54.1. Introduction

The existence of progressive aphasias has been known for more than 100 years. Pick (1892, 1904), Séreux (1893), Franceschi (1908), and Rosenfeld (1909) were among the first to report such patients. The current resurgence of 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 (Mesulam, 1982, 1987, 2007; Mesulam and Weintraub, 1992).

According to currently accepted criteria, the PPA diagnosis is made 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 term language in this definition is used in its technical neurological sense to refer to all component processes served by the left hemisphere language network, including phonology, morphology, syntax, semantics, naming, word-finding, reading and spelling. The language impairment in PPA 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. The recognition of familiar facts and objects is preserved (Adlam et al., 2006). 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, covering an interval of approximately 2 years after symptom onset.

Hundreds of PPA cases have been reported and a sizable research literature on this topic has appeared (Kertesz et al., 1994; Black, 1996; Westbury and Bub, 1997; Kertesz et al., 2000, 2002; Hillis, 2002, 2004; Grossman and Moore, 2005). Terms such as progressive nonfluent aphasia (PNFA), semantic dementia, aphasic variant of frontotemporal dementia (FTD), temporal variant of frontotemporal lobar degeneration (FTLD), Gogi aphasia and progressive aphasia have been used, mostly implicitly, to denote variants of PPA (Neary et al., 1998; Miller et al., 1999). We prefer the PPA term as a root diagnosis for two reasons: not all progressive aphasias fulfill the PPA criteria and not all PPA cases are caused by FTLD pathology. The word “primary” is a key descriptor that emphasizes the selective salience of the language disturbance and the relative preservation of other cognitive domains at initial stages.

Acquired language disorders are known as aphasias. Aphasias can be classified as being agrammatic, semantic, or anomic, depending on the specific aspect of language that is most severely affected. Progressive aphasias are not rare in neurological practice. Many patients with Alzheimer’s disease (AD) eventually develop an aphasia. Aphasia can also arise in the course of motor neuron disease (MND), corticobasal degenerations (CBD), behavioral variant of frontotemporal dementia (bvFTD), and dementia associated with the posterior cortical atrophy (PCA) of Benson et al. (1988). While all of these patients can be said to have progressive aphasias, the language impairment is not “primary”, either because it is of lesser importance in comparison to other more salient deficits or because it is a late manifestation of the disease.

In a unique group of patients, a slowly progressive aphasia arises in relative isolation, becomes the principal cause of restrictions in daily living activities (Wicklund et al., 2007), and remains the most salient...
aspect of the clinical picture for several years. This does not mean that all other cognitive and behavioral domains are intact, but that they are less severely 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 the behavioral variant of frontotemporal dementia (bvFTD), which designates a behavior-based (comportmental) dementia, PPA designates a language-based (aphasic) dementia.

54.2. Comments on the clinicopathological nomenclature used in this chapter

There are currently no reliable in vivo markers for the definitive identification of the underlying disease process in patients with non-familial neurodegenerative dementias. Furthermore, the same neuropathological entity can have multiple clinical manifestations depending on its regional distribution in the brain. These are two reasons why nomenclature in this field can become unusually confusing when the distinction between clinical and neuropathological levels becomes blurred. A physician can suspect that a dementia is caused by Alzheimer’s disease or Pick’s disease but cannot confirm this prediction until brain tissue is examined. This is of practical importance because the clinical patterns of the two diseases can partially overlap despite differences in the frequency of individual features (Weintraub and Mesulam, 1993). This state of affairs makes it imperative to distinguish clinical syndromes from neuropathological diagnoses. In this chapter, we will confine the use of acronyms such as PPA, bvFTD, and probable Alzheimer’s disease (PRAD) to clinically identified syndromes of aphasic (Mesulam, 2003), amnestic (McKhann et al., 1984) and comportmental (Néary et al., 1998) dementia, respectively. The acronyms AD and FTLD will be reserved for neuropathological patterns identified by microscopy. Specifically, AD will refer to the presence of amyloid plaques and neurofibrillary tangles in a certain density and distribution (Hyman and Trojanowski, 1997), whereas FTLD will refer to characteristic combinations of focal neuronal loss with gliosis, superficial spongiosis, Pick bodies, other tau inclusions, and tau-negative ubiquitinated TDP-43 inclusions (McKhann et al., 2001; Neumann et al., 2006).

