Pediatric Neurology 51 (2014) 192–197

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Topical Review

Congenital Myopathy With Cap-Like Structures and Nemaline Rods: Case Report and Literature Review

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ABSTRACT

BACKGROUND: Cap myopathy is a rare congenital myopathy characterized by cap structures located at the periphery of the muscle fiber. Cap structures consist of disarranged thin filaments with enlarged Z discs. The clinical presentation and natural history of cap myopathy is variable and overlaps with other congenital myopathies. **METHODS:** We describe a 10-year-old boy with cap myopathy and contrast him with 20 other individuals reported in the literature. **RESULTS:** Our patient presented at birth with hypotonia and weakness and subsequently developed respiratory failure in infancy. He is ambulatory but has increasing fatigue and requires a wheelchair by midafternoon. His muscle biopsy at 3 months revealed a nemaline myopathy and secondary fiber-type disproportion with type 1 hypotrophy and predominance. A repeat muscle biopsy at age 6 years revealed numerous peripherally located cap-like structures containing nemaline rods and exhibited a spectrum of Z-disk and myofibrillar abnormalities. Molecular genetic testing was performed for *NEB*, *TPM2*, *TPM3*, *ACTA1*, *TNNT1*, *SEPN1*, *SMN1*, *DMPK*, *FSHMD1A*, and *mtDNA*. A known pathogenic mutation, c.1152+1G>A, and a previously unreported variant, c.1782+4_1782+5delAG, were detected in *NEB*. **CONCLUSION:** Our patient has a more severe phenotype than most reported patients and is the first patient with cap myopathy to have a mutation in *NEB*. Our case supports the identification of cap myopathy as a congenital myopathy with significant overlapping features with nemaline myopathies and further elucidates the phenotype of this disease.

Keywords: cap myopathy, nemaline rods, *NEB*, case report, literature review

Pediatr Neurol 2014; 51: 192-197

Introduction

Cap myopathy, a congenital myopathy characterized by cap structures located at the periphery of the muscle fiber, was initially described in 1981 and came to light again in 2002.[1,2] To date, a total of 20 patients have been reported; of these, 13 were sporadic[2-11,13] and seven were familial.[12-14] One family had cap myopathy and nemaline myopathy occurring in the same kindred,[13] two familial cases of cap myopathy had features of both cap myopathy and nemaline myopathy,[12,14] and one sporadic case had features of both central core disease and cap myopathy.[11] The cap structures are disarranged myofibrils with enlarged and/or disorganized Z discs and no thick filaments. The coexistence of features of cap myopathy with nemaline myopathy and central core disease, in some cases, suggests there may be etiological overlap.

Congenital myopathies are a diverse group of congenital neuromuscular disorders that include slowly progressive or nonprogressive conditions secondary to mutations in various genes, including those for sarcomeric proteins.[15,16] Suggestive clinical features include hypotonia, hyporeflexia, diffuse weakness, often more proximal than distal, and poor muscle bulk. Morbidity is associated with complications from respiratory muscle involvement, bulbar weakness resulting in aspiration and swallowing difficulty, and orthopedic involvement including scoliosis and contractures. Intelligence is usually normal, and cardiac

Conflict of interest: The authors declare that they have no conflicts of interest that may be relevant to the submitted work.

Article History:
Received July 9, 2013; Accepted in final form April 3, 2014

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0887-8994/$ - see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pediatrneurol.2014.04.002

involvement is rare.[17] Muscle weakness ranges in severity from neonatal life-threatening disease to mild muscle weakness in adulthood. Diverse histopathologic and clinical phenotypes have been identified because of genetic and phenotypic heterogeneity.[15] Accordingly, definitive diagnosis requires muscle biopsy and/or molecular genetic testing.

We describe child with congenital myopathy with cap-like structures and nemaline rods and contrast him with 20 previously reported patients. Our patient supports the classification of cap myopathy as a category of congenital myopathy that overlaps with the nemaline myopathy family.[18]

Patient Description

This 10-year-old boy was born at 33 weeks gestation after an uncomplicated pregnancy and delivery. At birth, his clinical features included dolichocephaly, bilateral ptosis, low-set ears with attached lobes, a tented upper lip, downturned corners of the mouth, and a high arched palate. His hands demonstrated bilateral transverse palmar creases, fifth finger clinodactyly, hyperconvex nails, and prominent fetal pads. His first and second toes were overlapping and he had cryptorchidism. Neurological examination revealed hypotonia, generalized weakness, decreased deep tendon reflexes, and weak Moro, grasp, and suck reflexes.

His mother had a clinical and electrophysiological diagnosis of hereditary sensory neuropathy (HSN). His maternal grandmother and two maternal aunts also had a clinical evaluation of HSN. Genetic testing of his mother, including analysis for HSN type 1 (sequencing of *SPTLC-1* exon 5), CMT1A (duplication testing for *PMP22*), and myotonic dystrophy (analysis of *DMPK* CTG repeats), was normal. His father and two older brothers were healthy.

After his first week he developed recurrent respiratory infections and apneic episodes with evidence of reflux and aspiration felt to be secondary to a swallowing disorder. He experienced several episodes of respiratory arrest, at times requiring chest compressions, and ultimately he required continuous gastrojejunal tube feeds.

