Subcartical encefalopathy plus suicidal ideation: clinical presentation of uncommon genotype of CADASIL

V.Arnao[1], M.Maimone Baronello[1], G.Famoso[1], M.Romano[1], A.Romeo[1], S.Cottone[1],A.Gasparro[1]
[1]Neurology and Stroke Unit, Azienda Ospedaliera Ospedali Riuniti Villa Sofia-Cervello, Palermo, Italy.

BACKGROUND AND OBJECTIVES

Background: CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy) is a systemic artery disease responsible for more or less diffuse white-matter lesions associated with small deep infarcts. The disease affects middle-aged adults and it is caused by mutations of the Notch3 gene located on chromosome 19. CADASIL is clinically characterized by the recurrence of ischaemic stroke leading to a pseudobulbar palsy and subcortical dementia, attacks of migraine with aura and mood disorders.
Objectives: To describe a case of CADASIL with uncommon genotype

CASE REPORT: A 48-year-old-right-handed man, with familiar history of seizures, absence of brain damage in childhood and history of hypertension and behavioral disorders and suicidal ideation, was admitted to our department with a sudden left severe hemiparesis.

ON ADMISSION TO OUR DEPARTMENT:

- On neurological examination, sudden left severe hemiparesis, dysarthria (NIHSS=11). Depression mood was highlighted.
- First level laboratory tests were normal.
- First Brain CT was normal
- Brain CT after 48 hours showed: ipodensity in the right semioval center right and leukoencephalopathy
- Both heart and neck vassel ultrasonography examinations were normal
- 4-hour Holter ambulatory ECG monitoring was normal
- Serum research for tumoral markers was negative

MRI showed an extensive and diffuse DWI hyperintense signal in in the right semioval center and extensive small deep infarcts and leukoencephalopathy. (C-D-E)

CSF analysis including total proteins, count cell, glucose and isoelettrofocusing was normal

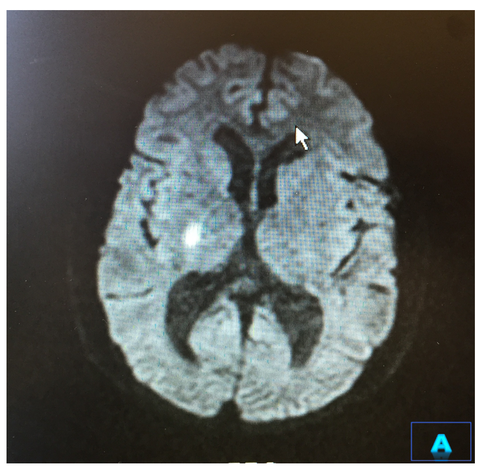
Genetic tests for Fabry disease and CADASIL showed: S497L in exon 9 for NOTCH3

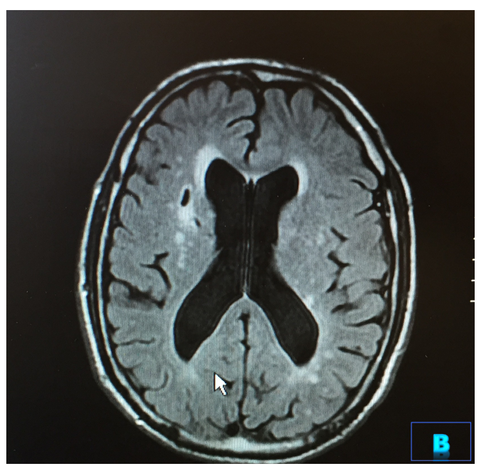
Over the next two weeks: Improve general condictions.

