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Diagnosis of a centronuclear myopathy case in Appalachia 20 years from symptom onset

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Abstract

Dynamin 2 (DMN2) mutations cause centronuclear myopathy (CNM) and Charcot Marie Tooth (CMT). Herein we discuss the details of a patient's case of adult onset CNM. We also highlight the unique features of this case with regard to the importance of electromyography (EMG), muscle biopsy and genetic testing in identifying CNM, as well as potential for improving outcomes by having a high index or suspicion and emphasizing better access to healthcare in underserved areas.

Keywords

Centronuclear myopathy, dynamin 2, DNM2, muscular dystrophy, weakness

Case Report

A 67-year-old Caucasian male was referred to us for progressive diffuse muscle weakness after an inconclusive work up done out of state three years prior. He was born full term without complications, and his parents were not consanguineous. He reported that he kept up with his peers but avoided sports; he preferred books. At age 42 he noticed inability to tiptoe. At 57 he had difficulty climbing stairs due to foot drop and had trouble arising from chairs. He worked at a call center despite hand weakness and obtained disability benefits citing depression. By age 62 he lost the ability to run. Family history included father with progressive foot weakness and loss of bulk in the lower extremities. Mother had heart failure. His paternal grandfather had a non-specific “gait problem”. This patient was not married, did not have any children, and had no awareness of any siblings with the same symptoms.

Neurologic exam

Patient had normal cognition. Quadriceps and foot dorsiflexors were atrophic. We noted presence of a left pectoral crease, mildly arched palate, nasal speech, but no scapular winging, pyramidal signs, ophthalmoparesis, ptosis, dysphagia, scoliosis, or Beevor’s sign. Moderately severe muscle weakness was seen in distal and proximal upper and lower extremities. There was no neck or facial weakness, grip or percussion myotonia. Strength testing showed full (MRC grade) strength in pectoralis and ankle plantar flexion muscles, but only 4+ power in the deltoids, biceps brachii, triceps brachii and wrist flexors, along with 4 power in finger flexors and ankle dorsiflexors, and 4- power in quadriceps. No fasciculations were noted. Tendon reflexes were 1+. Gait was significant for right foot drop.

Laboratory testing

Historically: ANA and antibodies to amphiphysin, CRMP5, calcium channels, acetylcholine receptor and voltage-gated potassium channels were negative.

Other labs revealed: CK 53, serum myoglobin 55, TSH 1.46, ESR 26, vitamin D 31.2; negative LDH and MUSK ab.

Imaging

MRI scans were obtained using a GE 1.5T machine. MRI of lumbar spine showed severe right neuroforaminal narrowing at L4-5 but no canal stenosis. EKG revealed sinus bradycardia (HR 56) with possible left atrial enlargement.

