Congenital Myopathies in Israeli Families

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The clinical features of 37 patients from 32 Israeli families with congenital myopathies evaluated between 1983 and 2004 are described: 13 children were diagnosed with congenital fiber type disproportion, 10 had myotubular myopathy, 7 had nemaline myopathy, 5 had central core disease, 1 had actin myopathy, and 1 had multi-minicore disease. There were 7 families (22%) that had parental consanguinity, and 4 families (12%) had more than 1 patient with congenital myopathy. Of the patients, 31 (84%) presented with clinical symptoms before 4 months of age, and 6 children (16%) presented after 1 year of age. Thirteen children (35%) had a severe phenotype with chronic ventilatory dependence or mortality before the age of 11 years. Facial weakness was associated with a severe phenotype. There was a high rate of a severe clinical phenotype in patients with myotubular myopathy (60%) and in patients with nemaline myopathy (57%), whereas in patients with congenital fiber type disproportion and in patients with central core disease, the proportion of a severe phenotype was lower (23% and 0%, respectively).

Keywords: congenital myopathies; Israel

C ongenital myopathies are a group of infantile or childhood onset muscle disorders characterized by a static nonprogressive course. They occur in a familial or in sporadic manner. The clinical presentation includes hypotonia, muscle weakness, and delayed motor milestones. Diagnosis is established according to the clinical presentation, muscle biopsy, and by identifying mutations in specific genes.1-3 There are over 40 different congenital myopathies. The most common are nemaline myopathy, myotubular myopathy, central core disease, and congenital fiber type disproportion. Other forms of congenital myopathies include multi-minicore disease and actin myopathy; these forms are less frequently encountered.1-3 In recent years, an etiologic classification of the congenital myopathies has emerged with at least 12 different genes identified to date.4 Significant variability exists in the clinical course in different cases within the same congenital myopathy and occasionally within the same family. Severity may range from severe hypotonia presenting immediately after birth, to childhood onset, mild muscle weakness or delayed motor milestones.1-3 The purpose of our study was to characterize the clinical features and course of patients with congenital myopathies in Israel.

Patients and Methods

The charts of 37 children diagnosed with congenital myopathies between 1983 and 2004 in 6 medical centers in Israel (Tel-Aviv Souraski Medical Center, Tel-Aviv; Hadassah Hebrew University Medical Center, Jerusalem; Alyn Pediatric Rehabilitation Hospital, Holon; Wolfson Medical Center, Holon; Rambam Medical Center, Haifa; Haemek Hospital, Afula) were reviewed. We contacted all University hospitals in Israel, and only those that follow congenital myopathy patients were included in the study. (Therefore, the above 6 medical centers follow the vast majority of congenital myopathy patients in Israel). The inclusion criteria were muscle weakness and hypotonia during infancy or childhood and muscle biopsies consistent with 1 of the congenital myopathies. The patients were classified as having either a severe or a nonsevere phenotype based on the requirement for ventilatory support. Subjects who were chronically dependent on mechanical ventilation or died of respiratory insufficiency during infancy or childhood were included in the severe phenotype group. Cases
who were ventilator independent were classified as having a nonsevere phenotype.\textsuperscript{5,6} Fischer's exact test was used for statistical analysis.

Results

The study cohort included 37 patients from 32 families (24 boys and 13 girls). There were 13 with congenital fiber type disproportion, 10 myotubular myopathy, 7 nemaline myopathy, 5 central core disease, 1 actin myopathy, and 1 multi-minicore disease. Table 1 summarizes their demographic and clinical data obtained from the medical records. There were 25 families of Jewish origin, 6 families were Moslem Arab, and 1 family was Druze Arab. In 7 families (22%), all of Arab origin, there was parental consanguinity. Four families (12%) had more than 1 child in the family with a congenital myopathy (9 children; 24%). In 31 patients (84%), the age of onset was before 4 months of age. The other 6 patients presented after 1 year of age. None presented between 4 months and 1 year of age. Seventeen patients (46%) had breathing difficulties. Facial weakness occurred in 23 children (62%), a high arched palate in 13 (35%), scoliosis in 12 (32%), and contractures in 8 (21%). Table 2 summarizes the major clinical features in the 4 most common subtypes of congenital myopathies in our study. Thirteen patients (35%) had a severe phenotype, with chronic ventilatory dependence or mortality due to respiratory insufficiency before 11 years of age. Nine children died during follow-up. Seven died before 1 year of age. Two died at the age of 11 years. Facial

