Case report

Challenges in diagnosis of primary progressive aphasia

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SUMMARY

Two 68-year-old men presented to the behavioral neurology clinic with memory complaints. The clinical picture was complicated by bilingualism and psychiatric comorbidities. Based on a combination of cognitive and language testing, 5-fluorodeoxyglucose positron emission tomography (FDG-PET), and/or magnetic resonance imaging (MRI) of the brain, both cases were initially diagnosed as having mild cognitive impairment (MCI). At follow-up, however, both cases' language profiles and neuroimaging had evolved to clearly indicate primary progressive aphasia (PPA) as the underlying condition rather than MCI. These cases underscore the importance of careful observation of clinical and neuroimaging data over time to reach an accurate diagnosis.

BACKGROUND

Primary progressive aphasia (PPA) is an atypical presentation of Alzheimer disease (AD) or fronto-temporal lobar degeneration (FTLD) that is characterised by a progressive language impairment and evolves to affect additional aspects of cognition. There are three subtypes of PPA.¹ Non-fluent/agrammatic PPA involves effortful speech, apraxia of speech, impaired use and understanding of grammar, and some anomia; comprehension and reading are intact for simple items. Semantic PPA is characterised by impaired comprehension of the meaning of words and objects, with some anomia; speech is fluent and grammatical, and repetition is intact. Logopenic PPA involves anomia due to impaired single-word retrieval; repetition of phrases and sentences is also impaired and phonological paraphasias are often present, however, speech is relatively fluent and grammatical, and comprehension and reading are intact for simple items.

The underlying pathology of PPA is heterogeneous and consists of either FTLD or AD pathology. Patients with non-fluent/agrammatic PPA or semantic PPA tend to have FTLD rather than AD pathology, whereas logopenic PPA is often due to AD pathology; however, exceptions have been documented.² These pathological changes lead to cortical atrophy and hypometabolism in areas of the brain that correspond to the patient's language deficits: left posterior frontoinsula cortex in non-fluent/agrammatic PPA, left anterior temporal cortex in semantic PPA and left temporoparietal cortex in logopenic PPA.^{1,3} Such findings on MRI and 5-fluorodeoxyglucose positron emission

tomography (FDG-PET), respectively, may be used to support a diagnosis of PPA.^{1,3}

There is no cure for PPA; differentiation from other conditions such as mild cognitive impairment (MCI) is important for treatment planning, which will mostly focus on treatment of aphasia rather than memory impairment. However, despite established criteria,¹ diagnosis of PPA can be challenging. Comorbidities can make it difficult to evaluate patients and differentiate PPA from other underlying conditions. Furthermore, identifying the particular variant of PPA is not always straightforward. Differentiating between non-fluent/agrammatic PPA and logopenic PPA may sometimes be difficult; both affect the dorsal language pathway, and logopenic PPA can also present with agrammatism.⁴ Semantic PPA can present late in the disease, because patients with this variant are often able to compensate for a long time. This report describes the diagnostic dilemmas encountered with two cases, and demonstrates the importance of following language and neuroimaging changes over time to diagnose PPA.

CASE PRESENTATION

What follows is a presentation of two cases, beginning with the history and including findings from clinical evaluations. A board-certified neurologist (author 2) performed the clinical evaluations, and a board-certified neuropsychologist performed the neuropsychological evaluations. Results of neuropsychological testing and other diagnostic investigations are presented in [table 1](#). In the neurology clinic and neuropsychological evaluations, various subtests of the Western Aphasia Battery⁵ were used to test naming, reading, writing, language production and comprehension. Naming was further evaluated using the Boston Naming Test.⁶ Verbal memory was assessed using the Three Words Three Shapes test⁷ in the neurology clinic, and the Hopkins Verbal Learning Test-Revised (HVLT-R)⁸ during neuropsychological evaluations. Speech fluency was evaluated in spontaneous speech and verbal responses throughout the evaluation. Semantic fluency was assessed by asking the patient to name as many animals as they could in 1 min, and then the same for fruits and vegetables.⁹ Repetition was evaluated using 11-word sentences on the Montreal Cognitive Assessment (MoCA).¹⁰ Visuospatial function was evaluated using the MoCA, the Wechsler Memory Scale-IV Visual Copy Test,¹¹ and Judgment of Line Orientation¹² in case 1, and the Brief Visuospatial Memory Test-Revised (BVMTR)¹³

