

Frontotemporal dementia

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Abstract

Frontotemporal dementia (FTD) is the prototypical behavioural disorder arising from frontotemporal cerebral atrophy. Depending on the age range, prevalence has been estimated between 3.6 and 15 per 100.000 persons. The clinical term FTD covers a heterogeneous group of sporadic and familial neurodegenerative diseases with respect to etiology, neuropathology and biochemical features. FTD occurs primarily between the ages of 35 and 75 years. The most common presentation is an early change in personality, social behaviour, and language dysfunction, with relative preservation of memory functions. It might be associated with clinical symptoms of Parkinsonism and the amyotrophic form of motor neuron disease. Degenerative lesions detected by cerebral imaging (MRI, SPECT) mainly involve the frontal and temporal lobes. The current consensus on the pathological classification of FTD is based on the morphology and the histochemical and biochemical characterization of inclusion bodies or their absence. To date 4 subgroups of FTD have been defined: 1) FTD with tau inclusions-[Pick's disease](#), [corticobasal degeneration](#), [progressive supranuclear palsy](#), [familial FTD with Tau gene mutations](#); 2) FTD lacking distinctive histopathology; 3) FTD with ubiquitin-positive motor neuron disease-type inclusions; 4) FTD with neurofilament-positive inclusions. Antibodies against tau, ubiquitin and neurofilaments are used for the specification of inclusions. The characterization of familial forms of FTD (25 to 40% of patients) enabled the identification of 3 gene loci with subsequent characterization of the tau gene as one FTD disease gene in 10-30% of familial cases. In spite of the progress in the clinical diagnosis, to date a definite diagnosis and discrimination of the single FTD entities is still only possible by neuropathological examination of the brain. Management is only symptomatic.

Keywords

Frontotemporal dementia (FTD), Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), dementia lacking distinct histopathology (DLDH), Pick's disease, ubiquitin, tau, neurofilament

Disease name / synonyms

Frontotemporal dementia

Frontotemporal lobe dementia

Frontal lobe dementia

Included diseases

[Pick's disease](#)

Pick complex

[Frontotemporal dementia and parkinsonism linked to chromosome 17 \(FTDP-17\)](#)
[Progressive supranuclear palsy \(PSP\)](#)
[Corticobasal degeneration \(CBD\)](#)

Definition, clinical description and diagnostic criteria

Frontotemporal dementia (FTD) is the prototypical behavioural disorder arising from frontotemporal cerebral atrophy. The clinical term FTD covers a heterogeneous group of sporadic and familial neurodegenerative diseases with respect to etiology, neuropathology and biochemical features.

The most common presentation of FTD is an early change in personality, social behaviour, and language dysfunction, with relative preservation of memory functions. It might be associated with clinical symptoms of Parkinsonism and the amyotrophic form of motor neuron disease.

Clinical diagnostic features of FTD are listed in **Table 1** (Neary *et al.*, 1998).

Table 1: Clinical diagnostic criteria for FTD

I. Core diagnostic features (all features must be present)

- Insidious onset and gradual progression
- Early decline in social interpersonal conduct
- Early impairment in regulation of personal conduct
- Early emotional blunting
- Early loss of insight

II. Supportive diagnostic features

Behavioral disorder

- 1. Decline in personal hygiene and grooming
- 2. Mental rigidity and inflexibility
- 3. Distractibility and impersistence
- 4. Hyperorality and dietary changes
- 5. Perseverative and stereotyped behavior
- 6. Utilization behavior

Speech and language

- 1. Altered speech output
 - A. Aspontaneity and economy of speech
 - B. Press of speech
- 2. Stereotype of speech
- 3. Echolalia
- 4. Perseveration
- 5. Mutism

Physical signs

- 1. Primitive reflexes
- 2. Incontinence
- 3. Akinesia, rigidity, and tremor
- 4. Low and labile blood pressure

III. Supportive features

- Onset before 65 years
- Positive family history of similar disorder in first-degree relatives
- Bulbar palsy, muscular weakness and wasting, fasciculations (associated motor neuron disease present in a minority of patients)

IV. Diagnostic exclusion features (all features must be absent)

- 1. Abrupt onset with ictal events
- 2. Head trauma related to onset
- 3. Early, severe amnesia
- 4. Spatial disorientation
- 5. Logoclonic, festinant speech with loss of train of thought
- 6. Myoclonus
- 7. Corticospinal weakness
- 8. Cerebellar ataxia
- 9. Choreoathetosis

V. Relative diagnostic exclusion features

- Typical history of chronic alcoholism
- Sustained hypertension
- History of vascular disease (*e.g.*, angina, claudication)

Differential diagnosis

[Alzheimer's disease \(AD\)](#) is characterized by early and profound difficulties in learning and retaining new information. In FTD memory loss is less prominent; however, memory difficulties often worsen as the disease progresses. The early appearance of behavioural symptoms, common in FTD, is unusual in AD. In addition, the occurrence of motor abnormalities is more likely in FTD than in AD patients (McKhann *et al.*, 2001).

