

## SHORT REPORT

# The Assessment of A Family With Myotonic Dystrophy

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Myotonic dystrophy (DM) is a neuromuscular disorder inherited autosomal dominantly. It affects multiple organs including skeletal muscle, heart, brain, eye, endocrine, and gastrointestinal systems (1). It is characterized by progressive muscle weakness and wasting and difficulty in muscles relaxation after contraction (myotonia). It is a rare disease and has an incidence of 1/8000 and a prevalence of 2.1 to 14.3/100,000 worldwide (1).

The onset commonly occurs during young adulthood; however, it can occur at any age and its clinic presentation shows extreme variability in degree of severity (2).

It is caused by an excessive number of CTG repeats at the location of chromosome 19q13.2-13.3. The normal number of these repeats is 5-35. When over 35, myotonic dystrophy can occur. The most severe congenital form of the disease has over 3000 repeats (1,3).

DM is a multisystem disorder. Its clinical manifestations include cardiac involvement, cataracts, testicular atrophy, respiratory impairment, difficulty in swallowing and gastrointestinal tract involvement, intellectual impairment, excessive output of insulin and abnormal carbohydrate metabolism, and excessive sleeping (1,3).

In this article, a family with myotonic dystrophy was described according to clinical and histopathological findings.

## Case

A 36-year-old female was admitted to our clinic with the complaints of inability to release a grasped object and easy fatigability since 11-12 years of age. In her past medical history, pre-, peri-, and postnatal periods were normal but she had had some difficulties in primary school. She had been married for 7 years, and had been given infertility treatment over the previous 3 to 4 years. About 40 days previously, she had given birth by Cesarean section.

In the family history, she had nonconsanguineous parents. She had 5 brothers and 4 sisters. Among them, there were 3 affected brothers and 3 affected sisters. She also had 8 nephews and 5 nieces. Two of them were affected and the other 2 had skeletal deformities such as pessequinovarus, as shown in the pedigree (Figure 1).

In the neurological examination, she had mild mental retardation, bilateral semiptosis, facial diplegia of moderate degree (especially in orbicularis oculi), hypophonic-nasonated speech, atrophy of masseter-temporal and sternocleidomastoid muscles, and a hatchet-shaped face. Motor power was 4/5 in neck flexion and distal muscle groups of the extremities. Deep tendon reflexes were hypoactive in the upper extremities, and abolished in the lower extremities. Percussion myotonia in the tongue and hands was seen. After gripping, action myotonia was observed in the hands.

In the laboratory examination, complete blood count, blood biochemistry including SGOT and SGPT, fasting

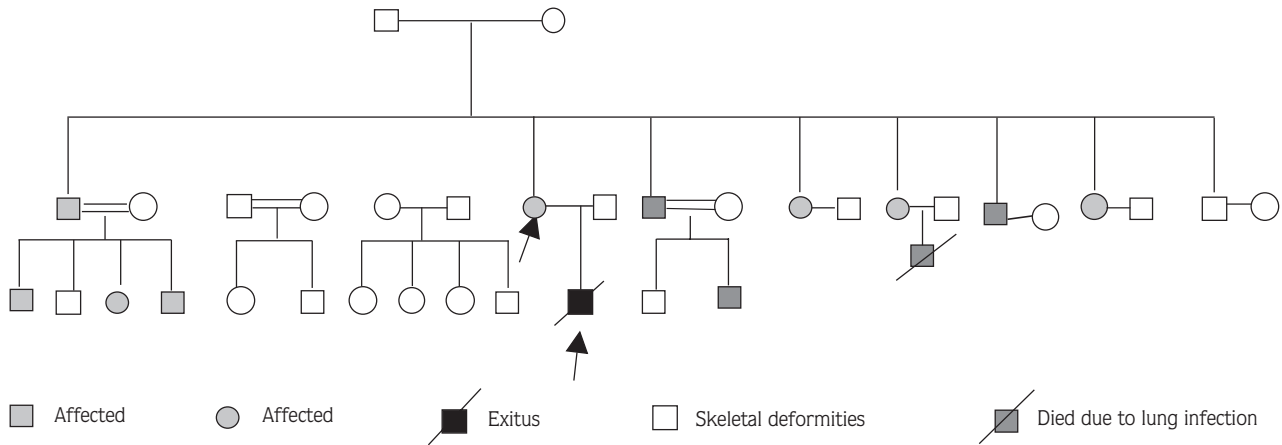


Figure 1. Pedigree.

