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Case Report

COQ7-Related Juvenile-Onset Motor Neuronopathy: A New Pathogenetic Dysfunction Associated with Motor Neuron Disease

Paulo Victor Sgobbi de Souza, Igor Braga Farias, Paulo de Lima Serrano, Bruno de Mattos Lombardi Badia, Ana Carolina dos Santos Jorge, Glenda Barbosa Barros, Hélvia Bertoldo de Oliveira, Samia Rogatis Calil, Isabela Danziato Fernandes, Roberta Correa Ribeiro, Vinícius Lopes Braga, Roberta Ismael Lacerda Machado, Marco Antônio Troccoli Chieia, Wladimir Bocca Vieira de Rezende Pinto * and Acary Souza Bulle Oliveira

Motor Neuron Disease Unit, Division of Neuromuscular Diseases, Federal University of São Paulo (UNIFESP), São Paulo 04039-060, SP, Brazil

* Correspondence: wladimirbvrpinto@gmail.com; Tel.: +55-(11)-5571-3324

Abstract: A 38-year-old Brazilian man presented with slowly progressive quadriparesis since age 11 years. He progressed over 15 years with symptoms restricted to the lower limbs, and since then, with a progressive compromise of the upper limbs. His deceased brother had a similar clinical presentation. Examination showed spastic dysarthria, global amyotrophy, brisk tendon reflexes in the lower limbs, symmetrical quadriparesis, and fasciculations in the four limbs. Neurophysiological studies disclosed acute and chronic signs of denervation and chronic reinnervation involving the cervical, thoracic, and lumbosacral myotomes, with normal sensory conduction study. Fibrillation potentials, fasciculations, and positive sharp waves involved mainly the upper limbs. A diagnosis of long-standing juvenile-onset motor neuronopathy was established. Genetic testing identified the possibly pathogenic variant c.3G>T (p.Met1?) in homozygosity in the *COQ7* gene. This report highlights the importance of considering a potentially treatable metabolic dysfunction as the primary mechanism in cases of juvenile motor neuron disease.

Keywords: juvenile amyotrophic lateral sclerosis; *COQ7*; neurometabolic disorder; inherited metabolic disorder; motor neuron disease; inborn errors of metabolism

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1. Introduction

Adult-onset motor neuron disease (MND) represents a complex challenge in clinical practice, and its most common presentation includes amyotrophic lateral sclerosis (ALS) [1]. Clinical suspicion for ALS diagnosis should be considered in patients with clinical symptoms and signs related to the dysfunction of both upper and lower motor neurons. Diagnostic work-up includes mainly neurophysiological testing and neuroimaging studies, which provide high diagnostic accuracy, despite the absence of a pathognomonic biomarker for diagnostic purposes. The presence of atypical clinical or laboratory features must make clinicians aware of the possibility of other underlying etiologies instead of a primary neurodegenerative basis [1].

During the evaluation of early-onset cases, especially in juvenile ALS (with the onset of motor symptoms before the age of 25 years), there is an imperative need to search for alternative differential diagnoses and secondary causes of MND, including rare inherited neurometabolic disorders [1]. Lower motor neuron impairment is often seen in inherited neurometabolic diseases, such as late-onset GM2 gangliosidosis, acid ceramidase deficiency (presenting as spinal muscular atrophy with progressive myoclonic epilepsy), and riboflavin transporter defects (including Brown–Vialetto–Van Laere syndrome and Fazio–Londe disease) [1]. Primary mitochondrial dysfunction of the oxidative phosphorylation due to respiratory chain defects and other energy production disturbances have very

rarely been correlated with the motor neuronopathy phenotype, and, in most cases, motor neuronopathy is only part of a complex multisystemic disorder [1]. Inherited metabolic disorders of coenzyme Q10 biosynthesis due to variants in the *COQ7* gene have been recently linked to distal hereditary motor neuronopathy (dHMN) [2,3]. Herein, we present the first description of juvenile motor neuronopathy associated with possibly pathogenic variants in the *COQ7* gene, reiterating the complex and heterogeneous pathophysiological basis of MND and the importance of proper diagnostic work-up for potentially treatable etiologies of juvenile MND.

