A Patient with Posterior Cortical Atrophy Possesses a Novel Mutation in the Presenilin 1 Gene

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Abstract

Posterior cortical atrophy is a dementia syndrome with symptoms of cortical visual dysfunction, associated with amyloid plaques and neurofibrillary tangles predominantly affecting visual association cortex. Most patients diagnosed with posterior cortical atrophy will finally develop a typical Alzheimer’s disease. However, there are a variety of neuropathological processes, which could lead towards a clinical presentation of posterior cortical atrophy. Mutations in the presenilin 1 gene, affecting the function of γ-secretase, are the most common genetic cause of familial, early-onset Alzheimer’s disease. Here we present a patient with a clinical diagnosis of posterior cortical atrophy who harbors a novel Presenilin 1 mutation (I211M). In silico analysis predicts that the mutation could influence the interaction between presenilin 1 and presenilin1 enhancer-2 protein, a protein partner within the γ-secretase complex. These findings along with published literature support the inclusion of posterior cortical atrophy on the Alzheimer’s disease spectrum.

Introduction

Posterior cortical atrophy (PCA) is a progressive neurodegenerative disorder of higher visual processing, both in terms of object and space perception [1,2]. At autopsy, a majority of the PCA patients are diagnosed with Alzheimer’s disease (AD) due to similar pathology including neuronal loss and accumulation of amyloid plaques, but with the special distribution to visual cortex [3]. The most PCA cases have intact episodic memory and insight early in the course of the disease, which enables differential diagnosis with typical (amnestic) AD [4,5].

For many years PCA has been regarded as an atypical visual variant of AD [6] or a distinct nosological entity such as non-AD pathologies including Lewy body disease, corticobasal degeneration and prion disease [7,8,9,10]. Recent epidemiological studies indicate that less than 5% of patients with AD are also affected with PCA [11].

PCA usually display the same cerebrospinal fluid (CSF) biomarker signature as AD, including elevated levels of total tau (t-tau) and phosphorylated tau (p-tau) and decreased levels of amyloid-β (Aβ) consisting of 42 amino acids (Aβ42). However, some studies have shown that a significant proportion of PCA and primary progressive non-fluent or logopenic aphasia patients may have atypical t-tau/Aβ42 and p-tau/Aβ42 profiles [12,13,14].

The genetic basis of PCA remains elusive [1,15], usually not showing autosomal dominant inheritance patterns and generally there is no family history of dementia [16]. This is in contrast to early-onset autosomal dominant AD, where mutations in the presenilin 1 gene (PSEN1) are the most common cause of familial AD (FAD). Patients bearing specific mutations may present different clinical phenotypes. Some patients with mutations in presenilin 1 or presenilin 2 (PSEN2) genes are clinically diagnosed with frontotemporal dementia or other neurodegenerative conditions [17,18]. Recently Crutch and colleagues reported on a PCA phenotype, which is associated with autosomal dominant FAD [1]. More recently it was shown that a mutation in prion protein gene (PRNP), or PSEN1 gene (Q223R) were associated with PCA phenotype [19,20].
Here we present a patient with clinically diagnosed PCA harboring a I211M mutation in PSEN1. *In silico* analysis, indicates that the I211M mutation could change the interaction between presenilin 1 (PS1) and the PS1 enhancer-2 protein (PEN-2), its partner within the γ-secretase complex.

**Materials and Methods**

**Case report**

A 67 year-old right-handed woman with university education reported a three-year history of progressive visual problems. Medical history included myopia, arterial hypertension, radioactive treatment for nontoxic multinodular goiter and diabetes type 2 (diagnosed at the age of 64). Her family history suggested several problems including managing objects in the near, as well as distant space. Because of visual problems, she turned to listening to the radio instead of watching TV. In the kitchen she recognized objects with touch due to the partially preserved spatial memory. She also experienced severe difficulties when eating and mild difficulties in dressing. She was unable to recognize faces, but compensated for this difficulty by correct voice recognition. In new surroundings, she had difficulties to orientate. Before hospitalization at the Neurology Department she continued to live on her own and was independent in the daily activities, except those in which accurate vision was indispensable and compensatory strategies were ineffective.

Neurological and neuropsychological examination revealed no abnormalities apart from visual agnosia, optic ataxia, simultanagnosia, prosopagnosia, unilateral neglect and alexia. A screening neuropsychological examination, as well as an interview with the proband's family (respectively; Mini Mental State Examination, MMSE 21/30, and Blessed Dementia Rating Scale, BDRS 4.5) indicated mild dementia. Neuropsychological assessment confirmed both the core and supporting symptoms of PCA. Visual deficits involved both object and space perception. The clock face filling test revealed severe optic ataxia, the Rey Complex Figure Test score was <10 percentile. The visuospatial dysfunction predominated in the clinical picture (Figure 1), while episodic memory, executive and language functions were mostly preserved.

