A case of presenile behavioural Frontotemporal Dementia with C9orf72 expansion and in vivo-evidence of cerebral amyloidosis

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Background: **C9orf72 hexanucleotide repeat expansion** is the most common cause of familial frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). There is a wide heterogeneity of clinical manifestations that includes also an early amnestic syndrome. The underlying neuropathology is a TAR DNA-binding protein (TDP) pathology irrespective of the clinical phenotype.

Aim: To describe a case of presenile dementia due to definite bvFTD caused by 100% penetrant C9orf72 expansion with evidences of **concurrent AD pathology.**

Case Description: A 48-year-old woman was admitted to our Memory Clinic because two years earlier she had developed difficulties in concentration and planning with anxiety and depression. Psychiatric symptoms were treatment-resistant and progressive cognitive impairment caused an early retirement.
Her past medical history was significant only for anxiety disorder in the last teen years.

Her brother died for ALS at 69 years old and a sister had suffered of major depressive disorder in early age then died at age 49 of myocardial infarction.

Her **neurological examination** revealed generally brisk deep tendon reflexes, bradykinesia and ideomotor apraxia; moreover she had postural finger micromyoclonus and slow saccades.

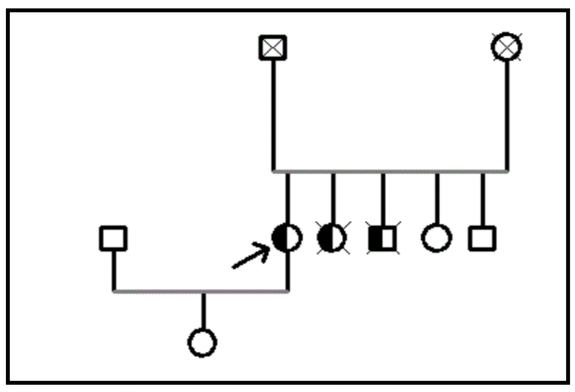

***Fig. 1**. Genealogic tree of patient's family. Half black symbols indicate the presence of neurological or psychiatric disease*

Neuropsychological assessment showed a global cognitive decline, more pronounced in amnestic and executive domains (MMSE 15/30).

Neuropsychological Test	raw score	ES (or z score*)
MMSE	15/30	0
Digit Span forward	3/8	-2.68*
Digit Span backward	0/8	-
Immediate Prose Memory	6/28	-2.25*
Delayed Prose Memory	7/28	-2.59*
RAVLT Immediate Recall	10/75	0
RAVLT Delayed Recall	0/15	-
ROCF Copy	5.5/36	0
ROCF Recall	1/36	0
Clock Test	6/10	0
Attentional Matrix	31/60	1
TMT A	130''	n.s.
FAB	7/18	0
Semantic Fluency	18	0
Phonemic Fluency	19	0

***Tab. 1**. Neuropsychological tests. ES: Equivalent Score; RAVLT: Rey Auditory Verbal Learning Test; ROCF: Rey–Osterrieth complex figure; FAB: Frontal Assessment Battery; TMT: Trail Making Test*

An **extensive diagnostic work-up** was performed comprehensive of biochemical, metabolic and immunological blood screenings that were unremarkable.

Chemical physical CSF analysis was normal.

A Beta 1-42	309 ng/L ↓	cut off < 500
P Tau 181	129 ng/L ↑	cut off > 60
Total Tau	1524 ng/L ↑	cut off > 450
A Beta/P Tau	2.4 ↓	cut off 6-7

***Tab. 2**. Levels of CSF biomarkers of amyloid and tau pathology*

CSF A-beta42 level was decreased while total-Tau and P-Tau levels were increased (**pattern suggestive for AD**).

