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Clinical Observations

Novel Homozygous Mutation of the *AIMP1* Gene: A Milder Neuroimaging Phenotype With Preservation of the Deep White Matter

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ABSTRACT

BACKGROUND: Mutations in *AIMP1*, which plays an important role in the development and maintenance of axon-cytoskeleton integrity and regulating neurofilaments, cause neurodegeneration of variable severity and white matter abnormalities.
METHODS: From the patient records we analyzed the clinical evaluation, molecular genetics, neurodiagnostic, and neuroradiological investigations.
RESULTS: We describe six members of a large consanguineous family with a phenotype of severe neurodegeneration in the form of developmental delays, progressive microcephaly, epilepsy, and failure to thrive. MRI showed callosal atrophy and T2 hyperintensity in the superficial white matter. The periventricular and deep white matter structures were, however, preserved. MR spectroscopy demonstrated *N*-acetylaspartate preservation without evidence of neuroinflammation. Exome sequencing showed a novel homozygous mutation of the *AIMP1* gene in all individuals: c.917A > G (p.(Asp306Gly)).
CONCLUSIONS: This novel homozygous mutation of the *AIMP1* gene is characterized by preserved development of the periventricular and deep white matter structures as demonstrated by MRI and MR spectroscopy correlation.

Introduction

AIMP1 is a crucial component of the multi-tRNA synthetase complex that consists of nine catalytic and three noncatalytic proteins: AIMP1/p43, AIMP2/p38, and AIMP3/p18. The complex plays an important role in various signaling pathways and functional protein synthesis.[1]

AIMP1 is a multifunctional polypeptide with both cytokine and tRNA-binding activities.[1] Several reports in the literature have documented *AMIP1* mutations causing neurodegeneration and leukoencephalopathy. Feinstein et al. reported seven individuals from a consanguineous family with infantile onset of a severe rapid hypomyelinating neurodegenerative disorder similar to

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Pelizaeus-Merzbacher disease.[2] All the affected individuals had severe failure to thrive, microcephaly, and severe global developmental delays with intellectual disabilities and lack of speech. Brain MRI and MR, and magnetic resonance spectroscopy (MRS) showed global cerebral atrophy, atrophy of the corpus callosum, and arrest of myelination and/or hypomyelination associated with decreased *N*-acetyl aspartate levels.

Armstrong et al. reported the same clinical presentation in a Filipino girl with a severe neurodegenerative disorder, intractable epilepsy, progressive microcephaly, and a rapid clinical course leading to premature death; however, the authors disagreed with Feinstein et al. as they considered the myelin deficiency as secondary to the neurodegeneration.[3] In 2016, Iqbal et al. reported two families with milder phenotypes and normal neuroimaging.[4]

To further characterize the *AIMP1*-related phenotype, we report six children from a large consanguineous family presenting with severe developmental delays, early onset seizures, failure to thrive, progressive microcephaly, and cerebral white matter abnormalities.

Methods

We reviewed the patients' charts, including their clinical evaluation and molecular genetics, neurodiagnostic, and neuroradiologic investigations. All the family members provided written informed consent. The diagnostic workflow used for all the patients and their parents is described in detail by Trujillano et al.[5] All the identified variants were verified by Sanger sequencing. The *AIMP1* mutation identified was absent from Centogene's proprietary database, which includes data from nearly 140,000 individuals of diverse geographic origins,[6] and from the Saudi genome database.[7]

Results

We evaluated six patients from a large consanguineous Saudi family (Fig 1). The main clinical, electroencephalogram, electroretinogram, and MRI features are summarized in Table.

Whole exome sequencing revealed the same novel homozygous mutation (c.917A > G p.(Asp306Gly)) of *AIMP1* in all six patients. This mutation was confirmed by Sanger sequencing to be homozygous in the six patients and heterozygous in the parents.

