PRIMARY PROGRESSIVE APHASIA

‘Primary progressive aphasia’ (PPA) refers to a group of degenerative brain disorders (dementias) in which loss of speech and language abilities is the leading and most prominent problem. ‘Aphasia’ refers to a neurological language problem; ‘progressive’, becoming worse over time; and ‘primary’, due to brain tissue changes rather than an external cause. PPA affects both sexes and usually starts between the ages of 50 and 70. However, it can also affect older people, and rarely, younger people.

Within PPA three main patterns of language loss are recognised:

1) **Progressive Non-fluent Aphasia (PNFA):** speech becomes effortful and distorted and there are often associated grammatical errors in speaking and writing

2) **Semantic dementia (SD):** there is a loss of vocabulary and ability to understand spoken and written words (though speech itself is fluent) and ability to recognise people or objects also becomes affected

3) **Logopenic aphasia (LPA):** there is a problem finding words leading to pauses in conversation and often associated mispronunciations and use of wrong words

PNFA and SD fall within a larger group of brain disorders collectively called **frontotemporal dementia (FTD),** or **frontotemporal lobe degeneration (FTLD),** indicating the parts of the brain mainly affected: the frontal and temporal lobes. Another form of FTD, behavioural variant frontotemporal dementia, mainly affects personality and social behaviour. However, as the disease spreads to other brain areas, people with these conditions often show overlapping symptoms. LPA, by contrast, is usually caused by Alzheimer pathology (it is an unusual form of **Alzheimer’s disease**).

All forms of PPA are caused by slow loss of brain cells due to accumulation and spread of pathological proteins, for reasons that remain poorly understood. At present, this process is not reversible by treatment and so all forms of PPA lead to a long term deterioration in language and other cognitive and neurological functions. Why pathological proteins accumulate and how cell changes lead to brain tissue loss and symptoms are vitally important questions that we need to answer to design effective treatments – the answers will only come through further research. However, it is important not to lose sight of the tremendous advances in understanding PPA that have already been made – advances that have been directly inspired and enabled by patients, their families and supporters.

The Dementia Research Centre team of neurologists, psychologists and nurses runs the NHS **Specialist Cognitive Disorders Clinic** at the National Hospital for Neurology and Neurosurgery on Queen Square in London for the clinical assessment and management of people with PPA and related conditions.

**Edited by Dr. Chris Hardy and Professor Jason Warren, November 2017**

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PROGRESSIVE NON-FLUENT APHASIA (PNFA)

Early symptoms of PNFA include:

- Difficulty producing words - although the person knows what they want to say, speech is non-fluent, hesitant or effortful, and speech is often distorted. This is due to a problem coordinating the movements of speech, sometimes called ‘speech apraxia’.
- Difficulty organising words - sentences may break down with omissions of words or other errors in the structure (grammar) of the sentence, though this is often much less affected than pronunciation.
- Difficulty understanding more complex messages - though understanding of others is usually much better than the production of speech.

Together these factors make speech difficult to understand and communication more difficult. Although written communication is often much better than speech to start with, writing usually becomes affected in time.

As the disease progresses, the person with PNFA tends to develop additional problems with other aspects of thinking, movement and neurological functions. These may include:

- Increasing difficulty understanding language, changes in behaviour, difficulty using tools and gadgets, and a decline in organisational skills and memory.
- Difficulty with swallowing and/or symptoms similar to Parkinson’s disease such as a slowing or clumsiness of movements, poor balance, tremor and difficulty using the hands.

Magnetic resonance imaging (MRI) of the brain often shows shrinkage (atrophy) mainly affecting the language production areas in the frontal and temporal lobes on the left side of the brain (see below).

In most patients, PNFA is ‘sporadic’ in that we do not know why it develops in that particular person. Rarely, there may be a family history and a gene mutation may be the cause.
SEMANTIC DEMENTIA

Early symptoms of SD include:

• Not knowing the word to use - often substituting a less precise word or a general term such as ‘thing’ instead of the specific word, with a ‘roundabout’ (though fluent) way of speaking
• Difficulty understanding words - loss of vocabulary and knowledge of word meanings, spoken and written. The person may ask the meaning of particular words that were well known to them. This is due to erosion of the brain’s ‘semantic’ (meaning) memory system, hence the name ‘semantic dementia’

As the disease progresses, the person with SD tends to develop additional problems with understanding and behaviour. These may include:

• Increasing difficulty recognising familiar people or everyday items, by sight or by sound
• Changes in personality, becoming more inflexible about time and routines, more obsessional or disinhibited in public
• Inability to recognise or react appropriately to other people’s emotions
• Development of a sweet tooth, changes in appetite or decline in table manners
• Development of intense new interests, for example in music or puzzles
• Changes in sensitivity to pain, temperature and bodily sensations, alterations of hearing

Sometimes non-language problems (such inability to recognise familiar people) may be prominent early in the illness or may even be the leading symptom. Over time, difficulties with understanding and behaviour limit the person’s independence even though physical strength, coordination and mobility remain relatively unaffected.

Magnetic resonance imaging (MRI) of the brain shows shrinkage (atrophy) mainly affecting the brain areas that store knowledge about words, people and objects in the temporal lobes – initially, the ‘dominant’ (in most people, the left) side of the brain is usually most affected and to a lesser extent, also the opposite temporal lobe and frontal lobes (see below).

