Clinical and pathologic aspects of congenital myopathies

Ikuya NONAKA MD

National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan

Abstract

The term "congenital myopathy" is applied to muscle disorders presenting in infancy with generalized muscle weakness and hypotonia followed by delayed developmental milestones. The myopathy has been differentiated diagnostically on the basis of their morphologic characteristics and includes nemaline myopathy, central core disease, myotubular (centronuclear) myopathy and congenital fiber type disproportion. In most of these disorders, there are 3 distinct subtypes: severe infantile, benign congenital and adult onset forms. The mode of inheritance and gene loci are variable, although each disorder shares the common clinical features including facial and prominent neck flexor weakness and preferential respiratory muscle involvement. All mutations identified in nemaline myopathy are localized to the actin filament components, suggesting that the disease is related to sarcoplasmic thin filaments or Z-protein abnormalities. On the other hand, X-linked myotubular myopathy has mutations in a family of tyrosine phosphatase (myotubularin gene) and central core disease in ryanodine receptor gene. In all these disorders, the common pathologic features are small muscle fibers with type 1 fiber atrophy and predominance, which account for the small muscle bulk and generalized muscle weakness.

INTRODUCTION

The term congenital myopathy is applied to muscle disorders presenting with generalized muscle weakness and hypotonia from early infancy with delayed developmental milestones. Dysmorphic features such as elongated face, scoliosis and contracture of joints are common. The congenital myopathies have been classified into various diseases based on pathologic characteristics, including nemaline myopathy, central core disease, myotubular myopathy and congenital fiber type disproportion. Although the clinical symptoms closely mimic each other, the genetic basis differs from disease to disease. This review will focus on nemaline myopathy, as it is the most common of the congenital myopathies.

INCIDENCE

The actual incidence of congenital myopathy is unknown. In my laboratory at the National Center of Neurology and Psychiatry, from 1979 to 2000, we have examined muscle biopsies from 449 patients with congenital myopathy (Table 1). During the same period, we had 511 cases of Duchenne muscular dystrophy, therefore congenital myopathy does not appear to be a rare disease, but is relatively common among the childhood myopathies.

NEMALINE MYOPATHY

Shy et al[1] and Conen et al[2] first described the disease in 1963. Because of the presence of thread or rod structures (Greek *nema* =thread) in muscle fibers, the term nemaline myopathy was coined by Shy et al[1] and this is now widely accepted. The disease has been classified into 3 major forms including the severe infantile (congenital), benign congenital (mild, nonprogressive or slowly progressive) and adult onset forms. A recent classification proposed by European Neuromuscular Center Workshop further subdivided the benign congenital form into 3 additional subtypes of intermediate congenital, typical congenital and childhood-onset forms.[3] However, this classification is not so clear-cut and is not of practical value in follow-up of these patients.[3]

1) Genetic aspects[4]

The disease is inherited through an autosomal dominant or recessive trait. In an Australian family with an autosomal dominant inheritance, a gene mutation was first found in slow alpha-tropomyosin *(TPM3)*.[5] Subsequently mutations were found in the Nebulin gene *(NEB)* in patients with an autosomal recessive trait[6], and alpha-actin gene *(ACTA1)* mostly in patients with the

**Table 1: Incidence of congenital myopathy
        (1979-2000: National Center of Neurology and Psychiatry)**

Types of congenital myopathy	Number of patients (%)
Nemaline myopathy	121 (27%)
Severe infantile form	43
Benign congenital form	53
Adult onset form	25
Central core disease	27 (6%)
Myotubular (centronuclear) myopathy	42 (9%)
Severe infantile myotubular myopathy	30 (7%)
Congenital fiber type disproportion	89 (20%)
Congenital myopathy without specific features (Minimal change myopathy)	31 (7%)
Miscellaneous	109 (24%)
Total number of patients	449
Duchenne muscular dystrophy diagnosed during the same period	551

severe infantile form and actinopathy.[7] Recently, a mutation in troponin T1 (*TNNT1*) was found in an autosomal dominant Amish family.[8] Since all mutations were found in genes encoding actin filament components, nemaline myopathy is a disorder of sarcomeric thin filaments or Z disc.

