A rare case of Centronuclear myopathy with DNM2 mutation
Genotype-phenotype correlation

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Abstract

Centronuclear myopathy (CNM) is a group of rare genetic muscle disorders characterized by muscle fibers with centrally located nuclei. The most common forms of CNM have been attributed to X-linked recessive mutations in the MTM1 gene, autosomal-dominant mutations in the DNM2 gene encoding dynamin-2 and the BIN1 gene, and autosomal-recessive mutations in BIN1, RYR1 and TTN gene. Dominant CNM due to DNM2 mutations usually follows a mild clinical course with onset in adolescence. Up to now, around 35 mutations of DNM2 gene have been identified in CNM; however, the underlying molecular mechanism of DNM2 mutation in the pathology of CNM remains elusive, and the standard clinical characteristics have not yet been defined. Here we describe a case of a 17 year old female manifest with proximal muscle weakness along with congenital anomalous pulmonary venus connection (which hasn't been described in previous cases of CNM), scoliosis and restricted lung disease without any positive family history. Creatine Kinase level was normal. Histology, special stains and electron microscope findings on the muscle biopsy showed CNM with characteristic features of DNM2 mutation which later on confirmed by Next Generation Sequencing. This case expands the known clinical and pathological findings of CNM with DNM2 gene mutation.

Background

Centronuclear myopathy (CNM) is a rare congenital myopathy, which was first described as myotubular myopathy by Spiro et al.[1] in 1966. Muscle biopsy was characterized by myofibers with centrally placed nucleoli which are reminiscent of the myotube stage of muscle development. So, they suggested that it is originated from an arrested maturation of embryonic muscle. Hence, the condition was called myotubular myopathy. Nobody could prove the muscle was arrested in its development, therefore the term of "Centronuclear myopathies" (CNM) was preferred especially for the late onset forms. The term "myotubular", is now kept to denote severe infantile cases and reserve CNM for milder cases arising in older patients, in whom the muscle biopsy tends to appear ''more mature.'' CNM are usually caused by mutation in myotubularin (MTM1), amphiphysin 2 (BIN1), and dynamin 2 (DNM2) genes which are involved in membrane remodeling and membrane trafficking, suggesting a common CNM pathophysiology[2]. In addition to CNM, dissimilar DNM2 mutations are associated with Charcot–Marie–Tooth (CMT) peripheral neuropathy (CMTD1B and CMT2M), suggesting a tissue-specific impact of the mutations. Defects in membrane trafficking due to DNM2 mutations potentially represent a common pathological mechanism in CNM and CMT.

Three main forms of CNM are recognized according to the mode of inheritance and clinical presentation[3,4,5]:

1- X-linked myotubular myopathy (XLMTM)

2- Autosomal recessive (ARCNM)

3- Autosomal dominant (ADCNM)

Centronuclear Myopathy	Mutation	Clinical presentation	Microscopic features
XLMTM	MTM1 gene (Xq27-q28)	Usually males, hypotonia, respiratory failure at birth, Facial weakness, ptosis, and extraocular muscle weakness	Fibers with central nuclei resembling myotubes which are frequently surrounded by a paler peripheral halo
		Heterozygous female carriers may present with limb girdle and facial weakness	Some muscle fibers that resembled a "necklace"
ARCNM	BIN1 gene (2q14)	Early onset with ophthalmoparesis: Tend to be more severely affected and may present with dysmorphic features	Large majority of rounded fibres with centralized nuclei and increase of endomysial fibrosis and some fibres have clusters of centrally placed nuclei
		Early onset without ophthalmoparesis	
	RYR1 gene (19q13.1)	Late onset without ophthalmoparesis: (similar to ADCNM)	
	TTN gene (2q31)		
ADCNM	DNM2 gene (19q13.2)	Classic form: It characterized by late onset (may present at 30's) and slow progression.	Numerous fibres with centrally located nuclei and sarcoplasmic strands radiating from the central nucleus ("spoke-like appearance"), hypotrophy of type 1 fibers
		With muscle hypertrophy: It presents at a younger age with a more rapid course.	

Case report

History and Physical Exam: 17 year old caucasian female with past medical history of Anomalous Pulmonary Venus Connection (Left to right shunt), Biphasic thoracolumbar Scoliosis and Restrictive Lung Disease presented with progressive proximal muscle weakness and lumbar pain. There was no specific family history of neurological disease. Upon physical examination, we observed levoscoliosis and weakness in bilateral upper extremities (4/5) and lower extremities (3/5). She was unable to walk on her toes or her heels, and unable to arise from a squatted position, although her gait is not grossly abnormal on observational gait. There was no facial weakness and extraocular movements were intact. Sensory examination show intact sensation bilaterally. There was no spasticity, Babinski sign or ankle clonus.

Imaging and Lab studies: X-ray showed Scoliosis and kyphoscoliosis. MRI findings were suggestive of paraspinal muscle edema suspicious for underlying myopathy process. Also was noted, partial anomalous pulmonary venous return with left to right shunt. EMG showed electrodiagnostic evidence of diffuse myopathic process. Creatine Kinase (CK) level was normal: 68 (Reference range: 0-250 U/L).

