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Case Report

AARS Novel Homozygous Variant in Two Lebanese Siblings with Isolated Transient Neonatal Axial Hypotonia

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Abstract

AARS mutations are associated with many clinical presentations that range from neuropathy to developmental syndromes and have either recessive or dominant patterns of inheritance. Here we present the first reported Lebanese patients with a novel AARS gene variant. The two female patients presented with a transient axial neonatal hypotonia with a muscle biopsy showing secondary mitochondrial dysfunction. The patients' symptoms showed a benign progression during the first year of life until reaching normal developmental milestones. The present case helps to widen the clinical spectrum of *AARS* gene mutations in order to include neonatal transient axial hypotonia.

***Keywords:** Alanyl-tRNA synthetase (AARS); Axial hypotonia; ARS genes; Lebanese patients*

Introduction

Alanyl-tRNA synthetase (AARS) belongs to the Aminoacyl-transfer RNA (tRNA) synthetases (aaRSs) family, which is the largest protein family causatively linked to neurodegenerative Charcot–Marie–Tooth (CMT) disease but can present with a wider and more heterogeneous spectrum than the peripheral neuropathy [1,2]. The loss-of-function mutations in the AARS gene can cause autosomal recessive disorders of the central nervous system ranging from simple hypomyelination to spasticity and progressive microcephaly as well as epilepsy [3].

Here we present the first two Lebanese patients reported with a novel *AARS* variant, presenting with transient severe axial hypotonia during the first year of life, and who showed a precipitated improvement with the treatment of their secondary mitochondrial dysfunction.

Case Report

Here we present the case of two sisters presenting with a previously unreported *AARS* mutation. The parents are first degree consanguineous originating from the same village in south Lebanon (Figure 1).

The older patient was born term by elective cesarean section, following a noneventful pregnancy. The patient presented at 2 months of life with a severe generalized hypotonia that persisted since birth. On physical exam severe axial hypotonia and peripheral hypotonia were noted, yet archaic reflexes and deep tendon reflexes were present with a very weak reactivity, the moro reflex was weakly perceived and the stepping reflex could not be elucidated. The child was able to breastfeed and was reactive to stimulation.

The patient's weight, height, and head circumference were following appropriately the growth curves at the 40th percentile. Clinical investigations including an extensive metabolic work up and brain imaging were performed and showed no anomalies. Physical therapy was started immediately while genetics studies and muscle biopsy were planned.

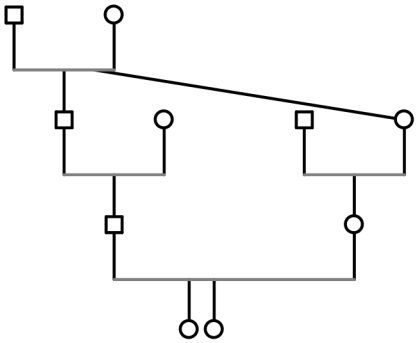

Figure 1: *The patients' pedigree.*

The patient showed a persisting severe axial hypotonia until the age of 6 months with an inability to hold her head or to elevate the head in prone position. Sessions of physical therapy were performed regularly three times per week by a professional therapist, and regular daily exercises at home by the parents. By the age of three months the only noted improvement was a mild increase in the lower limbs tone, the improvement of the upper limbs motricity was noted by the age of 4 months with trials to move hands up against gravity. At 6 months of age an improvement in the axial tone started to be noted, the child was able to hold her head, and to try to roll from side to side. A muscle biopsy done then showed a mitochondrial dysfunction with decrease in ATP synthase activity and supplementation with carnitine 100 mg/kg/day, co-enzyme Q 10 30 mg/day and vitamin B2 50 mg/day were started, along with the regular physical therapy sessions.

By the age of 9 months the patient was becoming more active and showing a better muscle tone, she was able sit alone and to stand assisted, and by the age of 1 year the patient was walking and saying her first words. At the age of 2 years genetic studies showed the presence of an AARS homozygous mutation. The patient showed a normal physical and neurological exam; medication as well as physical therapy sessions were stopped. The patient is still clinically followed regularly, now at the age of 6 years she still has a completely normal physical and neurological exam.

