Centronuclear myopathy and cardiomyopathy requiring heart transplant

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Abstract

Centronuclear myopathy has been extremely rarely associated with cardiomyopathy, which can lead to heart failure and premature death. We report the case of a 3.5-year-old girl with early-onset dilated cardiomyopathy, biventricular hypertrophy and histologic features suggestive of centronuclear myopathy. After unsuccessful medical treatment for heart failure, she underwent cardiac transplantation at the age of 4.5 years. Results of a skeletal muscle biopsy showed increased central nuclei and perinuclear vacuolations with aggregates of mitochondria. Examination of the heart at the time of transplantation confirmed a diagnosis of dilated cardiomyopathy. Histologic results revealed hypertrophic myocardiocytes, focal areas of infarction and endocardial fibroelastosis, most prominently in the left ventricle. Although cardiomyopathy is commonly associated with other childhood myopathies, to our knowledge, this is the youngest patient reported with centronuclear myopathy presenting with heart failure caused by cardiomyopathy, and the first patient to successfully undergo cardiac transplantation. One year after the heart transplant, there were no signs of rejection. We recommend detailed cardiac assessment with regular follow-up for children with histologic features consistent with centronuclear myopathy.

Keywords: Centronuclear myopathy; Myotubular myopathy; Congenital myopathy; Cardiomyopathy; Cardiac transplantation; Central nuclei

1. Introduction

Centronuclear myopathy (CNM) is a congenital myopathy, first described by Spiro et al. [1] in 1966. It is clinically characterized by generalized hypotonia, ptosis, ophthalmoplegia, and facial and limb weakness [2]. CNM has great clinical variability, ranging from a severe, fatal disorder (the neonatal X-linked form) to mild weakness with normal life expectancy (the autosomal recessive form). Classification is based on the age of onset, mode of inheritance, severity of involvement and rapidity of progress [3]. Three major patterns of inheritance have been described: the X-linked recessive form, called by some authors myotubular myopathy is linked to the Xq28 gene; the autosomal recessive form with childhood onset; and the autosomal dominant form, which has a milder course with adult onset [3–6].

Diagnosis of the disease is based on clinical suspicion and the results of appropriate muscle histopathological and electron microscopic studies, and exclusion of other causes of centrally nucleated muscle fibers [3,5]. CNM is suspected if the percentage of central nuclei in the muscle biopsy samples is increased (normal range ≤3%). This suspicion is supported by clinical evidence of facial and limb weakness and exclusion of other causes of muscular disorders associated with central nuclei [6].

The pathological features of CNM are an increased number of centrally nucleated muscle fibers, variation in the diameter of the muscle fibers, type I fiber predominance or atrophy, and a central area of the muscle cell devoid of activity on reaction with adenosinetriphosphatase (ATPase) [6,7].

We report a case of CNM in a young girl with a rare presentation of severe dilated cardiomyopathy that necessitated heart transplantation. To the best of our knowledge, this is the first reported patient with CNM to successfully undergo heart transplantation.

2. Case report

A 3.5-year-old girl, who presented with early-onset dilated cardiomyopathy, biventricular hypertrophy and CNM, was born at term; her birth weight was 3.4 kg. The pregnancy was uncomplicated; fetal movements were perceived to be normal; the postnatal period was uneventful; and her developmental history was normal.
At age 30 months, the patient presented with fever, cough, shortness of breath and lethargy. Subsequently, she developed acute congestive heart failure. After being diagnosed with dilated cardiomyopathy, she was treated with diuretics, digoxin, and captopril. While hospitalized, she had weakness of the neck and paraspinal muscles, with poor head control, and proximal limb weakness.

The patient had no history of cramps, stiffness, or exercise intolerance. She was the first born in the family, who had no family history of neuromuscular or cardiac disease and no consanguinity. The patient later had recurrent episodes of congestive heart failure that required admission to the intensive care unit and treatment with anti-heart-failure medications.

Physical examination of the patient at age 3.5 years, during her second admission for congestive heart failure, showed moderate hypotonia and diffuse muscle wasting, particularly in the neck and limb muscles. The muscle power in the neck flexors was 4, in the proximal muscles of the legs 3+, out of a possible 5 (measured on the Medical Research Council Scale from 0 to 5) [8]. Deep tendon reflexes were diminished. She had a positive Gower's sign, a waddling gait and no contractures. Her voice was weak and hoarse. She had no facial or extraocular muscle weakness. The results of a sensory examination were normal.

