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Review

Frontotemporal dementia and motor neurone disease: Overlapping clinic-pathological disorders

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ABSTRACT

Advances in genetics and pathology have supported the idea of a continuum between frontotemporal dementia (FTD) and motor neurone disease (MND), which is strengthened by the discovery of the trans-activating responsive (Tar) sequence DNA binding protein (TDP-43) as a key component in the underlying pathology of FTD, FTD–MND and sporadic and familial MND patients. MND is a multisystem disorder associated with cognitive and behavioural changes which in some instances reaches the criteria for FTD, while a proportion of patients with FTD develop frank MND. We review the overlap between FTD and MND, emphasizing areas of controversy and uncertainty.

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1. Introduction

Although traditionally regarded as very different entities, it is increasingly clear that frontotemporal dementia (FTD) and motor neurone disease (MND) are neurodegenerative conditions with overlapping clinical and neuropathological features. The pathological overlap has also been reinforced by the recent identification of a trans-activating responsive (Tar) sequence DNA binding protein (TDP-43) as the major component in the ubiquitinated inclusions in a major subgroup of FTD patients without tau pathology (so called ubiquitin-positive but tau-negative pathology, frontotemporal lobar degeneration-ubiquitin [FTLD-U]), as well as in sporadic and familial cases in MND.^{1–4} Recent advances in genetics have also enhanced our understanding of both entities, notably the discovery of mutations of the progranulin (*PGRN*) gene^{5,6} and the TDP-43 coding gene (*TARDBP*)^{7–9} in patients with familial FTD and MND, respectively although few, if any, of the members of these families appear to have MND with FTD.

Stronger evidence for the overlap comes from well documented families in which various members manifest either FTD, MND or both, in whom linkage has been shown to chromosome 9 but the causative gene mutation is yet to be identified.¹⁰

The clinical overlap can be considered from two perspectives: First, a subgroup of patients with FTD develops features of MND typically within 12 months or so of the onset of the cognitive and behavioural changes and show a rapidly downhill course.^{11,12} Second, is the issue of the degree and prevalence of cognitive impairment in patients presenting with classic motor features of

MND: it is well recognised that MND is a multisystem disorder^{13,14} with compromise of regions beyond the motor system, including cortical areas consistently involved in FTD. It comes as no surprise, therefore, that a proportion of patients presenting with MND manifest cognitive and/or behavioural changes which may be severe enough in some instances to reach criteria for frank FTD.^{15,16}

We review evidence for the overlap between these disorders drawing on neuropathological and cognitive changes reported in the literature and emphasizing areas of controversy and uncertainty.

2. Frontotemporal dementia

FTD, sometimes also referred to as frontotemporal lobar degeneration (FTLD), is the second commonest cause of dementia in younger people (< 65 years),¹⁷ and produces focal atrophy of the frontal and/or anterior temporal lobes, with concomitant cognitive features. Two major presentations are recognised: a behavioural variant (bvFTD) and a language variant, which in turn is divided in two different patterns: semantic dementia (SD) and progressive non-fluent aphasia (PNFA) (Fig. 1). These three forms of presentation differ in their clinical features and the pattern of underlying brain atrophy.

bvFTD is characterised by a prominent change in personality and social behaviour, with apathy and/or disinhibition, emotional blunting, stereotyped or ritualised behaviours, loss of empathy, alterations in appetite and food preference with limited or no insight.^{18,19} These changes reflect involvement of orbital and mesial frontal lobes which can be visualised on high resolution MRI.²⁰

In SD there is a profound loss in conceptual knowledge (or semantic memory) causing anomia and impaired comprehension

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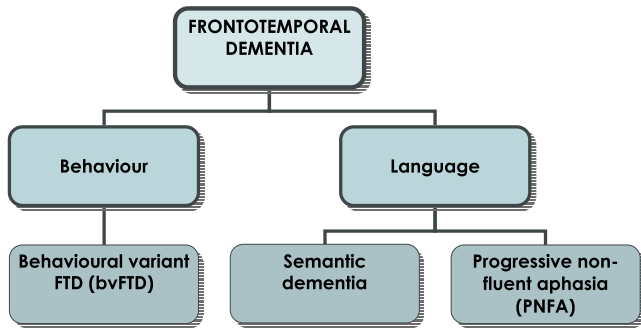


