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ScienceDirect

Neuromuscular Disorders 23 (2013) 955–961

www.elsevier.com/locate/nmd

'Double trouble': Diagnostic challenges in Duchenne muscular dystrophy in patients with an additional hereditary skeletal dysplasia

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Received 5 April 2013; received in revised form 2 August 2013; accepted 5 August 2013

Abstract

Duchenne muscular dystrophy (DMD) is caused by mutations in *Dystrophin* and affects 1 in 3600–6000 males. It is characterized by progressive weakness leading to loss of ambulation, respiratory insufficiency, cardiomyopathy, and scoliosis. We describe the unusual phenotype of 3 patients with skeletal dysplasias in whom an additional diagnosis of DMD was later established. Two unrelated boys presented with osteogenesis imperfecta due to point mutations in *COL1A1* and were both subsequently found to have a 1 bp frameshift deletion in the *Dystrophin* gene at age 3 and age 15 years, respectively. The third patient had a diagnosis of pseudoachondroplasia caused by a mutation in the *COMP* gene and was found to have a deletion of exons 48–50 in *Dystrophin* at age 9. We discuss the atypical presentation caused by the concomitant presence of 2 conditions affecting the musculoskeletal system, emphasizing aspects that may confound the presentation of a well-characterized disease like DMD. Additional series of patients with DMD and a secondary inherited condition are necessary to establish the natural history in this "double trouble" population. The recognition and accurate diagnosis of patients with two independent genetic disease processes is essential for management, prognosis, genetic risk assessment, and discussion regarding potential therapeutic interventions.

Keywords: Double trouble; Duchenne muscular dystrophy; Genetic counseling; Ostoegenesis imperfecta

Introduction

Duchenne muscular dystrophy (DMD) (OMIM#310200) is an X-linked disorder, caused by mutations in the *Dystrophin* gene, and affects 1 in 3600–6000 live male births [1,2]. DMD was first described in the early 19th century, and the causative gene was only identified in 1987 [3,4]. It is characterized by progressive muscle weakness leading to loss of ambulation, respiratory insufficiency, cardiomyopathy, and scoliosis. Boys typically present at age 3–5 years with evidence of proximal muscle weakness and calf hypertrophy. Diagnosis is made on the clinical presentation, elevated serum creatine kinase (CK) levels, and confirmatory genetic testing of the *Dystrophin* gene.

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http://dx.doi.org/10.1016/j.nmd.2013.08.003

In a small number of patients with intronic splice spite mutations interfering with normal splicing, confirmatory muscle biopsy staining or cDNA studies may be necessary. Immunohistochemistry on muscle biopsy tissue shows an absence of *dystrophin,* a large membrane-associated protein essential for muscle cell stabilization [5]. Frameshifting or terminating deletions and mutations are typically associated with the severe Duchenne phenotype, while frame-preserving deletions are typically associated with the milder Becker muscular dystrophy phenotype.

The clinical presentation of a well characterized disorder such as DMD may be masked and initially overlooked by the presence of another disorder of the musculoskeletal system. We present three patients with the rare combination of a hereditary skeletal dysplasia whose DMD diagnosis was delayed, illustrating the diagnostic challenges of their confounding phenotype.

Patients

Patient 1

A now 16-year-old boy presented at 4 months of age with a hairline fracture of the femur. After a second femoral fracture at 8 months of age, concerns arose about the possibility of osteogenesis imperfecta (OI). Further examination identified pale blue sclerea. The family history was negative for OI, neuromuscular, or neurological disease. Targeted genetic testing confirmed a mutation in *COL1A1* (c.3532-2A>G), associated with OI type IV at age 1 year. He started receiving Pamidronate at age 8 years. After a period of prolonged immobility while recovering from surgery for a right tibia and left femur fracture, he became non-ambulatory at age 8 years. He lost the ability to stand independently at age 10 years. At age 12 years, he sustained another fracture and he started complaining of a worsening of weakness in both upper and lower extremities, proximally more than distal, and lower extremity cramping. His examination was significant for short stature, bilateral blue sclerae, mild macroglossia, and a transverse smile. He also had contractures of jaw, shoulders, elbows, wrists, knees, and ankle dorsiflexors and bilateral distal finger laxity (Fig. 1A & D). Dextroconvex thoracic scoliosis and levoconvex lumbar scoliosis were present. At age 15 years he had generalized weakness, proximal more than distal, and diffuse global areflexia. Exam was limited due to his skeletal dysplasia and his history of fractures. His serum CK level was elevated at 1374 U/L (0–249 U/L). He had diffuse osteopenia and scoliosis on spine radiographs (Fig. 1F & G). Electrocardiogram showed right ventricular conduction delay; echocardiogram results were normal. Force vital capacity (FVC) was 50% of predicted value. Muscle ultrasound demonstrated moderately to severely increased echogenicity in all muscles, consistent with a dystrophic or myopathic process. Results of muscle biopsy at age 12 was consistent with muscular dystrophy showing extensive replacement of muscle with fatty tissue and the presence of only few muscle fibers. Tissue was stained for alpha-dystroglycan, beta-dystroglycan, merosin, collagen VI, perlecan and embryonic myosin heavy chain (Fig. 2A & D). Dystrophin staining was requested at age 15 when the suspicion of DMD was raised. Immunohistochemical staining revealed absent staining for the dystrophin in the majority of muscle fibers compared to a control sample (Fig. 2B–F). *Dystrophin* gene sequencing revealed a *de novo* out-of-frame 1 base pair deletion at c.1574 in exon 13.

Patient 2

The second patient is a now 12-year-old boy who was diagnosed with pseudoachondroplasia at age 1 year. His maternal family history was positive for pseudoachondroplasia, including the patient's mother, sister, grandmother and several first cousins. The family history was otherwise negative for neuromuscular or neurological disease. In 2012, molecular genetic testing identified a heterozygous c.1540T>G mutation in exon 13 of the cartilage oligomeric matrix protein (*COMP*) gene resulting in a change of Cysteine to Glycine at position 484 (p.Cys484Gly). He was enrolled in Early Intervention services at age 2 years for global developmental delays. He sat independently at age 1 year and walked at 18 months. He also had speech and learning difficulties. Following myringotomy at age 2 years, his verbal skills improved. He had difficulties rising from the floor or from a seated position, and required support climbing stairs. He also had difficulties with balance, excessive falling and was noted to lag behind his peers. At this time, his weakness was attributed to his underlying skeletal dysplasia. His medical history is significant for vitamin D deficiency, asthma, and at least 14 documented ear infections. The patient was referred for neuromuscular evaluation at age 8 years due to progressive weakness. He had a slight positional tremor in his fingers, hypotonia and weakness: grip was 4/5, deltoids 3+ to 4−/5, quadriceps 3/5, peroneals 3/5 bilaterally, and anterior tibialis 3/5 (MRC grading scale). He had a positive Gowers' sign and calf hypertrophy (Fig. 1E). Deep tendon reflexes were diminished with flexor plantar responses. Vibration and proprioception were intact. His feet exhibited *planus valgus* bilaterally and he showed an exaggerated lumbar lordosis (Fig. 1B–C). His CK level was markedly elevated at approximately 16,000 U/L. Muscle biopsy was not performed. Molecular genetic testing identified an out-of-frame deletion of exons 48–50 in the *Dystrophin* gene consistent with a diagnosis of DMD.

Patient 3

A now 3-year-old boy presented at age 15 months for concerns for external rotation of his left lower extremity and abnormal gait. Due to presence of blue sclerae noted at a few months of age and a paternal family history of