PROGRESSIVE APHASIA

Marsel Mesulam, Sandra Weintraub

Primary progressive aphasia (PPA) is a clinical syndrome diagnosed in any patient in whom a language impairment (aphasia), caused by a neurodegenerative disease (progressive), constitutes the most salient aspect of the initial clinical picture (primary). The language impairment can be fluent or non-fluent and may or may not interfere with word comprehension. Memory for recent events is preserved although memory scores obtained in verbally mediated tests may be abnormal. Minor changes in personality and behavior may be present but are not the leading factors that bring the patient to medical attention or that disrupt daily living activities. This selective clinical pattern is most conspicuous in the initial stages of the disease, and reflects a relatively selective atrophy of the language network, usually located in the left hemisphere. There are different clinical variants of PPA, each with a distinctive pattern of atrophy and neuropathology.

Progressive aphasias have been recognized for more than 100 years through case reports by Pick, Sérieux, Dejerine, Franceschi, and Rosenfeld. The current interest in this condition can be traced to a 1982 report of six patients with a slowly progressive aphasia and to the subsequent delineation of the primary progressive aphasia (PPA) syndrome. Soon after the 1982 report, clinical and imaging features of PPA started to be reported in many countries around the world, including Japan.

Primary progressive aphasia is diagnosed when language is the only area of major dysfunction early in the disease; when other mental faculties such as memory for daily events, visuospatial skills, face and object knowledge and basic comportment remain relatively intact; and when structural brain imaging does not reveal a specific lesion, other than atrophy, that can account for the language deficit. 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 few years, but the language dysfunction remains the most salient feature and deteriorates most rapidly through many years. PPA is a form of dementia since it causes 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 for many years. In contrast to many patients with amnestic dementias of the Alzheimer-type (DAT) who tend to lose interest in recreational and social activities, some patients with PPA 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 (13). It should also be differentiated from DAT and behavioral variant frontotemporal dementia (bvFTD) (14) 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 DAT) and behavior (in bvFTD).

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, sometimes in the form of “sympathetic dyspraxia” in the left hand can be encountered. A more frequent occurrence is the presence of an isolated buccofacial apraxia so that the command to “cough” 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.

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. Patients with these features may have the phenotypes of motor neuron disease (MND), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), DAT, bvFTD, or the syndrome of posterior cortical atrophy (PCA), each of which can be accompanied by a non–primary but progressive aphasia. Brain imaging is necessary since any finding other than atrophy that can account for the aphasia (such as neoplasm or ischemic lesions) rules out the diagnosis of PPA.

Additional cognitive, behavioral and motor deficits that independently influence daily living activities 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. Personality changes (inappropriate familiarity, impaired problem solving, blunted judgment) and extrapyramidal deficits reminiscent of CBD emerge quite commonly as the disease progresses and reflect the close anatomical association of PPA–causing diseases with those causing bvFTD and CBD.

Diagnosing PPA is easiest when the patient is examined in early stages when core criteria can be fulfilled explicitly. 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. In such cases, a structured interview with informants can be used to establish whether the aphasia had in fact emerged in relative isolation. A retrospective diagnosis of “possible PPA +” 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 now has other deficits as well.
SUBTYPING AND TERMINOLOGY IN PPA:

The study of patients with cerebrovascular lesions has led to the delineation of several aphasia subtypes, each characterized by a distinctive cluster of signs and symptoms linked to a preferred lesion site within the language network. The clustering of deficits and their clinicopathological correlates are slightly different in PPA, perhaps because the lesions are selective for specific neuronal types and also indolently progressive, leading to more complex dissociations of function and some reorganization of cortical circuitry. We are now subdividing our PPA cases into three variants: agrammatic, semantic and logopenic. The agrammatic subtype (PPA-G) is characterized by impairments of grammar (syntax and morphology) but not of word comprehension; the semantic subtype (PPA-S) by impairment of word comprehension but not of grammar and the logopenic subtype (PPA-L) by intermittent word-finding hesitations without impairments of comprehension or grammar. Fluency is low in PPA-G, normal in PPA-S, and variable in PPA-L. Repetition is impaired in both PPA-G and PPA-L, but not PPA-S.

