Clinical Case Report

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A case report with the peculiar concomitance of 2 different genetic syndromes

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Abstract

Rationale: Down syndrome (DS) is the most common chromosome disorder in live born infants, affecting several body systems, but usually sparing skeletal muscles. We present the case of a child with coexistence of DS and dystrophinopathy. Only 1 similar case has been reported so far.

Patient Concerns: An 8-year-old boy with DS had a history of incidental finding of increased serum creatine kinase levels up to 1775 U/L (normal values 38–174 U/L). He presented no delay in motor development; at the neurological examination, no muscle weakness or fatigability was detected in 2 different evaluations performed over a 6-month period.

Diagnoses: Skeletal muscle biopsy revealed marked dystrophic changes with patchy immunostaining for dystrophin. The Duchenne muscular dystrophy gene was screened for deletions by multiplex polymerase chain reaction, but no mutations were found. Sequence analysis of the Duchenne muscular dystrophy gene revealed a splice-site mutation c.1812+1G>A in intron 15 and confirmed a diagnosis of Becker muscular dystrophy.

Interventions: The patient has started a specific physiotherapy that avoided any deterioration in motor development and muscular wasting.

Outcomes: A multidisciplinary follow-up was initiated. The genetician that followed the patient for DS was supported by the neurologist, the physiotherapist, the pulmonologist, and the cardiologist.

Lessons: This peculiar "double trouble" case exemplifies the value of careful clinical evaluation and adequate clinical experience to identify the concomitance of 2 different genetic syndromes in the same patient, and it points out the significance of muscular strength assessment in DS patients to make the most correct prognosis, and, consequently, to organize the best long-term care.

Abbreviations: BMD = Becker muscular dystrophy, CK = creatine kinase, DMD = Duchenne muscular dystrophy, DS = Down syndrome.

Keywords: Becker muscular dystrophy, coinheritance, Down syndrome, Duchenne muscular dystrophy

1. Introduction

Down syndrome (DS, OMIM #190685) is 1 of the most common chromosome abnormalities in humans, occurring in about 1 per 1000 babies born each year.[1] It is caused by triplicate state (trisomy) of all or of a critical portion of chromosome 21, usually by nondisjunction.[2] It is characterized mainly by peculiar facial features, physical growth delay, mild to moderate intellectual disability, high rate of congenital heart defects and hypothyroidism, high risk for leukemia and lower, but significant rates of gastrointestinal malformations, which often require surgery within the first days to weeks of life.[3] Other surgical conditions that occur at higher rates include Hirschsprung disease, polydactyly, cleft palate, and cataracts.

Mutations in Duchenne muscular dystrophy (DMD) gene, which encodes the protein dystrophin and is located on chromosome X,[4] cause a spectrum of muscle diseases affecting male individuals and named dystrophinopathies. Two main forms are recognized, namely Duchenne and Becker muscular dystrophies (DMD and BMD, OMIM #310200 and #300376, respectively). DMD is the most common form of inherited muscle disease in childhood, with an estimated incidence of 1 in 3500 born males.[5] It presents in early childhood and it is rapidly progressive, with affected children being wheelchair-bound by 12 years of age. BMD is a generally milder and more variable form of dystrophinopathy, with an incidence of 1 in 18,518 male births.[5] Indeed, BMD phenotype can range from asymptomatic individuals with increased serum creatine kinase (CK) levels and muscle cramps, to more invalidating forms with severe muscle weakness and/or dilated cardiomyopathy. BMD patients usually remain ambulatory into their 20s.[6] The Duchenne phenotype is

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usually due to a mutation resulting in a shift of the reading frame of the mRNA transcript, leading to a truncated gene product.[7,8] In BMD, the mutation does not affect the reading frame; rather it results in the synthesis of shorter, but partly functional dystrophin molecules.[7,8]

We describe a peculiar case presenting a combination of chromosome 21 trisomy and in-frame DMD gene deletion. The patient has typical features of both DS and BMD.

2. Case

2.1. Presenting concerns

An 8-year-old boy with DS had been referred to us by an attentive neurologist for recurrent findings of increased serum CK levels. The patient was found to have an incidental elevation of serum transaminases that had led to a gastroenterological evaluation at around 6 years of age. During the same year, he was found to have elevated serum CK levels, up to 1775 U/L (normal values 38–174 U/L), confirmed in several serial assessments. Family history was negative for inherited diseases.

2.2. Clinical findings

Medical history was negative for delay in motor development and he did not show progressive muscular wasting. At the neurological examination, he showed characteristic DS facial features, but no muscle weakness or fatigability were detected in 2 different evaluations performed over a 6-month period.