2) Clinical findings

Severe infantile (congenital) form

All patients have obvious muscle weakness and hypotonia at birth. Most of the patients require respirator care and tube feeding. All have facial muscle involvement, including elongated, emotionless expression and high arched palate. Patients usually die before 1 year of age from respiratory failure or infection. Alpha-actin gene (*ACTA1*) mutations were reported to be common in this form. In our study, 4 of 14 patients examined had these mutations.

Benign congenital form

Most of patients with this form are floppy infants with delayed developmental milestones. They have facial muscle involvement and high-arched palate. Neck flexor weakness is prominent, therefore they cannot raise their head or have head lag when pulled up from the supine position (Figure 1). 95% of the patients have generalized or predominantly proximal muscle weakness and in 5% the weakness is predominantly distal. The disease is non-progressive or only slowly progressive. Respiratory muscles, especially the diaphragm may be involved leading to respiratory failure even in patients with mild limb muscle weakness.[9] We have followed 18 patients and 5 have died from respiratory failure by the age of 20 years.[10]

Adult onset form

Since the nemaline bodies themselves are not disease specific but can also be found in inflammatory myopathies and chronic muscular dystrophies, the adult form may include a variety of disorders with nemaline bodies in muscle biopsies. The most common disease is the benign congenital form which is asymptomatic in childhood but becomes symptomatic in adulthood. These patients usually have minimal to mild muscle weakness from childhood with facial

Figure 1: A patient with the benign congenital form of nemaline myopathy. Because of prominent neck flexor muscle weakness, she can not raise her head when pulled up from the supine position.
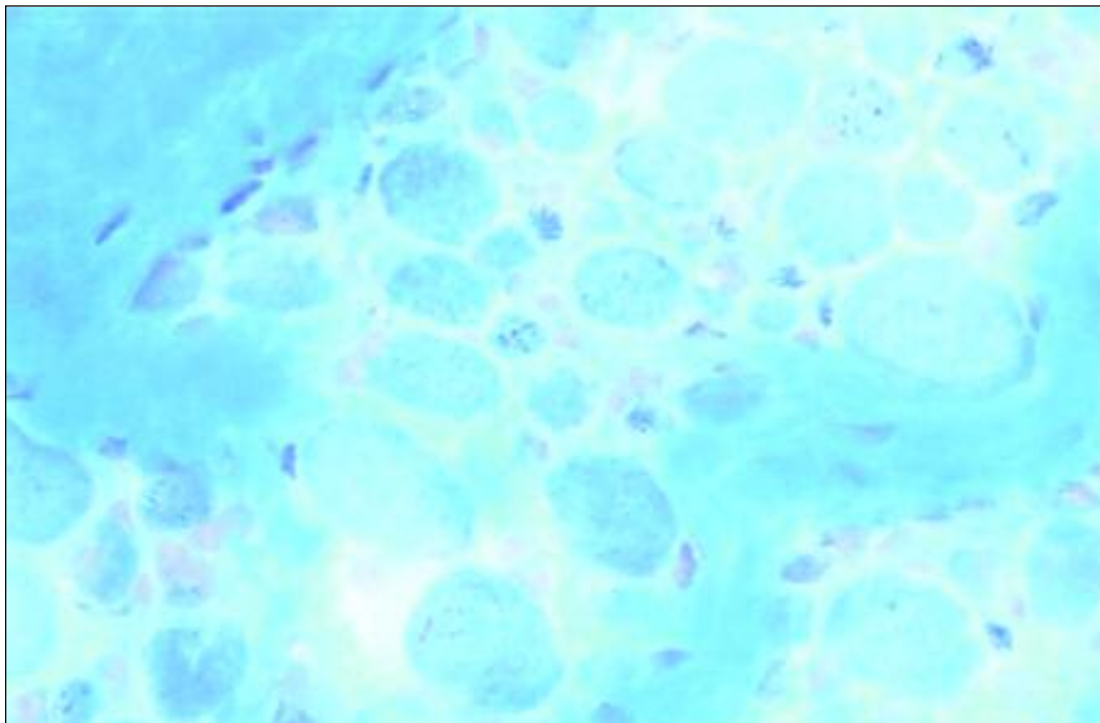

