Visual impairment as atypical presentation of CADASIL

C Romano[1], R Reniè[1], E Morena[1],M C Buscarinu[1], A Fornasiero[1], S Romano[1], M Ferraldeschi[1], G Ristori[1], M Salvetti[1]

[1] Department of Neurological Sciences, Mental Health and Sensory Organs (NESMOS)-AO Sant'Andrea-Sapienza University of Rome

Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common and best-known monogenic small vessel disease of the central nervous system. It is characterized by migraine with aura, cognitive impairment, seizures and subcortical ischemic events. The pathological hallmark is the deposition of granular osmiophilic material (GOM) near the vascular smooth muscular cells, as seen on electron microscopy, and NOTCH3 seems to be its major component. Consequently, skin biopsy is an important diagnostic tool. Mutations in the gene encoding the NOTCH3 receptor protein, predominantly expressed in adults by vascular smooth muscle cells and pericytes, are specific for CADASIL [1].

Case Presentation

A 44 year-old woman, with family history of headache, came to our attention in July 2015 for an episode of headache, vomiting and loss of consciousness happened in January 2015, followed by a sudden decrease in visual acuity fifth months later. She performed a fluoroangiography, that revealed enhancement of left optic nerve and MRI imaging that showed several and diffuse periventricular, sovratentorial, thalamic and pontine T2-hyperintensities without enhancement (Fig. 1-2). She was treated with Methylprendisone 1 g for 6 days with partial improvement of visual acuity. Meanwhile, there had been daily episodes of headache not responding to NSAIDs. A new contrast MRI scan in September showed no changes, while angio-MRI sequences were normal. She was then admitted to our Neurology Unit in December 2016 and the neurological examination demonstrated only a mild visual acuity reduction in the left eye. Infectious, toxic and autoimmune causes for optic neuritis were excluded [2]. Considering the clinical and imaging features, we considered also a differential diagnosis between metachromatic leukodystrophy and CADASIL. Spectroscopy MRI showed lactate and myo-inositol increase (Fig. 3). Lumbar puncture was normal, including oligoclonal bands and PCR for neurotropic viruses. Arysulfatase A was normal. A cutaneous biopsy was unremarkable for CADASIL, however pathogenic NOTCH 3 gene mutations were detected (Tab. 1).