2.3. Diagnostic focus and assessment

Electromyography findings revealed immediately a myopathic pattern. Because of the peculiarity and complexity of the clinical presentation, after the approval of the Ethics Committee of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico and upon parental signature of written informed consent, the child underwent a biceps brachial skeletal muscle biopsy that showed moderate dystrophic alterations consisting of scattered rounded opaque fibers, rare necrotic fibers undergoing phagocytosis, and basophilic muscle fibers. Immunocytochemical studies of dystrophin using DYS-1 (rod domain) and DYS-2 (C-terminus) monoclonal antibodies demonstrated normal immunoreactivity. DYS-3 (N-terminus) antibody showed weak immunostaining at the sarcolemma and a few dystrophin-negative fibers. Normal sarcolemmal immunostaining was observed with the antibodies against caveolin, and α and γ-sarcoglycan.

DNA analyses for DMD/BMD were performed after written informed consent. The DMD gene was screened for deletions by multiplex polymerase chain reaction, but no mutations were found. Sequence analysis of the DMD gene revealed a splice-site mutation c.1812+1G>A in intron 15. The mutation results in exon 15 skipping, a change that would leave the reading frame intact.

2.4. Therapeutic focus and assessment

The patient has started a specific physiotherapy that avoided any deterioration in motor development and muscular wasting. No other medical or surgical therapies were required.

2.5. Follow-up and outcomes

As soon as the diagnosis was performed, a multidisciplinary follow-up was initiated. The genetician that followed the patient for DS was supported by the neurologist, the physiotherapist, the pulmonologist, and the cardiologist.

2.6. Timeline

Figure 1 represents the skeletal muscle biopsy that permitted the diagnosis.

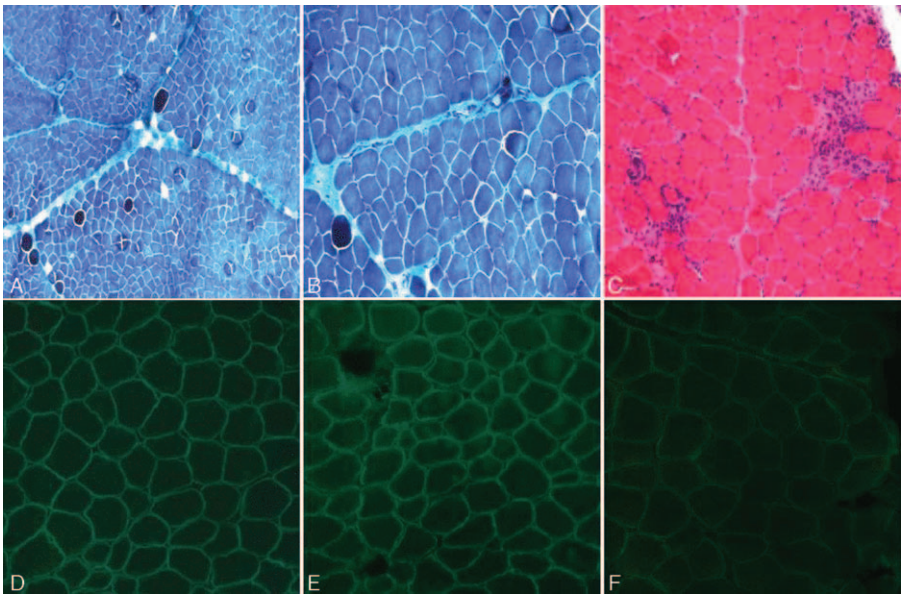

Figure 1. Skeletal muscle biopsy. Gomori trichrome (A, B) and H&E (C) staining showed typical histologic changes of muscular dystrophy (see the txt for description). Immunohistochemistry of dystrophin: DYS-1 (rod domain) (D) and DYS-2 (C-terminus) (E) were normal; DYS-3 (F) (N-terminus) antibody showed weak sarcolemmal immunostaining and a few dystrophin negative fibers.