2. Case Presentation

A 38-year-old Brazilian man presented with slowly progressive quadriparesis, cramps, and amyotrophy since age 11. His symptoms were markedly worse in distal muscle groups. He evolved over 15 years with symptoms mainly restricted to the lower limbs, and since then, with a progressive and symmetrical compromise of the upper limbs, mainly involving his hands and forearms. He denied dysphagia; however, dysphonia started after age 20 and has slowly evolved since then. No gastrointestinal or urinary complaints were reported. His parents were first-degree cousins. A detailed pedigree analysis disclosed that his deceased brother, with a similar phenotype at the age of 22 years, progressed with a progressive compromise of the distal upper limbs and became wheelchair-bound after 15 years.

Neurological examination showed spastic dysarthria, marked amyotrophy of the four limbs with distal predominance, brisk tendon reflexes in the lower limbs and normal reflexes in the upper limbs, bilateral Hoffmann and Trömner signs in the upper limbs, symmetrical quadriparesis with a predominance of distal involvement, bilateral split hand sign, bilateral foot drop, fasciculations in the four limbs, and bilateral postural and action tremor of the upper limbs. His tongue examination disclosed no fasciculations or atrophy. Sensory examination disclosed no superficial or deep sensation loss. Funduscopic examination was unremarkable.

As a long-standing juvenile MND was suspected, neuroimaging and neurophysiological assessments were performed. Needle EMG and nerve conduction studies disclosed acute and chronic signs of denervation and chronic reinnervation involving the cervical, thoracic, and lumbosacral myotomes, with normal sensory conduction study. Fibrillation potentials, fasciculations, and positive sharp waves involved mainly the upper limbs. There was a moderate reduction of compound motor action potential (CMAP) amplitude bilaterally in median, ulnar, and radial nerves and absent CMAP bilaterally in fibular and tibialis nerves. No signs of bulbar denervation were detected. Brain, cervical, and thoracic spinal cord MR imaging studies were unremarkable. Cerebrospinal fluid analysis was within normality. According to the revised El Escorial, Awaji-shima, and Gold Coast criteria, a diagnosis of ALS was established.

As a possible monogenic basis was suspected, two large multigene next-generation sequencing panels (including genes associated with ALS, non-5q spinal muscular atrophies (SMA), dHMN, and inherited metabolic disorders) were requested, including more than 120 different genes. The pathogenic variant c.3G>T (p.Met1?) was identified in homozygosity in the *COQ7* gene (16p12.3) (reference primary transcript: NM_016138.5) (Figure 1). ClinVar includes this missense variant product, possibly as p.Met1Ile. This variant is predicted as "deleterious" by several in silico prediction tools (Varity, SIFT, MutationTaster, BayesDel, GERP, GenoCanyon). It has not been observed in the gnomAD (aggregated) and was previously classified in ClinVar as pathogenic and of uncertain significance (variation ID: 1463095/VCV001463095.5). This variant, thus, fulfilled PM2, PVS1, and PP5 ACMG (American College of Medical Genetics and Genomics) criteria of pathogenicity. This possibly pathogenic variant has been recently correlated with dHMN phenotypes and had its functional impact and pathogenicity demonstrated by additional testing previously, disclosing coenzyme Q10 deficiency [2,3]. Our proband diagnosis was established as long-standing juvenile motor neuronopathy due to *COQ7* variants.

