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Frontotemporal dementia

Features, diagnosis and management

Background

Frontotemporal dementia is the third or fourth most common form of dementia in the 45–65 years age group. It causes significant morbidity as well as a six to eightfold increase in mortality risk.

Objective

This article provides an overview of the pathophysiology of frontal lobe function and the genetics of frontotemporal dementia. It also summarises the clinical features, diagnosis and management of frontotemporal dementia.

Discussion

While the clinical presentation of frontotemporal dementia was described as early as the nineteenth century, recent advances in genetics have resulted in greater understanding of the pathophysiology of this disease. While imaging may support the diagnosis of frontotemporal dementia, it is essentially a clinical diagnosis based on the presence of typical clinical features and the findings of neuropsychological tests. Clinical management of frontotemporal dementia remains a challenge and is largely centred on behavioural management. Pharmacological agents such as selective serotonin reuptake inhibitors and antipsychotics may be helpful, although evidence to support their use is minimal.

Keywords: frontotemporal dementia; middle aged; aged

CPD

With average life expectancy increasing it follows that the number of people who develop dementia is also increasing. It is estimated that 24.3 million of the world's population have dementia with 4.6 million new cases reported each year.[1] Based on the 2003 World Health Report, the global burden of disease estimates that dementia contributed to 11.2% of years lived with disability in people aged over 60 years.[1]

Although Alzheimer disease is the commonest cause of dementia, frontotemporal dementia (FTD) accounts for 9.7–12%[2,3] of early onset dementia, making it the third or fourth commonest form of dementia in people aged less than 65 years.[2,3] It affects approximately 15 per 100 000 people in the 45–64 years age group.[4]

Frontal lobe function

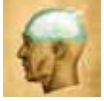
The conventional view of the frontal lobe is that its functions are localised. Anatomically, the frontal lobe consists of:

- the motor cortex (located posteriorly), which controls motor function
- the premotor cortex, and
- the prefrontal cortex (located anteriorly).

The frontal lobe can also be differentiated into two halves: the left, responsible for language related functions and the right, regulating social cognition and emotion.[5] The term 'frontal cortex' is frequently used synonymously with 'prefrontal cortex' as the centre for executive function, however the two are not precisely identical. While the prefrontal cortex contains areas that control executive function, there are additional parts to the prefrontal cortex that control other functions.

The prefrontal cortex can be subdivided into the following parts[6]:

- the medial frontal area of the prefrontal cortex, which contains the anterior cingulate gyrus and supplementary motor area. The anterior cingulate gyrus is, among other functions, responsible for motivation; damage can result in apathy
- the orbitofrontal area of the prefrontal cortex, in particular the right side, which governs social norms, attention and emotion
- the dorsolateral prefrontal cortex, which controls executive function such as organisation, choice selection, recollection of



past events and planning action. It also controls the programming of motor acts such as implementation, monitoring, and the decision to continue or stop a volitional act.

An established theory of how the brain functions shows that it is organised as a nested series of hierarchical units with the prefrontal cortex at the 'top' of the organisation.[7] More recently the concept of a 'flat network' was proposed.[8] More research is required to resolve the conflicting views of how the prefrontal cortex functions.

Other types of dementias can also affect frontal lobe function including Alzheimer disease, vascular dementia, dementia associated with supranuclear palsy, Parkinson disease and alcoholism (*Table 1*).

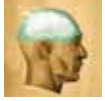
Classification of frontotemporal dementia

Frontotemporal dementia is a clinical syndrome that is clinically and pathologically distinct from Alzheimer disease. Arnold Pick first presented a case series with progressive language deterioration in 1892, and for many years the term 'frontotemporal dementia' has been used synonymously with Pick disease. However, Pick disease is now recognised as just one form of FTD and refers to a specific pathological diagnosis where tau-positive inclusions are present.[9] To date, the clinical classification of FTD has evolved to encompass at least three major subtypes[10]:

Table 1. Differentiating characteristics of some common dementias affecting frontal lobe function

	Alzheimer disease	Frontotemporal dementia	Vascular dementia	Progressive supranuclear palsy	Parkinson disease	Alcoholism
Age of onset	Incidence increases with age	40–60 years	Incidence increases with age	>60 years	Incidence increases with age (>55 years)	Incidence increases with age
Onset of frontal features	Later	Early	Variable but usually later	Early	Late	Later
Other features						
• Short term memory loss	Early	Usually not present but may occur as a late feature	Early	Later		
• Dysphasia	Occurs as disease progresses	Occurs in semantic FTD	Variable			
• Apraxia	Occurs as disease progresses	Not present	Depends on the location of lesion			
• Pyramidal	Very late	Not present		Falls Early loss of downward gaze Parkinsonism	Extra-pyramidal symptoms and signs	
• Others			Variable			History of alcoholism (including binge drinking)
Acetyl-cholinesterase inhibitor response	Yes, 20–30% of people	No	Yes	No	Some	
Pathology	Amyloid plaques and tangles (tau)	Tau and ubiquitin inclusions	Vascular White matter ischaemia Stroke	Tau pathologies	Lewy bodies	

Note: FTD can also overlap with 'tauopathies' where 'tau' inclusions are the dominant pathological feature. These diseases include progressive supranuclear palsy, corticobasal degeneration and motor neurone disease (amyotrophic lateral sclerosis). Clinical features of loss of conjugate eye movement (progressive supranuclear palsy), limb dystonia (corticobasal degeneration) or fasciculation (amyotrophic lateral sclerosis) may help the differentiation



- behavioural variant
- semantic dementia
- progressive nonfluent aphasia.

