Familial centronuclear myopathy associated with 'cardiomyopathy'

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Two cases of familial centronuclear myopathy are described. Both presented features of 'cardiomyopathy' and one had signs of slight congenital aortic stenosis. The 'cardiomyopathy' was fatal in one case. The clinical histological, and necropsy findings are presented and discussed.

In 1966, the first case of a congenital myopathy, histologically characterized by the presence of central nuclei in 85 per cent of the skeletal muscle fibres was reported (Spiro, Shy, and Gonatas, 1966). After this report, a number of identical cases were described and the general descriptive term of centronuclear myopathy was proposed (Sher *et al.*, 1967). Though the presence of cardiac abnormalities was mentioned in some cases, no clear description of these findings has been given.

The purpose of the present report is to describe the cases of two brothers with centronuclear myopathy associated with evidence of 'cardiomyopathy'.

Case reports

Case 1

The older of two brothers was born in 1957 after a normal pregnancy and delivery. His parents were in good health and there was no family history of any particular disease. The patient had difficulty in sucking, started walking late, and during childhood tired easily. After several weeks of increasing dyspnoea, he was admitted to our hospital at the age of 15 years.

The heart rate on admission was 140 beats/min and the systolic blood pressure 70 mmHg (9.3 kPa), with unrecordable diastolic blood pressure. There was striking distension of the neck veins, and the liver was enlarged to 3 cm below the costal margin, but there was no peripheral oedema. The heart was enlarged to the left and a diffuse left ventricular impulse was felt. Auscultation of the heart showed a summation gallop but no murmurs. Fine inspiratory râles were heard over the bases of both lungs. Both heart chambers were enlarged on the chest x-ray (Fig. 1). The electrocardiogram showed first degree atrioventricular block, extreme left axis deviation, and possible left atrial hypertrophy (Fig. 2a). The vectocardiogram showed left anterior hemiblock and intra-atrial conduction disturbances.

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Further clinical examination showed generalized muscle weakness and wasting, a waddling gait, winging scapulae, lumbar hyperlordosis, dorsal kyphoscoliosis, and slight bilateral ptosis of the eyelids (Fig. 3). Standing up from the supine position was impossible without the use of arms and hands. The tendon reflexes were weak or absent. Cutaneous sensibility and tests for cerebellar function were normal. His intelligence was normal.

Electromyography of the main muscle groups of the thigh and lower leg indicated only minor non-specific alterations. Over both temporal zones a theta arrhythmia with paroxysms during hyperventilation was found on the electroencephalogram. X-ray studies of the skeleton showed that the anterior arch of the atlas bone was absent. Routine biochemical studies, including determination of creatine phosphokinase, aldolase, and creatinuria, were normal. No autoimmune antibodies were present. The vital capacity of the lungs was 1.6 l and the 1 s forced expiratory volume 1.4 l, a restrictive pattern probably caused by muscle weakness. The karyotype was normal.

The signs of heart failure disappeared under treatment with digitalis, diuretics, and a sodium-free diet. The cardiac enlargement, however, persisted.

A biopsy of the right anterior tibial muscle revealed on histological examination a considerable variation in the diameter of the fibres, ranging from 10 to 80 μ . A few isolated small fibres showed regressive changes, like microvacuoles, or signs of regeneration (basophilia with vesicular nuclei). Short nuclear chains and small thick nuclear clumps were seen in some fibres. Of 500 muscle fibres examined in transverse section, 74 per cent presented central nuclei (Fig. 4a). This number varied between 30 and 92 per cent according to the examined field. Inflammatory changes, endomysial sclerosis or fat infiltration were not present. Spindles, nerves, and blood vessels had a normal aspect. The glycogen and protein contents of the muscle were within normal limits. Histochemically a pronounced, numerical predominance of type I fibres was found. Most type II fibres were atrophied (Fig. 4b).

FIG. 1 Chest x-ray of Case 1 shows obvious cardiomegaly and scoliosis.

