AARS2 mutation-related leukodystrophy: report of new adult-onset patients

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Background

The nuclear gene *AARS2* encodes for the mitochondrial alanine-tRNA synthetase (mtAlaRs), that charges the t-RNA with alanine during mitochondrial translation. In 2014, *AARS2* mutations, otherwise responsible of a recessive form of perinatal/infantile cardiomyopathy, have been found in patients with progressive leukoencephalopathy and ovarian failure. Very recently, Lynch *et al* discovered that mutations in *CSF1R* and *AARS2* may lead to a common clinical phenotype, characterized by neurodegeneration, axonal spheroids and pigmented glia. Considering these new discoveries, Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP), previously referred to as hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS) or pigmentary orthochromatic leukodystrophy (POLD), is the preferred unifying term for leukodystrophies due to mutations both in the *CSF1R* and *AARS2* genes.

Materials and methods

We selected 38 patients with clinical and Magnetic Resonance Imaging (MRI) findings of adult onset leukoencephalopathy and absence of *CSF1R* exons 12-22 mutations. All exons and intron-exon boundaries of *AARS2* gene were amplified and directly sequenced. The pathogenicity of the novel variant was tested in silico using Polyphen2, Mutation Taster, and SIFT software tools.

Results

We found three unrelated patients with compound heterozygous mutations of *AARS2* gene.

Patients 1: female with a mild cognitive delay and primary amenorrhea due to ovarian failure. At age 44, gait disturbances and cognitive deterioration. There was no family history of neurologic disease and no known consanguinity. Brain MRI is showed in Fig.1. She carried a missense mutation c.595C>T (p.Arg199Cys) in the exon 4 and an *in-frame* deletion c.390_392del(p.Phe131del) in exon 2.

Patients 2: female with secondary amenorrhea at age 32, when also cognitive decline and progressive spastic tetraparesis developed. She died at age 36. A sister had an overlapping phenotype. Brain MRI showed a severe leukoencephalopathy and atrophy. At MRI spectroscopy, marked decrease of N-acetylaspartate and marked increase of lactate was found. She harboured p.Arg199Cys variant and a substitution in exon 1 c.236T>A (p.Met79Lys) (2).

Patients 3: a 24 y-old woman with primary amenorrhea. At age 23 she presented a progressive gait disturbances, manifesting after a traumatic head injury, in the absence of cognitive decline. There was no family history of neurologic disease. Brain MRI is showed in Fig.1. She was heterozygous for the known pathogenic insertion (c.2611_2612insA), resulting in a frameshift mutation (p.Thr871Asnfs)[7] and p.Arg199Cys mutation.

