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Clinical Trajectories and Biological Features of Primary Progressive Aphasia (PPA)

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Abstract

Primary Progressive Aphasia (PPA) is a neurodegenerative syndrome characterized by a gradual dissolution of language, but relative sparing of other cognitive domains during the initial stages of the disease. Research has led to substantial progress in understanding the clinical characteristics, genetics, and neuropathology of this syndrome. This article reviews the clinical criteria for diagnosing PPA, discusses the utility of defining the *mild cognitive impairment* (MCI) stage of PPA, and highlights some of the more recent research advances particularly in the area of pathology and genetics.

Keywords

Frontotemporal dementia; dementia; anomia; semantic dementia; progressive nonfluent aphasia; primary progressive aphasia; frontotemporal lobar degeneration

INTRODUCTION

Primary Progressive Aphasia (PPA) is a clinical neurodegenerative syndrome initially described in a series of six patients for whom the term “slowly progressive aphasia” was coined [1]. The more descriptive term PPA was subsequently introduced [2]. More recently, core, ancillary, and exclusionary features have been specified (Table 1). These features are incorporated in the diagnostic criteria adopted by the National Alzheimer's Disease Coordinating Center (NACC) and the Uniform Data Set (UDS) of the Alzheimer's Disease Centers funded by the National Institute on Aging [3].

We use the term ‘dementia’ to denote any slowly progressive decline of cognition or behavior that undermines customary daily living activities and that is caused by neurological disease. Some dementias are characterized by salient memory loss, others are not. The characteristics listed in Table 1 help to differentiate the language-based dementia of PPA from the progressive amnesic syndrome also known as “dementia of the Alzheimer type” (DAT), and the behavioral variant of frontotemporal dementia (bvFTD). It is important to keep in mind that PPA, DAT and bvFTD are clinical syndromes, not neuropathological entities. In contrast terms such as frontotemporal lobar degeneration (FTLD) and Alzheimer's disease (AD) refer to neuropathological patterns identified by microscopy. This distinction helps to avoid at least some of the terminological inconsistencies encountered in the literature.

Perhaps one of the most confusing topics for caregivers, clinicians, and researchers has been the nomenclature associated with the PPA syndrome. Terms such as progressive nonfluent aphasia (PNFA), semantic dementia (SD), logopenic aphasia, aphasic variant of FTD, temporal variant of FTLT, Gogi aphasia, and Pick's disease (PD) have been used to describe various manifestations of the PPA syndrome [4,5]. In an attempt alleviate confusion, we propose the following scheme: 1) the term PPA should be used to refer to any patient who displays the overall *clinical syndrome* of a progressive language impairment that arises as the most salient initial feature of a neurodegenerative disease, 2) acronyms such as FTLT, AD and PD should be reserved for *neuropathological patterns* identified by microscopy; and 3) the subtyping into *clinical variants* (e.g. semantic, logopenic, and agrammatic) of PPA should be reserved for the specialist. We prefer the PPA term because of its descriptive transparency (clinicians can readily recognize an aphasia and determine it is progressive) and because it is free of preconceived notions about the underlying neuropathology [6,7].

THE PRECLINICAL AND PRODROMAL STAGES: AN APHASIC MCI?

Specifying the time of onset of a neurodegenerative syndrome is notoriously difficult. Upon taking a history, it is sometimes possible to identify a prodromal stage, prior to diagnosis. During that interval some patients report feeling that finding words became more effortful. There may be no word-finding pauses as the patient rapidly substitutes a slightly less apt word for one that cannot be retrieved. Colleagues and family members may be unable to detect the problem at that stage and may attribute the patient's complaints to stress. This "subjective" prodromal stage may last for up to a year. In other patients, the initial manifestations of PPA include infrequent word-finding pauses, occasional spelling errors, a slowing of reading, sporadic reversals of word order, and rare misinterpretations of word meaning. Friends and family may notice the problems but fail to pay much attention because of their transient nature. In most instances, it is the patients who have the greatest awareness of the language problems, substantially before they are noticeable by family or measurable by the clinician.

