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Biomarkers in the primary progressive aphasia

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Abstract

Background—Primary progressive aphasia (PPA) is a progressive disorder of language that is increasingly recognised as an important presentation of a specific spectrum of neurodegenerative conditions.

Aims—In an era of etiologically specific treatments for neurodegenerative conditions, it is crucial to establish the histopathologic basis for PPA. In this review, I discuss biomarkers for identifying the pathology underlying PPA.

Main Contribution—Clinical syndromes suggest a probabilistic association between a specific PPA variant and an underlying pathology, but there are also many exceptions. A considerable body of work with biomarkers is now emerging as an important addition to clinical diagnosis. I review genetic, neuroimaging and biofluid studies that can help determine the pathologic basis for PPA.

Conclusions—Together with careful clinical examination, there is great promise that supplemental biomarker assessments will lead to accurate diagnosis of the pathology associated with PPA during life and serve as the basis for clinical trials in this spectrum of disease.

Keywords

Frontotemporal degeneration; Primary progressive aphasia; Biomarker

Primary progressive aphasia (PPA) is an insidious worsening of language associated with a spectrum of disease processes described under the umbrella term of fronto-temporal lobar degeneration (FTLD), or with Alzheimer's disease (AD). There are no community-based surveys documenting the frequency of PPA in the population. Nevertheless, this condition is not uncommon. One rough estimate of the frequency of PPA, derived from autopsy-based studies, estimates that about 40% of cases FTLD pathology have PPA (Forman et al., 2006; Grossman et al., 2007, 2008; Hodges et al., 2004; Kertesz, McMonagle, Blair, Davidson, & Munoz, 2005; Knopman et al., 2005; Shi et al., 2005; Snowden, Neary, & Mann, 2007). This suggests a prevalence for PPA in the range of 1.1–6 per 100,000 and an incidence of about 0.88–1.4 per 100,000 with FTLD pathology, and additional cases with Alzheimer pathology. The average age of onset tends to be in the late 50s (Johnson et al., 2005), although a wide range of onset age is reported, and we know little about the factors

contributing to this substantial variability. Survival is about 7 years, although there are widely varying estimates of prognosis (Hodges, Davies, Xuereb, Kril, & Halliday, 2003; Josephs et al., 2005; Kertesz et al., 2005; Rascovsky et al., 2005; Roberson et al., 2005; Xie et al., 2008), and little is known about factors modulating survival other than the underlying pathological basis for the disease (Xie et al., 2008). There are no known environmental risk factors (Rosso et al., 2003). However, there is significant morbidity associated with PPA. We are highly dependent on language comprehension and expression in day-to-day functioning, and a language disorder limits self-care activities and independence in all aspects of daily living. There is also a significant reduction in quality of life. Poor communicative efficacy has profound consequences for psychological integrity and can be associated with overwhelming depression and anxiety. This impacts both the aphasic patient and the patient's family.

PPA represents a spectrum of language disorders (Gorno-Tempini et al., 2011). These are discussed in detail elsewhere in this volume. Several reports suggest that each specific PPA phenotype is associated statistically with a particular histopathologic abnormality (Grossman, 2010; Josephs et al., 2011; Snowden et al., 2011). In an era of disease-modifying treatments, it is crucial to know the histopathologic basis for PPA during life. However, phenotypic characterisations provide only a partial guide to estimate the probability of pathology in PPA (Grossman, 2010), because the clinical syndromes map imperfectly onto the different causes of PPA. Across the entire FTLN clinical spectrum, errors in the diagnosis of pathology on the basis of clinical presentation are in the range of 20–30% (Deramecourt et al., 2010; Forman et al., 2006; Hodges et al., 2004; Kertesz et al., 2005; Knopman et al., 2005; Snowden et al., 2007). While clinical assessment is useful for screening patients with PPA, other approaches thus are needed to provide a firmer basis for diagnosis. After a brief presentation of the most common forms of pathology found in PPA, this review will consider several additional sources of information that can contribute to diagnosing the histopathologic basis for PPA. First I will review the value of phenotype in predicting the underlying pathology of a patient with PPA. Then I will present genetically derived information that is informative for patients with PPA. Imaging studies also may play a role in estimating the histopathologic basis for disease in PPA, and I will focus here on magnetic resonance imaging (MRI) since it is so widely available. Finally, I will discuss biofluid studies. While no one approach appears to be foolproof in determining the histopathologic basis for disease in PPA, it is possible that these approaches taken together can increase the accuracy of predicting underlying pathology in PPA during life.