Special subtypes of vascular dementias, such as selective incomplete white matter infarctions (SIWI), [Binswanger's disease](#), multi-infarct dementia with frontal emphasis and strategic infarct dementia due to bilateral thalamic infarctions, may be misinterpreted as FTD (Larsson *et al.*, 2000).

Diagnostic methods

Imaging

Structural and functional brain imaging (MRI, SPECT) may show a predominant frontal and / or anterior temporal atrophy, sometimes with a striking asymmetry, and should be performed to exclude other causes for dementia such as vascular changes.

Neuropsychology

Significant impairment on frontal lobe tests in the absence of severe amnesia or perceptuospatial disorder.

Laboratory tests

Investigation of serum and cerebrospinal fluid (CSF) to exclude other diseases with brain involvement, such as inflammatory and metabolic disorders.

To date, a specific and sensitive serum and CSF marker enabling differentiation of FTD from other forms of neurodegenerative disorders is still lacking.

Post mortem examination of the brain

To date, the definite diagnosis of FTD as well as the determination of the single FTD subtypes is only possible by post mortem histological examination of the brain.

Epidemiology

FTD occurs primarily between the ages of 35 and 75 years (Van Deerlin *et al.*, 2003). Data on prevalence and incidence of FTD are scarce. In a recent study from the UK, the prevalence has been estimated at 15 cases per 100.000 persons in the 45- to 64-year-old-range (Ratnavalli *et al.*, 2002). The prevalence of FTD in another study from the Netherlands was 3.6 cases per 100.000 persons at ages 50-59 years, 9.4 per 100.000 at ages 60-69 years, and 3.8 per 100.000 at ages 70-79 years (Rosso *et al.*, 2003).

Both sexes are affected equally. About 25-40 % of patients have a positive family history of FTD, and approximately 10-30 % of these patients have a mutation in the *Tau* gene (Poorkaj *et al.*, 2001).

Etiology

Based on pathological and biochemical data, the clinical term FTD is a heterogeneous group of disorders and therefore the etiology is different in the specific subtypes. **Table 2** shows the current pathological classification of FTDs (modified after Munoz *et al.*, 2003).

Table 2: Classification of FTDs based on neuropathological and biochemical features

1. FTD with tau inclusions
 - [Pick's disease](#)
 - [Corticobasal degeneration](#)
 - [Progressive supranuclear palsy](#)
 - [Familial FTD with Tau gene mutations](#)
2. FTD lacking distinctive histopathology
3. FTD with ubiquitin-positive motor neuron disease-type inclusions
4. FTD with neurofilament-positive inclusions

1. FTD with tau accumulation

Several pathological entities of FTD are associated with filamentous deposits made of the hyperphosphorylated microtubule-associated protein tau: [Pick's disease](#) (PiD), [progressive supranuclear palsy](#) (PSP), [corticobasal degeneration](#) (CBD) and a subgroup of [familial FTD linked to chromosome 17q21-22](#). About 15-30 % of clinically diagnosed FTD cases show tau pathology (Munoz *et al.*, 2003; Cooper *et al.*, 1995). Tau is a microtubule-associated protein abundantly expressed in axons. Six tau isoforms are produced in the adult human brain by alternative mRNA splicing from a single gene (Goedert *et al.*, 1989). They differ from each other by the presence or absence of 29- or 58-amino acid inserts located in the amino-terminal

half (0N, 1N, 2N) and an additional 31-amino acid repeat located in the carboxy-terminal half. Inclusion of the latter, which is encoded by exon 10 (E10), gives rise to the 3 isoforms with 4 repeats each (4R); the other 3 isoforms have 3 repeats each (3R). The repeats and some adjoining sequences constitute the microtubule-binding domains of tau. In adult human brain, the ratio of 3R to 4R isoforms is ~ 1. The regulation of the binding of tau to microtubules is regulated by phosphorylation.

