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LETTER TO THE EDITORS

A rare case of congenital myopathy with excess muscle spindles: expanding the clinical spectrum of HRAS-associated neuromuscular disease

Julia M. Henry[1] · Nizar Chahin[1] · Yael Shiloh-Malawsky[1] · Zheng Fan[1] · Duygu Selcen[2]

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Introduction

HRAS is a member of the RAS family of GTP-binding proteins involved in cell signaling and growth promotion [1]. Costello syndrome (CS) (MIM#218040) results from activating mutations of the Ras–MAPK–ERK signaling cascade [2], often a gain of function mutation in HRAS (MIM*190020) [1]. A more recently discovered syndrome, congenital myopathy with excess of muscle spindles (CMEMS) (#218040), has also been linked to mutations of HRAS, and is considered a variant of CS. To date six cases of CMEMS have been reported [2]. We report a case of CMEMS who, to our knowledge, outlived all other reported cases of this devastating syndrome and who had autopsy results to further define the phenotype.

Case presentation

The male patient was born at 39-week gestation to non-consanguineous parents without a family history of neurological disease. The pregnancy was complicated by polyhydramnios and decreased fetal movement. Figure 1 shows the physical appearance. Nerve conduction studies were normal, needle examination showed fibrillation potentials and positive sharp waves in proximal muscles with rapidly recruited, short duration, small amplitude motor unit potentials. Quadriceps biopsy revealed excessive muscle spindles, consistent with CMEMS. Sequencing of the HRAS gene revealed the E63K mutation, c.187 G>A in exon 3. Both parents tested negative for HRAS mutations.

The patient was followed up closely by a multidisciplinary team. He required gastrostomy tube for feeding and eventually home mechanical ventilation. At 26 months, the patient was living at home. Developmentally, he could visually fix on and track faces and appeared to enjoy social interaction. He moved his fingers and toes independently, but had no improvement in his generalized weakness. He never developed the ability to roll over or sit unsupported.

At 31 months he expired after a cardiorespiratory arrest. Postmortem examination revealed a structurally normal brain. There was mild cardiomegaly and a patent foramen ovale, but the heart was otherwise normal. Besides narrowed distal ureters, no other significant abnormalities of the internal organs were found. The gastrocnemius muscle contained mostly normal-appearing tissue with clusters of spindles in few fascicles. It also showed type 1 fiber atrophy without fiber type preponderance. The rectus femoris (Fig. 2) was nearly replaced by muscle spindles. The muscle spindles were of varying size and composed of circular fibrous capsules containing few intrafusal muscle fibers. Some spindles were void of any muscle fibers. The intrafusal fibers were of either histochemical type. Rare extrafusal fibers could be seen among the spindles. Samples from the deltoid were normal.

Discussion

A phenotypic spectrum of HRAS mutations has been proposed with the classic CS at mild end and CMEMS on the severe end [2]. Identification of excess muscles spindles is thought rare in children with the classical phenotype of CS. The weakness in classical CS tends to be mild, and

✉ Julia M. Henry
JMHenry@unch.unc.edu

[1] Department of Neurology, University of North Carolina School of Medicine, Chapel Hill, NC, USA