glucose level and thyroid function tests were normal. Serum CPK was moderately increased (247 U/l, normal range: 24-195). Electrocardiogram (ECG), and echocardiography (EchoCG) were normal. Electromyography (EMG) showed pseudomyotonic discharges and myopathic units. Electroneurographic study was normal. Cerebral computerized tomography was normal.

A muscle biopsy sample was obtained from the biceps. Light microscopic examination showed variation in fiber size characterized by hypertrophy and atrophy, angular atrophy, muscle necrosis with myophagocytosis, increase in endomysial connective tissue, splitting of muscle fibers, increased internal nucleus in muscle biopsy specimens stained by hematoxylin and eosin, NADH, nonspecific esterase (Figure 2). Electronmicrographic examination showed subsarcolemmal aggregations, and myofibrillar structures (Figure 3).

DM is one of the most frequently encountered neuromuscular disorders and is characterized by multiple organ involvement, disturbance in muscle relaxation after percussion and/or voluntary muscle contraction (myotonia), muscle weakness and wasting.

It is a trinucleotide repeat disease caused by an increased number of cytosine-thymine-guanine (CTG) repeats on chromosome 19 (19p13.3) encoding dystrophia myotonia protein kinase (DMPK). It is inherited as an autosomal dominant disease (1,2,4). DMPK is a serine threonine proteine kinase formed by the phosphorylation of various proteins. It has been shown that it plays a role in the cellular signal mechanisms of

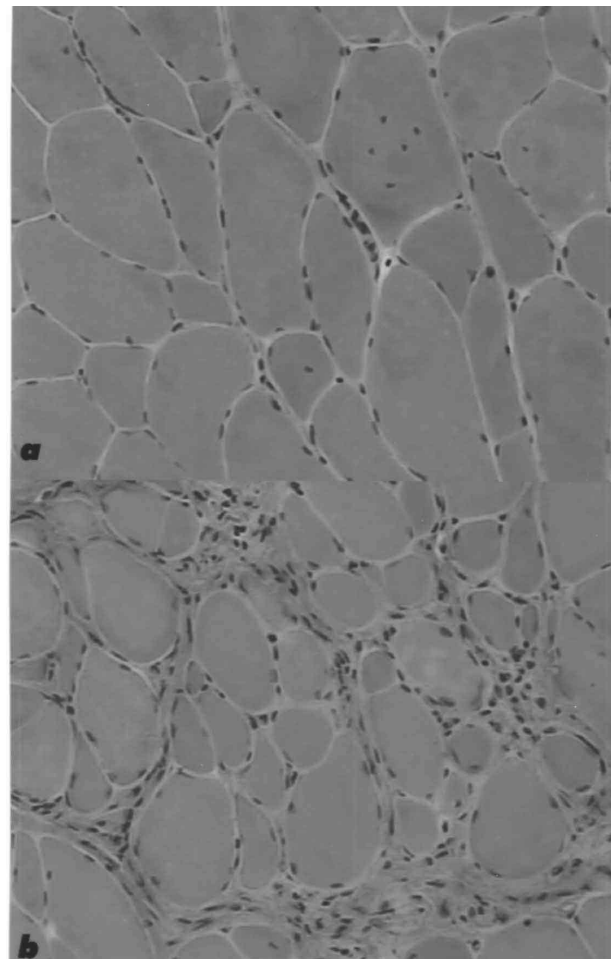


Figure 2. Hypertrophic and atrophic fibers, angular atrophy, splitting and increased connective tissue and internal nuclei (H&E, a X400 and b X200).