A comparison of copy/drawing to command provided clinically important information on the relatively well-preserved semantic knowledge (in comparison to semantic dementia), degree of optic ataxia, simultanagnosia and unilateral neglect. The patient had a preserved insight into her visual deficits which resulted in searching for compensatory strategies, and exhibited anxiety associated with the progressive nature of the disorder, albeit no depression (Montgomery Asberg Depression Rating Scale, MADRS 5).

A second neuropsychological evaluation six months later showed worsening of the visuospatial function and praxis and mild deficits of verbal memory and speech comprehension. The profile was still consistent with PCA and showed the predominant progression of visual deficits also in line with PCA diagnosis.

The third neuropsychological evaluation 2 years after the first assessment showed the global deterioration of cognitive status (MMSE 15, BDRS 9.5), and increasing of the visual deficits, both of visual agnosia and visuospatial dysfunction. The marked deterioration of visual function was accompanied by less severe, albeit significant, episodic memory decline and language impairment suggestive of transcortical sensory aphasia. Executive function was only mildly impaired. The patient’s anxiety and depressive symptoms increased over time (MADRS 16). The patient’s disability was still mostly due to visual dysfunction.

**Figure 1. Analysis of visuospatial dysfunction of the patient.**

Patient’s drawings in the context of drawings by a patient with semantic dementia. (SD) scoring 19 in MMSE were presented. A) flowers drawn by the patients from memory: A1) PCA patient, A2) SD patient; B) model, C) patients’ copy: C1) PCA patient, C2) SD patient. Copying pictures and drawing to command indicated severe optic ataxia and partial simultanagnosia. The test was performed at first neuropsychological assessment. During the second assessment (six months later) the patient was unable to draw even simple patterns and presented with complete simultanognosia.

doi:10.1371/journal.pone.0061074.g001

Magnetic resonance imaging (MRI) at the age of 67 revealed marked cortical and subcortical atrophy within both occipital and parietal lobes bilaterally. The atrophy was greater in the former. The right parietal lobe was more atrophic than the left one, with no asymmetry in the occipital lobes. The atrophy was less pronounced in the frontal and temporal lobes, and the hippocampal structures of the temporal lobes were mostly preserved. Single Photon Emission Computed Tomography (SPECT) demonstrated severe hypoperfusion within the parietal, occipital and temporal lobes bilaterally (Figure 2; compare with Figure 3 showing MRI/SPECT brain images from a control subject). Visual evoked potentials test showed reduced amplitude of P100 with prolonged latency (138 ms) on the left and normal amplitude with prolonged latency on the right (123 ms). The confrontation visual field examination revealed severe peripheral deficits bilaterally with central field vision preservation. Visual...
Acuity tests using a Snellen chart showed myopia (Vod and Vos = 0.3). Intraocular pressure and dilated fundus examination were normal.

The family history of the patient revealed no records of dementia, however, her father died at the age of 51, due to stroke, however no post-mortem examination was performed. The proband’s mother died at 80 due to leukemia, with no neurological problems recorded. An older brother of the patient died at the age of 78 due to a prostate cancer. An 82-year-old sister of the proband is neurologically healthy, and is not a carrier of the I211M mutation. Two children of the proband, aged 33 and 37 are healthy.

A written, signed consent was obtained from the proband and the family members. The genetic study was approved by the Ethics Committee of the CSK-MSWiA Hospital (Warszawa, Poland) in compliance with the national legislation and the Code of Ethical Principles for Medical Research Involving Human Subjects of the World Medical Association.

**Methods**

DNA was isolated from peripheral blood leucocytes of the proband and the family members using standard procedures. Intronic primers were used to amplify and sequence exons 3–12 of PSEN1, exons 16 and 17 of APP, exons 1–12 of PSEN2, and PRNP generally as described previously [17,21]. The absence of the mutation was confirmed in a group of 210 healthy subjects aged >65 (using RFLP method), and 170 early-onset AD patients (using fluorescent sequencing) from the Polish population. A written informed consent was obtained from all individuals.

![Figure 2. Results of MRI and SPECT examinations of the proband.](https://www.plosone.org/)

Magnetic Resonance Imaging revealed marked cortical and subcortical atrophy within both occipital and parietal lobes bilaterally. The atrophy was less pronounced in the frontal and temporal lobes, and the hippocampal structures of the temporal lobes were mostly preserved. Single Photon Emission Computed Tomography demonstrated severe hypoperfusion within the parietal, occipital and temporal lobes bilaterally.

