

Pathology in Primary Progressive Aphasia Syndromes

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Abstract ‘Primary progressive aphasia’ (PPA) refers to core linguistic disorders caused by neurodegenerative disease. Three main PPA variants are recognized: nonfluent/agrammatic, semantic and logopenic. Correctly classifying patients during life according to the underlying histopathology will become increasingly important as cause-specific treatments become available. This article reviews clinical and histopathological studies of PPA, with particular reference to updated PPA classifications. Currently, one-to-one relationships do not exist within PPA subtypes. The semantic variant has the best correspondence between the clinical syndrome and the underlying pathological cause and the logopenic variant the worst correspondence. The use of future biomarkers should facilitate accurate clinicopathological correlation of patients during life.

Keywords Primary progressive aphasia · Pathology · Frontotemporal lobar degeneration · Alzheimer’s disease · Semantic dementia · Progressive nonfluent aphasia

Introduction

Aphasia is defined as an impairment of language affecting the production and/or comprehension of speech caused by dysfunction of the brain. The term ‘primary progressive aphasia’

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(PPA) describes aphasias that are caused by neurodegenerative disease. The first descriptions of such progressive aphasias were published over 100 years ago by Arnold Pick [1, 2] and Paul Sérieux [3]. The term ‘primary progressive aphasia’ (PPA) was coined in the 1980s [4] following Marsel Mesulam’s seminal work in 1982 describing six cases of PPA [5]. In recent years, there has been a surge of scientific research into PPA that has enhanced our understanding of the clinical, genetic and pathological aspects of PPA.

Ideally, the clinical classification and diagnosis of neurodegenerative disorders would reflect the underlying neuropathology. This concept of clinicopathological correlation is vitally important in advancing our understanding of neurodegenerative disease. At a histopathological level, an ever-increasing range of specific proteinopathies are being identified, and hopes for future disease-modifying treatments in neurodegeneration rest heavily on targeting such protein-specific processes. Some conditions, such as Alzheimer’s disease (AD), are regarded as clinicopathological entities where the clinical diagnosis of AD strongly predicts Alzheimer-type pathology. However, in PPA the situation is more complicated, and it is necessary to recognize changes in clinical classification of PPA over time in order to understand the impact this has on clinicopathological relationships in PPA. In this review, we will describe each of the currently recognized subtypes of PPA, briefly recap the historical changes in nosology and explore their relationship to the underlying pathological causes.

Historical Perspective

Since Mesulam’s description of six cases in 1982, it has been apparent that PPA is a heterogeneous disorder. Mesulam’s initial work aimed to group PPAs together despite this clinical heterogeneity, principally in order to distinguish PPA from

aphasic AD [4]. Notably, Mesulam used ‘aphasic AD’ to refer to patients who present with aphasia, albeit without focal linguistic impairment, and in whom other cognitive deficits typical of AD can be appreciated. PPA subsequently came to be associated with frontotemporal lobar degeneration (FTLD) spectrum pathology. In 1998, clinical FTLT criteria were published with the aim of clinically identifying patients with underlying FTLT pathological features [6]. Consequently, the criteria included the three clinical syndromes associated with FTLT pathology: behavioural variant frontotemporal dementia (bvFTD)—which causes alterations in social behaviour/personality; progressive nonfluent aphasia—a primary linguistic disorder; and semantic dementia (SD), which affects semantic knowledge. SD can present with prominent deficits in verbal semantics and/or visual semantics, i.e. an associative agnosia [7, 8]. The visual/verbal distinction in SD is often presented in terms of asymmetry of atrophy, with visual disorders termed ‘right temporal lobe onset’ and with verbal disorders termed ‘left temporal lobe onset’. Historically, some investigators referred to this semantic group as ‘fluent’ aphasia in counterpoint to the nonfluent group. Although the 1998 criteria aimed to improve clinicopathological correlations, a proportion of patients meeting these criteria for SD and progressive nonfluent aphasia, particularly the latter, were found to have non-FTLT pathological diagnoses [9–16].

Such findings led to speculation that pathological heterogeneity will always exist within PPA subtypes and thus PPAs should be grouped together on the basis of clinical symptoms and separated from nonlinguistic disorders, i.e. bvFTD and right temporal lobe onset SD [17]. Together with an increasing interest in a third PPA subtype not included in the 1998 clinical FTLT criteria, this triggered a move towards updated classification of PPA focussing on clinical syndromes, without concern for attaining strict correspondence between PPA subtype and the underlying pathological diagnosis [17]. These contemporary classifications are presented in Table 1 and include basic PPA criteria and criteria for three PPA subtypes.

