Abstract. Frontotemporal dementia (FTD) is an important cause of non-Alzheimer’s dementia and is the second most common cause of young onset dementia. FTD presents with progressive changes in behavior and personality (behavioral variant FTD) or language deficits (also known as primary progressive aphasia), although both commonly coexist. Patients with progressive aphasia are subclassified according to the pattern of language deficits into those with progressive non-fluent aphasia (PNFA) and semantic dementia (SD). FTD is pathologically heterogeneous, both macroscopically and on a molecular level, with tau positive, TDP-43 positive, and FUS positive intraneuronal inclusions recognized on immunohistochemical analysis. TDP-43 positive inclusions are also a feature of amyotrophic lateral sclerosis pathology, corroborating the observation of overlapping clinical features between the two conditions and reaffirming the FTD-ALS disease spectrum. Most FTD cases are sporadic, but an important minority is inherited in an autosomal dominant fashion, most commonly due to MAPT or progranulin gene mutations. Familial clusters of FTD and amyotrophic lateral sclerosis are also recognized but poorly understood. This paper reviews the clinical phenotypes, assessment and treatment of FTD in light of recent pathological and genetic discoveries.

Keywords: Behavioral variant FTD, frontotemporal dementia, FTD-ALS, progressive non-fluent aphasia, semantic dementia, tau, TDP-43

INTRODUCTION

The recent demonstration of TAR-DNA binding protein 43 (TDP-43) as the constituent of ubiquitinated intraneuronal inclusions in frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) has stimulated a surge of clinical, pathological, and genetic research into these overlapping entities. FTD is the second most common cause of young onset dementia after Alzheimer’s disease [1,2], and three distinct clinical phenotypes of FTD are recognized, each with variable degrees of progressive behavior and language disturbance. A proportion of patients with FTD also develop clinical and neurophysiological evidence of motor neuron dysfunction and many satisfy the El Escorial criteria for the diagnosis of ALS [3]. The pathology of FTD is heterogeneous with variable degrees of focal frontal and temporal atrophy [4]. Three intraneuronal inclusions types have been characterized immunohistochemically as tau, TDP-43 or fused in sarcoma (FUS) positive [5–8]. TDP-43 positive inclusions are the most common type in FTD and are also identified in the majority of ALS cases [9,10].

Until recently, FTD was considered a rare cause of dementia and clinical distinction from AD was considered very difficult [11,12]. Over time, the defining clinical features of FTD have been elucidated and three clinical phenotypes are recognized (see Fig. 1). The behavioral variant of FTD (bvFTD) is character-
Fig. 1. Clinical Phenotypes of FTD. FTD is subclassified as behavioral variant (bvFTD) if behavior and personality changes predominate; Tau (green) and TDP-43 (blue) pathology are equally prevalent. Language variants include progressive non-fluent aphasia (PNFA), in which tau pathology is most prevalent and semantic dementia (SD), in which TDP-43 pathology is almost universal.

Fig. 2. MRI appearances in FTD. T1 weighted, coronal MRI images reveal: A) bvFTD – dorsolateral and orbitomesial, bifrontal atrophy, with dilatation of anterior horns of lateral ventricles (left > right); B) PNFA – moderate temporal atrophy (left > right) with subtle enlargement of the sylvian fissure due to insula atrophy (single arrow); C) SD – anterior temporal atrophy, severe on the left (double arrow) and moderate on the right with associated orbitofrontal atrophy.

ized by marked changes in behavior and personality, with relatively preserved language function. Alternatively, patients with semantic dementia (SD) and progressive non-fluent aphasia (PNFA) develop progressive language deficits, with more subtle personality and behavior changes. FTD is a progressive neurodegenerative disorder and the median survival from symptom onset is 6–8 years, but patients with FTD and ALS have an even worse prognosis [13,14].

This review cannot cover every facet of this rapidly evolving field, but rather attempts to place the recent pathological and genetic discoveries within the context of the clinical phenotypes of FTD and to outline an approach to clinical assessment and treatment.

