Frontotemporal dementia (FTD) is the most common of a group of clinical syndromes associated with circumscribed degeneration of the prefrontal and anterior temporal cortex. Onset is typically in the middle years of life and survival is about 8 years. The presence of microtubule-associated-protein-tau-based pathological features in some patients and the discovery, in some familial cases, of mutations in the tau gene links FTD to other forms of tauopathy, such as progressive supranuclear palsy and corticobasal degeneration. However, more than half of all patients with FTD, including some with a strong family history, show no apparent abnormality in the tau gene or protein, indicating pathological and aetiological heterogeneity. FTD provides a challenge both for clinical management and for theoretical understanding of its neurobiological substrate.

Introduction

Frontotemporal dementia (FTD) is the most common of a group of clinical syndromes associated with circumscribed degeneration of the prefrontal and anterior temporal lobes (figure 1) and non-Alzheimer disease type pathology, which has been called frontotemporal lobar degeneration (FTLD). Behavioural changes are the presenting feature and dominate the clinical picture throughout the disease course. Qualitative changes in language and cognitive impairments in executive function also occur. The absence of early neurological signs and findings of focal abnormalities in the frontotemporal lobes on neuroimaging, contribute to the clinical diagnosis (table).

Terminology and clinical criteria

Use of the term FTD is not consistent. The term was introduced by workers in Lund (Sweden) and Manchester (UK) to refer specifically to the progressive behavioural syndrome.7 The term—which superseded labels such as frontal-lobe dementia and dementia of frontal type pathlogy, which has been called frontotemporal lobar degeneration (FTLD). Behavioural changes are the presenting feature and dominate the clinical picture throughout the disease course. Qualitative changes in language and cognitive impairments in executive function also occur. The absence of early neurological signs and findings of focal abnormalities in the frontotemporal lobes on neuroimaging, contribute to the clinical diagnosis (table).

Clinical and pathological diagnostic criteria for FTD, developed by the Lund and Manchester groups,7 showed good discrimination between FTD and Alzheimer’s disease. However, no guide was given as to the number of clinical features necessary for diagnosis or the relative importance of symptoms, and no precise operational definitions of symptoms. Moreover, other clinical syndromes are also associated with FTLD, determined only by the distribution of the pathological process within the frontal and temporal lobes of the brain, namely progressive aphasia4,11 and semantic dementia.4,12,13 Non-fluent progressive aphasia is a disorder predominantly of expressive language, in which severe problems in word retrieval occur in the context of preserved word comprehension. This disorder is associated with asymmetric atrophy of the left hemisphere. Semantic dementia is a multimodal disorder of meaning, in which patients lose the abilities to name and understand words and to recognise the significance of faces, objects, and other sensory stimuli. This disorder is associated with bilateral, commonly asymmetric, atrophy of the middle and inferior temporal neocortex. Predictably, some patients have a mixed clinical picture of FTD, progressive aphasia, and semantic dementia,14 and these different syndromes may be seen within the same family.15,16 Because FTLD can be associated with degeneration of bulbar neurons and anterior horn cells of the spinal cord, the fact that MND, most commonly associated with FTD (FTD-MND), has also been described in the syndromes of semantic dementia and progressive aphasia, is not surprising.17–19

Clinical criteria published in 1998 (panel) recognised FTD as one of three major clinical syndromes of FTLD, and also provided some evidence of the pathologies in the brain.

Table: Clinical diagnostic features of frontotemporal dementia

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<th>Characteristic</th>
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<td>Sex distribution (men:women)</td>
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<td>Age of onset (years)</td>
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<tr>
<td>Duration of illness (years)</td>
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<tr>
<td>Family history</td>
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<tr>
<td>Presenting symptom</td>
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<td>Cognitive features</td>
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<td>Neurological signs</td>
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FTD=frontotemporal dementia; MND=motor neuron disease.
the other prototypical syndromes being non-fluent progressive aphasia and semantic dementia. A study of the criteria, based on 34 patients with pathologically diagnosed FTLD among a series of 433 individuals, reported good premortem diagnostic accuracy, with a sensitivity of 85% and specificity of 99%.\(^4\)