Surgical Pathology: Microscopic Examination of muscle biopsy (Left vastus lateralis) shows excess variability in fiber size (Fig.1), frequent myonuclei in the center of the muscle fibers(Fig.2), often forming chains when viewed longitudinally (Fig.3). Degenerating fibers, angulated, split fibers or nuclear bags are not present. Myophagocytosis is not present. Inflammatory infiltrates are not seen. Rare fibers contain central red stippling, however definitive ragged red fibers are not seen. NADH histochemistry shows increased reaction in the center of some fibers with radial arrangement of the intermyofibrillar network radiating from the central nucleus (spoke-like appearance on the fibres) (Fig.4). ATPase (pH 9.8, 4.6, 4.3) histochemical stains show type I fiber predominate (more than 90%) and type II fibers are normal in size or hypertrophic (Fig.5). Electron Microscopy with toluidine blue staining showed disruption of myofibers particularly around the central nuclei (Fig.6). Glycogen content appears mildly increased in areas. Scattered collections of mitochondria and occasional nonspecific inclusions were also noted.

Molecular study: Next Generation Sequencing showed a heterozygous missense (nucleotide change: 1393C->T) (Amino Acid change: p.Arg465Arg) variant in exon 11 of the DNM2 gene located on chromosome 19.

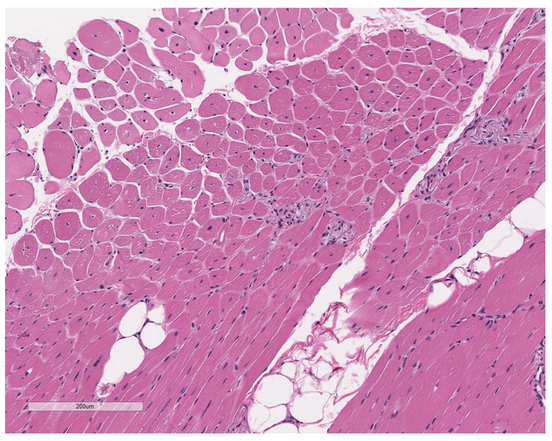

Fig.1 H&E stain; Fiber size variation and centralized nuclei especially in small fibers

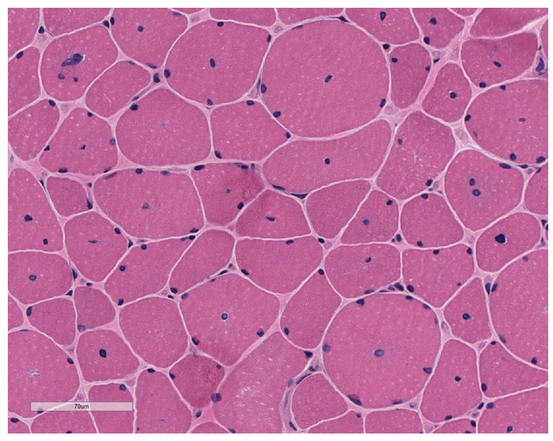

Fig.2 H&E stain; Central nuclei are observed in majority of cells

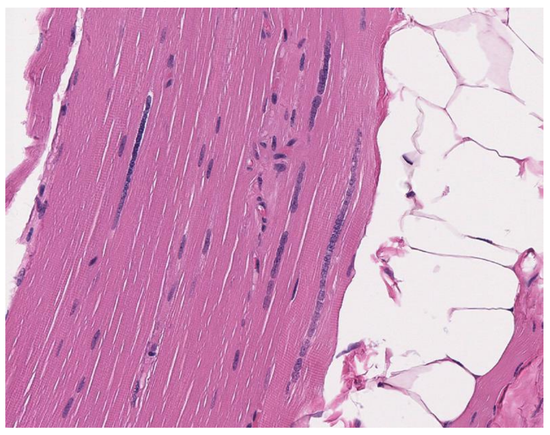

Fig.3 H&E stain; Centrally located nuclei often forming chains in longitudinal section

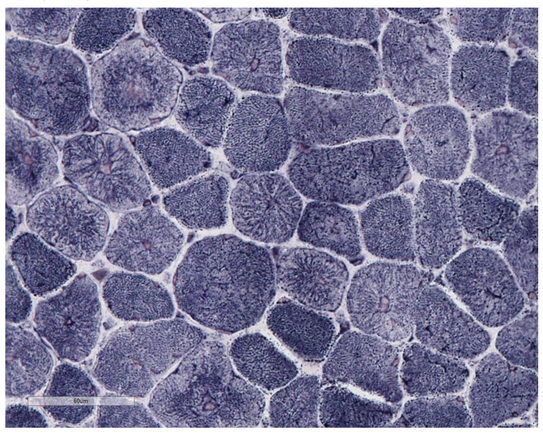

Fig.4 NADH stain; Radial arrangement of inter-myofibrillar network (spoke-like appearance)

