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A novel disease-causing variant associated with a milder phenotype of AARS2-related leukodystrophy — A case report

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A B S T R A C T

Background and objectives: Adult-onset leukodystrophies are a rare group of neurological disorders characterized by progressive degeneration of the cerebral white matter. One of these diseases is caused by biallelic pathogenic variants in the *AARS2* gene. We describe a patient with late-onset *AARS2*-related leukoencephalopathy, a milder phenotype and a novel disease-causing variant.

Methods: The patient was characterized during routine clinical practice.

Results: A 40-year-old male was evaluated for chronic headaches. Six years before, he was hospitalized for a major depression with psychotic features. The first neurological examination was normal, except for a slow downbeat nystagmus. Brain MRI revealed significant hyperintensities in T2 and T2-FLAIR bilaterally in the frontal lobes, with periventricular and corpus callosum involvement, and without restricted diffusion. A multigene panel for leukodystrophies based on whole-exome sequencing identified two heterozygous variants in the *AARS2* gene: one previously reported in the literature, already classified as pathogenic, NM_020745.4:c.595C > T (p.(Arg199Cys)), and one novel variant c.730G > A (p.(Val244Ile)), later reclassified as likely pathogenic. Nine years have passed since the first symptoms without clear clinical progression.

Discussion: This case underlines that adult-onset leukodystrophy caused by variants in *AARS2* may have a wide range of phenotypes and patterns of progression. The new variant c.730G > A (p.(Val244Ile)) herein described may induce a milder clinical picture and a less severe radiological pattern.

Practical implications: Adult-onset leukoencephalopathies may present with milder clinical signs than what is generally perceived, and novel disease-causing variants are being identified.

1. Introduction

Adult-onset leukodystrophies include a variety of disorders characterized by the progressive degeneration of cerebral white matter [1]. Among these, a rare form is caused by biallelic pathogenic variants in the AARS2 gene [2]. Typically, AARS2-related leukodystrophy leads to severe cognitive and motor decline, resulting in most patients becoming fully dependent within a decade [3]. However, some individuals exhibit milder phenotypes and slower radiological progression, which poses significant diagnostic challenges. We describe a patient with late-onset AARS2-related leukoencephalopathy, characterized by a milder phenotype associated with a novel disease-causing variant.

2. Case

A 40-year-old male and right-handed salesman was observed in a Neurology outpatient visit for chronic headaches. These headaches started in his early twenties but worsened in the previous 3 years. They had migrainous features and seldomly improved with over-the-counter acetaminophen. The patient was currently experiencing 20 days of headaches per month.

Six years before, he was hospitalized for a major depression with psychotic features and was temporarily medicated with a selective serotonin reuptake inhibitor and a second-generation antipsychotic that had already been tapered off. He also experienced mild attention complaints that didn't significantly interfere with his daily activities and work.

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He was born after an uneventful pregnancy and had normal motor and cognitive development. His past medical history also included C7-T1 arthrodesis following a car crash, with head trauma, when he was 19 years old. Family history was nonrevealing, and there was no history of premature ovarian failure in female relatives.

At the first neurological examination, he presented a slow downbeat nystagmus that was clearer in levo or dextroversion (video 1). The rest of the physical examination was normal, including no parkinsonism and no pyramidal syndrome.

Because of this clinical finding, a brain MRI (Fig. 1) was requested and revealed bilateral frontal periventricular T2 and T2-FLAIR hyperintensities, with subcortical extension, sparing the U-fibers, and involvement of the anterior portion of the corpus callosum (rostrum, genu and anterior part of the body). These lesions were not diffusion-restricted, and no hemorrhagic features were present. The usual biochemical, serological and immunological analyses in the workup of white matter diseases were unrevealing [4].