Based on results from *tau* gene mutations, three distinct mechanisms leading to tau dysfunction in disease have been proposed. Some mutations impair the ability of tau to bind to microtubules (MTs) and to promote MT assembly (Hutton *et al.*, 1998; Neumann *et al.*, 2001; Poorkaj *et al.*, 1998). Some of these mutations additionally promote tau aggregation. The third mechanism shown by some exonic and the intronic tau mutations might also play an important role in the pathogenesis of sporadic tauopathies. These mutations alter the splicing of E10 and therefore increase the ratio of 4R to 3R isoforms (Hutton *et al.*, 1998; Hong *et al.*, 1998). This argues that the correct ratio of the single tau isoforms seems to be important for the physiological functioning of the cells. Interestingly, different members of the same kindred often exhibit diverse clinical and neuropathological features, suggesting that additional disease modifying genetic or epigenetic factors influence the phenotypic manifestation of tauopathies (Bird *et al.*, 1999; Bugiani *et al.*, 1999; Spillantini *et al.*, 1998).

2. FTD lacking distinct histopathology

The most common subtype of FTD (about 50-65 %) is characterised by fronto-temporal atrophy without specific inclusion-types or diagnostic markers, therefore the term "dementia lacking distinct histopathology" (DLDH) was established (Knopman *et al.*, 1990).

The underlying pathological mechanisms involved in this subtype are so far not known. The disease has been linked to chromosome 17q21-22 (Lendon *et al.*, 1998; Rademakers *et al.*, 2002) and chromosome 3 in familial forms of DLDH (Gydesen *et al.*, 2002). So far, no tau mutation has been identified in the chromosome 17-linked families with the DLDH phenotype arguing for a second disease gene at 17q21 for FTD.

3. FTD with motor neuron-disease type inclusions

The second most common pathological entity of FTD (about 25 %) is characterized by ubiquitin-positive, tau-negative and α -synuclein-negative inclusions predominantly found in the dentate gyrus of the hippocampus. They are often

associated with typical inclusions found in the brainstem and spinal cord motor neurons as characteristically found in motor neuron disease (Munoz *et al.*, 2003). Clinical features of motor neuron disease may accompany or occasionally precede the onset of dementia or may be absent at all (Mackenzie and Feldman, 2003; Rosso *et al.*, 2001). Familial FTD cases showing this type of inclusions have been linked to chromosome 9q21-22 (Hosler *et al.*, 2000) and chromosome 17q21-22 (Rosso *et al.*, 2001). The protein components in the inclusion bodies as well as the pathological mechanisms involved in this FTD entity are so far unknown.

4. FTD with neurofilament-positive inclusions:

This subtype has been described very recently in a few cases with FTD (Cairns *et al.*, 2003; Cairns and Armstrong, 2003; Josephs *et al.*, 2003). It is characterized by intracytoplasmic neuronal inclusions predominantly found in the frontal and temporal cortex and in the hippocampus, which are strongly labelled by antibodies against neurofilaments. They are negative for tau and α -synuclein. The role of these neurofilament-rich inclusions in neurodegeneration is so far unknown but implicates novel mechanisms.

Genetic counseling

For familial forms of FTD, in which the disease is inherited as an autosomal dominant trait, classical Mendelian models of inheritance can be used to define the risk of transmission. Currently three gene loci (chromosome 17q21-22, 9q21-22 and 3) have been reported in familial FTD. So far, only mutations in the *Tau* gene have been identified as the underlying genetic defect in a subset of chromosome 17 linked FTD families. The finding of *Tau* gene mutations in 32% of patients with a positive family history for dementia in a Dutch cohort (Rosso *et al.*, 2003) justifies mutation screening in FTD patients with a positive family history.

Management including treatment

In the absence of large-scale clinical trials published on FTD, drug therapy remains controversial and hazardous. Serotonergic antidepressants, antipsychotics and monoamine oxidase (type B) inhibitors, may be useful in particular cases, but have to be studied more extensively (Allain *et al.*, 2003).

Unresolved questions

The mechanisms leading to neurodegeneration in the different subtypes of FTD are so far only poorly understood. Particularly, the identification of new disease genes and their associated mutations in the chromosome 3, 9 and 17-linked

familial FTDs will be helpful in understanding disease pathogenesis and may lead to the development of disease-specific tests and therapies.

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