Amyloid-PET: a possible biomarker in the PSEN1 Glu318Gly enigma

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Background and Objectives

Alzheimer's Disease (AD) is the most common dementia in the elderly. About 5% of cases are caused by autosomal dominant *APP*, *PSEN1* or *PSEN2* mutations, and may display clear familial aggregation and presenile onset. Here we describe the clinical and amyloid-PET aspects of a case of presenile AD associated with Glu318Gly *PSEN1* missense mutation, whose pathogenic role still remains uncertain.

Methods

Our patient underwent a complete diagnostic protocol including neurological and neuropsychological evaluation, extensive laboratory assays, EEG, structural (MRI) and functional (^{18}FDG-PET) neuroimaging. Genetic testing for *ApoE* polymorphism, *APP*, *PSEN1* and *PSEN2* mutations was performed. After the previous results were obtained ^{18}F-florbetapir amyloid PET was practiced.

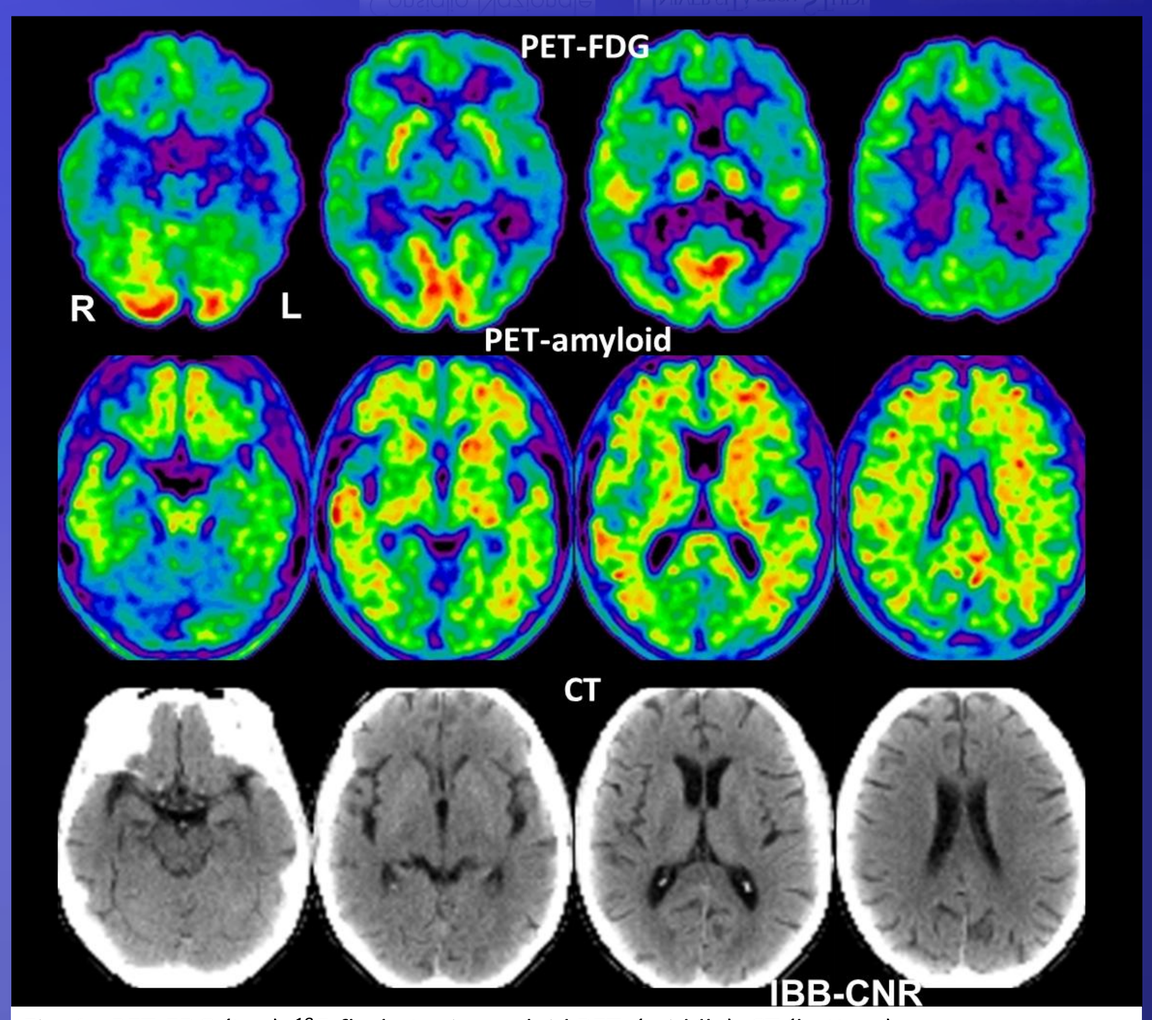

Fig. 1 - PET-FDG (top), ^{18}F-florbetapir amyloid PET (middle), CT (bottom)

