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LETTER TO THE EDITOR

Correspondence on "Expanded phenotype of *AARS1*-related white matter disease" by Helman et al

To the Editor:

We read with great interest the study by Helman et al,[1] which describes a series of 11 individuals with *AARS1*-related disease. The authors identify 2 main presentations in accordance with age at disease onset and neuroimaging findings. Patients with early infantile onset present in the first year of life with severe epileptic encephalopathy, developmental delay, microcephaly, visual impairment, hypotonia, and pyramidal and extrapyramidal signs. These patients also suffer from feeding problems, failure to thrive, gastroesophageal reflux, and muscle-skeletal complications. Brain magnetic resonance imaging (MRI) showed deficient myelination and early cerebral atrophy. Some patients also had brain calcification as seen on computed tomography scan. Patients belonging to the second group have later onset (beyond age 1 year) and milder clinical presentation but a progressive course. Brain MRI of these patients shows posterior predominant leukoencephalopathy and progressive brain atrophy.

We recently observed at our center a 4-year-old boy initially referred for diagnostic work-up of a genetic white matter disorder of unknown cause and finally diagnosed with a *AARS1*-related disorder. The child was second born from nonconsanguineous healthy parents. Pregnancy was uneventful; he was delivered at 36 gestational weeks by cesarean section because of cardiotocographic track alteration. He had normal weight-for-height parameters. Apgar score was 8 at 1 minute and 9 at 5 minutes. Immediately after birth, he suffered from acute respiratory distress and needed ventilatory support by continuous positive airway pressure for 24 hours. During the first months of life, developmental delay progressively became evident, together with oculomotor abnormalities (mainly instability of visual fixation and fragmented smooth pursuit) and acquired microcephaly. Over time, he presented a slowly improving evolution: he acquired head control at 9 months, sitting position at 14 months, standing at 20 months, walking with support at 2 years, and autonomous walking with wide base and instability at about 4 years. Babbling was reached at about 15 months. At age 4 years, he presented cognitive impairment, hyperactivity, and autistic-like features; he was able to babble but he could not pronounce any words, and he had not acquired pointing. He never experienced episodes of neurological deterioration.

The boy underwent 4 brain MRIs showing global myelination delay in the earliest scans (at age 6 and 11 months). Subsequently, at age 2 and 4 years, appropriate myelination for the age but progressive cerebellar atrophy associated with milder supratentorial brain atrophy and thinning of corpus callosum, chiasm, and optic nerves were detected (Supplemental Figures 1 and 2). Spinal cord MRI was normal, and brain computed tomography, performed at age 4 years, did not reveal intracranial calcification.

Visual evoked potentials at 2 years showed low amplitude waves, whereas electroretinogram was normal. Fundus oculi examination at 2 years showed small and pale optic discs, and at 4 years, it was unchanged.

Genetic tests, including karyotype and chromosomal microarray analysis, were negative. Trio-based exome sequencing disclosed 2 unreported variants on *AARS1* gene (NM_001605.2: c.1237dup; p.Leu413fs inherited from the father and c.145T>C; p.Phe49Leu from the mother) not detected in the general population and predicted in silico as damaging by different software and therefore, in accordance with American College of Medical Genetics and Genomics guidelines, considered likely to be pathogenic variants.

Alanyl-tRNA synthetase activity was measured on fibroblasts. A mild decrease in the AARS1 activity was detected in fibroblasts isolated from the patient. When compared with control fibroblasts, a 64% residual alanylation was detected in the patient fibroblasts.

In conclusion, our observation further enlarges the clinical spectrum of *AARS1*-related presentations. In accordance with age on onset, our patient should be classified in the group with early-onset encephalopathy, and indeed, it was seen that he shared features with this group of patients (developmental delay, acquired microcephaly, thinning of optic nerves and chiasma, myelination delay, cerebellar, and milder supratentorial atrophy). However, the clinical presentation seems to be significantly milder because he did not

have epileptic seizures, he had neither pyramidal nor extrapyramidal signs, he presented a slowly improving clinical picture with no episode of neurological deterioration, and his MRI mainly showed progressive cerebellar atrophy with transient deficient myelination during the first year of life. It is of note that the residual enzyme activity was higher than that reported in patients so far, suggesting a possible correlation between clinical severity and enzyme activity impairment. However, this hypothesis does not seem to be supported by the data from the large series published by Helman et al.[1] Further studies will be needed to better understand the pathophysiological basis of the wide phenotypic variability of this and other aminoacyl-tRNA synthetase–related disorders.

Data Availability

De-identified data are available on request by contacting the corresponding author.

Author Information

A.L. and R.P. wrote the first draft and performed data curation. C.P. performed formal neuroradiological analysis; F.R. performed clinical data curation; S.C., M.I.M., and G.S.S. performed cells culture and biochemical data curation; and M.I. performed genetic data curation. D.T. was responsible for conceptualization and supervision of the study. A.L., R.P., C.P., F.R., S.C., M.I.M., G.S.S., M.I., and D.T. reviewed and approved the manuscript before submission.

Ethics Declaration

The authors received and archived written consent by patient's parents (Institutional Review Board Milano Area 1, study number 2018/ST/117). The study adheres to the principles of the Helsinki Declaration and concerns data gathered during routine diagnostic activity.

Conflict of Interest

The authors declare no conflicts of interest.

Additional Information

The online version of this article (https://doi.org/10.1016/j.gim.2022.01.010) contains supplementary material, which is available to authorized users.

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Reference

1. Helman G, Mendes MI, Nicita F, et al. Expanded phenotype of AARS1-related white matter disease. *Genet Med*. 2021;23(12):2352–2359. http://doi.org/10.1038/s41436-021-01286-8.