### Table 1. Demographic and Clinical Data of Patients With Congenital Myopathies in Israel

<table>
<thead>
<tr>
<th>Age/Gender, Age at Presentation</th>
<th>Consanguinity/Family History</th>
<th>Ventilatory Support</th>
<th>Motor Development</th>
<th>Muscle Biopsy</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 3 y/M, neonate</td>
<td>--</td>
<td>Independent</td>
<td>Walks</td>
<td>CFTD</td>
<td>Nonsevere</td>
</tr>
<tr>
<td>2 1.5 y/F, neonate</td>
<td>--</td>
<td>Independent</td>
<td>Sits, does not stand</td>
<td>CFTD</td>
<td>Nonsevere</td>
</tr>
<tr>
<td>3 2.5 y/M, neonate</td>
<td>--</td>
<td>Independent</td>
<td>Does not roll or sit</td>
<td>CFTD</td>
<td>Nonsevere</td>
</tr>
<tr>
<td>4 6 mo/F, neonate</td>
<td>PC, 2 cousins died of RI</td>
<td>Independent</td>
<td>Does not sit or stand</td>
<td>CFTD</td>
<td>Nonsevere</td>
</tr>
<tr>
<td>5 6 mo/M, 2 mo (died at 6 mo)</td>
<td>PC</td>
<td>Independent</td>
<td>Does not roll or sit</td>
<td>CFTD</td>
<td>Nonsevere</td>
</tr>
<tr>
<td>6 1 y/M, neonate</td>
<td>PC</td>
<td>Independent</td>
<td>Does not roll or sit</td>
<td>CFTD</td>
<td>Nonsevere</td>
</tr>
<tr>
<td>7 1 y/F, neonate</td>
<td>--</td>
<td>Independent</td>
<td>Sits, does not stand</td>
<td>CFTD</td>
<td>Nonsevere</td>
</tr>
<tr>
<td>8 8 y/M, 2 mo</td>
<td>--</td>
<td>Independent</td>
<td>Walks</td>
<td>CFTD</td>
<td>Nonsevere</td>
</tr>
<tr>
<td>9 15 y/F, neonate</td>
<td>--</td>
<td>Independent</td>
<td>Walks</td>
<td>CFTD</td>
<td>Nonsevere</td>
</tr>
<tr>
<td>10 20 mo/M, 3 mo</td>
<td>PC, 1 sibling died of RI</td>
<td>Independent</td>
<td>Rolls, does not sit</td>
<td>CFTD</td>
<td>Nonsevere</td>
</tr>
<tr>
<td>11 3.5 y/M, 4 mo</td>
<td>--</td>
<td>Independent</td>
<td>Walks</td>
<td>CFTD</td>
<td>Nonsevere</td>
</tr>
<tr>
<td>12 11 y/F, 1 mo (died at 11 years)</td>
<td>Sister of Pt 13 and cousin of Pt 24</td>
<td>Dependent</td>
<td>Does not sit or stand</td>
<td>CFTD</td>
<td>Severe</td>
</tr>
<tr>
<td>13 2.5y/M, 2 mo</td>
<td>Brother of Pt 12 and cousin of Pt 24</td>
<td>Dependent</td>
<td>Does not sit or stand</td>
<td>CFTD</td>
<td>Severe</td>
</tr>
<tr>
<td>14 2 mo/M, neonate (died at 2 mo)</td>
<td>--</td>
<td>Dependent</td>
<td>Severe delay</td>
<td>MTM</td>
<td>Severe</td>
</tr>
<tr>
<td>15 5 y/M, neonate</td>
<td>--</td>
<td>Dependent</td>
<td>Does not roll or sit</td>
<td>MTM</td>
<td>Severe</td>
</tr>
<tr>
<td>16 1 mo/M, neonate (died at 1 mo)</td>
<td>--</td>
<td>Dependent</td>
<td>Severe delay</td>
<td>MTM</td>
<td>Severe</td>
</tr>
<tr>
<td>17 1 mo/M, neonate (died at 1 mo)</td>
<td>--</td>
<td>Dependent</td>
<td>Severe delay</td>
<td>MTM</td>
<td>Severe</td>
</tr>
<tr>
