Nemaline Myopathy With Dilated Cardiomyopathy in Childhood

abstract

We present a case of a 9-year-old boy with nemaline myopathy and dilated cardiomyopathy. The combination of nemaline myopathy and cardiomyopathy is rare, and this is the first reported case of dilated cardiomyopathy associated with childhood-onset nemaline myopathy. A novel mutation, p.W358C, in ACTA1 was detected in this patient. An unusual feature of this case was that the patient’s cardiac failure developed during early childhood with no delay of gross motor milestones. The use of a β-blocker did not improve his clinical course, and the patient died 6 months after diagnosis of dilated cardiomyopathy. Congenital nonprogressive nemaline myopathy is not necessarily a benign disorder: deterioration can occur early in the course of dilated cardiomyopathy with neuromuscular disease, and careful clinical evaluation is therefore necessary. Pediatrics 2013;131:e1–e5
Nemaline myopathy is a nonprogressive congenital skeletal muscle disorder defined by the presence of inclusions known as nemaline rods (Greek nema = thread) in muscle fibers. The combination of nemaline myopathy and cardiomyopathy is rare. The course of nemaline myopathy is often static or only very slowly progressive, and most patients with this disorder are able to lead an active life. A fatal course is usually due to respiratory failure and is rarely due to cardiac failure. In most cases, cardiomyopathy develops in adulthood; cardiomyopathy of childhood is rare.

The following case report describes a school-aged child who had dilated cardiomyopathy (DCM) associated with childhood-onset nemaline myopathy. This patient had DCM with minimal muscle involvement and no delay of gross motor milestones. Use of a β-blocker did not improve his clinical course. The disease was severe, and the patient died 6 months after the diagnosis of DCM. To our knowledge, this is the first report of DCM associated with childhood-onset nemaline myopathy.

**CASE PRESENTATION**

The patient was born by cesarean delivery at 37 weeks’ gestation. His birth weight was 3110 g. He was the second child of healthy, unrelated parents. There was no family history of neuromuscular disorders. He required oxygen inhalation due to mild respiratory distress at birth. He also required infusion of aminophylline hydrate due to apnea. The patient’s motor development was within normal limits (holds head steady at 4 months, rolls over at 5 months, stands up at 10 months) until he began walking at 13 months. Starting at 3 years of age, he would often fall over when running. At 4 years of age, his parents noticed that he ran slower than his friends. He could not open a bottle because he could not pinch with his thumb and index finger. His myopathy was mild, as his symptoms were not apparently progressive, and he could breathe, eat, and walk normally. He was learning karate and swimming before admission. A routine electrocardiography 2 years earlier was normal, and a chest radiograph 1.5 years earlier was also normal.

At 9 years of age, the patient was admitted to the hospital for acute deterioration of cardiac function. Two months before admission, he had an influenza virus infection, and at that time he was noted to have tachypnea at night and tachycardia. On admission, a chest radiograph demonstrated cardiomegaly (cardiothoracic ratio, 63%). Echocardiography confirmed the diagnosis of DCM with a left ventricular internal dimension at end diastole of 71.2 mm, moderate mitral regurgitation, and an ejection fraction of 18%.

Electrocardiography showed a sinus rhythm with negative T in V4, V5, and V6. Cardiac catheterization and myocardial biopsy were not performed. Serum creatine kinase, aldolase, and troponin T were normal. B-type natriuretic peptide was elevated at 1161 pg/mL. The patient was treated with milrinone, diuretics, angiotensin-converting enzyme inhibitors, and β-blockers.

The patient had reduced facial mimicry (myopathic facies) and a high arched palate but no reduction in muscle bulk. Motor examination revealed hypotonia, mild weakness of proximal and distal muscle strength, and atrophy of thenar muscles. Muscle biopsy of the left triceps brachii showed mild variation of muscle fiber size, with multiple cytoplasmic nemaline rods in some fibers visible with Gomori trichrome staining (Fig 1). Oxidative enzyme staining did not show any myofibrillar abnormalities or cores. A diagnosis of nemaline myopathy was made. Direct DNA sequence analyses showed a heterozygous mutation of c.1074G>T (p.W358C) in exon 7 of the α-actin gene (ACTA1), which has not been reported and was not found in a study of 50 normal Japanese controls.