Table 1 The 2011 primary progressive aphasia (PPA) classifications

• Basic PPA
Inclusions (all must be present):
1. Most prominent clinical feature is difficulty with language
2. These deficits are the principal cause of impaired daily living activities
3. Aphasia should be the most prominent deficit at symptom onset and in the initial phases
Exclusions (all must be absent):
1. Pattern of deficits is better accounted for by other nondegenerative or medical disorders
2. Cognitive disturbance is better accounted for by a psychiatric diagnosis
3. Prominent initial episodic memory, visual memory and visuosperceptual impairments
4. Prominent, initial behavioural disturbance

Table 1 (continued)

• Basic PPA
Nonfluent/agrammatic variant PPA
Clinical
Core features (at least one of the following): (a) agrammatism; (b) apraxia of speech
At least 2 of the following supportive features: (a) impaired comprehension of syntactically complex sentences; (b) spared single-word comprehension; (c) spared object knowledge
Imaging supported
Imaging showing (a) predominant left posterior fronto-insular atrophy on MRI and/or (b) left posterior fronto-insular hypoperfusion or hypometabolism on SPECT or PET
With definite pathological diagnosis
Histopathologic evidence of a specific neurodegenerative disease (e.g., FTLT-tau, FTLT-TDP-43, AD, other) and/or the presence of a known pathogenic mutation
SvPPA
Clinical
Core features (both required): (a) impaired confrontation naming and (b) impaired single-word comprehension
Supportive features (at least 3 required): (a) impaired object knowledge, particularly for low-frequency or low-familiarity items; (b) surface dyslexia or dysgraphia, (c) spared repetition; (d) spared speech production (grammar and motor speech)
Imaging supported
Imaging showing (a) predominant anterior temporal lobe atrophy and/or (b) anterior temporal hypoperfusion or hypometabolism on SPECT or PET
With definite pathological diagnosis
Histopathologic evidence of a specific neurodegenerative disease (e.g., FTLT-tau, FTLT-TDP-43, AD, other) and/or the presence of a known pathogenic mutation
LvPPA
Clinical
Core features (both required): (a) impaired single-word retrieval in spontaneous speech and naming and (b) impaired repetition of sentences and phrases
Supportive features (at least 3 required): (a) speech (phonologic) errors in spontaneous speech and naming; (b) spared single-word comprehension and object knowledge; (c) spared motor speech; (d) absence of frank agrammatism
Imaging supported
Imaging showing (a) predominant left posterior perisylvian or parietal atrophy on MRI and/or (b) left posterior perisylvian or parietal hypoperfusion or hypometabolism on SPECT or PET
With definite pathological diagnosis
Histopathologic evidence of a specific neurodegenerative disease (e.g., FTLT-tau, FTLT-TDP-43, AD, other) and/or the presence of a known pathogenic mutation

Adapted from Gorno-Tempini et al. [17]

AD Alzheimer’ disease, FTLT frontotemporal lobar degeneration, lvPPA logopenic variant PPA, svPPA semantic variant PPA SPECT single photon emission computed tomography, TDP-43 transactive-response DNA-binding protein of about 43 kDa

The basic PPA criteria comprise several inclusions and exclusions to ensure that only patients with circumscribed, progressive and sufficiently severe language impairments are included [17•]. If the basic PPA criteria are fulfilled, the next level of criteria can be applied, which includes criteria for three PPA subtypes: nonfluent/agrammatic variant PPA (nfvPPA; with similarities to progressive nonfluent aphasia), semantic variant PPA (svPPA; similar to left temporal lobe onset SD) and logopenic variant PPA (lvPPA). Within subtype criteria, there are three hierarchical levels of diagnosis: ‘clinical’, ‘imaging supported’ and ‘with definite pathology’. The latter allows evidence of any neurodegenerative disease as support for each of the three subtypes.

PPA Pathological Features

Gross pathological examination of brains in PPA demonstrates gross atrophy, typically centred on the perisylvian region in the left hemisphere. As mentioned already, most cases of PPA have a FTLD spectrum pathological change, yet some cases have been found to have other diseases, most commonly AD [10–16, 18–20].