54.3. Clinical features and diagnosis in primary progressive aphasia

The patient with PRAD comes to medical attention because of forgetfulness. Misplacing personal objects, repeating questions, and forgetting recent events are among the presenting symptoms. Although the patient may forget names of people, word-finding during conversation is usually not a major problem. In contrast, the patient with PPA comes to medical attention because of word-finding difficulties, abnormal speech patterns, or spelling errors of recent onset. Primary progressive aphasia is diagnosed when other mental faculties such as memory for daily events, visuospatial skills, face and object knowledge (assessed by the recognition of familiar faces and objects) 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 (Mesulam and Weintraub, 1992; Mesulam, 2001, 2003).

Standardized neuropsychological tests are helpful for reaching an early diagnosis (Weintraub et al., 1990; Weintraub and Mesulam, 1993, 1996). 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) (Folstein et al., 1975), 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 few years, but the language dysfunction remains the most salient feature and deteriorates most rapidly through many years (Weintraub et al., 1990). 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 PRAD 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 (Broussolle et al., 1996). It should also be differentiated
from PRAD and bvFTD 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 bvFTD).

54.3.1. Core diagnostic features and confirmatory investigations

The initial diagnostic criteria for PPA were descriptive. We have subsequently proposed a cluster of core, supportive, and exclusionary criteria for the diagnosis of PPA. These criteria have been incorporated into the Uniform Data Set (UDS) used by the National Alzheimer’s Disease Coordinating Center (NACC) of the National Institute on Aging (Morris et al., 2006). The salience of language impairments in the initial stages and the insidious onset and progression of symptoms over years are the two necessary core features (Table 54.1). The early stages during which the language disorder remains the most salient symptom and the principal source of restrictions in daily activities should have a minimum duration of approximately 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 length of utterance or slow output) and may or may not impair phonology, syntax or verbal semantics (comprehension of word meaning) (Mesulam, 1987; Mehler, 1988; Weintraub et al., 1990; Snowden et al., 1992; Thompson et al., 1997; Otsuki et al., 1998). Written language may be less impaired than spoken language but spelling errors (dysgraphia) are common.

Further neuropsychological confirmation of the aphasia can be obtained with instruments such as the Boston Diagnostic Aphasia Examination (BDAE: Goodglass et al., 2001), the Western Aphasia Battery

Table 54.1

Core, supportive and exclusionary criteria for primary progressive aphasia

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 initially (usually 2 years or more).

I. Core diagnostic features: These features are integral to the clinical syndrome. Both must be present for making the diagnosis.
   A. Insidious onset and gradual progression
   B. Early onset of aphasic disturbance (including any combination of the following):
      1. Word-finding pauses
      2. Word comprehension deficits
      3. Naming impairments
      4. Circumlocutious speech lacking specific nouns and verbs
      5. Speech and/or writing that has impaired grammar and syntax
      6. Syntactic comprehension deficits
      7. Dysgraphia

II. Supportive clinical features: These features are not present in all patients but their presence serves further to support the diagnosis.
   8. Onset before the age of 65
   9. Dysarthria
   10. Ideomotor apraxia
   11. Dyscalculia
   12. Mild facial flattening on the side opposite the language-dominant hemisphere (usually right face)
   13. Asymmetrical upper extremity posturing upon stressed gait on the side opposite the language-dominant hemisphere (usually right arm)
   14. Mild rigidity on the side opposite the language-dominant hemisphere (usually right side of body)

(Continued)
(WAB; Kertesz, 1982), the Boston Naming Test (BNT; Kaplan et al., 1983), the Token Test (De Renzi and Vignolo, 1962) and the F-A-S test of fluency (Benton and Hamsher, 1989). These can be supplemented by additional tests to demonstrate the relative preservation of other cognitive domains early in the course of the disease, especially memory for recent events. Listening to the patient’s speech, obtaining a short writing sample, assessing the comprehension of questions asked during the examination, and supplementing these with the BNT and F-A-S offer a rapid survey of language function that almost always reveals the presence of abnormalities. In many, but not all patients, neurodiagnostic investigations reveal asymmetric EEG slowing, hypoperfusion, hypometabolism and atrophy on the language-dominant (usually left) hemisphere (Fig. 54.1).

### 54.3.2. Supportive features

In addition to the core diagnostic criteria, 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 “sym pathetic dyspraxia” where the left hand cannot pantomime the movements related to the usage of the tool mentioned by the examiner. A more frequent occurrence 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.