THE SPECTRUM OF PATHOLOGY IN PPA

Detailed descriptions have characterised the FTLN spectrum of pathology underlying PPA (Mackenzie et al., 2009). The most common abnormality is FTLN-TDP. This refers to an accumulation of transactive response DNA-binding protein of ~43 kD, known as TDP-43 (Neumann et al., 2006) in central nervous system neurons. TDP-43 is an RNA-binding protein that functions normally in the nucleus, but can lose this location specificity with cleavage of the terminal portion of the protein. In other words, if the end of the chain of amino acids making up the TDP-43 protein is separated from the rest of the chain, TDP-43 can be deposited elsewhere in the cell, where it becomes ubiquitinated¹ and

hyperphosphorylated.² This migration and subsequent modification results theoretically in both a loss of function as well as a gain in dysfunction of affected cells, although pathophysiologic details remain to be specified.

Another common cause of FTLD is a family of conditions associated with the accumulation of the microtubule-associated protein tau (*MAPT*) in the neurons and glia. Although somewhat diverse biochemically, these pathologies are collectively known as FTLD-tau, or tauopathies (Forman et al., 2006). Tau ordinarily stabilises microtubules that are essential for structural and functional properties of neurons, but microtubules degrade without tau, and the tau becomes modified by hyperphosphorylation and ubiquitination. Thus, tau pathology is also associated with both a loss of function and a gain in dysfunction of affected cells. Conditions contributing to the family of tauopathies include dementia with Pick bodies, argyrophilic grain disease, corticobasal degeneration and progressive supranuclear palsy.

In the past, the remaining cases would have been classified as “Dementia Lacking Distinctive Histopathology” (DLHD). However, as knowledge of the pathologic basis for FTLD has rapidly accumulated over the past several years, the frequency of usage of this term has declined substantially. Several other, rare pathologies thus have been associated with FTLD. One less common histopathologic finding is FTLD-FUS, for example, related to aggregates of the fused-in-sarcoma (FUS) protein (Neumann et al., 2009). Like TDP-43, this too is an RNA-binding protein involved in a range of cellular functions. However, preliminary clinical descriptions of FTLD-FUS cases do not include aphasia (Mackenzie, Foti, Woulfe, & Hurwitz, 2007).

Beyond FTLD spectrum pathology, another major class of pathology associated with PPA is AD (Josephs et al., 2008; Mesulam et al., 2008; Rohrer, Rossor, & Warren, 2010). While first noted in large, clinical-pathological studies as a “diagnostic error,” aphasic variants of AD are now clearly recognised (Josephs et al., 2008), and these constitute a not infrequent number of cases. This has prompted the identification of an associated phenotype—the logopenic variant of PPA.

CLINICAL PHENOTYPE SCREENING FOR PATHOLOGY IN PPA

The recognition of PPA in the modern literature resulted in the publication of several detailed cases linking clinical and pathological data (Ikeda et al., 1996; Kertesz, Hudson, Mackenzie, & Munoz, 1994; Lieberman et al., 1998; Lippa, Cohen, Smith, & Drachman, 1991; Rossor, Revesz, Lantos, & Warrington, 2000; Turner, Kenyon, Trojanowski, Gonatas, & Grossman, 1996). Over time, it has become evident that there is some concordance between a particular clinical FTLD pheno-type and an underlying pathological abnormality. However, additional investigation has demonstrated that this association is only a statistical likelihood and not diagnostically definitive.

¹Ubiquitin is part of the proteosomal-lysosomal system in our cells that collects and clears “waste products” that does not belong in our cells.

²Phosphorylation adds a phosphate group to the protein, altering its activity.

For example, patients with the semantic variant of primary progressive aphasia (svPPA), also known as semantic dementia, frequently have FTLT-DTP (Deramecourt et al., 2010; Grossman, 2010; Grossman et al., 2008; Hodges & Patterson, 2007; Kertesz et al., 2005; Knopman et al., 2005; Mesulam et al., 2014; Shi et al., 2005; Snowden et al., 2007). For example, one series found that that all nine of their patients clinically diagnosed with svPPA had FTLT-DTP at autopsy (Snowden et al., 2007). However, there are exceptions. The Cambridge group reported that three patients with svPPA had FTLT-tau pathology in the form of Pick's disease (Davies et al., 2005; Hodges et al., 2004). Reports from the same institution (Alladi et al., 2007; Davies et al., 2005; Knibb, Xuereb, Patterson, & Hodges, 2006) also described histopathologic evidence for AD in several cases with a clinical diagnosis of svPPA (Alladi et al., 2007).