FTLD spectrum pathology can be broadly separated into tauopathies, transactive response DNA binding protein of about 43 kDa (TDP-43) proteinopathies and fused in sarcoma (FUS). The tauopathies most commonly observed in FTLD are Pick’s disease, corticobasal degeneration (CBD), progressive supranuclear palsy (PSP) and frontotemporal dementia and parkinsonism linked to chromosome 17. Until 2011, subclassification of FTLD TDP-43 proteinopathies according to the distribution of TDP-43 was difficult as two different systems existed which both used numbers 1–4 to denote different subtypes [21, 22]. These difficulties were overcome with publication of ‘a harmonized classification system’ which uses letters A–D [23]. In PPA, the subtypes of FTLD pathological change typically observed include TDP-43 types A, B and C and the following tauopathies: Pick’s disease, CBD and PSP. FUS and frontotemporal dementia and parkinsonism linked to chromosome 17 pathology are not commonly reported in PPA. The distribution of pathological deposits in cases of PPA, whichever specific proteinopathy is seen, has been found to be asymmetrical; the left hemisphere is more severely affected [24•].

AD pathology is characterized by amyloid β ($A\beta$) plaques and intracellular neurofibrillary tangles (NFTs), comprising hyperphosphorylated tau [25]. The density and location of NFTs have been found to correlate better than those of $A\beta$ plaques with the severity of disease and the areas of cognition affected [26–30]. Furthermore, grey matter volume loss correlates with NFT density in AD [31, 32]. In cases of PPA with AD pathological change, the gross pathology, Braak stage, neuritic plaque deposition, and TDP-43 immunoreactivity

with NFT and $A\beta$ plaques are the same as in typical AD clinical syndromes. However, there are some differences in PPA with AD versus typical AD: NFT density is higher in the left hemisphere than in the right hemisphere [33], particularly affecting the left temporoparietal cortex [15, 34], and there is a greater ratio of cortical to hippocampal NFT density [24•, 33, 34].

Relationship Between Subtypes of PPA and Pathology

Semantic Variant PPA

SvPPA is the most clinically and pathologically homogeneous of the PPA syndromes. The characteristic features of svPPA are marked anomia and impaired single-word comprehension. Patients are often garrulous with fluent speech, which conceals the magnitude of their disorder. When reading, patients may pronounce irregularly spelt words phonetically; such regularization errors are termed ‘surface dyslexia’. Although the patients’ main symptoms are in the language domain, additional deficits in object and face recognition, i.e. associative agnosia and prosopagnosia, are not uncommon, particularly with disease progression [35]. Patients with right temporal onset SD exhibit prominent associative agnosia, but typically also have some degree of verbal semantic impairment akin to that seen in svPPA.

In svPPA, neuroimaging studies typically report atrophy and hypometabolism of the anterior temporal and ventromedial frontal lobes predominantly in the left hemisphere [36–40]. As the name suggests, in right temporal onset SD the same regions are affected, but predominantly in the right hemisphere [7, 8].

Pathological examination in svPPA reveals predominant left lateralized atrophy of the temporal lobes and FTLD TDP-43, predominantly type C histological features [24•, 41•]. Right temporal onset SD is also associated with FTLD TDP-43 pathology, which accounts for more than 70 % of the svPPA and SD cases described [9, 11, 14, 42–45] (Table 2). Some patients with svPPA and SD have been found to have other FTLD pathological features, most frequently Pick’s disease, and patients have been reported with the pathological changes of AD [9, 11, 14, 42–45]. Notably, there is a large variation in pathological specificity reported by different research groups (50–100 %; see Table 2). This suggests that differences exist in the clinical diagnosis of svPPA/SD between groups. Interestingly, research studies evaluating the updated classifications have shown a higher concordance between svPPA and TDP-43 proteinopathy than studies prior to the updated classifications, although the numbers are small in the post-2011 studies (Table 2).

