

# Frontotemporal dementia<sup>†</sup>

JULIE S. SNOWDEN, DAVID NEARY and DAVID M. A. MANN

**Background** Frontotemporal dementia accounts for up to 20% of cases of dementia in the presenium, yet remains poorly recognised. Diagnostic criteria have been devised to aid clinical diagnosis.

**Aims** To provide an overview of clinical and pathological characteristics of frontotemporal dementia and its nosological status.

**Methods** The review summarises consensus diagnostic criteria for frontotemporal dementia and draws on the authors' clinical experience of 300 frontotemporal dementia cases, and pathological experience of 50 autopsied cases.

**Results** Frontotemporal dementia is characterised by pronounced changes in affect and personal and social conduct. Some patients also develop motor neuron disease. Mutations in the tau gene account for some but not all familial cases of frontotemporal dementia.

**Conclusions** Frontotemporal dementia is a focal form of dementia, which is clinically and pathologically distinct from other dementias. It represents an important model for understanding the functions of the frontotemporal lobes.

**Declaration of interest** None.

Over a century ago, Arnold Pick described focal syndromes associated with degeneration of the frontal and temporal lobes. For many years these focal disorders were unrecognised, were subsumed within the broad rubric of dementia, and typically assumed to be Alzheimer's disease. Their rediscovery (Gustafson, 1987; Neary *et al*, 1988) led to the development of clinical and neuropathological diagnostic criteria (Anonymous, 1994), the clinical criteria having undergone recent revision (Neary *et al*, 1998). Frontotemporal dementia denotes a clinical syndrome, characterised by behavioural change. Only a minority of patients exhibit Pick-type histological changes, hence the term 'frontotemporal dementia' is preferred to 'Pick's disease', which forms part of the ICD-10 and DSM-IV classifications of dementia (World Health Organization, 1992; American Psychiatric Association, 1994).

## OVERVIEW OF FRONTOTEMPORAL DEMENTIA

### Clinical features

Frontotemporal dementia is the most common form of primary degenerative dementia after Alzheimer's disease that affects people in middle age, accounting for up to 20% of presenile dementia cases. Onset occurs most commonly between the ages of 45 and 65 years, although the disorder can present before the age of 30 years as well as in the elderly. There is an equal incidence in men and women. The mean duration of illness is 8 years, ranging from 2 years to 20 years. A family history of dementia is present in about half of cases.

The salient clinical characteristic is a profound alteration in character and social conduct, occurring in the context of relative preservation of instrumental functions of perception, spatial skills, praxis and

memory. Behavioural features, specified in current consensus diagnostic criteria (Neary *et al*, 1998), are summarised in the Appendix. Decline in social conduct includes breaches of interpersonal etiquette, tactlessness and disinhibition. Impairment in regulation of personal conduct refers to departures from customary behaviour of a quantitative type and includes passivity and inertia as well as overactivity, pacing and wandering. Emotional blunting includes loss of the capacity to demonstrate both primary emotions such as happiness, sadness and fear, and social emotions such as embarrassment, sympathy and empathy. Impaired insight includes impairments both in explicit cognitive awareness of symptoms and in emotional awareness as defined by the lack of expression of concern or distress when confronted by difficulties.

Dietary changes typically take the form of overeating and a preference for sweet foods. Perseverative and stereotyped behaviours encompass simple repetitive behaviours such as humming, hand-rubbing and foot-tapping, as well as complex behavioural routines. Utilisation behaviour refers to stimulus-bound behaviour, in which patients grasp and use an object in their visual field, despite its contextual inappropriateness (e.g. drinking from an empty cup).

Speech output is attenuated and features of echolalia and perseveration may be present. Verbal stereotypies include repeated use of a word, phrase or complete theme. Mutism ultimately ensues. Cognitive changes are indicative of frontal lobe dysfunction. Patients show attentional deficits, poor abstraction, difficulty shifting mental set and perseverative tendencies. Although the primary tools of perception, spatial function and memory are preserved, performance on tests of these functions may be compromised by inattention, inefficient retrieval strategies, poor organisation, lack of self-monitoring, and lack of concern for accuracy.

