Frontotemporal dementia in the elderly

Frontotemporal dementia has been called by more names than any other degenerative dementia, reflecting nosological uncertainty. It is important to establish an accurate diagnosis as genetic counselling, symptomatology, risk assessment and management all differ from other types of dementia. In this article **Drs Saminathan Anand** and **Jerry Seymour** review the current status and understanding of this complex illness.

DR SAMINATHAN ANAND is a Specialist Registrar.
DR JERRY SEYMOUR is a Consultant Psychiatrist for Older Adults and Lead Consultant for Early Onset Dementia at Netheredge Hospital, Sheffield

Frontotemporal dementia (FTD) represents a group of neuropsychiatric syndromes arising from progressive degeneration of the frontal lobes, anterior temporal lobes or both. The clinical presentation is heterogeneous and leads to diagnostic uncertainty, which complicates epidemiological analysis.

Prevalence studies indicate FTD is more common than previously estimated and may be as common as Alzheimer's disease (AD) in younger onset dementia[1,2]. There is often delay in diagnosis because of the heterogeneity of presentation, and there is likely to be under diagnosis in older age groups.

Development of current nosology:

FTD was first described by Arnold Pick in 1892. Onari and Spatz introduced the term Pick's disease in 1926. The concept of Pick's disease required the presence of Pick's bodies (neuronal inclusion bodies) and Pick's cells (swollen neurons) for diagnosis, differentiating it from AD. With increased understanding of focal atrophies of the brain, frontotemporal dementia became the preferred term, as neuropathological studies showed only a minority exhibiting Pick's histology.

Other terms that have been used are:

> progressive subcortical gliosis;
> dementia of the frontal type;
> frontal lobe dementia of the non Alzheimer's type;
> thalamic dementia;
> dementia-disinhibition amyotrophy syndrome;
> frontotemporal dementia with parkinsonism linked to chromosome 17;
> multisystem tauopathy;
> dementia lacking distinctive histology; and
> frontotemporal lobar degeneration[3].

The constant change in nomenclature was driven by increasing neuropathological and genetic data. In the 1980s investigators from Lund in Sweden coined the term frontal lobe dementia of the non Alzheimer's type, whilst another group in Manchester, England, framed the term dementia of frontal type for the same disease. In 1994 the Lund/Manchester groups agreed the term frontotemporal dementia and proposed a consensus statement for research diagnostic criteria for the disorder (*Table 1*)[4].

Clinical characteristics:

The usual age of onset is between 45 and 65 with the mean in the 50s[5,6]. The disease affects both sexes approximately equally with some studies showing slight male preponderance. Family history is positive in up to 50 per cent suggesting the importance of a genetic aetiology. Tau gene mutations account for the

disease in 10-50 per cent of the families with FTD, leading to abnormal aggregation of the neuronal cytoskeletal tau protein. Tau mutations are linked to chromosome 17 and recently to other chromosomes, namely chromosome 3 and 9[7]. The median duration of illness from onset of symptoms to death is six to eight years, ranging from two years to 20 years[8].

Patients with FTD present with two patterns: either as progressive change in behaviour, or with progressive language dysfunction. There is relative preservation of memory and visuospatial skills in the early stages, which helps in distinguishing from other forms of early onset dementia. The clinical presentation of frontotemporal lobar degeneration is variable and depends on the site and the degree of involvement of frontal lobes, anterior temporal lobes or both. In many cases asymmetric involvement of both lobes is noticeable on brain scan. Neary *et al*[9] international consensus statement has classified three main subtypes:

1. FTD
2. semantic dementia (SD)
3. progressive non-fluent aphasia (PNFA).

FTD

Behavioural and personality change are usually the prominent presenting feature of this syndrome. Behavioural disturbances include disinhibition (including sexual disinhibition), apathy, blunted affect, lack of empathy, disregard for personal space, decline in personal care, rigidity, hyperorality, perseverative and repetitive behaviours, social inappropriateness and lack of insight[10].

According to the clinical behavioural presentation, this group can be further divided into disinhibited form (FTD-D) and apathetic form (FTD-A). The disinhibited form is associated with pathological changes confined to orbitomedial frontal and anterior temporal regions, whereas in apathetic form pathology is extensive throughout the frontal lobes and the dorsolateral frontal cortex[10,11].