**Figure 3. Results of MRI and SPECT examination of a control subject.** Magnetic Resonance Imaging and Single Photon Emission Computed Tomography demonstrating the normal scans of a control, age-matched patient with no signs of any neurodegenerative disorder.

**Figure 2. Results of MRI and SPECT examinations of the proband.** Magnetic Resonance Imaging revealed marked cortical and subcortical atrophy within both occipital and parietal lobes bilaterally. The atrophy was less pronounced in the frontal and temporal lobes, and the hippocampal structures of the temporal lobes were mostly preserved. Single Photon Emission Computed Tomography demonstrated severe hypoperfusion within the parietal, occipital and temporal lobes bilaterally.

doi:10.1371/journal.pone.0061074.g002

doi:10.1371/journal.pone.0061074.g003
The putative impact of the mutation on the transmembrane domains of PS1 was assessed using bioinformatic and in silico modeling approaches.

To elucidate an interface between human PS1 and PEN-2, residues 186–250 of PS1 (TM4–TM5) and 15–41 (TM1) of PEN-2 which are assumed to contain the transmembrane regions were investigated. The transmembrane part of PEN-2 was constructed as α-helix while the PS1 TM4–TM5 segment, including a loop, was modeled using membrane ab initio application from Rosetta package (v3.4) [22]. The resulting helices were antiparallel and not crossed. Since the experimental data show that the WNF motif in PS1 TM4 is crucial for binding [23,24] we used this side of TM4 as a part of a binding site with Pen-2. Residue N33, which was shown to be a part of ER retention signal, is also involved in the binding process on PEN-2 side [25,26]. The initial structures of the complex were pre-processed using a docking prepack protocol and subjected to a local docking procedure [27]. The best scored 200 of 500000 structures were clustered and filtered for correct orientation of both PS1 and PS2 fragments and for mutual positions of N204 and N33 residues. Selected structures of the complex characterized with the highest number of interactions in the interface were chosen for short 5 ns molecular dynamics refinement in POPC ([1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine] membrane. All simulations were conducted in Yasara program employing Amber03 force field [28,29].

The CSF levels of amyloid peptides (Aβ42 and Aβ40) were determined using the Aβ Triplex assay (Human Aβ peptide UltraSensitive Kits) provided and developed by Meso Scale Discovery (MSD, Gaithersburg, Maryland, USA) as described elsewhere [30]. Briefly, this assay uses C-terminus-specific antibodies to capture the different Aβ peptides and a SULFO-TAG-labeled anti-Aβ antibody (4G8) for detection with electrochemiluminescence. The CSF levels of total tau (t-tau), and tau phosphorylated at threonine 181 (p-tau) were determined using xMAP technology, as previously described [31]. For MesoScale (Karolinska Institute & University of Gothenburg, Sweden) measurements the cut-off ranges for healthy controls were Aβ12 > 400–1200 pg/ml and Aβ42 > 7000–15000 pg/ml. For xMAP measurements the cut-off values for p-tau was >30 pg/ml, and for t-tau >400 pg/ml.

Results

A patient with clinically diagnosed PCA, harboring a novel ATT>ATG mutation at codon 211 (I211M, g.44652T>G) of PSEN1 was identified. No other mutations were found in the PSEN1, PSEN2, APP or PRNP genes, except for already described polymorphisms. The proband is a carrier of the E3/E3 APOE background seems to predispose patients to early-onset AD

![Figure 4. In silico modeling of presenilin 1 and PEN-2 protein interaction.](image)

The proband presents Aβ signature atypical for AD: Aβ42 (787 pg/ml) and Aβ40 (14599 pg/ml) levels are in the range of healthy controls. In contrast, the elevated p-tau (97 pg/ml), and slightly elevated t-tau (418 pg/ml) levels are consistent with an AD signature.

Discussion

PCA is a descriptive term due to a lack of consistency between studies regarding the classification of PCA at the disease and syndrome level [1]. Recent recommendations from the National Institute of Aging and the Alzheimer’s Association (NIA-AA) workgroup include different non-amnestic symptoms such as visuospatial presentation as a possible core clinical criterion of atypical AD [10]. Atypical presentations and specific patterns of atrophy are frequently associated with early onset. However, little is known about risk factors. Genetic and/or environmental background seems to predispose patients to early-onset AD
interface with PEN-2, were also found to be in contact with PEN-2
PEN-2 binding, precedes the I211 position only by two helix turns.

