

# Frontotemporal dementia

*Synonyms: Pick complex, Pick's dementia, Pick's disease*

See the separate related [Dementia](#) article.

Frontotemporal dementia (FTD) defines a heterogeneous group of clinical syndromes marked by the progressive, focal neurodegeneration of the frontal and anterior temporal lobes<sup>[1]</sup>.

It is one of the more common causes of dementia before the age of 65<sup>[2]</sup>. This is now considered part of an overlapping collection of syndromes which are more common than has been thought in the past. Pick's disease (PiD) and frontotemporal dementia/degeneration should not be used interchangeably, as PiD is one type of frontotemporal dementia syndrome. The term 'Pick complex' is sometimes used to incorporate other frontotemporal dementias.

## Pathophysiology<sup>[3]</sup> <sup>[4]</sup> <sup>[5]</sup>

There is atrophy of the frontal and temporal lobes. Distribution is lobar, rather than the diffuse atrophy of Alzheimer's disease. There may be loss of neurons or gliosis but no increase in plaque formation. There is a spongy vacuolisation of the frontal and temporal cortex. There are protein inclusions in neurons and glial cells. Frontotemporal lobar degeneration (FTLD) describes the pathological syndromes, whereas frontotemporal dementia (FTD) describes the clinical syndromes.

The histological classification of FTLD into three different groups of diseases is based on the protein inclusions as follows:

- FTLD-TAU. Cellular inclusions contain the protein tau. Also called tau-positive or tauopathies. Includes:
  - Corticobasal degeneration (CBD).
  - Classic PiD. Pick bodies (tau-positive spherical cytoplasmic inclusions) and Pick cells (ballooned neurons) are typically seen.
  - Progressive supranuclear palsy (PSP).
- FTLD-TDP. Cellular inclusions contain trans-acting response (TAR) DNA-binding protein 43 (TDP-43). Also called TDP-opathies. There are subtypes A-D.
- FTLD-FUS. Cellular inclusions contain fused-in sarcoma (FUS) protein. FUS-opathies:
  - Rare - the other two types are equally the most common.
  - Includes atypical FTLD with ubiquitinated inclusions (aFTLDU).

There is a significant genetic component. Heritability, however, varies with the different clinical subtypes (discussed below) [6].

## Epidemiology [7]

- FTD is much less common than Alzheimer's disease and vascular dementia. Figures vary, but it probably accounts for less than 5% of all dementia [8]. It is, however, the second or third most common type of dementia presenting in those under the age of 65.
- The incidence of FTD is estimated to be 1.61 to 4.1 cases per 100,000 people annually [9].
- It is probably, however, significantly under-diagnosed. Current molecular techniques may now be able to distinguish the type of dementia at autopsy more accurately, and incidence and prevalence figures are likely to rise.
- It presents most commonly in the sixth decade, but may occur any time between the third and ninth decades.
- Up to 10% to 15% of cases are associated with an autosomal dominant genetic mutation [10].

# Presentation

Onset tends to be insidious and progression gradual. There are three main clinical syndromes of FTD. These are defined by the predominant symptom at presentation. They are<sup>[3]</sup> <sup>[7]</sup> :

- Behavioural variant frontotemporal dementia.
- Progressive non-fluent aphasia.
- Semantic dementia.

## **Behavioural variant FTD**

This is the most common clinical syndrome accounting for around one half to two thirds of cases.

Typical symptoms include:

- Loss of inhibition.
- Inappropriate social behaviour.
- Loss of motivation but without depression.
- Loss of empathy and sympathy.
- Change in preferences.
- Repetitive or compulsive behaviours, rituals.
- Loss of control over eating or drinking.
- Difficulties with planning, organisation or decision making.
- Memory and visuospatial skills usually preserved in early stages. Cognitive deficit less apparent than behavioural changes.
- Lack of insight.
- Loss of awareness of personal hygiene, and incontinence as the disease progresses.

On examination:

- There are usually no neurological signs, unless part of an overlap syndrome (see below).