PATHOLOGY

Focal frontal and temporal atrophy is identified in patients with FTD on autopsy [4], but the pattern of atrophy varies significantly among the clinical phenotypes. Bilateral mesial and orbitofrontal and temporal atrophy is the characteristic finding in patients with bvFTD. In SD, anterior and inferior temporal lobe atrophy is a universal feature, usually worse on the left than the right [15,16]. There may also be mild frontal atrophy. In PFNA, left-sided inferior frontal, insula, and perisylvian atrophy, is characteristic and is often severe [17].
Microscopically, FTLD is characterized by microvacuolation and neuronal loss, with variable degrees of white matter myelin loss and astrocytic gliosis [4], and intraneuronal as well as intraglial inclusions. The use of immunohistochemical staining has revolutionized the field and allows further categorization of the molecular pathology. Tau positive inclusions are present in approximately 40% of FTLD cases and the remainder are tau negative but ubiquitin positive [18]. Tau positive cases can be characterized biochemically as either predominantly three microtubule binding repeats (3R tau) or four microtubule binding repeat (4R tau), with further subclassification based on established morphologic criteria [4,19]. TDP-43 accounts for the majority of the ubiquitin positive cases and more than half of all FTD cases overall, but a minority FTD cases are both tau and TDP-43 negative [10]. Very recently, FUS positive inclusions have been demonstrated in these cases [6]. The search for FUS pathology was only initiated after FUS gene mutations were identified in cases of familial ALS, further emphasizing the links between FTD and MND [20–23]. Ubiquitin positive, TDP-43 negative inclusions have recently been demonstrated in patients with ALS due to mutations of FUS [24]. TDP-43 and FUS are RNA processing proteins, however, the link between these mutations and disease pathogenesis has not yet been elucidated [25].

The clinical phenotypes are associated with specific molecular pathologies to variable degrees. Tau positive and TDP-43 positive inclusions are equally prevalent in patients with bvFTD, whereas SD as well as FTD cases with coexistent ALS, are almost exclusively associated with TDP-43 pathology, although the distribution of inclusions differs between phenotypes [15,19,26,27]. In PNFA, tau positive inclusions are most commonly identified and can be further classified histopathologically as Pick’s disease (PiD) or non-PiD tau [26–28]. The small number of reported FUS positive FTD cases thus far have presented with bvFTD [6,29].

GENETICS

Up to 40% of patients with FTD may have a family history of dementia [1,30,31], but the high community prevalence of non-FTD dementia may account for a significant proportion of this family history. Patients with an autosomal dominant pattern (several affected first degree relatives across two generations) are much rarer, perhaps only accounting for 10% of FTD cases [32]. Known mutations can now be demonstrated in the majority of patients with this pattern of inheritance. Overall, mutations of the microtubule associated phosphoprotein tau (MAPT) and the progranulin (PGRN) gene each account for 5–11% of total FTD cases [32–35]. Although associated with TDP-43 pathology, PGRN mutations are not usually identified in patients with familial ALS [36]. Mutations of the gene encoding for TDP-43 (TARBP), recognized as a cause of familial ALS, have also been identified in cases of FTD-ALS [37], and rarely in FTD [38]. Rare genetic mutations causing FTD include valosin containing protein (VCP) and charged multivesicular body protein 2B (CHMP-2B). Mutation in the VCP gene causes FTD in association with inclusion body myopathy and Paget disease of bone [39], whereas the CHMP-2B gene mutation is confined to a large Danish cohort with FTD and other very rare patients with ALS [40]. In a recent study of patients with familial ALS due to FUS mutations, one mutation carrier presented with FTD [24]. The overall incidence of FUS mutations in FTD patients is currently unknown, however, no cases were identified in a recent mutation screening study of 225 FTD patients [32]. In addition to autosomal dominant inheritance of FTD, familial clusters of FTD and ALS are reported. Within these clusters, one individual may develop FTD and another ALS, or a third individual may develop FTD and subsequently ALS. Several linkage studies of FTD-ALS clusters have indicated a common locus in the region of chromosome 9p13.2–21.3 [41–44], but the responsible gene has not yet been identified.

