



Nemaline Myopathy in an Adult Patient: A Case Report

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Abstract

Introduction: Nemaline Myopathy (NM) is a muscle disorder part of a heterogeneous group of diseases classified according to the muscle biopsy result. They are caused by rod-shaped structures, which are rods accumulated in muscle fibers, visualized from a muscle biopsy. Nemaline myopathy is one of the most common subtypes of congenital myopathies. Still, it can also start in adult life, known as slow onset nemaline myopathy (SLONM), which remains without genetic confirmation and may therefore have another etiology. It is characterized by muscle weakness of a very variable spectrum and can be diagnosed in neonates in severe form to mild conditions in children and adults.

Case report: We present the case of a 27-year-old woman who presented muscle weakness with a progressive increase and underwent clinical, laboratory, electromyographic analysis, and muscle biopsy to confirm the diagnosis. The examination was suggestive of a myopathic pattern with signs of active denervation. Muscle biopsy: nonspecific neurogenic histological pattern. Expanded Genetic Panel for Dystrophinopathies: identification of undetermined clinical significance (VUS) variants in the NEB gene.

Conclusion: Late-onset nemaline myopathy is one of the most common subtypes of congenital myopathy. It may be present in all fibers or only in a percentage, and phenotypically it presents in a very variable way, with muscle weakness most often symmetrical and generalized with a predominance of the proximal and neck flexor muscles.

Keywords: Nemaline myopathy; Congenital myopathy; Late-onset nemaline myopathy

Introduction

Congenital myopathies are part of a clinically, histologically, and genetically heterogeneous group mainly affecting the muscle. The clinical phenotype alone is an inadequate basis for distinguishing between the different types of congenital myopathy since it is not very specific and consists of hypotonia and weakness, in addition to a static and little progressive clinical course [1,2]. The highest prevalence is of Congenital Myopathy, which manifests itself

right at birth or in the first days of life. It affects skeletal muscles, increasing weakness, hypotonia, and psychomotor retardation, but cognitive development remains normal [3]. Dysmorphic facial features secondary to muscle weakness are usually found in patients with congenital myopathies associated with an arched palate, micrognathia, and pectus carinatum or excavatum. In addition, abnormal extrinsic eye movements with eyelid ptosis and strabismus may develop later [4]. Nemaline Myopathy (NM) is a rare disease with an incidence of 1 in every 50,000 live births.

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However, it may be more common in specific populations (e.g., Ashkenazi Jews or the Amish community) and is the most common form of aggregate protein myopathy [3]. The diagnosis should be based on a careful review of the clinical symptoms and confirmed by further investigations and complementary examinations, excluding the diagnosis of other myopathies [5,6]. The characterization by Nemalino comes from the Greek prefix nema, which means “thread” [7]. Nemaline Myopathy is genetically heterogeneous and can present autosomal recessive or autosomal dominant inheritance, with a high proportion of sporadic dominant cases. Currently, more than 15 genes are related to NM: ACTA1, ADSSL1, CFL2, Filamin C, KBTBD13, KLHL40, KLHL41, LMOD3, MYH2, MYO18B, MYPN, NEB, RYR3, TNNT1, TPM2, TPM3, and TTN3 most encoding structural or regulatory proteins of the thin filament in the skeletal

muscle fibre. More recently, with next-generation sequencing, mutations in several other genes were identified [8]. The clinical aspect is vast and can vary between mild and severe phenotypes [9]. The most common form is the least severe, characterized by weakness of the limbs, trunk, and facial muscles, and a steady or slowly progressive course of the disease. Thus, adaptation to extrauterine life is usually adequate, but the acquisition of motor milestones is delayed. Although children affected by NM develop muscle contractures and bow feet, they can mostly walk. Respiratory involvement is the main prognostic factor [10]. According to clinical involvement, the disease can be classified as mild, moderate, severe, and late. The European Neuromuscular Center divided Nemaline Myopathy into six categories in a study (Table 1) [11].

Table 1: Division of Nemaline Myopathy into six categories according to The European Neuromuscular Center.