<td>18 1 mo/M, neonate (died at 1 mo)</td>
<td>--</td>
<td>Dependent</td>
<td>Severe delay</td>
<td>MTM</td>
<td>Severe</td>
</tr>
<tr>
<td>19 1 mo/M, neonate (died at 1 mo)</td>
<td>2 siblings of the mother died of RI</td>
<td>Dependent</td>
<td>Severe delay</td>
<td>MTM</td>
<td>Severe</td>
</tr>
<tr>
<td>20 10 y/M, 2 years</td>
<td>No family history</td>
<td>Independent</td>
<td>Walks</td>
<td>MTM</td>
<td>Nonsevere</td>
</tr>
<tr>
<td>21 13 y/F, 2 years</td>
<td>PC, sister of Pt 22</td>
<td>Independent</td>
<td>Walks</td>
<td>MTM</td>
<td>Nonsevere</td>
</tr>
<tr>
<td>22 14 y/F, 1.5 years</td>
<td>PC, the sister of Pt 21</td>
<td>Independent</td>
<td>Walks</td>
<td>MTM</td>
<td>Nonsevere</td>
</tr>
<tr>
<td>23 17 y/F, neonate</td>
<td>PC</td>
<td>Independent</td>
<td>Walks</td>
<td>MTM</td>
<td>Nonsevere</td>
</tr>
<tr>
<td>24 7 y/M, neonate</td>
<td>The cousin of Pts 12, 13</td>
<td>Dependent</td>
<td>Does not sit or stand</td>
<td>NM</td>
<td>Severe</td>
</tr>
<tr>
<td>25 3 y/F, 3 mo</td>
<td>--</td>
<td>Independent</td>
<td>Walks</td>
<td>NM</td>
<td>Nonsevere</td>
</tr>
<tr>
<td>26 15 y/M, neonate</td>
<td>--</td>
<td>Dependent</td>
<td>Does not sit or stand</td>
<td>NM</td>
<td>Severe</td>
</tr>
<tr>
<td>27 8 y/F, 2 mo</td>
<td>--</td>
<td>Independent</td>
<td>Walks</td>
<td>NM</td>
<td>Nonsevere</td>
</tr>
<tr>
<td>28 4 y/F, neonate</td>
<td>--</td>
<td>Independent</td>
<td>Walks</td>
<td>NM</td>
<td>Nonsevere</td>
</tr>
<tr>
<td>29 11 y/M, 3 mo (died at 11 years)</td>
<td>2 siblings died of RI</td>
<td>Dependent</td>
<td>Walks</td>
<td>NM</td>
<td>Severe</td>
</tr>
<tr>
<td>30 1 y/M, neonate (died at 1 year)</td>
<td>PC, 1 cousin died of RI</td>
<td>Dependent</td>
<td>Does not roll or sit</td>
<td>NM</td>
<td>Severe</td>
</tr>
<tr>
<td>31 9 y/M, 4 years</td>
<td>--</td>
<td>Independent</td>
<td>Walks</td>
<td>CCD</td>
<td>Nonsevere</td>
</tr>
<tr>
<td>32 10 y/M, 3 mo</td>
<td>--</td>
<td>Independent</td>
<td>Sits does not stand</td>
<td>CCD</td>
<td>Nonsevere</td>
</tr>
<tr>
<td>33 16 y/M, 1 year</td>
<td>Half sibling of Pts 34, 35</td>
<td>Independent</td>
<td>Walks</td>
<td>CCD</td>
<td>Nonsevere</td>
</tr>
<tr>
<td>34 2.5 y/F, 4 mo (twin)</td>
<td>--</td>
<td>Independent</td>
<td>Sits does not stand</td>
<td>CCD</td>
<td>Nonsevere</td>
</tr>
<tr>
<td>35 2.5 y/F, 4 mo (twin)</td>
<td>--</td>
<td>Independent</td>
<td>Sits does not stand</td>
<td>CCD</td>
<td>Nonsevere</td>
</tr>
<tr>
<td>36 10 y/M, neonate</td>
<td>--</td>
<td>Independent</td>
<td>Walks</td>
<td>AM</td>
<td>Nonsevere</td>
</tr>
<tr>
<td>37 7 y/M, 7 years</td>
<td>--</td>
<td>Independent</td>
<td>Walks</td>
<td>MmD</td>
<td>Nonsevere</td>
</tr>
</tbody>
</table>