Clinically and pathologically, FTD can also overlap with motor neurone disease, corticobasal degeneration or progressive supranuclear palsy.[11] Recent advances in genetics may aid the diagnosis of a small number of familial FTD.

Pathophysiology

Molecular biology research has led to the important discovery of abnormal 'tau' and 'ubiquitin' inclusions in the brains of people with FTD. Linkage studies in families with FTD have identified mutations in the MAPT gene (responsible for tau inclusion)[12] and progranulin gene (responsible for ubiquitin inclusion).[13] Both mutations are found on chromosome 17 and are the commonest genetic causes of FTD.

Clinical features

Frontotemporal dementia has no gender predilection. The usual age of onset is in the fifth and sixth decades. As a result, patients with FTD may be misdiagnosed with psychiatric illness or other types of dementia. Younger patients may also pose challenges in the management of some symptoms such as behavioural problems. History is important; subtle frontal lobe symptoms may be missed when a detailed history from relatives, friends and the patient is not obtained. Frontal lobe signs may aid diagnosis but are frequently absent early in the course of the illness. Clinical features vary depending on the subtype. If a diagnosis of FTD is suspected, bedside tests can be used to more objectively assess frontal lobe function (*Table 2*).

Clinical features of the behavioural variant of frontotemporal dementia

Patients with the behavioural variant of FTD may demonstrate a gradual change in personality and behaviour, including loss of emotional reactivity, disinhibition and loss of insight. The ability to plan and organise may also be affected, however memory may essentially be intact. Patients may also lack basic emotions and empathy or have changes in eating habits (eg. preferring sweet foods).[14]

Clinical features of the semantic variant of frontotemporal dementia

Patients with the semantic variant of FTD exhibit early difficulties with language, particularly semantic paraphasias (ie. substituting similar words for the intended word, such as 'aunt' for 'sister') and difficulties with the meaning of words, naming and comprehension.[15] Speech is fluent but devoid of meaning, and patients may have problems with visual recognition of unfamiliar objects or faces. Memory and behavioural symptoms are evident later.

Clinical features of progressive nonfluent aphasia

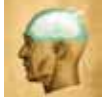
Progressive nonfluent aphasia is characterised by slow, hesitant and effortful speech. Phonemic paraphasic errors are common, but naming and comprehension are not as severely affected as in semantic dementia. Problems with abstract reasoning, mental arithmetic, memory and behavioural symptoms become evident later.

Investigations

Neuroimaging (magnetic resonance imaging [MRI]), computerised

Table 2. Bedside testing to assess frontal lobe function

Go-no-go test	This test requires a patient to perform an action under certain stimuli and inhibit that action under a different set of stimuli. For example, the patient is asked to hold up one finger when the examiner holds up two or vice versa
Anti-saccade trials	Anti-saccade trials require the patient to fix their gaze on a central object then a novel stimulus appears from either the left or the right. Before the stimulus appearing, the patient is instructed to look away from the stimulus – thus inhibiting the reflexive saccade. Failure of inhibition is an error
Letter fluency (lexical fluency)	The patient is asked to say as many words (but not proper nouns) as they can in 1 minute that start with a single letter, eg. 'F', 'A' and 'S'. They are instructed that words changed only by the addition of a suffix will not be counted (eg. jump, jumps, jumping). The minimum number of words should be equal to or more than eight words that start with the chosen letter. Repetitions and rule violations (eg. words beginning with other letters or nouns) are common mistakes
Attention test	The patient is instructed to do serial seven subtractions, or spell the word 'world' backwards. Alternatively, a digit span test (a normal span is 6–7 digits forward and 4–5 backward) can be used
Alternate sequence test	The patient is asked to draw a segment with alternating Ms and Ns or perform the Luria's three-step test of alternating hand movements – fist, then edge, then palm
Similarities and differences	This examines the patient's ability to perform abstract reasoning. The patient is asked to describe the difference between a dwarf and a child, or the similarity between a table and a chair
Frontal lobe reflex	These behavioural motor responses are normal in infants but subsequently inhibited. They may re-emerge with cerebral damage or degeneration. Examples include suck, grasp, snout, groping and palmer mental reflexes and reflexive utilisation behaviour which involve the automatic, unthinking use of an object



tomography (CT) or single photon emission computed tomography (SPECT) may show selective atrophy or hypoperfusion in the frontal and/or temporal areas. While a positive test may aid diagnosis it is by no means specific, as other dementias affecting the frontal lobe may show similar results. On the other hand, a negative test does not necessarily rule out diagnosis in early disease. Therefore, while imaging may be supportive of a diagnosis of FTD, the diagnosis is essentially a clinical one based on demonstration of impaired frontal lobe functioning on neuropsychological testing. The role of genetic studies to identify familial FTD is best dealt with in a specialist centre.