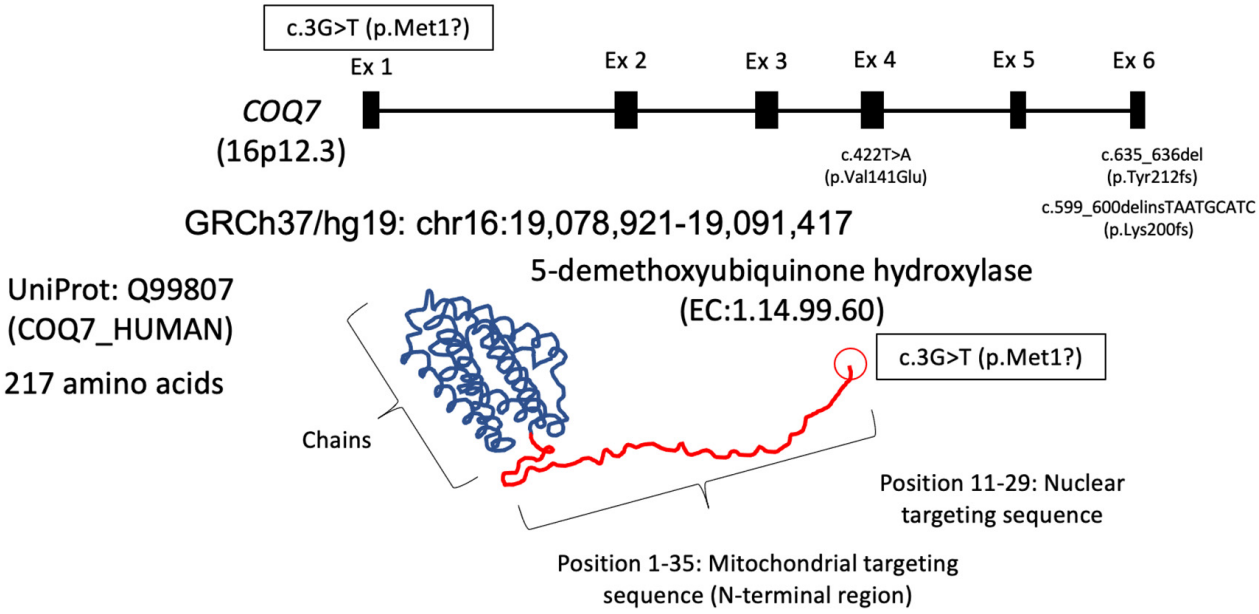

Figure 1. *COQ7* gene structure (exons and introns) and its coded protein structure. The homozygous pathogenic variant c.3G>T (p.Met1?) is located at the first codon of exon 1 and involves the mitochondrial targeting sequence at the N-terminal region.

3. Discussion

Pathogenic variants in the *COQ7* gene were associated previously with primary coenzyme Q10 deficiency type 8 (MIM #616733), leading to a neonatal or infancy-onset severe multisystemic disorder with complex mitochondrial dysfunction [4]. The presentation generally includes growth retardation, early and severe renal dysfunction, left ventricular hypertrophy, pulmonary hypertension, lung hypoplasia, hearing loss, joint contractures, global hypotonia, neurodevelopmental delay, and chronic sensorimotor axonal and demyelinating polyneuropathy [5,6]. There is a variable clinical and laboratory impact of 2,4-dihydroxybenzoic acid or coenzyme Q10 supplementation [5]. COQ7 participates in the regulation of oxidative phosphorylation and in the production of reactive oxygen species (ROS) [7]. The COQ7 enzyme catalyzes the second step of the CoQ10 biosynthesis pathway in the hydroxylation of 5-demethoxyubiquinone-10 [3].

