Essentials of Primary Progressive Aphasia

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INTRODUCTION

Acquired language disorders are known as aphasias. Progressive aphasias can arise in the course of many neurodegenerative diseases, including Alzheimer's disease (AD), motor neuron disease (MND), corticobasal degenerations (CBD), frontotemporal dementia (FTD) and dementia associated with posterior cortical atrophy (PCA). While such patients can be said to have progressive aphasias, their language impairment is neither the dominant component of the clinical picture nor its initial feature.

In a unique group of patients, a slowly progressive aphasia arises in relative isolation, becomes the principal cause of restrictions in daily living activities, and remains the most salient aspect of the clinical picture for many months. Other cognitive and behavioral domains, while not necessarily intact, are less impaired than language. Such patients are said to have a *primary* progressive aphasia or PPA. In contrast to the clinical syndrome of probable Alzheimer's disease (PRAD), which designates a memory-based (amnestic) dementia, or frontotemporal dementia

(FTD), which designates a behavior-based (comportmental) dementia, PPA designates a language-based (aphasic) dementia. The PPA syndrome has been described in native speakers of nearly all major language groups, including Turkish.[1]

CLINICAL FEATURES AND DIAGNOSIS

Primary progressive aphasia is diagnosed when other mental faculties such as memory for daily events, visuospatial skills (assessed by tests of drawing and face recognition), and comportment (assessed by history obtained from a third party) remain relatively intact; when language is the only area of major dysfunction early in the disease; and when structural brain imaging does not reveal a specific lesion, other than atrophy, that can account for the language deficit.[2-4]

Standardized neuropsychological tests are helpful for reaching an early diagnosis.[5-7] However, a strict reliance on neuropsychological tests, most of which depend on verbal instructions, verbal responses, or covert verbal reasoning, may occasionally lead to the erroneous conclusion that areas other than language are also impaired. Scores on the Mini Mental Status Examination (MMSE),[8] for example, can exaggerate the degree of disability. Although the language disorder in primary progressive aphasia may interfere with the ability to memorize word lists or solve reasoning tasks, the patient typically has no difficulty recalling daily events or behaving with sound judgment, indicating that explicit memory, reasoning and social skills remain relatively intact.

In some patients, the principal signs and symptoms are confined to the area of language for as many as 10-14 years. In others, impairments in other cognitive functions can emerge after the initial couple of years, but the language dysfunction remains the most salient feature and deteriorates most rapidly through many years.[5] Primary progressive aphasia is a form of dementia since it causes a gradual cognitive decline to the point where daily living functions become compromised. It is also an unusual dementia since core memory functions remain largely preserved. In contrast to many patients with AD who tend to lose interest in recreational and social activities, some patients with primary progressive aphasia maintain and even intensify their involvement in complex hobbies such as gardening, carpentry, sculpting and painting.

Primary progressive aphasia should be differentiated from states of pure progressive dysarthria, speech apraxia, or phonological disintegration where the formation rather than usage of words becomes disrupted.([9]) It should also be differentiated from the syndromes of probable Alzheimer's disease (PRAD) and frontotemporal dementia (FTD) where word-finding disturbances (anomia) or a paucity of speech output (economy of speech) may arise, but on a background of more salient impairments of memory (in PRAD) and behavior (in FTD).

Core Diagnostic Features and Confirmatory Investigations

The *prominence of language impairments in the initial stages* and the *insidious onset and progression of symptoms over months to years* are the two necessary core features. The early stages during which the language disorder remains the most salient symptom and the principal source of restrictions in daily activities should last 1-2 years. In many instances, the patient is the first to detect a problem, usually in the form of word-finding hesitations. These initial complaints are occasionally attributed, by family members and even physicians, to stress or depression. No single type of language disorder is pathognomonic of PPA. The most common initial sign of primary progressive aphasia is a word-finding and naming impairment known as "anomia." As the language impairment becomes established, it can be fluent (that is, with normal articulation, flow, and number of words per utterance) or non-fluent (that is, with decreased mean lenght of utterance or slow output) and may or may not impair phonology, syntax or verbal semantics (comprehension of word meaning).([5,10-14]) Written language may be less impaired than spoken language but spelling errors (dysgraphia) are common. In many, but not all patients, neurodiagnostic investigations reveal asymmetric EEG slowing, hypoperfusion, hypometabolism and atrophy on the language-dominant (usually left) hemisphere.

