Autosomal dominant cerebral small vessel disease associated with HTRA1 gene mutation in an Italian family

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Introduction

Cerebral small vessel diseases (CSVDs) are an important cause of stroke, cognitive impairment, and mood disorders among the elderly. Usually CSVD is sporadic, but early-onset monogenic forms of CSVD have been reported (1).

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is one of the most common hereditary CSVD caused by autosomal dominant NOTCH3 gene mutations, while Cerebral Autosomal Recessive Arteriopathy with Subcortical Infrarcts and Leukoencephalopathy (CARASIL) is a rare autosomal recessive CSVD caused by HTRA1 gene mutations.

HTRA1 is a member of High Temperature Requirement serine proteases which plays an important role in the degradation of intracellular proteins. More than 200 mutations are known in NOTCH3 gene and only 12 HTRA1 mutated CARASIL families have been reported so far. Recently, heterozygous HTRA1 mutations have been described associated with an autosomal dominant form of CSVD with reduced penetrance, showing clinical features differing from those of CARASIL (2-3).

Patients and methods

We report a family with three affected individuals, referred for stroke and cognitive impairment segregating as an autosomal dominant disorder (fig 1).

Mutations in NOTCH3 and HTRA1 genes have been screened by Sanger sequencing.

In silico prediction tools PolyPhen and SIFT have been used to predict the pathogenicity of the variants found. Skin biopsy of two patients were examined with transmission electron microscope

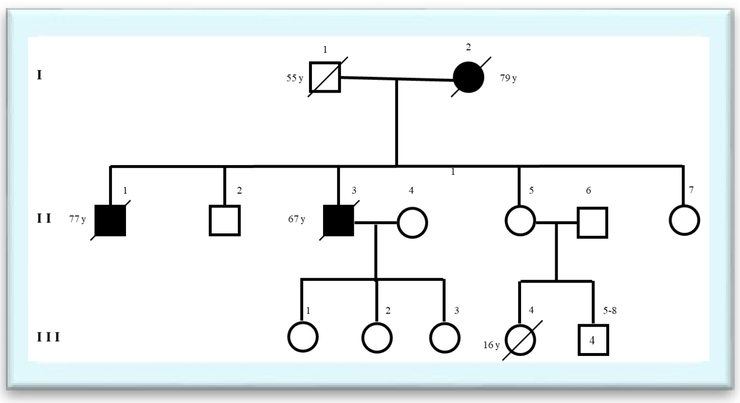

FIG. 1

Genealogical tree of the two patients with R166C HTRA1 mutation.

Filled symbol = clinically and MRI proven affected individual;

Empty symbol = clinically healthy relative;

Results

A heterozygous HTRA1 missense mutation predicted to be deleterious has been found (fig 2) in the two affected brothers. The variation c.496C>T p.Arg166Cys , absent in 1000 genomes database, affects a highly conserved aminoacid, which, if mutated, strongly reduce the HTRA1 proteolytic activity (3).

In silico prediction tools: (PolyPhen-2: probably damaging with a score of 0.998; SIFT: deleterious with a score of 0.00).

The biopsy showed deposits of osmophilic material in the arterial wall, very similar to those characterizing CADASIL (fig 3). MRI examination, performed using axial T1, T2 and FLAIR sequences revealed an extensive high intensity lesions in the white matter specifically in the corona radiata, centrum semiovale, and basal ganglia. See MRI FLAIR sequences, showing the neuroradiological pattern of a CADASIL patient with NOTCH3 mutation sharing the same features of our patients with R166C HTRA1 mutation (fig 4).

Conclusions

Clinical and neuroimaging features of Notch3 and HTRA1 dominant mutations were found to be very similar, both disease belonging to the category of small vessel diseases. The present data show, for the first time, that the hystological alterations of small arteries seen at electronic mycroscope, typical of CADASIL, including deposits of granular osmiophilic material and degeneration of muscle cell of tunica media, are found also in the disease due to dominant HTRA1 mutations. This appears to be rather surprising given the diversity of the 2 gene functions and may constitute a hint to better understand the pathophysiological mechanisms underlying the alterations of small arteries.

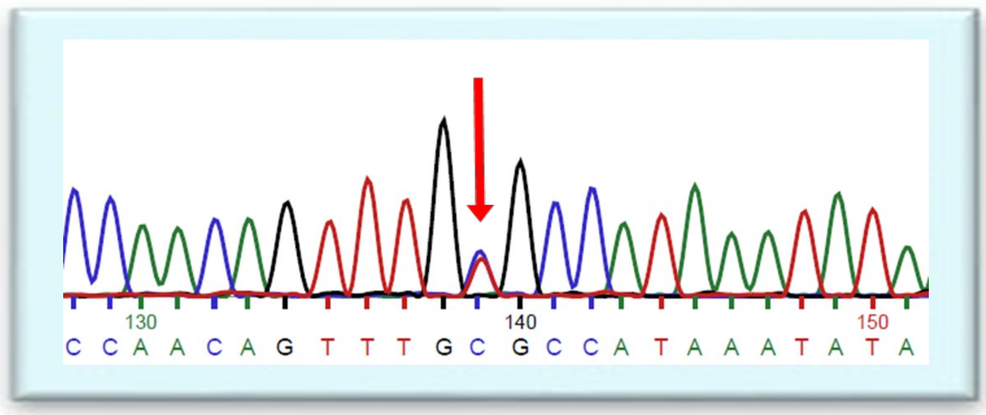

FIG. 2

DNA sequencing chromatogram of a part of HTRA1 exon 2 showing the heterozygous mutation found in our patients.