Despite maximal conventional therapy, the patient’s condition continued to deteriorate, and he was referred for treatment with experimental inotropic agents. Heart transplantation was contraindicated because of ventricular failure, elevation of bilirubin, and a prolonged prothrombin time. He died of severe heart failure 6 months after diagnosis.

An autopsy was performed, and the diaphragm and heart were examined. In the diaphragm, a few nemaline rods were found in muscle fibers. Using electron microscopy, a few definite nemaline rods could be detected (Fig 2).
The explanted heart was large and flaccid with a widely dilated left ventricle. By light microscopy, the myocardial fibers were varied in size and showed atrophy to hypertrophy. Active myocarditis was ruled out because neither inflammation nor myocardial necrosis was observed. Using electron microscopy, a few electron-dense fine structures related to Z lines and polymorphic materials (suspicious of nemaline bodies) were observed in the myocardium and skeletal muscle (Fig 3). These findings were consistent with nemaline myopathy and associated DCM.

**DISCUSSION**

Nemaline myopathy is a congenital nonprogressive skeletal muscle disorder defined by the presence of inclusions known as nemaline rods in muscle fibers. Most patients with nemaline myopathy have clinical characteristics of generalized muscle weakness and hypotonia involving facial muscles. The existing classification defines 6 forms that include severe congenital (neonatal), Amish, intermediate congenital, typical congenital, childhood-onset, and adulthood-onset forms. These forms are classified according to onset and severity of motor and respiratory involvement. Patients with the severe congenital form usually die in early infancy of respiratory failure or of an infection due to involvement of the diaphragm and intercostal muscles. Conversely, the course of the typical congenital form is often static or only very slowly progressive, and most patients can lead an active life.

The combination of nemaline myopathy and cardiomyopathy is rare. In Table 1, a review of 16 other patients with nemaline cardiomyopathy is presented. Six patients developed cardiac involvement in infancy and childhood. Ten patients developed cardiac failure in adulthood. Five of the 6 pediatric patients had hypertrophic cardiomyopathy (HCM), and only 1 pediatric patient had DCM. Conversely, 7 of the 10 adult patients had DCM. In children, the combination of nemaline myopathy and DCM is extremely rare. The current case is the first report of DCM associated with childhood-onset nemaline myopathy. Specifically, patients with the “childhood-onset” form of nemaline myopathy have normal infantile and early development and then develop weakness of ankle dorsiflexion and foot drop in the late first decade or early second decade of life.1 Our patient had a somewhat atypical presentation of the childhood-onset form of nemaline myopathy, as he started to fall over at 3 years of age; therefore, he could possibly be classified as having the typical mild congenital form of the disorder. This patient represents

**FIGURE 3**

Electron microscopy of the cardiac muscle. A few electron-dense fine structures related to Z lines and polymorphic materials are observed in the myocardium, as in the diaphragm. Although a large amount of mitochondria occupy the sarcoplasm, mitochondrial abnormalities are not found.