In time, the impairments, although still very mild, become chronic and allow the clinical diagnosis to be reached, according to the features listed in Table 1. The clinical diagnosis of very early PPA is usually based on the presence of mild but persistent word-finding pauses initially confined to low-frequency words, impaired object naming (anomia), abnormalities of syntax, poor spelling, and word comprehension errors. These impairments can be dissociated so that one patient may initially have only syntax problems, another only single word comprehension impairments and still others only word-finding impairments even in the absence of object naming problems. Upon formal neuropsychological evaluation the patient shows isolated difficulty on tests of language with relative preservation of other cognitive domains and activities of daily living (ADL).

These prodromal and early stages could conceivably be designated the "mild cognitive impairment (MCI)" stage of PPA. However, the usefulness of such a designation is unclear. The MCI designation is of considerable value in the Alzheimer-type amnesic dementias (DAT) because declining memory is also a feature of "normal" aging. It is therefore useful to have a specific designation for the borderland between normal aging and an amnesic dementia, especially because some MCI cases may never progress to the dementia stage. The same cannot be said for PPA. Word finding, spelling and syntax abnormalities are not part of normal aging. In fact language is quite resistant to age-related changes. The presence of a new language disorder is therefore always abnormal and deserves the PPA designation if it can be attributed to a neurodegenerative process.

ADVANCED STAGES

As the disease progresses the severity of the language impairment becomes more pronounced (Fig. 1). However, the rate of progression and pattern of decline vary by patient [8,9]. In some patients, language may be the only area of major impairment for up to 10 years. It has been suggested that decline may be more rapid in woman than men [10].

Since PPA is caused by progressive neurodegeneration, patients may eventually display additional deficits. Some PPA patients may develop memory disorders (reminiscent of DAT), others personality changes (reminiscent of bvFTD), motor neuron disease (of the type seen in ALS), or asymmetric extrapyramidal deficits (of the type seen in the corticobasal degeneration syndrome, CBDS), underlining the lack of rigid boundaries in neurodegenerative syndromes. We use the term “PPA+” to designate these patients who initially fulfilled the diagnostic criteria for PPA, but currently show clinical deficits that are no longer confined to aphasia, Fig (1). This practice allows us to fit clinical diagnostic terms to the presenting features of the neurodegeneration rather than to the less specific and widespread distribution of advanced disease. Recent studies examining the trajectory of PPA progression suggest that the semantic subtype may have a closer association with behavioral dysfunction typical of bvFTD (including manifestations such as disinhibition and eating disorders) [11] whereas the agrammatic subtype (also known as PNFA) may be more closely associated with corticobasal degeneration (CBD) [8].

In other patients a progressive aphasia may emerge almost simultaneously with equally prominent memory, behavior, motor neuron, or extrapyramidal deficits. These patients do not fit the diagnostic criteria for PPA. We tend to describe them as “DAT with aphasia”, “bvFTD with aphasia,” “MND with aphasia” or “CBDS with aphasia”.

CHALLENGES IN DIAGNOSIS AND SUBTYPING

The diagnostic criteria for PPA specify the relative preservation of non-language cognitive domains. One hurdle in assessing such cognitive abilities is that most neuropsychological tests are verbally mediated, creating a distinct disadvantage for individuals with PPA. Modification of standardized tests, development of nonverbal measures, and caregiver interviews may help to circumvent this problem. Through such a strategy, it became possible to demonstrate the preservation of reasoning and cognitive flexibility in PPA [12].

Patients with PPA resist easy classification into the traditional subtypes used in the stroke literature such as Wernicke's or Broca's Aphasia. We currently use a modification of a classification proposed by Gorno-Tempini and colleagues [13], according to which the *agrammatic*, *semantic*, and *logopenic* subtypes can be delineated. The agrammatic subtype (partially overlapping PNFA) is characterized by poor syntax and fluency but good comprehension; the semantic subtype (partially overlapping SD) is characterized by poor comprehension but good syntax; and the logopenic subtype (partially overlapping PNFA) is characterized by good syntax and comprehension but frequent word-finding pauses. A considerable number of patients with the logopenic subtype may display prominent deficits in phonological loop functions such as digit, letter and word span [14]. Subdividing PNFA into the agrammatic and logopenic subtypes is useful in predicting the underlying neuropathology as will be shown below. Patients who have abnormalities of syntax and single word comprehension can be described as having a *mixed* form of PPA. This subtyping system is still evolving and some PPA patients fail to fit neatly into these subtypes, or may transit from one to the other in time.

