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Novel *AARS2* Gene Mutation Producing Leukodystrophy: A Patient with Peripheral Demyelinating Polyneuropathy

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Abstract

Novel *AARS2* gene mutations encoding mitochondrial alanyl-tRNA synthetase are important in the spectrum of different phenotypes expressed in the nervous system. Leukodystrophy and ovarian failure in females are common phenotypes. Peripheral demyelination is not a recognized aspect of the *AARS2* phenotype. A patient with preceding Lyme neuroborreliosis developed progressive leukodystrophy and peripheral demyelinating motor polyneuropathy. Serial magnetic resonance imaging showed progressive inflammatory demyelination extending to the corticospinal tracts. Treatment with a standard of care of antibiotics and immune-modulatory therapy employing intravenous immune globulin was employed. The contribution of neuroborreliosis is not well understood in the expression of the *AARS2* phenotype.

Keywords

AARS2 Mutation, Leukodystrophy, Lyme Neuroborreliosis, Magnetic Resonance Imaging, Electrodiagnostic Studies, Cerebrospinal Fluid, Epidermal Nerve Fibers, Sural Nerve, Muscle Biopsy, IVIg

1. Introduction

The *AARS2* gene encodes mitochondrial alanyl-tRNA synthetase (mtARSs). Gotz and colleagues [1] identified a homozygous mutation in the *AARS2* gene at 6p21.1 in unrelated Finnish female infants with fatal infantile hypertrophic mitochondrial cardiomyopathy and homozygous mutations affecting the editing and catalytic aminoacylation domains of combined oxidative phosphorylation deficiency-8. Dallabona and coworkers [2] described progressive leukoencepha-

lopathy among five women with premature ovarian failure and compound heterozygous mutations in the *AARS*2 gene, which in direct sequencing identified pathogenic biallelic mutations.

2. Patient Report

An adolescent male developed combined leukodystrophy and peripheral nerve demyelination in association with a novel compound heterozygous mutation in the *AARS*2 gene. In 2013, a 16-year-old male with normal birth and development noted a rash and high fever. He resided in rural areas endemic for tick borne disease (TBD). Soon afterward he developed symptoms of stiffness, spasticity and incoordination of the legs followed by involvement of the arms. He was wheelchair bound within two years of onset. Non-contrast magnetic resonance imaging (MRI) suggested a leukodystrophy and genetic analysis (Baylor College of Medicine, Medical Genetics Laboratories, TX) showed a deleterious combined heterozygote frame shift mutation, c.701dupC (p.0236Pfs*50) at exon 4; and a heterozygote novel variant, c.452T > C (p.M151T) at exon 3. Neurological examination in 2015 showed nystagmus with horizontal gaze, scanning speech, intact language and cognition. There was generalized hyperreflexia, bilateral Babinski signs, and hypertonicity of the left arm and both legs with bilateral foot drop and action tremor on attempted movement. He was unable to stand without assistance. Sensation was intact. Babinski signs were elicited. Further evaluation at New York University in 2015 showed the following.

Nerve conduction studies of the legs and left arm showed left fibular distal motor latency (DL) 9 ms and right fibular DL 7.3 ms (normal [nl] ≤ 6.8 ms). Right tibial compound muscle action potential amplitude was 0.3 mV (nl ≥ 3.0 mV) with a motor conduction velocity (CV) of 38 m/s (nl ≥ 42 m/s). Sensory conductions were normal. Electromygraphy showed chronic neurogenic changes. A subsequent study 3 and 6 months later showed progressive absence of the left and right fibular motor responses. Epidermal nerve fiber density in the calf was 2.7/mm of skin (nl ≥ 20/mm) and thigh density was 6.6/mm (nl ≥ 31/mm). Soleus muscle tissue showed collections of subsarcolemmal mitochondria. Sural nerve tissue showed segmental demyelination with CD68 immunoreactivity in the endoneurium, and excessive thinly myelinated nerve fibers in epoxy embedded plastic sections and segmental remyelination in teased nerve fiber analysis. Cerebrospinal fluid was acellular with normal protein, glucose, and IgG, and negative oligoclonal bands and cultures. The Lyme index was 2.14 (nl < 1.1) indicating the intrathecal production of *Borrelia*-specific antibody.