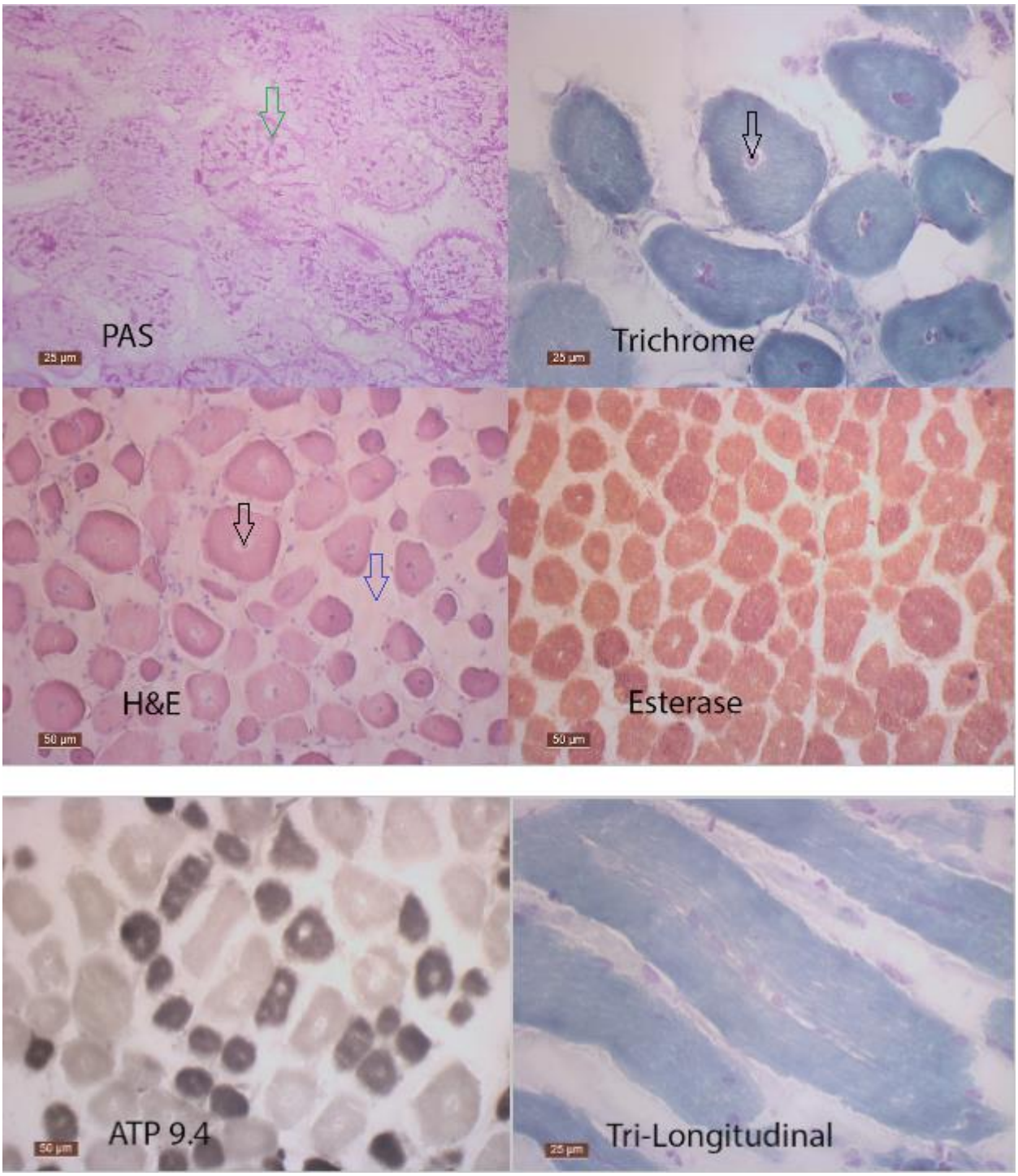
EMG

Historically, he had a normal repetitive nerve study. EMG was performed using standard routine technique on a Viking EDX EMG machine (2010 Carefusion Corporation, 20.1.32). Nerve conduction studies (NCS) of the right side of the body were normal. Needle EMG study of most muscles tested including cervical, thoracic and lumbar paraspinals showed small units, with short duration and early recruitment pattern indicative of a diffusely myopathic process. Fibrillations and positive sharp waves were seen in the right first dorsal interosseous, abductor policis brevis, lumbar and thoracic paraspinals. Waning discharges (pseudomyotonia) were detected in a right triceps brachii and semitendinosus muscles.

Muscle biopsy

Skeletal muscle was analyzed at University of Colorado Hospital with standard routine staining protocols for light microscopy. The right quadriceps showed marked variation in fiber size on the modified trichrome and H&E stains. (Figure 1) There were centrally placed nuclei in 70% of fibers. There was no necrosis, inflammation or phagocytosis. There was no increased connective tissue or endomysial fat on VVG stain. NADH-TR stain revealed mild coarsening of the intermyofibrillary network. ATPase series (pH 9.4 and 4.6) revealed a normal distribution of fiber types without type grouping but did show type 1 fiber hypotrophy. The non-specific esterase and acid phosphatase reactions were normal. PAS, Oil Red 0, and cytochrome oxidase reactions were all normal.

Figure 1. Muscle biopsy of a quadriceps muscle showing large central nuclei in fibers (black arrows) and type 1 fiber hypotrophy with increased space between muscle fibers (blue arrow) Rare radial strands seen on PAS stain indicate disruption of myofibrillar network (green arrow).



