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SHORT COMMUNICATION

Pathogenic variants in *AIMP1* cause pontocerebellar hypoplasia

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Abstract
Aminoacyl-tRNA synthetase-interacting multifunctional protein 1 (AIMP1) is a non-catalytic component of the multi-tRNA synthetase complex which catalyzes the ligation of amino acids to the correct tRNAs. Pathogenic variants in several aminoacyl-tRNA synthetases genes have been linked to various neurological disorders, including leukodystrophies and pontocerebellar hypoplasias (PCH). To date, loss-of-function variants in *AIMP1* have been associated with hypomyelinating leukodystrophy-3 (MIM 260600). Here, we report a novel frameshift *AIMP1* homozygous variant (c.160delA,p.Lys54Asnfs) in a child with pontocerebellar hypoplasia and simplified gyral pattern, a phenotype not been previously described with AIMP1 variants, thus expanding the phenotypic spectrum. *AIMP1* should be included in diagnostic PCH gene panels.

Keywords AIMP1/p43 · Hypomyelinating leukodystrophy · Pontocerebellar hypoplasia · Aminoacyl-tRNA synthetases

Introduction

Aminoacyl-tRNA synthetases (AaRSs) catalyze the attachment of an amino acid to its cognate tRNA, ensuring accurate translation of genetic information into functional proteins. Pathogenic variants in both cytosolic and mitochondrial AaRSs have been linked to a broad range of neurologic disorders [1], including hypomyelinating leukodystrophies [2] and pontocerebellar hypoplasias (PCH) [3]. Aminoacyl-tRNA synthetase-interacting multifunctional protein 1 (AIMP1), is one of the three non-catalytic components (AIMP1, 2, and 3) that, combined with nine aminoacyl-tRNA synthetases, form the mammalian multi-tRNA synthetase complex [1]. Bi-allelic frameshift and nonsense variants in *AIMP1* cause hypomyelinating leukodystrophy-3 (MIM 260600), characterized by early neurodegeneration, hypomyelination, cerebral atrophy, progressive microcephaly, and epilepsy [4–6], whereas homozygous missense variants have been recently associated with intellectual disability either without neurodegeneration [7] or with neurodegeneration but showing a milder neuroimaging phenotype [8]. Here, we report a patient harboring a novel homozygous frameshift *AIMP1* variant, presenting with PCH and simplified gyral pattern, a clinical phenotype that has not been previously associated with AIMP1 disease-causing variants, thus broadening the phenotypic spectrum.

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Case description

This boy was the only child of healthy parents. Mother was French-Canadian, father was of Portuguese and French-Canadian ancestry. Prenatal ultrasounds were unremarkable. Delivery was spontaneous and vaginal at term. APGAR scores were 7, 7, and 9 at 1, 5, and 10 min, respectively. Birth weight was 3250 g (− 0.5 SD), length 53 cm (+ 1.1

SD), and head circumference 32 cm (−1.7SD). Within a few hours, the baby presented with seizures and was admitted to the neonatal intensive care unit. EEG during ictal events showed epileptic activity in the posterior left quadrant. Interictally, there was epileptic activity in the bilateral posterior quadrants and severe disturbance of the background consisting of excessive discontinuity for age. His seizures were initially well-controlled on phenobarbital. During hospitalization, he also had recurrent episodes of central apnea, as well as severe feeding intolerance with gastroesophageal reflux and vomiting requiring gavage feeds. Brain MRI at 3 days of life revealed pontocerebellar hypoplasia with simplified gyral pattern, hypomyelination, and thin corpus callosum (Fig. 1). The patient was discharged at 2 months of age. His seizures became more frequent, up to 30 per day, and were resistant to treatment with lorazepam, levetiracetam, topiramate, and phenobarbital. The patient developed increased spasticity in his limbs and dystonia. He had severe developmental delay and failure to thrive. He was partially gavage-fed because of aspiration. At 7 months, his head circumference was 35 cm (− 7.1 SD) and his weight 4.0 kg (− 5.1 SD). He was not dysmorphic. He could fix and follow intermittently. He had no head control. Neurologic exam revealed severe central hypotonia, spastic quadriparesis, and hyperreflexia. His hands were fisted and he could not hold any objects. Intermittent dystonic posturing of the limbs was noted. The patient died at the age of 8 months from respiratory failure in the context of a febrile pulmonary illness. Investigations including extensive metabolic work-up, isoelectrofocusing of transferrin, and brain malformation panel including PCH genes yielded negative results.