The non-fluent/agrammatic variant of PPA (naPPA), also known as progressive non-fluent aphasia, is said to be associated with a tauopathy (Grossman, 2012; Grossman et al., 2013; Josephs, Duffy, et al., 2006; Mesulam et al., 2014; Yokota et al., 2009). In some work, the clinical feature of apraxia of speech appears to be a useful marker for tau-positive forms pathology (Josephs, Duffy, et al., 2006), particularly when associated with a movement disorder such as progressive supranuclear palsy syndrome and corticobasal syndrome (Deramecourt et al., 2010; Mesulam et al., 2014). However, TDP-43 pathology was seen at autopsy in several reports of patients with naPPA (Grossman et al., 2008; Josephs, Petersen, et al., 2006; Josephs, Stroh, Dugger, & Dickson, 2009; Kertesz et al., 2005; Knibb et al., 2006; Knopman et al., 2005; Mackenzie et al., 2006; Mesulam et al., 2008; Shi et al., 2005; Snowden et al., 2007), and several have reported a large proportion of naPPA patients TDP-43 pathology (Deramecourt et al., 2010; Snowden et al., 2007). Others have described AD pathology (Knibb et al., 2006; Mesulam et al., 2014) and Lewy body pathology (Grossman, 2010; Kertesz et al., 2005) in patients with naPPA.

Yet another group of PPA patients have an aphasic form of AD called logopenic progressive aphasia, also known as the logopenic variant of PPA (lvPPA) (Josephs et al., 2008; Mesulam et al., 2008; Rohrer, Rossor, et al., 2010). This is frequently confused with other forms of PPA that are due to FTLT spectrum pathology. In one series, investigators identified patients with PPA who had AD pathology (Josephs et al., 2008), and all five of these patients had a lvPPA phenotype. By comparison, other series found mixed pathologies in association with lvPPA, including tau-positive inclusions, FTLT-DTP pathology and AD (Grossman, 2010; Mesulam et al., 2008).

Syndromic phenotypes typically represent a bundle of co-occurring attributes, and failures to confirm clinical-pathological correlations may be due to the association of a syndrome with a subset of clinical feature, or cases may have additional characteristics that disqualify them from a diagnosis. To address this problem, several studies assessed specific aspects of language and cognition quantitatively in autopsy-proven cases of FTLT. Patients with TDP-43 pathology were significantly more impaired than patients with tau pathology or AD pathology on measures of confrontation naming and category naming fluency guided by the letters F, A and S (Grossman et al., 2007, 2008; Josephs et al., 2008). By comparison, patients with tau-positive pathology (FTLT-tau) were significantly more impaired than patients with a TDP-43 pathology and patients with AD pathology on non-linguistic

measures of executive functioning involving visual constructions and reverse digit span (Grossman et al., 2007, 2008). Episodic memory was relatively impaired in lvPPA patients with AD pathology compared to PPA patients with FTLN-tau or FTLN-TDP pathology, although it should be noted that memory in the AD pathology-PPA patients was significantly superior to that found in typical AD patients (Forman et al., 2006; Rascovsky et al., 2002). While patterns such as those described above are highly suggestive at a group level, follow-up observations showed that quantitative neuropsychological measures are unreliable at identifying histopathology in individual patients (Hu et al., 2010).

BIOMARKERS HELP IDENTIFY THE CAUSE OF PPA

While the clinical phenotype provides useful screening information suggesting a possible pathology, additional information is needed to improve our ability to define the etiology of an individual patient with PPA with greater confidence. Biomarkers thus must be developed to supplement the clinical examination. A biomarker is a validated measure that reliably reflects the underlying pathology of a disease associated with several different pathologies like PPA. An ideal biomarker should have several characteristics: (1) The marker should be sensitive and thus should be able to detect the presence of a disease state; (2) The marker should be specific and thus should be capable of identifying those without the target disease state; (3) The marker should be effective at defining sensitivity and specificity in an individual patient; (4) The marker should be minimally invasive in order to minimise the risk of morbidity and mortality—while this is obviously important for those with the disease state, it is equally valuable for those who are tested and do not have the disease state since these individuals would not even have the potential to benefit from a treatment for the disease; (5) The marker should be widely available; and (6) The marker should be inexpensive.

Some biomarkers are categorical and thus provide only diagnostic information. This class of biomarkers should be sensitive to the distinction between healthy controls and patients, and also should be specific enough to distinguish patients with PPA from patients with other, age-associated neurodegenerative conditions like Parkinson's-associated dementias. Other biomarkers are graded and may reflect disease severity. This class of biomarkers may be useful for prognosis. Moreover, this graded feature may be valuable in treatment trials where it is necessary to determine whether the disease is responding to the treatment. Biomarkers that are graded in their informativeness are not necessarily categorical in their diagnostic informativeness. Several biomarker modalities are potentially available to help determine the neuropathological basis for a case of PPA. These include genetic studies, neuroimaging, and studies of blood, serum and cerebrospinal fluid analytes.³ I discuss each of these below.