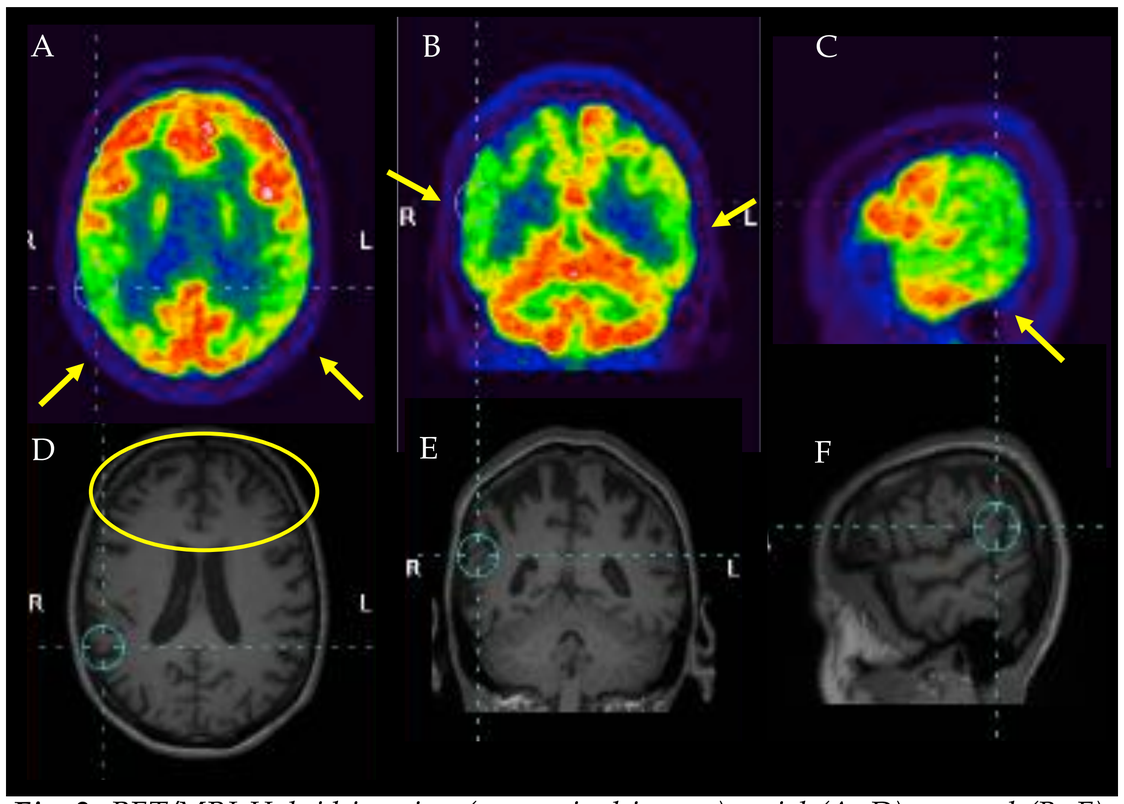

***Fig. 2**. PET/MRI Hybrid imaging (co-acquired images), axial (A, D), coronal (B, E), and sagittal (C, F) scan. Arrows point to bilateral parieto-temporal hypometabolism, no correspondent cortical atrophy was detect at visual qualitative analysis; mild mesial frontal atrophy was noted (circle)*

***Fig. 3**. PET scan (A) and NEUROSTAT output (B) (differences between patient's scan and a standard atlas brain), blue areas indicate the grater standard deviations*

