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Myopathy, lactic acidosis and sideroblastic anemia 1 (MLASA1): A 25-year follow-up

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ABSTRACT

Mitochondrial myopathy, lactic acidosis and sideroblastic anemia 1 (MLASA1) is a rare disease caused by biallelic pathogenic variants in the *PUS1* gene. There are eleven MLASA1 patients reported worldwide with the majority of the patients originating from the Shiraz region of Iran. The rarity of this disease poses challenges to counseling patients due to a lack of natural history data. This report reviews what is known regarding MLASA1 and describes two brothers with MLASA1 who were cared for over the course of 10 years at the University of California Los Angeles. The brothers suffered from chronic anemia, transfusion dependency and muscle wasting that lead to respiratory insufficiency and death in one of the brothers.

1. Introduction

Inbal et al. first biochemically described a new condition with myopathy, lactic acidosis and sideroblastic anemia (MLASA) in 1995 [1]. The disorder now classified as MLASA1 is caused by biallelic pathogenic variants in the nuclear gene *PUS1* as described by Bykhovskaya et al. in [2]. The gene product of *PUS1* (the PUS1 protein) is responsible for the tRNA pseudouridination of tRNA species in both the mitochondrion and cytoplasm and its deficiency causes a defect of functional mitochondrial activity [3,4,5]. Unlike other mitochondrial deficiency disorders, it is a condition primarily affecting the skeletal muscle and the erythrocyte lineage of the bone marrow [1,2]. MLASA1 is phenotypically similar to two other disorders, which are MLASA2 due to biallelic pathogenic variants in the nuclear gene *YARS2* and MLASA3 due to pathogenic variants in the mitochondrial gene *MTATP6* [3,4].

Six of the eleven patients previously reported in the literature have come from a single, culturally homogeneous community of Jews from the city of Shiraz in Iran. MLASA1 has also been reported in families from Italy and Turkey. Iranian patients were homozygous for the most commonly reported "Persian" missense pathogenic variant (*PUS1* c.656C > T, p.Arg116Trp) [1,2, 7]. Two Italian patients were homozygous for a nonsense pathogenic variant (*PUS1* c.658G > T, p.Glu220X) and were more seriously affected than patients with missense variants [8]. Another less severely affected Italian patient was compound heterozygous for a frameshifting deletion and a missense pathogenic variant (*PUS1* c.487delA, p.Ile163Leufs*4 and c.884 G > A, p.Arg295Glu) [9]. The first Turkish patient was homozygous for a missense pathogenic variant (*PUS1* c.883C > T, p.Arg295Trp) while the second Turkish patient was homozygous for a different missense pathogenic variant (*PUS1* c.302A > G, p.Gln301Arg) [10,11].

MLASA1 is an ultra-rare autosomal recessive disease, with only 22 pathogenic and six likely pathogenic variants reported in ClinVar as of May 2019. There are no known cases of disease caused by mono-allelic pathogenic variants in *PUS1*. The mathematical concepts of pLI and pRec may be utilized to predict whether or not a gene is susceptible to mono-allelic or biallelic loss of function variants with a score closer to 1.0 indicative of intolerance of loss of function. The fact that the *PUS1* gene has only been implicated in disease with an autosomal recessive pattern is supported by the fact that it has a pRec score of 0.9, indicating that the gene is highly intolerant of biallelic loss of function variants [12]. Conversely, the pLI score for *PUS1* is 0.0, indicating that the gene is highly tolerant of monoallelic loss of function variants [12]. The low pLI score is consistent with the fact that no autosomal dominant disease has yet to be associated with *PUS1*.

In this paper we will discuss the two patients described by Casas and Ghodsian who were homozygous for the *PUS1* p.Arg116Trp pathogenic variant. These patients were eventually seen and followed to the present by one of us (SC) for a period of 10 years up to the time of this report [7].

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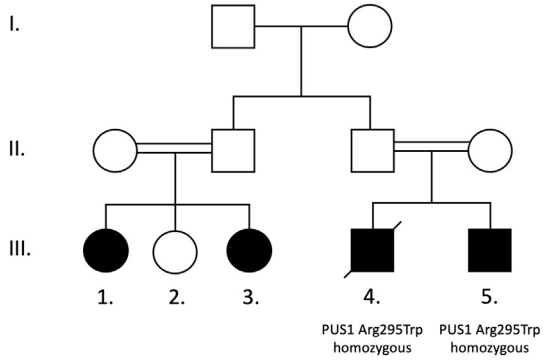

Fig. 1. Pedigree of a family originating from the Shiraz region of Iran affected by MLASA1. The two brothers described herein are individuals III-4 and III-5. They had similarly affected paternal cousins (Individuals III-1 and III-3). Individual III-4 died at the age of 37 due to respiratory failure secondary to MLASA1.