Cardiac examination revealed a heart rate of 150 beats per minute. Systolic blood pressure was 84 mmHg. The brachial pulse was reduced in volume. She had diffuse biventricular heave, normal heart sounds, and grade 2/6 apical heart pansystolic murmurs. A chest X-ray showed moderate cardiomegaly. Her electrocardiogram showed a sinus rhythm and combined atrial and ventricular hypertrophy. Results of echocardiography showed progressively poor ventricular function and elevated mean pulmonary artery pressure; the left ventricular ejection fraction was 6%.

The patient's liver was 3 cm below the right costal margin. Her height was at the 50th percentile; her weight, at the 3rd percentile.

Results of laboratory tests showed serum creatine phosphokinase levels of 42 U/l (normal 60–305 U/l); results of her urine and serum amino acid screens were normal. Her erythrocyte sedimentation rate was 32 mm/h (normal 1–10 mm/h). Serum electrolyte and liver enzyme levels were normal, as were her levels of serum complements C3 and C4, and antinuclear antigen. The results of DNA analysis for dystrophin, α, β, γ and δ sarcoglycans were all normal. Electron microscopy revealed many fibers with central nuclei surrounded by aggregates of mitochondria and glycogen. CNM was diagnosed on the basis of all these findings.

The patient suffered progressive cardiac decompensation from age 3.5 to 4.5 years, which resulted in orthotopic cardiac transplantation. Pathologic studies of her native heart (Fig. 2) showed dilated cardiomyopathy with a markedly dilated right ventricle. The left ventricle had diffuse endocardial fibroelastosis. The anatomy of the valves was normal. Microscopic examination showed hypertrophic myocardocytes in both ventricles, subendocardial myocytolysis and vacuolar degeneration (Fig. 3). No evidence of myocarditis or storage disorders was found.

The patient's postoperative course was complicated by neurologic sequelae, including seizures and acute cardiopulmonary arrest. One year after the transplant, her neurologic and cardiac status had both improved. Her gait is more stable. She can run and she no longer exhibits Gower's sign. Her mental function and speech are appropriate for her age.

3. Discussion

Although cardiomyopathy is commonly associated with other childhood myopathies, our patient is the youngest reported with CNM presenting with heart failure caused

![Fig. 1. A light microscopic image of the muscle shows muscle fibers with abnormally increased central nuclei (50%) surrounded by aggregates of mitochondria and glycogen. Also evident is myofiber atrophy without grouping and variation in fiber size (hematoxylin-eosin staining, ×250).](image-url)
by cardiomyopathy. CNM is rarely associated with cardiomyopathy: only three reports [2,7,9] have indicated this association. Almost all reported patients with CNM and cardiac manifestations die because of congestive heart failure. Our patient was the first patient with CNM and congestive heart failure to successfully undergo cardiac transplantation.

3.1. Cardiac involvement

The few reported cases of CNM-associated cardiomyopathy [2,7,9] and their clinical findings and outcome are summarized in Table 1. The disease has great clinical variability. The onset of illness in all patients was early in infancy or childhood. Four patients had cardiac symptoms at 14–15 years of age, but our patient presented with cardiac symptoms at a younger age; she had a rapidly progressive cardiomyopathy at 3.5 years of age that required heart transplantation. From the other four patients, two died because of severe cardiomyopathy that developed over a period of 12 months; the other two had slowly progressive symptoms.

Fig. 2. A pathological picture of the heart muscle tissue shows that the right ventricle is markedly dilated with accentuated trabecula. The left ventricle has diffuse marked endocardial fibroelastosis. The right atrioventricular valve is a tricuspid valve. The aortic valve is normal.
Early reports of CNM documented variable presentations of progressive muscle disease, but cardiac symptoms were only rarely described. The first case of CNM [1] was reported in an adolescent male with external ophthalmoplegia, facial diplegia, areflexia and progressive muscle weakness. Bethlem et al. [2] described cardiomyopathy in a 16-year-old girl with CNM; she presented with hypotonia, developmental delay, muscle atrophy and weakness of the extremities. At the age of 14 years, she had developed congestive heart failure. Gospe et al. [9] described the case of a 15.5-year-old adolescent boy with wasting of limb muscles, difficulty running and acute congestive heart failure. Results of his muscle biopsy showed an increased number of central nuclei. The patient developed rapidly progressive congestive heart failure with ventricular tachycardia and died 24 months after his initial evaluation. Verhiest et al. [7] reported two male siblings with developmental delay. One developed congestive heart failure at age 15 years and died 1 year later; the other had mild valvular aortic stenosis and asymptomatic cardiomegaly at age 14 years.