Results

Our patient was a 57-year-old woman with a two-year history of short-term memory deficit, apathy and lack of initiative with insidious onset. Albeit unaware of her difficulties, she could not work as a physician as before. Her familial history was negative. Epstein sign was present. Neuropsychological assessment revealed deficits in long- and short-term memory, language, abstract reasoning, executive functions, and marked anosognosia. Only moderate folic acid and B12 vitamin deficiencies were found. Brain MRI showed diffuse cortical atrophy. FDG-PET scan revealed significant hypometabolism in bilateral superior parietal, temporo-parietal, posterior cingulate and frontal dorso-lateral cortex with slight left prevalence. Glu318Gly *PSEN1* exon 9 mutation was found. Amyloid PET imaging showed increased cortical uptake of the radiotracer more marked in the lateral temporal regions.

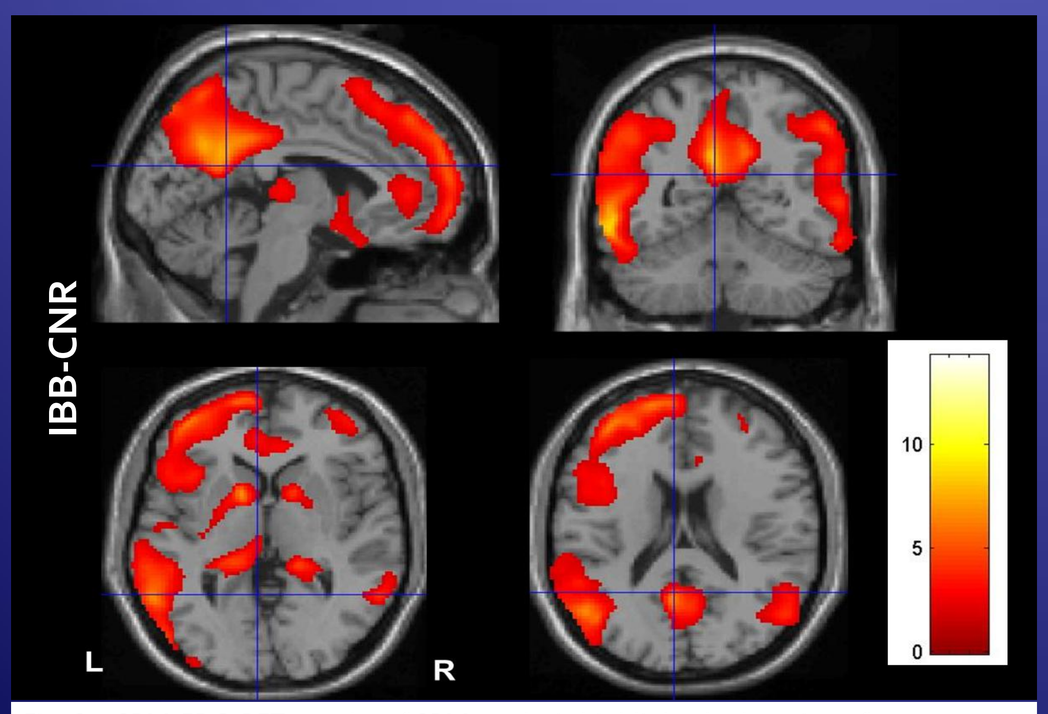

Fig. 2 – SPM-FDG-PET: results of SPM analysis highlight the location of hypometabolic deficit in our patient as compared to controls and clearly show reduced relative glucose metabolism in the posterior cingulate bilaterally (p 0.02 uncorrected; patients vs 14 healthy controls, age range of controls 27–70, age was considered in the statistical model of SPM as nuisance covariate)

Discussion and conclusions

Despite the uncertain pathogenicity of the Glu318Gly *PSEN1* mutation reported in the literature, the clinical history of our patient is highly suggestive of a genetically inherited form of AD, mainly due to presenile onset. In support of this, amyloid PET scan confirms the presence of remarkable amyloid pathology in some of the areas typically involved in Alzheimer's disease.

Therefore we believe that amyloid PET could prove to be a very useful pathophysiological biomarker especially in cases possibly associated to "uncertain" mutations. However the ultimate evidence of a true pathogenic role for this and other enigmatic mutations derives only from further *in vitro* studies.

References

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