McKhann and colleagues\(^{11}\) suggested that, although these criteria are useful for research, simpler guidelines are needed for general physicians to facilitate recognition of FTD and expedite referral to a specialist centre. Their simplified criteria subsume progressive aphasia and semantic dementia under the rubric of FTD and consist of the following six features: (1) early and progressive change in personality or language; (2) impairment in social and occupational functioning; (3) a gradual and progressive course; (4) exclusion of other causes; (5) presence of deficits in the absence of delirium; and (6) exclusion of psychiatric causes such as depression.\(^{21}\)

The usefulness of these latter criteria for the general physician has yet to be assessed. The criteria are sufficiently broad that they are likely to have high sensitivity, yet inevitably at the expense of diagnostic specificity. The criteria would, for example, incorrectly include patients with Alzheimer’s disease who present with language rather than memory impairment. Moreover, the heuristic value of submerging highly distinct clinical syndromes under the single diagnostic label of FTD is open to question.

Some investigators have adopted the terms frontal-variant FTD for the behavioural syndrome of FTD and temporal-variant FTD to refer to the clinical syndrome of semantic dementia.\(^{22,23}\) Use of these terms draws attention to the link between the two syndromes, and the fact that the syndromes merely indicate differences in the distribution of pathological changes.\(^{13}\) A potential source of confusion is that there is not an exclusive relation or one-to-one correspondence between the syndrome and atrophy. Patients with semantic dementia always have temporal-lobe atrophy, but the presence of temporal-lobe atrophy does not inevitably denote the clinical syndrome of semantic dementia. Patients with the behavioural disorder of FTD invariably have both frontal-lobe and temporal-lobe atrophy, and in some cases the temporal-lobe atrophy is greater, even in the absence of obvious semantic impairment.\(^4\) Predominant frontal or temporal atrophy, as determined by MRI of the brain, cannot therefore be used as a reliable predictor of the clinical syndrome, which can only be determined by neuropsychological examination. As a consequence, reports of temporal variant FTD denote different groups of patients depending on whether they are defined on neuropsychological or neuroimaging grounds.\(^{22,25,26}\)

In this review, we use the term FTD in its originally defined sense to refer to the behavioural syndrome associated with degeneration of the frontal and temporal lobes (figure 2). However, comparison of results from independent studies of FTD is potentially confounded by differences in the definition of patients, as described above. The designation FTLD is used here in preference to Pick’s disease, because Pick’s type histological changes (comprising Pick’s bodies and ballooned neurons) are seen in only a small proportion of cases. Moreover, Pick’s type features can be distributed outside the prefrontal and anterior temporal cortices (the sites of FTLD), for example, in the parietal lobes and premotor cortices leading to apraxia,\(^{27}\) as seen in progressive apraxia and corticobasal degeneration.

**Neuropathological characteristics**

FTLD comprises atrophy of the prefrontal and anterior temporal neocortex. Differences in topographical distribution of atrophy determine the clinical syndromes
Review of FTD, semantic dementia, and progressive aphasia (figure 2). Routine histology shows microvacuolation of the outer cortical laminae (microvacuolar-type features), due to large neuronal cell loss, or less commonly, transcortical gliosis.

Immunohistochemical analysis defines four major types of pathological features (figure 3). (1) Microvacuolation without neuronal inclusions, that is, dementia lacking distinctive histological features. (2) Microvacuolation with ubiquitinated rounded intraneuronal inclusions and dystrophic neurites within layer 2 of frontal and temporal neocortex and hippocampal dentate gyrus cells. This is designated FTD-ubiquitinated (FTLD-U) type. (3) Transcortical gliosis with tau-reactive rounded intraneuronal inclusions and swollen achromatic neurons (Pick’s cells). These histological features are referred to as being of Pick’s type.2 (4) Microvacuolation and tau-positive neurofibrillary tangles or Pick-like bodies in neurons, and sometimes tangles in glial cells of the cerebral cortical white matter. This is associated with familial FTD because of mutations in the tau gene. Types 3 and 4 are referred to as tauopathies.