Genetically related biomarkers in blood

Genetic analysis can reveal information about the pathology causing a FTLN syndrome. It can identify an inherited mutation in the portion of a chromosome coding for a particular protein, and many of these proteins are associated with one of the specific histopathologic abnormalities leading to PPA. This is particularly useful because familial disorders are

³An analyte is a constituent that is of interest in an analysis.

frequent in FTLT. Using a weak criterion of any family member with a dementia, up to 45% of index cases may have a positive family history (Chow, Miller, Hayashi, & Geschwind, 1999; Seelaar et al., 2008). Using more rigorous criteria such as the presence of a specific form of dementia in two first-degree family members in a three-generation family history, our series of over 300 index cases demonstrates a high-risk family history in 25.1% of probands (Wood et al., 2013). Testing for the most common genetic etiologies in all of these cases revealed a specific mutation in about 80% of cases.

The genetic status of an individual is valuable because each mutation reliably predicts a specific underlying histopathologic abnormality. Mutations of progranulin (*GRN*) on the q arm of chromosome 17 are invariably associated with FTLT-TDP pathology (Baker et al., 2006; Davidson et al., 2007; Gass et al., 2006; Mackenzie, 2007). Also, the recently identified hexanucleotide repeat abnormality in an open reading frame on chromosome 9 (*C9orf72*) is associated with FTLT-TDP pathology. Less common mutations associated with FTLT-TDP pathology include the gene coding for valosin-containing protein (*VCP*) on chromosome 9, for *CHMP2B* on chromosome 3, and a mutation in the region coding for TDP itself (*TARDDBP*) on chromosome 1. Other familial patients with a FTLT syndrome have a mutation in the region coding for the *MAPT* on chromosome 17. This is associated with FTLT-tau histopathology (Hong et al., 1998; Lee, Goedert, & Trojanowski, 2001; Zhukareva et al., 2001).

Several studies have investigated inherited causes of PPA, but a few studies have identified families with a mutation that specifically causes PPA. Moreover, PPA has been associated with an inherited abnormality in several carefully studied families. One report described two families with a mutation of *GRN* (Snowden et al., 2006). Both families had naPPA combined with a behavioural disorder. A second study reported two families where most individuals had a naPPA phenotype in association with a *GRN* mutation (Mesulam et al., 2007). There has been an attempt to define the clinical characteristics of PPA associated with a *GRN* mutation (Rohrer, Crutch, Warrington, & Warren, 2010). This is important because *GRN* mutations are invariably associated with FTLT-TDP pathology. It is important to note in this context that the clinical FTLT syndrome can be highly variable even in members of a single family with the identical mutation of *GRN* (LeBer et al., 2008; Leverenz et al., 2007). Indeed, the presence of a *GRN* mutation and a PPA phenotype do not appear to be highly correlated. Sixty per cent of 25 patients in one family with a *GRN* mutation and a progressive neurological disease were found to have reduced speech production for a variety of reasons, although only half of these patients had speech difficulty at presentation (more common was behavioural variant frontotemporal degeneration with apathy), and only three of these patients appeared to have PPA at presentation without accompanying inappropriate social behaviour (Becket et al., 2008). In another series of patients with a *GRN* mutation, PPA appeared to be relatively uncommon at presentation (initial diagnoses were frontotemporal degeneration, corticobasal syndrome and AD), although a language disorder did eventually emerge in many individuals (Rademakers et al., 2007).

Importantly, progranulin levels can be measured in plasma and cerebrospinal fluid (Carecchio et al., 2011; Finch et al., 2009). Thus, this may be a marker of disease

emergence and progression because levels of progranulin appear to decline as carriers of *GRN* mutations age. Moreover, in therapeutic trials for carriers of a *GRN* mutation, plasma progranulin levels can be used as a potential marker of response to a treatment intervention. Care must be taken in measuring progranulin levels in plasma because of significant background contaminants, and cerebrospinal fluid measures may be more reliable.

In patients with a *MAPT* mutation, characteristics of svPPA were observed more frequently, although this never appeared to occur without a preceding behavioural impairment (Pickering-Brown et al., 2008). A contrast of phenotypes across mutations showed a significant reduction of speech less often in patients with an *MAPT* mutation than a *GRN* mutation, although only about one third of patients with a *GRN* mutation exhibited characteristic aphasic features of a PPA variant, typically naPPA.

