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Tıtınopathy wıth Centronuclear Myopathy in Two Sıblıngs

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Abstract

Titin is a large and important protein in the sarcomere structure, which is involved in the development, structure, elasticity, and signalization of the heart and skeletal muscle. Titin mutations can present with different, pathological, and clinical findings inheritance patterns.In this article, we present two siblings who had significant generalized muscle weakness, contractures, and respiratory failure with centronuclear myopathy findings in muscle biopsy. However, it should be known that the same type of mutation can cause different clinical phenotypes even within the same family. In patients with TTN mutation, limited ambulation may prevent us from detecting respiratory and cardiac dysfunctions at early stages. Therefore regular and close monitoring is vital in these patients.

Keywords: Titin; Myopathy; Genetic Mutation

Abbrevation: TTN - Titin ; LGMD-2J - Limb-Girdle muscular dystrophy 2J; CK - Creatine kinase

Introduction

Titin (TTN) is a large and important protein in the sarcomere structure, interacting with multiple scaffolding proteins including calpain-3 and nebulin. Mutations in the titin gene cause clinical signs and symptoms that are related to the cardiac and skeletal muscle or both. TTN mutations can present with different inheritance patterns, pathological and clinical findings as listed below [1].

-Late-onset autosomal dominant tibial muscular dystrophy,
- Young or early adult-onset recessive distal titinopathy,
- Limb-Girdle muscular dystrophy 2J (LGMD-2J),
-Congenital centronuclear myopathy,
- Early-onset myopathy with fatal cardiomyopathy,
- Multi-mini core disease with heart involvement,
- Childhood-juvenile-onset Emery-Dreifuss-like phenotype without cardiomyopathy,
-Hereditary myopathy with early respiratory failure,
-Adult-onset recessive proximal muscular dystrophy.

In this article, we present two siblings diagnosed with centronuclear myopathy and report a new mutation in the titin gene.

Cases

A 17-year-old girl was admitted to our hospital because of scoliosis and the inability to walk. It was learned from the parents, who were second-degree relatives, that she was born healthy as a second child, there was a delay in all her motor milestone development. She could walk at the age of 3, started falling frequently at 5, and was non-ambulatory at the age of 12. The first baby of the family was lost in the newborn period due to respiratory distress. At the same time, it was stated that our patient's 7-year old brother could not walk at all. On physical examination, Her mental development was normal for her age. Facial muscle weakness, ptosis, and ophthalmoparesis were not detected. The muscle weakness of the patient with generalized muscle atrophy was evident at especially in the proximal parts and at lower extremities. Scoliosis and flexion contractures in the bilateral elbow and knees were detected (Figure 1). Creatine Kinase (CK) was normal and, findings of myogenic involvement were detected in electromyoneurography. The muscle biopsy was interpreted as consistent with centronuclear myopathy. On echocardiography, she was found to be normal. Nocturnal hypoventilation was observed in our patient who had a headache in the morning. Genetic screening with the next-generation sequencing technique revealed homozygous mutation for c.15218-2A> G in the TTN gene on the 2nd chromosome. This mutation in the TTN gene is reported for the first time in the literature as far as we know.

Figure 1: 17 years old girl with centronuclear myopathy(Tininopathy), she is demonstrating scoliosis with no fascial myopathy or ptosis.

Her 7-year-old brother who had a history of an uneventful pregnancy was incubated in the neonatal intensive care unit for 45 days due to postpartum respiratory distress and jaundice. In the neonatal period, he was diagnosed with G6PD deficiency. Despite his normal mental development, there was a delay in the motor milestones. He could sit without any support at 3 years of age, but he could never walk. He had knee contractures since the age of 5. The patient was hospitalized many times due to frequent respiratory infections. On physical examination, facial muscle weakness, ptosis, and ophthalmoparesis were not detected. There was severe generalized muscle atrophy and weakness in the lower extremities and mild scoliosis and flexion contracture in both knees (Figure 2). Similar results were found in the genetic study of the patient. CK was within normal ranges. Myogenic involvement in electromyoneurography was detected. Echocardiography showed newly trace mitral insufficiency at age of 7 which was newly developed. Daytime respiratory function tests were consistent with restrictive respiratory disease.

Figure 2: 7 years old boy with centronuclear myopathy (Titinopathy), he is demonstrating generalized muscle atrophy and scoliosis with no fascial weakness or ptosis.

Discussion

Our patients had clinicopathologic features of centronuclear myopathy. Centronuclear myopathy is a congenital myopathy in muscle fibers, characterized by over 25% central nuclei. The disease can be caused by mutations in many genes such as MTM1, DNM2, BIN1, and RYR1 [2]. Ceyhan-Birsoy et al described five patients with generalized infantile muscle weakness and muscle biopsy findings consistent with centronuclear myopathy [3]. The disease manifests itself as generalized muscle weakness at an early age, scoliosis, and respiratory failure that can be developed at young ages. However, clinical findings may range from severe hypotonia and respiratory failure at birth to the late onset of mild muscle weakness. Titinopathy could have different clinical presentations even in the same family [4]. In the first patient, the findings began in infancy, the walking age was delayed, and at the age of 12, she couldn't mobilize and started to use a wheelchair. The 7-year-old brother showed respiratory system dysfunction signs in the neonatal period, scoliosis appeared at an earlier age and he could never walk. While the 17-year-old patient had no signs of cardiac involvement, her brother had signs of newly developed mitral insufficiency. However, Fattori et al. reported a patient with compound heterozygous nonsense TTN mutations, who was diagnosed with dilated cardiomyopathy at age of 8 years [5]. But it is known that cardiac involvement may be delayed until the 4th decade [6,7]. Facial, extraocular, and bulbar involvement findings were not detected in both siblings. CK values were normal. In previous cases, it has been reported that facial and extraocular involvement may not occur and CK values are generally normal. Scoliosis is generally a common finding as in these patients [3]. And in our patients, contractures appeared to be developed earlier. As a result, centronuclear myopathies can develop due to different genetic mutations, and the type of mutation determines the patient's clinical manifestations. However, it should be remembered that the same type of mutation can cause different clinical phenotypes even within the same family. In patients with TTN mutation, limited ambulation may prevent us from detecting respiratory and cardiac dysfunctions at early stages. Therefore regular and close monitoring is vital in these patients.

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Authors' contributions

Bilge S. Duygu GüneÖzcanyüz, Fatma kaya, Gülen gül Mert, FarukİncecikSuzan Zorludemir, Özlem hergüner. contributed equally to the acquisition, analysis, and interpretation of the data and the drafting and revision of this review. The authors have read and approved the submitted version.

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