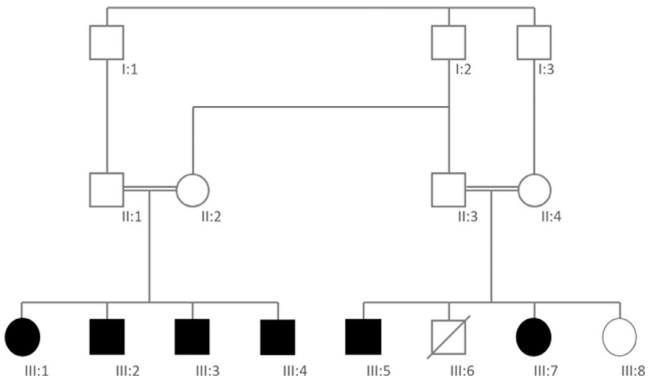

FIGURE 1.
Pedigree of the study family showing the degree of consanguinity between the parents.

Clinically, our patients presented with the features of progressive microcephaly, severe developmental delays with intellectual disabilities and lack of speech acquisition, seizure disorders, and esotropia. All of the patients presented early in the first year of life after an unremarkable perinatal period. The seizures appeared in the first year of life but the semiology varied: tonic in three patients, generalized tonic-clonic in two patients, myoclonic in one patient, and mixed in one patient. The seizures have been under control since then by using one or two antiepileptic drugs.

At the last examination, the patients were wheelchair bound and exhibited spastic quadriplegia, microcephaly (−3 to −4SD), and severe failure to thrive.

Neuroimaging revealed multiple abnormalities. The most common findings included a markedly thinned but fully developed corpus callosum, T2 hyperintensity of the superficial white matter, and normally myelinated periventricular and deep white matter (Fig 2). MRS obtained from patient III5 showed normal metabolites with no signs of decreased cellularity, metabolic impairment, or inflammation. A follow-up MRI and MRS showed progression of the normal myelination in the periventricular and deep white matter, respectively (not shown).

Discussion

We describe six patients from a large consanguineous family with a novel homozygous mutation of *AIMP1*. All the affected individuals presented early in life with severe developmental delays with lack of speech acquisition, progressive microcephaly, seizure disorders, and white matter changes detected via neuroimaging.

AIMP1 genetic mutations are associated with two main phenotypes. The patient phenotype reported by Armstrong et al. and Feinstein et al. is similar to that of our patients, with early neurodegeneration, progressive microcephaly, seizures, and neuroimaging abnormalities.[2,3] However, their neuroimaging phenotype differs in which the abnormal white matter involved the superficial, periventricular, and deep white matter, while in our patients the periventricular and deep white matter structures (i.e., internal capsules) were invariably preserved, showing normal patterns of myelination on MRI and MRS and progression of the myelination process with age. This observation suggests that our novel homozygous mutation of the *AIMP1* gene is associated with a more benign neuroimaging phenotype. Iqbal et al. reported a milder clinical phenotype in two families. Their patients presented mainly with moderate to severe intellectual disabilities, but without seizure disorders, microcephaly or neurodegeneration, or MRI abnormalities.[4] This neuroimaging phenotype is similar to that caused by *AIMP2*/p38, another key component of the multiaminoacyl-tRNA synthetase complex. However, the neuroimaging features are different, in the form of atrophy of the cerebrum, cerebellum, and spinal cord, prominent retrocerebellar cyst, symmetric

TABLE.
The Clinical and Genetic Characteristic of *AIMP1*-Associated Neurophenotypes