4 years after, the couple had another daughter who presented at 2 weeks of life with a severe axial hypotonia similar to the first patient's presentation. Physical therapy as well as supplementation with carnitine, coenzyme Q 10 and vitamin B2 were immediately started while waiting for the genetic study that showed the presence of the same homozygous mutation. The second patient started to hold her head at the age of 3 months, she was able to sit unassisted at the age of 6 months, at the age of 12 months she had her first steps without any sign of hypotonia, and at the age of 18 months the child is walking unassisted, she has a normal physical and neurological exam, and she is following accurately her developmental mile stones.

Investigations

For the older child, the regular hematological work up showed no anomalies. The complete blood count showed no anomalies, creatinine 0.1 mg/dl, uric acid 3.2 mg/dl, AST 37 IU/L, ALT 30 IU/L. GGT 19 IU/L, CPK 56 IU/L, Lactic acid 8 mg/dl, pyruvic acid 0.80 mg/dl, ammonia 88 µg/dl, HCO3 23 mEq/L, the chromatography of the amino acids in blood and the chromatography of organic acids in urine were within normal ranges as well. The karyotype was normal.

A brain MRI with spectroscopy was performed and showed no morphological anomalies neither maturational defects. A repeated MRI at the age of 2 years showed a mild widening of the ventricles without any associated anomalies (Figures 2 and 3).

A muscle biopsy for the older sibling performed at the age of 6 months showed mitochondrial myopathy with a decrease in ATP synthase expression, and an increase in lipid deposits within myofibers.

A cardiac ultrasound was performed and was within the normal limits.

In the first patient Whole exome sequencing showed the presence of a previously unreported homozygous mutation in the *AARS* gene c.5A>G, both parents were asymptomatic carriers. The younger sister was homozygous for the same mutation.

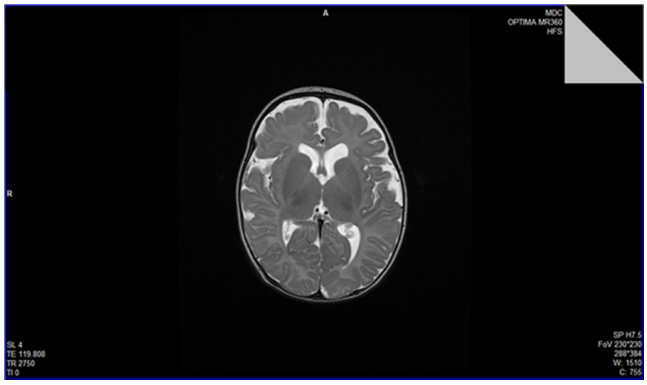

Figure 2: *Sequence T2 of the Brain MRI of the older Sibling, showing mild ventricular dilation.*

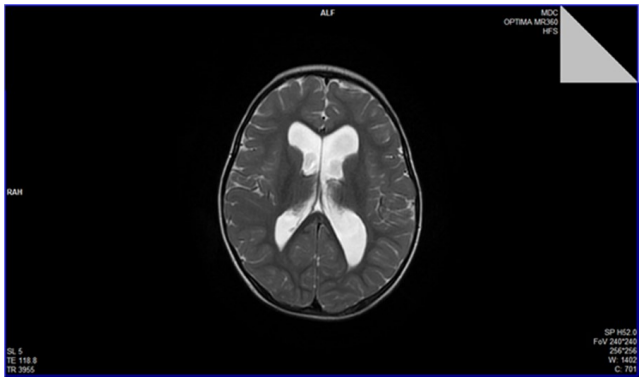

Figure 3: *Sequence T2 of the Brain MRI of the Younger Sibling, showing mild ventricular dilation.*

Discussion

Despite its high rate of emigration and multiple demographic displacements, the Lebanese society still presents a high rate of consanguinity, and subsequently a very high rate of rare diseases, with possibility of concomitant presence of multiple pathogenic, clinically expressed, mutations in the same patient [4,5,6,7]. With the advent of the next generation sequencing, the genetic homogeneity of the Lebanese population has allowed us to discover the occurrence of new variants of multiple mutations that seem to have wider clinical spectrums than previously described.

Here we present the first reported Lebanese patients with AARS-relate disorder where two affected sisters had a novel variant c.5A>G.