Non-contrast MRI of the brain serially from 2015 to 2018 showed extensive, increasing confluent T_2/fluid-attenuated inversion recovery (FLAIR) signal abnormality with severely decreased diffusion restriction in the corpus callosum, bilateral corona radiate, centrum semiovale, periatrial white matter and posterior limb of the internal capsule, extending into the cerebral peduncles and corticospinal tracts consistent with Wallerian degeneration. These findings were

consistent with inflammatory demyelination and corresponding volume loss and brain atrophy Apparent diffusion coefficient measures on diffusion weighted imaging (DWI) shown in **Figure 1** were consistent with active inflammatory demyelination. MRI of the spinal cord was normal.

The patient received a standard of care antibiotic treatment with parenteral ceftriaxone for earlier Lyme exposure. He has receives monthly 2 grams per kilogram intravenous immune globulin (IVIg) for 36 months. In followup, this regimen led to stabilization of neurocognitive and clinical motor manifestations.

3. Discussion

Mutation in mtARS is an important cause of a spectrum of different phenotypes affecting the central nervous system (CNS). Among 9 female and 8 male cases of reported *AARS2*-associated leukoencephalopathy [2]-[7], the age at onset ranged from 3 to 35 years. Prominent clinical manifestations included cognitive deficits in 15 patients, CST signs in 14 patients, psychiatric and cerebellar signs each in 12 patients, ovarian failure in all 9 females, and epilepsy in 1 patient. Spinal cord MRI was described in only one other patient [7], and that showed signal abnormality in the cervicothoracic region. Treatment with corticosteroids, azathioprine and mycophenolate mofetil were given to one patient. In none however, was peripheral neuropathy ascertained clinically, electrodiagnostically, or histopathologically, in life or at postmortem examination.

The accuracy of mitochondrial protein synthesis is dependent on the coordinated action of nuclear-encoded mtARSs and the mitochondrial DNA-encoded tRNAs. Whole-exome sequencing shows the importance of the mtARS proteins for mitochondrial pathophysiology, as nearly every nuclear gene for mtARS recognizes a disease gene for mitochondrial disease, and defects in each, are identified in a tissue-specific disease that commonly affects the brain.

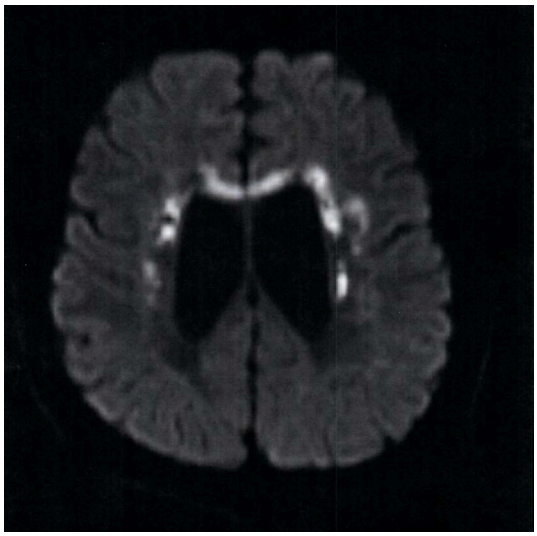

Figure 1. Persistent periventricular increased diffusion restriction consistent with active demyelination.

The contribution of Lyme neuroborreliosis (LNB) to *AARS*2-associated leukodystrophy and peripheral neuropathy is uncertain. It is useful to consider LNB in two dimensions, anatomic and temporal with the former leading to peripheral neuropathy and encephalomyelitis; and the latter resulting in abrupt and early onset of clinical manifestations and a later indolent progression when untreated. Most patients with early LNB are seropositive by conventional two-tiered testing at the time of initial clinical presentation, while intrathecal antibody production directed against *Borrelia* (*B.*) *burgdorferi*, with an elevated Lyme index, and is highly specific for CNS involvement. That index may remain elevated for years following successful treatment. Treatment with a standard of care regimen of antibiotics may not halt the progression of subsequent post-infectious *Borrelia* immunity by activated cerebral microglia and reactive astrocytes in widespread cortical areas [8]. Patients with enhanced immunity or autoimmunity, triggered by *B. burgdorferi* (https://www.cdc.gov/lyme/postlds/index.html), are candidates for IVIg therapy [9].

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Disclosure

The author has nothing to disclose.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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