NEUROPSYCHOLOGICAL PROFILES

Standardized neuropsychological tests are helpful for reaching an early diagnosis. 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), 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. The neuropsychological examination of the patient with suspected PPA should demonstrate the aphasia, characterize its subtype, and identify non language cognitive domains of strength.

Aphasia can be tested with one of the several clinical batteries designed for this purpose. The Western Aphasia Battery (WAB-R) includes subtests that measure spontaneous speech, word and sentence comprehension, naming, reading and writing. An Aphasia Quotient provides a measure of aphasia severity that can be tracked over time. The clinical aphasia tests, however, lack quantitative measures of conversational fluency and grammar that contribute to subtyping. These can be calculated from analysis of spontaneous narratives generated in the course of telling the “Cinderella Story” or other spontaneous speech sample. Based on a subtyping algorithm previously described, grammatical production can also be tested with the Northwestern Anagram Test (NAT), a measure of sentence construction that does not place demands on working memory or speech output. Single word comprehension can be tested with items from the Peabody Picture Vocabulary Test (PPVT-IV), which provides a range of item difficulty. Finally, we have used the Boston Naming Test (BNT) as a measure of object naming.

Non verbal functions should be tested with instruments that minimize interference from aphasia. Episodic memory can be tested with the Three Words Three Shapes (3W3S) test, a measure we previously designed to be useful in differentiating DAT from healthy cognitive aging since it tests memory for words and shapes, both in the visual modality. Reasoning can be assessed with selected items from the Visual Verbal Test, a non verbal test of recognition.
of similarities and cognitive flexibility. Visuoperceptual functions can be tested with Judgment of Line Orientation. Finally, behavioral changes can be assessed with the Frontal Behavior Inventory. Behavioral changes, salient in early stages of bvFTD, are not typically apparent until later stages of illness in PPA.

FUNCTIONAL AND STRUCTURAL NEUROANATOMY

Structural neuroimaging can show asymmetric atrophy of the left perisylvian region that can progress over time (Fig. 1). According to quantitative morphometry, the PPA–G subtype is most closely associated with atrophy in the posterior frontal lobe, including Broca’s area; the PPA–S subtype with atrophy in the anterior temporal components of the language network, including the temporal pole; and the PPA–L subtype with atrophy in the temporo-parietal component of the language network, including Wernicke’s area.

Abnormalities of blood flow and metabolism may emerge prior to the detectable atrophy. SPECT or PET may therefore provide more sensitive diagnostic

Fig 1. Legend for Figure - Top - two coronal sections, showing the asymmetric atrophy of the left perisylvian cortex in a PPA patient. Bottom - two axial sections showing the progression of atrophy.
information than structural MRI or CT scans. 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, including Broca’s and Wernicke’s areas. However, the functional connectivity between these two major nodes of the language network becomes disrupted. It appears, therefore, that disrupted language processing in PPA may initially reflect an impairment of information transfer within the language network rather than a failure of activation within the network nodes. In comparison to neurologically intact subjects, the PPA patients also display additional aberrant activations within regions of the brain outside of the classic language network.

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.

NEUROPATHOLOGY

Post-mortem examinations show that PPA patients have the pathology of either frontotemporal lobar degeneration (FTLD) or of AD. In 70–80% of PPA–G the neuropathology is of the FTLD type with tauopathy of the Pick or CBD/PSP types. In 70–80% of PPA–S, the neuropathology is also of the FTLD type but with TDP–43 inclusions. The remaining 20–30% of patients in these two variants show the neuropathology of AD, occasionally in an atypical distribution. In PPA–L, more than half of the cases have AD pathology and the rest FTLD. There is no clinical distinction between PPA patients with and without AD pathology. Determining the underlying pathology in an individual patient is quite challenging, especially in PPA–L. ApoE genotyping or F18–DG metabolic scans do not help in this differentiation. Amyloid imaging with PET and cerebrospinal fluid evaluations for phosphotau and beta amyloid may be helpful but this remains to be proven in neuropathologically verified cases. A rapidly progressive language disorder with all the initial characteristics of PPA has also been described in conjunction with Jacob–Creutzfeldt disease. However, the course is much more rapid than in the usual cases.