Supportive Features

In addition to the core diagnostic features, PPA patients display common features that support the diagnosis without being necessary for it. Age of onset has ranged from the 40s to 80s. However, the majority of patients have had a *presenile onset*, before the age of 65. *Dysarthria* can occasionally arise and becomes one of the factors undermining fluency. *Ideomotor apraxia* is common. In some patients, it takes the form of "sympathetic dyspraxia" where the left hand cannot pantomime the movements related to the usage of the tool mentioned by the examiner. A

more frequent ocurrance is the presence of an isolated buccofacial apraxia so that the commands to "cough" or "lick crumbs from the lips" cannot be followed even though the patient understands the instructions and can perform the movements spontaneously when the need arises. *Dyscalculia* is very common, reflecting the anatomical proximity of the brain areas necessary for language and calculations. In some patients, the dyscalculia emerges early and becomes as prominent as any other of the aphasic impairments. A careful neurological examination can reveal subtle *asymmetrical pyramidal or extrapyramidal signs* reflecting the dysfunction of the language-dominant (usually left) hemisphere. These signs include mild flattening of the nasolabial fold, widening of the palpebral fissure, asymmetrical posturing of the hand while walking on the heels or edge of the feet, and mild cogwheeling rigidity induced when the other hand is engaged in repetitive tapping movements. In some instances, asymmetric extrapyramidal findings can be quite prominent, confirming the strong relationship of PPA to CBD.([15])

Exclusionary Criteria

An abrupt onset of the aphasia excludes the diagnosis of PPA. Additional exclusionary criteria include the *early* salience of motor deficits, amnesia, abnormal comportment, associative agnosia, or visuospatial disorientation. Such patients are said to have motor neuron disease, progressive supranuclear palsy, typical CBD, probable AD, frontotemporal dementia, semantic dementia (agnosic variant) or the syndrome of posterior cortical atrophy, accompanied by a non-primary progressive aphasia. Brain imaging is necessary since any finding other than atrophy that can account for the aphasia (such as neoplasm, ischemic lesions or cortical ribboning) rules out the diagnosis of PPA.

The "PPA-Plus" Diagnosis

Additional cognitive, behavioral and motor deficits that independently influence daily living activities eventually arise in the middle or late stages of the disease. We have used the descriptive term "PPA-plus" (PPA+) to designate the fact that the patient had initially fulfilled the diagnostic criteria for PPA but that the current clinical deficits are no longer confined to the aphasia.

Retrospective Informant-Based Diagnosis

Diagnosing PPA is easiest when the patient is examined in early stages. Occasionally, the clinician will see a patient at a more advanced clinical stage, at a time when the selectivity of aphasia may no longer be ascertainable because of language comprehension deficits or because deficits in other domains have emerged after the initial stages of relatively isolated aphasia. In such cases, a structured interview with informants can be used to establish whether the aphasia had emerged in relative isolation. A diagnosis of PPA-Plus is made if such an interview confirms that the diagnostic criteria had been met during an earlier phases of the disease in a patient who has since developed additional deficits.

SUBTYPES OF PPA

PPA patients generally resist classification into traditional subtypes such as Broca's, Wernicke's, or Conduction Aphasia. Following the lead of Gorno-Tempini and colleagues,[16] we currently recognize three PPA subtypes, agrammatic, semantic, and logopenic. It should be pointed out, that the clinical diagnosis of PPA is quite straightforward whereas the assignment of an individual patient to one of these subtypes may be quite challenging, and may best be reserved for research purposes.