### 54.3.3. Exclusionary clinical and imaging criteria

An abrupt onset of the aphasia excludes the diagnosis of PPA. Additional exclusionary criteria include the early salience of motor deficits, amnesia, abnormal comport ment, associative agnosia, or visuospatial disorienta tion. Patients with these features deserve a primary diagnosis of motor neuron disease (MND), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), PRAD, bvFTD, or the syndrome of posterior cortical atrophy (PCA), each accompanied by a non-primary progressive aphasia. In many cases, however, PPA patients may eventually display some features of these syndromes, indicating the considerable clinical overlap among these entities. 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.
54.3.4. The “PPA-plus” diagnosis

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.

54.3.5. Retrospective informant-based diagnosis

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 PPA+ is made if such an interview confirms that the diagnostic criteria had been met during an earlier phase of the disease in a patient who now has other deficits as well.

54.4. Subtyping and terminology in primary progressive aphasia

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.

In contrast to stroke-induced syndromes where dysarthria is a frequent component of non-fluent aphasias, for example, the low fluency in PPA is usually due to word-finding pauses or to a characteristic non-dysarthric slow and labored output as if the patient is struggling to form the word. In such patients single syllables such as “pa”, “ta”, or “ka” can each be repeated in rapid succession, but their combination into “pataka” may not be possible, reflecting a high-order deficit in articulatory programming of phonological sequences.

Components of language may dissociate in unusual ways. For example, a PPA patient may be non-fluent but without the agrammatism that usually accompanies stroke-induced non-fluent aphasias. Conversely, the agrammatism may be more pronounced and dramatic than in any stroke-induced aphasic syndrome. In contrast to patients with stroke-induced loss of fluency who are consistently dysfluent, the impaired fluency in PPA may be intermittent. Such patients can produce fluent speech when allowed to engage in small talk and circumlocution, but become non-fluent because of word-finding hesitations when forced to be precise. The neologism “logopenia” was coined to describe this state of fluctuating fluency (Mesulam, 1982). The intermittent interruption of fluency in these patients also shows that the fluent vs. nonfluent distinction, a gold standard for the classification of stroke-based aphasias, may be of more limited usefulness in the classification of PPA. When present, comprehension deficits are usually confined to single words and rarely lead to the profoundly impaired comprehension of conversation characteristic of Wernicke’s aphasia. These are some of the reasons why PPA patients do not easily lend themselves to classification into traditional subtypes such as Broca’s, or Wernicke’s aphasia.

The progressive non-fluent aphasia (PNFA) of Neary et al. (1998) fulfills the PPA criteria and can be considered a PPA subtype. If the original Neary et al. criteria for semantic dementia, namely the requirement to have both poor word comprehension and also an associative agnosia, are interpreted literally, semantic dementia does not fit the PPA criteria. However, a revision of these criteria by the Cambridge group has led to a reformulation of semantic dementia as a fluent form of PPA (Adlam et al., 2006). According to this reformulation, semantic dementia leads to a recognition deficit for grammatically complex sequences.

The PNFA and semantic dementia subtypes do not account for all of PPA. The “logopenia” term introduced in the initial 1982 paper on PPA (then known as slowly progressive aphasia) described a clinical state intermediate between non-fluent and fluent aphasia (Mesulam, 1982). The most comprehensive recent development to take this “third” form of PPA into account is the work of Gorno-Tempini and colleagues who codified a “logopenic” variant of PPA (Gorno-Tempini et al., 2004).

Based on these developments, we are now subdividing our cases into three variants: agrammatic-dysfluent, semantic and logopenic. In our clinical practice, the agrammatic-dysfluent variant (representing a subset of PNFA) is characterized by impairments of syntax and fluency but preserved word comprehension; the semantic variant by poor word comprehension but preserved syntax and fluency; and the logopenic variant by variable fluency, frequent word-finding pauses and/or anosmia but relatively intact syntax and word comprehension.

The steps we use in clinical diagnosis are listed in Table 54.2. The practicing neurologist or psychiatrist may want to stop at the end of Step 1 after establishing the root diagnosis of PPA. This is the key step in differentiating the patient’s clinical picture from other major dementia syndromes such as PRAD and bvFTD. The further subtyping of PPA is a laborious exercise that should probably be reserved for research purposes.

54.4.1. PPA: agrammatic-dysfluent subtype

This variant is a subset of PNFA. It 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 head and cut up. Writing syntax errors. Edit my work computer.”