Methods

This study was approved by the Montreal Children Hospital ethics committee and informed consent was obtained from the parents. Genomic DNA extracted from blood samples from the affected child and his parents were exome-captured and sequenced at the McGill University and Genome Quebec Innovation Center (Montreal, Canada) using the Agilent SureSelectXT CRE kit and the Illumina HiSeq platform. Exon-level read counts were determined using GATK v4 depth of coverage. Removal of duplicate reads, alignment, and variant annotation were performed using analytical pipelines that include publicly available tools and custom scripts. To identify potentially pathogenic variants, we filtered out (1) synonymous or intronic variants other than those affecting the consensus splice sites, (2) variants with a minor allele frequency greater than 0.001 in gnomadAD database, (3) variants

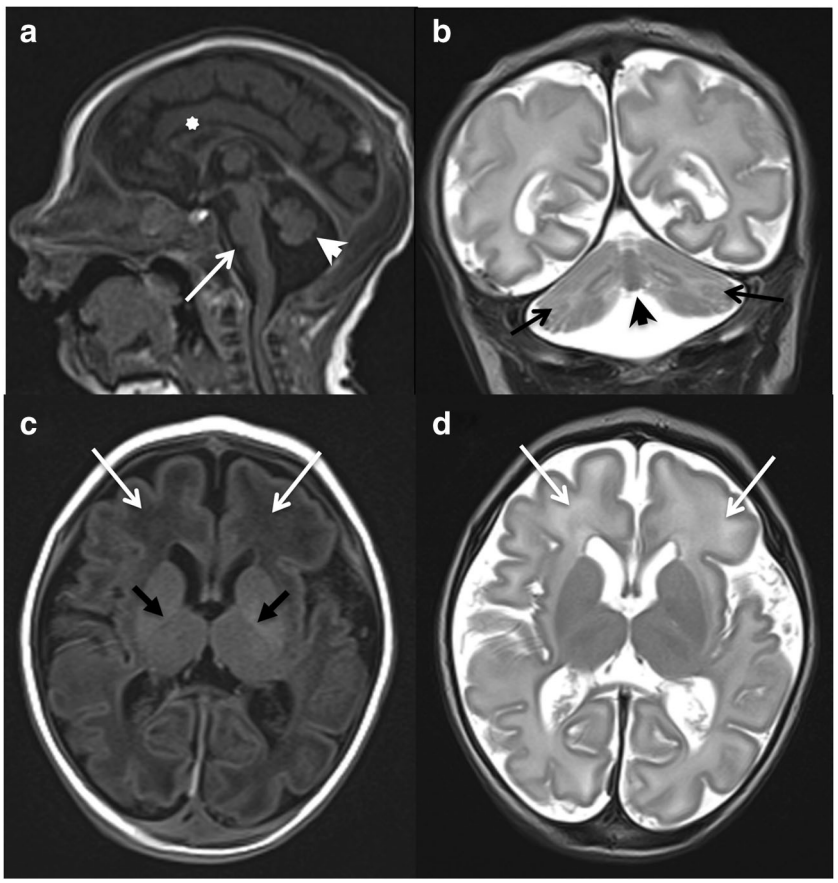

Fig. 1 3T brain MRI images at 3 days of life of patient with *AIMP1* mutations. **a** Sagittal T1 and **b** coronal T2 images illustrate hypoplasia of the pons (white arrow), vermis (arrowhead), and hemispheres (black arrows on T2) of the cerebellum consistent with pontocerebellar hypoplasia. **a** Sagittal T1 also shows thin corpus callosum (asterisk). Axial **c** T1 and **d** T2 images show diffuse decreased gyration and sulcation of the brain, with increased extra-axial spaces in keeping with simplified gyral pattern. In addition, there is abnormal delayed myelination with absence of the expected hyperintense T1 signal of the posterior limb of the internal capsule (black arrows) normally seen at term, **c** hypointense T1, and **d** hyperintense T2 signal of the frontal white matter (white arrows)

seen in homozygous state in our in-house exomes ($n = 1000$) from unrelated projects. We first looked at OMIM genes. All patterns of inheritance were considered in our analysis.

Results

Stepwise filtering retained a single homozygous frameshift deletion in exon 3 of *AIMP1* (NM_001142415 c.160delA, p.Lys54Asnfs*2) which introduces a nonsense codon 2 positions downstream in all three isoforms, likely resulting in a degraded protein through mRNA decay. This variant is rare as it is reported in the heterozygous state in 9/277046 alleles (MAF = 0.003%) and absent in homozygous state in the gnomAD dataset. No further variants in genes linked to known neurodevelopmental disorders were identified. Sanger sequencing confirmed that the c.160delA variant was homozygous in the proband and heterozygous in the parents.

