Young-onset frontotemporal dementia with aphasia and Alzheimer-related copathology with a discordant CSF/PET amyloid status

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Background

Accurately identifying the clinical variants of Primary Progressive Aphasia (PPA) may suggest the underlying neuropathology although the use of biomarkers is essential to differentiate between Alzheimer disease and frontotemporal lobar degeneration. A correct biological diagnosis of these variants is crucial for appropriate prognostic and therapeutic management. Here, we report a case of a young-onset patient presenting with advanced PPA and a challenging differential diagnosis and/or co-pathology.

Case report

A 53-year-old woman experienced an insidious onset of language decline over the course of three years, initially marked by subtle semantic and phonemic paraphasias, along with mild apathy and loss of volition. Family history was negative for neurological diseases.

Neurological examination revealed severe global cognitive impairment (MoCA score: 5), primarily caused by significant reduction in speech fluency, semantic and phonemic paraphasias, and attention deficits and frontal lobe behaviour. No motor symptoms were detected.

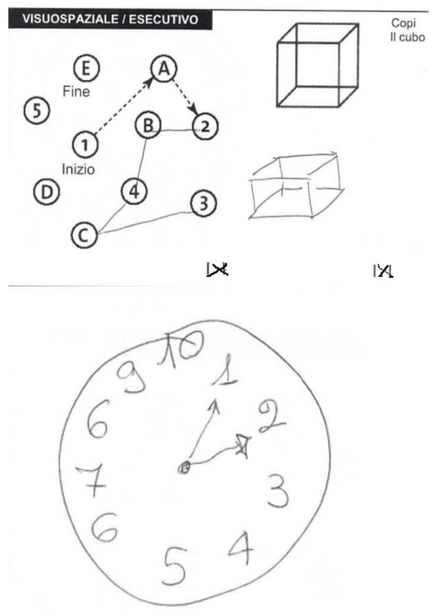
Investigations

Neuropsychological examination revealed impaired frontal lobe functions (FAB), immediate and delayed memory deficits, and impairment in social cognition. Speech evaluation identified significant naming difficulties and altered phrase repetition, while phonetic-articulatory function and semantic association were preserved, consistent with a logopenic pattern. Figure 1

MRI showed atrophy in the frontal and lateral temporal regions, with relative sparing of the mesial temporal regions and mild parietal atrophy.

FDG-PET showed left fronto-temporal and parietal pattern of hypometabolism. Genetic testing was negative. **CSF** analysis revealed a A+T+N+ status although qualitative and quantitative **amyloid-PET** was negative for amyloid deposition.

A diagnosis of frontotemporal dementia with PPA onset and Alzheimer-related copathology according to CSF was made.