NEUROPSYCHOLOGY

Measurements of basic and instrumental activities of daily living (ADL) showed that PPA patients are functionally independent in most activities other than those that rely on communicative abilities. This study suggested that the ADL scale may capture the functional capacities of PPA patients more accurately than language-based cognitive tests that tend to overstate deficits because of the aphasia [15].

In our experience, autobiographical memory and nonverbal memory are relatively preserved whereas verbal memory is often compromised, probably as a consequence of the aphasia [16]. Object naming difficulties (anomia) in PPA can be attributed, at least in part, to semantic interference caused by noisy lexical encoding so that the appropriate noun cannot be differentiated from semantically related distracters [16-18]. This phenomenon is akin to the gradual slowing of target detection in a spatial detection task as distracters look more like the target. Other factors contributing to the anomia include phonological disintegration and abnormalities of lexical retrieval.

STRUCTURAL AND FUNCTIONAL NEUROANATOMY

Structural and functional imaging show that the clinical focality of PPA is matched by the anatomical selectivity of damage to the language network. Voxel based morphometry (VBM) studies, have confirmed that PPA is characterized by strongly asymmetrical atrophy revolving around the left perisylvian cortex but also extending into neighboring areas [13,19]. Functional studies, such as the one by Sonty and colleagues [20], suggest that disrupted language processing in PPA may reflect an impairment of information transfer within the language network rather than a failure in the activation of major network nodes such as Wernicke's and Broca's areas.

Structural and metabolic imaging (single photon emission computed tomography, SPECT and positron emission tomography, PET) usually shows a distinctly asymmetric distribution of atrophy and hypometabolism favoring the language-dominant (usually left) hemisphere [19, 21]. Metabolic imaging may reveal abnormalities prior to the development of atrophy in structural scans. Magnetic resonance spectroscopy showed axonal pathology in the left hemisphere arcuate fasciculus, an axonal bundle that interconnects perisylvian and temporal components of the language network [22]. Nearly all components of the distributed perisylvian/temporal language network can become involved, the exact pattern differing from patient to patient.

The cortical atrophy tends to be mostly in the perisylvian region in the agrammatic and logopenic variants of PPA but extends into anterior and medial temporal cortex in the semantic variant [13,23,24]. In the perisylvian region the atrophy is most prominent in the temporoparietal junction in the logopenic subtype and in the inferior frontal gyrus in the agrammatic subtype [13,25].

NEUROPATHOLOGY

Most patients (60-70%) with PPA who have come to autopsy show changes consistent with a diagnosis of frontotemporal lobar degeneration (FTLD). The FTLD pathology is characterized by tauopathy in some patients (FTLD-T), and TDP-43 proteinopathy in others (FTLD-TDP). The tauopathy in the FTLD-T group may include Pick-, CBD- or PSP-type inclusions. The FTLD-TDP group is characterized by tau-negative nuclear and cytoplasmic inclusions containing the TDP-43 protein. This subtype used to be known as FTLD-U because the inclusions were initially identified through their ubiquitin content. The other 30-40% of PPA patients have shown AD pathology [1,26,31].

A recent study in our laboratory investigated factors that could predict AD versus FTLT pathology in 23 consecutive autopsies in patients with the clinical syndrome of PPA [32]. Patients were classified into PPA subtypes and results showed that all of the agrammatic patients had FTLT pathology, 80% with FTLT-T, while the majority of the logopenic patients had AD. Results from other autopsy series show that the semantic PPA subtype is most commonly associated with FTLT-TDP [33].