SD

Deficits in language and visual perception are the prominent clinical presentation. There is a progressive loss of semantic memory affecting naming, word comprehension and object recognition, accompanied by sensory impairment of non verbal sounds, tastes and smells. In the early stages, patients are aware of their diminishing expressive vocabulary and often present with word finding difficulties. Grammar and

Table 1. Diagnostic features of FTD

A. 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 preservative 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

B. Affective symptoms:
- Depression, anxiety, excessive sentimentality, suicidal and fixed ideation, delusions
- Hypochondriasis, bizarre somatic preoccupation
- Emotional unconcern (emotional indifference and remoteness, lack of empathy and sympathy, apathy)
- Amimia (lack of facial expression)

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

D. Spatial orientation and praxis preserved

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

F. 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.

SEITE *Arabisch

Table 2. Difference between FTD and AD

	Frontotemporal dementia	Alzheimer's dementia
Sex distribution	> Equal	> Increased prevalence in females
Duration of illness	> 6-8 years	> 5-9 years
Presenting symptom	> Early change in personality and behavioural disturbance	> Gradual memory loss with late personality change.
Memory	> Relative preservation in early stages with inconsistent and patchy memory loss	> Gradually deteriorating pervasive memory loss
Activities of daily living	> Tendency for stereotypical behaviour like wandering, usually able to find their way back	> Progressive difficulty in finding their way in unfamiliar and later familiar surroundings
	> Relatively intact visuospatial and praxis skills	> Dyspraxias like dressing dyspraxia are common
	> No Dysgraphia until late stages	> Early difficulties in writing skills
Appetite	> Changes in appetite and food preferences	> Variable and decreased appetite
Affect	> Noticeable mood disturbance, with irritability, withdrawal and alexithymia. Absent guilt feelings and relative lack of judgement	> Mood changes may not be prominent Depressed mood is characterised by sadness tears, insomnia and guilt
Neuroimaging	> Mood changes may not be prominent. Depressed mood is characterised by sadness, tears, insomnia and guilt	> Generalised atrophy with increased atrophy of temporoparietal areas
Neuropsychological	> Perseveration during testing more pronounced, may exhibit apathy or disinhibition compromising ability to complete task	> Can become anxious and overwhelmed and unable to complete tests

structure of the language seem intact with increased use of paraphrasias to cover the deficits[12].

Neuropathologically, SD is associated with circumscribed degeneration of the anterior temporal lobes, with inferior and middle temporal gyri being predominantly affected.

PNFA

In contrast to SD, PNFA is a disorder of expressive language. It is characterised by speech dysfluency, phonologic and grammatical errors, and word retrieval difficulties in the context of relative preservation of single word comprehension and non linguistic cognitive abilities. Other noticeable features are impaired repetition, reading and writing; and stuttering.

Clinically, in the early stages of disease the patients present with difficulty in phoneme discrimination, usually attributed to hearing problems. However, with the progression of the disease this leads to muteness and word deafness. Neuropsychological testing show non fluent aphasia in the absence of severe amnesia or perceptuospatial deficits[13]. Neuroimaging studies in PNFA have produced variable results, though focal pathology of the left insular region and frontal operculum is likely to be significant.

Management

There is limited rational pharmacological treatment for FTD. In the absence of specific curative treatment the management include targeted symptomatic treatment for the patient and psychosocial support for the carers.

Unlike AD, comparative neurochemical studies in FTD have failed to find a deficiency of acetyl cholinesterase and choline acetyl transference in the temporal, frontal or parietal lobe. Hence anticholinesterase inhibitor drugs used in treatment of AD are not beneficial in FTD[14]. There is evidence of decreased serotonin binding both pre- and post-synaptically in the frontal, temporal lobes and the hypothalamus in patients with FTD. Selective serotonin reuptake inhibitor (SSRI) drugs seem to benefit behavioural symptoms like disinhibition, overeating, compulsions and depression implicating serotonin neurotransmission disturbance in FTD[15]. Antipsychotics and benzodiazepines have been used symptomatically for behavioural problems like agitation. These agents need to be used as an adjunct to behavioural and psychosocial interventions. Patients with FTD may be sensitive to the effects of neuroleptics, which have been reported to accelerate cognitive decline and even hasten death. Hence these medications should be used cautiously starting at a low dose under specialist supervision[16].

There is theoretical evidence that FTD may be the end result of abnormalities of tau aggregation in the frontal lobes[17]. Specifically, overactivity of the enzyme glucose synthase kinase 3 (GSK-3), causing selective hyperphosphorylation of tau protein, has been postulated as aetiologically significant[18]. Lithium carbonate inhibits GSK-3[19] and trials are under way to see if lithium has clinical benefit in FTD patients, i.e. if this theoretical manipulation of brain neurochemistry provides clinical benefit.

Carers support

Patients with FTD frequently place excessive strain on the carers because of the distressing behavioural disturbances associated with the illness. Though there is not much evidence for improved outcome, it is likely that clear information on the nature of the illness and support available for carers can be helpful in managing patients, potentially delaying institutional care[20]. Behavioural disturbance such as aggression, disinhibition (especially sexual disinhibition) are particularly distressing for carers.

Key points

- Frontotemporal Dementia (FTD) is a group of neuropsychiatric syndromes due to progressive degeneration of the frontal lobes, anterior temporal lobes or both.
- The usual age of onset is between 45 and 65 years of age and is a relatively common cause of dementia.
- Clinically present either with progressive change in behaviour or language dysfunction.
- FTD cause excessive carer strain due to behavioural disturbance.
- No curative pharmacological treatment. Management involves individually tailored psychosocial support for the patient and carers.