Table 2 Clinicopathological correlations in PPA

Study	Number of cases	NfvPPA % (N)				SvPPA % (N)				LvPPA % (N)				Unclassifiable and mixed PPA % (N)			
		Tau	TDP-43 ^a	AD	Other	Tau	TDP-43 ^a	AD	Other	Tau	TDP-43 ^a	AD	Other	Tau	TDP-43 ^a	AD	Other
Pre-2011 PPA classifications																	
Hodges et al. [45]	17 (8 PNFA, 9 SD)	87.5 (7)	12.5 (1)	0.0 (0)	0.0 (0)	33.3 (3)	66.7 (6)	0.0 (0)	-	-	-	-	-	-	-	-	-
Knibb et al. [11]	38 (23 PNFA, 15 SD)	43.5 (10)	21.7 (5)	30.4 (7)	4.4 (1)	13.3 (2)	53.3 (8)	33.3 (5)	-	-	-	-	-	-	-	-	-
Josephs et al. [49]	10 (3 PNFA, 7 unspecified)	100 (3)	0.0 (0)	0.0 (0)	0.0 (0)	-	-	-	-	-	-	-	-	28.6 (2)	71.4 (5)	0.0 (0)	-
Josephs et al. [99]	13 PNFA	76.9 (10)	23.1 (3)	0.0 (0)	0.0 (0)	-	-	-	-	-	-	-	-	-	-	-	-
Alladi et al. [14]	53 (26 PNFA, 20 SD, 7 mixed)	38.5 (10)	15.4 (4)	46.2 (12)	0.0 (0)	20.0 (4)	70.0 (14)	10.0 (2)	-	-	-	-	-	28.6 (2)	0.0 (0)	71.4 (5)	-
Yokota et al. [100]	9 (2 PNFA, 7 SD)	100.0 (2)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	100.0 (7)	0.0 (0)	-	-	-	-	-	-	-	-	-
Deramecourt et al. [92]	11 (6 agrammatic variant PPA, 4 SD, 1 lvPPA)	0.0 (0)	100.0 (6)	0.0 (0)	0.0 (0)	50.0 (2)	50.0 (2)	0.0 (0)	0.0 (0)	0.0 (0)	100.0 (1)	0.0 (0)	-	-	-	-	-
Hodges et al. [43]	24 (SD)	-	-	-	-	12.5 (3)	75.0 (18)	12.5 (3)	-	-	-	-	-	-	-	-	-
Grossman [44]	26 (11 PNFA, 9 SD, 6 lvPPA)	54.5 (6)	0.0 (0)	36.4 (4)	9.1 (1)	0.0 (0)	55.6 (5)	44.4 (4)	0.0 (0)	16.7 (1)	83.3 (5)	0.0 (0)	-	-	-	-	-
Snowden et al. [50]	17 (8 PNFA, 9 SD)	12.5 (1)	87.5 (7)	0.0 (0)	0.0 (0)	0.0 (0)	100 (9)	0.0 (0)	-	-	-	-	-	-	-	-	-
Rohrer et al. [42]	33 (10 PNFA, 23 SD)	70.0 (7)	30.0 (3)	-	-	17.4 (4)	82.6 (19)	-	-	-	-	-	-	-	-	-	-
Total	251 (110 nfvPPA, 120 svPPA, 7 lvPPA, 14 unclassified)	50.9 (56)	26.4 (29)	20.9 (23)	1.8 (2)	15.0 (18)	73.3 (88)	11.7 (14)	0.0 (0)	14.3 (1)	85.7 (6)	0.0 (0)	28.6 (4)	35.7 (5)	35.7 (5)	35.7 (5)	35.7 (5)
Post-2011 PPA classifications																	
Mesulam et al. [24]	58 cases (17 agrammatic variant PPA, 3 svPPA, 32 lvPPA ^a , 6 mixed)	64.7 (11)	17.6 (3)	11.8 (2)	5.9 (1)	0.0 (0)	66.7 (2)	33.3 (1)	15.6 (5)	25.0 (8)	56.3 (18)	3.1 (1)	16.7 (1)	16.7 (1)	16.7 (1)	66.7 (4)	66.7 (4)
Harris et al. [41•]	30 (8 nfvPPA, 4 svPPA, 13 lvPPA, 5 unclassified)	50.0 (4)	25.0 (2)	0.0 (0)	25.0 (2)	0.0 (0)	100.0 (4)	0.0 (0)	0.0 (0)	23.1 (3)	53.8 (7)	23.1 (3)	0.0 (0)	60.0 (3)	40.0 (2)	40.0 (2)	40.0 (2)
Caso et al. [55]	11 (nfvPPA)	81.8 (9)	18.2 (2)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Total	99 (36 nfvPPA, 7 svPPA, 45 lvPPA, 11 unclassified)	66.7 (24)	19.4 (7)	5.6 (2)	8.3 (3)	0.0 (0)	85.7 (6)	14.3 (1)	11.1 (5)	24.4 (11)	55.6 (25)	8.9 (4)	9.1 (1)	36.4 (4)	54.5 (6)	54.5 (6)	54.5 (6)