[2] Mayo Clinic Rochester, Rochester, MN, USA

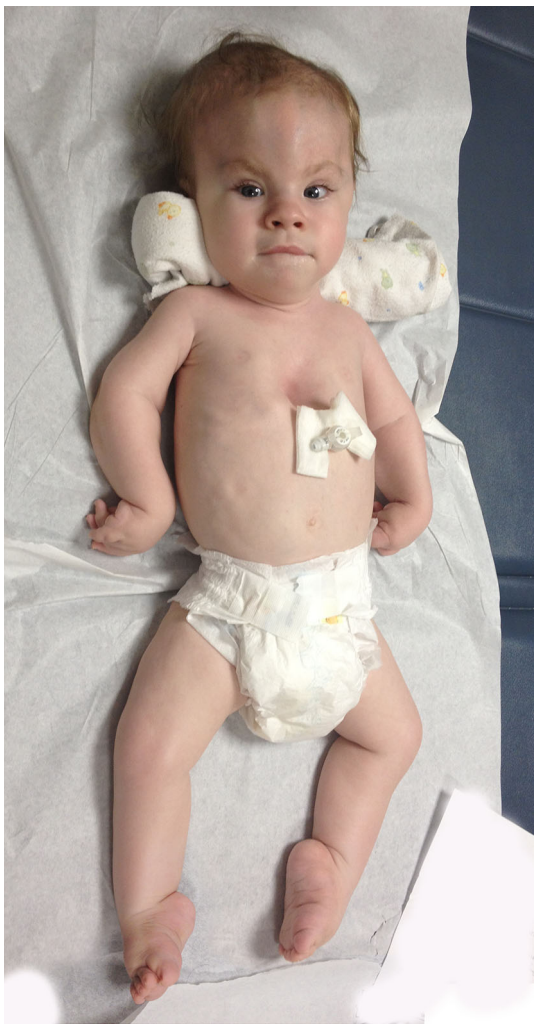

Fig. 1 The patient at age 11 months showing many of the features of Costello syndrome, broad high forehead, fine curly hair, long eye lashes, upturned nose, ulnar deviation of wrists and fingers, plantar flexion contractures and pectus excavatum

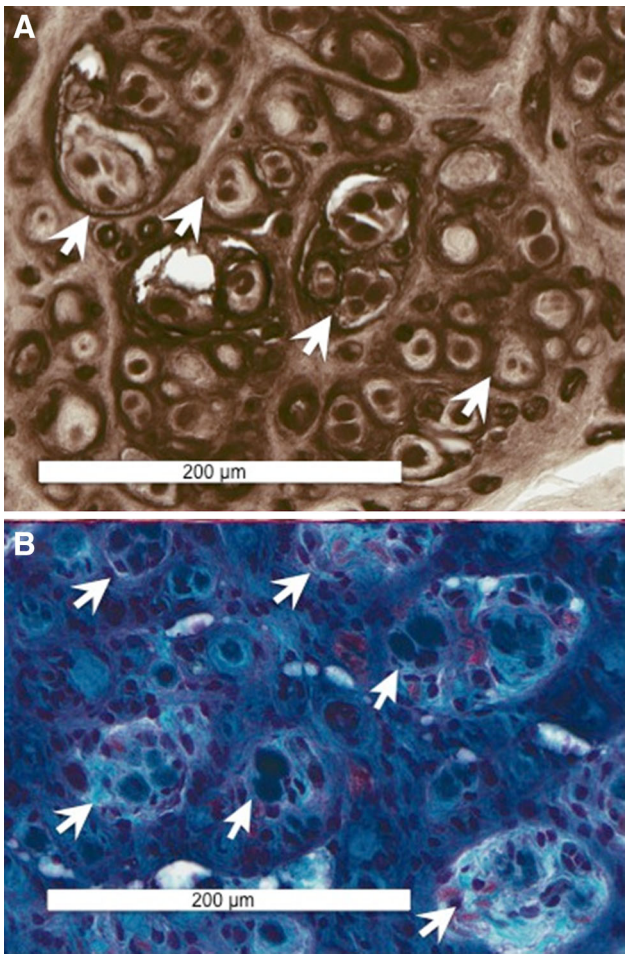

Fig. 2 **a** ATPase 9.4 stain and **b** Masson's trichrome stain: the rectus femoris muscle is nearly replaced by muscle spindles of varying sizes containing few muscle fibers. Some of the spindles are atrophic and only contain fibrous and connective tissue without any apparent muscle fibers

thus does not prompt invasive testing such as muscle biopsy [2]. Perhaps many patients with CS would have some degree of spindle excess on pathology were they to undergo muscle biopsy.

An additional case of CMEMS with the E63K HRAS mutation has been reported [3]. This patient had many features in common with ours, including diffuse body edema, arthrogryposis, congenital fractures and dependence on mechanical ventilation. Our patient lacked cardiomyopathy, which likely explains his longer survival.

An additional case with the E63K mutation was recently reported in a 5-year-old child with hypotonia, delayed gross motor development, joint contractures, hyperlaxity of distal joints and normal cognitive function [4]. Excess of muscle spindles was found on her muscle biopsy. At the time of the report the patient was clinically well.

It appears that CMEMS is a very severe phenotypic subtype of CS. None of the reported cases of CMEMS lived past infancy/toddlerhood, whereas it is not uncommon for patients with classic CS to live into their 20s or 30s [5]. Cardiomyopathy, respiratory failure and severe skeletal muscle weakness contribute to the shortened life span of children with CMEMS. One major barrier to comparison is that children with CMEMS have not lived past infancy. Given that our patient and two other reported patients [3, 4] shared an identical HRAS mutation which had also been reported in CS, it stands to reason that there is a broader spectrum of possible phenotypes than previously thought for CS, and that mild excess spindle may be underrecognized in CS. Observations of our patient may provide insight to the relationship between these two genetically similar syndromes, and further our understanding of their phenotypic ranges.

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Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standard This study was carried in accordance with ethical standards as set out in the 1964 Declaration of Helsinki and its later amendments.

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