Another patient who happened to be a nurse gave the following description of her difficulties: “Syntax errors and no articles. . . Words in the my head and cut up. Writing syntax errors. Edit my work computer.”

Patients in this subgroup may also show a selective comprehension deficit for grammatically complex sen-
sentences such as those with passive voice, possessives, and embedded clauses. For example, when looking at a pair of pictures, one of a girl chasing a boy, and the other of a boy chasing a girl, the patient correctly points to “boy chasing the girl” but frequently gets confused when asked to point to the “girl chased by the boy”. 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 “it”.

Fluency, as determined by word outflow per minute or by mean length of utterance, is consistently decreased and speech may be halting, labored and effortful but not necessarily dysarthric. Speech apraxia and phonological disintegration may distort speech. Frequent word-finding pauses may emerge and naming is more impaired for verbs than nouns (Hillis et al., 2004). The critical findings for this subtype include low fluency and agrammatism in the presence of preserved comprehension for single words and sentences with canonical syntax (Mesulam, 2001; Hillis et al., 2002; Gorno-Tempini et al., 2004).

Neuropsychological instruments useful for identifying this PPA subtype include tests of speech production (Wertz et al., 1984; Duffy, 1995), the Token Test for assessing grammatical comprehension (De Renzi and Vignolo, 1962), subtests of the WAB (Kertesz, 1982) and the Curtiss-Yamada Comprehensive Language Evaluation (Curtiss and Yamada, unpublished results; Gorno-Tempini et al., 2004). The BNT can be abnormal in these patients, as in nearly all cases of PPA.

54.4.2. PPA: semantic subtype

This subtype fits the criteria for semantic dementia as redefined by Adlam et al. (2006). The core feature is the early onset of prominent word comprehension deficits in the absence of major agrammatism (Hodges et al., 1992; Mesulam, 2001; Gorno-Tempini et al., 2004). Fluency is usually preserved when the patient is allowed to produce circumlocutions and simplifications but word-finding pauses may emerge as the patient struggles to retrieve a word. At the initial stages, the patient may follow most conversation except for an intermittent inability to interpret individual words. 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 “two-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 successfully subgroup objects they cannot name into appropriate semantic categories and since they experience no difficulty (until late in the disease) using the objects they cannot name. Nonetheless, such patients may display recognition deficits when

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**Table 54.2**

The steps involved in the clinical diagnosis and subtyping of primary progressive aphasia

**Step 1:** Does the patient have an impairment in word-finding, object naming, syntax or word comprehension, caused by a neurodegenerative disease, and that initially constitutes the most salient aspect of the clinical picture?
- if yes, diagnose PPA and proceed to step 2

**Step 2:** Does the patient have word comprehension deficits and preserved fluency?
- if yes, classify as “PPA, semantic variant”
- if not, proceed to step 3

**Step 3:** Does the patient have consistently decreased fluency and selective impairments in the production and comprehension of syntax?
- if yes, classify as “PPA, agrammatic-dysfluent variant”
- if not, proceed to step 4

**Step 4:** Does the patient have object naming deficits or intermittent dysfluency because of word-finding pauses?
- if yes, classify as “PPA, logopenic variant”
- if not, classify as “PPA, unspecified”
shown unfamiliar faces or objects (Adlam et al., 2006). 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.

The WAB (Kertesz, 1982) contains naming and word comprehension subtests that can be used to test whether naming alone is impaired or whether the patient is also unable to comprehend the spoken words for objects, numbers, colors, and geometric shapes. Performance in the Pyramids and Palm Trees (Howard and Patterson, 1992) can be used to assess semantic associations and is usually abnormal in this PPA subtype, at least in part because it relies on extensive verbal processing. The Regularity and Reading subtest of the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA) (Kay, 1992) can be used to demonstrate the surface dyslexia characteristic of these patients. This PPA subtype is associated with the most severe abnormalities on the BNT. A distinctive feature is the failure to point to an object named by the examiner, a process that is preserved in the other PPA subtypes. These are the most challenging patients to evaluate since the inability to comprehend questions may give the mistaken impression of global cognitive deficits.

54.4.3. PPA: logopenic-anomic subtype

The core features of this subtype include an anomia without early agrammatism or comprehension deficits. 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 perceived by the patient. These two types of anomia can be dissociated from each other. Extrinsic anomia is diagnosed by poor performance on naming tests such as the BNT. Intrinsic anomia is characterized by word-finding pauses during spontaneous speech. 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 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. The BNT is abnormal in patients with extrinsic anomia but may be normal in some patients with a predominantly intrinsic anomia. This is almost always a one-way deficit so that the patient cannot name the object but can point to it when the name is given by the examiner. Spelling errors are common.