Abbreviations: CFTD, congenital fiber type disproportion; MTM, myotubular myopathy; NM, nemaline myopathy; CCD, central core disease; MmD, multi-minicore disease; AM, actin myopathy; PC, parental consanguinity; Pt, patient; RI, respiratory insufficiency.
Table 2. Proportion of Typical Clinical Features Among the Common Congenital Myopathies in Israel

<table>
<thead>
<tr>
<th>Condition</th>
<th>CFTD (13 Cases)</th>
<th>MTM (10 Cases)</th>
<th>NM (7 Cases)</th>
<th>CCD (5 Cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breathing difficulties</td>
<td>5 (38%)</td>
<td>7 (70%)</td>
<td>5 (71%)</td>
<td>0</td>
</tr>
<tr>
<td>Facial muscles weakness</td>
<td>6 (46%)</td>
<td>9 (90%)</td>
<td>6 (85%)</td>
<td>0</td>
</tr>
<tr>
<td>High arched palate</td>
<td>4 (36%)</td>
<td>4 (40%)</td>
<td>4 (44%)</td>
<td>0</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>3 (23%)</td>
<td>1 (10%)</td>
<td>5 (71%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Contractures</td>
<td>3 (23%)</td>
<td>2 (20%)</td>
<td>1 (14%)</td>
<td>2 (40%)</td>
</tr>
</tbody>
</table>

Abbreviations: CFTD, congenital fiber type disproportion; MTM, myotubular myopathy; NM, nemaline myopathy; CCD, central core disease.

weakness was noted in 95% (12/13) of the patients with a severe phenotype and 54% (13/24) with a nonsevere phenotype (P = .017). Presentation at birth was noted in 69% (9/13) of severe patients and 41% (10/24) of nonsevere patients (P = 1, nonsignificant).

**Congenital Fiber Type Disproportion**

A total of 13 children from 12 families were diagnosed with congenital fiber type disproportion (8 boys and 5 girls). Muscle biopsies showed significant smallness of type 1 muscle fibers in comparison to type 2 as interpreted by the pathologist. Eight families were of Jewish origin, and four were of Arab origin. All patients presented with hypotonia and muscle weakness before 4 months of age. Five had breathing difficulties, and two required chronic mechanical ventilation. Facial weakness was reported in 6 children and a high arched palate in 4. There were 3 congenital fiber type disproportion children who had severe phenotype: 1 (patient 5) died at the age of 6 months and 2 (patients 12 and 13, brother and sister) presented at 2 months of age with general hypotonia and facial weakness, both of whom gradually developed respiratory difficulties requiring chronic mechanical ventilation. The girl died at 11 years of age due to respiratory insufficiency. Their first degree cousin (patient 24) had a similar clinical course and a biopsy consistent with nemaline myopathy. The rate of a severe phenotype in the congenital fiber type disproportion group was 23% (3/13).

**Myotubular Myopathy**

A total of 10 children from 9 families (7 boys and 3 girls) had a centrally located nucleus in their muscle fibers on muscle biopsy. This finding is consistent with the diagnosis of myotubular myopathy, which includes 2 main forms: the “X-linked myotubular myopathy” characterized by a severe phenotype and the “centronuclear myopathy” characterized by a milder phenotype.5

All boys were of Jewish origin, and 6 presented with severe hypotonia in the neonatal period requiring early ventilatory support (patients 14–19). All 6 had facial weakness, 2 had contractures in the upper and lower limbs, and 5 died before 2 months of age. In 3 of 6 of these patients, genetic analysis revealed a mutation in the MTM1 gene (X-linked myotubular myopathy). The seventh male child (patient 20) had a different clinical course. He presented at 2 years of age with difficulty in walking long distances and climbing stairs. The child was adopted, and no family history was available. A diagnosis of centronuclear myopathy is more probable in this patient.