CLINICAL PHENOTYPES OF FTD

Behavioral variant FTD

Approximately half of patients with FTD present with the bvFTD [45]. The symptom profile reflects progressive disintegration of the neural circuits involved in social cognition, emotion regulation, motivation, and decision making [46–48]. The orbitomesial frontal cortex, insula, and amygdala are increasingly recognized as key structures undergoing degeneration [49]. The behavioral and personality changes of bvFTD develop insidiously and may initially be mistaken for symptoms of depression [50,51]. Over time, symptoms accumulate and become more obvious. Patients usually lack insight into their cognitive symptoms and often dismiss carer or family concerns as unfounded. Apathy is al-
most universal and manifests as inertia, reduced motivation, lack of interest in previous hobbies, and progressive social isolation. Disinhibition often coexists with apathy, and may manifest as impulsive actions, tactless or socially inappropriate remarks, and socially embarrassing behavior. Changes in eating habits are common, with a narrowed repertoire of favored foods and meals. Patients may become gluttonous with food hoarded and even snatched from others. Excessive weight gain is common. Repetitive or stereotypic behaviors may be apparent and patients may perseverate, frequently repeating phrases, stories or favorite jokes. Patients often lack empathy and an inappropriately subdued grief reaction is a common early symptom. Mental rigidity is common and patients may have difficulty adapting to new situations or routines. Psychotic features (delusions and hallucinations) are relatively unusual overall [52], but in cases of FTD associated with ALS psychiatric features have been reported in up to 50% of patients [53]. Uncommonly, patients may present with symptoms suggestive of dementia with Lewy bodies such as hallucinations, fluctuating cognition, and parkinsonism [54].

Language disturbance may be present, most commonly characterized by adynamism, but does not dominate the clinical picture. Impaired executive function, manifest as difficulties in planning, organization, and goal-setting, is common. Unlike AD, episodic memory is preserved in the early stages of bvFTD and visuospatial deficits are not prominent. It is increasingly apparent that not all patients with the clinical features of bvFTD actually progress to frank dementia [55]. Such patients are almost always men and a proportion remain stable over many years or actually improve [56,57]. Over recent years a number of features have emerged that distinguish these non-progressive or phenocopy cases, for example, they show normal structural and functional imaging brain imaging [55,56,58]. The etiology of the phenocopy syndrome is a matter of debate. A proportion of patients appear to have a developmental personality disorder in the Asperger’s spectrum (personal observation). Some may have a chronic low grade mood disorder, but others remain a mystery.

The most commonly used diagnostic criteria for bvFTD, the Neary criteria [59], have recently come under criticism and are currently under review [60]. It is anticipated that the revised criteria will distinguish possible/probable and definite bvFTD, be easier and more flexible to apply with clearer operational definitions, and will include imaging and genetic findings.

Progressive Non-Fluent Aphasia (PNFA)

In PNFA, the presenting features reflect the breakdown of processes vital for effortless verbal communication, centering on Broca’s area, the anterior insula and the perisylvian structures. While some patients have a predominantly motor speech disorder (or apraxia of speech), others have mainly syntactic problems [61]. Their speech is labored and they often stumble over certain words, make grammatical errors, and have variable degrees of dysarthria. Word-finding difficulty and word pauses are common, further contributing to reduced speech fluency. Phonemes, the most elemental components of verbal language, may be inappropriately selected or substituted, and such phonemic errors and paraphasias are common. For example, the patient with PNFA may say “kanbaroo” rather than “kangaroo” or “wrisk” rather than “whisk”. Minor naming difficulties are apparent, but the severe anoma as encountered with SD is not a feature. Word repetition is typically impaired, particularly when attempting multisyllabic words such as “hippopotamus”, “chrysanthemum”, or “methodist episcopal” but comprehension of word meaning is preserved. Syntax (sentence construction) may be impaired and patients use simplified grammar with occasional inflectional errors and omissions, but severe agrammatism is uncommon. Although typically not reported by patients, sentence comprehension is often impaired. This is best observed when testing sequencing of tasks with more complex sentence structures, for example “Touch the pen after handing me the razor”.