Form	Movement
severe congenital	Poor spontaneous drive; Fetal akinesia, difficulty swallowing, respiratory support at birth. They may present tendon retractions and fractures.
Intermediate Congenital	Spontaneous movement and respiratory movements at birth, but evolve to the need for ventilatory support. Poor motor acquisitions. Most need to manage to acquire a gait.
typical congenital	Delay in the acquisition of motor milestones, neonatal hypotonia, and progressive muscle weakness.
Take with onset in childhood. adult onset other types	Insidious proximal weakness and exercise intolerance. No delay in motor milestones

Case Report

A 27-year-old man, a machine operator with no comorbidities, reports that two years ago, she started a loss of muscle strength in the right lower limb when performing bodybuilding activities at the gym. He sought medical help and noticed that even with physical exercise, the weakness was intensifying. Weakness is more pronounced in the proximal third of the brachial and crural regions, with difficulty walking (gait with a myopathic pattern). He does not present frequent gagging, alteration in the timbre and intensity of his voice, and does not report myofasciculations; does not present findings of pyramidal distress. Neurological examination: amyotrophy and paresis, grade 3, in the proximal third of the brachial and crural limbs (Figure 1). Hypoactive Deep Reflexes (Wexler +). Superficial and deep sensitivity normal. Peripheral Nerves: normal. Gait: anserine. Gowers sign present. Word and Mental State: Normal. Laboratory results: Normal except for CPK 954u|l; Creatine Phosphokinase – MB Fraction 30.6 U|L. Electroneuromyography reveals signs of chronic denervation, mainly in the muscles of the lower limbs. However, it is also present in the upper groups – predominantly proximal

(Figure 2): low amplitude potentials, short duration, and incomplete motor unit recruitment pattern. The examination was suggestive of a myopathic pattern with signs of active denervation. Muscle biopsy: nonspecific neurogenic histological pattern.



Figure 1: Amyotrophy in the proximal brachial and crural third.



Figure 2: Scoliosis with shoulder girdle melting.

Protein aggregates compatible with nemaline bodies were not observed in the material. Doppler echocardiogram: Normal. Electrocardiogram: Normal. Expanded Genetic Panel for Dystrophinopathies (208 genes): identification of undetermined clinical significance (VUS) variants in the NEB gene. Clinical Condition: Nemaline Myopathy 2 (OMIN: 255030), Autosomal recessive inheritance, NEB gene, chromosomal position chr2:152.5000.357, NM variant 001164508.1:c.7931G>A;p.Arg2644GLn, zygosity (heterozygosity 40.30%). Sequencing Coverage: 761,444; Average coverage of the target region 92.34%; % target region with coverage greater than or equal to 20x: 99.34%.

Discussion

Depending on the case, the patient has loss of muscle strength, and one may suspect late-onset sporadic Nemaline Myopathy (SLONM) since the patient presented the onset of symptoms mildly and already in adulthood. However, according to the patient's genetic findings, this diagnostic suspicion is disregarded since SLONM may not have a genetic basis, presenting subacutely in adults with progressive weakness and, in most cases, with immunological abnormalities. The most common genetic causes of nemaline myopathy are autosomal recessive mutations in NEB and autosomal dominant de novo mutations in ACTA1. Mutations in NEB, which encode nebulin, are the most frequent cause of autosomal recessive nemaline disease and may represent up to 50% of cases, but Genetically, NM is very heterogeneous, including more than 15 genes. The molecular screening of variants in the NEB gene is very laborious since this gene contains 183 exons, a triplicated region (TRI) of 8 exons, and three areas with alternatively spliced exons. Although next-generation sequencing significantly improved the capacity to

identify genetic alterations in NEB, in some cases, it would be necessary to combine additional tools, such as CGH microarray and RNA analysis. After the exome analysis of 208 genes associated with MUSCULAR DYSTROPHIES, only the c.7931G>A variant was found in the NEB gene. This variant has been classified as uncertain significance (VUS). However, the clinical and molecular findings in this patient suggest that variant c.7931G>A has an impact on causing nemaline myopathy 2. No occurrence of c.7931G>A in individuals affected with Nemaline Myopathy 2, and no experimental evidence demonstrating its effect on protein function have been reported. Some patients have predominantly distal weakness, and homozygous mutations in NEB have been identified in individuals with distal myopathy without evidence of rods [12], as is the case of the patient in the present report since nemaline bodies were not found in the biopsy. As it is a disease that can present itself in ways that are incompatible with life, it is important that genetic counseling be carried out if the patient intends to have children since, in the reported case, the main cause of the disease is hereditary.

Conclusion

Nemaline Myopathy is a rare disease difficult to diagnose since nemaline bodies are not always present in the patient's muscle tissue biopsy. The resolution of the suspicion is carried out through the patient's clinic and genetic screening. This case report supports the theory that the NEB gene variation is the most common cause of NM. Therefore, more studies should be done regarding the correlation between the gene and the disease phenotype since it is difficult to diagnose.

Declaration of Conflict of Interest

The authors declare no conflicts of interest regarding this manuscript.

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