When reviewing the different publications in the literature, the mutations relating to *AARS* gene are mainly linked to several progressive diseases and neuropathies like Charcot-Marie-Tooth and leukoencephalopathies [8] or to a severe infantile epileptic encephalopathy with a central myelin defect and peripheral neuropathy [2], as well as an indolently progressive, mild myeloneuropathy [9].

The clinical presentation in our two patients seems to vary in what seems to be a natural course of the disease. The encephalopathy seen in these patients had only a motor component with a progressive resolution of the symptoms that eventually lead to a normal healthy child in the first case, in the second child the achievement of the normal developmental milestones was rapidly reached with the early introduction of the treatment for the secondary mitochondrial dysfunction. This clinical variation can lead to the possible conclusion that defects of alanyl-tRNA charging can result in a wide spectrum of disease manifestations.

AARS belongs to the aminoacyl-tRNA synthetase family proteins, and it ligates alanine to the cognate tRNA, whose backbone sequence contains anticodon for alanine [10]. Aminoacyl-tRNA synthetases are ubiquitously expressed, essential enzymes responsible for charging tRNA molecules with cognate amino acids—the first step of protein translation. These enzymes are present in both mitochondria and the cytoplasm and, interestingly, certain tRNA synthetases have non-canonical functions in biological processes such as angiogenesis, regulation of gene transcription, and RNA splicing [2]. Aminoacyl-transfer RNA (tRNA) synthetases are enzymes that ligate amino acids to specific tRNAs and are essential for protein synthesis [3]. more than 20 ARSs have been found to be associated with human diseases [11,12]. While mutations in mitochondrial ARSs lead to disorders affecting various organ systems, mutations in cytoplasmic ARSs have mainly been associated with autosomal dominant peripheral neuropathies [3] Thus, AARS mutations appear to lead to two distinct phenotypes, a peripheral nervous system disorder that is a dominant trait and a central nervous system condition that is a recessive trait. [3,13]. *AARS* gene has also been found to cause a form of recessive ataxia starting at 6 weeks of age and with concomitant Purkinje cell loss [14].

The mutant AARS exhibits reduced aminoacylation activity and might engender reduced translation and consequent neurodegeneration, due to widespread protein aggregation and neuron loss, Reduced aminoacylation activities of some mutant ARSs could intensify the symptoms but might not be sufficient or required [11,15]. The proposed mechanism of the precipitated neural cellular apoptosis could be the accumulation of misfolded proteins and the disruption of translational fidelity in terminally differentiated neurons [16].

Human cytoplasmic and mitochondrial AlaRS are encoded by two different nuclear genes, *AARS* and *AARS2*. Latour *et al.* report that a mouse model showed that a homozygous defect in AlaRS editing is responsible for mischarging of tRNAAla with serine or glycine and leads to protein misfolding and neurodegeneration, leading to sensory-motor distal degeneration secondary to predominant axonal neuropathy and with absent or slight demyelination [17]. While Simons *et al.* [2] also report hypomyelination in all the patients with *AARS* gene mutations, our patients did not have any cerebral anomalies apart from a benign widening of the ventricles.

Meyer *et al* report that the mutations in ARS genes encoding cytoplasmic enzymes also cause a spectrum of recessive disorders with hypomyelination, microcephaly, seizures, sensorineural hearing loss, and developmental delay, liver dysfunction and lung disease [18], but this series does not include transient hypotonia, like in our two patients. On the other hand, Fuchs *et al* report mitochondrial dysfunction in more than 30% of the different *AARS* deficiencies, but with normal respiratory chain enzymes activities [19]. This secondary mitochondrial dysfunction found on the muscle biopsy of the younger sibling can explain the response to the mitochondrial cocktail treatment given to the patient, and the faster improvement of her younger sibling when initiated at a younger age.

Conclusion

Here we report the first two cases of Lebanese patients with a novel AARS gene mutation, presenting with signs of a transient peripheral neuropathy with a secondary mitochondrial dysfunction. The present report allows us to widen the clinical spectrum of the AARS mutation to include a benign form of transient infantile hypotonia, With a very good resolution of the symptoms within the first year of life. The treatment of the secondary mitochondrial dysfunction might not be essential as the progression can be the natural course of the mutation, but it can hasten the improvement of the hypotonia. This report also highlights the persisting increased risk of inherited disorders in consanguineous marriages in genetically homogenous populations.

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Conflict of Interest

The authors have indicated they have no potential conflicts of interest to disclose.

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