PPA- Agrammatic/Dysfluent Subtype

This subtype is characterized by early and prominent agrammatism (in spoken and written language) in the absence of single word comprehension deficits. Output tends to be impoverished in function words but may be enriched in meaning-appropriate nouns and verbs, giving speech a "telegraphic" and pithy quality. Sentences display abnormal word order (syntax) and the inappropriate deployment of *bound morphemes* (word endings used to denote tenses, possessives, or plurals). For example, the daughter of one of our patients first realized that there was something wrong with her mother when she received the following e-mail: "I will come my house in your car and drive my car into Chicago…You will back get your car and my car park in my driveway. Love, Mom."

Patients in this subgroup may also show a selective comprehension deficit for grammatically complex sentences such as those with passive voice, posessives, and embedded clauses. In general, these patients have no difficulty understanding casual conversation or single words. Some patients in this group display the remarkable finding of grammatical alexia: they can read nouns such as "alligator" or "house" but not pronouns such as "he" or "she."

Fluency, as determined by word outflow per minute or by mean length of utterance, is usually decreased and speech may be halting, labored and effortful but not necessarily dysarthric. Speech apraxia and phonological disintegration may distort speech but not in any recognizable pattern of dysarthria. Frequent word-finding pauses may emerge and naming is more impaired for verbs than nouns.[17] The critical findings for this subtype include agrammatism (usually associated with low fluency) in the presence of preserved comprehension for single words and sentences, except those that are grammatically complex.[3,16,18] Thus subtype overlaps with the progressive nonfluent aphasia (PNFA) term in the literature.[19]

PPA- Semantic Subtype

The core feature is the early onset of prominent word comprehension deficits in the absence on major agrammatism.[3,16,20] Fluency is usually preserved, but circumlocutions and word-finding pauses can also emerge, leading to intermittently dysfluent, halting speech. At the initial stages, the patient may follow most conversation except for frequent "lexical-semantic lacunes." In the course of an otherwise uneventful conversation, for example, the patient may suddenly assume a perplexed expression and ask: "school? What does 'school' mean?" Many of the naming deficits at this stage are "2-way" so that the patient can neither name an object nor point to it when the examiner provides the name. This represents a state where the semantic "knowledge" related to the object cannot be accessed through the verbal route. In contrast, the knowledge related to the same object can be accessed through the visuoperceptual route since the patient can describe (through circumlocutions, paraphasias and pantomime) the nature of the object shown by the examiner. The preserved ability to surmise the nature of the object shows that the patient has no associative agnosia. In time, even the most common words fail to be understood and the comprehension of sentences during conversation becomes impossible. Reading and writing are frequently impaired but may initially remain relatively more preserved than spoken language.

These are the most challenging patients to evaluate since the inability to comprehend questions may give the mistaken impression of global cognitive deficits.

PPA- Logopenic/Anomic Subtype

The core features of this subtype include an anomia without early agrammatism or comprehension deficits. In our experience, the majority of PPA patients belong to this group. The anomia can be *intrinsic*, in which case the patient cannot find the word to express the intended verb or noun, leading to halting but syntactically correct speech interspersed with word-finding pauses, or *extrinsic,* in which case the major difficulty is in naming objects and actions in the environment. These two types of anomia can be dissociated from each other. Extrinsic anomia is diagnosed by poor performance in naming tests such as the BNT. Intrinsic anomia is characterized by word-finding pauses in the absence of agrammatism, a pattern for which we coined the term logopenic.([21]) Patients with intrinsic anomia learn to circumvent the use of words they cannot retrieve and can produce fluent but circumlocutious and simplified sentences lacking in verbs and nouns (for example, a patient who says "the thing that you use to put it in" instead of "hammer"). When asked to be specific (for example, about the technical details of their occupation) paraphasias and word-finding pauses emerge and the patient becomes non-fluent. Conversely, patients with an extrinsic anomia may be quite fluent when describing complex ideas but may become non-fluent when asked to describe a scene (such as the one depicted in the Cookie Theft) where objects need to be named. Comprehension is preserved well into the middle and late stages. Object naming is abnormal in patients with extrinsic anomia but may be normal in some patients with a predominantly intrinsic anomia. This is almost always a 1-way deficit so that the patient cannot name the object but can point to it when the name is given by the examiner. It therefore represents a lexical access deficit.