	Patient III1	Patient III2	Patient III3	Patient III4	Patient III5	Patient III7
Perinatal history	Unremarkable	Unremarkable	Unremarkable	Unremarkable	Unremarkable	Unremarkable
Age at presentation	In the first year of life	In the first year of life	In the first year of life	In the first year of life	In the first year of life	In the first year of life
Age at assessment	11 years	13 years	16 years	23 years	2 years	8 years
Progressive microcephaly	−3SD	−3.5SD	−4SD	−4SD	−3SD	−3SD
Seizures	Tonic seizures starting in the first year of life. Controlled with 1 AED.	GTC seizures starting at age 1 year. Controlled with 1 AED.	Tonic seizures starting at age 1 year. Controlled with 1 AED.	GTC seizures starting in the first year of life. Controlled with 1AED.	Myoclonic seizures starting at age 1 year. Controlled with 1 AED.	Tonic and GTC seizures starting in the first year of life requiring 2 AEDs.
EEG	Discharges within the temporal lobes	Discharges within the temporal lobes	Discharges within the occipital lobes	Discharges within the temporal lobes	Discharges in both temporal and occipital lobes	Multifocal discharges
Squint	Esotropia	Esotropia	Esotropia	Esotropia	Esotropia	Esotropia
ERG	Normal	Normal	Normal	Normal	Normal	Normal
Developmental milestones	Severely global psychomotor retardation	Severely delayed, mainly gross motor and language	Severely delayed, mainly gross motor and language	Severely delayed, mainly gross motor and language	Severely delayed, mainly gross motor and language	Severely delayed, mainly gross motor and language
Brain MRI	Global thinning of the corpus callosum -Normal extra-axial spaces -Moderate subcortical white matter T2-hyperintensity with deep white matter	Global thinning of the corpus callosum - Normal extra-axial spaces -Moderate subcortical white matter T2-hyperintensity with deep white matter	Global thinning of the corpus callosum - Normal extra-axial spaces -Moderate subcortical white matter T2-hyperintensity with deep white matter	Global thinning of the corpus callosum - Normal extra-axial spaces -Moderate subcortical white matter T2-hyperintensity with deep white matter	-Global thinning of the corpus callosum -Normal extra-axial spaces -Extensive subcortical white matter T2-hyperintensity with deep white matter	Global thinning of the corpus callosum -Normal extra-axial spaces -Mild subcortical white matter T2-hyperintensity with deep white matter
***AIMP1* mutation Protein**	c.917A > G (homozygous) Asp306Gly	c.917A > G (homozygous) Asp306Gly	c.917A > G (homozygous) Asp306Gly	c.917A > G (homozygous) Asp306Gly	c.917A > G (homozygous) Asp306Gly	c.917A > G (homozygous) Asp306Gly

Abbreviations: AED = Antiepileptic drug; EEG = Electroencephalogram; ERG = Electroretinogram; GTC = Generalized tonic-clonic; SD = Standard deviation.