The 3 girls with centronuclear myopathy are of Arab origin. Two of them are sisters (patients 21, 22). One case presented in infancy with moderate hypotonia and a high arched palate. The 2 sisters (patients 21, 22) presented at 2 years of age with hypotonia and muscle weakness. All 3 had facial weakness and walked at 2 years of age. The percentage of a severe phenotype in the myotubular myopathy group was 60% (6/10), 85% among the boys and no severe phenotype among the girls.

**Nemaline Myopathy**

There were 7 children from 7 families were diagnosed with nemaline myopathy (4 boys and 3 girls). They consisted of 6 families of Jewish origin and 1 family of Arab origin. Muscle biopsies stained with modified Gomori trichrome showed nemaline rods in the cytoplasm of muscle fibers, without nuclear rods. All patients in this group presented with hypotonia and muscle weakness before 3 months of age. There were 5 children who had breathing difficulties, 2 requiring constant mechanical ventilation. A total of 6 children had facial weakness, 4 had scoliosis, 4 a high arched palate, and 3 dolicocephaly. Two patients died from respiratory insufficiency at 1 year and 11 years of age. Genetic analysis in a female patient of Ashkenazi origin showed a 2502-bp deletion type mutation in the nebulin gene, including exon 55 and parts of intron 54 and 55. This mutation was recently described in nemaline myopathy in the Jewish Ashkenazi population.7 This previously described child5 had no breathing difficulties, walked at 18 months of age, and in addition had a suspected mitochondrial disease (complex 1 deficiency). In the nemaline myopathy group, we found a severe phenotype in 57% (4/7).

**Central Core Disease**

A total of 5 children from 3 families were diagnosed with central core disease (3 boys and 2 girls). Oxidative enzyme staining of the muscle biopsies showed rounded areas of abnormal myofibrillar architecture and an absence of mitochondria typical of central core disease. The 3 families were of Jewish origin. Three children (patients 33–35) were from the same mother. Two were twin sisters and their older...
brother was from her previous marriage. All 3 were born after a normal pregnancy with congenital dislocation of the hip. The twin sisters presented at the age of 3 months, and their older brother presented at 1 year of age. Their clinical course differed. The twins did not walk by 2.5 years of age (1 had severe scoliosis and contractures). The brother had a mild course with starting to walk at 14 months and difficulties in running and climbing stairs. Their mother also has mild proximal muscles weakness. In this group, there were neither breathing difficulties nor facial muscles weakness and no severe phenotype.

### Multi-Minicore Disease

One boy of Jewish origin diagnosed as multi-minicore disease had multiple small cores of abnormal myofibrillary architecture on muscle biopsy. His parents were unrelated, and family history for hypotonia and muscle weakness was negative. He presented at age 7 years with muscle weakness, difficulties walking long distances and climbing stairs, and facial weakness without breathing difficulties.

### Actin Myopathy

One boy of Jewish origin was diagnosed as having actin myopathy (previously described). Presentation was at birth with hypotonia and arthrogryposis, and family history was negative. He walked at 2 years of age, and by the age of 10 years, he had no breathing difficulties. A muscle biopsy at 10 years age of showed numerous large subsarcolemmal particles on a modified Gomori trichrome stain with abnormal actin aggregates on electron microscopy. Molecular DNA analysis had a missense mutation in the skeletal muscle alpha actin gene (ACTA1) consistent with an actin myopathy.

### Discussion

The congenital myopathies are a group of rare, early onset, nonprogressive muscle disorders with familial or sporadic inheritance. The affected children present in infancy as floppy babies or later with features of muscle weakness. However, the presentation is nonspecific, and clinically one cannot readily distinguish between the various subtypes. The purpose of this study was to delineate the clinical features of the Israeli cohort of congenital myopathies from 1983 to 2004. Of 37 children in our group, 35 had 1 of the 4 common forms: congenital fiber type disproportion (13 cases), myotubular myopathy (10 cases), nemaline myopathy (7 cases), and central core disease (5 cases). Myotubular and nemaline myopathy each have an incidence of 1 in 50,000 live births worldwide. With an average rate of 120,000 live births per year in the past 20 years in Israel, the presumed incidence of the above subtypes of congenital myopathies in Israel is lower than previously reported in the literature. This finding is probably due to the retrospective nature of the study, even though attempts were made to retrieve all congenital myopathy patients in Israel.