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Table 1 Clinical findings

	Visit	Symptoms	Neuropsychological evaluation	MRI	FDG-PET	CSF	Diagnosis
Case 1	V1	Word-finding and memory difficulty	<ul style="list-style-type: none"> ▶ Memory: mildly impaired encoding of verbal information. ▶ Speech fluency: intact. ▶ Semantic fluency: mildly impaired. ▶ Naming: moderate anomia in English, but not Farsi. ▶ Repetition: intact in Farsi, difficult in English. ▶ Comprehension: intact. ▶ Visuospatial function: intact. ▶ Executive function: mildly impaired. 	Read as normal.	Read as normal.	Non-Alzheimer	MCI, non-amnestic, with contribution from OSA and anxiety.
	V2	Worse	<ul style="list-style-type: none"> ▶ Memory: mildly impaired encoding of verbal information. ▶ Speech fluency: intact. ▶ Semantic fluency: moderately impaired. ▶ Naming: severe anomia in both languages. ▶ Repetition: intact. ▶ Comprehension: intact. ▶ Visuospatial function: intact. ▶ Executive function: intact. 	N/A	Left anterior temporal hypometabolism.		PPA with anomia (likely early semantic PPA).
Case 2	V1	Word-finding and memory difficulty	<ul style="list-style-type: none"> ▶ Memory: severe retrieval-based verbal memory impairment. Speech fluency: intact. ▶ Semantic fluency: severely impaired. ▶ Naming: moderate anomia. ▶ Repetition: intact. ▶ Comprehension: intact. ▶ Visuospatial function: mildly impaired. ▶ Executive function: intact. 	Mild bilateral temporoparietal atrophy.	N/A	Alzheimer	MCI
	V2	Worse	<ul style="list-style-type: none"> ▶ Memory: severe retrieval-based verbal memory impairment. ▶ Speech fluency: moderately impaired. ▶ Semantic fluency: mildly impaired. ▶ Phonemic paraphasias, circumlocutory paraphasias present. ▶ Naming: severe anomia. ▶ Repetition: impaired for long sentences. ▶ Comprehension: intact. ▶ Visuospatial: mildly impaired. ▶ Executive function: intact. 	<ul style="list-style-type: none"> ▶ Worse bilateral temporoparietal atrophy. ▶ Left perisylvian atrophy. 	Severe L>R temporoparietal hypometabolism.		Logopenic PPA-plus.

Summary of diagnostic workup for two cases. In both cases, word-finding and verbal memory difficulties worsened over the two visits and the diagnosis was changed from MCI to PPA. Neuropsychological, MRI, and CSF findings differed across the two cases, but FDG-PET in both cases showed asymmetrical (L>R) hypometabolism in the temporal cortex at the second visit. CSF, cerebrospinal fluid; FDG-PET, 5-fluorodeoxyglucose positron emission tomography; MCI, mild cognitive impairment; OSA, obstructive sleep apnea; PPA, primary progressive aphasia.

in case 2. Executive function was assessed using the Wechsler Adult Intelligence Scale (WAIS-IV),¹⁴ the Trail Making Test, the Wisconsin Card Sorting Test,¹⁵ the months of the year forwards and backwards, and forwards and backwards digit span.

Case 1 was a 68-year-old right-handed, Persian-English bilingual business owner with a history of obstructive sleep apnea (OSA), hypertension and anxiety/depression who presented to the Neurobehavior and Memory Clinic with a 3-year history of forgetting names of places and details of conversations. He denied difficulty remembering events, or people or places familiar to him. He had no issues with driving or finances. He continued to run his own cabinetry business and reported difficulty sleeping due to stress. He denied any history of head trauma or change in medications. His family history was significant for dementia in

his 66-year-old sister. He was fluent in English, having moved to the USA 30 years prior; therefore, he was tested in English. Evaluation in the neurology clinic and neuropsychological testing demonstrated mild impairments in verbal memory and executive function; neuropsychological evaluation also revealed moderate anomia (table 1). Because his naming was better in his first language, Farsi, the impaired naming in English was cautiously attributed to English being his second language. Therefore, the clinical diagnosis was non-amnestic MCI with contributions from OSA and anxiety.¹⁶

Case 2 was a 68-year-old right-handed native English-speaking businessman with a history of coronary artery bypass who presented with a 2-year history of progressive forgetfulness and reduced name recall. A few months prior, while delivering

Figure 1 Results of neuroimaging investigations for cases. Images are in radiological orientation with the left side of the image corresponding to the patient's right side. V1, visit 1, V2, visit 2. (A) In case 1, the MRI on visit 1 (MRI, V1) shows slight apparent temporal atrophy, which was read as unremarkable. FDG-PET shows slight left > right hypometabolism in the temporal pole that was read as normal at the first visit (FDG-PET, V1) and more pronounced after a year (FDG-PET, V2; blue arrows). (B) In case 2, MRI shows mild bilateral atrophy of the temporoparietal cortex on visit 1 (MRI, V1). On visit 2, there was worsening superior and middle temporal gyri and widening of the left sylvian fissure (MRI, V2; red arrows). FDG-PET shows severe left > right hypometabolism of the temporoparietal cortex on visit 2 (FDG-PET V2; blue arrows). FDG-PET, 5-fluorodeoxyglucose positron emission tomography.

a lecture to a large audience, he suddenly struggled to come up with words. A full workup for transient ischaemic attack was negative. He denied issues with driving or finances, but endorsed some anxiety and depression. Three years prior, he sustained a head injury on a golf course, but denied any associated amnesia or change in consciousness. He also denied recent changes to his medications. Evaluation in the neurology clinic and neuropsychological testing showed moderate anomia, severely impaired verbal recall and mild visuospatial impairment; neuropsychological evaluation also revealed severely impaired semantic fluency (table 1). Based on these findings, the patient was clinically diagnosed as having an amnesic multidomain MCI.¹⁶

INVESTIGATIONS

The diagnostic workup for both cases is summarised in table 1. Laboratory tests and general neurological examinations were unremarkable. In case 1, brain MRI and FDG-PET (figure 1) findings were read as unremarkable. In case 2, MRI showed mild atrophy that was most pronounced in the temporoparietal junction bilaterally, and FDG-PET was not obtained. Cerebrospinal fluid (CSF) analysis revealed underlying Alzheimer pathology in case 2, but not case 1.