Some studies are from the same research laboratories and therefore some cases may be counted more than once.

lvPPA logopenic variant primary progressive aphasia, nfvPPA nonfluent/agrammatic variant primary progressive aphasia, PNFA progressive nonfluent aphasia, SD semantic dementia, svPPA semantic variant primary progressive aphasia, TDP-43 transactive response DNA binding protein of about 43 kDa

^a Frontotemporal lobar degeneration with Ubiquitin (FTLD-U), Dementia lacking distinctive histology (DLHD) and Motor neurone disease type inclusion (MNDI) were used prior to the discovery and widespread use of TDP-43 in 2006. These disorders are grouped here under TDP-43.

^b These patients include patients without repetition deficits who would therefore not fulfil the criteria for lvPPA.

SvPPA and right temporal onset SD are usually sporadic [43]. This is in contrast to bvFTD, where a positive family history may be seen in up to 40 % of cases [46].

New PPA classifications force a separation between right temporal onset SD and svPPA. Yet they share a significant number of clinical features, have neuroimaging that demonstrates asymmetrical temporal lobe atrophy and are frequently caused by the same pathological disease. The presence of behavioural changes in right temporal lobe onset SD can lead to such patients being diagnosed with bvFTD. By the same token, semantic impairments seen in patients with mutations in *MAPT* (microtubule-associated protein tau gene), associated with symmetrical temporal lobe atrophy [47], can lead to such patients being clinically diagnosed with SD. Therefore, the prediction of the underlying pathology in patients with progressive semantic impairment remains difficult, and current clinical criteria do not fully aid clinicians in teasing out the differences in such cases.

Nonfluent/Agrammatic Variant PPA

NfvPPA encompasses clinical syndromes characterized by problems in grammar/syntax and or problems with speech production, and is associated with various underlying pathological changes (Table 2). Distinctive features of nfvPPA include agrammatism, phonemic paraphasias, impaired articulatory planning or apraxia of speech (AOS) and dysprosody [6, 37, 48–54]. Understanding the relationship between nfvPPA and the underlying pathological diagnosis is greatly hampered by the broad range of clinical syndromes that can be subsumed under the rubric of ‘nonfluent’ aphasia. It is perhaps best to consider the pathology encountered in the nfvPPA group as a whole and then look at whether splitting the nfvPPA group up further leads to greater understanding of the pathological relationships.

Neuroimaging studies suggest patients with nfvPPA have atrophy and hypometabolism of the left posterior inferior frontal lobe [37, 49, 52, 55, 56]. When AOS is a prominent feature, the premotor and supplementary motor cortex are also affected [49].

At autopsy, atrophy of the temporal and frontal lobes with an asymmetric, left-sided emphasis is seen. Histology in the FTLT spectrum is typically observed in over 70 % of cases (Table 2) [24•, 41•, 42, 57]. Within the FTLT spectrum, over 50 % of nfvPPA patients have FTLT tau (including Pick’s disease, CBD, PSP), but a reasonable proportion of patients (around 20 %) are reported with TDP-43 proteinopathy (predominantly type A).

It therefore seems that, compared with svPPA, the overall diagnosis of nfvPPA does not predict a specific underlying disease with a great deal of accuracy. In the past, some patients now classified as having lvPPA might have been diagnosed with progressive nonfluent aphasia. This may

account for the significant variation in the proportion of nfvPPA patients reported with AD over the years (Table 2). Clinicopathological correlation in nfvPPA may therefore improve further with implementation of the updated classifications and improved recognition of lvPPA. However, the misattribution of lvPPA as nfvPPA does not account for the variability of the diseases within the FTLT spectrum encountered at autopsy.

Given that nfvPPA seems to encompass at least two subtypes (agrammatic and AOS predominant), it is reasonable to explore whether such subdivision on clinical grounds leads to better specificity of aetiological diagnosis. Indeed, some studies have reported a significant association between AOS and FTLT tau [42, 49]. In a large series of PPA patients, the link between FTLT tauopathies and AOS was limited to PSP histology; the majority of patients with other FTLT tauopathies (CBD and Pick’s disease) exhibited prominent agrammatism [24•]. The suggestion from this observation is that clinicopathological correlations may be found between some specific clinical and pathological subtypes rather than between general PPA groups and overarching pathological groupings. Further complicating the understanding of the relationships between AOS, agrammatism, and specific proteinopathy in nfvPPA is a recent study reporting that AOS was the commonest feature in 11 cases of nfvPPA with FTLT, including both tau and TDP-43 (nine tau, two TDP-43 type A) [55], whereas some degree of agrammatism was present in the tau and TDP-43 groups [55]. AOS and agrammatism can be difficult to diagnose and quantify. It is possible that some of the discrepancies in the literature are due to inconsistencies between research laboratories in identifying these clinical features. Further work describing and outlining how best to identify these features is required.