Congenital myopathies occur frequently in a familial manner, with onset mostly during infancy and occasionally during childhood, but rarely in adulthood. In this study, more than 1 patient with a congenital myopathy was found in 4 families (12%), detecting 9 children (24%). The majority of cases (84%) presented before 4 months of age, and the rest between 1 and 7 years of age.

Clinical features differed between the different common forms of congenital myopathies in this study (see Table 2). Patients with myotubular myopathy and nemaline myopathy had a high incidence of breathing difficulties and facial weakness with a high percentage of a severe phenotype. A severe clinical course is the common phenotype among patients with X-linked myotubular myopathy. This finding was demonstrated in 1 study of 116 patients with X-linked myotubular myopathy with 99 patients (85%) requiring ventilatory support. Therefore, a high rate of a severe phenotype in the myotubular myopathy male subgroup is expected. Studies show the majority of nemaline myopathy patients have a “typical” phenotype characterized by hypotonia, proximal muscle weakness, facial weakness, delayed motor milestones, and nocturnal hypoxia without respiratory dependence. In a study of 143 patients with nemaline myopathy, 66 patients (46%) had a typical phenotype, and 52 (36%) had either severe or intermediate phenotypes. Severe and intermediate phenotypes in nemaline myopathy are characterized by the inability to maintain respiratory independence at birth or during childhood. In our study, there was a slightly lower ratio of typical cases (3/7) compared with more severe ones (4/7), possibly due to the small size of this group.

Patients with central core disease and congenital fiber type disproportion had a lower percentage of a severe phenotype (Table 2). The common presentation of central core disease is mild proximal and facial weakness. Congenital dislocation of the hips and skeletal deformities are also characteristic. In our study, 4 of 5 central core disease patients had a skeletal deformity (congenital dislocation of the hip or contractures). None had breathing difficulties, facial weakness, or a severe phenotype. It is possible that facial weakness in mild cases may be observed at a later age. Thirteen cases were diagnosed with congenital fiber type disproportion. Because congenital fiber type disproportion is not a single entity and molecular genetic diagnosis of most cases is unavailable, the classification of this type of congenital myopathies is still ill defined. Clarke and North reviewed the literature for cases with congenital fiber type disproportion and found that, of a total of 64 patients, 30% had some
level of respiratory weakness, 44% had facial muscles weakness, and 25% had a severe phenotype. These findings are similar to our results (38% respiratory and 46% facial weakness). Four of our patients of Arab origin had parental consanguinity, which could support autosomal recessive inheritance.

A positive correlation between facial weakness and a severe phenotype has been noted in congenital fiber type disproportion patients. We found a similar positive correlation between facial weakness and the severe phenotype in our congenital myopathies cohort \( (P = .017) \). A trend toward a positive correlation was also found between onset at birth and a severe phenotype. However, statistical significance was not attained.

There were 3 children (patients 12, 13, and 24) from a large extended family who had similar presentations with a severe clinical course, a muscle biopsy with congenital fiber type disproportion and a mutation in the ACTA1 gene. An ACTA1 gene mutation could be a possible explanation in a family with both congenital fiber type disproportion and nemaline myopathy. A 2502-bp deletion mutation in the nebulin encoding gene was detected in a girl of Ashkenazi descent (patient 25) with a typical nemaline myopathy phenotype. The same mutation was found by Anderson et al in 5 families of Ashkenazi Jewish descent with nemaline myopathy and a typical phenotype from Brooklyn New York.

A total of 37 patients from 32 Israeli families with congenital myopathies were diagnosed in Israel in the past 20 years, with an incidence of 1 in 60 000 live births. Clinical manifestations in our cohort were similar to those described in previous series from other ethnic backgrounds. Most children presented clinical symptoms in the first months of life.

References