Figure 2: Muscle pathology in severe infantile form of nemaline myopathy. Note small muscle fibers with nemaline bodies and dense interstitial fibrosis. Modified Gomori trichrome stain.

muscle involvement, but they are rarely aware that they have muscle disease.

3) Muscle pathology

Although muscle fiber immaturity and fibrosis can be seen in early infancy in the severe infantile form (Figure 2)[11], the overall histological and histochemical findings are almost the same.[12] There is type 1 fiber atrophy (hypotrophy) with type 1 fiber predominance (type 1 fibers comprise more than 55% of the total number of fibers) (Figure 3). Nemaline bodies, demonstrated with modified Gomori trichrome stain, are present in both type 1 and 2 fibers in half of the biopsies, and in type 1 fiber only in the other half. The amount of nemaline body is not proportional to disease severity.

Even in patients with nebulin or alpha-actin gene mutations, nebulin and actin were normally expressed immunohistochemically and by immunoblotting. Therefore, gene analysis is necessary to establish the definitive diagnosis of nemaline myopathy.

By electron microscopy, the nemaline bodies have the same structure as the Z line and is sometimes connected to the Z line. Since the nemaline bodies react immunologically with a Z-protein, alpha-actinin, these bodies are formed by an overproduction of the Z-protein. However, the significance of nemaline body formation remains unknown.

CENTRAL CORE DISEASE

Shy and Magee[12] first described this disease in 1956. Some patients were proven to have mutations in the ryanodine receptor gene (*RYR1*).[13] The C-terminal of *RYR1* acts as calcium-releasing transmembrane channel in the sarcoplasmic reticulum. Interestingly patients with malignant hyperthermia have mutations in *RYR* gene.[13-15] Patients with central core disease tend to have malignant hyperthermia during generalized anesthesia. Therefore, the two diseases appear to be closely related to each other in its pathogenesis.