GENETICS AND RISK FACTORS OF PPA

Progressive aphasia can be seen in patients with autosomal dominant dementias linked to chromosome 17. In some kindreds, this has been called familial dysphasic dementia, or hereditary dysphasic disinhibition dementia. There is also a unique autosomal dominant disorder, linked to chromosome 9, where inclusion body myopathy and Paget’s disease is seen in conjunction with a progressive aphasia. However, the early emergence of prominent memory, behavior, and motor impairments in these familial cases differs from the pattern seen in typical PPA.

In two recently reported kindreds, 3 of 4 siblings (in the PPA1 kindred) and 2 of 3 siblings (in the PPA3 kindred) developed typical PPA. In both kindreds, a mutation in the progranulin gene (GRN) on chromosome 17 was found to segregate with the presence of PPA. Neuropathological evaluations in affected siblings showed characteristic left perisylvian atrophy and FTLD with TDP–43 inclusions. The number of these inclusions was higher in neocortical than in hippocampo–entorhinal areas and higher in the left than the right hemisphere.

In larger groups of patients show that PPA is a major clinical manifestation of GRN mutations. In most of the families with GRN mutations, one family member may have PPA, and another bvFTD. How can the same mutation target
the language network in one family member and the prefrontal cortex in another? 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 \(^{1,56}\). In some of these families, the concentration of dyslexia was striking, affecting the majority of children or siblings. Furthermore, two patients with PPA onset in their 60’s 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 \(^{57}\).

These observations have led us to wonder whether PPA could represent the tardive manifestation of genetic or acquired vulnerabilities of the language network that remain functionally compensated during most of adulthood but that become the locus of least resistance for the distribution of neurodegeneration. In other patients with a different set of prior vulnerabilities the same neurodegenerative process may have a different distribution and therefore different clinical manifestations.

**CONTRIBUTIONS OF PPA TO NEUROLINGUISTICS AND COGNITIVE NEUROSCIENCE**

Classic aphasiology has been based on observations in patients with focal cerebrovascular lesions where site of injury, usually including cortical as well as subcortical areas, is abruptly and completely destroyed. In primary progressive aphasia, the gradual and selective loss of cortical neurons in the language network leads to more specific and subtle perturbations of language function. Research on PPA has already led to several new insights concerning language function. One of the most consequential new insights has been the realization that the classic neurological account of language is incomplete and that the anterior temporal lobe of the left hemisphere needs to be inserted into the language network as a third major hub with a critical role in language comprehension, especially of words denoting concrete entities \(^{38-41}\). In fact, some of these observations have cast serious doubts on existing characterizations of Wernicke’s area and its role in language comprehension \(^{62}\).

Another equally important insight has been the realization that grammatical ability and fluency can be dissociated neuropsychologically as well as anatomically \(^{26,63}\). Numerous experiments have also shown that the retrieval (or access) anoma in PPA–G and PPA–L has a definite associative component, which reflects a blurring of the pre-phonological “lemma” so that the object name can be recognized but not retrieved \(^{64}\). It is quite likely that future research in PPA will lead to additional insights into the functional organization of the language network.

**PATIENT CARE**

The manifestations of PPA are distinctly different from those of DAT. 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 DAT 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 caregivers cope with the patient’s impairments. We find that psychosocial interventions, support groups and targeted educational programs are necessary components of a comprehensive approach to patients and families. Although many patients with PPA may have atypical AD, cholinesterase inhibitors have not been particularly useful. However, a new trial of these agents in patients with PPA is underway, with positive results expected. Anecdotal reports of success with omental transplants, intraspinal ethanercept, steroids and transcranial magnetic stimulation have appeared but need to be confirmed. Advances in developing truly effective therapies for AD and FTLD pathology will obviously also affect the treatment of PPA. A very special feature of PPA is the relative sparing of the right hemisphere for many years during the course of the disease. Stimulating the plasticity of the right hemisphere so that it can take over some of the impaired language functions is a major and futuristic goal for treatment in PPA.

REFERENCES

5) Sérieux P. Sur un cas de surdité verbale pure. Revue de Medecine 1893; 13: 733–750.
21) Weintraub S, Mesulam M-M. From neuronal networks to dementia: four clinical profiles. In: Föret F,


