

Short Communication

The Presenilin 1 P264L Mutation Presenting as non-Fluent/Agrammatic Primary Progressive Aphasia

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Abstract. Primary progressive aphasia (PPA) represents a diverse group of language-led dementias most often due to frontotemporal lobar degeneration. We report clinical, neuropsychological, and neuroimaging data in the case of a 47-year-old woman presenting with non-fluent PPA due to a genetically confirmed pathogenic presenilin 1 P264L mutation. This case highlights an unusual clinical presentation of familial Alzheimer's disease and a novel presentation of the P264L mutation. The case adds to accumulating evidence that particular mutations can promote specific brain network degeneration, with wider implications for understanding the sporadic forms of Alzheimer's disease and PPA.

Keywords: Familial Alzheimer's disease, Presenilin 1, primary progressive aphasia

INTRODUCTION

The primary progressive aphasias (PPA) are language-led dementias comprising three major clinical syndromes [1]: a non-fluent/agrammatic variant (nv-PPA) associated with apraxia of speech, agrammatism, and left peri-sylvian atrophy; a semantic variant (sv-PPA) associated with loss of semantic knowledge and anterior temporal lobe atrophy; and a logopenic variant (lv-PPA) associated with single-

word retrieval deficits, impaired phonological working memory, and left temporo-parietal atrophy. nv-PPA and sv-PPA are typically associated with pathology in the frontotemporal lobar degeneration (FTLD) spectrum [2], while lv-PPA is most often associated with Alzheimer's disease (AD) pathology [2]. Autosomal dominant forms of PPA are uncommon but are most often attributable to mutations in the *progranulin*, *microtubule associated protein tau* or *C9ORF72* genes [3–5]. Autosomal dominant AD is also uncommon, typically presenting as a progressive amnesic syndrome [6] and results from mutations in the *presenilin 1* (PSEN1), *presenilin 2* (PSEN2), or *amyloid precursor protein* (APP) genes. In particular, the P264L

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Table 1
Summary of patient's neuropsychological performance. Raw scores and percentile rankings are shown. Results <5th percentile of published norms are shown in bold

	Raw Score	Percentile [†]
<i>IQ</i>		
WASI Verbal IQ	77	
WASI Performance IQ	68	
<i>Episodic memory</i>		
Recognition Memory Test-Words (/50)	45	50th
Recognition Memory Test-Faces (/50)	43	25–50th
<i>Executive function</i>		
D-KEFS Stroop word	60	<1st
D-KEFS Stroop inhibition	150	<1st
<i>Semantic processing</i>		
British Picture Vocabulary Test (/150)	136	25–50th
<i>Language skills</i>		
Graded non-word repetition /20	12	<1st
Graded non-word reading /25	13	1–5th
Sentence repetition /10	6	<1st
Verb Naming /20	19	<1st
Graded Word Repetition /45	39	1–5th
PALPA 55 sentence comprehension /24	20	<25th
Graded Naming Test (/30)	0	<1st
Boston Naming Test (/30)	6	<1st
<i>Other Skills</i>		
Digit Span-Forward (/12)	4	<5th
Digit Span-Reverse (/12)	3	5–25th
Addition	0	<1st
Subtraction	1	1st–5th
Visual Object Spatial Perception	13	1st–5th

D-KEFS Stroop (word and inhibition), Delis-Kaplan executive function system; PALPA 55, Psycholinguistic Assessment of Language Processing in Aphasia; WASI, Wechsler Abbreviated Scale of Intelligence. [†]Where published normative percentile data are unavailable, percentile values relative to local control data ($n = 75$) are listed.

PSEN1 mutation usually presents with typical amnesic AD, and rarely with less typical phenotypes such as dementia with Lewy bodies or frontotemporal dementia (see Supplementary Table 1; available online: <http://dx.doi.org/10.3233/JAD-122092>) [7–15]. Here, we report clinical, neuropsychological, and neuroimaging data signifying a novel presentation of this mutation in a patient with PPA. Ethical approval for the study was obtained from the London Queen Square Ethics Committee and the subject gave written informed consent to participate in accordance with the Declaration of Helsinki.

CASE REPORT

The patient, a right handed charity administrator, presented initially at age 45 with an approximately three year history of increasingly effortful speech and word-finding difficulty. The patient had no relevant

past medical history. At that stage, there was no objective language or other cognitive deficits demonstrable on bedside assessment. Over the following two years, she suffered an insidious deterioration in her expressive speech and handwriting with prominent errors of grammar and spelling, and she developed significant anxiety around these symptoms. However, no concerns were raised by family members regarding her episodic memory or behavior. When reassessed at age 47, her speech was effortful and marred by speech sound and grammatical errors. There was a potentially relevant family history: one of her parents had developed cognitive decline with onset around 60 marked by insidious behavioral change and episodic memory difficulties and a clinical duration of 14 years.