Neurological signs are typically absent early in the disease or limited to the presence of primitive reflexes. However, Parkinsonian signs of akinesia and rigidity develop with disease progression and may be marked in a proportion of patients. A minority of patients with frontotemporal dementia develop neurological signs of motor neuron disease.

Routine electroencephalography is invariably normal. Brain imaging reveals abnormalities in the frontal and temporal

<sup>†</sup>See editorial, pp. 97–98, this issue.

regions that are bilateral but sometimes asymmetrical. Functional imaging techniques such as single-photon emission computed tomography (SPECT) are most sensitive to such changes. Structural imaging using magnetic resonance imaging is more sensitive than computed tomography.

### Neuropathology

Post-mortem pathological examination reveals bilateral atrophy of the frontal and anterior temporal lobes and degeneration of the striatum. Histological findings are of three main types (Anonymous, 1994). The most common (microvacuolar) type, accounting for about 60% of cases, is characterised by loss of large cortical nerve cells and a spongiform degeneration or microvacuolation of the superficial neuropil; gliosis is minimal and there are no distinctive changes (swellings or inclusions) within the remaining nerve cells. The limbic system and the striatum are affected but to a relatively mild degree. A second histological pattern (Pick type), accounting for approximately 25% of cases, is characterised by a loss of large cortical nerve cells with widespread and abundant gliosis but minimal or no spongiform change or microvacuolation. Swollen neurons or inclusions that are positive for both tau and ubiquitin are present in most cases, and the limbic system and striatum are more seriously damaged. The two different histological types share a similar distribution within the frontal and temporal cortex. In about 15% of cases, clinical features of both frontotemporal dementia and motor neuron disease are present during life, and microvacuolar (or very rarely Pick type) histological features are combined with those of motor neuron disease.

### SUBTYPES OF FRONTOTEMPORAL DEMENTIA

There is evidence of heterogeneity of clinical presentation. Some patients are disinhibited, fatuous, purposelessly overactive, easily distracted, socially inappropriate and lacking in concern. At the other extreme, patients are bland, apathetic, inert, lacking volition and mental effort, mentally rigid and perseverative. In a proportion of patients the salient presenting characteristic is stereotyped, ritualistic behaviour. The

disinhibited form of frontotemporal dementia is associated with pathological changes confined to orbitomedial frontal and anterior temporal regions, whereas the apathetic form occurs when pathological change is extensive throughout the frontal lobes and extending into the dorso-lateral frontal cortex. The stereotypic form of frontotemporal dementia occurs in association with marked striatal changes and variable cortical involvement, often with the emphasis on temporal rather than frontal lobe pathology.

These broad behavioural subtypes reflect regional but not hemispheric differences between patients. There is, however, some evidence that hemispheric asymmetries too may influence the behavioural presentation. Social behaviour has been shown to be more disrupted in patients with predominantly right-hemisphere pathological changes (Edwards-Lee *et al*, 1997), suggesting a particular role of the right hemisphere in social behaviour.

### RELATED CLINICAL SYNDROMES

Patients with the behavioural disorder of frontotemporal dementia account for the largest proportion (at least 70%) of patients with non-Alzheimer frontotemporal lobar degeneration. However, other clinical syndromes share the same histopathological characteristics (Snowden *et al*, 1996; Neary *et al*, 1998). One is semantic dementia, in which there is progressive loss of concepts, affecting the ability to understand the meaning of words, objects, faces, non-verbal environmental sounds, smells, tastes and tactile stimuli. Pathological change is pronounced in the temporal neocortices, particularly the inferior and middle temporal gyri. Another syndrome is progressive non-fluent aphasia, in which a highly circumscribed disorder of language is associated with markedly asymmetric atrophy affecting the left hemisphere extensively. Occasionally patients may present with a circumscribed apraxia, in association with atrophy of the frontoparietal regions. These syndromes are less common than the behavioural disorder of frontotemporal dementia. Semantic dementia accounts for about 15%, progressive aphasia 10% and progressive apraxia 2% of cases of frontotemporal lobar degeneration.