In the same series of 23 patients, the distribution of AD pathology in patients with the clinical diagnosis of PPA was charted and quantitatively compared to that of patients with the amnesic DAT profile and a neuropathological AD diagnosis. The goal was to determine whether AD pathology in PPA is atypically distributed to fit the uncharacteristic aphasic phenotype [32]. In other words, we wanted to find out whether the AD pathology in these patients was more extensive in the preferentially atrophied left perisylvian areas than in the corresponding areas of the right hemisphere. Secondly, we also wanted to find out whether the ratio of perisylvian to entorhinal pathology was greater in the PPA patients (i.e., patients who did not have a salient amnesia) than in the characteristically amnesic DAT patients. Results indicated that there was no consistent asymmetry or neocortical preponderance of AD pathology in PPA. It appears, therefore, that there is no clinicopathological concordance between the anatomic distribution of AD markers and either the behavioral neuroanatomy of the aphasia or the preferential location of atrophy. Equally puzzling was the finding that the e4 allele of apolipoprotein E, a major risk factor for AD pathology in the DAT population, was not a risk factor for AD pathology in the PPA group. These findings raise the possibility that the AD markers detected by the neuropathologist 10-15 years after disease onset, at a time when the clinical picture has lost all specificity, may not reflect the nature of the disease process responsible for the initial PPA phenotype and that there may be another concomitant process that eventually becomes overshadowed by age-related accumulations of AD markers.

GENETICS, EPIDEMIOLOGY, AND RISK FACTORS OF PPA

The vast majority of PPA cases are sporadic. A very small minority belong to families with point mutations on chromosome 17 in genes that encode tau or progranulin (PGRN) [34]. In many of the genetic forms, some family members have the bvFTD phenotype, others the PPA phenotype. Recently, two families, PPA1 and PPA3, have been reported where all affected family members had PPA. Three of 4 siblings in one kindred and 2 of 3 in the other had typical PPA and mutations in the progranulin gene (PGRN) on chromosome 17, leading to a haploinsufficiency syndrome [34]. In the PPA1 family, in which 3 autopsies were performed, tau-negative but ubiquitin-positive FTLT neuropathology was found in the 2 affected members but not in the unaffected sibling. Although these autopsy results were obtained before the role of TDP-43 in FTLT was discovered, it is quite likely that the neuropathology in this family is also characterized by TDP-43 proteinopathy and that the pathology will be classified as consistent with FTLT-TDP. Language fluency and comprehension varied among patients in the PPA1 and PPA3 families and changed as the disease progressed so that the PGRN mutation was not associated with a particular subtype of PPA.

Neither age nor the e4 allele of apolipoprotein E are risk factors for typical PPA. Symptom onset usually occurs before the age of 65 and more men than women are reported as having PPA [35,36]. This demographic profile differs from that of the DAT syndrome, an amnesic dementia in which the majority of patients have disease onset after the age of 65, in which prevalence is slightly higher in females and in which the e4 allele is a major risk factor [37, 38].

Learning disabilities, especially dyslexia, may be more frequent in PPA patients and their first degree relatives, suggesting a familial vulnerability of the language network to developmental

delay and degeneration [35,39]. Men with PPA were found to have a higher incidence of vasectomy than those without PPA. According to one speculation, vasectomy may be a risk factor through an autoimmune phenomenon based on shared antigens expressed by brain and semen [40].

TREATMENT AND THERAPEUTIC STRATEGIES

There are currently no approved medications for the treatment of PPA or FTLD. A controlled clinical trial with bromocriptine yielded marginal results [38] and preliminary analyses of a recently completed study with memantine are not promising. Our uncontrolled clinical experience with cholinesterase inhibitors has been negative.

Some patients can learn sign language, others find it useful to carry laminated cards with specific messages, still others benefit from voice synthesizers or laptops containing digitally stored words and phrases. An evaluation by a speech therapist is useful for exploring alternative communication strategies [41].

MOOD, CAREGIVER BURDEN AND PSYCHOSOCIAL IMPACT OF PPA

Given the relatively early age of onset, the preservation of insight, and the relentless progression of the disorder, it is not surprising that depression is common among patients and their families. A factor analysis of the Geriatric Depression Scale (GDS) showed that many patients endorsed symptoms of social withdrawal and lack of mental and physical energy, suggesting that patients with PPA should be evaluated for depression so that they may be appropriately treated [42].

