Primary progressive aphasia: misdiagnosis with ‘normal imaging’

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Aphasia, an acquired disorder of language function, has a potentially broad differential diagnosis. We present two cases in which primary progressive aphasia in its most common variant – the non-fluent form – was misdiagnosed as other cognitive disorders, with consequent implications for patient lifestyle and activities. Greater awareness of this disorder is required in the assessment of patients presenting to memory clinics.

Aphasia or dysphasia may be defined as a disorder characterised by an acquired loss or impairment of language function. While this is most frequently a consequence of stroke, neurodegenerative disorders can sometimes present with early and relatively isolated language impairment.

Although there are some controversies, three clinical variants of primary progressive aphasia (PPA) are generally recognised: the non-fluent/agrammatic variant (nfvPPA or avPPA), in which there may or may not also be an apraxia of speech (AOS); the semantic variant (svPPA), and the logopenic variant (lvPPA). While nfvPPA and svPPA are characterised as linguistic variants of frontotemporal dementia (FTD), lvPPA is most often associated with Alzheimer-type pathology and is therefore classified with Alzheimer’s disease (AD). Progressive apraxia of speech without aphasia may be a separate disorder from nfvPPA.

The three clinical variants of PPA may be distinguishable on clinical grounds (Table 1). However, because these disorders are relatively rare, particularly when compared with amnestic AD and vascular cognitive disorders, diagnosis may prove challenging for those clinicians not familiar with the clinical phenotype. Neuroimaging signatures may also be discriminative in differential diagnosis. We present two cases in which PPA was initially misdiagnosed, and in which misinterpretation of neuroimaging contributed to delayed diagnosis.

Case 1
A 78-year-old right-handed man presented with a three-year history of language problems. He had been seen elsewhere prior to neurological referral and given a diagnosis of Alzheimer’s disease, as a consequence of which he was told not to drive.

Listening to him give his account, it was evident that his narrative speech was effortful and halting, with some word finding difficulties but no long pauses. His comprehension appeared intact, and despite the linguistic problems he was still working and all his activities of daily living were preserved. He could repeat single letters (eg puh, tuh, kuh) but there were problems with rapid repetition of strings of letters (puh-tuh-kuh, puh-tuh-kuh, puh-tuh-kuh; also known as
the ‘pataka’ test) indicating impaired articulatory agility, reflecting an apraxia of speech. There were also problems repeating some multisyllabic words (e.g. ‘statistician’). General neurological examination was otherwise normal.

Brain imaging (CT) from two years earlier (Figure 1) showed focal left inferior frontal lobe atrophy as did MR brain imaging (Figure 1) from one year previously. Functional imaging (SPECT) from one year earlier showed relative hypoperfusion of the left frontal and temporal lobes.

The clinical phenotype and neuroimaging findings suggested a diagnosis of PPA, specifically the non-fluent variant, combined with apraxia of speech, rather than AD.

Case 2
A 65-year-old right-handed lady presented with a four-year history of ‘forgetting words’. Speech output had become difficult for her husband to understand, with impaired fluency and apparent loss of confidence, but she had no evident problem in understanding speech. The patient was otherwise in good health, with all activities of daily living preserved. She had been seen elsewhere for these symptoms prior to neurological referral and given a diagnosis of vascular dementia, as a consequence of which she was told not to drive.

On examination she had reduced rate and accuracy of speech output, with some impairments in articulatory agility (pataka test) and repetition of some multisyllabic words, but no other neurological signs.

Brain imaging (CT) performed three years earlier, reported to be normal, was reviewed and found to show mild left inferior frontal lobe volume loss, with a more prominent sylvian fissure. Functional imaging (SPECT) performed six months prior to neurological referral showed reduced perfusion in the left hemisphere. Subsequent MR brain imaging showed left insular and periopercular loss of volume. No significant ischaemic changes were seen.

In light of the clinical and neuroimaging findings, diagnosis was revised from vascular dementia to PPA, non-fluent variant with apraxia of speech.

Discussion
We present these cases to raise awareness of PPA. While it is a truism that ‘common things are common’, it is also the case that rare disorders do occur and may be missed if the diagnosis is not considered.

Although prototypical forms of frontotemporal dementia are relatively easily recognised by clinicians with experience of these conditions, diagnosis may often be challenging and delayed. Because of an overlap of symptoms, occasional misdiagnosis of FTD as AD may occur, even in experienced hands. Relatively acute aphasic presentations may occur on occasion, suggestive of stroke, presumably because of sudden decompensation of slowly progressive and hitherto subclinical disease, but a slowly progressive course is the usual presentation.

Phenotypic similarities between cognitive disorders with differing pathology and pathogenesis are well recognised. Diagnostic errors based on over-reliance on, or over-interpretation of, investigations may sometimes occur, particularly structural neuroimaging reported to show brain atrophy. However, in contrast to such false positive diagnoses, in the cases reported here the problem was under-interpretation of brain imaging findings, hence false negative diagnosis. We suspect that the initial diagnostic labels of Alzheimer’s disease and vascular dementia, applied respectively to each of these reported cases, were suggested at least in part by default.

Any diagnostic test may be associated with false positives or false negatives, possibilities that may be denoted by various test measures, explicitly so in the ‘number needed to misdiagnose’ and the ‘likelihood to be diagnosed or misdiagnosed’ metrics. The current cases emphasise the importance of trying to contextualise investigation results in terms of the clinical history and neurological examination when making diagnoses in order to avoid false positives or negatives.
Are there other simple investigations that might assist in diagnosis of PPA, accepting that examinations by speech and language pathologists and FDG-PET functional brain imaging, which may achieve a more fine-grained classification of patients, are not widely available? Cognitive testing may possibly help: item scores on the Mini-Mental State Examination (MMSE) suggest better word recall compared with AD patients who performed better on object naming and repetition. However, MMSE and many other brief cognitive screening instruments that are heavily weighted to language function and overall scores, rather than item scores, may not discriminate between different disorders. A recent review of PPA suggested that MMSE and the Montreal Cognitive Assessment (MoCA) should be used with caution in these cases because of the risk of overestimating cognitive impairment, although the Addenbrooke’s Cognitive Examination (ACE) and its revision (ACE-R) have been reported to be of use in the differential diagnosis. Assessment and investigation results should then be considered in that light, attempting to correlate clinico-radiological findings.

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Declaration of interests
No conflicts of interest were declared.

References