### BEHAVIOUR AND DIFFERENTIAL DIAGNOSIS

The overriding feature of frontotemporal dementia is the profound character and behavioural changes and it is the historical account of these changes that plays the most critical part in diagnosis. In a study of the original consensus statement (Anonymous, 1994), Miller *et al* (1997a) made a comparison of 30 patients with frontotemporal dementia and 30 with Alzheimer's disease, classified clinically on the basis of SPECT findings; 8 of the patients with frontotemporal dementia had subsequent confirmation of diagnosis at autopsy. The behavioural features of loss of social awareness, hyperorality, stereotyped and perseverative behaviour, reduced speech output and preserved spatial orientation best discriminated the two groups, with sensitivity for frontotemporal dementia ranging between 63% and 73% and specificity between 97% and 100%. A discriminant function analysis correctly classified 100% of patients with frontotemporal dementia or Alzheimer's disease on the basis of these behavioural features.

Our own more recent studies provide further evidence of the importance of dietary changes and repetitive and stereotyped behaviours in differential diagnosis. We have found too that the loss of affective response (generalised blunting of emotions) is a key factor in distinguishing frontotemporal dementia from both Alzheimer's disease and cerebrovascular dementia. It is known that emotional unconcern may be heralded in the prodromal and early stage of frontotemporal dementia by symptoms of anxiety, depression and hypochondriacal rumination (Anonymous, 1994). However, these symptoms are typically transient, and provide a less reliable diagnostic marker than the blunting of affect. Similarly, although irritability may be reported in some patients with frontotemporal dementia, it is not more frequent than in other forms of dementia, and is therefore a relatively poor diagnostic marker. In line with the loss of social emotions, social behaviour is highly disordered in frontotemporal dementia, and is a valuable factor in differential diagnosis (Miller *et al*, 1997b; Sjögren *et al*, 1997).

### REPETITIVE AND COMPULSIVE BEHAVIOURS

Repetitive behaviours in frontotemporal dementia take a variety of forms. They

include simple motor mannerisms as well as complex behavioural routines. They occur in the verbal domain in the form of stereotyped use of words or phrases, and in the motor domain as wandering and pacing. Some repetitive behaviours have a distinctly compulsive quality. Compulsive-type behaviours may take the form of clock-watching and adherence to a fixed routine, superstitious rituals such as avoiding standing on cracks in the pavement, or may involve a complex sequence of actions, such as tapping each wall twice upon entering a room.

At first sight the presence of compulsive behaviours seem at odds with the prevailing lack of emotional concern. However, ritualistic and compulsive behaviours are not present in all patients with frontotemporal dementia. Our own experience (Snowden *et al*, 1996) suggests that they occur in patients with predominantly striatal rather than neocortical pathological changes and in patients with the disinhibited form of frontotemporal dementia, in whom there are orbitofrontal and anterior temporal lobe changes, rather than in those with apathetic frontotemporal dementia who have widespread frontal changes extending into dorsolateral frontal cortices. That the temporal lobes, in addition to the striatum, may have an important role in compulsive behaviours is suggested, moreover, by the high frequency of these behaviours in patients with semantic dementia, in whom the predominant pathology is temporal rather than frontal (Snowden *et al*, 2001). In these patients clock-watching and adherence to a fixed routine are prominent features. Although the compulsive behaviours in frontotemporal dementia and related syndromes have affinities with those of obsessive-compulsive disorder, patients with frontotemporal dementia do not typically experience the feelings of anxiety and release from anxiety characteristic of obsessive-compulsive disorder.

## TREATMENT

Rational treatments for frontotemporal dementia are currently limited. Neurochemical studies indicate no abnormality of the cholinergic system, so that pharmacological agents designed for Alzheimer's disease are unlikely to benefit patients with frontotemporal dementia. Nevertheless, there is some evidence that behavioural symptoms, such as disinhibition, overeating and compulsions, may

benefit from treatment with selective serotonin reuptake inhibitors (Swartz *et al*, 1997), suggesting that a modicum of symptomatic improvement can be achieved at least in some cases.