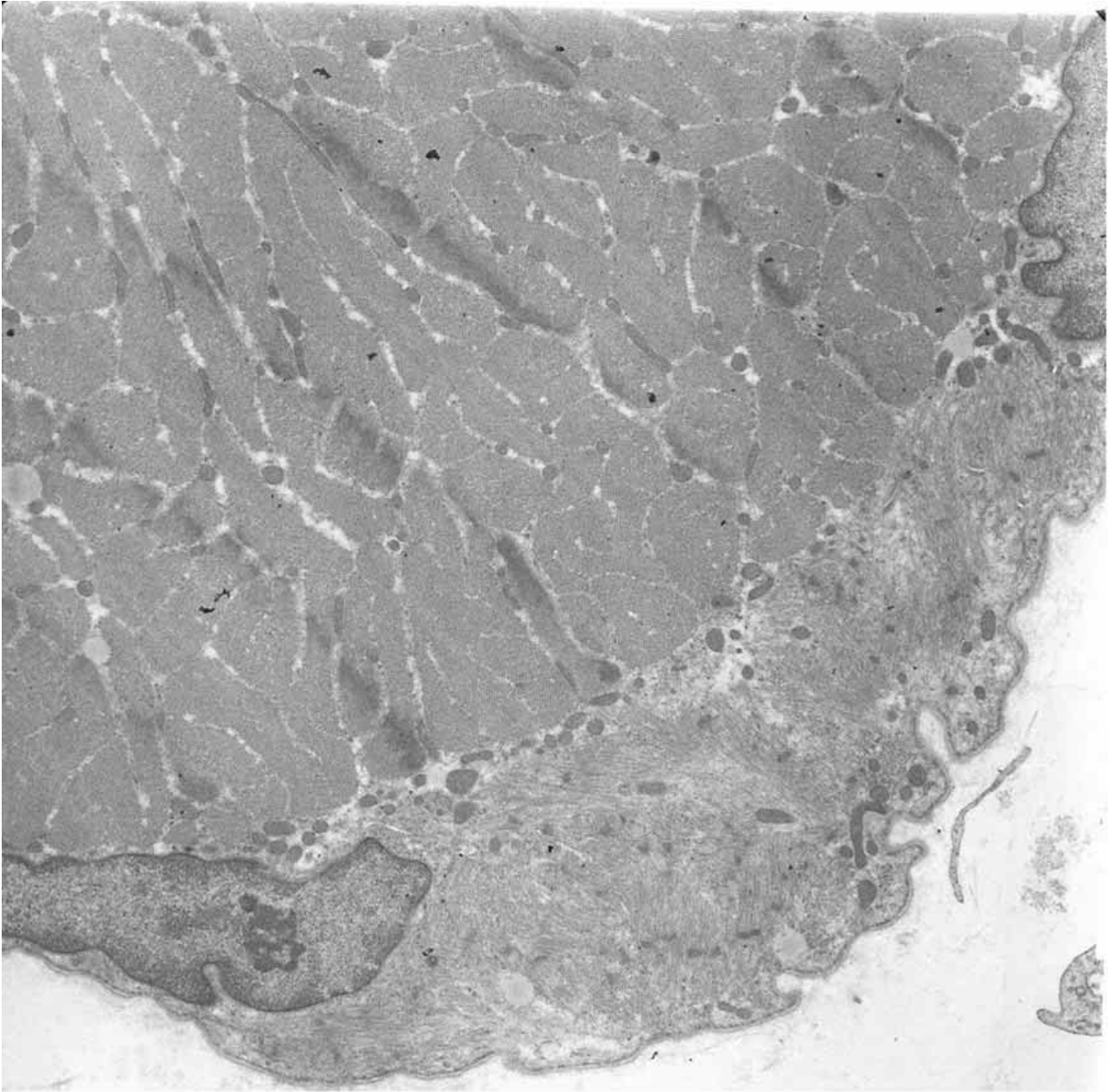


Figure 3. Subsarcolemmal aggregations and myofibrillar structures (Electron micrograph, X8800).

protein kinases, in the control of ion channels, and in the activation of secondary messengers. By experimental studies performed in cell cultures, it has been demonstrated that DMPK has some effects on sodium and calcium channels in skeletal muscles. However, the pathophysiologic mechanism underlying DM has not yet been completely understood.