Fig. 1. Classification of frontotemporal dementia.

of words, objects, or faces. The patient typically complains of “loss of memory for words” and has fluent, empty speech with substitutions such as “thing”, and “one of those”, but the grammatical aspects are preserved. Naming is impaired with semantically based errors (such as “animal” or “horse” for zebra). Patients are unable to understand less frequent words and fail on a range of semantically based tasks such as matching words to pictures and matching pictures according to their meaning. Repetition of words and phrases is normal even though patients are unaware of their meaning. Unlike patients with Alzheimer’s disease, day-to-day memory (episodic memory) with good visuospatial skills and non-verbal problem-solving ability is relatively preserved, at least in the early stages. MRI imaging in SD shows very consistent pattern of anterior and inferior temporal lobes which is typically asymmetric (left greater than right).^{21,22}

In PNFA, by contrast, there is a gradual loss of expressive language abilities with impairments in phonological (sound-based) and grammatical aspects of language production. This leads to non-fluent, agrammatical, and poorly articulated speech with phonological errors (e.g. “sitter” for sister or “fencil” for pencil). Repetition of multisyllabic words and phrases is impaired but, in contrast to SD, word comprehension and object recognition are well preserved.^{23,24} MRI changes are much more subtle than in SD with widening of the left Sylvian fissure due to atrophy of the insular and inferior frontal regions.²⁵ These distinctions are clear when patients first present the symptoms, but with progression of the disease, most patients manifest both behavioural and language features.

3. Motor neurone disease

MND comprises a group of conditions with progressive motor neuronal loss.²⁶ Amyotrophic lateral sclerosis (ALS) is the most frequent form of presentation (>75%), and is characterised by progressive loss of lower motor neurones (LMN) in the anterior horn of the spinal cord and brainstem motor nuclei, and loss of upper motor neurones (UMN) in layer V of the motor cortex. Clinically, MND produces progressive weakness, muscular wasting, fasciculations, spasticity, breathing and swallowing problems, with a survival of 3 to 5 years in 50% of the patients. A second variant of MND is progressive muscular atrophy (PMA), characterised by purely LMN degeneration and represents around 10 to 20% of the cases. Primary lateral sclerosis affects exclusively UMN and has a slower progression (10 years from the onset). Finally, progressive bulbar palsy, present in 1 to 2% of the patients, involves bulbar nuclei.²⁷

4. Pathological findings in FTD and MND: the role of TDP-43

The gross pathological appearance of FTD is that of profoundly atrophied frontotemporal regions that may be so severe as to pro-

duce the so-called knife-edged gyri and deep widened sulci. The histopathological hallmarks are widespread cortical and subcortical gliosis, loss of large cortical nerve cells and microvacuolation.

Immunohistochemical staining reveals two major patterns based on the presence of intraneuronal inclusions.

The first pattern is characterised by the accumulation of the microtubular binding protein tau, either in the form of classic Pick bodies, or diffuse neuronal and glial pathology. The latter is typically seen in patients with mutations of the tau gene.²⁸

The second major pattern consists of FTLN-U, first identified in patients with MND without dementia, but then later found in those with MND-FTD and in FTD patients with progranulin gene mutations. The recent discovery of TDP-43 as the major underlying protein associated with ubiquitin in these tau-negative patients has led to a reclassification of the ubiquitin-positive tau-negative patients as discussed more fully below in this section.

