CONSENSUS STATEMENT

Clinical and neuropathological criteria for frontotemporal dementia

The Lund and Manchester Groups

Clinical and neuropathological descriptions of patients with non-Alzheimer's disease atrophy of the frontotemporal lobes have emerged chiefly from Lund, Sweden and Manchester, UK. The nosology of both the clinical syndrome and the underlying histological change is in danger of becoming confused in the medical literature and terminological distinctions between clinical and pathological criteria are not always strictly kept. Accordingly, the workers in both centres have shared their clinical and pathological findings and have decided upon commonly agreed criteria for neuropsychiatric and pathological diagnosis. These are based on clinical evaluation of several hundreds of patients and upon pathological analysis of more than 60 brains. Together these represent the largest series in the world and have been the focus of interest in the two international conferences on Frontotemporal Dementia held in Lund in 1986[1] and 1992[2].

Frontotemporal dementia is the prototypical behavioural disorder arising from frontotemporal cerebral atrophy and is associated in a few cases with the clinical manifestations of the amyotrophic form of motor neuron disease. Two types of histological change underlie the atrophy and both share an identical anatomical distribution in the frontal and temporal lobes. The commonest pathology is that of nerve cell loss and spongiform change (microvacuolation), together with a mild or moderately severe astrocytic gliosis in the outer cortical layers, and is designated frontal lobe degeneration. This is to distinguish it from the typical Pick-type histology characterised by intense astrocytic gliosis in the presence of intraneuronal inclusion bodies and inflated neurons in all cortical layers. Cases of frontotemporal dementia with a similar level of astrocytosis but without inclusions or inflated neurons should be best included in this Pick-type category pending a more definitive histological identification. When spinal motor neuron degeneration occurs, the cerebral pathology is almost always that of frontal lobe degeneration.

This formulation distinguishes the clinical syndrome of frontotemporal dementia from other disorders that may also affect frontotemporal structures, such as Alzheimer's disease, Creutzfeldt-Jakob disease, subcortical vascular disease and Huntington's disease as well as affective and schizophreniform psychoses.

The application of descriptive labels to the three major histological patterns avoids the imputation of aetiological significance. Future studies may indicate that there is a spectrum of non-specific histology involving both, or alternatively, that each may reflect a distinct process governed by different genetic or molecular mechanisms. To consider the Pick's-type of change as a histological variant of frontotemporal atrophy, manifesting clinically as frontotemporal dementia, avoids the vexed clinical and pathological arguments as to what constitutes, so-called "Pick's disease".

Frontotemporal dementia results from bilateral and more or less symmetrical distribution of pathology in the frontotemporal lobes.

Asymmetrical degeneration, however, may, influence the clinical picture. Predominant involvement of the language dominant frontal and temporal lobes leads to linguistic rather than behavioural symptoms.[3,4] The clinical entity of progressive aphasia and the link between this condition and frontotemporal dementia is essentially determined anatomically, both forming part of the clinical spectrum of lobar atrophy and sharing the same spectrum of histology.[5] The criteria for, and the different forms of language breakdown in, progressive aphasia are not discussed here. We describe the clinical and pathological criteria for frontotemporal dementia.

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Clinical diagnostic features of frontotemporal dementia[6–12]

CORE DIAGNOSTIC FEATURES

Behavioural disorder

- Insidious onset and slow progression
- Early loss of personal awareness (neglect of personal hygiene and grooming)
- Early loss of social awareness (lack of social tact, misdemeanours such as shoplifting)
- Early signs of disinhibition (such as unrestrained sexuality, violent behaviour, inappropriate jocularity, restless pacing)
- Mental rigidity and inflexibility
- Hyperorality (oral/dietary changes, overeating, food fads, excessive smoking and alcohol consumption, oral exploration of objects)
- Stereotyped and perservative behaviour (wandering, mannerisms such as clapping, singing, dancing, ritualistic preoccupation such as hoarding, toileting, and dressing)
- Utilisation behaviour (unrestrained exploration of objects in the environment)
- Distractibility, impulsivity, and impersistence

- Early loss of insight into the fact that the altered condition is due to a pathological change of own mental state.

Affective symptoms
- Depression, anxiety, excessive sentimentality, suicidal and fixed ideation, delusion (early and evanescent)
- Hypochondriasis, bizarre somatic preoccupation (early and evanescent)
- Emotional unconcern (emotional indifference and remoteness, lack of empathy and sympathy, apathy)
- Amimia (inertia, aspontaneity).

Speech disorder
- Progressive reduction of speech (aspontaneity and economy of utterance)
- Stereotypy of speech (repetition of limited repertoire of words, pharases, or themes)
- Echolalia and perseveration
- Late mutism.

Spatial orientation and praxis preserved (intact abilities to negotiate the environment).

Physical signs
- Early primitive reflexes
- Early incontinence
- Late akinesia, rigidity, tremor
- Low and labile blood pressure.