Test somministrati	Punteggi grezzi (P. G.)	P. C.	Z score	P.E.	Cut-off	Esito
FUNZIONI COGNITIVE GLOBALI						
MoCA (Conti et al., 2014)	5/30	2,82		0		Alterato
MMSE convertito			12/30			
LINGUAGGIO						
Fluenza verbali (Costa et al., 2014) semantica	13	8,95		0		Alterato
SAND (Screening for Aphasia in Neurodegeneration, Catricalà et al., 2017)						
Denominazione	1/14	0,71			≤9,969	Alterato
Comprensione di frasi	3/8	2,95			≤6,157	Alterato
Comprensione di parole	11/12	10,9			≤10,258	Nella norma
Ripetizione di parole e non parole	7/10	6,64			≤6,349	Nella norma
Ripetizione di frasi	0/6	-0,17			≤2,455	Alterato
Scrittura	2/6	1,64			≤2,132	Alterato
Associazione semantica	3/4	2,89			≤1,166	Nella norma
Descrizione di figura	2/8				≤3	Alterato
Lettura	9/16	8,82			≤13,489	Alterato
FUNZIONI ATTENTIVE ED ESECUTIVE						
Matrici Attentive (Spinnler e Tognoni, 1987)	30/60	26		0		Alterato
Trail Making Test (ENB-2 Mondini et al., 2011)						
TMT-A	42,73", 0 err		-0,042			Nella norma
TMT-B	494", >3 err		13,98			Alterato
FAB (Apollonio, 2005)	9/18	8,30		0		Alterato
Fluenza verbale (Costa et al., 2014) fonemica	10	7,16		0		Alterato
MCST (Caffarra 2004)	1				3	Alterato
N. categorie raggiunte						
Errori perseverativi	13	13			0	Alterato
MEMORIA						
Digit span (Monaco et al., 2013)						
avanti	3/9	2,83		0		Alterato
indietro	4/8	3,79		2		Nella norma (i)
Memoria di Prosa (ENB-2 Mondini et al., 2011)						
immediata	2/28		-2,93			Alterato
differita	4/28		-2,92			Alterato
Richiamo Figura Complessa di Rey (Caffarra et al., 2002)	3,5/36	4,75		0		Alterato
FUNZIONI VISUO-SPAZIALI/PERCETTIVE E VISUO-COSTRUTTIVE						
Test dell'orologio (ENB-2 Mondini et al., 2011)	4/10		-4,95			Alterato
Figura Complessa di Rey (Caffarra et al., 2002)	19,5/36	19,25		0		Alterato
Copia di disegno (ENB2, Mondini et al., 2011)	2/2		0,39			Nella norma
SOCIAL COGNITION						
Face Test (Terruzzi 2023)						
Versione A - Lunga equivalente	10/36	9,96	22,69	0		Alterato

Fig. 1. The MoCA and second-level neurocognitive assessments reveal a globally impaired cognitive profile, characterized by multiple-domain deficits primarily affecting language abilities, with impairments in both production and comprehension of syntactically complex sentences. Additional frontal deficits are present, involving executive functions—particularly cognitive flexibility—and social cognition (theory of mind). Memory and visuospatial abilities are also impaired.

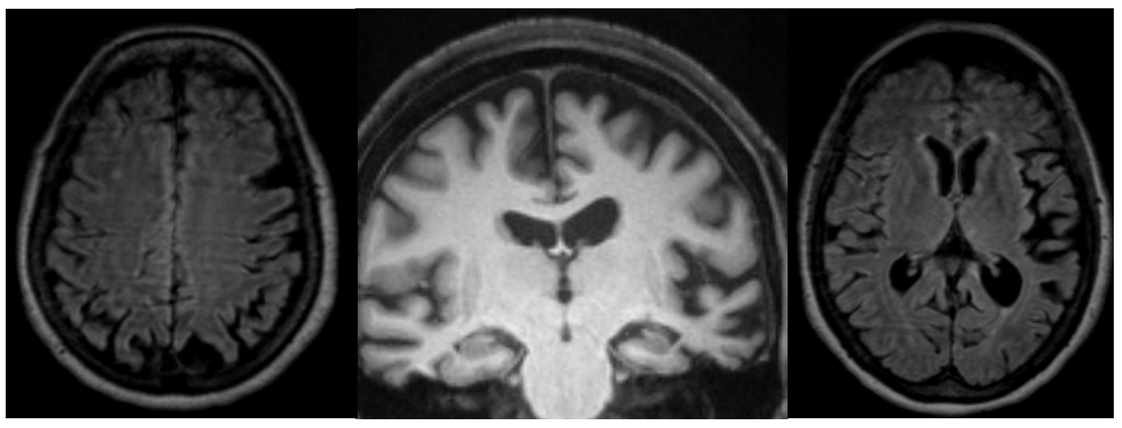


Fig. 2. MRI showing severe left frontotemporal atrophy with relative preservation of the hippocampus.