1) Clinical findings

All patients with central core disease have milder generalized muscle weakness and less marked facial muscle involvement than those with nemaline myopathy. Patients with the severe congenital form have not been reported. Scoliosis and contracture of joints can be seen even in patients with minimal limb muscle weakness
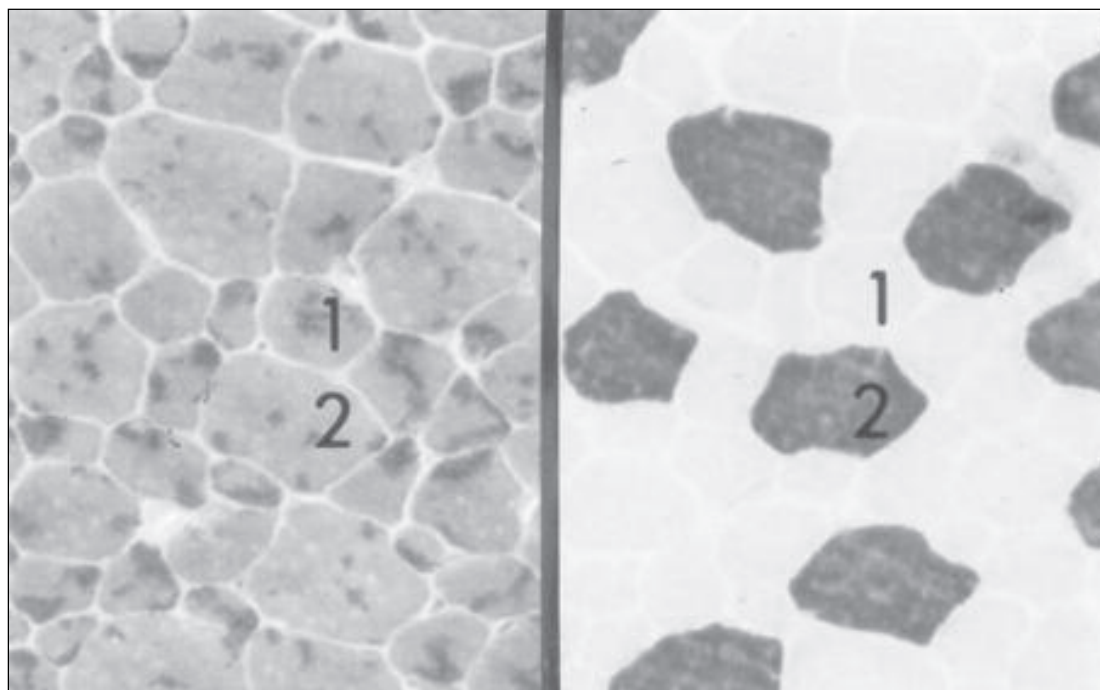

Figure 3: A typical muscle pathology in the benign congenital form of nemaline myopathy. Nemaline bodies are seen in all muscle fibers with modified Gomori trichrome stain (left). Type 1 (1) fibers predominate and atrophic (right) (routine ATPase stain).

Figure 4: A patient with central core disease manifesting with marked scoliosis.

(Figure 4).[16,17] The disease is usually nonprogressive and respiratory failure is uncommon.

2) Muscle pathology

"Core" structure is most clearly demonstrated with oxidative enzyme stains such as NADH-TR, succinate dehydrogenase (SDH), and cytochrome c oxidase (COX) (Figure 5). Since mitochondria and sarcoplasmic reticulum are absent in the core region, oxidative enzyme activity is markedly reduced to absent. In addition to the core formation, almost all of patients have significant type 1 fiber predominance. In one family, the father had mild muscle weakness and only type 1 fibers and no core structures, but his son had typical central core disease.[18] Congenital neuromuscular disease with uniform type 1 fibers may be related or is identical to central core disease. Interstitial fibrosis is prominent from the early stages of the disease.

By electron microscopy, mitochondria and sarcoplasmic reticulum are absent in the core region where A-I-Z band structure is disorganized with occasional Z-streaming. Since patients with malignant hyperthermia but without congenital myopathy have core-like structures in about half of the muscle biopsies, core formation may be related to ryanodine receptor abnormality.
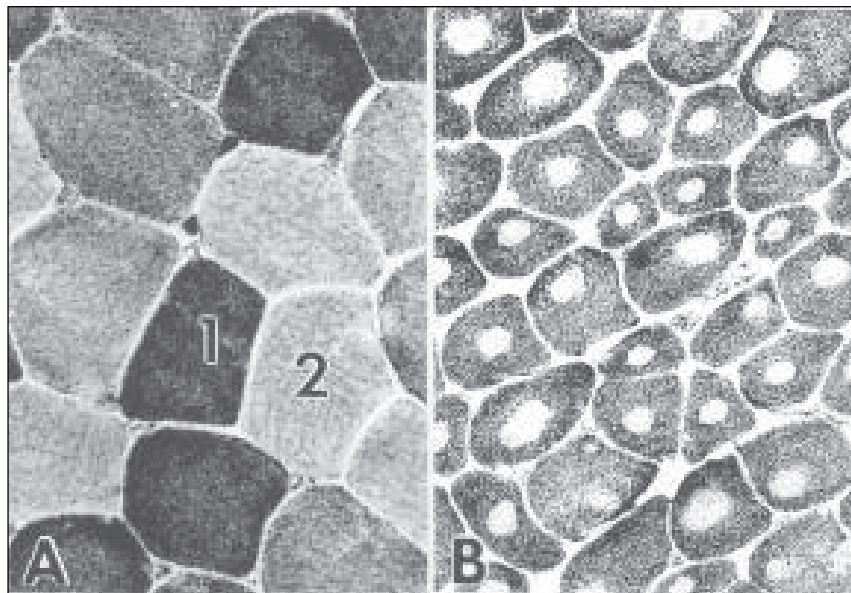