- Neurological examination may show primitive reflexes (forced grasping, rooting, sucking) in later stages.
- There may be echolalia (repetition of sounds made by another person), perseveration (continued repetition of a particular response) or mutism.
- There may be inappropriate or disinhibited behaviour during consultation.

### **Semantic dementia**

Common early symptoms include:

- Loss of vocabulary with fluency of speech maintained.
- Asking the meaning of familiar words.
- Difficulty finding the right word and having to talk around it or describe it.
- Loss of recognition of familiar faces or objects.
- Memory and visuospatial skills comparatively well preserved.

Neurological examination is usually normal.

### **Progressive non-fluent aphasia**

Common early symptoms include:

- Slow, hesitant, difficult speech.
- Grammatical errors in speech.
- Impaired understanding of complex sentences, although recognition of individual words is preserved.
- Loss of literacy skills.

On examination:

- There may be impairment of orofacial movements such as swallowing, coughing or yawning on command (although still present as a reflex).

- There may be stuttering, impairment of ability to write or read, or impaired repetition ability.

## Overlap syndromes

FTD frequently overlaps with:

- [Progressive supranuclear palsy](#). There is impairment of vertical gaze, postural instability, falls, behavioural change, and cognitive impairment.
- Corticobasal syndrome. There is asymmetric apraxia, accompanied by rigidity, myoclonus and involuntary movements of the affected side.
- [Motor neurone disease](#). Both behavioural and language problems may develop alongside the motor disorders. Fasciculations of upper arm musculature may be an early feature. There may be both cognitive and behavioural impairment.

In overlap syndromes there may be [Parkinsonian](#) symptoms and signs with rigidity, apraxia and dystonia, along with other motor disorder changes.

## Differential diagnosis

Includes:

- [Alzheimer's disease](#).
- [Cerebrovascular disease](#).
- Conditions affecting the frontal lobes, including frontal lobe epilepsy, frontal lobe syndromes, infections or abscesses, frontal lobe tumours, olfactory groove meningiomas, etc.
- Primary psychiatric illness.
- [HIV](#)-related disease such as [AIDS](#) dementia complex.
- [Huntington's disease](#).
- [Hydrocephalus](#).
- [Herpes simplex encephalitis](#).
- Tertiary neurosyphilis.

- Sequential bilateral thalamic strokes.
- [Lyme disease](#).
- [Multiple sclerosis](#).
- Prion-related diseases such as [Creutzfeldt-Jakob disease](#).
- Substance abuse.
- Metabolic disturbances and nutritional deficiencies.

## Investigations

Blood and urine tests:

- Dementia screen which should include B12, U&Es, TFTs, ANF and TPHA (if appropriate).
- If encephalopathy is suspected, note particularly FBC, LFTs, biochemistry, ammonia level, erythrocyte sedimentation rate (ESR) and urine toxicology.
- If Parkinsonism is present, add caeruloplasmin and serum copper (to exclude Wilson's disease) with a peripheral blood screen for acanthocytes.

Genetic tests for Huntington's disease may be indicated.

Lumbar puncture with extensive testing of CSF is done routinely by some specialists in the field.

- Measurement of biomarkers in the CSF has been useful in Alzheimer's disease (raised levels of phosphorylated tau protein and low levels of beta-amyloid are found). This may help distinguish FTD from Alzheimer's disease. However, levels of tau and beta-amyloid in the CSF of patients with FTDs have been less useful in diagnosis and assessing prognosis<sup>[11]</sup>.
- Further tests may include CSF examination (for chronic meningitis and HIV-related disease) and, if inattention is prominent, exclusion of Lyme disease (Lyme serology) and metastatic carcinoma may be necessary.

Imaging is essential to exclude other causes of symptoms, confirm the diagnosis and help try to differentiate between the types of dementia:

- MRI is preferred, as CT scans can miss relevant pathology - for example, metastases and subcortical infarcts<sup>[3]</sup>. CT scan of the brain if MRI is contra-indicated.
- Metabolic brain imaging with single-photon emission computerised tomography (SPECT) or fluorodeoxyglucose positron emission tomography (FDG-PET) may be more accurate in further determining the area of pathology<sup>[12]</sup>.
- If the diagnosis is uncertain and frontotemporal dementia is suspected, the national Institute for Health and Care Excellence (NICE) recommends FDG-PET or perfusion SPECT. FTD should not be ruled out solely on the results of structural, perfusion or metabolic imaging tests<sup>[13]</sup>.