Clinical and histological correlations

In individual cases of FTD, progressive aphasia, or semantic dementia the underlying histological changes cannot be precisely inferred on the basis of the clinical syndrome. Each histological type can be associated with each clinical syndrome (figure 2). In purely pathological studies of FTLD, without clinical data, there are substantial differences in the reported proportion of cases showing each histological type, particularly if progressive supranuclear palsy and corticobasal degeneration are included as FTLD. Moreover, there

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**Figure 2: Relation between the different levels of description of frontotemporal lobar degeneration (FTLD)**

DLDH = dementia lacking distinctive histological features; FTD = frontotemporal dementia; FTLD-U = frontotemporal lobar degeneration, ubiquitinated type.

**Figure 3: Histological changes in the cerebral cortex**

Microvacuolation (dementia lacking distinctive histological features) in upper layers of the cerebral cortex (A). Ubiquitin inclusions in the cerebral cortex (B). Pick’s bodies in patient with frontotemporal dementia and parkinsonism associated with chromosome 17 (FTDP-17; Q336R mutation; C). Neurofibrillary tangles in patient with FTDP-17 (+16 exon 10 splice mutation; D).
may be variations in clinical designation. Nevertheless, some broad generalisations can be drawn from the published research and our own data based on 68 necropsied patients.\textsuperscript{36–41} In cases that fulfil the strict clinical criteria for FTD,\textsuperscript{3} the most common histological feature is tauopathy. In clinical cases of FTD-MND the histological features are typically non-tau, about 50% of patients have FTLD-U changes in the cerebral cortex and brainstem. Initially this was termed as being of MND type.\textsuperscript{7} However, FTLD-U features are present in many patients without clinical evidence of MND during life. Moreover, half of cases of clinical FTD-MND have no distinct histological features. Accordingly, the term FTLD-U should be reserved for the histological description and FTD-MND to denote the clinical disorder. Patients with semantic dementia and progressive aphasia show a preponderance of non-tau features.

### Epidemiology

Prevalence studies of FTD are currently limited. One study, based on 17 patients with clinically diagnosed FTD in the Cambridge area of the UK, reported a prevalence of 15 cases per 100 000 in people age 45–64 years.\textsuperscript{14} A study from the Netherlands of 245 patients with FTD in the Zuid-Holland province (the Netherlands), reported much lower prevalence: 3·6 per 100 000 at age 50–59 years, rising to 9·4 per 100 000 at age 60–69 years, and falling to 3·8 per 100 000 at age 70–79 years.\textsuperscript{15} The high prevalence arising from the Cambridge study led the authors to suggest that FTD may be as common as Alzheimer’s disease before the age of 60 years. However, clinical data from other centres do not support this view. In Lund (Sweden), 36 (9%) of 400 consecutive dementia patients with postmortem confirmation had FTD and 168 (42%) had Alzheimer’s disease.\textsuperscript{2} Japanese investigators have reported a ratio about one case of FTD to four of Alzheimer’s disease.\textsuperscript{16} In Manchester (UK) in patients with dementia onset before age 65 years, 147 had FTD compared to 498 with Alzheimer’s disease (ratio about one to three). The ratio fell to one to 1·7 in patients with dementia onset before 50 years (69 Alzheimer’s disease vs 40 FTD). Differences in cohort and population size and in the criteria used for patient definition are likely to contribute to differences in findings across centres.

A high familial incidence in FTD is common (table).\textsuperscript{14–18} Familial incidence is likely to be influenced by geography. FTD families with +16 exon 10 splice mutation of \textit{tau}, from the UK, USA, and Australia, have been traced to a common founder in North Wales.\textsuperscript{17}

### Demographics

A study of 245 patients from the Netherlands indicated an equal distribution of FTD among men and women (49% men, 51% women), similar to findings in the Manchester series of 210 patients (50% men, 50% women).\textsuperscript{15,21} Age at onset is typically 45–65 years, with a mean in the 50s.\textsuperscript{3,15–18} However, pathologically confirmed and clinically presumed FTD has been recorded in individuals as young as 21 years and as old as 85 years.\textsuperscript{3,15} Age at onset in familial and sporadic cases does not differ significantly.\textsuperscript{15,21} Interestingly, the youngest-onset cases have been sporadic.\textsuperscript{3,15} The median duration of illness from onset to death is 6–8 years with a range of 2–20 years.\textsuperscript{15} The presence of neurological abnormalities is associated with shorter survival.\textsuperscript{41} FTD-MND is associated with a median survival of only 3 years.\textsuperscript{4,35}