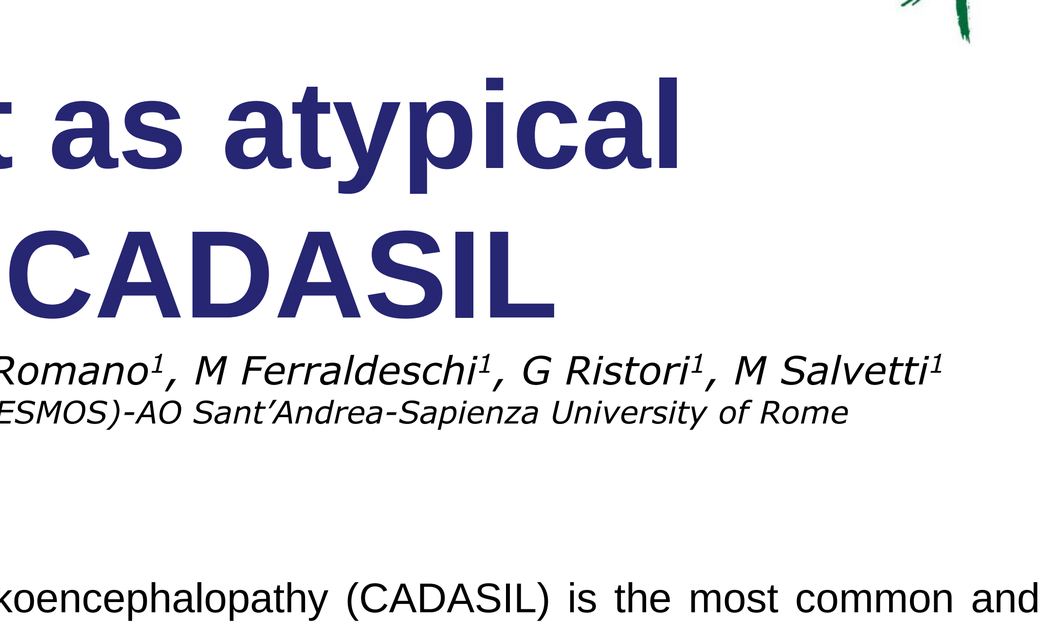

Fig.1

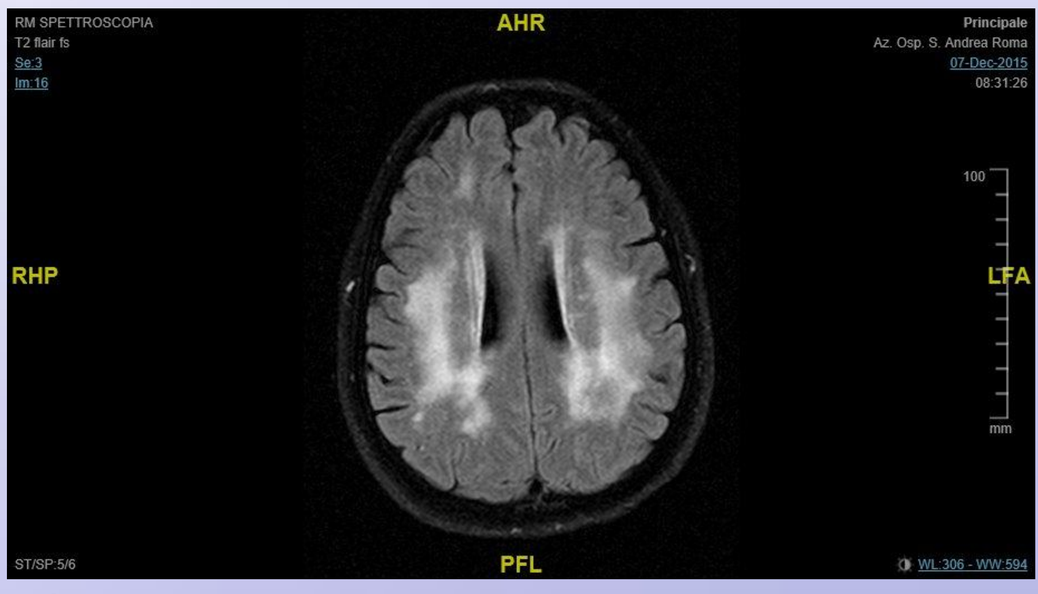

Fig. 2

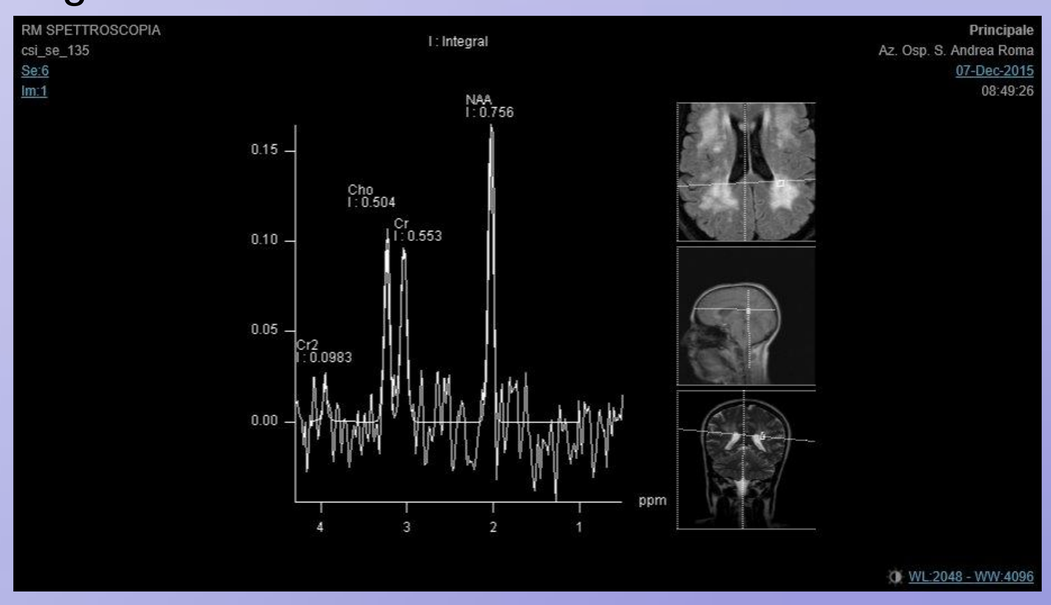

Fig. 3

Genetic result	Interpretation
Molecular analysis of NOTCH3 gene revealed the presence of heterozygosis mutation **c.1708T>C (p.Cys570Arg)**	The NOTCH3 missense mutation, c.1708T>C, determines cysteine loss at 570 position (p.Cys570Arg) with consequent formation of aberrant intramolecular disulphide bonds, resulting in abnormal folding of Notch3 (Joutel et al., 1997). This mutation can be considered **PATHOGENETIC**. It is neither described in literature nor present in dbSNP, LOVD, HGMD, CLinVar, EXAC, 1000 genomes databases.

Tab. 1

Conclusions

Although not typical of CADASIL, family history of headache, MRI findings and mutation of NOTCH3 gene, even in absence of GOM evidence in skin biopsy, suggest the diagnosis of CADASIL in a patient with visual impairment. However, the presence of a resilient mutation cannot be excluded[3].

References

1. Joutel A, Corpechot C, Ducros A, Vahedi K, Chabriat H, Mouton P, et al. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. Nature. 1996;383:707–10.
2. Toosy AT, Mason DF, Miller DH. Optic Neuritis. Lancecrt Neurol. 2014 Jan; 12 (1):83-99.
3. Chen R, Shi L, Hakenberg J, Naughton B et al. Analysis of 589,306 genomes identifies individuals resilient to severe Mendelian childhood diseases. Nature Biotech. 2016; 34:

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