A NEW VARIANT IN EXON 14 OF NOTCH3 IN A PATIENT WITH BRAIN WHITE MATTER HYPERINTESITY

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Background

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a white matter disease with cephalalgia and ischemic infarcts, linked to mutations in the *NOTCH3* gene, mostly located in exons 2-24. Because MRI can show areas of increased signal on T2 weighted sequences, differential diagnosis with demyelinating diseases is required. Atypical clinical cases are reported and electromicroscopic granular osmiophilic materials (GOMs) are frequent on skin biopsy

Case report

We describe an hispanic, 32 years old female affected for three years by pain and weariness of the right shoulder, hands' paresthesia, painful electric shocks, dizziness, weakness of the left lower limb, diffuse myalgia, headache. She was a smoker but any relevant disease was sign out in the past. In family's history (fig 1): the mother was affected by senile dementia with white matter alterations on brain-MRI (fig 2), a brother had migraine with normal MRI and a sister presented an unspecified MRI brain white matter alterations. Neurological examination was normal in the patient but neuropsycological profile showed a decrease of one's concentration and of the diffusion inhibitory control. Submitted to a brain MRI, numerous, multiple, non enhancing subcortical hyperintensity's areas on T2-wighted sequences, sometime confluent, located prevalently on the left frontal region and the centrum semiovale were seen (fig 3). Spinal cord and brain angioMRI were both normal. EMG showed bilateral C5, C8, D1 chronic neurogenic alterations but EEG, Evoked Potential, Carotid Artery's and Transcranial ultrasound were normal. Ematic exams, including metabolic, coagulation, lipid profile, folate, B12, thyroid, thrombophilia and tests for collagenopathies and vasculitis were all negative. Also CSF analysis with IgG-Oligoclonal Bands by IEF and HSV-1,2, VZV, CMV, EBV,HHSV-6 real time PCR were normal. Because of subcortical brain MRI alterations and cephalagia, the patient was submitted to genetic testing for CADASIL. Sequencing of *NOTCH3* revealed the presence of c.2180C>T change in exon 14, causing the novel missense substitution p.Pro727Leu at codon 727 of putative protein (fig 4). To confirm the diagnosis of CADASIL the woman underwent to skin and muscle biopsy that were both normal: in particular GOMs were absent on electromicroscopic analysis. The patient had a poor compliance but a treatment with ASA and analgesic drugs was start with clinical stability. Also brain MRI was unchanged during the last 4 years. Genetic analysis not confirmed the new variant in the brother with migraine (fig 5). No other family's members have been studied to date.

Fig 1

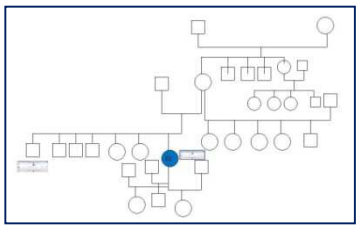


Fig 2

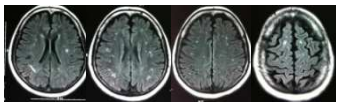


Fig 3

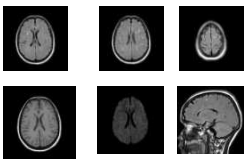


Fig 4

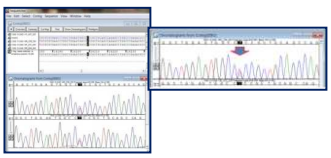
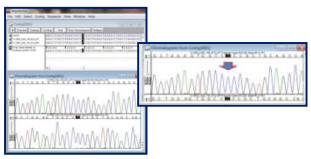


Fig 5



Conclusions Phenotype of our patient was atypical regarding clinical, neuroradiological and pathological manifestations. Also the new *NOTCH3* variant (c.2180C>T) found was no typical because it doesn't insert/abolish a Cys codon. Moreover it didn't segregate with the migraine phenotype in the brother of the patient. Since no additional relatives have been analysed, we actually don't still know if the variant arose *de novo* in the proband. Further follow-up of the patient and genetic analysis of additional family's members would be helpful in order to strengthen the association with clinical phenotype.