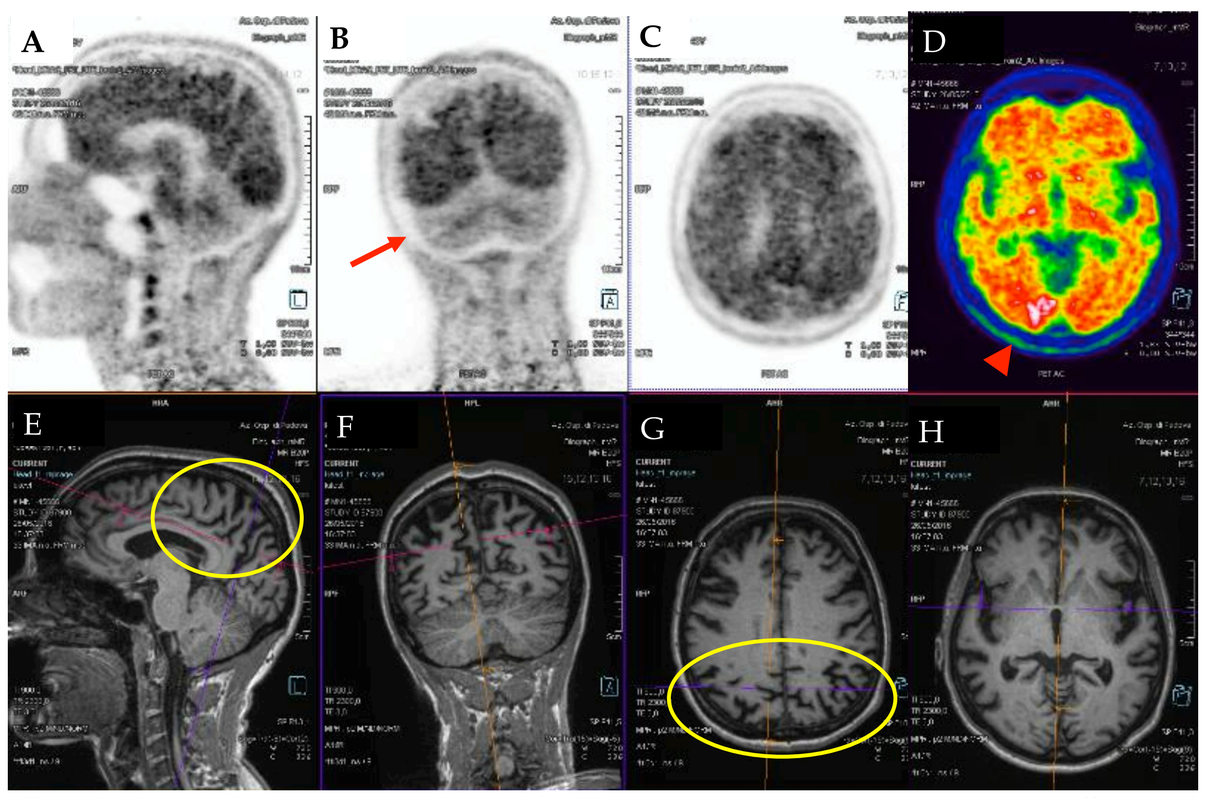

***Fig. 4**. PET/MRI amyloid imaging with 18F-Florbetaben (A, B, C, D) show diffuse and significant cortical Florbetaben retention (note the cerebellar cortex as a reference region, arrow), with semiquantitative measures (D): z scores (vs 10 normal controls with age < 60) max values for: R occipital 20.1, L occipital 15.8, R parietal 14.6, L parietal 15.5 (arrow point on R occipital lobe). Note on MRI images, precence of mild parietal cortical atrophy (circles)*

A brain **FDG-PET/MRI** scan showed a marked bilateral parieto-temporal hypometabolism and, 1 year later she performed **Florbetaben PET** that was rated amyloid-positive.

She tested positive for C9orf72 expansion

She was treated with Sertraline (50 mg/day) and Quetiapine (25 mg/day); anticholinesterase therapy was started with memory improvement. Six months later she continued to experience panic attacks, and developed **psychotic symptoms** (she projected aggressive and negative thoughts onto an another external self that became so real that she spoke and argued with), so quetiapine dosage was titrated up to 300 mg/day.

Conclusion: to our knowledge this is the first report of FTLD and AD mixed pathology occurring in a patient under 50 years of age. This case broadens the clinical complexity related to C9orf72 expansion, and suggests considering the unpredictable interactions between more proteinopathies.

Rohrer JD et al. Lancet Neurol. 2015;14(3):291-301.