A few patients have neither tau nor ubiquitin-positive inclusions.²⁹

In MND, the pathology also includes Bunina bodies and ubiquitin immunoreactive inclusions (“skein-like” or round “Lewy body-like”) in the LMN; meanwhile in the UMN, these ubiquitinated inclusions are less frequent.²⁸

A major breakthrough has been the recent discovery that ubiquitin (a proteasomal linked protein) binds to a specific protein called TDP-43, a 414 amino acid nuclear protein of 43 kD. TDP-43 participates in a range of different biological process binding DNA, RNA and other proteins. Normally, it is detectable in the nuclei of neurons and glial cells. The pathological state is associated with a reduction of normal nuclear TDP-43 staining and presence of cytoplasmic and nuclear inclusions. Recent genetic studies have identified mutations of the TDP-43 coding gene (*TARDBP*) on chromosome 1p36, in a subset of patients with familial and sporadic MND^{30,31} but not in patients with FTD or MND-FTD. The presence of TDP-43 inclusions in patients with familial FTD and *PGRN* mutations might be explained by a different metabolic process – suppression of progranulin expression leading to caspase-dependent accumulation of TDP-43 fragments.³²

The finding of TDP-43 has also contributed to a revised classification of the FTLN-U patients, depending of the pattern and distribution of staining as shown in Table 1. According to the Mackenzie classification, type 1 is present in FTLN and PNFA patients, and type 2 is associated with SD whereas type 3 is related to FTLN-MND and typically has pathology involving superficial and deep cortical laminae with abundant intracytoplasmic neuronal inclusions.^{4,28,33–35}

In summary, TDP-43 positive pathology, also called FTLN-TDP,³⁶ is present in virtually all patients with FTD associated with MND, a significant proportion of FTD patients without overt MND and in most patients with sporadic and familial MND (but notably not those with a superoxide dismutase 1 [*SOD1*] gene mutation).

5. Clinical overlap

5.1. MND in patients presenting with FTD

An important minority of patients present with features of FTD and go on to develop frank MND. This subform of FTD was described in detail by Japanese neurologists in 11 consecutive patients,³⁷ but has been increasingly recognised globally. In 61 patients from Cambridge and Sydney, with FTD pathologically confirmed, 15% had known FTD-MND in life.³⁸ Experience from Cambridge since 2000 suggests that these FTD-MND patients share unique characteristics. The dementia is of unusually rapid progression, even before motor features declare themselves, raising the differential diagnosis of prion disease or a paraneoplastic syndrome. There is a mixture of prominent language features (usually

Table 1

Pathological classification of frontotemporal lobar degeneration with TDP-43-positive inclusions (FTLD-TDP)

Pathology classification	Inclusion localisation	Disease association
Mackenzie ^{28,33} Sampathu ^{28,34} Neumann ^{28,35}		
1	3	Numerous NCIs and DNs in superficial cortical layer. Variable NIIs.
2	1	Abundance of long DNs in superficial cortical laminae.
3	2	Few or no NCIs or NIIs. Numerous NCIs in superficial & deep cortical laminae. Few DNs. Sparse or no NIIs.
	Neumann ^{28,35} Cairns ^{4,28}	
	4	Numerous NIIs, infrequent NCIs and DNs in neocortical areas. Relative sparing of hippocampus.

DNs = dystrophic neurons, FTLD = frontotemporal lobar degeneration, GCIs = glial intracytoplasmic inclusions, MND = motor neurone disease, NCIs = neuronal cytoplasmic inclusions, NIIs = neuronal intranuclear inclusions, PGRN = progranulin, PNFA = progressive non-fluent aphasia, VCP = valosin-containing protein.

within the PNFA rather than SD spectrum)^{39–42} and behavioural changes. Language impairment in verb rather than noun processing is common^{41,42} and some patients have a high prevalence of psychotic features, such as hallucinations and delusions. The mean duration between diagnosis with FTD and the onset of bulbar or limb motor symptoms is 6 months to 12 months.^{11,38,43}

There have been few formal attempts to systematically examine cohorts of FTD patients for features of MND but one such study involving 36 patients with FTD found that 14% met the criteria for a definitive diagnosis of MND/ALS and 36% had electromyography findings suggesting MND/ALS.⁴⁴

5.2. Cognitive and behavioural findings in patients presenting with MND

Estimates of the prevalence of cognitive impairment in MND have ranged from as low as 10% to as high as 75%.⁴⁵ These differences almost certainly reflect differences in the neuropsychological assessment instruments employed to define cognitive impairment, variability in the number of patients and, particularly, methods of case ascertainment. In one of the largest studies, involving 279 patients with sporadic MND/ALS, cognitive impairment was reported in 50% of the patients while 15% of the patients met criteria for FTD.⁴⁶