After discharge from the neonatal intensive care unit at 3 months, he gained developmental milestones but suffered regression after a cardiac arrest at 18 months of age. Subsequently, his developmental milestones progressed such that by 2.3 years of age he was ambulatory. Currently (at 10 years old), he has global developmental disability consistent with an 18- to 24-month old child. He is able to walk but has increasing fatigue requiring a wheelchair by midafternoon. He communicates using about 15 signs consistently. He is able to say about five words. He demonstrates his needs by showing his parents and by pointing.

The child's ongoing medical issues include recurrent aspiration pneumonia, asthma, and chronic hypoventilation requiring BiPAP at night. He is exclusively G-tube fed because of dysphagia and risk of aspiration and continues to have significant hypotonia, diffuse weakness (proximal more than distal muscle groups), and muscle wasting. His reflexes are present symmetrically in the upper and lower extremities but are decreased.

Investigations including nerve conduction studies, electromyography, and a brain magnetic resonance imaging were normal. With respect to the nerve conduction studies, his right median sensory nerve showed a latency of 0.9 ms, an amplitude of 9.5 mV, and a conduction velocity of 33 m/second. His right tibial motor nerve showed a distal latency of 2.1 ms, a proximal latency of 4.7 ms, an amplitude of 10.7 mV, and a conduction velocity of 25 m/second. With respect to the electromyography, his right tibialis anterior and medialis vastus muscles showed normal motor unit potentials. His creatine kinase level was 66 U/L (reference range: 90-395 U/L). Laboratory tests including lactate, urinary oligosaccharides, urinary mucopolysaccharides, very long chain fatty acids, and phytanic acid were normal. Analysis of leukocytes for sulfatase, β-galactosidase, arylsulfatase A, and galactocerebrosidase revealed normal levels. Cerebrospinal fluid analysis was normal for amino acids and lactate. Anti–acetylcholine receptor antibodies test results were negative.

A muscle biopsy of the right thigh at 7 months of age (Fig 1) revealed fiber-type disproportion, characterized by type 1 fiber predominance and hypotrophy. Nemaline rods were observed in many fibers, with preferential involvement of type 1 fibers, even allowing for their numerical predominance. A repeat muscle biopsy of the left thigh at 6 years of age (Fig 2) revealed a much lesser degree of fiber size variation compared to the earlier biopsy. Pale-staining cap-like structures were observed in many fibers with ATPase (Fig 2A,B), cytochrome oxidase, and succinate dehydrogenase histochemical staining. On resin-embedded sections most of the cap-like structures were observed to contain nemaline rods (Fig 2D), although occasional more subtle areas of sarcoplasmic disarray were seen. Individual or small groups of nemaline rods were also observed within the sarcoplasm of frequent fibers unassociated with cap-like areas. A similar distribution of nemaline rods was observed on modified Gomori trichome–stained frozen sections (Fig 2C). Electron microscopy confirmed the presence of accumulations of nemaline rods in subsarcolemmal cap-like regions (Fig 2E). At their ends the rods showed characteristic continuity with thin filaments (Fig 2F). Disorganized bundles of thin filaments and a paucity of thick filaments were also evident between nemaline rods. There was Z-band thickening, irregularity, and streaming adjacent to cap-like structures and focally within sarcomeres unrelated to such.

Chromosomal analysis revealed a normal 46,XY karyotype. Sequencing was performed for *TPM2* and *SEPN1*. Sequencing and deletion and/or duplication analysis was performed for *TPM3*, *ACTA1*, and *TNNT*. No abnormalities were detected. Deletion testing of *SMN1* exon 7 and *FSHMD1A* was normal. *DMPK* testing revealed no expansion of CTG repeats. *FMR1* testing revealed no expansion of CGG repeats. Sequencing and Southern blot analysis revealed no mitochondrial DNA point mutations, deletions, or rearrangements.

Sequencing of *NEB* revealed two sequence variants. The c.1152+1G>A pathogenic variant was previously reported in an individual with nemaline myopathy. This variant affects the splice site and is expected to be disease causing.[19] The patient's father had the same variant. The c.1782+4_1782+5delAG variant had not been reported in individuals with nemaline myopathy or as a variant in the general population, so it was classified as a variant of unknown significance. The patient's mother had the same deletion. Consistent with a pathogenic change, the c.1782+4_1782+5delAG variant had not been observed in the general population, and the data from the splice prediction tool suggested that the donor site of the exon-intron junction may be destroyed. Parental testing revealed the variants were in *trans*, which further supported the pathogenicity of the variant of unknown significance. Comparative genomic hybridization performed to identify deletions and duplications in *NEB* revealed no abnormalities.

Discussion

The diagnosis of cap myopathy is established by typical histopathologic features in muscle. The subsarcolemmal cap structures at the periphery of muscle fibers in our patient are consistent with the reports of cap myopathy in the literature. The position of the peripherally situated myofibrils, as well as their abnormal sarcomere pattern, seems to point to an error in fusion and muscle protein synthesis.[2]

Our patient shares many features with previously reported patients with cap myopathy.[2-6,9-14] The clinical presentation and progression of cap myopathy is variable. Affected individuals typically present with neonatal or infantile hypotonia and, in some cases, feeding difficulties. Patients can have nonprogressive, slowly progressive, or progressive facial weakness and associated long face and high arched palate. They also have weakness of the axial and skeletal muscles, with proximal preceding distal limb