Figure 5: Muscle pathology in central core disease. Type 1(1) and 2(2) fibers are distributed in a mosaic pattern in normal muscle (A). Almost all fibers are small and have core structures, and are darkly stained behaving as type 1 fiber in central core disease (B). NADH-TR stain.

MYOTUBULAR (CENTRONUCLEAR) MYOPATHY

Spiro et al[19] described a patient with the clinical characteristics of the benign congenital myopathy who had small muscle fibers, most with centrally placed nuclei. Since fetal muscle fibers, the myotubes, have central nuclei, the term myotubular myopathy was suggested. The muscle fibers in this milder form differ from true "myotubes". They have a mature morphology and are well differentiated into either type 1 or 2 fibers, therefore the term centronuclear myopathy is now more commonly used rather than myotubular myopathy.

The disease is inherited through either autosomal recessive or dominant manner. The responsible gene has not been cloned. The clinical features do not significantly differ from those seen in the benign congenital form of nemaline myopathy except for marked facial muscle involvement. About 30% of patients have ptosis. Mental retardation is common.[10]

Muscle pathology shows type 1 fiber atrophy and predominance. Most of the fibers have centrally placed nuclei. Myofibrils occasionally show a radiating structure on NADH-TR staining (Figure 6).

CONGENITAL MYOTUBULAR MYOPATHY (SEVERE INFANTILE MYOTUBULAR MYOPATHY)

This disease is different from the centronuclear myopathy just discussed because patients have marked muscle weakness and hypotonia since birth. Except for a few patients, most are males suggesting an X-linked recessive inheritance. Most of the patients have respiratory failure and feeding difficulties at birth. They have generalized muscle weakness and hypotonia with marked facial muscle involvement. Mental retardation is common. Patients die before the age of 1 year without respirator assistance. The gene was recently cloned and the gene product was named myotubularin, a family of tyrosine phosphatase.[20,21] It is still unknown why this enzyme defect induces muscle fiber immaturity.

Muscle fibers are small with occasional central nuclei and are immature having "myotube" characteristics. The most prominent feature is the presence of peripheral haloes by NADH-TR staining because oxidative enzyme activity is deficient at the periphery of the sarcoplasm (Figure 7).[21]
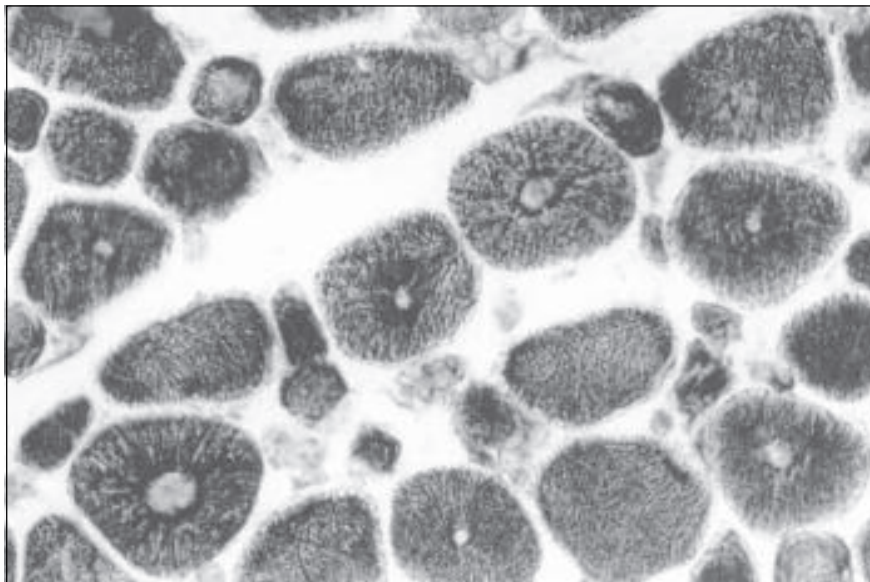