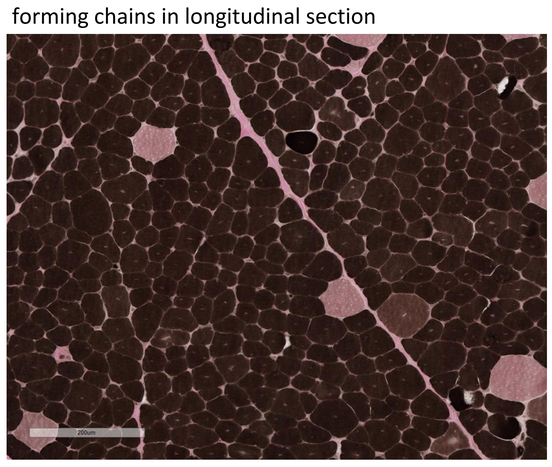

Fig.5 ADPase stain; type II fiber hypertrophy and type I fiber predominance (>90%)

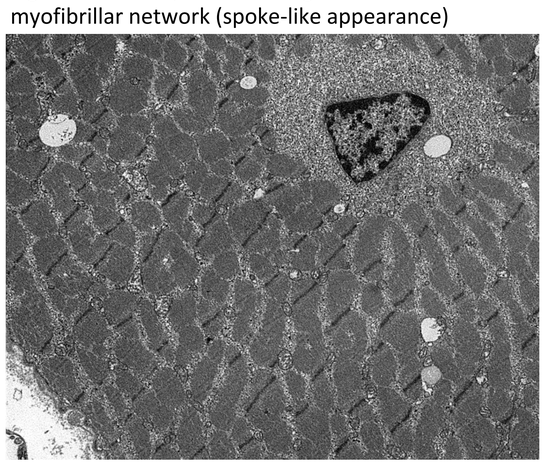

Fig.6 EM; Fibres with central nuclei and radial sarcoplasmic strands. (x6300)

Discussion

Centronuclear myopathy (CNM) is a rare congenital myopathy that is characterized by centrally placed nuclei in the muscle fibers. Three forms of the disease are clinically recognized; X-linked severe neonatal form caused by MTM1 mutation, Autosomal Recessive childhood onset form which usually caused by BIN1 mutation, and Autosomal Dominant adult-onset caused by DNM2 mutation. Genotype–phenotype correlation hypotheses are drawn from the published and new data, and allow an efficient screening strategy for molecular diagnosis. Here, we report the clinical, pathological and molecular characteristics of a 17 year old patient with DNM2-related CNM. Patient presents with muscle weakness and associated disabilities (thoracolumbar Scoliosis with Restrictive Lung Disease), as well as cardiac abnormalities (has not been described in patients with DNM2-related CNM). EMG study was consistent with myopathy and lab workup showed normal blood CK levels. Microscopic and histochemistry study on the muscle biopsy showed centronuclear myopathy with features suggestive of DNM2-related changes ; radial oxidative staining of sarcoplasmic strands (on NADH staining) and type I muscle fiber predominance with type II muscle fiber hypertrophy (on ADPase staining). Next Generation DNA Sequencing (NGS) showed DNM2 mutation on Chr 19 which confirmed the Autosomal dominant type of centronuclear myopathy (ADCNM).

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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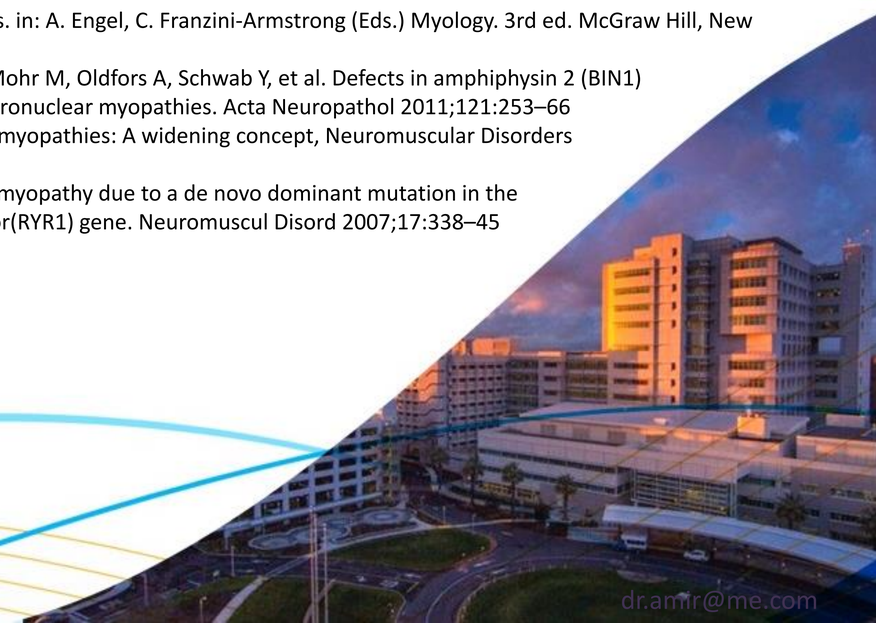

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