Severity varies with the number of repeats: normal individuals have from 5 to 35 repeats, mildly affected persons from 50 to 80, and severely affected individuals 2,000 or more. In other words, the number of CTG repeats is correlated with the clinical findings (2-4).

DM is generally classified into 3 distinct types as congenital/early childhood, juvenile/adult and late-onset.

Conjugal/early childhood type, the most severe, appears from birth to 10 years, Juvenile/adult type is seen in the late 10's to early 40's while late onset is seen after the 40's (1,2).

In the juvenile/adult type, the main clinical features are myotonia and muscle weakness. Myotonia is commonly seen in the hands. Myotonia is paradoxical in DM. It decreases with continuation of movement (1,2,5). The predominancy of weakness in distal group muscles distinguishes DM from other muscle dystrophies. In particular, it involves the neck muscles. Sternocleidomastoid muscles are often atrophic. Atrophy in masseter and temporal muscles causes a hatchet-shaped face. In advanced disease, ptosis, dropped jaw, and facial diplegia are typical findings (2).

Our patient had had myotonia since 11-12 years of age. She had bilateral ptosis and facial diplegia, and her speech was hypophonic and nasonated due to weakness in the palatal and pharyngeal muscles. Muscle power in the distal muscle group of the extremities was 4/5.

Manifestations of other system involvements in addition to muscle weakness are also found in DM. Among these, the most life threatening is cardiac involvement. Mitral valve prolapsus, cardiac conduction defects, and arrhythmias may be seen. Electrocardiographic findings such as prolonged P-R interval, widening of QRS complex, changes in ST segment, and atrioventricular conduction defects can be detected. These findings may cause hypotension, syncope, palpitation, and sudden death (5,6). In our patient, ECG and EchoCG were normal.

In patients, respiratory distress may develop due to either alveolar hypoventilation or respiratory muscle involvement. Disturbance of the hyperpneic response to increased carbon dioxide concentration in adults may result in a tendency to sleep (7). Both cardiac conduction defects and impaired respiratory functions form the main risk factors in anesthesia. Barbiturates and other respiratory depressant medicines should be used carefully in these patients during anesthesia because of their evident effects and risk of arrhythmias (8).

Dysphagia, aspiration, cholelithiasis, bladder dysfunction, esophagogastrointestinal dysmotility, anal incontinence, and incoordinated contractions of the uterus have been reported due to smooth muscle involvement (1,3).

In DM patients, ocular involvement includes polychromatic lens opacities, retinal degeneration, decreased ocular pressure, extraocular muscle weakness, and mild extraocular myotonia (1,3). Our patient had no cataracts but her elder brother, 43 years old, did.

Endocrine abnormalities such as testicular atrophy, infertility, increased insulin production due to abnormal insuline receptor resistance, postprandial hyperinsulinemia, and abnormal gonadotrophic hormone levels may occur (9). Frontal balding may be seen.

In our patient, the hormone profile, fasting blood glucose level, and oral glucose tolerance test were normal. She did not have diabetes mellitus, but she had been treated for infertility for 4 years, and as a result she became pregnant. She stated that her 2 brothers and 1 sister were married, and they were infertile. She also reported that her 2 brothers had frontal balding in addition to infertility.

The serum CPK level may be normal or 3 times higher than normal. In our patient, serum CPK was moderately increased.

There are nonspecific changes in the muscle biopsy. Most commonly, central nuclei and ring fibers are seen. Necrosis, regeneration, and increase in collagen are not as severe as in Duchenne muscular dystrophy. In 70% of patients, there is hypotrophy of type I muscle fibers; less commonly there are markedly atrophic fibers. In many cases, there are target fibers suggesting neurogenic dysfunction, but intramuscular nerves appear histologically normal. Ultrastructural studies show dilatation of T tubules or sarcoplasmic reticulum, whose contents may be unusually dense. In some cases the surface membrane may be irregular, with reduplication of the basal lamina. Muscle biopsy findings in our case were compatible with the findings mentioned above (Figures 2 and 3).

In neuroimaging studies, cerebral atrophy in both computerized tomography and magnetic resonance imaging, white matter lesions (WMLs) and large Virchow Robin spaces (VRSs) may be seen in magnetic resonance imaging (10). In addition to these findings, neurochemical changes may be detected in proton spectroscopy and the involvement increases directly with the number of CTG repeats. In our case, cerebral computerized tomography was normal.