At the age of 16, the patient presented progressive heart failure and was readmitted with pulmonary oedema and unrecordable blood pressure. The electrocardiogram was unchanged, except for a sinus tachycardia of 140/min. Chest x-ray examination showed pulmonary oedema and further progression of the cardiac enlargement. The patient perished three days after admission as a consequence of extreme left heart failure, which did not respond to digitalis and diuretics.

At necropsy, the heart was extremely dilated, with displacement of both lungs. On gross examination the pericardium appeared normal and contained a small amount of serous fluid. The heart weighed 450 g. The right atrium, right ventricle, and left ventricle were very dilated. The thickness of the right ventricular wall was 2 to 3 mm and the left ventricular wall 7 to 10 mm. All heart valves had a normal appearance. No mural thrombi were present. The coronary and pulmonary arteries and the aorta were normal. Microscopical examination (Fig. 5) of the myocardium revealed extensive fibrosis in both heart chambers. Though this fibrosis occurred throughout the entire thickness of the myocardium, it was particularly dominant around the blood vessels. Some myocardial fibres showed hypertrophy without attenuation. No degenerative changes were found. The endocardium was slightly thickened (mean thickness at the level of the left ventricular outflow tract: 20–50 μ , and of the right ventricular outflow

FIG. 2a) Electrocardiogram of Case 1 shows first degree atrioventricular block, extreme left axis deviation, and an rS pattern in the chest leads across to V6. b) Electrocardiogram of Case 2: left axis deviation and chest lead pattern similar to that of Case 1.

FIG. 3 Case 1: muscular atrophy of the shoulder girdle and winged scapulae.

tract: 10–30 μ). The pericardium presented a completely normal aspect. No microscopical examination of the conducting system was made.

Case 2

The second brother was born in 1959. He also had difficulty in sucking and started walking at the age of 4 years. Mild congenital valvular aortic stenosis was suspected at the age of 6 years, but the left ventricular ejection time measured on a carotid pulse recording, the electrocardiogram, the chest x-ray film, and right heart catheterization were normal.

At the age of 14 years, after the death of his older brother, he was admitted to our hospital. He presented the same general pattern of muscle wasting and weakness as his older brother, but somewhat less pronounced.

Neurological examination revealed a myopathic gait. Achieving the standing position was impossible without the aid of arms and hands. There was also a striking lumbar lordosis and dorsal kyphoscoliosis. The tendon reflexes were weak or absent. Cutaneous and deep sensitivity were normal as were the cerebellar tests. Speech was difficult for the letters G, K, B, and R. Intelligence was normal.

The serum creatine phosphokinase was 420 units (upper limit of normal: 55 units). Serum transaminases and aldolase were normal. The karyotype was normal. No autoimmune antibodies were found. Physical examination of the heart showed slight cardiac enlargement and the signs of mild valvular aortic stenosis.

The heart was moderately enlarged on a chest x-ray film. The left ventricular ejection time was now 110 per cent. The electrocardiogram (Fig. 2b) was completely altered: extreme left axis deviation of -50° was present without any evidence of left ventricular hypertrophy. The vectocardiogram showed the pattern of a left anterior hemiblock. Electromyography showed a typical myopathic pattern. An x-ray survey of the skeleton showed an absent anterior arch of the atlas bone. The electroencephalogram was slightly disturbed by a diffuse slow arrhythmia.

A biopsy of the anterior tibial muscle was performed. On microscopical examination the diameter of the muscle fibres varied from 10 to 60 μ . The smaller basophilic fibres were not grouped but dispersed, and isolated basophilic fibres with vesicular nuclei were seldom found. In some fibres the number of myofibrils was reduced and the sarcoplasm presented focally or diffusely granular or hyaline alterations. The most prominent feature was the internal location of nuclei in 66 per cent of 400 fibres examined on transverse sections. This percentage varied from 61 to 71 when the fibres were examined in groups of 50. Some fibres also contained long nuclear chains and thickened nuclear clumps. In some areas a slight endomysial fibrosis and rare fat cells were found. Histochemically, type I fibres were predominant in number but generally smaller than type II fibres. Internal nuclei were present in both type I and II fibres.

