Thyrotoxic myopathy

A variety of neuromuscular disorders has been described in adults in association with overactivity of the thyroid (Millikan and Haines, 1953; Ramsay, 1966; Engel, 1972). The most common of these disorders is a chronic myopathy, characterized by muscular atrophy and weakness involving predominantly proximal muscles (Adams and Rosman, 1971). The myopathic symptoms may precede the symptoms of thyrotoxicosis by many months, and the atrophy and weakness may be so pronounced that it suggests a diagnosis of progressive muscular atrophy or a limb-girdle type muscular dystrophy. Less commonly, myasthenia gravis and periodic paralysis may be associated with thyrotoxicosis. The chronic myopathy and periodic paralysis are always improved by establishing a euthyroid state, suggesting that thyroid dysfunction induces the neuromuscular disorder. The myasthenia gravis, however, is not cured by controlling the thyroid dysfunction and any departure from the euthyroid state increases the severity of the myasthenia (Engel, 1972).

Chronic thyrotoxic myopathy has hitherto been reported exclusively in adults. The purpose of this paper is to report that a similar disorder can be associated with thyrotoxicosis in childhood.

Case reports

Case 1. This 6-year-old girl was referred to the neuromuscular clinic with a 4-month history of progressive muscular weakness. The birth history and neonatal period were uncomplicated, and the developmental milestones were normal. The parents became concerned when at the age of 5 years 8 months the patient seemed to be having difficulty in lifting objects which her sister, aged 3 years, was lifting with ease. During the 4 months before referral she had increasing difficulty with running, she was only able to walk without resting for about 100 yards, and only able to climb stairs slowly with assistance. She had considerable difficulty in getting up from the floor or the sitting position. General health was good. No weight loss, diarrhoea, or increased appetite was noted. Though the child had obvious proptosis, the parents had not noted this.

Both parents were well. A paternal grandmother had thyrotoxicosis diagnosed at age 32 years.

Examination showed the following. Height 25th centile. Weight 3rd centile. There was bilateral proptosis with lid lag. The ocular movements were full. Pulse rate 120/min; the sleeping rate was 100/min. The thyroid isthmus was palpable, but there was no enlargement of the gland. No tremor of outstretched hands. Neuromuscular examination revealed generalized hypotonia with poor muscle bulk, particularly of proximal muscle groups. The gait was slightly waddling with a

marked Gower's manoeuvre on getting up from the floor. Muscle strength of proximal muscle graded at 4/5 on M.R.C. scale. The distal muscles were of normal strength. The reflexes were normal.

Bone age 6 years. Protein bound iodine (PBI) 13.6 $\mu\text{g}/100\text{ ml}$ (normal 3.8–8.0); total thyroxine 17.7 $\mu\text{g}/100\text{ ml}$ (normal 4.5–13.6); T_3 uptake 77%; LATS not detectable. IgG and IgM normal, but IgA low at 12 mg/100 ml (normal 73–250). Thyroglobulin antibodies negative by electroprecipitin test, the tanned red cell titre positive to 1/25. Thyroid microsome immuno-fluorescence, antinuclear factor, mitochondrial antibody, smooth muscle antibody, and gastric parietal cells were all negative.

Creatine phosphokinase (CPK) 16 mIU/ml (normal up to 140). Electrodiagnostic studies showed normal motor nerve conduction. Concentric needle electrode recordings showed a definite myopathic pattern with action potentials of small amplitude, short duration, and increased polyphasicity. Muscle biopsy of the quadriceps showed normal appearance to routine and histochemical stains. The electron microscopy revealed some increase in fibre splitting, but the mitochondria were normal. In culture the muscle showed an increased rate of growth with the formation of very mature, large, multinucleate myotubes (Professor V. Dubowitz, Hammersmith Hospital, London).

Clinical improvement was noted 3 weeks after starting carbimazole 5 mg three times daily. Muscle strength gradually returned to normal during the next 3 months, with the most marked improvement in the first month. Increased strength was accompanied by increase in muscle bulk. Weight increased by 2 kg in 2 months and the sleeping pulse fell to 80/min. PBI returned to normal range by the fourth week of treatment, and has remained so. CPK, which was initially low at 16 mIU gradually increased to 97 mIU/ml during a 5-month period.