## Management<sup>[3]</sup> <sup>[13]</sup>

There is no treatment to stop the progression of FTD. Anticholinesterase (AChE) inhibitors or memantine should not be used<sup>[13]</sup>.

Management is therefore directed at alleviating symptoms, providing support and information for those with FTD and their families, and keeping them safe. This will involve multidisciplinary health and social care, which needs to be co-ordinated. Referrals to other agencies will be required, which may include geriatric medicine, psychiatry, psychology, social work, occupational therapy, speech and language therapy, physiotherapy and community nursing.

### Non-pharmacological management

This should incorporate:

- Provision of information to the patient and family, with full discussion of investigations, results, diagnosis, prognosis and management.
- Helping with organisation of social and family care.
- Help with forward planning: financial, occupational, housing, care, etc. Lack of insight means this should be considered early, and should involve family.

- Considering safety issues which may become a problem due to lack of insight or behavioural changes: driving, dependants, occupation, consequences of antisocial or psychopathic behaviour.
- Advising a stable routine.
- Anticipating motor and gait difficulties – consider practical aids, physiotherapy, occupational therapy. Consider further mobility and continence aids as disease progresses.
- Speech and language therapy referral for swallowing difficulties or communication difficulties.
- Considering the needs of the family and carers – provide regular respite, referral for counselling or psychological support, and advice about support groups, and also consider genetic counselling.

## Pharmacological management

- Stop drugs which may be exacerbating memory problems or confusion (anticholinergics, CNS drugs).
- Selective serotonin reuptake inhibitors (SSRIs) may be helpful in modifying behavioural symptoms. Evidence is limited to small studies.
- Atypical antipsychotics are used where there are severe behavioural problems such as agitation and psychosis. These are only used cautiously and when SSRIs have failed, as those with FTD are at higher risk of extrapyramidal side-effects.
- Levodopa/carbidopa may be tried where there are Parkinsonian symptoms, and dopamine agonists where this is not effective.

## Prognosis<sup>[3]</sup> <sup>[14]</sup>

FTD shows poor life expectancy but with survival comparable to that of Alzheimer's disease<sup>[15]</sup> .



Slow progression of symptoms, with increased disability both at work and home, is usual. There is gradual decline in social, cognitive and neurological abilities. The eventual outcome is usually complete dependency requiring institutional care. Average survival is 8–10 years. However, there is great variation across the spectrum of clinical syndromes. Best prognosis tends to be in those with the semantic type, and survival may be as long as ten years or more. Worst prognosis is associated in the overlap syndrome with motor neurone disease, and there may only be 3–5 years between onset and death.

The distinct clinical syndromes tend to converge as the disease progresses, with those with the behavioural variant developing speech problems, and those with the semantic type developing behavioural changes. It is a particularly difficult disease for family and friends to come to terms with, due to behavioural changes, physical as well as cognitive disability, and loss of communication.

## Prevention

Where there is a strong family history of FTD, genetic testing should be discussed. Genetic counselling should be undertaken before testing is undertaken.

For the future, it has recently been shown that increasing levels of the protein progranulin (PGRN) may be beneficial to neurons and prevent FTLD. Mutations in the progranulin gene (GRN) are a cause of some types of FTLD. Because these mutations have been linked to abnormal deficiencies in the production of PGRN, researchers are looking for therapies which could increase PGRN levels in affected individuals, potentially alleviating the symptoms associated with disease<sup>[16]</sup> .

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## Further reading

- [Cardarelli R, Kertesz A, Knebl JA](#); Frontotemporal dementia: a review for primary care physicians. *Am Fam Physician*. 2010 Dec 1;82(11):1372–7.

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