### Behavioural changes

Abnormal behaviour is, by definition, the dominant feature of FTD (table). Changes in affect and lack of concern and insight are strong discriminators between FTD, Alzheimer’s disease, and vascular dementia.\textsuperscript{44–46} Patients lack appropriate basic emotions, such as sadness, and social emotions, such as sympathy and empathy. Other strong discriminators are the presence of repetitive, stereotyped behaviours (motor mannerisms, repeated use of a phrase or saying, complex behavioural routines)\textsuperscript{4,44–46,48–51} and changes in eating habits (gluttony, food fads, sweet food preference).\textsuperscript{4,22,24,44–46,52} An additional feature, with high specificity for FTD although low sensitivity, is an altered response to sensory stimuli. This includes both reduced pain response,\textsuperscript{44,45} ascribed to a decrease in motivational and affective components of pain,\textsuperscript{44,45} and hypersensitivity to neutral stimuli.\textsuperscript{44,45,53} Behavioural inventories of FTD highlight the unique characteristics of FTD for differential diagnosis.\textsuperscript{44,45,53–55}

### Phenotypic variations

Patients with FTD may present as overactive, socially disinhibited, and fatuous, or conversely as apathetic, inert, and emotionally blunted.\textsuperscript{40,45} Attention has also been drawn to a third behavioural phenotype, characterised by marked stereotyped and associated with muscular rigidity.\textsuperscript{4} These behavioural variants may indicate differences in the topographical distribution of pathological features. Functional imaging and post-mortem pathological examination show involvement predominately of orbital frontal and anterior temporal cortices in socially disinhibited patients, but widespread frontal involvement, extending into dorsolateral frontal cortex in apathetic patients.\textsuperscript{4} Reports of stereotypic patients have indicated that atrophy is greatest in the anterior temporal lobes and striatum.\textsuperscript{4} Patients with FTD with more right-hemisphere atrophy have greater behavioural change than those with more left-sided atrophy.\textsuperscript{4} In keeping with this finding, a correlational study (involving patients with FTD and those with semantic dementia) found a correlation between so-called aberrant behaviour and loss of grey-matter in the dorsomesial frontal lobe that was greatest on the right.\textsuperscript{41}
Cognitive changes
Executive dysfunction characterises FTD, and patients show impairments in planning, judgment, problem solving, organisation, attention, abstraction, and mental flexibility. By contrast, primary instrumental abilities of language, elementary visual perception, spatial skills, and memory are well preserved. Spatial skills in particular are strikingly well preserved, even in advanced disease. Patients negotiate their environment, localise, orientate, and align objects with ease, providing a striking contrast to the spatial impairments typical of Alzheimer’s disease. Performance is poor on frontal executive tests4,23,46 and typically well preserved on visuoconstructual tests65 and memory23,46 compared with that in Alzheimer’s disease.

Test performance in FTD is characterised by failure to adhere to the rules of the task, impaired generation and sequencing of information, inattention, impulsivity of response without checking, concreteness of thought, impaired set shifting, and response perseveration,4 features that compromise performance not only on executive tests but also on tasks designed to test other cognitive domains. Language changes in FTD include economy of output, concreteness of thought, verbal stereotypes, echolalia, perseveration, and eventual mutism (panel). On memory tests, poor attention and lack of active generation of information impairs efficiency of recall. On drawing tests, reproductions of figures may be impaired by poor organisation and perseverative strokes, whereas spatial configurational features of performance are well preserved.49 Consequently, despite notable differences in behaviour, neuropsychological test scores may not always reliably differentiate FTD and Alzheimer’s disease.50–71 Reliance on test scores alone predictably mask qualitative differences in the reasons for test failure.68,72

Executive test failure in FTD is greatest in patients with widespread frontal-lobe atrophy extending into the dorsolateral frontal cortex. By contrast, patients with relatively restricted orbitofrontal frontal-lobe atrophy may do surprisingly well on traditional frontal-lobe cognitive tests, despite gross behavioural change.14,77 Although executive impairments provide support for a diagnosis of FTD, their absence does not preclude one.