In the treatment of DM, a membrane stabilizer such as phenytoin, procainamide, mexiletine has been used (1,3). These drugs act through the inhibition of voltage-gated sodium channels. In our case, improvement of myotonia was observed by phenytoin given after birth in a dose of 300 mg/day tid po.

Congenital myotonic dystrophy (CMD) is characterized by hypotonia, myopathic face, feeding and respiratory problems, skeletal deformities and polyhydramnios. CMD accounts for 10% to 15% of DM. It has an incidence of approximately one per 3,500 live births (11). Patients with CMD generally have affected mothers rather than affected fathers. During pregnancy, decreased fetal movements, breech presentation, prematurity, and preterm labor may frequently be seen. In CMD, the risk of maternal obstetric complications such as placenta previa, abruptio placenta,

and polyhydramnios are increased. The diagnosis can be confirmed by examining the mother, but sometimes a diagnosis cannot be made because she might be asymptomatic.

Following birth, hypotonia is the most predominant finding. Neonatal respiratory distress is commonly seen and severe cases may need mechanical ventilation. CMD should be considered in a neonate having feeding and respiratory problems with hypotonia, and their parents should be examined with respect to myotonia (1,3).

In CMD, serum CPK level is usually normal. Muscle biopsy does not show changes seen in the typical adult type cases and may appear considerably normal apart from nonspecific changes such as selective atrophy of type 1 fibers with internal nuclei. It may also show some evidence of maturational delay in the muscle (myotubular pattern) (12).