Relationship to the "Neary Criteria"

In 1998, an influential set of criteria were proposed for three major subtypes of frontotemporal lobar degeneration (FTLD).([19]) Two of the three FTLD subtypes, progressive non-fluent aphasia (PNFA), and semantic dementia (SD) have characteristics that overlap with PPA. The PNFA

subtype is almost completely overlapping with the agrammatic PPA subtype. The relationship to SD is more complex. Neary and colleagues listed a loss of language comprehension, prosopagnosia and associative agnosia as core features of SD, stipulating that "all features must be present to fulfill the criteria for diagnosis." If these instructions are taken literally, no SD patient would fit the PPA diagnosis because of the concommitant and presumably early prosopagnosia and associative agnosia. In common practice, however, many clinicians use the SD designation in a variant sense, making this diagnosis when a patient has an isolated fluent aphasia that impairs word comprehension even in the absence of any agnosia. Such patients (constituting an aphasic variant of SD) would overlap with the semantic subtype of PPA.

Neither the SD nor PNFA subtypes of Neary et al. incorporate the logopenic/anomic subtype of PPA.[16] The logopenic/anomic subtype does not fit the PNFA criteria because the patients can be halting and dysfluent (due to word-finding pauses) but not agrammatic, and it does not fit the SD criteria because comprehension is preserved. The logopenic subtype encompassed approximately a third of the Gorno-Tempini et al. sample[16] and is by far the most common subtype seen in our clinical paractice.

LONGITUDINAL COURSE

Early-Stage PPA
The distinctive features characteristic of the PPA subtypes are most clearly identified in the early stages of the disease, usually within the first two years after symptom onset. This is the stage at which the predominance of the aphasia is most obvious. Even at these early stages, however, all other domains need not be absolutely normal. On occasion, patients with early PPA may also show mild ideomotor (usually buccofacial) apraxia, dyscalculia, disinhibition, and constructional deficits. These additional signs reflect a spread of dysfunction to prefrontal and parietal cortices immediately adjacent to the language network. However, deficits in non-language domains, if present, are minor relative to the language impairment and do not contribute to the limitations of daily living activities in any major way.

Mid-Stage PPA

As the symptomatology progresses, more pronounced deficits in other domains may emerge. The most common are in the areas of executive function and comportment. Some of our patients develop apathy, start to show signs of poor judgment, excessive joviality, inappropriate conviviality, and blunted foresight. Others may show memory deficits for recent events. Still others may develop face and object recognition deficits that compound the impact of the aphasia. In the majority of our patients these non-language deficits have been less salient than the aphasia, progressed less rapidly, and had a lesser impact on daily living activities. Mild pyramidal and especially extrapyramidal deficits on the side of the body contralateral to the hemisphere dominant for language (usually left) may tend to emerge. This is the stage at which the diagnosis of PPA+ may be considered as described above.

End-Stage PPA

As the end-stages are reached, all patients gravitate toward a state of global aphasia characterized by severe comprehension deficits and and a severe loss of fluency. Output becomes limited to single words, pallilalic syllables, or grunts. It becomes impossible to infer cognitive state. Behavior may range from apathy to severe agitation.

FUNCTIONAL AND STRUCTURAL NEUROANATOMY

The majority of patients with PPA display focal atrophy, EEG slowing, hypoperfusion (measured by SPECT) and hypometabolism (measured by PET) centered in the perisylvian region of the language-dominant hemisphere (usually left) where the core components of the language network are located. These structural and physiological abnormalities frequently extend into the adjacent frontal, insular, temporal, and parietal components of the language network.[2,22-24] Two voxel based morphometry studies, involving a total of 42 patients have confirmed that PPA is characterized by strongly asymmetrical atrophy revolving around the left perisylvian cortex but also extending into neighboring areas.[16,25] Other parts of the brain, including the entire right hemisphere, may remain relatively intact well into the middle and late stages of the disease.[22,23] In the rare patients with right hemisphere dominance for language, the atrophy is centered in the right perisylvian region.[26] The clinical focality of PPA is thus matched by the anatomical selectivity of the underlying pathological process for components of the language network.

