changes such as increased central nuclear counts, type 1 fibre predominance, or type 2 fibre atrophy. Common abnormalities on electron microscopy are accumulation of glycogen and lipids, abnormal mitochondria, increased numbers of mitochondria in perinuclear and subsarcolemmal regions, dilated sarcoplasmic reticulum, proliferation of T-tubules, and focal myofibrillar degeneration. Ono *et al* described large irregularly shaped cores to occur in five patients with hypothyroidism, which disappeared following treatment with thyroxine.¹ They were seen in eccentric positions or in the periphery of type 1 fibres. They were unreactive with ATPase and PAS staining whereas with haematoxylin-eosin and modified Gomori trichrome staining the regions were more strongly reactive than the rest of the fibre. Electron microscopy of the cores showed Z disc streaming, poorly defined myofibrils, and absent mitochondria.

Nemaline myopathy is an uncommon muscle disorder characterised by weakness

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.