## NOSOLOGICAL ISSUES

Uncertainties regarding the nosological status of frontotemporal dementia have arisen for a number of reasons. The clinical syndromes arising from frontotemporal lobar degeneration are not uniform. The disorder itself can be separated into disinhibited, apathetic and stereotypic forms. In a minority of patients with frontotemporal dementia, extrapyramidal signs occur early and are marked, leading to distinct designations of dementia with parkinsonism. Clinically distinct syndromes such as progressive non-fluent aphasia and semantic dementia share the same pathological findings. Moreover, the pattern of histological change also is not uniform, being characterised by microvacuolation (frontal lobe dementia (FLD) type), sometimes combined with histological changes of motor neuron disease (MND type), or severe gliosis with or without inclusions and ballooned cells (Pick type). The clinical syndrome does not predict histological type, so that clinical distinctiveness itself does not imply aetiological difference. Nevertheless, the presence of distinct histological characteristics raises the question whether frontotemporal dementia reflects a single or multiple entities. Advances in molecular genetics are beginning to unravel this issue.

Genetic linkage studies have established the presence of a causative gene on the long arm of chromosome 17 (17q21–22) in some families with autosomal dominant inheritance, and mutations in the tau gene have been identified in some cases (Hutton *et al*, 1998). The identification of mutations in tau associated with Pick type as well as microvascular histological changes links the two histological patterns into the same disease entity. Nevertheless, tau pathology, as shown by immunohistochemistry and mutations in tau, accounts for only a proportion of patients with frontotemporal dementia (Mann *et al*, 2000). Moreover, a frontotemporal dementia clinical phenotype has shown linkage to chromosome 3 (Brown *et al*, 1995) and frontotemporal dementia occurring in association with motor neuron disease has shown linkage

to chromosome 9 (Hosler *et al*, 2000). There is thus a need for caution in assuming that all cases of frontotemporal dementia represent tauopathies and have a common aetiology. The clinical and pathological variants of frontotemporal lobar degeneration may reflect different phenotypic expressions of particular genetic changes, some of which involve the tau gene while others relate to as yet undefined genetic variations at this or other chromosomal loci.

## CLINICAL AND THEORETICAL IMPORTANCE

Until recently patients presenting with primary degenerative dementia in the presenium were invariably believed to have Alzheimer's disease. It is now recognised that approximately 20% of those patients have frontotemporal dementia. These patients' relative youth, physical well-being and bizarre, socially disruptive behaviour represent a unique challenge for medical, social and therapeutic management.

The nature of frontotemporal dementia forces re-evaluation of the traditional assumption of dementia as an undifferentiated impairment of intellect. Dementia syndromes have highly distinct characteristics, reflecting the regional distribution of atrophy, allowing accurate differentiation between dementing conditions on clinical grounds. Frontotemporal dementia gives rise to characteristic behavioural changes, which include altered emotions, changes in social functioning, altered eating habits, and a spectrum of repetitive and compulsive behaviours. Characterisation of behavioural changes may increase understanding not only of frontotemporal dementia but also of other neuropsychiatric disorders in which parallel changes occur. Future clinical research is likely to shed further light on the functions of the frontotemporal lobes, while basic scientific research may lead to identification of additional genetic loci and to effective treatment strategies.

## REFERENCES

- American Psychiatric Association (1994)** *Diagnostic and Statistical Manual of Mental Disorders (4th edn)* (DSM-IV). Washington, DC: APA.
- Anonymous (1994)** Consensus Statement. Clinical and neuropathological criteria for fronto-temporal dementia The Lund and Manchester Groups. *Journal of Neurology, Neurosurgery and Psychiatry*, **4**, 416–418.

**Brown, J., Ashworth, A., Gydesen, S., et al (1995)** Familial non-specific dementia maps to chromosome 3. *Human Molecular Genetics*, **4**, 1625–1628.

**Edwards-Lee, T., Miller, B. L., Benson, D. F., et al (1997)** The temporal variant of frontotemporal dementia. *Brain*, **120**, 1027–1040.

**Gustafson, L. (1987)** Frontal lobe degeneration of non-Alzheimer type II. Clinical picture and differential diagnosis. *Archives of Gerontology and Geriatrics*, **6**, 209–223.

**Hosler, B. A., Siddique, T., Sapp, P. C., et al (2000)** Linkage of familial amyotrophic lateral sclerosis with frontotemporal dementia to chromosome 9q21–q22. *JAMA*, **284**, 1664–1669.

**Hutton, M., Lendon, C. L., Rizzu, P., et al (1998)** Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature*, **393**, 702–705.