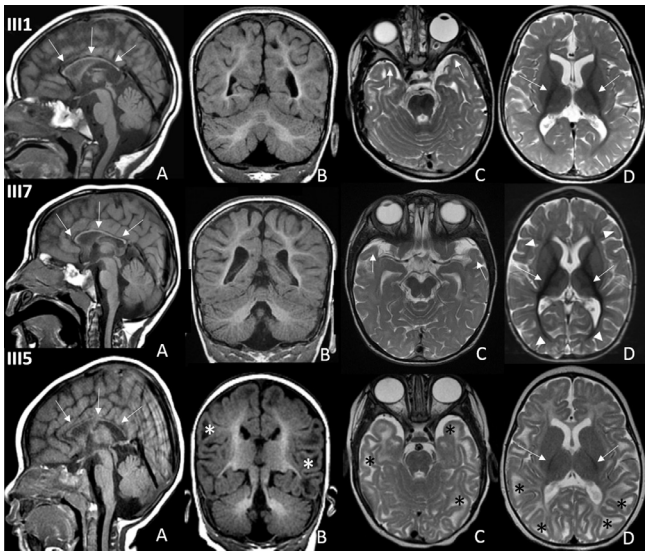

FIGURE 2.
Patient III1. Images from a four-year, nine-months-old patient: There is diffuse thinning of the corpus callosum (A, arrows). There is white matter hyper intensity affecting the subcortical U fibers as seen at the level of the temporal lobes white as observed on T2-weighted images (C, arrowheads). However, there is a normal appearing white matter within the internal capsules (D, arrows). The brainstem and cerebellum are normal. **Patient III7**. A 22-months-old patient: The corpus callosum is thin (A, arrows). Mild diffuse supratentorial atrophy from periventricular white matter loss resulting in mild ventricular enlargement, more pronounced posteriorly, in the absence of significant delay in the expected myelination milestones. Mild hyper intensity is noted in the U fibers (C, arrows, and D, arrowheads) while the internal capsules show normal appearing myelin (D, arrows). **Patient III5**. An eight-months-old patient: Diffuse thinning of the corpus callosum (A). Sulci are nonefaced and diffuse subcortical and periventricular white matter abnormality/impaired myelination is observed on T1- (B, asterisks) and T2-weighted images (C and D, asterisks). In D normally myelinated posterior capsules are clearly identified (arrows).

T2 hypointensities in the bilateral basal ganglia, and thinning of the corpus callosum.[8]

Regarding the variability of the phenotype and the possible correlation of phenotype and/or genotype, Iqbal et al. suggested that frameshift and stop codon *AIMP1* mutations are associated with severe phenotypes, while missense mutations are associated with milder phenotypes.[4] This fact was not confirmed in our study, as the mutation was missense and associated with a more severe clinical phenotype but with a less aggressive neuroimaging presentation.

The white matter abnormalities observed in patients with *AIMP1* have been debated.[9] Our patients showed preserved myelination in the periventricular and deep white matter as supported by T1- and T2-weighted images and serial MRS (although the latter obtained only in patient one). The high T2, low T1 signal areas in the subcortical white matter observed in our variant of *AIMP1* resemble the neuroimaging features, described by van der Knaap et al. in patients with megalencephalic leukoencephalopathy with subcortical cysts (MLC) related white matter edema.[10] One possible mechanism regarding the myelination of deep structures is an abnormal myelin formation of the usual lated myelinated structures, which is likely secondary hypomyelination due to early axonal impairment with decreased density of myelinated axons. Interestingly, also in MLC patients the central white matter structures are preserved.[10] However, in the patient from our series, who underwent serial MRS, we did not observe signs of neuroinflammation or gliosis, and the MRS was within normal limits for age, while in MLC, MRS demonstrates decreased metabolites reflecting increased water content per volume.[10]

The phenotype in the patients corresponds well to findings observed in mice lacking the *AIMP1* and/or *P43* orthologue. Zhu et al. observed that *AIMP1*-null mice showed weight loss and developed multiple motor defects, including tremors, spasticity, slow gaits, and decreased motor activity.[11] Histologic studies showed reduced size and abnormalities of myelinated axons of the ventral roots of the spinal cord and axonal defects of both sensory and motor neurons. These findings indicated that *AIMP1* plays an important role in the development and maintenance of axon-cytoskeleton integrity and regulating neurofilaments.[9] Thus we speculate that this novel homozygous mutation of the *AIMP1* gene may selectively target the axons within the superficial white matter and corpus callosum and that the imaging findings may reflect decreased size of the axons rather than delayed myelination or neuroinflammation.[2,3]

In conclusion, this study identifies a novel neuroimaging phenotype characterized by the exclusive involvement of the superficial white matter.

Authors' contributions

Ahmed BoAli, Kalthoum Tlili-Graiess, Amal AlHashem, Saad AlShahwan, Giulio Zuccoli, and Brahim Tabarki participated in the design, writing, and review of this article.

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Sutures

When the last bit of gauze was gone and I saw the cuts upon cuts, scars in between from her last bout of self-inflicted wounds, blood dripping from her arm onto the bed, my eyes widened and my heart hurt for this poor girl. We looked up at each other, mutually shocked at the extent of her wounds, for a few moments of unspoken conversation. Hurt and compassion and question in my eyes; sadness and embarrassment in hers. As I went to work on her sutures she seemed to calm down, as did I, with the methodical work of pulling the needle through, wrapping, tying, wrapping, tying, wrapping, tying…

Cassie Turnage