54.4.4. Other subtypes

Some patients will fulfill criteria for PPA but will not fit into the semantic, agrammatic-dysfluent or logopenic subtypes. For example, some patients may have agrammatism or loss of fluency together with comprehension deficits, others a loss of comprehension for spoken but not written words. These patients can be classified as having “mixed” or “word-deaf” subtypes of PPA. Still other patterns may exist, illustrating the complexity of the language network and the heterogeneity of its response to the underlying neurodegenerative disease.

54.4.5. Varieties of naming impairments and paradoxical priming in PPA

Anomia is one of the most common deficits in PPA. A rich and bewildering variety of naming deficits can be encountered in PPA. Some patients may name objects but not actions; others may be able to write the name of objects they cannot name verbally; still others can display dissociations in the naming of living versus non-living objects. Psycholinguistic experiments in neurologically intact subjects show that brief exposure to a word may speed up the subsequent naming of a picture depicting a semantically related object. This process is known as priming. In PPA, priming with a semantically related word causes the subsequent picture naming to be slower than when primed by a semantically unrelated word (Vandenberghe et al., 2005). This phenomenon of semantic interference was not seen in controls or PRAD patients tested with the same task. In order to explain this paradoxical effect, we postulated that PPA interferes with the discriminability of semantically related words during naming. According to this scenario, the prime activates the proper semantic field but paradoxically slows the naming of related objects because the correct choice becomes embedded in a field of semantically related nouns. This phenomenon resembles the gradual slowing of target detection in a spatial attention task as
distracters look more and more like the target. A basic mechanism for the logopenia and anomia in PPA may thus be a deterioration of the signal to noise ratio during lexical retrieval. In keeping with this finding, PPA patients showed abnormalities in recognizing previously encountered words mostly because of false positive identification of semantically related distracters (Rogalski et al., 2007).

54.5. Longitudinal course

54.5.1. Early-stage primary progressive aphasia:

The distinctive features characteristic of the PPA subtypes are most clearly identified in the early stages of the disease, usually within the first 2 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.

54.5.2. Mid-stage primary progressive aphasia

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 recognition deficits even for familiar faces and objects. 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 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.

54.5.3. End-stage primary progressive aphasia

As the end-stages are reached, all patients gravitate toward a state of global aphasia characterized by severe comprehension deficits and usually a severe loss of fluency. Output becomes limited to single words, palilalic syllables, or grunts. In others with fluent onset, speech deteriorates into meaningless logorrhea. Behavior may range from apathy to severe agitation.

54.6. Non-PPA progressive aphasias

Occasionally, patients with otherwise typical motor neuron disease (MND) may display anomia and other features of aphasia (Caselli et al., 1993; Rakowicz and Hodges, 1998; Strong et al., 1999). In some patients, the earliest stages will raise the suspicion of PPA but signs of motor neuron disease will soon emerge, usually within the first year, and dominate the clinical picture. This is the one group of progressive aphasics where a rapidly progressive course leading to death within a few years may be encountered. Asymmetry of pathology is common in corticobasal degeneration (CBD). When the disease targets the left hemisphere, right-sided motor deficits can be accompanied by prominent and progressive aphasic disturbances (Frattali et al., 2000; Kertesz et al., 2000). Patients who fit the diagnostic criteria for PRAD, bvFTD, and posterior cortical atrophy (PCA) can also develop aphasias. However, the language disturbance in these patients either emerges late in the course of the disease or does not represent the most salient aspect of the clinical picture. These patients can be designated as having a progressive aphasia in addition to the relevant primary diagnosis.

In PRAD the language disorder usually takes the form of a fluent aphasia with or without comprehension deficits (Weintraub et al., 1990; Price et al., 1993), in bvFTD the language disorder is characterized by an economy of expression and occasional agrammatism, in CBD the aphasia is usually dysfluent, and in MND the aphasia may be associated with dysarthria or dysphonia.