Semantic Dementia (SD)

Although the predominant features of SD are anoma and impaired word comprehension, there is breakdown of the amodal knowledge system, the hub of which is located in the anterior temporal lobe. In contrast to PNFA, SD presents with progressive fluent aphasia and word comprehension deficits. Initially patients may report “loss of memory for words” or difficulty remembering the names of people. Anoma, the inability to name objects, is an integral component of SD with the names of infrequently used objects usually affected first. For example, the patient may be unable to name a stethoscope but is able to name a pen. As SD progresses, the names of more common objects become difficult to produce and patients often resort to circumlocutions to express their meaning. For example, when asked to name a can opener, a patient with SD may
Logopenic Progressive Aphasia (LPA)

Not all cases of primary progressive aphasia can be neatly classified as either PNFA or SD. In recent years, a third group of patients with progressive aphasia characterized by hesitant speech with prominent word finding difficulty, anomia, intact word but impaired sentence repetition and markedly impaired auditory verbal short-term memory has been described [69,70]. This syndrome, called logopenic progressive aphasia (LPA), while sharing some clinical features with PNFA and SD, appears to represent an atypical variant of AD, rather than a clinical phenotype of FTD [71].

ASSESSMENT

The bedside or clinic cognitive assessment involves a detailed patient and informant interview, simple testing of cognitive domains, and a neurological examination [72,73]. It is preferable to interview the patient and informant separately in order to confirm or elaborate on elements of the history which may prove sensitive or embarrassing. Even in advanced cases an assessment of insight, spontaneous speech, and social interaction can usually be attempted. As the interview proceeds, speech fluency, word-finding difficulties or pauses, and phonemic paraphasias are noted. Other symptoms such as apraxia or visuospatial disturbance should also be explored. A family history of dementia, mental illness, or ALS should be sought and clarified when identified.

Cognition can be assessed surprisingly well in the clinic or at the bedside [72,73]. Naming and semantic knowledge should be examined using pictures or, even better, toy animals and household objects, but it is important to use both familiar and less familiar items. Comprehension of simple commands and grammatical understanding, often mildly abnormal in patients with PNFA, should be examined with multi-step commands such as “Touch the razor and then the scissors” or “Give me the razor after you have touched the pencil”. Single word repetition is often impaired in PNFA. In contrast, patients with SD are generally able to repeat but not define the word. Reading aloud may reveal surface dyslexia, a feature of SD. Executive function is assessed with verbal fluency tests (letter and category), proverb interpretation, or testing the patient’s ability to inhibit alternating hand movements.

The bedside cognitive assessment should be complemented with a neuropsychological examination, which is reviewed elsewhere [73,74]. The Mini-Mental Status Examination (MMSE), although commonly used in clinical practice, is insensitive to the cognitive deficits encountered in FTD [75]. The Addenbrooke’s Cognitive Examination (ACE-R) incorporates elements of the MMSE, but includes a more thorough assessment of language (with fluency, naming, and semantic knowledge tasks), visuospatial ability, and memory, is effective in the distinction of FTD from AD [76,77]. The ACE-R is freely available online for clinical use [78].

Traditional neuropsychological assessments are not particularly sensitive to the deficits in social cognition encountered in patients with FTD, especially early bvFTD [79]. However, a new generation of tasks testing complex decision making [80,81], emotion process-
ing [49,82,83], sarcasm detection [49,84], and “Theory of Mind” [80,85] have been developed to address this. Similarly, new tasks have been developed to demonstrate and characterize the speech output and semantic deficits encountered in PNFA and SD [86]. Physical examination may be normal in patients with FTD. In some cases of bvFTD, or rarely PNFA, features of motor neurone dysfunction such as hyper-reflexia, muscle wasting, weakness, fasciculations, or dystonia may be detected [3]. Other patients, particularly those with PNFA, may demonstrate the parkinsonian features of corticobasal syndrome or progressive supranuclear palsy such as rigidity, bradykinesia, gait disturbance, and eye movement abnormalities [87–90].