**Mann, D. M. A., McDonagh, A. M., Snowden, J. S., et al (2000)** Molecular classification of the dementias. *Lancet*, **355**, 626.

**Miller, B. L., Ikonte, C., Ponton, M., et al (1997a)** A study of the Lund–Manchester research criteria for frontotemporal dementia: clinical and single-photon emission CT correlations. *Neurology*, **48**, 937–942.

—, **Darby, A., Benson, D. F., et al (1997b)** Aggressive, socially disruptive and antisocial behaviour in frontotemporal dementia. *British Journal of Psychiatry*, **170**, 150–154.

**Neary, D., Snowden, J. S., Northen, B., et al (1988)** Dementia of frontal lobe type. *Journal of Neurology, Neurosurgery and Psychiatry*, **51**, 353–361.

—, —, **Gustafson, L., et al (1998)** Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology*, **51**, 1546–1554.

**Sjögren, M., Wallin, A. & Edman, A. (1997)** Symptomatological characteristics distinguish between FTD and vascular dementia with a dominant frontal lobe syndrome. *International Journal of Geriatric Psychiatry*, **12**, 656–661.

**Snowden, J. S., Neary, D. & Mann, D. M. A. (1996)** *Frontotemporal Lobar Degeneration: Frontotemporal Dementia, Progressive Aphasia, Semantic Dementia*. New York: Churchill Livingstone.

—, **Bathgate, D., Varma, A., et al (2001)** Distinct behavioural profiles in frontotemporal dementia and semantic dementia. *Journal of Neurology, Neurosurgery and Psychiatry*, **70**, 323–332.

**Swartz, J. R., Miller, B. L., Lesser, I. M., et al (1997)** Frontotemporal dementia: treatment response to serotonin selective reuptake inhibitors. *Journal of Clinical Psychiatry*, **58**, 212–216.

**World Health Organization (1992)** *Tenth Revision of the International Classification of Diseases and Related Health Problems (ICD–10)*. Geneva: WHO.

## CLINICAL IMPLICATIONS

- Frontotemporal dementia can be distinguished from other forms of dementia on clinical grounds.
- The frontotemporal lobes play a critical role in emotion, social functioning, dietary behaviour, and in giving rise to stereotyped and compulsive behaviours.
- Familial frontotemporal dementia is associated with genetic mutations at different loci.

## LIMITATIONS

- Referral bias may distort estimates of prevalence of frontotemporal dementia and patients' demographic characteristics.
- There may be geographical variation in the proportion of familial cases.
- Diagnostic criteria for frontotemporal dementia require validation, in independent samples of autopsy-verified cases.

JULIE S. SNOWDEN, PhD, DAVID NEARY, MD, DAVID M. A. MANN, PhD, Greater Manchester Neuroscience Centre, Hope Hospital, Salford, UK

Correspondence: Dr Julie Snowden, Cerebral Function Unit, Greater Manchester Neuroscience Centre, Hope Hospital, Salford M6 8HD, UK. Tel: +44 (0)161 787 2561; +44 (0)161 787 2993; e-mail: julie.snowden@man.ac.uk

(First received 10 April 2000, final revision 11 December 2000, accepted 18 April 2001)

## APPENDIX

### Behavioural features of frontotemporal dementia specified in diagnostic criteria

#### Core features

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

#### Supportive features

(a) **Behavioural disorder**  
Decline in personal hygiene and grooming  
Mental rigidity and inflexibility  
Distractibility and impersistence  
Hyperorality and dietary changes  
Perseverative and stereotyped behaviour  
Utilisation behaviour

#### (b) **Speech and language**

Altered speech output:

- (i) asynchrony and economy of speech
- (ii) press of speech

Stereotypy of speech

Echolalia

Perseveration

Mutism

#### (c) **Physical signs**

Primitive reflexes

Incontinence

Akinesia, rigidity and tremor

Low and labile blood pressure

#### (d) **Investigations**

Neuropsychology: significant impairment on frontal lobe tests in the absence of severe amnesia, aphasia or perceptuospatial disorder

Electroencephalography: normal on conventional electroencephalography despite clinically evident dementia

Brain imaging (structural and/or functional): predominant frontal and/or temporal abnormality