The arrow indicates the c496C>T nucleotide substitution leading to p.Arg166Cys mutation, predicted to be pathogenic by in silico prediction tools (PolyPhen-2 and SIFT)

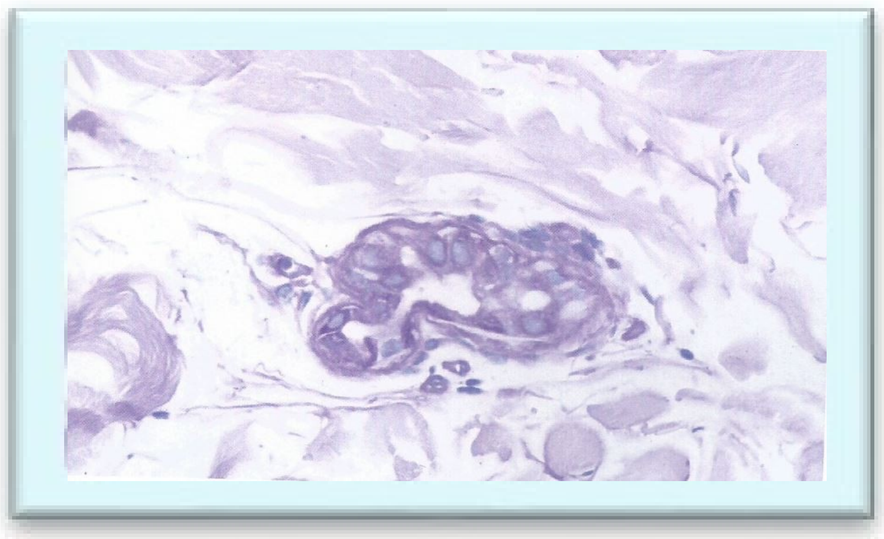

Fig. 3

Ultrastuctural analysis showing the deposition of GOMs in the dermal arterioles closely associated to the CSVDs

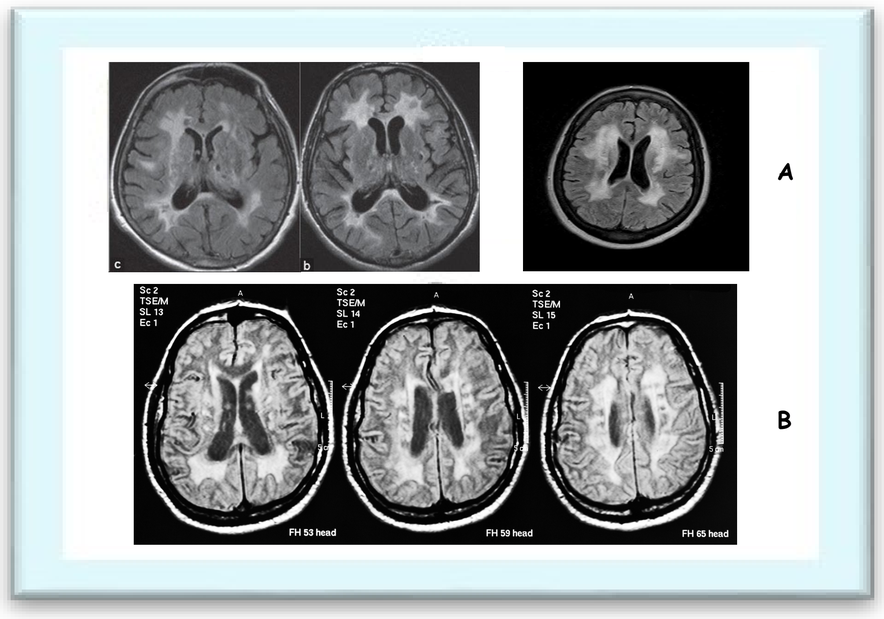

FIG 4

MRI examination. FLAIR sequences showing the neuroradiological pattern of a CADASIL patient with NOTCH3 mutation (A) sharing the same features of our patients with HTRA1 mutation (B).

Subject	Onset	Death	Symptyoms	Alopecia	Cerebral ischemic attacks	Cognitive defects	Epilepsy	MRI findings suggestive of CADASIL	Skin biopsy (GOMs)
I-2	57 y	79 y	Paresthesias, weakness of left arm and leg	-	+	N/A	-	N/A	N/A
II-1	57 y	77 y	tetraparesis	-	+	++	+	+	+
II-3	57 y	67	Piramidal signs, cerebellar ataxia	-	+	++	+	+	+

Table 1.

Clinical and diagnostic findings of the patients.

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