A multigene panel for 152 *loci* (115 leukodystrophy-associated genes and 37 mitochondrial genes) based on whole-exome sequencing was requested. Two heterozygous variants in the *AARS2* gene were identified: the variant NM_020745.4:c.595C > T (p.(Arg199Cys)), which is already well-known as pathogenic variant [5]; and the variant NM_020745.4:c.730G > A (p.(Val244Ile)) not previously reported in the literature and initially classified as a variant of uncertain clinical significance (VUS). Given that compound heterozygosity was confirmed through variant segregation analysis performed in both parents, the PM3 criterion from the ACMG variant classification system was fulfilled (when, for recessive disorders, a variant is detected in trans with a pathogenic variant). Together with other previously assigned criteria (PM1, PM2 and PP3) this variant was classified as likely-pathogenic. Neuropsychological evaluation at 41 revealed mild dysfunctions in attention, semantic verbal fluency, and inhibitory control.

The patient, now 43 years old, underwent a follow-up brain MRI (Fig. 2) which revealed an increase in bilateral frontal periventricular white matter hyperintensities on T2 and T2-FLAIR, with new extension to the internal capsule. These changes are associated with moderate enlargement of the lateral ventricles, suggesting atrophy. Additionally, the anterior portion of the corpus callosum appears slightly thinner, indicating possible atrophic progression.

Clinically, migraine headaches have become infrequent, and prophylactic therapy with propranolol was discontinued after one year. The patient is employed as a salesman, and the only notable symptom reported during medical evaluations and by his family is mild apathy. Considering his hospitalization for psychotic depression as the onset of symptoms, nine years have passed without any significant impairment.

3. Discussion

Adult-onset leukodystrophies are a rare group of neurological disorders characterized by progressive degeneration of cerebral white matter [1]. One of such diseases is caused by autosomal recessive gene disease causing variants in the alanyl-transfer RNA synthase 2 (*AARS2*) gene, which is located on chromosome 6p21.1. This nuclear gene encodes a mitochondria-specific synthetase enzyme, which plays a crucial role in mitochondrial translation and protein synthesis [4]. Despite being increasingly reported in recent years, *AARS2*-related leukodystrophy (OMIM:612035) is still an extremely rare white matter disorder, with 48 cases documented globally [5].

The overall spectrum of clinical presentation includes movement disorders (78 %), cognitive impairment (67 %), corticospinal signs (64 %), behavioral changes or overt psychiatric symptoms like depression, psychosis, anxiety (46 %), and abnormal eye findings such as nystagmus or ophthalmoplegia (38 %) [6]. The age of onset is between the third and the fourth decades of life, and there is usually a severe cognitive and