Genetically associated biomarkers also may play a role in defining the risk associated with a particular pathologic basis for a FTLN syndrome in sporadic cases. Tau haplotypes⁴ are derived from the region of chromosome 17 that spans the portion where the *MAPT* gene is represented. One haplotype, the H1 haplotype is over-represented in conditions associated with tau pathology such as corticobasal syndrome, progressive supranuclear palsy syndrome and sporadic FTLN (Houlden et al., 2001 ; Hughes, Mann, & Pickering-Brown, 2003; Pittman et al., 2004). Although relationships between tau haplotypes and tau pathology have been verified only rarely (Morris et al., 2002), the tau haplotype may play a role in defining the pathologic basis for PPA. One study associated the H1 haplotype with sporadic PPA (Sobrido et al., 2003).

Another potential genetically associated biomarker is the apolipoprotein E— ϵ 4 (ApoE ϵ 4) allele (form of the gene) of apolipoprotein E. This biomarker is associated with AD pathology, and thus the frequency of the ApoE ϵ 4 allele could potentially distinguish PPA due to AD from PPA due to FTLN spectrum pathology. The frequency of the ApoE ϵ 4 allele is not elevated in PPA due to FTLN spectrum pathology. However, it has also not yet been shown to be disproportionately elevated in PPA due to AD (Mesulam, Johnson, Grubic, & Weintraub, 1997; Mesulam et al., 2014, 2008; Rogalski, Rademaker, et al., 2011), so there is no evidence for ApoE ϵ 4 as a PPA biomarker to date. Indeed, all atypical presentations of early-onset AD, including lvPPA and posterior cortical atrophy with modest episodic memory deficits at presentation, have a lower frequency of ApoE ϵ 4 than late-onset AD (Mendez, 2012; van der Flier, Pijnenburg, Fox, & Scheltens, 2011).

A recent study proposed a risk biomarker associated with TDP-43 pathology. In this genome-wide association study of >500 autopsy-proven cases with FTLN-TDP pathology, the investigators reported that transmembrane protein 106B (*TMEM106B*) is a protein-coding gene, coded on chromosome 7p21, and is associated with an increased risk for the presence of TDP-43 pathology. However, this does not appear to be associated with a particular phenotype of frontotemporal degeneration.

⁴A haplotype is a set of DNA variations, or polymorphisms, that tend to be inherited together.

It is possible to measure TDP-43 levels directly in plasma. The proportions of FTLN patients (46%) and AD patients (22%) with elevated plasma levels of TDP-43 corresponded roughly to the percentages of these populations with TDP-43 detected in the brains at autopsy (Foulds et al., 2008). A follow-up study found significant correlations between plasma levels of phosphorylated TDP-43 and the density of FTLN-TDP brain pathology, although, critically, plasma levels of TDP-43 did not distinguish between patients with autopsy-proven FTLN and AD (Foulds et al., 2009).

Imaging biomarkers

While 20% of patients with FTLN have a genetic disorder that predicts underlying pathology (Wood et al., 2013), it is important to develop additional methods that can define the specific pathology responsible for sporadic cases of FTLN. Structural imaging such as MRI and functional imaging studies of glucose metabolism with positron emission tomography (PET) can reflect the distinct features of each PPA syndrome. While this work largely reflects the distribution of disease responsible for the clinical features of PPA, recent advances using multimodal MRI and PET radioligands (radioactive biochemical marker) have begun to provide information the pathology underlying PPA in an individual patient.

Consider first the distribution of grey matter disease associated with each PPA syndrome. naPPA appears to be related largely to anterior peri-Sylvian atrophy involving inferior, opercular and insular portions of the left frontal lobe (Gorno-Tempini et al., 2004; Peelle et al., 2008; Rohrer et al., 2011). This includes cases with autopsy-proven FTLN spectrum pathology (Grossman et al., 2013). This atrophy appears to extend to adjacent, anterior-superior regions of the left temporal lobe. svPPA has a different anatomic distribution of disease. Imaging studies associate this syndrome with left anterior temporal atrophy, affecting lateral and ventral surfaces of the temporal lobe as well as the anterior hippocampus and the amygdala (Agosta et al., 2012; Desgranges et al., 2007; Galton et al., 2001; Grossman et al., 2004; Mummery et al., 2000; Rohrer et al., 2009). lvPPA tends to be associated with atrophy in a left posterior-peri-Sylvian distribution affecting posterior temporal and inferior parietal regions (Bonner & Grossman, 2012; Gorno-Tempini et al., 2008, 2004; Rogalski, Cobia, et al., 2011 ; Rohrer, Ridgway et al., 2010).