Abnormalities of blood flow and metabolism may emerge prior to the detectable atrophy. When asked to identify homonyms or synonyms in the course of functional MRI experiments, PPA patients and age-matched controls activate the same components of the language network.[25] However, in contrast to neurologically intact subjects, the PPA patients display additional aberrant activations within regions of the brain outside of the classic language network.[25,27] It is not yet clear whether these aberrant activations reflect compensatory processes or abnormal disinhibition. The latter possibility is supported by the fact that the intensity of the aberrant activations is inversely correlated with performance on a naming test.[25]

Non-fluent patients with intact comprehension tend to have atrophy and metabolic dysfunction within the frontal and perisylvian components of language areas, whereas fluent patients with comprehension deficits tend to have atrophy and dysfunction also in the temporal parts of the language network.[28,29] The 3 PPA subtypes described above may each have distinctive neuroanatomical patterns. According to a voxel based morphometry study, the agrammatic/dysfluent subtype is most closely associated with atrophy in the anterior parts of the language network, including Broca's area; the semantic subtype with atropy in the middle and anterior temporal cortices bordering the perisylvian region; and the logopenic/anomic subtype with atrophy in the temporo-parietal component of the langguage network, including Wernicke's area.[16]

NEUROPATHOLOGY

More than 100 patients with the clinical syndrome of PPA have yielded neuropathological information.[2,30-34] The single most common neuropathological picture associated with PPA, seen in 60-70% of the patients, is one that fits the FTLD spectrum of diseases.[2,15,32,35-42] These patients do not have plaques and neurofibrillary tangles in quantities that warrant a diagnosis of AD.

The FTLD spectrum of neuropathology can be divided into at least three major groups based on the presence and nature of neuronal inclusions. One group has no inclusions (also known as

dementia lacking distinctive histopathology [DLDH]), a second has tau-positive inclusions that are different from neurofibrillary tangles (e.g., Pick bodies), and a third has tau-negative ubiquiting positive inclusions (FTLD-U). In familial cases, linkage to chromosome 17 can be associated with tauopathy if the mutation is in the tau gene and with FTLD-U if the mutation is in the progranulin gene (*PRGN*), also on chromosome 17.[43,44]

In two unrelated families, each with multiple affected siblings, typical PPA was associated with *PRGN* mutations.[45] In the PPA1 family, where 3 autopsies were performed, FTLD-U was found in the affected members but not in the unaffected sibling. Language fluency and comprehension varied from patient to patient and also changed in the same individual as the disease progressed. There was no consistent fit with the PNFA or SD designations, the one common denominator being the aphasia that initially emerged in relative isolation. In each family, some of the affected members developed right-sided motor impairments suggestive of CBD. These two families show that *PRGN* mutations may emerge as important genetic causes of familial PPA. Whether *PRGN* gene expression also plays a role in sporadic PPA remains to be seen but there are preliminary findings suggestive of such an association.

PPA and AD Neuropathology
The frontotemporal family of neuropathologies does not seem to account for all cases of PPA. Approximately 30-40% of PPA patients that have been examined post-mortem have shown the pathology of AD. Some of the patients in this group have neuropathological features that are not seen in typical AD, such as neurofibrillary tangle distributions favoring neocortical rather than limbic areas and the absence of senile plaques.[46] However, the currently cited 30-40% frequency of AD in PPA may overemphasize the importance of this relationship since the neuropathological examination is usually performed many years after disease onset, at an age when the plaques and tangles of AD are endemic. In fact, the primary neuropathological diagnosis of AD in a patient with the clinical picture of PPA and a limbic concentration of neurofibrillary tangles typical of AD should be met with skepticism since such a diagnosis would have failed to establish a credible clinicopathological correlation. The nosological distinction of PPA from AD is supported by the observation that patients with PPA have different patterns of

apolipoprotein E and prion protein genotypes.([47,48]) However, the possibility that there is a distinct subgroup of PPA caused by an atypical manifestation of AD cannot yet be dismissed.

