**Title: PSEN2 mutations may mimic frontotemporal dementia: two new case reports and a systematic review.**

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**DECLARATIONS:**

**Statement 1:**

All coauthors listed in the “Title page – authors” have seen and agree with the contents of this manuscript and all the following data.

**Statement 2:**

This whole submission is not under review at any other publication.

**Limitations and strengths of the study:**

This study has the limitations of an observational, descriptive, single-center study, as well as the biases of a systematic review (for example, the possible variability in the collection of certain data, extracted from documents produced by more than one professional). The solid clinical characterization and the complete diagnostic study of the patients presented are its most important strengths.

**Compliance with Ethical Standars:**

**Informed consent:**

Although this is a case report, properly anonymized, it should be mentioned that both patients and their relatives and/or legal guardians have given written consent for this publication.

**Research involving human participants and/or animals:**

Although this work was designed in a retrospective and non-intervencionist way, this study was approved by the research ethics committee of our Hospital and we certify that the study was performed in accordance with the ethical standards.

**Potential conflicts of interest:**

The authors declare that they have any conflicts of interest.

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**Author’s contributions:**

AMMP performed the systematic review. AMMP and JMPP got in contact with patients and families and also were the main contributors in writing the manuscript. JMAV and MAG supervised the process and helped with the conceptualization of this paper. AO, MAN and TSM helped with the data management, basic investigation assessment and experimental blood biomarkers in AD. BQ was in charge of genetic testing and results analysis, additionally as the assessment in this field. JCH was, on the other hand, responsible for all the PET images and nuclear medicine complementary tests. JMPP and TSM have contributed equally as senior and corresponding authors, as well as AMMP as corresponding author. ISM performed the neuropsychological assessments and assisted in the formal drafting of this manuscript.

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**ABSTRACT:**

**Background:** Monogenic Alzheimer's disease (AD) has severe health and socioeconomic repercussions. Its rarest cause are *presenilin 2* (*PSEN2*) gene mutations. We present two new cases with presumed *PSEN2*-AD, with unusual clinical and neuroimaging findings in order to provide more information on the pathophysiology and semiology of these patients.

**Methods**: Women aged 69 and 62 years at clinical onset, marked by prominent behavioral and language dysfunction, progressing to severe dementia within three years. Neuroimaging, laboratory study, genetic testing. In addition, a systematic review of the *PSEN2*-AD were performed.

**Results**: Neuroimaging revealed pronouncedfrontal white matter hyperintensities (WMH) and frontotemporal atrophy/hypometabolism. The genetic study unveiled PSEN2 variants: c.772G>A (p.Ala258Thr) and c.1073-2\_1073-1del.Both cerebrospinal fluid (CSF) and experimental blood biomarkers shouldered AD etiology.

**Conclusions**: Prominent behavioral and language dysfunction suggesting frontotemporal dementia (FTD) may be underestimated in the literature as a clinical picture in PSEN2 mutations. Thus, it may be reasonable to include PSEN2 in genetic panels when suspecting FTDL.

PSEN2 mutations may cause striking WMH, arguably related with myelin disruption induced by amyloid accumulation.

1080 total articles after database searching

802 items

87 items

67 studies selected for in-depth review and analysis.

216 studies excluded:

- Full text not available.

- Animal studies.

- Written in a language other than: English, Spanish, French or Portuguese.

715 articles excluded due to low statistical quality, accepting only:

- Meta-analysis.

- Systematic reviews.

- Multicenter studies.

- Clinical trials.

20 duplicated articles

**Figure 5.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Cut-off points | None proposed | None proposed | < 0.083 | > 2 pg/mL |
| ID | Aβ 1-42 | Aβ 1-40 | β-amyloid ratio (1-42/1-40) | pTau |
| Case A | 18.31 | 318.71 | 0.057 | 2.39 |
| Case B | 2.96 | 265.42 | 0.011 | 2.91 |

**Table 1.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Cut-off points | <638 pg/mL | None proposed | < 0.069 | >56.5 pg/mL | >404 pg/mL |
| ID | Aβ 1-42 | Aβ 1-40 | β-amyloid ratio (1-42/1-40) | pTau | t-tau |
| Case A | 988 | 10693 | 0.092 | 122.5 |  |

**Table 2.**