**TABLE 1 Previous Case Reports on Nemaline Myopathy with Cardiomyopathy**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Investigator</th>
<th>Age (y)</th>
<th>Gender</th>
<th>Myopathy</th>
<th>Cardiomyopathy</th>
<th>Rods in Cardiac Muscle</th>
<th>Classification of NM</th>
<th>Outcome</th>
<th>Gene Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mir et al‡2</td>
<td>0</td>
<td>Male</td>
<td>+</td>
<td>HCM</td>
<td>Not ex.</td>
<td>Typical</td>
<td>Survived</td>
<td>Not ex.</td>
</tr>
<tr>
<td>2</td>
<td>Nakajima et al∥3</td>
<td>1</td>
<td>Male</td>
<td>+</td>
<td>HCM</td>
<td>Not ex.</td>
<td>Severe</td>
<td>Survived</td>
<td>Not ex.</td>
</tr>
<tr>
<td>3</td>
<td>D’Amico et al∥4</td>
<td>2</td>
<td>Male</td>
<td>+</td>
<td>HCM</td>
<td>Not ex.</td>
<td>Typical</td>
<td>Died</td>
<td>ACTA-1 K336E</td>
</tr>
<tr>
<td>4</td>
<td>Ishibashi-Ueda et al∥5</td>
<td>5</td>
<td>Male</td>
<td>+</td>
<td>DCM</td>
<td>+</td>
<td>Typical</td>
<td>Died</td>
<td>Not ex.</td>
</tr>
<tr>
<td>6</td>
<td>Van Antwerpen et al∥7</td>
<td>5</td>
<td>Male</td>
<td>+</td>
<td>HCM</td>
<td>Not ex.</td>
<td>Typical</td>
<td>Survived</td>
<td>Not ex.</td>
</tr>
<tr>
<td>*</td>
<td>Our case</td>
<td>9</td>
<td>Male</td>
<td>+</td>
<td>DCM</td>
<td>+</td>
<td>Childhood</td>
<td>Died</td>
<td>ACTA-1 W358C</td>
</tr>
<tr>
<td>7</td>
<td>Kim et al∥8</td>
<td>20</td>
<td>Male</td>
<td>+</td>
<td>HCM</td>
<td>Not ex.</td>
<td>Typical</td>
<td>Survived</td>
<td>ACTA-1 E239K</td>
</tr>
<tr>
<td>8</td>
<td>Rosenson et al∥9</td>
<td>22</td>
<td>Male</td>
<td>+/-</td>
<td>DCM</td>
<td>Not ex.</td>
<td>Typical</td>
<td>Died</td>
<td>Not ex.</td>
</tr>
<tr>
<td>9</td>
<td>Müller-Höcker et al∥10</td>
<td>26</td>
<td>Male</td>
<td>+</td>
<td>DCM</td>
<td>+</td>
<td>Adult</td>
<td>Survived</td>
<td>ACTA-1 (transplanted)</td>
</tr>
<tr>
<td>10</td>
<td>Meier et al∥11</td>
<td>29</td>
<td>Sisters</td>
<td>-</td>
<td>DCM</td>
<td>+</td>
<td>Adult</td>
<td>Died</td>
<td>Not ex.</td>
</tr>
<tr>
<td>11</td>
<td>Meier et al∥11</td>
<td>37</td>
<td>Sisters</td>
<td>-</td>
<td>Sudden death</td>
<td>+</td>
<td>Adult</td>
<td>Died</td>
<td>Not ex.</td>
</tr>
<tr>
<td>12</td>
<td>Stoessl et al∥12</td>
<td>46</td>
<td>Female</td>
<td>+</td>
<td>DCM</td>
<td>-</td>
<td>Adult</td>
<td>Died</td>
<td>Not ex.</td>
</tr>
<tr>
<td>13</td>
<td>Nagata et al∥13</td>
<td>47</td>
<td>Male</td>
<td>+</td>
<td>DCM</td>
<td>+</td>
<td>Adult</td>
<td>Survived</td>
<td>Not ex.</td>
</tr>
<tr>
<td>14</td>
<td>Simpson et al∥14</td>
<td>50</td>
<td>Male</td>
<td>+/-</td>
<td>Cardiac failure</td>
<td>-</td>
<td>Adult</td>
<td>Died</td>
<td>Not ex.</td>
</tr>
<tr>
<td>15</td>
<td>Jones and Factor∥15</td>
<td>53</td>
<td>Brothers</td>
<td>-</td>
<td>DCM</td>
<td>+</td>
<td>Adult</td>
<td>Died</td>
<td>Not ex.</td>
</tr>
<tr>
<td>16</td>
<td>Jones and Factor∥15</td>
<td>69</td>
<td>Brothers</td>
<td>-</td>
<td>DCM</td>
<td>+</td>
<td>Adult</td>
<td>Died</td>
<td>Not ex.</td>
</tr>
</tbody>
</table>