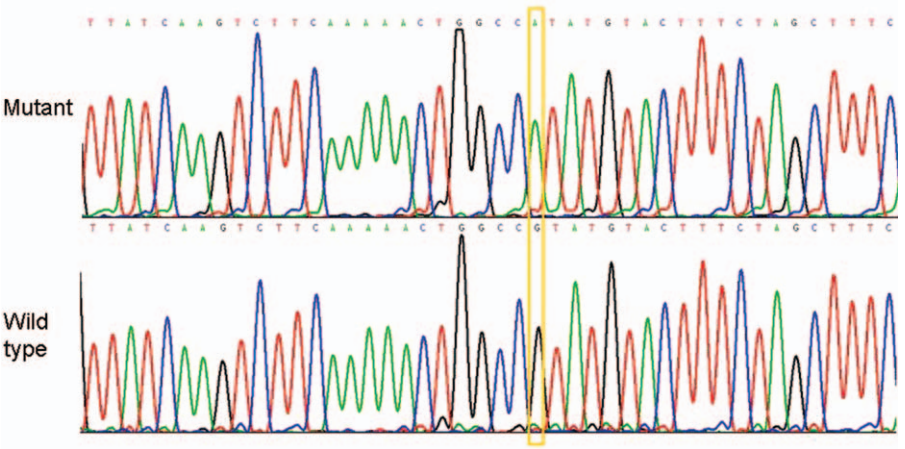

Figure 2. Molecular genetic analysis of the cDNA DMD gene. BMD exon/intron 15, base change c,1812+1G>A. BMD = Becker muscular dystrophy, DMD = Duchenne muscular dystrophy.

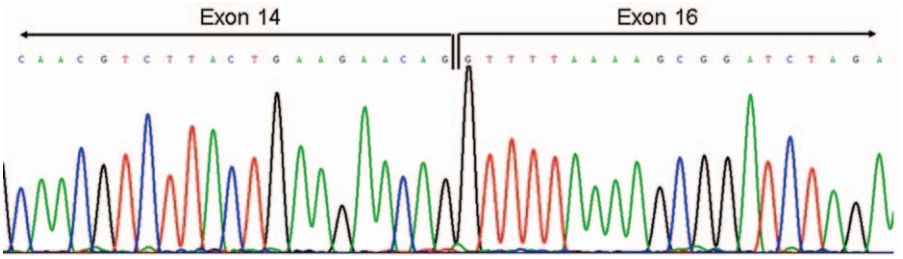

Figure 3. Molecular genetic analysis of the mRNA DMD gene. Base change c.1812+1G>A leads to a splice site mutation in intron 15, resulting in exon 15 deletion. DMD = Duchenne muscular dystrophy.

As soon as the results of the skeletal muscle biopsy were available, molecular genetic analysis was performed and documented a splice-site mutation c.1812+1G>A in intron 15. Figure 2 shows the molecular genetic analysis of the cDNA DMD gene, whereas Fig. 3 reports molecular genetic analysis of the mRNA DMD gene.

3. Discussion

We report the case of a 8-year-old boy with coinheritance of DS and BMD. An increase in CK serum levels is not a typical feature of DS, although a significant increase in CK values is reported in obese DS patients compared with nonobese ones.[9] Our patient, who had both high serum CK levels and a myopathic electromyography pattern, underwent skeletal muscular biopsy, which revealed a weak Dys 3 immunostain compatible with a diagnosis of BMD. The diagnosis was confirmed by DMD gene analysis, which revealed an intronic splice-site mutation causing exon 15 skipping and keeping the reading frame intact. The typical BMD great phenotype variability[10] may account for the normal muscular strength in the patient.

In DS patients, considerable evidence underlines the common presence of reduced muscle strength, only partially explained by degree of intellectual disability.[3] Also, Cowley et al[11] showed lower expression of cytochrome-c oxidase in Soleus muscles of DS murine model, Ts65Dn, our patient, however, has normal COX activity. Despite these data, neuromuscular anomalies are very uncommon in DS, although DS has been previously described in 2 independent patients affected by DMD[12] and BMD,[13] respectively.

The concomitant presence of DS and BMD in a single patient is logically assumed to be coincidental. The incidence of DS is 1 per 1000 birth,[1] and the frequency of BMD is estimated to be 1 in 18,518 male births.[5] However, the possibility of being affected with 2 relatively common inherited genetic conditions, although rare, should be considered when findings are incoherent with the primary diagnosis. Although the genetic etiology is different, dystrophinopathies have been reported in males with chromosomal abnormalities, more specifically DMD in Turner and Klinefelter syndrome,[14–16] and BMD in Noonan syndrome.[17]

The rarity of this disease association underlines the value of adequate clinical experience; even more, it emphasizes how a multidisciplinary approach is essential in managing and treating these patients. Because reduction in muscle strength interferes with everyday activities and limits opportunities for independent living, it is extremely important to assess DS patients' muscle strength and to detect any genetic comorbidities to make the most correct prognosis and, consequently, organize the best long-term care.

4. Patient's and parents' perspective

We were happy to identify the cause of the increase in CK in our child and we are confident in the multidisciplinary follow-up that has been started.

5. Informed consent

The patient's parents provided their written informed consent for the publication of this study.

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