It has been argued that the classification of primary progressive AOS should be separate from PPA classifications [58]. Owing to the overlap between primary progressive AOS and nfvPPA with prominent AOS, the separation of these disorders may be difficult and would likely cause a degree of diagnostic confusion. However, as we gain a better understanding of the clinicopathological relationships in nfvPPA and AOS, further subdivision of nfvPPA may prove useful.

Special attention ought to be brought to those rare instances of familial nfvPPA. Most cases of nfvPPA are sporadic, but some familial forms of nfvPPA are associated with progranulin (*GRN*) mutations, which are also found in some familial cases of bvFTD [59–66]. Interestingly, members of the same family with known *GRN* mutations have been found to present with different clinical syndromes [61, 64]. In addition, a handful of nfvPPA patients have been described with the *C9ORF72* GGGGCC hexanucleotide repeat expansion [67, 68]. The presence of such mutations is helpful in predicting the underlying disease

as patients with *GRN* and *C9ORF72* mutations typically have FTLTDP-43.

Logopenic Variant PPA

LvPPA is a heterogeneous clinical and pathological entity. ‘Logopenia’, the characteristic feature of lvPPA, is defined by slowed speech rate due to marked word-finding difficulties. This leads to fluent speech interspersed with nonfluent periods. Cases of PPA described with this feature date back to Mesulam’s initial descriptions of PPA in 1982 [5], but lvPPA was only presented as a discrete clinical syndrome in 2004 [37]. Single-word comprehension and syntax are typically not affected in lvPPA.

Atrophy and hypometabolism of the left posterior temporal lobe and inferior parietal atrophy is typically reported in neuroimaging studies of lvPPA [37, 69–73].

LvPPA is a relatively new entity, and therefore there are only a few published studies of clinicopathological case series which include lvPPA. Gross inspection has shown atrophy of the temporal and parietal regions with a left-sided preponderance [24•]. Most patients with lvPPA have AD (around 60%), but a significant minority of patients have other diseases (Table 2) [24•, 41•]. Non-AD proteinopathies in patients with lvPPA are varied and include FTLTDP-43 type A, dementia with Lewy bodies, cerebrovascular disease and Creutzfeldt–Jakob disease [41•]. Owing to the association between lvPPA and AD, several studies have used biomarkers to detect AD pathology during life. Similarly to pathology studies, around 60% of lvPPA patients have been found to have CSF biomarkers of AD (i.e. elevated tau levels and reduced A β 42 levels) [74, 75]. In contrast, studies using positron emission tomography with the ligand Pittsburgh compound B to detect A β have found a much higher proportion (between 90 and 100%) of lvPPA patients to be positive for Pittsburgh compound B, suggestive of underlying AD pathological change [76–78].

There are no genetic mutations known to cause lvPPA. The presence of an apolipoprotein E (*APOE*) ϵ 4 allele is a risk factor for AD [79, 80]. Findings have been mixed as to whether the same is true for lvPPA, with some authors finding a similarly high frequency of *APOE* ϵ 4 carriers in lvPPA versus typical AD [34, 37] and other authors reporting a lower frequency [24•, 81, 82].

Unclassifiable PPA

Recent studies evaluating the 2011 PPA classifications have found that a PPA subtype cannot be ascribed to all patients with PPA [41•, 83–85], and some patients meet the criteria for more than one PPA subtype [83–85]. In unclassifiable and mixed PPA cases, predicting the underlying disease is especially challenging.