**NEUROIMAGING**

Neuroimaging has been increasingly applied to the assessment of patients with FTD. Structural imaging, most typically with magnetic resonance imaging (MRI), reveals relatively well circumscribed, but varied, frontal and temporal lobe atrophy. The distribution of frontal and temporal atrophy observed on MRI correlates with the clinical phenotype [91]. In bvFTD, bilateral frontal and temporal atrophy is encountered [58], with the orbitofrontal cortex, superior frontal gyrus, temporal pole, insula, entorhinal cortex, hippocampus, and the head of the caudate affected [92,93]. Sophisticated MRI imaging techniques have identified dysfunction of differing neural circuits in FTD phenotypes [94], and selective vulnerabilities of specific circuits may underpin the clinical features and distribution of neuropathologic appearance of FTD [95]. For example, selective atrophy of the anterior cingulate cortex and anterior insula, corresponding with the location of von Economo neurons – a unique neuron type identified in humans and higher primates, has been identified in early bvFTD using MR techniques [96]. The neural correlates of behavioral symptoms have been studied using voxel based morphometry. For example, apathy has been associated with atrophy of right dorsolateral frontal structures, whereas disinhibition has been associated with grey matter loss of the right temporal lobe, particularly of the amygdala and hippocampus [97]. White matter changes on diffusion tensor imaging (DTI) have also been correlated with symptoms in bvFTD. For example, the superior longitudinal fasciculus has been linked with behavioral symptoms in bvFTD [98].

In PNFA, atrophy is most marked in the left superior temporal and inferior frontal lobes, as well as the left insula [17,99,100]. SD is characterized by asymmetrical temporal lobe atrophy (worse on the left than the right) with atrophy of the perirhinal cortex, as well as the parahippocampal, fusiform, and inferior temporal gyri [17,99]. Functional imaging with F18 fluorodeoxyglucose positron emission tomography (FDG-PET) in FTD reveals frontal and temporal hypometabolism, and FDG-PET is a useful adjunct in the distinction of FTD from other dementias [101–103]. Recently, the use of carbon 11-labeled Pittsburgh compound B positron emission tomography (PiB-PET) has been used to distinguish atypical presentations of AD from FTD [99]. Patients with AD pathology demonstrated increased PiB binding, but patients with FTD do not [71,104,105]. Positron emission tomography ligands to detect tau, TDP-43, or FUS pathology are not currently available.

**TREATMENT**

Currently there are no disease specific treatment interventions for FTD. Consequently, treatment largely remains supportive and involves a combination of non-pharmacological and pharmacological measures, aimed at reducing the effect of troublesome behaviors [106]. The impact of FTD on family members is enormous with high levels of stress and burden [107,108]. Carer education and support are essential and have been enhanced by the publication of a free booklet, “Understanding Younger Onset Dementia” [78]. The role of pharmacological interventions in FTD remains uncertain, and only small and often conflicting treatment trials have been conducted thus far. Selective serotonin reuptake inhibitors (SSRIs) such as paroxetine have been used to treat disinhibition and challenging behaviors, but evidence for their use remains contradictory [109,110]. Atypical antipsychotics such as olanzapine have been used for behaviors unresponsive to SSRIs or in patients with prominent delusions [111]. Anticholinesterase inhibitors, the mainstay of AD therapy, do not have an established role in the treatment of FTD. One study reported improvement in measures of behavioral disturbance and carer stress with rivastigmine [112], however, deterioration in neuropsychiatric symptoms without cognitive improvement was demonstrated with donepezil [113].
Table 1
Clinical features of FTD phenotypes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Behavioral FTD (bvFTD)</th>
<th>Progressive Non-Fluent Aphasia (PNFA)</th>
<th>Semantic Dementia (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heritability</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Behavior</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Severe Apathy</td>
<td></td>
<td>- Relatively preserved in early stages</td>
<td>- Preference for sweet foods, (late)</td>
</tr>
<tr>
<td>- Disinhibition</td>
<td></td>
<td></td>
<td>- Apathy (late)*</td>
</tr>
<tr>
<td>- Reduced empathy</td>
<td></td>
<td></td>
<td>- Disinhibition (late)*</td>
</tr>
<tr>
<td>- Stereotyped behavior and perseveration</td>
<td></td>
<td></td>
<td>- Impaired facial recognition*</td>
</tr>
<tr>
<td>- Changed food preference, weight gain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Literal proverb interpretation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mental rigidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Executive dysfuction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Adynamism</td>
<td></td>
<td>- Non-Fluent speech</td>
<td>- Fluent speech</td>
</tr>
<tr>
<td>- Non-Fluent speaking</td>
<td></td>
<td>- Hesitancy</td>
<td>- Severe anomia</td>
</tr>
<tr>
<td>- Hesitancy</td>
<td></td>
<td>- Apraxia of Speech</td>
<td>- Circumlocutions to express meaning</td>
</tr>
<tr>
<td>- Phonemic errors</td>
<td></td>
<td>- Syntactic errors</td>
<td>- Surface dyslexia</td>
</tr>
<tr>
<td>- Syntactic errors</td>
<td></td>
<td>- Mild anomia</td>
<td>- Normal word and sentence repetition</td>
</tr>
<tr>
<td>- Mild anomia</td>
<td></td>
<td>- Impaired single word and sentence repetition</td>
<td></td>
</tr>
<tr>
<td>MRI features</td>
<td>- Frontal atrophy</td>
<td>- Severe left temporal atrophy*</td>
<td>- Bilateral anterior temporal atrophy (usually left &gt; right)</td>
</tr>
<tr>
<td>- Orbitomesial</td>
<td>- Perisylvian</td>
<td></td>
<td>- Parietal cortex</td>
</tr>
<tr>
<td>- Temporal atrophy</td>
<td></td>
<td></td>
<td>- Fusiform gyrus</td>
</tr>
<tr>
<td>- Temporal pole</td>
<td></td>
<td></td>
<td>- Inferior temporal gyrus</td>
</tr>
<tr>
<td>- Hippocampus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Amygdala</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Caudate (head)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Tau positive cases</td>
<td>&lt; 50%</td>
<td>70%</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>% TDP-43 cases</td>
<td>&lt; 50%</td>
<td>30%</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>% FUS positive cases</td>
<td>5–10%</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