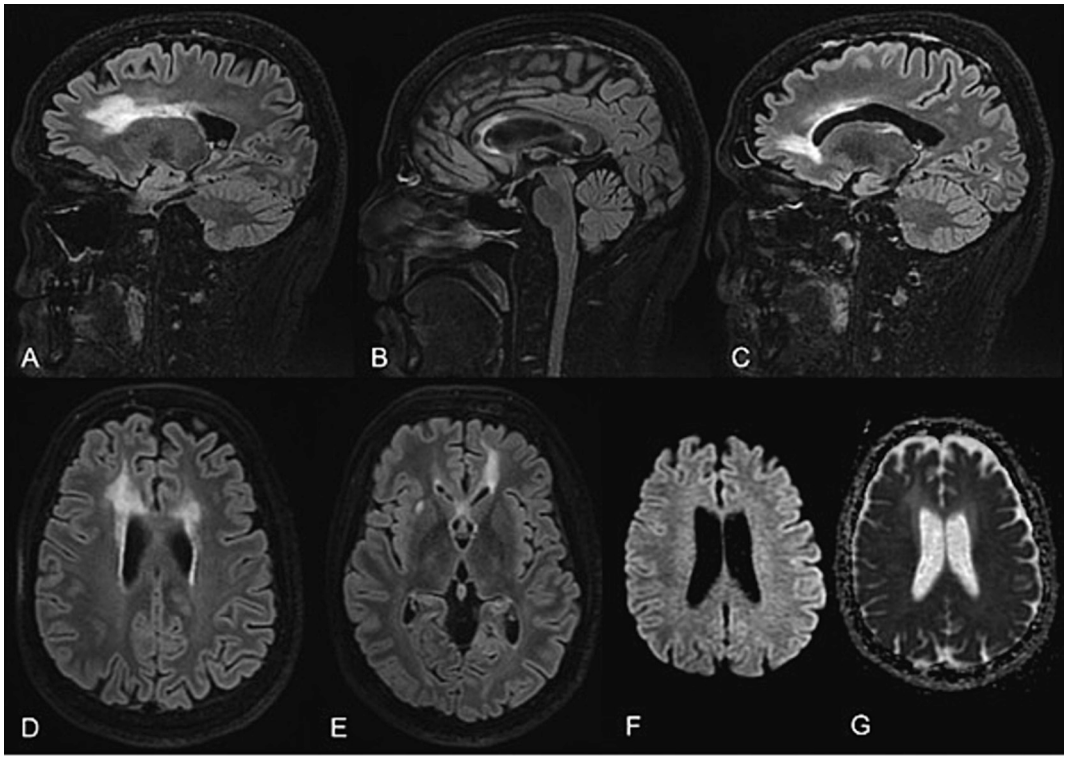

Fig. 1. Brain MRI. A-C T2-weigted fluid-attenuated inversion recovery (T2-FLAIR) sagittal scans show extended white matter hiperintensities at bilateral frontal periventricular areas (right parasagittal plane – A; left parasagittal plane – C) and involvement of the rostum, genu and anterior part of the body of corpus callosum (midsagittal plane – B); D-E T2-FLAIR weighted axial scans show asymmetrical confluent high signal involving bilateral anterior periventricular areas, with subcortical extension, sparing the U-fibers (corona radiata level – D; basal ganglia level – E); F-G The diffusion-weighted image (DWI – F) and apparent diffusion coefficient (ADC – G) map show absence of restricted diffusion in the abnormal white matter.