Comparative imaging studies of grey matter atrophy across subtypes have been rare. These are important because they evaluate the specificity of disease and whether imaging characterisations can reflect specific forms of pathological disease. Some reports have focused on the distinction between FTLN and AD. One study compared patients with a fluent form of PPA, including five cases with AD pathology and five with FTLN with ubiquitinated⁵ (FTLN-U) pathology presumably due to TDP-43 (Josephs et al., 2008). Patients with AD pathology had T1 cortical atrophy in a temporal-parietal distribution with sparing of the hippocampus, but FTLN-U cases had sparing of parietal cortex. Likewise, reduced parietal cortex functioning was reported in PET or SPECT (single-photon emission computed tomography) scans of patients with pathologically confirmed naPPA due to AD compared to naPPA patients with non-AD pathology (Nestor et al., 2007), while FTLN-U

⁵Before it was possible to determine that ubiquitinated pathology was due to TDP-43, the neuropathological subtype testing positive for ubiquitin was referred to as FTLN-U.

cases had sparing of parietal cortex. A second report described cortical thinning in small groups of naPPA patients with tau-positive disease and svPPA patients with FTLN-U pathology (Rohrer et al., 2009). The naPPA patients showed superior temporal and inferior frontal thinning that was more prominent in the left hemisphere than the right hemisphere, and the svPPA patients showed prominent left anterior and inferior temporal thinning.

Another study assessed the validity of T1-weighted (which highlights contrast between grey and white matter in brain tissue) structural MRI to identify pathology in individual patients. This report examined 34 non-fluent PPA patients with autopsy- or cerebrospinal fluid-based evidence consistent with underlying FTLN or AD pathology (Hu et al., 2010). Subtle but statistically significant differences in the anatomic distribution of cortical atrophy in the FTLN and AD subgroups were observed, consistent with the findings described above. However, a receiver operating characteristic (ROC) curve analysis of MRI cortical atrophy revealed an area under the curve of only .64, with 72.7% sensitivity and 66.7% specificity. This suggests that assessments of grey matter disease for the purpose of defining the associated pathology are not likely to prove informative in individual patients with PPA.

Recent work also has demonstrated the utility of diffusion tensor imaging (DTI) studies of white matter to distinguish clinical syndromes. Studies of patients with naPPA have been reported to show reduced fractional anisotropy.⁶ In patients with autopsy-confirmed naPPA associated with FTLN spectrum pathology, for example, reduced fractional anisotropy has been demonstrated in superior longitudinal fasciculus, inferior frontal-occipital fasciculus, and uncinate fasciculus (Grossman et al., 2013). Studies of svPPA have shown reduced fractional anisotropy in white matter projections of the anterior temporal lobe (Acosta-Cabronero et al., 2011 ; Agosta et al., 2010). Several comparative studies have shown different patterns of white matter disease in patients with naPPA compared to patients with svPPA (Agosta et al., 2012; Borroni et al., 2007; Galantucci et al., 2011; Mahoney et al., 2011 ; Schwindt et al., 2013; Whitwell et al., 2010). Comparative DTI studies in patients with autopsy-confirmed disease have been very rare. Clinically diagnosed patients who had autopsy- or cerebrospinal fluid-based biomarkers consistent with FTLN or AD were evaluated with T1 MRI for grey matter disease and DTI fractional anisotropy for white matter disease (McMillan, Avants, et al., 2013). Significantly reduced fractional anisotropy was seen in FTLN compared to AD in the anterior corpus callosum and the inferior longitudinal fasciculus in the area of the uncinate.

While grey matter disease and white matter disease are each informative, analytic approaches that combine these two imaging techniques are statistically more informative (McMillan et al., 2014). One recent report combined T1 grey matter atrophy and DTI studies of white matter to classify 50 individual cases of clinically diagnosed FTLN who had autopsy- or cerebrospinal fluid-based findings consistent with FTLN or AD pathology (Avants, Cook, Ungar, Gee, & Grossman, 2010). These investigators used a statistical approach based on sparse canonical correlation analysis that selects the voxels from T1 and

⁶Fractional anisotropy is a measure often used in diffusion imaging studies that is thought to quantify the diffusion of water molecules along axonal tracts, where reduced fractional anisotropy reflects more random water diffusion thought to be seen in white matter disease.