Figure 6: Muscle pathology in centronuclear myopathy. In addition to centrally placed nuclei (empty area in the center), most of the fibers have striated intermyofibrillar networks. NADH-TR stain.
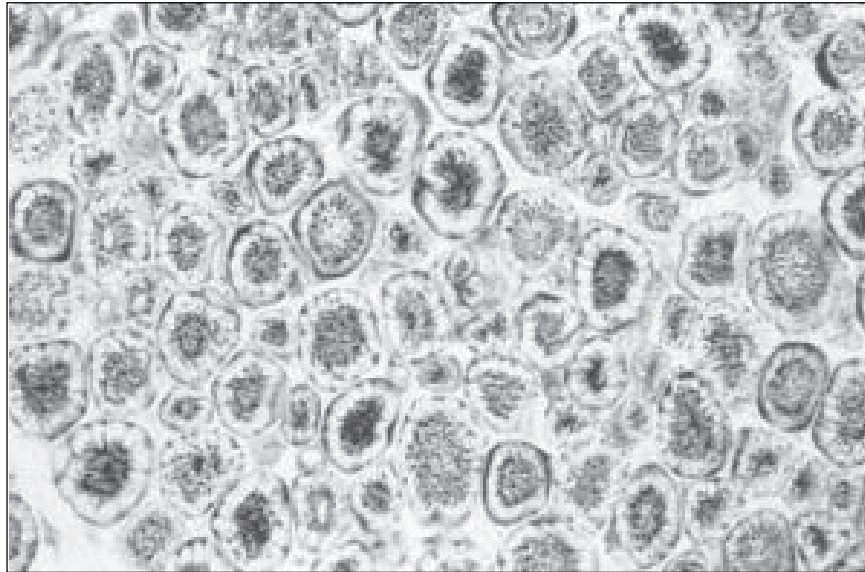
Figure 7: Muscle pathology in congenital myotubular myopathy. All muscle fibers are small with peripheral halo showing "myotube" structure. NADH-TR stain.

CONGENITAL FIBER TYPE DISPROPORTION (CFTD)

When patients have the typical clinical features of congenital myopathy and the diameter of type 1 fibers is smaller than that of type 2 fibers by more than 12% on average, they are diagnosed as having CFTD.[22]

Most of patients with various congenital myopathies have type 1 fiber atrophy. If the muscle biopsy sample is too small to demonstrate nemaline bodies, a diagnosis of CFTD is given. Similarly if a patient has occasional muscle fibers with centrally placed nuclei, the pathologist may have difficulty in differentiating between centronuclear myopathy and CFTD. There are no definite criteria to distinguish between these two disorders. Therefore CFTD is probably a group of heterogeneous disorders, but we need this category to give a diagnosis to patients with congenital myopathy who have no disease characteristic morphology other than small type 1 fibers.