The patient has been seen every 6 months at the outpatient department. No special treatment, except for a sodium-free diet, has been instituted. Until now he has been doing well and no progression of his muscular or cardiac abnormalities has occurred.

Discussion

With rare exceptions (Vital *et al.*, 1970), centronuclear myopathy is clinically characterized by slow and progressive wasting and weakness of the skeletal muscles beginning at birth. Ptosis of the eyelids is present in the majority of the reported cases. Hypo- and areflexia are constant findings. The only biochemical abnormality reported in some patients is a rise in the level of serum creatine phosphokinase. Electromyography is usually normal or reveals atypical abnormalities, which do not permit a distinction between pathological processes of the peripheral nerves or muscle fibres; on the other hand it can show a myopathic pattern as in our Case 2. The electroencephalogram is usually disturbed and seizures were reported in two cases (Coleman *et al.*, 1968; Sher *et al.*, 1967). The central or internal location of nuclei in a high percentage of the fibres is the dominant histological abnormality. A pronounced variation of the diameter of the muscle fibres is often found. Necrosis is almost absent; sometimes discrete fibrosis and fat infiltration are observed as in our

FIG. 4 Muscle biopsy of Case 1 (right anterior tibial muscle). a) Variation in fibre diameter and centralization of the nuclei in most fibres. (Cryostat section: H and E. $\times 330$.) b) Type II fibres (darkly stained) are less numerous and atrophied. (Cryostat section, myofibrillar ATPase pH 9.4. $\times 330$.)

second case. Campbell, Rebeiz, and Walton (1969) described perinuclear myofibrillar degeneration, but this was not found by other authors.

The clinical and histological findings of our two patients correspond to the published descriptions of centronuclear myopathy. However, in most patients, histochemical studies show a normal

distribution of type I and II fibres. Atrophy of type I fibres was clearly found in 6 cases (Badurska *et al.*, 1969; Bethlem *et al.*, 1969, 1970; Engel, Gold, and Karpatis, 1968; Karpatis, Carpenter, and Nelson, 1970). In our 2 cases we found an obvious numeral predominance of type I fibres. The atrophy was usually of type II fibres in the first

case, and type I fibres in the second case. A special feature in our patients was the absence of the anterior arch of the atlas vertebra, which has not been described until now.

The familial occurrence of the disease was noted by several authors. Though different modes of inheritance have been proposed, insufficient data are available for definite conclusions to be drawn.

The clinical, radiological, electrocardiographic, and necropsy findings in the first patient clearly indicate the presence of 'cardiomyopathy', with diffuse cardiac dilatation, extensive fibrosis, and compensatory focal hypertrophy of the myocardium. In the second patient slight congenital aortic stenosis was present. This diagnosis was based on the clinical findings and the character of the carotid pulse recording. Nevertheless, it is reasonable to suspect that this patient also presented some degree of 'cardiomyopathy'. Indeed, the cardiac enlargement at the age of 14 was out of proportion to the degree of the aortic stenosis. Further, extreme left axis deviation without other signs of left ventricular hypertrophy was the main electrocardiographic abnormality in both brothers. This electrocardiographic pattern suggests intraventricular conduction disturbance of the left anterior hemiblock type.

Although the association of peripheral muscle disease such as progressive muscular dystrophy and

'cardiomyopathy' is well known, until now this association has received only slight attention in centronuclear myopathy.