DTI imaging that optimally explain the variance in each data set, and applies the resulting algorithm to categorise individual participants. In FTLT, changes were most prominent in frontal and anterior temporal regions, while changes in temporal–parietal brain areas were more evident in AD. The algorithm combining T1 and DTI accurately categorised 49 (98%) of the 50 participants. A follow-up study used the same, multimodal, canonical correlation analysis to relate imaging to language and cognition in a large cohort of patients (Avants et al., 2014). PPA patients with a language disorder showed grey matter and white matter changes in frontal and temporal regions of the left hemisphere, while AD patients with an episodic memory disorder showed changes in bilateral medial temporal lobe and precuneus distribution.

More recently, an analytic approach known as eigenanatomy used singular value decomposition to identify clusters of voxels in T1 imaging of grey matter and DTI studies of white matter that classified 35 patients with autopsy-proven or genetically identified FTLT-tau or FTLT-TDP (McMillan, Irwin, et al., 2013). A white matter region contributing significantly to the classification of patients was identified in the superior longitudinal fasciculus, and grey matter regions were in the angular gyrus, anterior temporal neocortex and the amygdala, and caudate. Consistent with the known intense burden of disease in FTLT-tau compared to FTLT-TDP, cross-validation using a leave-one-out approach demonstrated that the identified white matter region in superior longitudinal fasciculus was highly effective at predicting FTLT-tau or FTLT-TDP pathology. Classification was confirmed in the autopsy cohort by direct inspection of histopathology in these radiologically defined regions. The investigators thus validated their imaging studies by examining pathology in the superior longitudinal fasciculus identified by the imaging study, and demonstrated extensive tau pathology in the FTLT-tau cases but little TDP pathology in the FTLT-TDP cases.

While a variety of different histopathologic abnormalities can accumulate in each of the anatomic regions implicated in PPA, recent advances in PET metabolic imaging are poised to provide important advances in determining the specific cause of a PPA syndrome. This is because of the development of a tracer known as Pittsburgh Compound B (PiB) that can tag beta-amyloid ($A\beta$). $A\beta$ is one of the proteins that accumulates in AD, and thus PiB uptake is evident in AD (Klunk et al., 2004). By comparison, $A\beta$ should not accumulate in neurodegenerative conditions from the FTLT pathologic spectrum, including both tauopathies and TDP-43 proteinopathies, since these cases do not have $A\beta$ pathology. One report comparing patients with clinically diagnosed FTLT and patients with AD found reduced PiB uptake in eight of 12 FTLT patients (Rabinovici et al., 2007). A recent study of PPA by this group reported PiB uptake in a previously unreported four lvPPA patients, as would be predicted (Rabinovici et al., 2008). Signal was strongest in a left temporal-parietal distribution, consistent with the anatomic distribution of pathology in lvPPA due to AD. By comparison, PiB uptake was less common in other PPA syndromes: Left frontal uptake was seen in only one of six naPPA patients, and left temporal uptake was seen in only one of five svPPA patients. This is consistent with the results of reported clinical-pathological correlations. However, significant caution should be exercised since the results of imaging studies with PiB have only rarely been validated with autopsy confirmation. Moreover, in PPA patients with AD pathology, quantitative analyses of histopathologic burden do not

always correspond to the expected anatomic distribution of the PPA syndrome (Forman et al., 2006; Mesulam et al., 2008; Munoz, Woulfe, & Kertesz, 2007). Finally, PiB may be associated with false-positive results in ageing. Recently, tau radioligands have been developed for PET imaging (Maruyama et al., 2013), and the results of these studies may be informative for defining the histopathologic basis for other PPA cases with FTLT-tau pathology. Nevertheless, additional biomarker information is needed to help specify the cause of PPA syndromes during life.

Cerebrospinal fluid biomarkers

Another potential source of biomarker information comes from cerebrospinal fluid. This fluid bathes the brain. Moreover, cerebrospinal fluid contains crucial proteins such as tau and beta-amyloid ($A\beta$) that may directly reflect the underlying pathology of a patient with a PPA syndrome. Many studies have now shown that AD is associated with elevated cerebrospinal fluid levels of total tau and tau phosphorylated at its 181 phosphorylation site. This is combined in AD with reduced levels of $A\beta_{1-42}$ (a particular subtype of $A\beta$), and a ratio of total tau to $A\beta_{1-42}$ that is greater than .34 is highly indicative of underlying AD pathology.