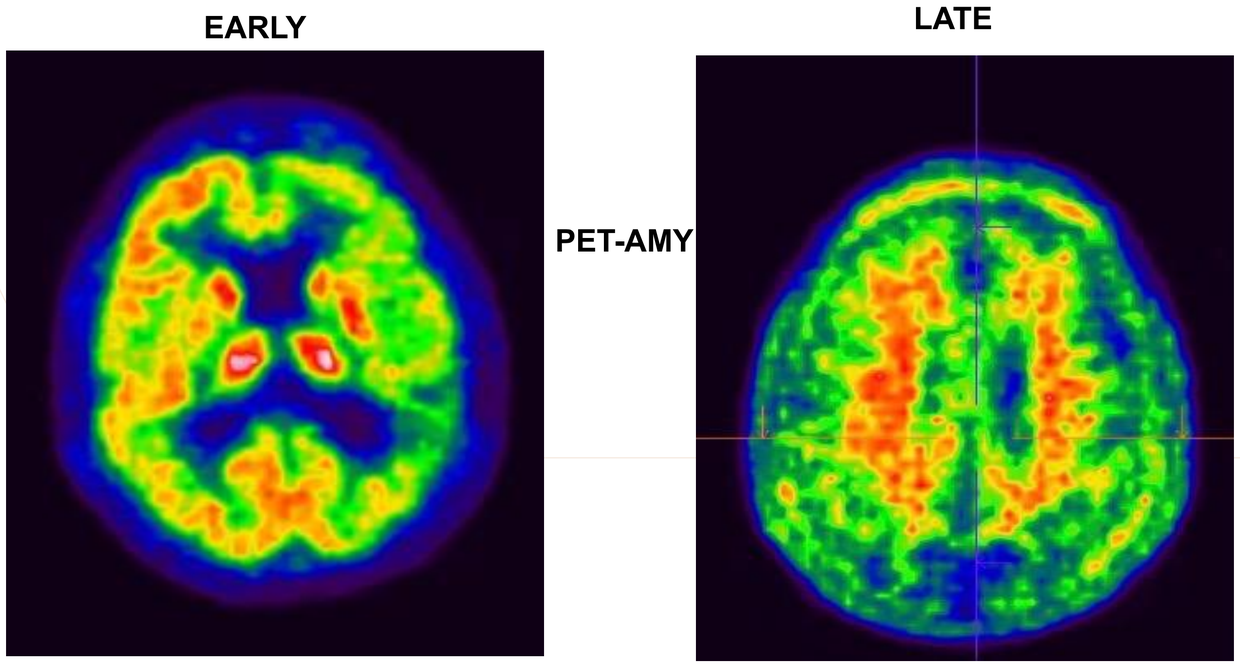


Fig.4. Amyloid-PET: early-phase image (left) show marked hypoperfusion of the left parietotemporal cortex and the left ventral frontal cortex. Late-phase image (right) do not reveal significant cortical tracer accumulation for β-amyloid.

DIAGNOSTICA DELLA MALATTIA DI ALZHEIMER

CSF-TAU TOTALE	***747***	ng/L	
	Liv. decisionale:		> 404
CSF-TAU FOSFORILATA (181)	***95***	ng/L	
	Liv. decisionale:		> 56,5
CSF-B-AMILOIDE (1-42)	***223***	ng/L	
	Liv. decisionale:		< 599
Rapporto (1-42)/Tau Fosforilata	***2,347***		
	Liv. decisionale:		<8,1
CSF-B-AMILOIDE (1-40)	***5 076***	ng/L	
Rapporto B-Amiloide (1-42)/(1-40)	***0,044***		
	Liv. decisionale:		< 0,069

Fig.3. CSF profile: A+/T+/N+

Discussion and conclusions

Although the speech profile more consistent with the logopenic variant of PPA frontal symptoms raise suspicion for Frontotemporal Degeneration (FTD). On the other hand, while fluid biomarkers (elevated pTau, abnormal CSF amyloid ratios) support an Alzheimer's disease diagnosis, a negative Amyloid-PET may be indicative an early stage of amyloid related pathology, nor responsible for the clinical symptoms. Further in depth biological study of amyloid fragments and their characteristics of solubility may explain the discordant CSF/AMY-PET pattern.

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