Prognosis

Adjusted for age, FTD had a six to eightfold increase in mortality risk compared to Alzheimer disease, which has a fourfold increase.[16]

Management

There are no available disease modifying agents to treat FTD. Therefore treatment is based on managing difficult behaviours. Unfortunately, there is a paucity of clinical trials examining behavioural or pharmacological interventions in FTD. It may be necessary to use medications 'off label' to manage the range of behaviours that may present.

Behavioural strategies are first line in the management of difficult behaviours in FTD, with pharmacological agents added as second line as necessary. The patient should be reviewed every 3–4 months to assess the effectiveness of the management plan. Some behaviours may become worse as memory loss progresses. For example, poor personal hygiene may initially relate to an unwillingness to bathe, and then be exacerbated by a forgetfulness to bathe.

As well as managing the patient, it is important to provide ongoing support for the carer, who will often be stressed and require help to cope with changes in the patient (see *Resources*). Accepting the changing behaviour that does not cause any harm is just as important as dealing with difficult or harmful behaviour. Consider referral to a specialist centre if the diagnosis is uncertain, for carer stress or for unmanageable behaviour. Common behavioural changes and their management are outlined below.

Aggression

Aggression can be a major problem. In severe aggression it is often not helpful to confront or discuss the behaviour with the patient (who will not understand). If possible and appropriate, suggest 'time out' for the carer. Ask the carer to remain calm, distract the patient if it is feasible or simply let the patient play it out and do not take abusive language personally. If there is no response to behavioural strategies, consideration can be given to trialling a specific serotonin reuptake inhibitor (SSRI) or an atypical antipsychotic at a low dose. It is paramount to assess if the carer is able to cope with a patient who is aggressive. Carers often find aggression extremely stressful and may require management and referral to a psychiatrist or psychologist for stress management, depression or anxiety. In clinical practice, patients with aggressive behaviours often require referral to a psychogeriatrican.

Wandering

Wandering can be a nuisance but can also be dangerous (eg. if patient encounters a traffic danger). A useful strategy to discourage people who wander from getting out is to paint doors in the same colour as the surrounding walls and to place a 'no exit' sign on the door. A child-safe barrier device could also be used. Patients may still wander, so a name tag should be worn detailing an address and contact telephone number. If wandering is due to restlessness, redirection of the patient's energy to productive activity or exercise can be trialled. If wandering is due to disorientation, an orientation device such as a clock, large print calendar or signage can be used. Reduction of noise levels is a general strategy to reduce overstimulation and may help reduce restlessness.

Sexual disinhibition

Sexual disinhibition is often very challenging to manage. If distraction or other behavioural strategies (such as modification of clothing to hamper disrobing) fail, pharmacological interventions such as SSRIs or antipsychotics can be trialled.[17]

Apathy

Apathy is a common but frequently ignored symptom. Maintaining interaction with others and continuing activities of interest can reduce social isolation and feelings of loneliness or boredom. Encourage patients to join group activities at a local day activity centre (see *Resources*).

Personal hygiene

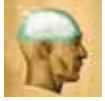
Personal hygiene difficulties usually require a pragmatic approach rather than a pharmacological solution. For example, if a patient refuses daily bathing, a strategy may be to shower on a needs basis and substitute with a sponge-down on other days. Poor personal hygiene can lead to unwanted effects such as urinary tract infection (in females), but overzealous persuasion from the carer may cause unwanted tension. Therefore, a compromise may be needed.

Repetitive behaviours

Repetitive and compulsive behaviours similar to those seen in obsessive compulsive disorder can be a feature of FTD, particularly in patients with striatal or temporal atrophy on neuroimaging.[18] While open label trials describe improvement with SSRIs,[19] a double blinded placebo controlled crossover trial found no difference.[20] Redirection, distraction and engagement in activities may reduce repetitive behaviour.

Conclusion

Frontotemporal disorders are the result of a disruption to a neurocircuit comprising the prefrontal area and subcortical structures, hence lesions in different anatomical areas may lead to the same clinical



phenotype. Other types of dementia often present with symptoms of frontal dysfunction and differentiation can be a challenge. Behavioural management remains a challenging aspect of managing FTD.

Resources

- Carers Australia: 1800 242 636
- National Dementia Helpline: 1800 100 500
- Carer Respite Centres: 1800 059 059
- Carer Resource Centres: 1800 242 636.

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