Case 2. This boy, aged 10 years 8 months, presented with a 3-month history of progressive weight loss increasing lethargy, and emotional lability. Some prominence of his eyes had been noted for about the same length of time. An enlargement of the thyroid was seen only 2 weeks before presentation. He had been seen in the clinic since the age of 9 years with the nephrotic syndrome which had responded to steroids and cyclophosphamide, and had been off treatment for one year without relapse. No family history of thyroid disorders, but the mother has pernicious anaemia.

Examination showed the following. Height 90th centile. Weight 25th centile. Marked proptosis with lid lag. Pulse 136/min. He was a nervous boy with excessive sweating. The thyroid gland was enlarged, firm, and smooth without nodules. The musculature was generally poorly developed. Although muscle strength was reduced proximally, the boy had not complained of weakness. There was some difficulty with stairs, but no Gower's manoeuvre. Reflexes were normal. Marked fine tremor of outstretched hands.

Bone age 12.5 years. PBI 12.8 $\mu\text{g}/100\text{ ml}$; T_3 uptake

76%. IgA, IgG, IgM normal. Immunofluorescent test for antibody to nuclei, mitochondria, smooth muscle, and gastric parietal cells negative. Thyroglobulin antibodies positive by electroprecipitin test. The tanned red cell titre was positive to 1/25,000. Immunofluorescent test positive for thyroid microsomes.

CPK 43 mIU/ml. Motor nerve conduction normal. The electromyogram was grossly myopathic. Muscle biopsy was normal to routine, histochemical, and ultrastructural techniques.

4 months after starting on carbimazole 10 mg twice daily he had gained 3 kg, and clinically and biochemically was euthyroid. Muscle strength improved rapidly, returning to normal within a few weeks.

Discussion

Both these children have, in addition to the manifestations of thyrotoxicosis, evidence of a chronic myopathy. In the first the neuromuscular symptoms predominated and the child was referred as a possible muscular dystrophy. The second case presented with classical thyrotoxic symptoms, the myopathy only being recognized on clinical examination.

Many adult thyrotoxic patients have some mild reduction in muscle power, and show increased muscle fatigability (Swank and Bergner, 1946), making it difficult to define the criteria for the diagnosis of chronic thyrotoxic myopathy. Nor is the electromyogram of help for it is abnormal in about 80% of the patients whether or not there is clinical muscle involvement (Ramsay, 1966). Since the majority of thyrotoxic patients have some evidence of muscle involvement it is the extent and severity of the weakness and atrophy which determine the diagnosis of 'myopathy'.

There are relatively few reports of muscle pathology in either uncomplicated thyrotoxicosis or in patients in whom the muscle weakness has become so severe as to constitute a chronic myopathy. The principal change seen in about half the biopsies is one of mild atrophy, sometimes with fatty infiltration (Adams and Rosman, 1971). Electron microscopy has added little, but in 2 cases an excessive number of abnormal mitochondria were seen (Engel, 1966). In the present cases light microscopy, including the histochemical profile, was normal. The first child showed minimal ultrastructure abnormality with occasional atrophic fibres and splitting and degeneration of some myofibrils.

The increased growth and maturation rate in culture is an unexpected finding, and may be an effect of the thyroid hormone. The second case showed no ultrastructural changes. The activity of creatine phosphokinase in the Case 1 was initially low, gradually increasing as she became euthyroid and muscle strength returned to normal. CPK has an important role in the synthesis of phosphocreatine, which is an intermediary in the energy cycle for muscle contraction. Whether the low serum CPK reflects a low intracellular level and is responsible for the metabolic disturbance of failure of storage and utilization of creatine is not known (Kuhlback, 1957). The reverse, with raised CPK levels occurring in myxoedema (Fleisher, McConahey, and Pankow, 1965) suggests that the low enzyme activity in the toxic state is a nonspecific effect and not directly related to the muscle disorder.

Summary

Two children aged 6 and 10 years presented with muscle weakness which proved to be due to thyrotoxic myopathy. One case illustrated the most severe form with masked hyperthyroidism, while the other had classic thyrotoxic symptoms with only mild muscle weakness.

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