A variety of underlying diseases have been reported in unclassifiable PPA, including FTLTDP-43, FTLTDP-43 and AD (Table 2) [24•, 41•, 49]. In the clinicopathological study from our centre, two ‘unclassified’ PPA patients had *GRN* mutations [41•]. Interestingly, two other PPA patients in the study also had *GRN* mutations, but a PPA subtype could be ascribed to them (one nfvPPA patient and one lvPPA patient). The most salient feature of PPA with *GRN* mutations is typically reported to be anomia; agrammatism may be present, in which case patients may fall into the nfvPPA category [61–63, 86, 87]. However, if agrammatism is not present, it is conceivable that these patients would fulfil the lvPPA criteria. Indeed, one study has reported a high proportion *GRN* mutations in patients who met the criteria for lvPPA [88]. These findings suggest that patients may present with a syndrome akin to lvPPA owing to their marked anomia. The characterization of the language disorder associated with *GRN* mutations may require further study. Future criteria could include separate PPA–*GRN* criteria or include characteristic features of PPA–*GRN* within the nfvPPA criteria.

Patients with *GRN* mutations can account for some but not all cases of unclassifiable PPA. It was postulated in the 2011 classifications publication that patients with early stages of PPA may not fulfil the criteria [17•]. However, in a study from our research group, although a PPA subtype could be ascribed to some ‘unclassified’ PPA patients with disease progression, this was not invariably the case [41•]. Since unclassifiable PPA cannot simply be accounted for by mild/early disease stage, this suggests that more than three PPA syndromes exist.

In a recent study, unclassified PPAs were grouped together, and the investigators found group-level patterns of atrophy predominantly involving the posterior temporal and parietal lobes on the left side, i.e. a pattern similar to that reported for lvPPA [89]. The suggestion from the authors was that such unclassifiable patients probably had AD. However, the study from our centre found that unclassifiable PPA patients have a range of clinical syndromes and underlying pathological diagnoses when evaluated individually [41•]. Therefore, simply assigning patients who do not fit the current PPA criteria to a single group may not help tease out clinicopathological correlations. Looking for trends within unclassifiable patients in order to subdivide these patients, such as those with *GRN* mutations, is more likely to improve our understanding of the difficult relationship between clinical symptoms and the underlying pathological diagnosis.

Since different PPA subtypes are predominantly associated with different underlying proteinopathies (Table 2), understanding clinicopathological correlations in patients who fulfil the criteria for more than one PPA subtype is problematic. Recent studies evaluating the updated criteria have found that some patients meet the criteria for both lvPPA and another PPA subtype [83–85], and some patients who initially meet the criteria for lvPPA subsequently fulfil the criteria for

nfvPPA with disease progression [24]. Indeed, the core features of lvPPA are nonspecific (Table 1) and can occur in nfvPPA and svPPA [85]. It seems increasingly obvious that the lvPPA classification recommendations are not specific enough to describe a discrete clinical syndrome, and therefore there is little chance of predicting a specific pathological diagnosis. It has been recommended that lvPPA should be defined by word-finding difficulties in the absence of agrammatism or impairments in single-word comprehension [90]. Whether this will improve accurate classification of lvPPA is yet to be determined; however, relying on the absence of core features of the other PPA subtypes to define lvPPA does not seem ideal. Future work characterizing the language disorder seen in patients with PPA with underlying AD is therefore required.

PPA with Significant Behavioural, Cognitive and/or Neurological Features

The PPA classifications are specific to linguistic features and thereby no features outside the language domain are referenced (excepting AOS). Although this narrows down the features to assess and anticipate, other features, which may help pinpoint a specific aetiology, are neglected.