The patient's neuropsychological assessment confirmed a predominantly language-led cognitive syndrome consistent with current consensus criteria and diagnostic formulations for nv-PPA (Table 1) [1]. She showed evidence of impaired repetition of single polysyllabic words and sentences particularly affecting non-words. Her comprehension of syntactically complex sentences was also impaired. Despite severe anomia, the patient's semantic knowledge as measured by a test of single word comprehension (British Picture Vocabulary score) was preserved. In addition she exhibited executive dysfunction, while her performance on verbal and visual recognition memory tests was good. The general neurological examination was unremarkable.

Volumetric MR brain imaging (Fig. 1A) revealed global volume loss accentuated within the left cerebral hemisphere. In particular, there was left-sided anterior peri-Sylvian volume loss extending caudally to involve parietal cortex. Metabolic brain imaging using FDG-PET (Fig. 1B) identified asymmetric hypometabolism within the left hemisphere, most strikingly within the left temporal and parietal lobes. Diffusion weighted imaging ($B = 1000 \text{ s/mm}^2$) was also carried out (see Supplementary Figure 1). No areas of restricted diffusion were identified, nor was there any cortical ribboning consistent with prion disease present.

The clinical and neuroimaging evidence here suggested a neurodegenerative disease with asymmetric involvement of the cerebral hemispheres.

MATERIALS AND METHODS

Cerebrospinal fluid (CSF) was assayed to determine levels of marker proteins associated with neurodegeneration and of value in discriminating FTLD from AD.

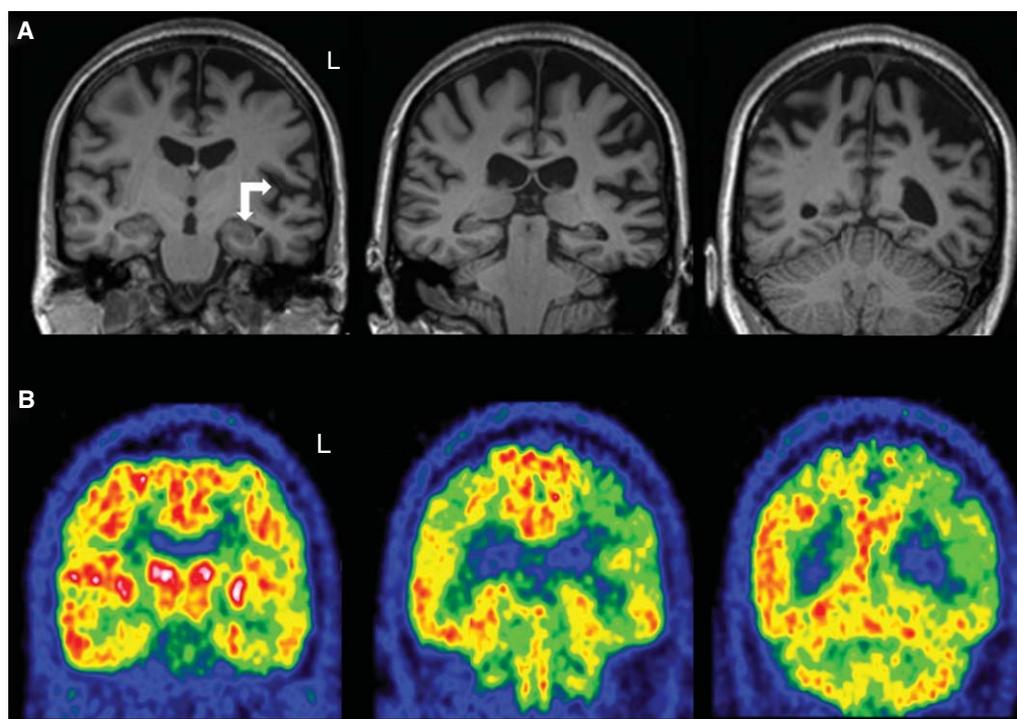


Fig. 1. A) Representative coronal volumetric MRI and B) FDG-PET slices from patient with nv-PPA carrying the P264L presenilin mutation. Arrow indicates left peri-sylvian volume loss and preserved hippocampi. B) FDG-PET scan indicating patterns of hypometabolism particularly in left temporal and parietal cortices.