*Features of the right temporal variant of SD.

OUTSTANDING ISSUES

Although disease specific treatments for FTD are not available, the development of anti-tau therapies in the context of AD holds promise for future FTD therapeutics [114]. Should specific anti-tau or anti-TDP-43 therapies be developed, the ability to predict underlying neuropathologic processes at an early stage will become crucial [115]. Careful refinement of FTD phenotypes is one attempt to achieve this. For instance, it is clear that SD is associated with TDP-43 pathology [116] but has very low heritability and gene mutations are consequently rare [32]. PNFA, by contrast, appears to be more commonly associated with tau pathology, especially when apraxia of speech is present [117]. Sensitive and specific biomarkers are clearly needed. CSF biomarkers such as total tau and ratios of tau to amyloid-\(\beta\) have been demonstrated to distinguish FTD from AD \textit{in vivo} [118,119], but their utility in individual cases is unproven. Serum TDP-43 has also been studied as a potential biomarker for FTD and ALS [120–122]. Serum progranulin levels, which are low in patients with \(\textit{PGRN}\) mutations [123], may provide a useful screening test for these mutations. PET and MRI imaging may support the clinical diagnosis of FTD, to distinguish FTD from AD and to aid FTD phenotype classification [99,102,124,125]. Accurate prediction of underlying pathology is likely to require a combined approach using a range of investigative techniques.

CONCLUSION

Developments in the field of FTD are proceeding rapidly. Consequently, efforts to revise the diagnostic criteria, taking into account clinical features, genetic, imaging, and pathologic characteristics are underway. The revised criteria will hopefully allow the distinction of “phenocopy” FTD patients from those with progres-
sive dementia. The shared clinical, genetic, and pathological features of FTD and ALS have provided new insights into both disorders which together form a single clinicopathological spectrum. Although tau positive intraneuronal inclusions were identified initially, TDP-43 positive inclusions are now recognized as the most frequent underlying histopathology in FTD and ALS. The observed familial clusters of FTD and ALS have not yet been definitively explained. Furthermore, the incidence of subclinical motor dysfunction in FTD, or cognitive symptoms in ALS, has not yet been definitively established and is the subject of further study.

The combination of FTD and ALS is associated with a poorer prognosis, but whether the prognosis of TDP-43 positive cases differs significantly from tau positive FTD cases remains controversial. Moreover, the role of neuropsychologic examination in the assessment of ALS patients is yet to be established. The need for suitable biomarkers in life of distinctive pathological entities, and their relationship to prognosis, is clear and will be necessary for the future development of disease specific treatments.

ACKNOWLEDGMENTS

Dr. James R. Burrell gratefully acknowledges the support of the National Health and Medical Research Council of Australia and the Motor Neurone Disease Research Institute of Australia.

Professor John R. Hodges is in receipt of an Australian Research Council Federation Fellowship Grant.


REFERENCES