PPA and Creutzfeldt-Jacob Neuropathology

A rapidly progressive language disorder with all the initial characteristics of PPA has also been described in conjunction with Creutzfeldt-Jacob disease. However, the course is so rapid that death usually occurs within a year and the criteria of a few initial years of indolently progressive isolated aphasia cannot be fulfilled.([49])

HYPOTHESES ABOUT ETIOLOGY

Is PPA a syndrome or a disease? It is quite possible that the common denominator is not necessarily the nature of the molecular/cellular process but the a selective vulnerability of the language network. Such selective vulnerabilities may have genetic or developmental origins. For example, we reported that learning disabilities, including dyslexia, were overrepresented in patients with PPA and their first degree relatives when compared to controls and AD patients.([2]) Many patients we have seen since then have reported prominent spelling problems during school years, but not necessarily at a level of severity that warranted a diagnosis of learning disability. Others have reported unusually strong family history of dyslexia in first degree relatives. Furthermore, two patients with PPA onset in their 60s were found to have left hemi-craniosynostosis, a mild developmental abnormality that interferes with the normal growth of the underlying cortex. In these two patients, the left hemisphere hypoplasia was functionally compensated throughout most adulthood but appears to have provided the neural background for the emergence of PPA in the 7th decade of life.([50]) Such tardive manifestations of remote vulnerabilities are not unknown in neurology. One study, for example, showed that patients who had recovered from childhood hemiplegia reported the progressive emergence of hemiparkinsonism later in life on the side of the original weakness.([51])

Potential insights into possible molecular bases of regional susceptibilities come from a study showing that the MV polymorphism in codon 129 of the prion protein gene is more prevalent in PPA than in normals or AD.([47]) This does not imply that PPA is a prion disease, but that

polymorphisms in the prion protein may influence the anatomical distribution of susceptibility to degeneration, as they do in fatal familial insomnia and familial Creutzfeld-Jacob disease.([52,53]) The possibility that the language network has a unique and identifiable molecular fingerprint that would make it the target of selective vulnerability in some genetic backgrounds but not in others is not as implausible as it may sound, especially in view of recent observations on the KE family where a speech and language disturbances are linked to a FOXP2 gene mutation.([54])

Collectively, these observations raise the possibility that PPA may reflect the tardive manifestation of a genetic or developmental vulnerability centered within the language network. This putative vulnerability seems to remain functionally compensated through most adulthood but eventually provides a locus of least resistance for the anatomical distribution of a degenerative disease that becomes identified as PPA. In other individuals with other vulnerabilities the same cellular pathology might lead to a different anatomical distribution of brain damage and therefore to a different clinical picture. The discovery of progranulin gene mutations in families with typical PPA offers a molecular handle for investigating some of these questions.

CONCLUSIONS AND PATIENT CARE

Primary progressive aphasia needs to be considered in the differential diagnosis of dementia. The diagnosis is easily made on the basis of an initially isolated progressive aphasia. 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. Primary progressive aphasia has a broad spectrum of clinical manifestations. Early in the course of the disease, agrammatic, semantic, and logopenic variants can identified.

The manifestations of primary progressive aphasia are distinctly different from those of typical Alzheimer's disease. Different aspects of daily living activities are impaired and require different sorts of intervention. 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. In contrast to Alzheimer's disease where new information cannot be retained in memory, the recall and evaluation of recent events remains intact although the patient may not be able to express this knowledge verbally. Explaining this phenomenon to the family and offering an objective assessment of how the aphasia interferes with verbal expression and language comprehension tends to help the family cope with the patient's impairments.

The epidemiology and risk factors of PPA are largely unknown. There is currently no effective pharmacological treatment for this condition but clinical trials with potentially promising drugs are being initiated. In the meantime, PPA provides a unique syndrome for investigating the pathological mechanisms of focal degenerations, the molecular fingerprints of the language network, and the neuropsychological organization of aphasias.

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