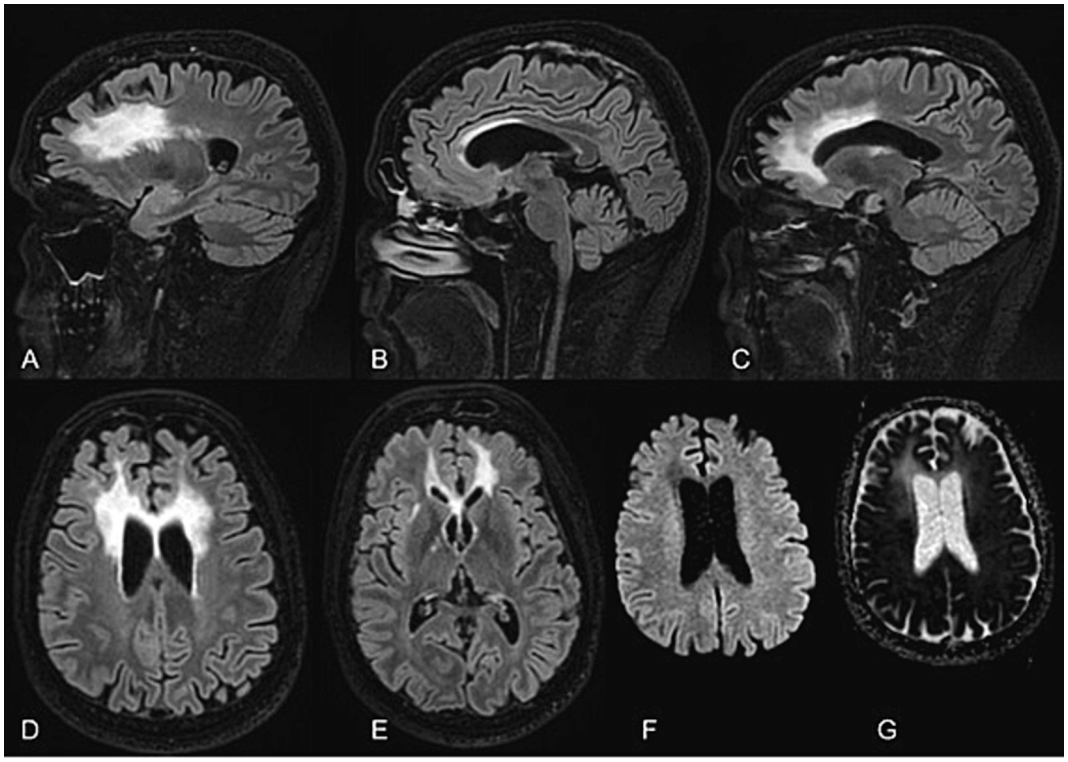

Fig. 2. A follow-up brain MRI was performed three years later, using sequences and positions similar to those in Fig. 1. Compared to the previous study, there is an increase in T2-FLAIR white matter hyperintensities in the bilateral frontal periventricular areas, now extending to the internal capsule. This is accompanied by moderate enlargement of the lateral ventricles, suggesting atrophy. Additionally, there is a greater posterior extension of T2-FLAIR hyperintensity within the body of the corpus callosum, while the anterior portion appears slightly thinner, consistent with atrophic progression. No restricted diffusion is observed in the abnormal white matter.

motor decline, with most patients being dependent within 5–10 years [3].

In our case, the patient presented with a depression with psychotic features, followed by an unusual nystagmus and executive dysfunction complaints. The migrainous headaches, which prompted the first consultation, may not be related with the leukodystrophy *per se*. However, what was striking in this particular case was the mild phenotype, with little progression when compared with the previously reported cases [2,5,6].

It is interesting to notice that in this case there is a head trauma prior to the onset of the disorder. Accordingly, we could find 4 other cases with head trauma preceding the onset of symptoms [2,6–8].

The MRI findings included significant white matter hyperintensities involving the bilateral anterior frontal lobes, including the periventricular region and the anterior portion of the corpus callosum, associated to moderate enlargement of the lateral ventricles (Figs. 1 and 2). However, unlike most described cases, our patient didn't have diffusion-restricted lesions. This imagiological finding is in contradiction with De Cocker LJL et al., that state that restricted diffusion spots are mandatory [9].

Some known genetic variants can cause *AARS2*-related leukodystrophy, and the most commonly reported is the c.595C > T (p.(Arg199Cys)) [5]. In our case, the patient is a compound heterozygote for this known pathogenic variant, and for the new variant c.730G > A (p.(Val244Ile)). We believe that this new likely pathogenic variant may be related to a milder phenotype and slower progression of the clinical picture. Accordingly, it may also justify the absence of restricted-diffusion lesions in the MRI, which are generally markers of a more aggressive physiopathological process.

In summary, this clinical case underlines that AARS2-related leukodystrophy is a heterogeneous disease with a wide range of phenotypes and patterns of progression. The new variant c.730G > A (p.(Val244Ile)) herein described may induce a milder clinical picture and a less severe radiological pattern.

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CRediT authorship contribution statement

Joana Fernandes: Writing – original draft, Investigation, Formal analysis. **João Moura:** Writing – review & editing. **João Tarrio:** Writing – review & editing, Investigation. **Jorge Oliveira:** Writing – review & editing. **Ana Lopes:** Writing – review & editing. **João Parente Freixo:** Writing – review & editing. **Gonçalo Videira:** Writing – review & editing, Validation, Supervision, Project administration, Formal analysis, Conceptualization.

Declaration of competing interest

The authors report no disclosures. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

Data availability

Data will be made available on request.

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