Support groups, educational care conferences and other initiatives for expanding awareness of non-Alzheimer dementias are becoming increasingly more common. The Cognitive Neurology and Alzheimer's Disease Center (CNADC) at Northwestern University conducts education and support conferences focusing on PPA and bvFTD for caregivers, patients and health care professionals [43]. A list of programs can be found at www.brain.northwestern.edu.

The University of California at San Francisco (UCSF) Memory and Aging Center has launched a YouTube channel on the internet to promote the spread of knowledge and understanding of PPA and FTD. Using this link, <http://www.youtube.com/ucsfmemoryandaging> one can find short video summaries relating to PPA including, symptoms of the disorder, tips for caregiving, and the importance of autopsy.

The Association for Frontotemporal Dementias (AFTD), which was founded in November of 2002, has initiated a national effort to raise public and legislative awareness, educate patients and caregivers, and search for effective treatments. The AFTD has produced a newsletter, launched a website (www.ftd-picks.org) and started annual meetings. Their website serves as a hub for distributing news relevant to PPA and FTD.

CONCLUSIONS

Primary progressive aphasia is a clinical syndrome that needs to be considered in the differential diagnosis of dementia. The diagnosis is easily made on the basis of an initially isolated progressive language impairment. Other neurodegenerative syndromes can also become associated with language disturbances but the resultant aphasias are not "primary" because they are neither the most salient feature of the clinical picture nor early in onset. Four clinical variants, agrammatic, semantic, logopenic and mixed, can be identified. The rules for subtyping are still evolving and will impact the ability to predict the underlying neuropathology in PPA patients. The utility of delineating prodromal and early stages of PPA may be useful in understanding progression and allow earlier therapeutic interventions.

Despite the clear advances in the understanding of the clinical syndrome, there is currently no effective pharmacological treatment for PPA and this remains the single most important challenge facing this field. Hopefully, the increased interest in this disorder will lead to significant advances in clinical recognition, pathophysiological elucidation, and therapeutic intervention.

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Fig. (1).
Clinical trajectory of PPA. Not all patients progress to the PPA+ stage.

Table 1

Core, Ancillary, and Exclusionary Criteria for Primary Progressive Aphasia (Adapted from Mesulam and Weintraub 2008)

<p>Descriptive clinical profile: An aphasic dementia where the language impairment (aphasia) emerges in relative isolation and is the major determinant in the limitation of daily living activities. Perception, memory, personality are relatively preserved during the initial 1-2 years.</p>
<p>Core diagnostic features: These features are integral to the clinical syndrome. Both must be present for making the diagnosis.</p> <ul style="list-style-type: none"> ∞ Insidious onset and gradual progression. ∞ Early onset of aphasic disturbance (including any combination of the following): <ul style="list-style-type: none"> ○ Word-finding pauses, word comprehension deficits, naming impairments, circumlocutions, impaired grammar and syntax, syntactic comprehension deficits, new spelling errors.
<p>Ancillary Clinical features: These non-linguistic features are not present in all patients but their presence is consistent with the diagnosis.</p> <ul style="list-style-type: none"> ∞ Onset before the age of 65, dysarthria, ideomotor apraxia, dyscalculia, mild facial flattening on the side opposite the language-dominant hemisphere (usually right side of the face), asymmetrical upper extremity posturing upon stressed gait on the side opposite the language-dominant hemisphere, mild rigidity on the side opposite the language-dominant hemisphere.
<p>Investigations: The neuropsychological findings are present in all patients if the proper tests are used. The other test findings may not be present in all</p> <ul style="list-style-type: none"> ∞ <u>Neuropsychology</u>: findings of aphasia in the absence of equally prominent amnesia, prosopagnosia, associative visual agnosia, apathy, and disinhibition. ∞ <u>MRI or CT</u>: perisylvian atrophy that can extend to parietal cortex and/or inferior or anterior temporal cortex on the side of language dominance (usually left). ∞ <u>PET or SPECT</u>: asymmetrical hypometabolism in the language-dominant hemisphere (usually left). ∞ <u>EEG</u>: asymmetrical slowing in the temporal leads of the language dominant hemisphere (usually left).
<p>Exclusionary features:</p> <ul style="list-style-type: none"> ∞ Abrupt onset ∞ Brain imaging showing lesions other than focal atrophy that can account for the aphasia.