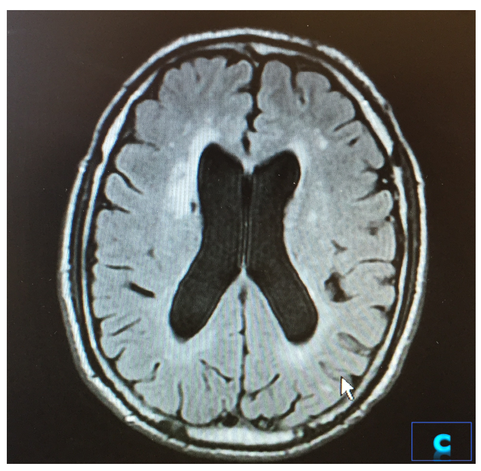
Motor and logopedic rehabilitation therapy associated with farmacological therapy for depressive symptoms and behavioral disorders was started as soon as possible with improvement of motor impairmant

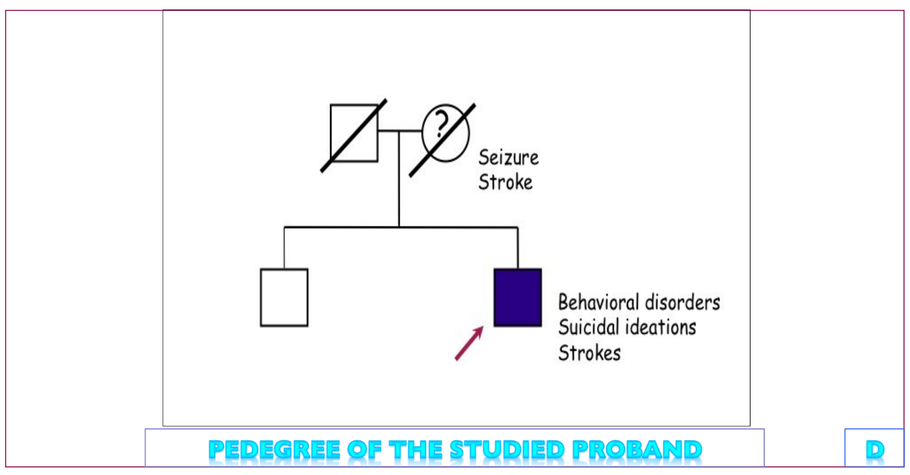
According to publish literature data

FINAL DIAGNOSIS WAS: CADASIL









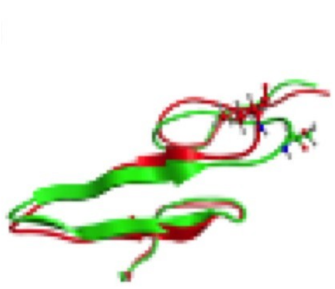
REVIEW OF LITERATURE

- NOTCH3 has 33 exons but all CADASIL mutations occur in exons 2–24, which encode the 34 EGF like region.

All mutations lead to an odd number of cysteine

- ✓ 95% missense mutations
- ✓ 5% small in-frame deletions or splice-site mutations
- ✓ polymorfisms

- In one series of 229 CADASIL Italian patients, an heterogeneous mutational spectrum has been observed.
- A new type of mutation has been showed recently: no-cys mutations
- A silico-model study has revelead a no-cys mutation for the variation S497L



Structural superposition of the wild type (green) and Ser497Leu (red) Notch3 protein.

An "in silico study" has revealed a rather complex molecular mechanism of Notch3 on the structural level; based on the nature and position of S497L mutation, a consensus significant loss of beta-sheet structure is observed.

A series of Notch3 mutations in CADASIL; insights from 3D molecular modelling and evolutionary analyses

Journal of Molecular Biochemistry (2014) 3, 97-105

DISCUSSION AND CONCLUSION

- We described a case of CADASIL with psychiatric onset and stroke due to no-cys mutation S497L in exon 9 for NOTCH3.
- Strokes and behavioral disorders are the most common symthoms in CADASIL in a large series from Italy, but cognitive impairment, migraine with aura and seizures can occur.
- All classic mutations for NOTCH3 lead to an odd number of cysteine EGFR.
- No-cys mutations could be a key to undestand polymorfisms and new mutations for NOTCH3.
- Full sequencing of exons 2-24 is mandatory for CADASIL screening.

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