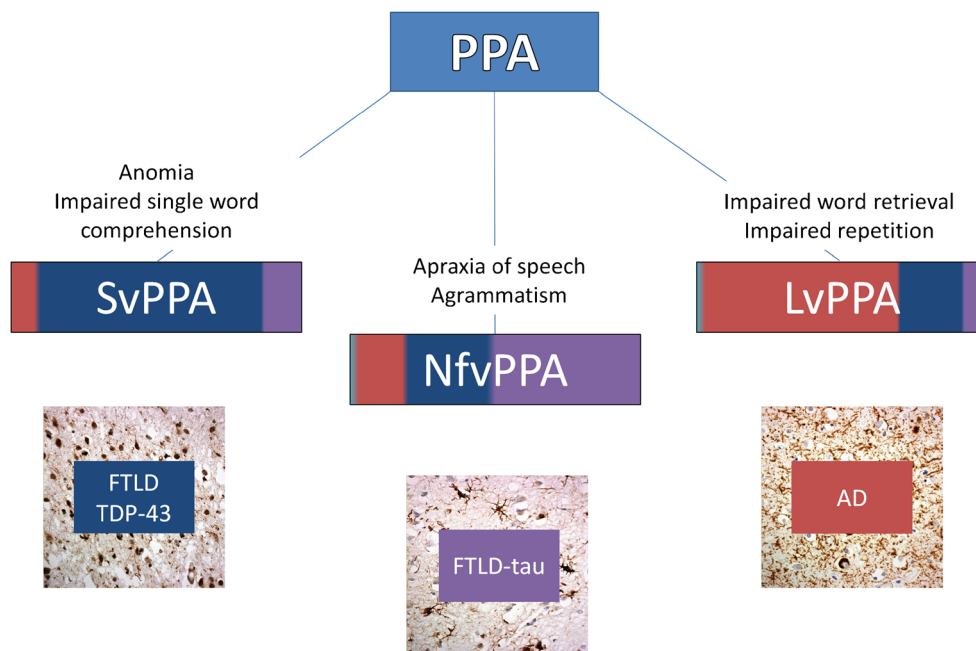
Behavioural features are not uncommon in PPA, and the presence of behavioural features is much commoner in PPA with FTLD than in PPA without FTLD [41, 91]. Conversely, the presence of certain linguistic features, such as semantic impairment, in a progressive behavioural disorder will increase the certainty that the underlying disease belongs to the FTLD spectrum.

NfvPPA has been linked with disorders of vertical gaze associated with PSP syndrome [49, 92] and symmetric apraxia associated with corticobasal syndrome. If patients with PPA exhibit prominent extrapyramidal motor disorders FTLD tau is more likely than FTLD TDP-43 [55]. Similarly, examining patients for signs of motor neurone disease (MND)/amyotrophic lateral sclerosis (ALS) can be useful since some patients with mixed nfvPPA and MND/ALS [93–95] and svPPA and MND/ALS [96–98] have been reported, and these patients are likely to have FTLD TDP-43. Therefore, monitoring neurological signs and possibly including some of these features in the clinical criteria may be a helpful way of trying to predict pathological diagnosis.

Conclusions

It is likely that as and when potential disease-modifying treatments for PPA become available they will be targeted at specific proteins, and thus accurate clinicopathological diagnosis will be essential. Therefore, the aim of the clinical PPA criteria should be to achieve accurate differentiation of FTLD PPA from non-FTLD PPA, and ideally to distinguish between different pathological diseases in the FTLD spectrum during life. This is a seemingly impossible task, and current PPA classifications do not provide one-to-one correspondence between pathological aetiology and PPA subtypes. However, some patterns between the clinical PPA syndrome and the underlying proteinopathies are recognized. NfvPPA and svPPA are predominantly linked with FTLD, nfvPPA more commonly with FTLD tau and svPPA with FTLD TDP-43

Fig. 1 Clinicopathological correlations in primary progressive aphasia (PPA). AD Alzheimer’s disease, FTLD frontotemporal lobar degeneration, lvPPA logopenic variant PPA, nfvPPA nonfluent/agrammatic variant PPA, svPPA semantic variant PPA, TDP-43 transactive response DNA binding protein of about 43 kDa



type C (Fig. 1). Although most lvPPA patients have AD, this group is in fact the most pathologically heterogeneous. In part this seems to be due to the nonspecific features included in current classifications, and a better understanding of language features in typical and focal presentations of AD would be useful. PPA is typically sporadic, but some genetic associations are recognized; PPA patients with *GRN* or *C9ORF72* mutations indicate underlying FTLTDP-43.

So far, improvements in clinicopathological correlation have been largely dependent on cognitive and postmortem neuropathology research. In life, clues to an underlying proteinopathy can be gleaned through the use of biomarkers. Structural MRI can be helpful and may disclose characteristic patterns of atrophy, such as the left anterior temporal volume loss seen in svPPA. In other PPA syndromes, left-sided perisylvian atrophy is often seen but may not help differentiate one underlying disease from another. CSF measurements of A β and tau, together with PET ligands that bind amyloid are now becoming increasingly used to identify the pathological changes of AD in vivo. There is hope that in due course biomarkers will become available for TDP-43 and FTLTDP-43 tauopathies. The combined approach of careful clinical characterization and selective use of biomarker technology will hopefully make accurate clinicopathological diagnosis a reality in the future.

Compliance with Ethics Guidelines

Conflict of Interest Jennifer M. Harris and Matthew Jones declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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