Comparative studies have found a different pattern in FTLT relative to AD. About 20% of clinically diagnosed patients with FTLT had a significantly low level of cerebrospinal fluid tau compared to healthy controls, although this was never seen in patients with AD (Grossman et al., 2005). In a population of patients with known pathology, moreover, the ratio of total tau to $A\beta_{1-42}$ was significantly lower in FTLT compared to AD, and a ROC curve analysis demonstrated excellent sensitivity and specificity for distinguishing FTLT from AD (Bian et al., 2007). However, this study was unable to dissociate tau-positive disease from TDP-43 proteinopathies. This may have been due in part to the analytic platform (enzyme-linked immunosorbent assay, or ELISA) traditionally used to quantify these analytes in cerebrospinal fluid which has a relatively broad coefficient of variance. More recently, a multiplex assay based on flow-cytometry of antibody-coated fluorescent beads known as Luminex (INNO-BIA AlzBio3 xMAP; Luminex, Innogenetics) was developed that has a much narrower coefficient of variance (Shaw, Korecka, Clark, Lee, & Trojanowski, 2007). We were able to transform values obtained from ELISA to equivalent Luminex units using linear regression to create a larger autopsy/genetic-confirmed FTLT data set. This confirmed our previous observations of the diagnostic utility of the total tau to $A\beta_{1-42}$ ratio to differentiate FTLT from AD (Irwin et al., 2012). The higher $A\beta_{1-42}$ level found in FTLT compared to AD most likely reflects the absence of significant amyloid deposits in the brain. However, the biological basis for observed low cerebrospinal fluid total tau in some FTLT patients is uncertain. Nevertheless, while cerebrospinal fluid total tau may reflect non-specific CNS disease, cerebrospinal fluid level of total tau does appear to be related to underlying FTLT pathophysiology as total tau levels in FTLT patients correlate with relevant areas of grey matter atrophy on MRI studies (Grossman et al., 2005; McMillan, Avants, et al., 2013).

Recent cerebrospinal fluid studies have begun to differentiate between FTLT-tau and FTLT-TDP. This work is based on the principle that phosphorylated tau is abnormal and is

specifically related to hyperphosphorylation that is seen in neuro-degenerative diseases. In two studies assessing patients with clinical diseases highly associated with isolated FTLD-tau or FTLD-TDP, investigators demonstrated significantly elevated levels of phosphorylated tau in patients with presumed FTLD-tau pathology but negligible levels of phosphorylated tau in patients with presumed FTLD-TDP pathology (Grossman et al., 2014; Hu et al., 2013).

CONCLUSIONS

Taken together these findings suggest the importance of a multimodal approach to defining the pathology in cases of PPA during life. First, the diagnosis of PPA should be made clinically, and the specific PPA syndrome should be identified. Based on clinical-pathological studies, the specific variant of PPA will provide important screening information about the most likely cause of PPA. The presence of additional clinical features can be helpful in identifying the underlying pathologic abnormality in cases of PPA, and just as importantly, help identify less expected causes of PPA. Unfortunately, many of the useful clinical features tend to emerge later in the course of PPA. Longitudinal studies of PPA patients thus indicate that episodic memory difficulty suggests AD (Grossman et al., 2008), extrapyramidal features are consistent with corticobasal syndrome or progressive supranuclear palsy syndrome forms of tauopathy (Armstrong et al., 2013), and motor features are evident in amyotrophic lateral sclerosis/motor neuron disease that is associated with TDP-43 proteinopathy (McCluskey et al., 2014), but these clinical features tend to become evident well after the initial presentation and precluding their use as early diagnostic markers for pharmacological treatments (Brettschneider et al., 2013; Murray et al., 2007). Moreover, clinical observations such as these are less than definitive: corticobasal syndrome is difficult to diagnose (Armstrong et al., 2013; Boeve et al., 1999; Litvan et al., 1997), impaired memory can be difficult to ascertain in language-impaired patients (Libon et al., 2007; Nestor, Fryer, & Hodges, 2006), and motor neuron disease may be subclinical (Josephs, Parisi, et al., 2006; Lomen-Hoerth, Anderson, & Miller, 2002; Quinn et al., 2012).

This emphasises the urgent need for additional biomarkers that can be obtained routinely early in the course of PPA. Although no one biomarker is definitive in PPA, a combination of these biomarkers may be effective at defining the basis for disease in PPA. The identification of a genetic mutation in blood consistent with a tauopathy or a TDP-43 proteinopathy can provide definitive information about the etiology of a PPA syndrome, although a mutation leading only to PPA has not been identified. Recent multimodal neuroimaging work emphasises the informativeness of combined imaging studies of grey matter disease and white matter disease at defining the histopathologic basis for PPA. Metabolic imaging with agents such as PiB have the potential to identify lvPPA as well as unusual cases of AD presenting as a variant of naPPA or svPPA, although there are false-positives. Finally, the presence of a particular cerebrospinal fluid analyte profile also can contribute to defining the histopathologic cause of PPA during life. This will open the way for the administration of etiologically specific treatments for the underlying conditions and thus help us achieve a potential cure for the disease processes that cause PPA.

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