Discussion

To date, four homozygous loss-of-function (Lof) variants have been described in *AIMP1* in 10 patients from four families [4–6]. Apart from one individual with Charcot-Marie-Tooth (CMT) [9], all patients had a hypomyelinating leukodystrophy. Recently, a missense homozygous variant has been reported in six members of a large consanguineous family presenting with severe neurodegeneration but showing preserved development of the periventricular and deep white matter on brain MRI [7].

We describe a patient with a novel homozygous Lof variant in *AIMP1*, a progressive neurodegenerative phenotype and brain imaging compatible with PCH, which has never previously been described in AIMP1-related disorders. Similar to other AIMP1 cases harboring bi-allelic Lof variants, our patient had severe global developmental delay, progressive microcephaly, epilepsy, spasticity, and failure to thrive since first months of life (Table 1). Of note, he presented with neonatal seizures similar to a previously reported patient [5]. He did have mild white matter abnormalities noted on his neonatal brain MRI, not sufficient to prompt investigation of an underlying leukodystrophy. It is possible that with the progression of neurodegeneration, the hypomyelination may have become more obvious with time in our patient. Indeed, hypomyelination in AIMP1 deficiency is likely due to both a primary neuronal disorder and an inability to produce normal myelin following neurodegeneration [6].

PCH is a group of autosomal recessive disorders with prenatal onset of cerebellar and pons hypoplasia or atrophy. To date, there are 11 formally recognized PCH types that have been recently reviewed [3]. Most PCH genes play a role in RNA processing and protein translation [3], thus it is not surprising that pathogenic variants in *AIMP1,* which encodes a component of mammalian multi-tRNA synthetase complex, result in PCH. Mutations in *RARS*, which encodes the mitochondrial arginyl-tRNA synthetase, also result in PCH and hypomyelination and are associated with PCH6. *EXOSC3* and *EXOSC8*, associated with PCH1, have a role in mRNA degradation and *TSEN4*, *TSEN2*, and *TSEN34*, associated with PCH2, PCH4, and PCH5, are involved in tRNA splicing. The pathogenic mechanism underlying pons and cerebellar atrophy is not fully understood. Mice with an editing defect in the alanyl-tRNA synthetase gene, *AARS*, develop progressive neurodegeneration and ataxia, and show evidence of neuronal accumulation of misfolded proteins leading to Purkinje cell death [10]. Similarly, knockout of *tsen54* and *rars2*, two other genes involved in protein translation, results in neuronal cell death in zebrafish [11]. In line with the above findings, postmortem neuropathological studies in individuals with PCH2 and PCH6 reveal arrest of cerebellar development, followed by degeneration during early developmental stages [12, 13].

Among the 37 known AaRSs, 10 cytosolic and 14 mitochondrial AaRSs have been implicated in a wide range of central and peripheral nervous system disorders [14] including hypomyelinating leukodystrophies [15–18], PCH [19], Alpers syndrome (MIM 203700), Leigh syndrome (MIM 256000), intellectual disability [20], hereditary spastic paraplegia [21], and CMT [22, 23]. Mutations in the AaRSs not only lead to abnormal protein synthesis and misfolding but it can also affect non-canonical functions outside protein synthesis [14]. Besides its tRNA-binding activity, AIMP1 has non-canonical effects in several biological processes [24] including neurogenesis. AIMP1 is highly expressed in the central nervous system and is essential for the assembly of neurofilaments (NF), the major neuronal intermediate filaments (IFs). IFs are dynamic structures of the cytoskeletal network, crucial for neuronal development and function [25]. IF defect is a well-identified physiopathological mechanism in several neurodegenerative disorders, such as Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, and CMT [26]. AIMP1 deficiency results in disruption of neuronal cytoskeleton and AIMP1 null mice exhibit motor axon degeneration, defective neuromuscular junctions, muscular atrophy, and motor dysfunction, similar to human patients [25, 27]. The role of NF in cerebellar development is not well understood. Mice lacking light neurofilament (NF-L) show enzymatic activity alterations in hindbrain regions, mainly in the cerebellum and its connecting brainstem regions [26, 28]. Heavy neurofilament (NF-H) proteins are expressed in Purkinje cells during the first weeks of life, defining different stages of postnatal cerebellar patterning [28, 29]. Together, these observations suggest a critical role of NF in cerebellar development and homeostasis, which may be altered when AIMP1 is deficient.