Bethlem *et al.* (1969) described a 16-year-old girl with centronuclear myopathy and heart failure, attributed to a 'cardiomyopathy' of unknown origin. No further data were given. In 2 other patients, right ventricular hypertrophy was mentioned (Bradley, Price, and Watanabe, 1970; Brooke and Williamson, 1969). Though not discussed by the authors, this could have been secondary to ventilatory dysfunction caused by chronic respiratory muscle weakness and not to 'cardiomyopathy'. In a study on skeletal muscle in idiopathic cardiomyopathy, Shafiq *et al.* (1972) described one case (No. 11) with type I fibres which were hypotrophic but more numerous than normal (type I fibre predominance). Though not mentioned in the description by these authors, numerous internal nuclei are visible in the illustrated figure of this case, which possibly could be considered as a 'cardiomyopathy' associated with a centronuclear myopathy.

The present two cases and the cases of Bethlem *et al.* (1969) and Shafiq *et al.* (1972) clearly indicate that centronuclear myopathy may be associated with 'cardiomyopathy', which can cause death at an early age. This implies that centronuclear myopathy cannot always be considered as a benign disease.

FIG. 5 Case 1: Extensive fibrosis and focal hypertrophic fibres are present in the myocardium (fixation about 10 hours after death, Masson trichrome. $\times 50$).

Cardiological examination to look for the possible presence of cardiac involvement seems mandatory in all cases of centronuclear myopathy.

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References

- Badurska, B., Fidzianska, A., Kamieniecka, Z., Prot, J., and Strugalska, H. (1969). Myotubular myopathy. *Journal of the Neurological Sciences*, **8**, 563.
- Bethlem, J., Van Wijngaarden, G. K., Meijer, A. E. F. H., and Hülsmann, W. C. (1969). Neuromuscular disease with type I fiber atrophy, central nuclei, and myotube-like structures. *Neurology (Minneapolis)*, **19**, 705.
- Bethlem, J., Van Wijngaarden, G. K., Mumenthaler, M., and Meijer, A. E. F. H. (1970). Centronuclear myopathy with type I fiber atrophy and 'myotubes'. *Archives of Neurology*, **23**, 70.
- Bradley, W. G., Price, D. L., and Watanabe, C. K. (1970). Familial centronuclear myopathy. *Journal of Neurology, Neurosurgery and Psychiatry*, **33**, 687.
- Brooke, M. H., and Williamson, T. (1969). An adult case of type I muscle fiber hypotrophy: an abnormality of mono-synaptic reflex function. *Neurology (Minneapolis)*, **19**, 280.
- Campbell, M. J., Rebeiz, J. J., and Walton, J. N. (1969). Myotubular, centronuclear or peri-centronuclear myopathy? *Journal of the Neurological Sciences*, **8**, 425.
- Coleman, R. F., Thompson, L. R., Niehuis, A. W., Munsat, T. L., and Pearson, C. M. (1968). Histochemical investigation of 'myotubular' myopathy. *Archives of Pathology*, **86**, 365.
- Engel, W. K., Gold, G. N., and Karpati, G. (1968). Type I fiber hypotrophy and central nuclei. A rare congenital muscle abnormality with a possible experimental model. *Archives of Neurology*, **18**, 435.
- Karpati, G., Carpenter, S., and Nelson, R. F. (1970). Type I muscle atrophy and central nuclei. A rare familial neuromuscular disease. *Journal of the Neurological Sciences*, **10**, 489.
- Shafiq, S. A., Sande, M. A., Carruthers, R. R., Killip, T., and Milhorat, A. T. (1972). Skeletal muscle in idiopathic cardiomyopathy. *Journal of the Neurological Sciences*, **15**, 303.
- Sher, J. H., Rimalovski, A. B., Athanassiades, T. J., and Aronson, S. M. (1967). Familial centronuclear myopathy: a clinical and pathological study. *Neurology (Minneapolis)*, **17**, 727.
- Spiro, A. J., Shy, G. M., and Gonatas, N. K. (1966). Myotubular myopathy. *Archives of Neurology*, **14**, 1.
- Vital, C., Vallat, J. M., Martin, F., Le Blanc, M., and Bergouignan, M. (1970). Étude clinique et ultrastructurale d'un cas de myopathie centronucléaire (myotubular myopathy) de l'adulte. *Revue Neurologique*, **123**, 117.

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