Emotion processing and social cognition
Two domains that affect social behaviour are emotion processing and social cognition. Patients with FTD have impaired recognition of both facial74–78 and vocal76 expressions of emotion and have difficulty inferring what other people feel or think,79–81 consistent with a loss of so-called theory of mind. Such impaired social cognition occurs in patients with restricted orbitofrontal atrophy who succeed on traditional tests of frontal-lobe function, highlighting the importance of this region in social functioning.79

Physical signs and investigations
FTD is commonly associated with an early absence of neurological signs (table).1 However, primitive reflexes and striatal signs of akinesia and rigidity emerge with progression of disease. Muscular wasting occurs in the few patients who develop MND. Myoclonus, corticospinal weakness and ataxia are absent.

On electroencephalogram, an absence of slow waves is commonly thought of as valuable in differentiating between FTD and Alzheimer’s disease.1,82 However, this differentiating feature has recently been questioned on the basis of findings of comparable EEG abnormalities in FTLD and Alzheimer’s disease.83

MRI shows atrophy in the frontal and temporal lobes,84,85 which may be asymmetric.86 Abnormalities in the anterior cerebral hemispheres are also present on functional imaging with single-photon-emission CT,86 and may be detected even at an early stage of disease by functional MRI when structural MRI is normal.87 PET studies have indicated the ventromedial frontal cortex as the critical affected area common to all patients, supporting the view that this is the earliest site of disease.88

Genetics
In 1998, research showed that familial FTD, linked to a chromosome-17 locus, was associated with mutations in tau.89,90 Since then, further families and mutations in tau have been identified (figure 4) —about 35 different mutations in around 100 families in total. The tau mutations can be classified according to whether their primary effect is exerted either at the level of the translated protein or on alternative RNA splicing of tau involving exon 10, or both.

Molecular genetics
Tau, also known as microtubule-associated protein tau (MAPT), is involved in the regulation of microtubule assembly and disassembly, and the transport of proteins and organelles. In healthy adults, six isoforms of tau are produced. Three isoforms have three microtubule-binding regions (known as 3R tau), and the others have four repeats (known as 4R tau). If one or more of the various isoforms fails to function, or if there is an...
imbalance in the different variants, microtubule formation becomes more difficult and the stability of microtubules formed becomes compromised. Excess or unused tau can accumulate into indigestible residues and inclusions, which choke the cell, leading to neuron dysfunction and death.

Many of the tau mutations exist as missense mutations within coding regions of exon 1 (R5H, R5L), exon 9 (K257T, I260V, L266V, G272V), exon 11 (L315R, S320F, K317M), exon 12 (Q336R, V337M, E342V, K369I) and exon 13 (G389R, R406W). These genetic changes affect all tau isoforms, generating mutated proteins that fail to promote microtubule assembly or facilitate axonal transport. Some of the mutations also increase the propensity of the mutated tau to self-aggregate into neurofibrillary inclusions or Pick’s bodies composed of a mix of 3R and 4R tau.

Other tau mutations lie close to the splice donor site of the intron that follows the alternatively spliced exon 10 or in exon 10 itself. These mutations destabilise this region, leading to an imbalance or deletion of tau isoforms, thereby compromising microtubule binding and function. This results in the aggregation of excess tau formed into neurofibrils composed of 4R tau. Conversely, the ΔK280 mutation destroys the function of a splice-enhancing region and results in the abolition of all transcripts containing exon 10.

Clinical genetics

Linkage to chromosome 9 in several families clinically sharing an FTD-MND phenotype has been claimed by some investigators, but not confirmed by others, and linkage to chromosome 3p11–12 has been reported in a Danish family showing FTD with frontotemporal atrophy, neuronal loss, and gliosis. For FTD has been associated with inclusion body myopathy and Paget’s disease, a dominant disorder mapping to chromosome 9p21.1–12 and caused by mutant valosin-containing protein. A combination of behavioural and language disorders has been described, and neuropathological examination has shown frontotemporal lobar atrophy, cortical and subcortical gliosis, and intranuclear inclusion bodies containing valosin-containing peptide and ubiquitin in the cerebral cortex, but sparing the hippocampal dentate gyrus.