Genetic testing

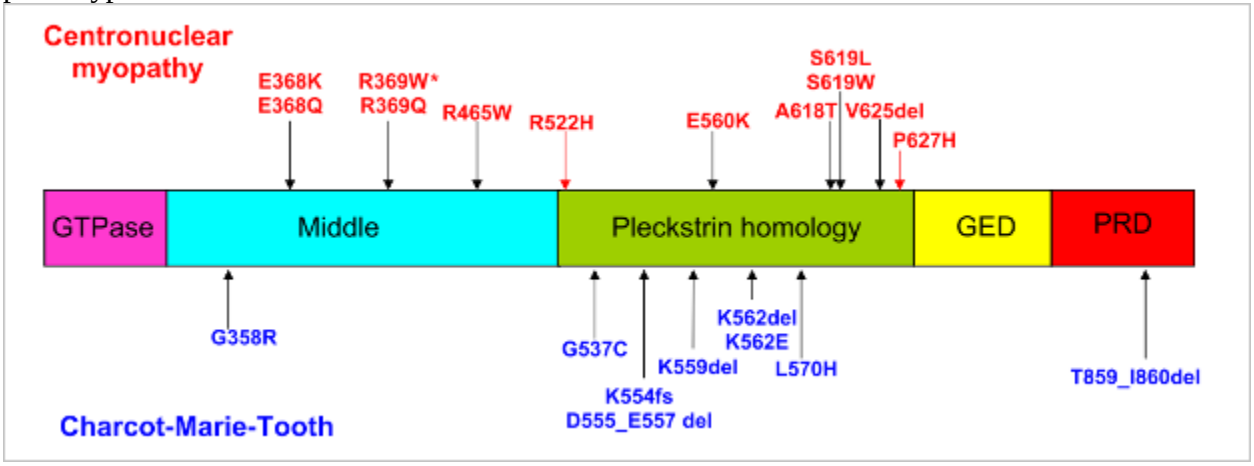
Informed verbal consent was obtained prior to extraction of DNA from blood using an Invitae kit according to manufacturer's instructions. The Comprehensive Neuromuscular Disorders Panel and Comprehensive Neuropathies Panel was negative for CMT and spinal muscular atrophy. A heterozygous pathogenic variant was found: c.1105C>T (p.R369W). Parental genetic data was unavailable.

Discussion

CNM is a rare congenital disease, with heterogenic etiology varying in phenotype and muscle histopathology. This condition is characterized by muscle weakness and may present at any point during life. There are several different forms. MTM1 mutations cause infantile x-linked CNM known as myotubular myopathy which is the most severe form leading to hypotonia, respiratory issues, contractures, feeding difficulties and cardiomyopathy.[1] MTM1 mutation also causes late onset CNM with typical necklace fibers created by basophilic deposits. DNM2 mutations cause autosomal dominant (AD) or sporadic CNM with centralized nuclei in muscle fibers, type 1 hypotrophy and radial sarcoplasmic strands (RSS). (Figure 1) DNM2 mutations predominantly involve distal weakness but sometimes limb girdle, ptosis, and muscle hypertrophy too with milder progression in adolescents and adults.[2] BIN1 or RYR1 mutations also cause CNM.

In our case AD inheritance was suspected due to presence of male to male transmission. DNM2 mutation on chromosome 19p13.2 is allelic for CMT and CNM (Figure 2). However, CMT was thought unlikely given no large fiber neuropathy found on NCS and preserved reflexes. EMG abnormalities led us to order a muscle biopsy, and the histopathology was diagnostic.

Figure 2. Protein structure of DNM2 composed of five domains including an N-terminal GTPase domain, a middle domain, a pleckstrin homology domain, a GTPase effector domain, and a C-terminal proline-rich domain.[9] R369W resides in the middle domain resulting in an attenuated form of the disease compared to the plekstrin homology domain which results in a more severe phenotype.[10]



Our patient had normal cognition and no cardiac complaints, however cognitive delay was reported in a family with a DNM2 mutation by Tranchant et al.[3] Another cohort of ten Italian patients showed no obvious cognitive impairment, and only one had cardiac involvement

(tachycardia).[4] Gal et al. reported a case of a DNM2 mutation manifesting at age 30 with cognitive delay, severe cardiomyopathy, axonal neuropathy and distal weakness, however that patient also had several mitochondrial DNA deletions.[5] DNM2 mutation may exert these effects by causing disrupted cellular organization due to its role in endocytosis, membrane trafficking and cell motility.[6]

Encouraging data from animal experiments using DNM2 knockdown, with anti-sense oligonucleotide to DNM2, showed prevention of myotubular myopathy in Mtm1KO mouse model by extending the lifespan and restoring muscle force in a dose-dependent manner.[7] However, currently we can only offer supportive care with cardiac surveillance as management for DNM2. A right ankle-foot orthotic was prescribed to correct our patient's foot drop, and an echo is pending. Muscle MRI is non-invasive and is becoming more popular in identifying patterns of muscle involvement; it could facilitate subspecialty referrals to avoid delay in diagnosis.[8]

Difficulty accessing specialty clinic resources in underserved regions is mainly due to lack of transportation and access to subspecialists. EMG, muscle biopsy and genetic testing are instrumental in making the diagnosis of CNM given variability of phenotypic expressions.

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