The NF motif within this domain, which is critical for
and two other membrane components: nicastrin and anterior
obtained results strongly suggest that the mutated residue 211, as
in silico analysis of the I211M mutation suggests that the

To make our claim on the true disease-causing nature of the
is highly conserved in evolution and functional.
ConSurf programs (http://consurf.tau.ac.il/) suggest that I211
toleration in position 211. However, analyses using ConSeq and
properties of amino acids, suggests that methionine could be

Also an in silico analysis of the I211M mutation suggests that
changes the hydrophobic isoleucine into the nonpolar methionine and thus potentially could
be tolerated without changing the global transmembrane domain
Analysis of the protein variant sequence using Sorting
into the nonpolar methionine and thus potentially could

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corresponded with more severe atrophy and hypoperfusion in the
in silico analysis of the I211M mutation suggests that the

To test this hypothesis we quantified the core CSF biomarkers for
the 82-year-old proband’s sister, presenting no neurological
in public DNA sequence variation databases, including Archive

In summary, we report a novel PSEN1 I211M mutation, which
could be causally connected with the PCA phenotype. It could

Author Contributions
Conceived and designed the experiments: JS CZ. Performed the

Novel PSEN1 Mutation in a PCA Patient

(EOAD) [32]. Some authors have suggested that it could be due to
different age-related vulnerability to amyloid toxicity [33,34].
In the PCA patient presented here the structural and functional
neuroimaging data correlated with the observed clinical features,
reflecting dysfunction of both dorsal and ventral visual streams,
which is quite common in PCA [35]. However, the predominance of
ventral stream dysfunction was evidenced by prominent visual
object agnosia, alexia and less pronounced spatial disorientation. It
Corrugated from PEN-2 and possibly can result in a similar clinical phenotype of
AD, as it was recently shown in case of Q223R [20]. However, it
should be noted that the Q223R mutation was identified for the
first time in an EOAD patient with spastic paraplegia [30].

It was recently proposed that over-expression of PEN-2 or PS1
mutation in vivo altered the equilibrium between PS1- and PS2-γ-
secretases, resulting in a profound effect on the enzyme activity and
the Aβ42:Aβ40 ratio [39]. It could be speculated that I211M-
mutated PS1, due to the conformational changes in PS1, has
a reduced ability to compete with native PS1 and PS2 for PEN-2,
therefore favoring the PS2 γ-secretase complex formation. This
could result in a reduction of the overall γ-secretase activity and
an increase of the Aβ42:Aβ40 ratio [36]. It could be further speculated that
the neurons, selectively damaged in PCA, could be those
particularly vulnerable to the disruption of the equilibrium between
PS1- and PS2-containing γ-secretases [40].

To test this hypothesis we quantified the core CSF biomarkers for
AD. The proband presents a biomarker signature atypical for
AD, albeit, with elevated p-tau (97 pg/ml) and slightly elevated
t-tau (418 pg/ml) levels, which is consistent with an AD signature.
For instance the Q223R mutation identified in a patient diagnosed
with AD with spastic paraparesis displayed a biomarker profile
which was different from the profile of our patient i.e. low Aβ42
and normal t-tau [30]. Furthermore, a patient with the same
mutation and PCA-like phenotype had decreased Aβ42 levels
together with increased t-tau and p-tau [20]. Also in a recently
published study of 22 patients with clinical diagnosis of PCA, in
four cases Aβ42 and t-tau, p-tau levels were not typical for AD
[41]. Therefore, the atypical CSF biomarkers presentation should
not exclude the possibility of causative link between PCA and AD.

Moreover, the profile of cognitive deterioration of the proband
supports the assumption that PCA phenotype should be
interpreted within AD spectrum. Despite the predominance of
visual dysfunction throughout the 2-year observation period, in the
follow-up testing episodic memory decline, was evident.

The putative influence of I211M mutation on PS1:PEN-2
interaction and on γ-secretase activity as a result, is supported by
the recent findings that Pen-2 could directly modulate the pore-
like structure around the catalytic center formed by PS1
transmembrane domains [42].

In summary, we report a novel PSEN1 I211M mutation, which
could be causally connected with the PCA phenotype. It could

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Conceived and designed the experiments: JS CZ. Performed the
experiments: EJS EN AB MS KM MJ DR EP BB KM. Analyzed
the data: SF CZ MB JS EP BP AB ES EN MB. Wrote the paper: SF ES JS
CZ BP.
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Novel PSEN1 Mutation in a PCA Patient