Recently, Jacquier et al. [2] described two brothers and a sister with typical features of dHMN associated with the same pathogenic variant c.3G>T in the *COQ7* gene [2]. The COQ7 substrate 6-demethoxycoenzyme Q10 was also assessed as a possible serum biomarker[2]. Furthermore, the authors showed the in vitro pathogenicity of the variant and the effect of 2,4-dihydroxybenzoic acid to normalize COQ7 substrates and coenzyme Q10 levels[2]. Although the impact of such therapeutic proposals on clinical outcomes and prognosis in the scenario of motor neuronopathies is not yet recognized, it has shown to be highly promising, given the progressive and irreversible clinical course usually seen in that group of diseases. Smith et al. have also described a family with three siblings with autosomal-recessive juvenile-onset dHMN due to homozygous pathogenic variant c.1A>G in the *COQ7* gene, confirming the expansion of this group of metabolic motor neuronopathies [3]. The impact of such therapeutic proposals on clinical outcomes and prognosis in patients with JALS and an undetermined monogenic basis is not yet established. It is of note, however, that a previous randomized, placebo-controlled, double-blind, Phase II trial showed that high doses of coenzyme Q10 supplementation for ALS patients did not result in significant changes in the values and rates of decline observed in the ALS Functional Rating Scale Revised (ALSFRS-R) score compared to the placebo group over 9 months of follow-up [8].

Inherited neurometabolic disorders may present with motor neuron involvement, mimicking clinical and neurophysiological features observed in dHMN, non-5q SMA,

and juvenile ALS [1]. Oxidative stress due to the abnormal production of ROS is a well-established phenomenon in the pathogenesis of both sporadic and familial ALS [9]. COQ7 is a well-known membrane-bound hydroxylase involved in coenzyme Q10 biosynthesis and has been previously demonstrated to participate in the regulation of oxidative phosphorylation and in the production of ROS. Mitochondrial respiratory chain dysfunction, abnormal oxidative phosphorylation, and the generation and accumulation of mitochondrial ROS may certainly play a key role in the pathophysiology of the juvenile ALS case described as that observed in dHMN [2,3,5]. Furthermore, there are possibly additional pathophysiological mechanisms that lead to the development of clinical heterogeneity in the *COQ7*-related spectrum of disorders, including environmental factors and epigenetic changes.

Several clinical and genetic subtypes of juvenile ALS have been previously described, highlighting *FUS* pathogenic variants in ALS type 6 as the most common presentation in young-onset cases [10]. Other autosomal recessive forms, similar to the *COQ7* variants described in this report, have been previously correlated with juvenile ALS, including compound heterozygous or homozygous variants in *SPG11* (ALS type 5), *ALS2* (ALS type 2), *SIGMAR1* (ALS type 16), *SYNE1*, *GNE*, *ERLIN1*, *DDHD1*, and *VRK1* genes. Most autosomal-recessive presentations in JALS were previously associated with upper motor neuron-dominant phenotypes, mimicking several features of hereditary spastic paraplegia, especially in *SPG11*, *ALS2*, *ERLIN1*, and *DDHD1* variants [10]. The main genetic subtype representative of this context is juvenile ALS type 5 related to *SPG11* variants [11]. These cases commonly correspond to group 2 of juvenile ALS, described previously by Ben Hamida as the spastic paraplegia phenotype with distal amyotrophy [12]. The clinical profile observed in our case description has several clinical and neurophysiological findings correlated to Ben Hamida's group 1 of juvenile ALS, described as upper limb and bulbar amyotrophy with bilateral corticospinal tract involvement [12]. Thus, COQ7-related juvenile motor neuronopathy must be included in the differential diagnosis of early-onset MND with predominant involvement of lower motor neuron signs in distal muscle groups and mild signs of corticospinal tract dysfunction.

4. Conclusions

Juvenile MND presentation may be secondary to rare inherited neurometabolic disorders, including the *COQ7* pathogenic variants presented in this description. A comprehensive genetic investigation is essential to enable the proper diagnostic evaluation of potentially treatable severe inborn errors of metabolism. This manuscript contributes to the current knowledge about juvenile MND pathogenesis and sheds light on the necessary effort to identify potentially treatable neurometabolic causes of MND [1].

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Abbreviations

ACMG	American College of Medical Genetics and Genomics.
ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	ALS Functional Rating Scale-Revised.
CMAP	Compound Motor Action Potential
dHMN	Distal Hereditary Motor Neuronopathy
MND	Motor Neuron Disease
ROS	Reactive Oxygen Species
SMA	Spinal Muscular Atrophy

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