3.2. Histologic features

In our patient, the results of a muscle biopsy revealed increased central nuclei (50%) in muscle fibers. The results of muscle biopsies from patients with CNM may be variable, but there is no relation between the severity of the disease and the percentage of central nuclei in muscle fibers.

Table 1
Summary of patients with CNM and cardiomyopathy

<table>
<thead>
<tr>
<th>Case report</th>
<th>Time of onset of weakness</th>
<th>Percentage of central nuclei</th>
<th>Age (years) at onset of cardiac symptoms</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verhiest et al. [7] 1st patient</td>
<td>Early infancy</td>
<td>74</td>
<td>15.0</td>
<td>Death at 16 years</td>
</tr>
<tr>
<td>Verhiest et al. [7] 2nd patient</td>
<td>Early infancy</td>
<td>66</td>
<td>14.0</td>
<td>Slowly progressive</td>
</tr>
<tr>
<td>Gospe et al. [9]</td>
<td>Early childhood</td>
<td>90</td>
<td>15.5</td>
<td>Death at 17.5 years</td>
</tr>
<tr>
<td>Bethlem et al. [2]</td>
<td>Early infancy</td>
<td>70</td>
<td>14.0</td>
<td>Slowly progressive</td>
</tr>
<tr>
<td>Our case</td>
<td>Early childhood</td>
<td>50</td>
<td>3.5</td>
<td>Rapidly progressive; heart transplant</td>
</tr>
</tbody>
</table>

Two siblings with CNM [7] had increased central nuclei in the muscle fibers (74 and 71%), but different levels of severity of CNM. The presence of central nuclei in skeletal muscle fibers may not be pathognomonic of any muscle disease; instead, they may signify a primary abnormality of the muscle fiber.

3.3. Diagnosis

A good approach for patients with clinical features of muscle disease and evidence of increased central nuclei on their muscle biopsies is to exclude other causes of the centrally located nuclei. Central nuclei are found in the results of the muscle biopsies of patients with inflammatory myopathies, myotonic dystrophy and Charcot-Marie-Tooth disease, and in small amounts in the regenerating fiber of normal muscles [9].

In our patient, a diagnosis of myotonic dystrophy was unlikely because the results of the DNA test were normal; moreover, there is no family history of muscle diseases. Other causes of central nuclei in the skeletal muscles of our patient were less likely because the results of the muscle biopsy showed no evidence of inflammatory myopathy or neurogenic atrophy.

3.4. Pathogenesis

It has been postulated that CNM involves a maturational arrest of muscle in the myotubular stage of development; however, the myofibers of patients with CNM are actually mature in their histochemical differentiation and ultrastructure, except for the persistence of a centronuclear architecture [6,9]. If CNM were secondary to maturational arrest, the condition should be static, but for many patients the course of the disease is progressive. Consequently, if the muscle fibers with central nuclei are much larger than fetal myotubes and the number of central nuclei on a repeat muscle biopsy decreases, the disease process is thought to be degenerative [5,6].

3.5. Prognosis and severity

CNM is a clinically variable disorder, the severity of which correlates with age of onset, the rapidity of progression and the mode of inheritance. The most severe form, the X-linked recessive type, is characterized by the perinatal onset of severe generalized muscle hypotonia and its usually...
fatal course [4,5]. Poor outcome for patients with CNM has been reported [3,7]; the prognosis for CNM, however, depends on the mode of inheritance (X-linked) and the severity of cardiac or respiratory involvement.

3.6. Conclusion

Our patient is the first report of a young girl with skeletal muscle involvement and early-onset severe cardiomyopathy that would have been fatal without cardiac transplantation. Our case and the other reported cases [2,7,9] clearly indicate that CNM may be associated with cardiomyopathy at any age. We recommend that patients with CNM have a full cardiovascular assessment for possible cardiac involvement.

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References