5.2.1. Frontal executive abilities

The strongest evidence related to cognitive impairment comes from the study of frontal dysfunction in cohorts of patients with MND.^{44–47}

As summarised in Table 2, the impairment in executive function is evidenced by a range of tests including: verbal fluency,⁴⁸ verbal free recall, problem solving, cognitive flexibility, planning, and working memory.^{13,49,50} Verbal fluency, in which subjects generate as many words as possible in a given time period either beginning with certain letters of the alphabet or from a defined semantic category, had been studied extensively with adjustments for dysarthria.

Table 2

Studies of cognitive impairment in motor neurone disease

Study	MND/ALS patients (n)	Cognitive impairment	Cognitive function impaired	Neuropsychological assessment
Gallassi et al. 1985 ¹³	22	27%	Verbal fluency, immediate recall	COWA, RAVLT, verbal reasoning, short term verbal memory, short term visual recall
Massman et al. 1996 ⁴⁷	146	35.6%	Problem solving, attention/mental control, recognition memory, word generation, verbal free recall	Short category booklet test, VSAT, CMRT, FAS, CVLT
Rakowicz and Hodges 1998 ⁵⁰	18	28%	Verbal fluency, attention, syntactic comprehension, confrontation naming, conceptual semantic processing	Verbal fluency, reverse digit span, graded naming test, TROG
Ringholz et al. 2005 ⁴⁶	279	51% frontal impairment 15% met FTD criteria	Attention, verbal fluency, working memory, naming	VSAT, FAS, visual recall, verbal recall, BNT
Murphy et al. 2007 ⁸³	23	22% met criteria for FTD	17% subtle behavioural changes, 9% subtle cognitive dysfunction	BNT, COWA, NPI, WCST, category fluency

BNT = Benton naming test, CMRT = continuous recognition memory test, COWA = the controlled oral word association test for fluency, CVLT = California verbal learning test, FAS = Verbal fluency test, FTD = frontotemporal dementia, MND/ALS = motor neurone disease/amyotrophic lateral sclerosis, NPI = neuropsychiatric inventory, RAVLT = Rey auditory verbal learning test, TROG = test of reception of grammar, VSAT = verbal series attention test, WCST = Wisconsin card sorting test.

Moreover, the degree of executive impairment correlates closely with hypometabolism of the frontal lobe in studies using FDG-positron emission tomography,^{51–53} reduced isotope uptake in the frontal region in single-photon emission computed tomography (SPECT) studies⁵⁴ and impaired activation in the frontal lobe on functional MRI (fMRI).⁵⁵ Frontal atrophy has been demonstrated in MND using quantitative structural MRI.^{56,57}

5.2.2. Language

The spectrum of language impairment in MND is wider than simply problems in speech production due to dysarthria but it is yet to be fully characterised. Reduced verbal output (adynamism) evolving into mutism has been reported, as well as echolalia, perseverations and stereotypical expressions.¹² True non-fluent aphasia with phonological and/or syntactic deficits and comprehension impairment has been reported in isolated cases.^{40,41,58,59} These deficits mirror those found in patients with FTD-MND who show consistent deficits on the Test for the Reception of Grammar particularly in the sections probing knowledge of verb meaning and the on the “Kissing and Dancing Test” of action verb comprehension.^{12,59,60}

MND has also been associated with apraxia of speech, in which there is breakdown in articulatory planning, producing slowed, effortful and dysprosodic speech with problems repeating multisyllabic words. Apraxia of speech is often accompanied by orobuccal apraxia but not necessarily with aphasia.^{61,62} The prevalence of subtle phonological, syntactic or semantic deficits remains unknown. Given the prominence of language deficits in FTD, it is surprising that this aspect of cognition has been studied much less in MND than frontal executive function. There are, of course, considerable problems given that many patients become severely

dysarthric and that hand weakness may also limit the ability to test comprehension using pointing tasks or language output via the modality of writing.