Individually tailored care plans based on psychosocial strategies with adequate risk management need to be formulated to reduce risk and ease carer strain. The constant demands, both physical and emotional, placed on the carer can be exhausting. Day centre/day hospital involvement and regular

respite care can ease the burden. Patients and carers can also benefit greatly from support groups, such as the Pick's disease support group. Speech therapy is an important component for both establishing the diagnosis, and management of SD and PNFA. Carers are usually grateful for the support of a speech therapist in understanding the nature of the language deficit and improving communication.

Conclusion

Diagnosing FTD is challenging because of the heterogeneity of presentation and overlap of clinical syndromes. Though there is no curative treatment, accurate diagnosis is important to predict the course and to provide correct information for the patients and carers, avoiding unnecessary drug treatment. It is also important for aiding and facilitating further clinical research. It is likely that genetic engineering and treatments for tauopathy targeted at GSK-3 will hold the greatest hope for future treatment interventions.

Conflict of interest: none declared

References

1. Ratnavalli E, Brayne C, Dawson K, Hodges JR. The prevalence of frontotemporal dementia. *Neurology* 2002; **58**:1615-21
2. Swieten JC, Rosso SM. Epidemiology of Frontotemporal Dementia. *Advances in Clinical Neurosciences and Rehabilitation* 2006; **6**: 9-10
3. Greicius MD, Geschwind MD, Miller BL. Presenile dementia syndromes: an update on taxonomy and diagnosis. *Journal of Neurology, Neurosurgery, and Psychiatry* 2002; **72**: 691-700
4. Brun A, England B, GustafsonL, *et al*. Consensus statement: clinical and neuropathological criteria for frontotemporal dementia; the Lund and Manchester Groups. *Journal of Neurology, Neurosurgery and Psychiatry* 1994; **57**: 416-418
5. Rosso SM, Kaat LD, Baks T, *et al*. Frontotemporal dementia in The Netherlands: patient characteristics and prevalence estimates from a population-based study. *Brain* 2003; **126**: 2016-2022
6. Snowden JS, Neary D, Mann DMA. Frontotemporal dementia. *British journal of Psychiatry* 2002; **180**: 140-143
7. Neary D, Snowden J, Mann D. Frontotemporal dementia. *Lancet Neurology* 2005; **4**: 771-780
8. Hodges JR , Davies R, Xuereb J, *et al*. Survival in frontotemporal dementia. *Neurology* 2003; **61**: 349-354
9. Neary D, Snowden JS, Gustafson L, *et al*. Frontotemporal lobar degeneration: A consensus on clinical diagnostic criteria. *Neurology* 1998; **51**: 1546-1554
10. Snowden JS , Neary D , Mann DMA. *Fronto-temporal lobar degeneration: frontotemporal dementia, progressive aphasia, semantic dementia*. 1996; Churchill Livingstone, New York
11. Snowden JS, Bathgate D, Varma A, *et al*. Distinct behavioural profiles in frontotemporal dementia and semantic dementia. *Journal of Neurology, Neurosurgery and Psychiatry* 2001; **70**: 323-332
12. Hodges JR, Patterson K, Oxbury S, *et al*. Semantic dementia: Progressive fluent aphasia with temporal lobe atrophy. *Brain* 1992; **115**: 1783-1806
13. Grossman M. Frontotemporal dementia: A review. *Journal of the International Neuropsychological Society* 2002; **8**: 566-583
14. Perry RJ, Miller BL. Behaviour and treatment in frontotemporal dementia. *Neurology* 2001; **56**: S46-51
15. Swartz JR, Miller BL, Lesser IM, *et al*. Frontotemporal Dementia: treatment response to serotonin selective reuptake inhibitors. *Journal of Clinical Psychiatry* 1997; **58**: 212-216
16. Pijnenburg YA, Sampson EL, Harvey RJ, *et al*. Vulnerability to neuroleptic side effects in frontotemporal lobar degeneration. *International Journal of Geriatric Psychiatry* 2003; **18**: 67-72
17. Vandeerlin VM, Gill LH, Farmer JM, *et al*. Familial Frontotemporal Dementia: From Gene Discovery to clinical Molecular Diagnostics. *Clinical Chemistry* 2003; **49**: 1717-1725
18. Noble W, Planel E, Zehr C, *et al*. Inhibition of glycogen synthase kinase-3 by lithium correlates with reduced tauopatfehy and degeneration in vivo. *Proceedings of the National Academy of Science* 2005; **102**: 6990-6995
19. Perez M , Hernandez F, Lim F, *et al*. Chronic lithium treatment decreases mutant tau protein aggregation in a transgenic mouse model. *Journal of Alzheimer's Disease* 2003; **5**: 301-308
20. Litvan I. Therapy and management of frontal lobe dementia patients. *Neurology* 2001; **56**: 42-45