Case 1 returned 1 year later and case 2 returned 2 years later complaining of worsening symptoms. Clinical and neuropsychological examinations in both cases revealed aphasia with worsening deficits on tests of word-finding, semantic fluency and verbal memory. In case 1, the mild executive function impairment seen on visit 1 had resolved after undergoing treatment for anxiety and OSA. In addition, case 2 had word-finding pauses and moderately impaired speech fluency with several phonemic paraphasias (table 1).

In case 1, repeat FDG-PET revealed more pronounced left-predominant anterior temporal hypometabolism, a pattern seen in individuals with semantic PPA. Repeat MRI was not obtained. In case 2, repeat MRI showed persistent mild atrophy of the temporoparietal cortex, and new atrophy of the left perisylvian cortex. FDG-PET in case 2 revealed severe left-predominant

temporoparietal hypometabolism. Based on the progression of deficits predominantly in the language domain and correlation with neuroimaging findings, the diagnosis was changed from MCI to PPA with anomia in case 1 and logopenic PPA in case 2.

OUTCOME AND FOLLOW-UP

In case 1, the patient was started on escitalopram for symptoms of anxiety and depression. He also received tele-speech therapy through the University of Austin Aphasia Research and Treatment Laboratory and facilitated by a Persian speech pathologist. He and his wife have reported improvement with speech and language therapy interventions.¹⁷ His language deficits are currently stable and his diagnosis remains PPA with anomia. Based on the pattern of hypometabolism in the anterior temporal cortex, we expect his condition will most likely evolve into semantic PPA.

In case 2, the patient was started on rivastigmine and memantine for AD management. He has been working with a speech-language pathology team to improve his word finding and communication. His condition has now worsened to include memory impairment, which is a target of his intervention by the memory rehabilitation team.

DISCUSSION

In the present cases, PPA was ultimately distinguished from the initial diagnosis based on the lack of significant functional limitation and progressive impairment mostly in the language domain. At the first encounter, neither patient met diagnostic criteria for PPA. In case 1, imaging findings were interpreted as unremarkable; cognitive evaluation in English revealed a mild word-finding difficulty that was attributed to English being the patient's second language. In case 2, poor performance on tests of verbal recall and mild bilateral temporoparietal atrophy on MRI led to a diagnosis of amnesic MCI. By the second encounter, however, both patients' deficits were clearly attributed to aphasia, with memory concerns secondary in nature. Furthermore, in case 1,

FDG-PET on the second visit revealed left anterior temporal hypometabolism, raising the possibility that this case may have early semantic PPA. In case 2, the worsening left temporoparietal atrophy on MRI and the severe left temporoparietal hypometabolism on FDG-PET aligned with clinical findings in supporting a diagnosis of logopenic PPA. Had FDG-PET been obtained on the first visit, perhaps hypometabolism in this region would have been detected and PPA been diagnosed earlier.

Although both cases were found to have PPA, only case 2 had CSF changes consistent with AD as the underlying pathology. In case 1, the underlying cause would most likely be FTLT, seen in patients with semantic PPA. These findings support the characterisation of PPA as a clinical syndrome rather than by the specific pathology.

Despite established diagnostic criteria,¹ by the first visit, the diagnosis remained challenging in both cases. In patients with PPA, poor performance on tests of verbal and working memory may actually be due to aphasia and difficulty with lexical retrieval rather than a retentive memory deficit, especially in patients with Alzheimer pathology.¹⁸ Non-native English speakers may perform poorly on neuropsychological tests normed on native English speakers, making it difficult to differentiate aphasia. Presentation may also be impacted by concomitant psychiatric diagnoses, such as anxiety and depression, which can impact executive function, memory and attention. These cases underscore the importance of close follow-up and the use of neuroimaging modalities for an accurate diagnosis of PPA. The earlier patients receive an accurate diagnosis of PPA, the sooner these patients and their families can be referred for services (eg, speech-language therapy, social work) that can be tailored to their individual needs and improve their quality of life.

Learning points

- In patients with aphasia, poor performance on tests of verbal memory may actually be due to language impairment.
- Bilingualism and concomitant psychiatric diagnoses can make it difficult to interpret cognitive testing.
- In patients with unclear clinical presentations, close follow-up is recommended. The evolution of symptoms and imaging findings over time are helpful in differentiating primary progressive aphasia from other conditions.

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EC prepared the initial manuscript and contributed to the discussion. Both parties edited the final manuscript.

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