2. Clinical course

At the time of publication in 2004, the two brothers described by Casas and Ghodsian with the missense mutations were 19 and 17 years old [7]. The oldest (Individual III-4 in Fig. 1) presented with mild anemia at age 6, with a hemoglobin of 10 g/dl and over a period of years was found to have short stature, progressively worsening kyphoscoliosis, increasing exercise intolerance, hypothyroidism, erythroid hyperplasia in the bone marrow and distal muscle wasting. At age 19 he had begun to require blood transfusions for hemoglobin levels as low as 6–7 mg/dl and had an adult height of 163 cm, in the normal range but below his mid-parental height.

When he was first seen at the University of California Los Angeles in 2009 he was of normal intelligence and graduated from college with a bachelor degree in business. He was employed as an accountant and business manager. He had diminution in muscle mass and weighed 44 kg and complained of lack of energy and stamina and could walk less than one city block. He had lordosis that mitigated the weakness of his strap muscles and allowed him to remain erect. He had surprising muscle strength on formal testing with 3.5–4/5 in most groups. He walked by swinging rather than lifting his legs. There was elevation of ferritin, high iron in the blood and he was under treatment for hemosiderosis. He worked out regularly with a personal trainer. The most troublesome issues were his lack of stamina, his difficulty working a full day and his transfusion requirement of 2 units of packed red blood cells every 6–8 weeks.

Over the subsequent decade he continued to decline, his muscle wasting progressed, his muscle strength diminished, and his posture worsened. His weight at his hospital admission and death was 37.2 kg. He had chronic osteoporosis, but suffered no intellectual decline, no neurological abnormalities, diabetes, intrinsic pulmonary disease or diminution of renal function. He developed cardiomyopathy late in his course, likely secondary to chronic iron overload in the setting of transfusion dependence. No treatment specific to his mitochondrial defect was available. The patient died at 37 years of age due to respiratory failure secondary to weakness of his diaphragm and accessory respiratory muscles. When it became clear that he was to become permanently ventilator-dependent, he declined further treatment and expired.

The younger brother (Individual III-5 in Fig. 1) was 17 when his case was first reported [6]. He presented at age eight with easy fatigability and was short prior to a growth spurt that resulted in a normal adult height of 157 cm. When seen at UCLA at age 26 he was of normal intelligence and had a master's degree. His hemoglobin remained in the 9–10 g/dl range and he had no transfusion requirement, but he had macrocytosis and his ferritin was elevated. Compared to when he was first reported in the literature at eight years of age his muscle symptoms had progressed and he had developed a lordotic posture, similar to, but less severe, than his brother. He was exercising and his muscle strength was good. His weight was 58 kg and has remained stable over the subsequent decade. Over the period of the decade there was some minimal progression of his muscle wasting and worsening of his posture, but except for loss of stamina, he was working substantially full-time and doing well. He has osteoporosis for which treatment was begun.

3. Discussion

Reports of patients with uncommon disorders often present their antecedent history and current status, but unless they are part of a treatment protocol, no long-term followup is given. In those disorders relatively more frequent, a picture of the longer term can be inferred from the broader cross-section of presented cases. In rare conditions such as the present MLASA1 patients, such cross-sectional inferences are impossible, and follow up reports are necessary.

The previous reports of MLASA1 permitted us to conclude that biallelic nonsense mutations resulted in a more severe condition in which the nervous system was affected as well. It was also clear that the disorder in the patients with the “Persian” mutation had a condition that was later onset, was variable between individuals and was almost certainly progressive. In this report we confirm the progressive nature of the disorder in one individual, the variability between individuals with the same mutation and the fact that the progression of the disorder may be relentless and that there is no plateau of severity. Despite the limited data on MLASA1 our experience suggests that such patients may benefit from regular pulmonary function testing as well as monitoring of bone mineral density along with hemoglobin and ferritin levels.

The pattern of relentless deterioration in MLASA1 follows the example of the more common MELAS and MERFF syndromes, which cause a similar pattern of progressive mitochondrial functional decline [2]. Wallace et al. demonstrated that with age the efficiency of energy generation diminishes, and the outcome is expected [13]. Thus, a combination of natural ageing and genetic metabolic derangement can account for the progressive neuromuscular decline seen in patients with MLASA1.

Declaration of Competing Interest

None.

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