NM, nemaline myopathy. +, existed; -, not existed; +/-, unknown; Not ex, not examined.
the second case of DCM associated with
nemaline myopathy presenting during
childhood. The only other reported case
of DCM presented in a child with the
typical congenital form of nemaline
myopathy. That patient had generalized
muscular hypotonia and weakness, and
died at age 3 years, 10 months.5 In
children, most reported cases of
nemaline cardiomyopathy have severe
skeletal muscle symptoms. The afore-
mentioned child remained dependent
on intermittent positive pressure ven-
tilation.3 He was unable to sit un-
assisted and demonstrated poor head
control until 4 years of age.6 The child
did not walk until 3 years of age, and he
was unable to rise from a sitting posi-
tion.7 The boy was able to sit un-
supported at 2.5 years of age.4 In
contrast, an unusual feature of the
current patient was that cardiac failure
developed during early childhood with
no delay of gross motor milestones.
Electron microscopy studies of car-
diac muscle were performed in 7
cases,5,10,11,13–15 but the typical rod-like
structures were found in 4 cases.5,10,11,13
The results of the current case illus-
strate that rod-like structures may be
rare in the heart compared with skele-
tal muscle. At the ultrastructural
level, abnormal cardiomyocytes showed
an accumulation of rod-like electron-
dense material, similar to the skele-
tal muscle. It should be noted that
there is no correlation between the
number of nemaline rods and the
severity of cardiac failure in nema-
line cardiomyopathy.
Nemaline myopathy is a clinically and
genetically heterogeneous disorder.

Mutations of 7 genes have been iden-
tified in nemaline myopathy: α-actin
(ACTA1), nebulin (NEB), α-tropomyosin
(TPM3), β-tropomyosin (TPM2), tropo-
nin T1 (TNN1), coflin 2 (CFL2), and
Kelch repeat and BTB domain-
containing protein 13 (KBTBD13).1 The
majority of individuals with nemaline
myopathy have no family history (de
novo dominant mutations). ACTA1
mutations have been reported as au-
tosomal dominant and autosomal re-
cessive inheritance. NEB mutations
have all been inherited in an autosom-
al recessive manner. Genotype–
phenotype correlations in nemaline
myopathy remain largely unclear be-
cause of the clinical overlap between
differing forms of the disease. NEB
mutations are more commonly asso-
ciated with typical congenital form,
whereas ACTA1 mutations are asso-
ciated with variable presentations
ranging from severe neonatal to
adulthood-onset form.1
In the current case, a novel mutation of
ACTA1 was found. To our knowledge,
this is the first case in which DCM was
associated with nemaline myopathy
and a heterozygous mutation of ACTA1,
although association of ACTA1 muta-
tions with nemaline myopathy and
HCM was previously reported in
a 2-year-old male and a 20-year-old
male.4,8 Among these patients, this
finding raises the hypothesis that
mutation possibly affects actin poly-
merization.4 However, the mechanism
by which DCM or HCM develops as
a result of ACTA1 mutations in each
case with nemaline myopathy is still
unknown. To date, there have been no
obvious functional or biochemical pat-
terns seen in ACTA1 mutations that
result in the common pathology for
cardiomyopathy.16 Further functional
analysis of ACTA1 with the mutation in
our case would clarify the underlying
genetic mechanism of nemaline my-
opathy with DCM.
The prognosis of patients with DCM and
nemaline myopathy is extremely poor.
Seven of 9 cases (including the 1 in this
report) of DCM with nemaline myop-
athy died. One patient underwent
heart transplantation and survived.10
The use of a β-blocker did not improve
the clinical course of the current pa-
tient, and he died 6 months after the
diagnosis of DCM. The deteriora-
tion can happen early in the course of
DCM with neuromuscular disease,
and careful clinical evaluation is
therefore necessary. Congenital non-
progressive nemaline myopathies are
not necessarily benign disorders be-
cause some patients show rapid pro-
gression that leads to death due to
aggressive involvement of cardiac
muscles.

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