CSF total tau (a measure of neuronal loss, reflecting non-specific neurodegeneration) and amyloid- β_{1-42} ($A\beta_{42}$, a measure of amyloid deposition specific for AD pathology) were assayed (Innotest platforms, Innogenetics, Ghent, Belgium). Total tau was elevated (1400 pg/ml; >90% of all patients ($n = 238$) at our center who have CSF and a clinical diagnosis of AD have a total tau >1200 pg/ml), corroborating the clinical impression of a neurodegenerative process. $A\beta_{42}$ was low (379 pg/ml; 85% of patients ($n = 238$) at our center who have CSF and a clinical diagnosis of AD have an $A\beta_{42} < 400$ pg/ml) and in keeping with previous reports of abnormal $A\beta_{42}$ levels [16]. The ratio of tau: $A\beta_{42}$ was raised (3.7), consistent with AD pathology (>90% all patients at our center who have CSF and a clinical diagnosis of AD have a total tau/ $A\beta_{42} > 1$). 14-3-3 protein was negative.

The first diagnostic consideration in this case in light of the clinical and neuroimaging evidence was a disease in the FTLN spectrum; the patient's age and family history further suggested a genetic basis for her presentation, although there were no other living affected relatives and no family members in the previous generation had undergone genetic testing.

However, the CSF profile with a raised total tau: $A\beta_{42}$ ratio favored underlying AD pathology. We therefore undertook direct Sanger sequencing of exons 16 and 17 of APP, exons 2–12 of PSEN1, and exon 4, 5, and 7 of PSEN2 using previously published methods [17]. We identified a heterozygous pathogenic point mutation at exon 8 (g.49976C > T) in the PSEN1 gene (the P264L mutation). Given the atypical presentation we also screened for other mutations within the following genes MAPT, GRN, C9ORF72, *fused-in-sarcoma*, *valosin-containing protein*, *prion protein*, *TAR DNA-binding protein 43*, and *colony stimulating factor 1 receptor*, with next generation sequencing technology using Life Technology's Ion Torrent PGM sequencing. We found no further mutations or obvious variants of unknown significance.

DISCUSSION

This case raises a number of important issues. First, the clinical phenotype, consistent with nv-PPA, represents a novel presentation of the PSEN1 P264L mutation. Schema for classifying familial AD

mutations and functional cellular work have suggested that this mutation is pathogenic. It is therefore highly unlikely that another disease process accounted for the atypical clinical phenotype in this case [18, 19]. While language deficits, in particular anomia, are common in familial AD, these tend to manifest later in the illness with only one previous case due to a different mutation (PSEN1 R278I) reported as presenting with nv-PPA [20, 21]. Second, this case highlights the heterogeneity of the P264L mutation. This is evident both in relation to previously published cases (Supplementary Table 1) [7–15, 20] and reported clinical phenotypes within the patient's family. While detailed clinical information about the previous generation is lacking, the substantially later age of the patient's father at clinical onset and his clinical phenotype (a memory/behavioral led syndrome) suggests that if (as is plausible) he also carried the P264L mutation, then the clinical phenotype of the mutation varied within this family. Indeed, a recent report has highlighted the potential heterogeneity of this mutation among members of a single family; one member had word comprehension deficits, while another had more typical features of AD with poor episodic memory and apraxia [14].

The present case supports the idea that genetic lesions may cause relatively focal cognitive presentations resulting from targeted degeneration of specific vulnerable brain networks, here the left temporoparietal language network as demonstrated by clinical and neuroimaging findings. This hypothesis is supported by studies of the language-led forms of sporadic AD, most often presenting as lv-PPA, which also show a similar distribution of neurodegeneration [1, 2, 22]. Indeed our patient's phenotype overlapped on clinical and neuroimaging grounds with lv-PPA, although did not fulfill current criteria for lv-PPA (owing to the presence of impaired motor speech production and expressive agrammatism [1]). The frequently observed overlap of neurodegenerative syndromes might plausibly reflect disease propagation through distributed functional networks [22, 23]. The mechanisms by which brain networks are rendered vulnerable and subsequently degenerate remain to be elucidated. It may be that a pathogenic protein change alters a vulnerable brain network via direct toxicity or that protein alterations confer vulnerability to existing protein species (e.g., A β). Once the degenerative process is triggered, the intrinsic network connectivity may facilitate propagation of the process, initially to locally connected brain regions but ultimately, more diffusely. Rare genetic presentations may help us understand how more common

sporadic disease develops and propagates within the brain.

From a clinical perspective, the present case suggests that screening for AD mutations should be considered in patients presenting with PPA, particularly where there is suspicion of a family history with CSF or other pointers to underlying AD pathology or when screens for other mutations causing FTLD are negative.

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Authors' disclosures available online (<http://www.j-alz.com/disclosures/view.php?id=1724>).

SUPPLEMENTARY MATERIAL

Supplementary material can be found here: <http://dx.doi.org/10.3233/JAD-122092>

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