54.7. Functional and structural neuroanatomy

The vast 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 (Chawluk et al., 1986; Kempler et al., 1990; Tyrrell et al., 1990; Mesulam and Weintraub, 1992). 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 (Sonty et al., 2003; Gorno-Tempini et al., 2004). Other parts of the brain, including the entire right hemisphere, may remain relatively intact well into the middle and late stages of the disease (Chawluk et al., 1986; Tyrrell et al., 1990). In the rare patients with right hemisphere dominance for language, the atrophy is centered in the right perisylvian region (Mesulam et al., 2005). 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. SPECT or PET may therefore provide more sensitive diagnostic 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 (Sonty et al., 2003). However, the functional connectivity between these two major nodes of the language network becomes disrupted (Sonty et al., 2007). It appears, therefore, that disrupted language processing in PPA may 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 displayed additional aberrant activations within regions of the brain outside the classic language network (Sonty et al., 2003). 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 (Sonty et al., 2003).

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 (Abe et al., 1997; Rosen et al., 2002). According to voxel-based morphometry, 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 atrophy in the middle and anterior temporal cortices bordering the perisylvian region as well as the inferior temporal lobe; and the logopenic-anomic subtype with atrophy in the temporoparietal component of the language network, including Wernicke’s area (Gorno-Tempini et al., 2004; Adlam et al., 2006).

54.8. Neuropathology

Is PPA a single disease linked to a unitary neuropathology or is it a syndrome arising from a common anatomical distribution of multiple disease entities? This question has not yet been resolved. Despite the tendency to rely on the post-mortem examination as the final arbiter, it is necessary to consider the possibility that the cellular changes noted at death, 10–15 years after symptom onset, may not necessarily reflect the initiating cellular changes that triggered the distinctive clinical picture in the beginning.

54.8.1. PPA and the FTLD spectrum of neuropathology

More than 100 patients with the clinical syndrome of PPA have yielded neuropathological information (Mesulam and Weintraub, 1992; Chin et al., 1994; Harasty et al., 1996; Turner et al., 1996; Kertesz et al., 2005; Knibb et al., 2006). 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 (McKhan et al., 2001). These patients do not have plaques and neurofibrillary tangles in quantities that warrant a diagnosis of AD. In some, the findings are confined to a focal (lobar) degeneration characterized by neuronal loss, gliosis, and mild spongiform change within superficial cortical layers. This pattern was once known as nonspecific focal atrophy or dementia lacking distinctive histology. In other cases, the cerebral cortex may contain ballooned neurons filled with phosphorylated neurofilament protein, tau-positive Pick bodies, CBD- or PSP-like tau inclusions, or tau-negative but TDP-43-immunoreactive and ubiquitinated inclusions (Lippa et al., 1991; Mesulam and Weintraub, 1992; Kertesz et al., 1994, 2000; Ikeda et al., 1996; Kinoshita et al., 1996; Turner et al., 1996; Molina et al., 1998; Rossor et al., 2000; McKhan et al., 2001; Boeve et al., 2003; Neumann et al., 2006). The tau-negative ubiquitin/TDP-43 inclusion pattern is also known as FTLD-U or FTLD-MND type.

54.8.2. 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 who have been examined post mortem have shown the pathology of AD
A very small number 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 (Galton et al., 2000). 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. Some of the patients in this group may have had another neuropathological process that may have been responsible for the clinical picture of progressive aphasia but that could have been overlooked in the presence of the more conspicuous age-related plaques and tangles (Munoz et al., 2007). 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 than patients with the PRAD syndrome (Mesulam et al., 1997; Li et al., 2005). However, the possibility that there is a distinct subgroup of PPA caused by an atypical manifestation of AD cannot be dismissed.

54.8.3. Relationship of PPA subtype to neuropathology and differentiating AD from FTLD

In non-familial cases, some autopsy series show that the dysfluent subtypes are more closely associated with tauopathy and the semantic subtypes with FTLD-U (Knibb et al., 2006). However, there is considerable overlap. Furthermore, in familial cases FTLD-U pathology is more closely associated with the dysfluent rather than the semantic variants (Van der Zee et al., 2006). Some autopsy series have suggested that the non-fluent forms (PNFA) have a particularly high frequency of AD pathology (Knibb et al., 2006), others that the association is mostly with the logopenic subtype (Gorno-Tempini et al., 2004). Our experience tends to favor the latter. Conceivably, CSF biomarkers or amyloid-binding PET ligands may assist in determining whether PPA is caused by AD or FTLD.

