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Congenital muscular dystrophy phenotype with neuromuscular spindles excess in a 5-year-old girl caused by HRAS mutation

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Abstract

We report on a 5-year-old girl who presented with an association of symptoms reminiscent of an Ullrich-like congenital muscular dystrophy including congenital hypotonia, proximal joint contractures, hyperlaxity of distal joints, normal cognitive development, and kyphoscoliosis. There was an excess of neuromuscular spindles on the skeletal muscle biopsy. This very peculiar feature on muscle biopsy has been reported only in patients with mutations in the *HRAS* gene. Sequence analysis of the subject's *HRAS* gene from blood leukocytes and skeletal muscle revealed a previously described heterozygous missense mutation (c.187G>A, p. Glu63Lys). The present report thus extends the differential diagnosis of congenital muscular dystrophy with major "retractile" phenotypes and adds congenital muscular dystrophy to the clinical spectrum of HRAS-related disorders.

Keywords: CMD; Ullrich congenital muscular dystrophy; HRAS; Excess of neuromuscular spindles

1. Introduction

Congenital muscular dystrophies (CMD) are a heterogeneous group of inherited muscle disorders clinically characterized by muscle weakness, hypotonia, and contractures at birth or during the first months of

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life with a dystrophic pattern on muscle biopsy. Muscle histopathology from patients with CMD shows a dystrophic pattern characterized by a necrosis/regeneration process with reduced number of muscle fibers and replacement of muscle by fat and fibrous connective tissue [1].

Ullrich congenital muscular dystrophy (UCMD; OMIM# 254090) is one of the most common types of CMD. The typical features of UCMD include a combination of congenital contractures of proximal joints, associated with hyperlaxity of distal joints, weakness, and early respiratory failure. It is caused by mutations in the *COL6A1-A3* genes encoding the α1–3 (VI) chains that constitute the major form of collagen type VI (COLVI) [2].

A peculiar histopathological observation of an excess of neuromuscular spindles in the muscle biopsies has only been previously described in patients with a variant form of Costello syndrome (OMIM# 218040), the so-called congenital myopathy with excess of muscle spindles associated with mutations in HRAS (official full name: Harvey rat sarcoma viral oncogene homolog) [3]. Costello syndrome is clinically characterized by developmental delay, postnatal growth retardation, severe failure to thrive, typical coarse facial features, mental retardation, cardiac defects, musculoskeletal, and skin abnormalities, and predisposition to certain malignancies including rhabdomyosarcoma and neuroblastoma [4].

In the present study, we report on a 5-year-old girl who presented with a rare clinico-pathological phenotype associating an Ullrich-like congenital muscular dystrophy phenotype with an excess of neuromuscular spindles on muscle biopsy. The patient carried the heterozygous c.187G>A (p. Glu63Lys) missense mutation in the *HRAS* gene in muscle and blood leukocytes. This mutation has already been reported by other investigators in a patient with a severe infantile presentation of myopathy with excess of neuromuscular spindles [3].

2. Case report

The patient was the second child of non-consanguineous Algerian parents. There was no informative family history. Polyhydramnios and weak fetal movements were noticed throughout the gestation. The girl was born at term following a spontaneous vaginal delivery. Birth weight was 3350 g (40th centile), length was 45 cm (5th centile), and head circumference was 37 cm (90th centile). At birth, moderate hypotonia, pectus carinatum, mild facial dysmorphism, protruded calacanei, clubfoot, adducted thumbs, and generalized proximal arthrogryposis were noted. No respiratory failures or episodes of hypoglycemia were reported. Motor milestones were markedly delayed. She was able to sit at the age of 2 years, but she never stood or walked. At the last assessment, at 5 years 2 months, her weight and height were 13.3 kg and 94 cm, respectively (both below the 3rd centile). Head circumference was normal.

The girl shows a normal cognitive development. She presents with facial dysmorphism characterized by high forehead, epicanthus, hypertelorism, thick lips, micrognathia, depressed nasal bridge, short philtrum, full cheeks, and short neck. She also presented with sunken eyes, mild right strabismus, pectus carinatum, hypertrichosis, severe kyphosis, mild scoliosis, ulnar deviation of wrists, severe shoulder, hip, and knee contractures, protruded calacanei, and distal joint hyperlaxity (Fig. 1). Weakness was generalized with sparing of the facial musculature; deep tendon reflexes were reduced throughout. No skin abnormalities or organomegaly were noticed. Laboratory studies included normal karyotype and normal serum creatine kinase, urine mucopolysaccharides, and oligosaccharide levels. A brain MRI performed at the age of 2 years 4 months showed enlarged third and lateral ventricles but no evidence of brain malformation. An X-ray examination showed delayed bone age, brachymetacarpia, hypoplasia of distal phalanges, and sequelae of femoral fractures. A mitral valve dysplasia characterized by mitral insufficiency grade III-IV was surgically treated when the patient was 5 years old.

Electromyography revealed a myopathic pattern with action potentials of low amplitude and normal motor and sensory nerve conduction. Two muscle biopsies were taken from the quadriceps at ages 28 months and 5 years. The first muscle biopsy failed to collect sufficient muscular tissue for analysis; mostly fat tissue was obtained. Given the muscular phenotype and clinical presentation, immunolabelling of collagen VI was performed on cultured skin-derived fibroblasts; it revealed the absence of secretion of COLVI associated with intracellular retention (Fig. 2A–F). However, no mutations were detected in the *COL6A1-A3* genes. Due to difficulties in obtaining muscular tissue samples, whole body muscular MRI was performed, which revealed diffuse hypotrophy of muscles with no selective pattern of involvement. No abnormalities suggestive of other known myopathies were identified; in particular the specific pattern associated with COLVI-related myopathies was absent (Fig. 3). In the second muscle biopsy taken at age 5, dense connective tissue harboring numerous ovoid formations corresponding to neuromuscular spindles and only very few extrafusal muscle fibers were observed in the absence of necrotic/regenerative fibers (Fig. 2G–I). Genomic DNA was isolated from peripheral lymphocytes and skeletal muscle using standard techniques. Sequencing of the *HRAS* gene revealed the heterozygous c.187G>A (p. Glu63Lys) missense mutation in skeletal muscle and leukocyte derived DNA from patient (Fig. 4). Sequencing was not performed in other tissues. Blood samples were taken from the patient's parents to screen mutations in the *HRAS* gene. Neither parent carries the mutation (data not shown).