A TREVISO DEMENTIA (TREDEM) REGISTRY CLINICAL CASE SHOWING A FRONTOTEMPORAL PHENOTYPE WITH GENETIC AND ELECTRON MICROSCOPY EVIDENCES OF CADASIL

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INTRODUCTION

We describe an unusual case of a patient exhibiting a clinical, neuropsychological and neuroimaging phenotype consistent with the frontotemporal spectrum, associated with multiple minute subcortical ischemic lesions not typical for vascular pathology of genetic nature, but with a NOTCH3 genetic variation and with the presence of osmiophilic deposits in the skin biopsy, suggestive for Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

CASE PRESENTATION

An 83-year-old right-handed man, a retired engineer, reported the occurrence, three years earlier, of memory difficulties, anxiety and loss of interests, such as reading and watching movies. He also began to eat in a hurry despite his wife's recommendations. The patient also showed high blood pressure and hypercholesterolemia. His mother became demented at the age of 60. The patient presented a substantially normal neurological objective examination.

METHODS AND CLINICAL INVESTIGATION

Clinical, neuropsychological, neuroimaging, biomarkers, genetic and ultrastructural analysis were conducted.

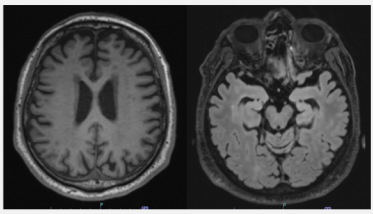

Fig. 1

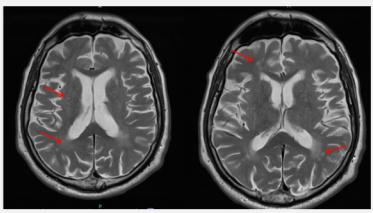

Fig. 2

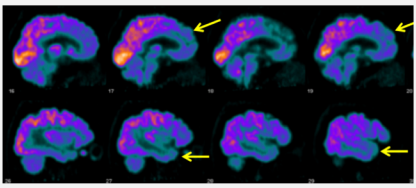

Fig. 3

Brain MRI showed mild frontotemporal atrophy and multiple hyperintense focalities in FLAIR and T2 in the subcortical area. (fig. 1, 2)

18F-FDG PET imaging showed reduced glucose metabolism in the temporal and frontal lobes bilaterally (fig. 3).

CSF tau and amyloid measurements did not show pathological values. The serum progranulin assay was in the normal range.

Four neuropsychological assessments showed loss of memory, and worsening of anxiety, apathy, and hyperphagia, with loss of autonomy in instrumental activities of daily living.

APOE E3/E4 genotype was identified. After excluding C9ORF72 by Repeat-Primed PCR, targeted Next-Generation Sequencing identified a heterozygous c.3691C>T rare variant (MAF $8*10^{-4}$) in the Notch3 gene which is predicted to cause an Arg1231Cys substitution; in the literature associated with mild or full-blown forms of CADASIL in heterozygosity or homozygosity respectively.

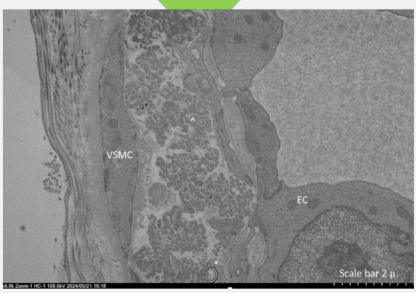

Fig. 4 - Diffuse granular material (GOM ^2) deposits located on the cell membrane of a VSMC with an inhomogeneous morphology and calcification (*). EC = epithelial cell; VSMC= vascular smooth muscle cell.

A skin biopsy was then performed in the deltoid region of the arm. Electron microscopy of the skin and subcutis showed some arterioles with evidence of osmiophilic granular material associated with calcific spherules near the smooth muscle cells of the middle tonaca, supporting the diagnosis of CADASIL (fig. 4).

DISCUSSION & CONCLUSION

Our patient had an older age of symptoms' onset than the classic age of onset of CADASIL symptoms (40-50 years). The multiple hyperintense focalities in FLAIR and T2 in the subcortical area did not show the confluent appearance typical of CADASIL nor the characteristic hyperintensities in the external capsule. There were no cerebral microbleeds (CMBs) in SWI. Clinical, neuropsychological aspects and hypometabolism on brain 18F-FDG PET scan suggested frontotemporal disease. On the other hand, two diagnostic gold standards of the CADASIL (genetic analysis and electron microscopy) were met in our patient. The report expands the genotype-to-phenotype borders of Notch3 associated CADASIL.

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