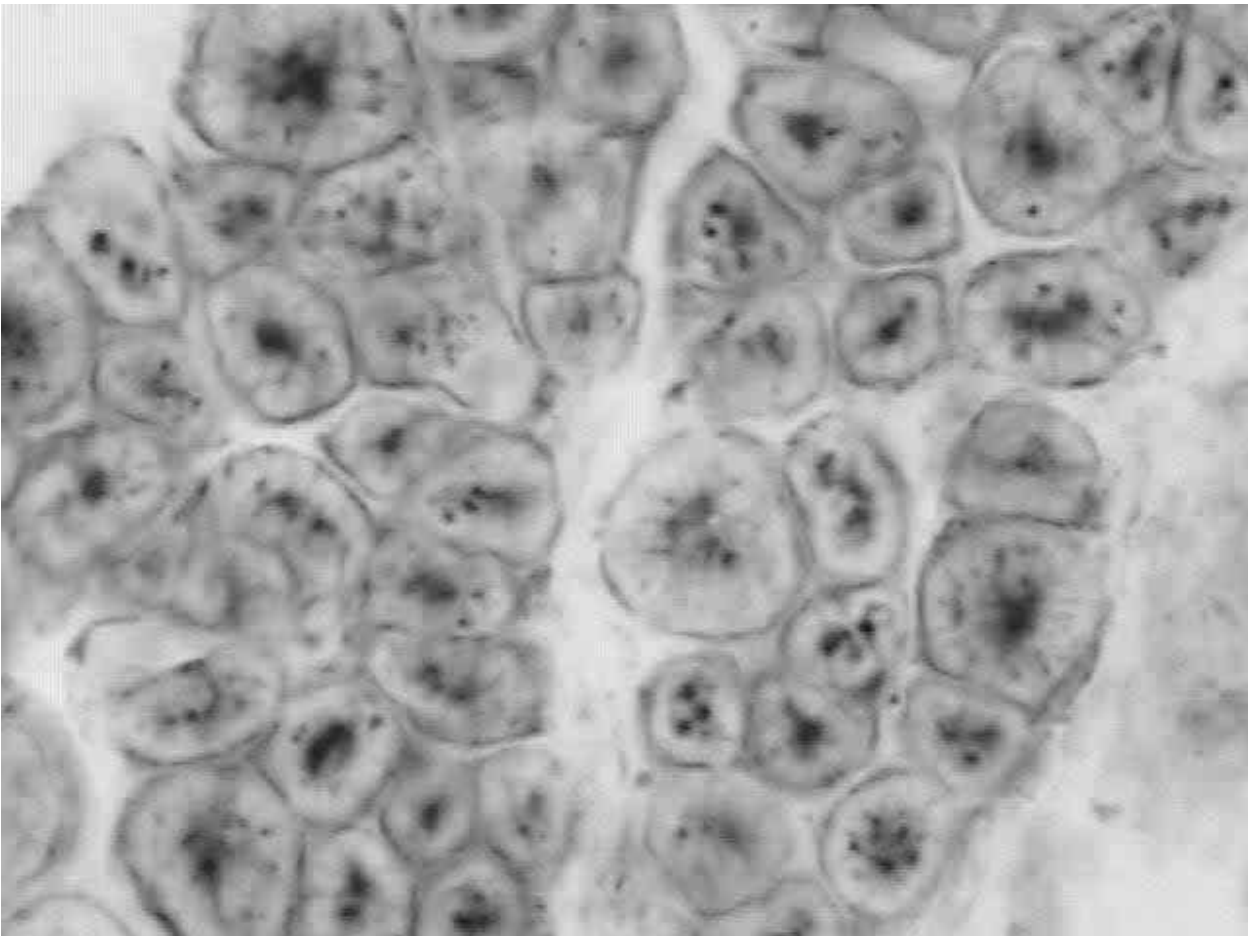


Figure 4. Myotubular pattern characterized by rearrangement of substrate in muscle fibers forming dense central areas surrounded by a substrate-free halo (NADH X200).

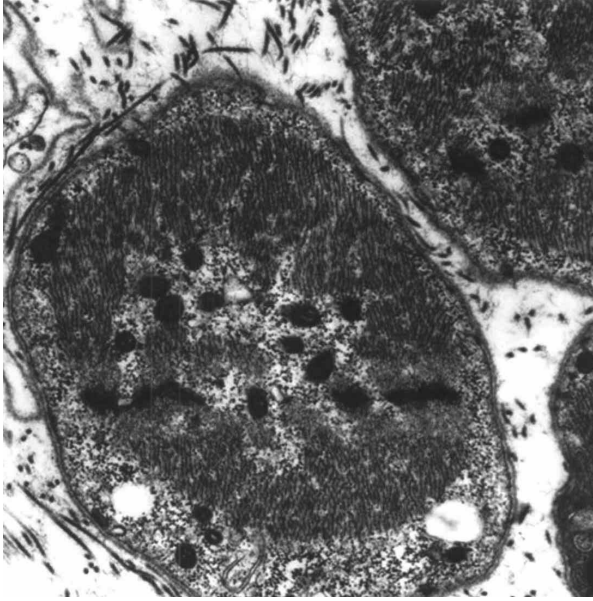


Figure 5. Myofilaments forming a compact rim around the mitochondria located in the center of the myofiber (Electron micrograph X10,000).

Our patient reported that during her pregnancy, routine obstetric ultrasonographies showed polyhydramnios. She gave birth to a boy at 36 weeks of gestation by Cesarean section. The baby had an apgar score of 4 and 6 at 5 and 10 min, and had skeletal deformities such as pesquinovarus. He presented with respiratory and feeding difficulties at birth. He needed to be intubated due to respiratory distress, and hospitalized

in the NICU. He was diagnosed with congenital myotonic dystrophy based on his family history. A muscle biopsy was obtained from the infant. On light microscopic examination, there were variations in fiber size and a central halo or nucleus in the middle of the muscle fibers by hematoxylin-eosin. NADH stain showed the myotubular pattern characterized by rearrangement of substrate in muscle fibers forming dense central areas surrounded by a substrate-free halo (Figure 4). On electron micrograph study, myofilaments forming a compact rim around the mitochondria located in the center of the myofiber were seen (Figure 5). In spite of all the supportive treatment, he died at the age of 2.5 months.

In summary, a family with several members affected by DM, which is a rare neuromuscular disease, was described according to history, and clinical and histopathological findings. The most striking feature in this family report is this: it shows the importance of taking a thorough history while evaluating a family with multiple affected members and examining each parent when making a diagnosis in a newborn.

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