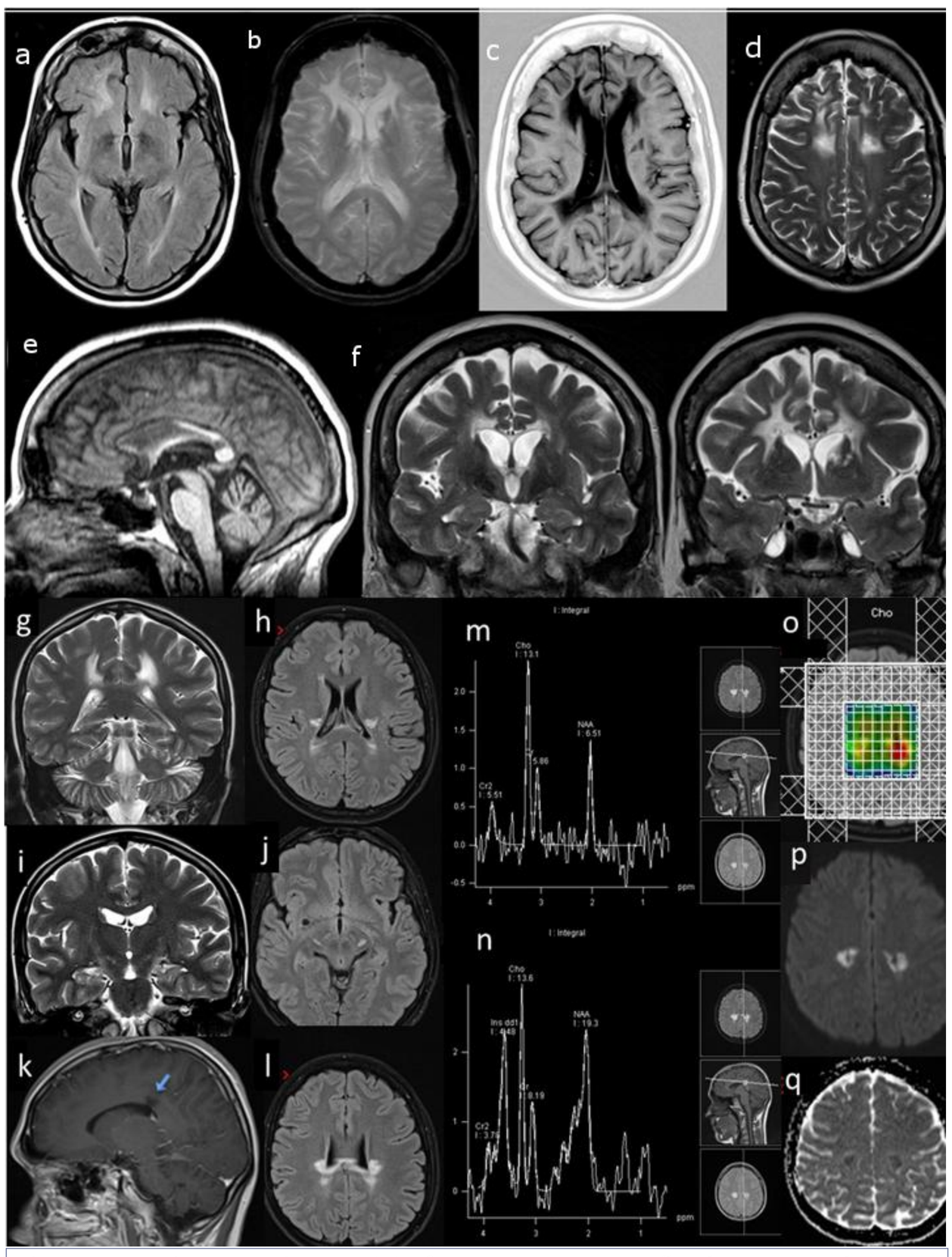

Figure 1. Brain MRI: Patient 1 (a-f): Nonconsecutive fluid attenuated inversion recovery (a), gradient echo (b), inversion recovery (c), and T2-weighted (d) axial, T1-weighted sagittal (e), and nonconsecutive T2-weighted coronal (f) MRI images. Patient 3 (g-q) Coronal T2 images (g;i), axial FLAIR images (h;j;l).

Discussion

Our report is remarkable for the following reasons: a) the finding of three patients carrying *AARS2* mutations suggests that this form may be underestimated; b) the absence in our case 3 of cognitive decline and/or behavioral changes as invariably reported in the majority of patients at onset; c) the peculiar brain MRI pattern with only focal white matter involvement in case 3; and d) the presence of high brain lactate at MR spectroscopy in two patients. we recommend screening for mutations in *CSF1R* and *AARS2* genes in patients with clinical or pathological suspicious of ALSP, also in absence of a clear family history and more characteristic MRI changes. Our results also suggest that MRI spectroscopy may be useful in addressing the genetic screening.

References: **1)** Lynch DS, et al. Analysis of Mutations in **AARS2** in a Series of CSF1R-Negative Patients With Adult-Onset Leukoencephalopathy With Axonal Spheroids and Pigmented Glia. JAMA Neurol. 2016 Dec 1;73(12):1433-1439. **2)** Gaudiano C, et al. A case of ovarioleukodystrophy without eIF2B mutations. J Neurol Sci. 2008 May 15;268(1-2):183-6. Epub 2007 Dec 3. **3)** Dallabona C, et al. Novel (ovario) leukodystrophy related to AARS2 mutations. Neurology. 2014 Jun 10;82(23):2063-71.