Alzheimer's Disease with incidental *MAPT* mutation: hidden phenotype or co-pathology?

Giorgia Brodini[1], Fausto Roveta[1], Silvia Boschi[1], Aurora Cermelli[1], Salvatore Gallone[2,3], Giulio Mengozzi[3], Michela Zotta[4], Guido Rovera[4], Silvia Morbelli[4], Innocenzo Rainero[1], Elisa Rubino[1,2]

1. Department of Neuroscience "Rita Levi-Montalcini", University of Torino, Torino, Italy.
2. Centre for Cognitive Disorders and Dementias, Department of Neuroscience and Mental Health, AOU Città della Salute e della Scienza di Torino, Turin, Italy.
3. Department of Laboratory Medicine, Clinical Biochemistry laboratory "Baldi e Riberi", A.O.U. Città della Salute e della Scienza di Torino, Torino, Italy.
4. Nuclear Medicine Unit, AOU Città della Salute e della Scienza di Torino, Turin, Italy.

Patient ID

♂ 63 years old.
Education = 8 years.

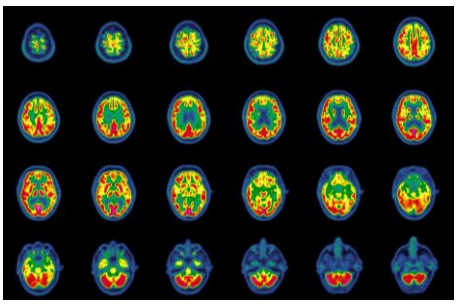
Clinical history
- Benign Prostatic Hyperplasia;
- Dyslipidemia.

Family history:
Mother with dementia (late onset).

Imaging

Brain Magnetic Resonance Imaging
Non-specific gliosis, no recent ischemic lesions, cortical convexity atrophy.

Brain 18-FDG-PET
No definite pattern of glucose hypometabolism. Minimal cortical convexity asymmetry (left predominant hypometabolism), currently of uncertain clinical significance.

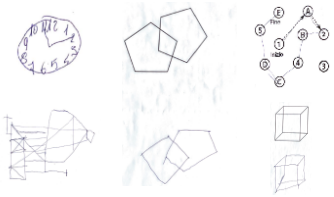


Clinical Presentation

Patient's Perspective
- Progressive working memory impairment;
- Mild mood deflection, likely reactive to a recent family loss.

Neurological examination
Unremarkable.

Neuropsychology evaluation
- Mini-Mental State Examination: **23** p.c. (n.v. ≥ 23.8)
- Clock Drawing Test: 12 p.c. (n.v. ≥ 7.57);
- Frontal Assessment Battery: **9.74** p.c. (n.v. ≥ 12.02);
- Montreal Cognitive Assessment: **17.18** p.c. (n.v. ≥ 18.58).
- Conclusions: Mild Cognitive Impairment predominantly affecting **memory functions** with additional **executive** and **praxic-constructive** deficits. Mild concomitant mood deflection. **CDR = 0.5**



CSF Biomarkers

- Aβ40: **350** pg/ml (n.v. > 500)
- Aβ42/40: **0.036** (n.v. 0.068-0.115);
- Total tau: **569** pg/ml (n.v. < 450);
- P-tau181: **88.5** pg/ml (n.v. < 61).

→ Diagnosis: Mild Cognitive Impairment due to Alzheimer's Disease (A+ T+ N+) ←

Given the presenile onset, genetic testing was performed

APOE genotype: ε4/ε4

Next Generation Sequencing dementia panel: **MAPT** p.(Val968Ile)

- **Frequency**: 0.0028% in the gnomAD v2.1 database;
- **Biological effect**: mutation affecting an evolutionarily conserved residue;
- **Inheritance**: autosomal dominant with incomplete penetrance;
- **ACGM classification**: likely pathogenetic variant, considered a probable cause of the patient's phenotype.

Discussion

MAPT gene mutations are mostly associated with Frontotemporal Lobar Degeneration (FTLD) spectrum, although considerable phenotypic variability has been described [1]. Our patient's mutation has been reported only few times in literature, but – to our knowledge – always with an FTLD phenotype [1]. In contrast, other *MAPT* variants (e.g. R406W) have been described to produce an Alzheimer's Disease (AD) – like clinical syndrome, sometimes even with amyloid pathology [2]. Our patient is homozygous for APOE ε4 and shows an AD-type CSF profile, findings that mirror the AD-like biomarker pattern described in some *MAPT* cases [2]. The presence of APOE ε4 has been associated with earlier onset and a modified clinical course in tauopathies independent of amyloid-β co-pathology, suggesting APOE may accelerate tau-mediated neurodegeneration [3].

Conclusions

Our patient likely represents a case of AD with the incidental presence of a *MAPT* variant, but a co-occurring AD and FTLD pathologies cannot be excluded. Implications for patient's offspring need to be carefully considered.

References:

[1] van Swieten JC, Stevens M, Rosso SM, Rizzu P, Joosse M, de Koning I, Kamphorst W, Ravid R, Spillantini MG, Niermeijer, Heutink P. Phenotypic variation in hereditary frontotemporal dementia with tau mutations. Ann Neurol.

[2] Ishida C, Kobayashi K, Kitamura T, Ujike H, Iwasa K, Yamada M. Frontotemporal dementia with parkinsonism linked to chromosome 17 with the MAPT R406W mutation presenting with a broad distribution of abundant senile plaques. Neuropathology.

[3] Koriath C, Lashley T, Taylor W, Druyeh R, Dimitriadis A, Denning N, Williams J, Warren JD, Fox NC, Schott JM, Rowe JB, Collinge J, Rohrer JD, Mead S. ApoE4 lowers age at onset in patients with frontotemporal dementia and tauopathy independent of amyloid-β copathology. Alzheimers Dement (Amst).