Autosomal dominant mutations in the presenilin-1 gene (PSEN1) are generally associated with early-onset familial Alzheimer’s disease. Nevertheless, in many such cases, frontal-lobe signs are prominent within the constellation of more typical Alzheimer’s disease symptoms. Two PSEN1 mutations with prominent frontal-lobe signs have been recently reported. One patient had an M146L mutation with both Pick’s bodies and typical Alzheimer’s disease plaques, and another had a G183V mutation and Pick’s bodies alone. Neither case showed neurofibrillary tangles typical of Alzheimer’s disease.

Several polymorphisms in tau are in complete linkage disequilibrium and form extended haplotypes, H1 and H2. H1 has been widely associated with progressive supranuclear palsy and corticobasal degeneration. Tau haplotypes, and perhaps specifically the tau H1H1 genotype, may promote tau dysfunction leading either towards the 4R tau neurofibrillary tangles of progressive supranuclear palsy and corticobasal degeneration, or towards that in FTD with Pick’s type features, in which the Pick’s bodies are composed typically of 3R tau, but also of 4R tau in some cases.

Although the apolipoprotein E (APOE) ε4 allele is a well established risk factor for late-onset sporadic and familial Alzheimer’s disease, the presence of this allele does not seem generally to increase the risk of developing FTLD. However, there is evidence that the ε4 allele may selectively increase the risk of FTLD in men. Many patients with this allele have (sometimes prominent) deposition of amyloid β plaques when disease onset is after age 65 years, or duration of illness is long and stretches into later life.

Clinical phenotypes

The clinical phenotype in familial cases of FTD is generally similar to that in sporadic cases. Patients with tau mutations, both those with missense mutations leading to Pick’s type histological changes, and those with mutations affecting exon 10 splicing leading to tangle-type changes, have been noted to display the behavioural change of FTD combined with the comprehension and naming loss of semantic dementia. Differences in clinical phenotype, with neurological presentations resembling progressive supranuclear palsy or corticobasal degeneration have been reported. However, it is not clear to what extent specialist bias gives rise to apparent phenotypic differences, or whether genuine differences represent the effects of genetic modifiers.

Despite the varying histological features associated with FTD, it is likely that all feed a shared neurodegenerative cascade. Tau mutations devastate the neurons’ ability to organise microtubule assembly and disassembly, and therefore crucially disrupt axonal transport. Genes and proteins involved in producing FTLD-U features or dementia lacking distinctive histological features might likewise adversely affect this fundamental cytoskeletal function, converging on the same physiological problem, and thereby generating a similar clinical disorder.

Treatment

Pharmacological treatments for FTD are limited. Data from neurochemical studies of necropsied brains and functional imaging using PET have indicated abnormalities in serotonin metabolism, which have led to clinical trials of drugs with serotoninergic effects. The results of trials of modulation of serotonin in FTD using...
selective serotonin reuptake inhibitors have been equivocal.117–141 Interestingly, concentrations of serotonin and its metabolites are high in some cases of FTLD.142 A reduction in serotonin receptors on glutamatergic cortical pyramidal neurons may simply indicate neuronal cell loss. However, the preservation of serotonin afferents, which are inhibitory, could lead to an excess of extraneural serotonin, causing underactivity of a depleted pool of surviving glutamatergic pyramidal neurons. Accordingly, trials of treatment with serotonin antagonists may be indicated.

Management of patients with FTD concentrates mainly on the construction of a support network through social, psychiatric, and voluntary services, enabling provision of such facilities as day, respite, and ultimately residential care, to relieve the immense burden on families. Services are often best provided by psychiatry services for elderly people, regardless of patients’ ages, although access to those services may be limited for people with early-onset dementia and behavioural impairment.

Conclusions

Growth in interest in FTD in recent years indicates the rapid advances in the understanding of its pathological and molecular basis. Better understanding has, however, revealed increased complexity. FTD is associated with distinct histological features, different immunohistochemical characteristics, and different genetic bases. FTD presents a challenge for management. There is a need for better symptomatic treatment and better resources for care of these patients and their families.

Authors’ contributions
JS and DM did the literature search. DM provided the pathological figures. All authors contributed to the selection of references and the writing of the review.

Conflicts of interest
There are no conflicts of interest.

References


Snowden JS, Neary D, Mann DM. Autopsy proven sporadic frontotemporal dementia due to microvascular-type histology, with onset at 21 years of age. J Neurol Neurosurg Psychiatry 2004; 75: 1337–39.