Table 1 Clinical, neuroradiological, and molecular features of patients with *AIMP1* pathogenic variants

	Feinstein et al. 2010							Armstrong et al. 2014	Gonzaga Jauregui et al. 2015	Iqbal et al. 2016		
Patient	Kindred1 III-16	Kindred1 III-25	Kindred1 IV-3	Kindred2 II-1	Kindred2 III-6	Kindred2 III-5	Kindred2 III-26		3664	PKMR60 VI-1	PKMR60 VI-2	PKMR60 VI-3
Ethnicity	Israeli Bedouin							Filipino	Turkish	Pakistani		
Alive	+	+	+	+	+	–	–	–	na	+	+	+
GDD/ID	Severe							Severe	na	mod	mod	mod
Neurodegeneration	+	+	+	+	+	+	+	+	na	–	–	–
Age of onset	First months of life							3rd weeks	na	–	–	–
Microcephaly (SD)	−4	−4	−4	−2.5	na	na	na	−5	–	–	–	–
Spasticity	+	+	+	+	+	+	+	+	–	–	–	–
Neuropathy	na	na	na	na	na	na	na	na	+	na	na	na
Ambulation at follow-up	na	na	na	na	na	na	na	–	na	+	+	+
Epilepsy	–	+	+	–	–	na	na	+	–	–	–	–
Dysmorphism	Coarse face							Coarse face	na	–	–	–
Others	Nystagmus							Optic nerve hypoplasia	CMT2	Dental caries	Dental caries	Dental caries
Hypomyelination	+	+	+	+	+	+	+	+	na	–	–	–
Cerebral atrophy	+	+	+	+	+	+	+	+	na	–	–	–
Corpus callosum hypoplasia	+	+	+	+	+	+	+	–	na	–	–	–
Homozygous *AIMP1* variants (NM_001142415)	c.292_293delCA p.(Gln98Valfs*30)							c.115C>T, p.(Gln39*)	c.334C>T, p.(Gln112*)	c.895G>A p.(Gly299Arg)		

	Iqbal et al. 2016				Accogli et al. 2018	Boali et al. 2019						Current case
Patient	PKMR60 VI−4	PKMR60 VI-5	M105 V-1	M105 V-5	II3	III1	III2	III3	III4	III5	III7	
Ethnicity	Pakistani		Iranian	Iranian	French-Canadian	Saudis						Portuguese/ French-Canadian
Alive	+	+	+	+	+	+	+	+	+	+	+	–
GDD/ID	mod	mod-severe	mod	mod	Severe	Severe						Severe
Neurodegeneration	–	–	–	–	+	+	+	+	+	+	+	+
Age of onset	–	–	–	–	2nd month	First years of life						1st day of life
Microcephaly (SD)	–	–	–	–	−4.8	From −3 to −4						−7.1
Spasticity	–	–	–	–	+	+	+	+	+	+	+	+
Neuropathy	na	na	na	na	+	na						na
Ambulation at follow-up	+	+	+	+	–	–	–	–	–	–	–	na
Epilepsy	–	–	–	–	+	+	+	+	+	+	+	+
Dysmorphism	–	–	–	–	*	–	–	–	–	–	–	–
Others	–	Behavioral issues			Optic nerve hypoplasia	Esotropia						Pontocerebellar hypoplasia

Table 1 (continued)

Hypomyelination	–	–	–	–	+		T2 hyperintensity of the subcortical white matter, but normally myelinated periventricular and deep white matter						+	
Cerebral atrophy	–	–	–	–	+		–	–	–	–	–		+	
Corpus callosum hypoplasia	–	–	–	–	+		+	+	+	+	+		+	
Homozygous *AIMP1* variants (NM_001142415)	c.895G>A p.(Gly299Arg)		c.527T>G p.(Val176Gly)		c.191_192del p.(Gln64Argfs*25)		c.917A>Gp.(Asp306Gly)						c.160delA p.(Lys54Asnfs*2)	

+Present

–Absent

*Thin eyebrows, right epicanthal fold, broad nasal tip, thin upper lip

mod, moderate; *na*, not available; *CMT2*, Charcot-Marie-Tooth type 2

In summary, we report that pathogenic variants in *AIMP1* can be associated with a PCH phenotype. Testing for *AIMP1* variants should be considered as part of the work-up of patients with PCH spectrum, and *AIMP1* should be included in diagnostic PCH gene panels. The co-occurrence of PCH and hypomyelination in our patient suggests a common physiopathological mechanism involving defective protein translation and protein misfolding underlying impaired myelin sheet formation and pontocerebellar cell death. In addition, NF abnormalities related to AIMP1 deficiency might contribute to cerebellar atrophy. Further studies are needed to better define the phenotypic spectrum of *AIMP1* mutations and uncover the common underlying cellular pathophysiological mechanisms linking pontocerebellar atrophy and hypomyelination.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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