Investigations
- Normal EEG despite clinically evident dementia
- Brain imaging (structural or functional, or both): predominant frontal or anterior temporal abnormality, or both
- Neuropsychology (profound failure on "frontal lobe" tests in the absence of severe amnesia, aphasia, or perceptual spatial disorder).

SUPPORTIVE DIAGNOSTIC FEATURES
- Onset before 65
- Positive family history of similar disorder in a first degree relative
- Bulbar palsy, muscular weakness and wasting, fasciculations (motor neuron disease).

DIAGNOSTIC EXCLUSION FEATURES
- Abrupt onset with ictal events
- Head trauma related to onset
- Early severe amnesia
- Early spatial disorientation, lost in surroundings, defective localisation of objects
- Early severe apraxia
- Logoclonic speech with rapid loss of train of thought
- Myoclonus
- Cortical bulbar and spinal deficits
- Cerebellar ataxia
- Choreo-athetosis
- Early, severe, pathological EEG
- Brain imaging (predominant post-central structural or functional deficit. Multifocal cerebral lesions on CT or MRI)
- Laboratory tests indicating brain involvement or inflammatory disorder (such as multiple sclerosis, syphilis, AIDS and herpes simplex encephalitis).

RELATIVE DIAGNOSTIC EXCLUSION FEATURES
- Typical history of chronic alcoholism
- Sustained hypertension
- History of vascular disease (such as angina, claudication).

Neuropathological diagnostic features of fronto-temporal dementia

FRONTAL LOBE DEGENERATION TYPE[5 13–17]

Gross changes

These include slight symmetrical convolutional atrophy in frontal and anterior temporal lobes, neither circumscribed nor of a knife blade type; atrophy can be severe in a few cases. The ventricular system is widened frontally. Usually there is no gross atrophy of the striatum, amygdala or hippocampus although, in some instances, severe involvement of these regions can occur.

Distribution of microscopic changes

Changes are seen in the frontal convexity cortex, sometimes in the orbitofrontal cortex, often in the anterior third of the temporal cortex, and the anterior, but rarely the posterior, cingulate gyrus. The superior temporal gyrus is conspicuously spared.

The parietal cortex is mildly involved in a few patients, more so in rare, advanced cases.

In some patients with pronounced stereotypic behaviours, there is less neocortical involvement, with mostly striatal, amygdala, and hippocampal changes. These may represent a possible subtype.

Microscopic characteristics, grey matter

Microvacuolation and mild-to-moderate astrocytic gliosis affecting chiefly laminae I–III are seen, sometimes one or the other change prevailing.

There is atrophy/loss of neurons in laminae II and III, whereas those of lamina V are mildly affected, being atrophic rather than lost. Occasionally there are a few dystrophic neurites.

There are no Pick bodies, inflated neurons or Lewy bodies. Immunohistochemistry for tau or ubiquitin reveals no distinctive features.

In the substantia nigra of some patients, there is mild-to-moderate loss of pigmented neurons.

Microscopic characteristics, white matter

White matter astrocytic gliosis, moderate to mild, is seen in subcortical u-fibres. There is very mild astrocytic gliosis in deeper white matter, sometimes with slight attenuation and loss of myelin. The distribution is related to grey matter changes. Sometimes there is also ischaemic white matter attenuation.

PICK-TYPE

Gross changes

These have the same topographic localisation as frontal lobe degeneration, but generally more intense and usually more circumscribed. Asymmetry and striatal atrophy is common.

Distribution of microscopic changes

These are the same as frontal lobe degeneration, in agreement with the gross distribution.

Microscopic characteristics, grey and white matter
The main characteristics are the same as frontal lobe degeneration, but with intense involvement of all cortical layers. Inflated neurons and Pick bodies, which are silver positive, tau and ubiquitin immunoreactive, are present. There is more intense white matter involvement. Patients with intense astrocytosis but without inflated neurons or inclusions, or both, may for the present be included.

MOTOR NEURON DISEASE TYPE[18]

Gross changes
These are the same as frontal lobe degeneration, although usually less severe.

Distribution of microscopic changes and microscopic characteristics in grey and white matter
These are the same as for frontal lobe degeneration. There is spinal motor neuron degeneration, affecting cervical and thoracic levels more than lumbar or sacral. There is greater cell loss in medial than lateral cell columns. Motor neurons, layer II neurons in frontal and temporal cortex, and hippocampal dentate gyrus neurons show inclusions that are ubiquitin positive but not silver or tau reactive. Nigral cell loss is severe in many patients. There is also hypoglossal degeneration in some.

DIAGNOSTIC EXCLUSION FEATURES
There are senile plaques, diffuse amyloid deposits, and amyloid angiopathy with anti-β-protein antibodies, tangles, and neuropil threads, with anti-tau and ubiquitin antibodies, more than normal for age. Prion protein are present with anti-prion antibodies.

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