CHALLENGING THE BOUNDARIES: C9ORF72 MUTATION PRESENTING AS ALZHEIMER'S DISEASE

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BACKGROUND

Frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) represent a spectrum of neurodegenerative disorders sharing clinical, genetic, and pathological features. The *C9orf72* hexanucleotide repeat expansion is a major genetic factor, with carriers potentially exhibiting a pure ALS phenotype, a pure FTD phenotype, or a combination of both (1). However, in a few cases, the *C9orf72* expansion has also been linked to Alzheimer's disease (AD), particularly in early-onset forms (EOAD) (2, 3). We present a case of EOAD associated with a *C9orf72* expansion.

CASE PRESENTATION

- **53 y.o.** Caucasian **M** with pervasive mood disorder and anxiety impacting autonomy (job demotion) and memory and language disturbances. **FHx** notable for maternal ALS. Neurological examination showed mild anomia.
- **NPS testing:** MCI with deficits in memory, language, and executive function. MoCA: 19/30; BNT: 31/60; CDT: 4/10). Progression at 6 mo.
- **Brain MRI:** mild bilateral F-T-P atrophy.
- **CSF:** amyloidopathy (A+T−N+), with reduced Aβ42/Aβ40 ratio.
- **FDG-PET** and **AmyPET**: bilateral T-P and precuneus hypometabolism (AD-like). Amy-PET with marked brain amyloid deposition.
- **Genetics:** pathogenic C9orf72 expansion (>80 repeats) via NGS.
- **Six-month follow-up:** neuropsychological decline progression in memory, language and executive functions.

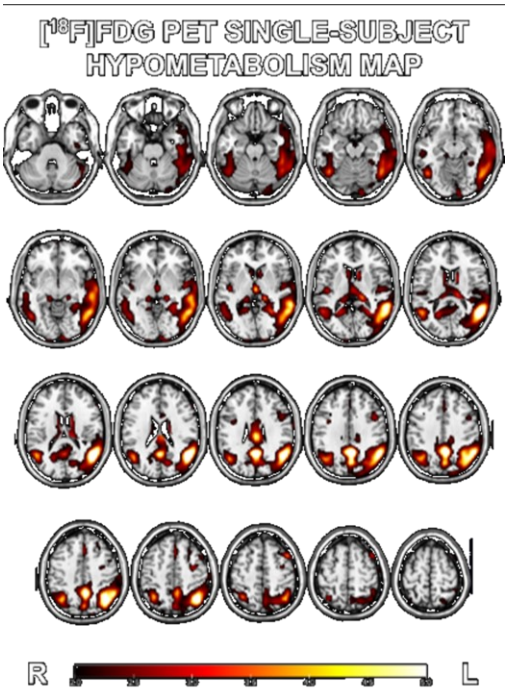
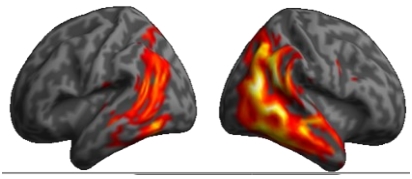


Fig. 1-2: Single-subject Statistical Parametric Mapping brain hypometabolism map



DISCUSSION

NPS testing, clinical presentation and biomarkers profile support EOAD diagnosis. However, T- and *C9orf72* expansion complicate the diagnostic interpretation. Only a few cases with a biomarker-based diagnosis of AD and a *C9orf72* expansion has been reported (2, 3). This rare case highlights the phenotypic heterogeneity of *C9orf72*-related disorders and suggests a potential contributory role of amyloid pathology in their clinical expression.

REFERENCES

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