54.8.4. PPA and Creutzfeldt-Jakob neuropathology

A rapidly progressive language disorder with all the initial characteristics of PPA has also been described in conjunction with Creutzfeldt-Jakob disease. However, the course is so rapid that death usually occurs before the criteria of approximately 2 years of indolently progressive isolated aphasia can be fulfilled (Mandell et al., 1989).

54.9. Genetics and risk factors of PPA

Progressive aphasia can be seen in patients with autosomal dominant dementias linked to chromosome 17 (Basun et al., 1997; Bird et al., 1997; Lendon et al., 1998; Murrell et al., 1999). 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 are seen in conjunction with a progressive aphasia (Kovach et al., 2001). 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, three of four siblings (in the PPA1 kindred) and two of three siblings (in the PPA3 kindred) developed typical PPA (Mesulam et al., 2007). In both kindreds, a mutation in the progranulin gene (PGRN) on chromosome 17 was found to segregate with the presence of PPA. Neuropathological evaluations in affected siblings showed characteristic left perisylvian atrophy and ubiquinated intracellular and intranuclear inclusions characteristic of the FTLD-U pattern. Investigations in larger groups of patients show that PPA is a major clinical manifestation of PGRN mutations (Gass et al., 2006). Such mutations can also be encountered in PPA patients with no known family history (Davion et al., 2007).

In some families with PGRN mutations, one family member may have PPA, and another bvFTD (Van der Zee et al., 2006). How can the same mutation target the language network in one family member and the prefrontal cortex in another? The common denominator may not be the nature of the molecular/cellular process but a selective vulnerability of the language network that makes it a locus of least resistance. Such selective vulnerabilities may be genetic or acquired. For example, we reported that learning disabilities, including dyslexia, were overrepresented in patients with PPA and their first-degree relatives when compared with controls and AD patients (Mesulam and Weintraub, 1992; Rogalski et al., in press). 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 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 (Alberca et al., 2004). 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 (Klawans, 1981).

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.

Additional risk factors for PPA have also been suggested. The H1/H1 haplotype of tau may be overrepresented in PPA (Sobrido et al., 2003). Furthermore, the MV polymorphism in codon 129 of the prion protein gene is more prevalent in PPA than in normals or AD (Li et al., 2005). 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 (Parchi et al., 1996; Hauw et al., 2000). 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 observations on the KE family, where speech and language disturbances are linked to a FOXP2 gene mutation (Fisher et al., 1998). In men with PPA, the frequency of vasectomy was found to be increased (Weintraub et al., 2006). As a possible underlying mechanism for this association it was pointed out that sperm and brain tissue share some common antigens and that the hypothesized vasectomy-related neurodegeneration may have an autoimmune basis similar to that of neoplastic diseases. The E4 allele of apolipoprotein E, a major risk factor for AD, is not overrepresented in PPA (Mesulam et al., 1997).

54.10. Conclusions and patient care

The diagnosis of PPA is easily made on the basis of an initially isolated progressive language impairment. Other degenerative diseases can also eventually lead to 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-dysfluent, semantic, logopenic variants can be identified.

The manifestations of primary progressive aphasia are distinctly different from those of PRAD. 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 PRAD, 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. We find that psychosocial interventions, support groups and targeted educational programs are necessary components of a comprehensive approach to patients and families (Weintraub and Morhardt, 2005).

The epidemiology of PPA is largely unknown. Hundreds of patients have been reported in the literature and many thousands are likely to be receiving care in clinics around the world. There is currently no effective pharmacological treatment for this condition but clinical trials with potentially promising drugs are being initiated. A controlled bromocriptine trial did not yield positive results (Reed et al., 2004). A trial with memantine in our clinic is nearing completion but is unlikely to yield promising results. Transcranial magnetic stimulation of the left prefrontal cortex appears to have led to improvement in one patient (Finocchiaro et al., 2006). Discovering effective pharmacological treatments constitutes the most critical challenge facing this field.

While we await the appearance of effective therapies, PPA offers a unique experiment of nature for exploring the molecular fingerprints that make the language network a primary disease target and for probing the cognitive architecture of human language as it undergoes a slow but relentless dissolution. Considering the progress achieved during the past 25 years, it is safe to predict that future work on PPA will yield pivotal insights into human language, the mechanisms
of neurodegeneration, and the molecular underpinnings of system-based selective vulnerabilities.

Acknowledgements

Supported by grants DC008552 from the National Institute on Deafness and other Communication Disorders and AG13854 from the National Institute on Aging.

References