REFERENCES

1. Shy GM, Engel WK, Somers JE, Wanko T. Nemaline myopathy, a new congenital myopathy. *Brain* 1963;86:793-810
2. Conen PE, Murphy EG, Donohue WL. Light and electron microscopic study of "microgranules" in a child with hypotonia and muscle weakness. *Can Med Assoc J* 1963;89:983-6
3. Ryan MM, Schnell C, Strickland CD, et al. Nemaline myopathy: A clinical study of 143 cases. *Ann Neurol* 2001;50:312-20
4. Sanoudou D, Beggs AH. Clinical and genetic heterogeneity in nemaline myopathy - A disease of skeletal muscle thin filaments. *Trends Mol Med* 2001;7:362-8
5. Laing NG, Wilton SD, Akkari PA, et al. A mutation in the alpha-tropomyosin gene TPM3 associated with an autosomal dominant nemaline myopathy NEM1. *Nat Genet* 1995;9:75-9
6. Pelin K, Hilpela P, Donner K, et al. Mutations in the nebulin gene associated with autosomal recessive nemaline myopathy. *Proc Natl Acad Sci USA* 1999;96:2305-10
7. Nowak KJ, Wattanasirichaigoon D, Goebel HH, et al. Mutations in the skeletal muscle alpha-actin gene in patients with actin myopathy and nemaline myopathy. *Nat Genet* 1999;23:208-12
8. Johnston JJ, Kelly RI, Crawford TO, et al. A novel nemaline myopathy in the Amish caused by a mutation in troponin T1. *Am J Hum Genet* 2000;67:814-21
9. Sasaki M, Takeda M, Kobayashi K, Nonaka I. Respiratory failure in nemaline myopathy. *Pediatr Neurol* 1997;16:344-6
10. Akiyama C, Nonaka I. A follow-up study of congenital non-progressive myopathies. *Brain Dev* 1996; 18:404-8
11. Nonaka I, Tojo M, Sugita H. Fetal muscle characteristics in nemaline myopathy. *Neuropediatrics* 1983;14:47-52
12. Shimomura C, Nonaka I. Nemaline myopathy: comparative muscle histochemistry in the severe neonatal, moderate congenital and adult-onset forms. *Pediatr Neurol* 1989;5:25-31

12. Shy GM, Magee KR. A new congenital non-progressive myopathy. *Brain* 1956;79:610-21
13. Zhang Y, Chen HS, Khanna VK, et al. A mutation in the human ryanodine receptor gene associated with central core disease. *Nat Genet* 1993;5:46-50
14. Quane KA, Healy JM, Keating KE, et al. Mutations in the ryanodine receptor gene in central core disease and malignant hyperthermia. *Nat Genet* 1993;5:51-5
15. McCarthy TV, Quane KA, Lynch PJ. Ryanodine receptor mutations in malignant hyperthermia and central core disease. *Hum Mutat* 2000;15:410-7
16. Merlini L, Mattutini P, Bongfiglioli S, Granata C. Non-progressive central core disease with severe congenital scoliosis: a case report. *Dev Med Child Neurol* 1987;29:106-9
17. Nagai T, Tsuchiya T, Murayama A, Takemitsu M, Nonaka I. Scoliosis associated with central core disease. *Brain Dev* 1994;16:150-2
18. Tojo M, Ozawa M, Nonaka I. Central core disease and congenital neuromuscular disease with uniform type 1 fibers in one family. *Brain Dev* 2000;23:262-4
19. Spiro AJ, Shy GM, Gonatas NK. Myotubular myopathy. Persistence of fetal muscle in an adolescent boy. *Arch Neurol* 1966;18:435-44.
20. Laporte J, Hu LJ, Kretz C, et al. A gene mutated in X-linked myotubular myopathy defines a new putative tyrosine phosphatase family conserved in yeast. *Nat Genet* 1996;13:175-82
21. Nishino I, Minami N, Kobayashi O, et al. *MTM1* gene mutations in Japanese patients with the severe infantile form of myotubular myopathy. *Neuromuscul Disord* 1998;8:453-8
22. Brooke MH. Congenital fiber type disproportion. In: Kakulas BA ed: Clinical studies in myology. Amsterdam: *Excerpta Medica*, 1973:145-59