5.2.3. Memory

It has been difficult to categorise the pattern of memory impairment, but current evidence suggests that memory problems are related to abnormalities in retrieval of the information secondary to frontal dysfunction.^{63,64} Memory problems involve primarily immediate recall,^{49,65} but visual memory also has been implicated.^{53,66}

In a cohort of 146 sporadic MND cases, 20% of the patients performed below cut off (5th percentile) on the California Verbal Learning Test, with difficulties on the free recall learning trials, meanwhile on the Delayed Verbal Recognition Memory Test the performance was good.⁴⁷ Frontal, temporal and thalamic hypoperfusion on SPECT has been shown to correlate with the severity of memory impairment.⁶⁷

5.2.4. Behavioural changes

Behavioural changes in MND patients, when present, fit within the spectrum of symptoms that characterise bvFTD. For instance, one study assessing a group of 45 patients with MND/ALS with the Frontal Systems Behaviour Scale, reported that 56% of the patients had a significant degree of apathy that was mood independent.⁶⁸ In another recent study, an informant based behavioural interview was administered to the carers of 16 patients with MND: the authors reported an increase in self-centredness and reduced concern for the feelings of others in 69%, while 63% were more irritable. Emotional lability was reported in 50%, 38% were apathetic and 25% showed blunting of emotions. Less common changes were gluttony, behavioural stereotypes and compulsions.⁶⁹

Emotional lability is a long-established finding in MND associated particularly with pseudobulbar palsy, occurring in about 10% to 20% of MND/ALS patients.⁷⁰ This raises the possibility that those with emotional lability may have problems with the appreciation, or processing, of emotions in faces or voices. Impaired emotion has been consistently shown in patients with FTD.⁷¹ It is logical, therefore, that a recent study demonstrated an alteration in emotional faces recognition in bulbar MND patients.⁷² In another study, using affective pictures and fMRI, MND patients showed an increased response in the right supramarginal area representing an altered sensitivity to social-emotional cues.⁷³

Verbal emotional judgments are also impaired. Using pictures from the International Affective Picture System, MND patients' ratings were more positive than controls. They tended to neutralise extreme pictures, rating calm pictures as more exciting than controls and exciting pictures as calmer. These changes of emotional processing were, however, unrelated to depression or frontal lobe dysfunction.⁷⁴

A review of 28 studies of mood in MND suggested that patients present with hopelessness and concern about the end of life, more than clinical significant depression.⁷⁵ In a one small-scale study, using the Beck Depressive Inventory and the Hospital Anxiety and Depression Scale, four of 18 MND patients (23%) had significant levels of depression but there was no clear relation between depression, other life events or illness progression.⁷⁶

6. Predictors of cognitive dysfunction in MND: Bulbar onset versus limb onset

While it is generally believed that bulbar onset patients seem to have more cognitive impairment than those with limb onset, this association remains controversial. In one study bulbar-onset patients showed greater impairment in several domains including working memory, problem-solving/cognitive flexibility, episodic

memory and visual-perceptual skill.⁷⁷ In another, distractibility and frontal lobe impairment was positively correlated with dysarthria and bulbar symptoms.⁷⁸ Several other studies have failed to replicate this distinction.^{46,47,79}

7. Conclusions

In the last few years a tremendous effort has been directed towards characterising the clinical overlap between FTD and MND. There remain, however, important issues to resolve. For example, is cognitive impairment an inherent aspect of MND which is an inevitable accompaniment at some stage, or is the dysfunction only present in a subgroup of MND patients with different clinical phenotype? One longitudinal study suggested that cognitive impairment in MND becomes more prominent over time,⁸⁰ but it has not been possible, so far, to determine if patients manifesting mild cognitive and/or behavioural impairment progress to frank FTD. Changes in social cognition and complex reasoning, which have been shown to occur consistently in bvFTD, have not been systematically explored in MND and there have been very few studies of language in MND. By analogy, central and peripheral motor function has not been investigated using modern sensitive methods in populations of patients with FTD.

A fuller characterisation of the extent of cognitive and behavioural dysfunction in MND is not simply of academic interest but has important implications given that the burden and stress for carers of patients with FTD is very great.⁸¹ It also has relevance to effective communication, legal issues and end-of-life decision making by patients with MND.⁸²

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