In most patients, SD is ‘sporadic’ in that we do not know why it develops in that particular person.
LOGOPENIC APHASIA

Early symptoms of LPA include:

- Difficulty finding the right word – the person’s conversational speech often contains long pauses or trails off, as they search for the word they need. The Greek term for ‘lack of words’ (‘logopenia’) gives the condition its name.
- Producing the wrong words – these may contain the wrong sounds or substitute the wrong word entirely.
- Difficulty understanding more complex messages and holding information in mind.
- Less marked difficulties with memory and other functions, such as spatial awareness, arithmetic and use of tools and gadgets.

As the disease progresses, these problems tend to become generally more severe and a more widespread picture of cognitive difficulties develops, resembling Alzheimer’s disease.

Magnetic resonance imaging (MRI) of the brain shows shrinkage (atrophy) mainly affecting brain areas in the temporal and parietal lobes that link language stores to language production – the brain areas we use to find words when we are speaking. Initially, the ‘dominant’ (in most people, the left) side of the brain is usually most affected (see below).

In most patients, LPA is ‘sporadic’ in that we do not know why it develops in that particular person.

Because most people with LPA have Alzheimer changes in the brain, this opens up the possibility of using the medicines prescribed for Alzheimer’s (Donepezil and related drugs) to try to help the symptoms of LPA. Most patients find that any benefit is quite modest and unfortunately these medicines do not affect the associated changes in brain tissue or the course of the illness.

The picture to the right shows a "slice" of the brain on an MRI scan, as if a cut was taken through the brain as shown above
FREQUENTLY ASKED QUESTIONS

How is a diagnosis of PPA made?
At our Specialist Cognitive Disorders Clinic there will initially be a clinical assessment by an experienced team of neurologists, nurses and psychologists. We regard brain scanning (ideally, MRI) as a key step in making an accurate diagnosis of PPA (see pictures above). In some circumstances, other tests such as a lumbar puncture (spinal tap) or more specialised scanning may also be useful.

Is there a treatment for PPA?
There remains no cure for PPA despite intense worldwide research. We recommend speech therapy to help with communication, particularly in PNFA, where people can often use electronic devices and other strategies to help ‘bypass’ their speech difficulty. Co-existing depression, anxiety or behavioural problems can often be managed effectively with a combination of medicines and/or non-medical strategies. It is important to anticipate and manage associated neurological problems such as swallowing difficulty and hearing loss and the help of speech therapists, audiologists, dieticians and/or occupational therapists can be extremely valuable – ideally, under the coordinating eye of an involved GP or local psychiatry team. In LPA and PNFA, we often recommend a trial of Alzheimer medicines (such as Donepezil) as these forms of PPA are more likely to have Alzheimer changes in the brain. However, any benefit from these medicines is modest and they do not alter overall outlook – so it is important people do not feel pressured to take them.

What causes PPA?
The symptoms of PPA are caused by slow loss of brain cells in the language areas of the brain – particularly the left temporal and frontal lobes, and their connections. However, the processes that cause cell loss are not well understood. It is known that there is an abnormal accumulation in brain cells of certain proteins (most often the proteins TDP-43 or tau). The pattern of language difficulty is determined by where in the brain these proteins accumulate, but what makes these proteins deposit, why they occur in particular areas, and how their deposition leads to nerve damage are still being investigated.

Does PPA run in the family?
Some people with PPA have a family history of the same condition or another form of frontotemporal dementia. Recently, mutations in genes causing other forms of frontotemporal dementia have been shown to be associated with PNFA and (rarely) other forms of PPA. However, overall (and particularly where there is no known family history) most people with PPA will not have a hereditary illness. It is much less likely to be hereditary than the behavioural form of frontotemporal dementia.

What is the prognosis for people with PPA?
This is difficult to answer as it can be extremely variable from person to person. However, we know that from the onset of symptoms many people will live over ten years. SD seems in general to have longer life expectancy than other forms of PPA. The onset of other neurological problems tends to be associated with a shorter life expectancy. But there is still no reliable way to estimate life expectancy in an individual person with PPA. There are also practical questions about how long communication and independence will be maintained – again, we lack useful information and staging the disease is an important research priority.
RESEARCH PROGRAMME FOR PPA

Much more research in PPA is needed and will be crucial if we are to arrive at effective treatments. There is currently a team of neurologists, neuropsychologists, brain imaging experts and geneticists researching PPA at the Dementia Research Centre and Institute of Neurology in London. You may be asked to participate in one of the ongoing studies. These studies focus on understanding how symptoms arise in PPA, how abnormalities of brain physiology develop and how these can be detected, how the diagnosis can be made earlier and more reliably, and how PPA can be tracked over time. Our research projects generally involve clinical and psychology assessments and MRI brain scanning (see below) and there may be opportunities to give a blood sample or do other more specialised tests. We ask people volunteering for research to come to a research visit spread over two days, and if possible, repeated the following year so we can measure changes directly.

If you would like further information, please contact our research coordinator, Lucy Russell, by phone on 020 344 83653, or by email at l.russell@ucl.ac.uk

BRAIN DONATION PROGRAMME

Together with pathologists at the Queen Square Brain Bank we are continuing to research the causes of PPA in brain cells and tissues. This research relies on people with PPA offering to donate their brain to research after death. If you are interested in helping out with this research please discuss it with us and we will be able to provide you with more information.