

Frontotemporal lobar degeneration: current perspectives

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Abstract: The term frontotemporal lobar degeneration (FTLD) refers to a group of progressive brain diseases, which preferentially involve the frontal and temporal lobes. Depending on the primary site of atrophy, the clinical manifestation is dominated by behavior alterations or impairment of language. The onset of symptoms usually occurs before the age of 60 years, and the mean survival from diagnosis varies between 3 and 10 years. The prevalence is estimated at 15 per 100,000 in the population aged between 45 and 65 years, which is similar to the prevalence of Alzheimer's disease in this age group. There are two major clinical subtypes, behavioral-variant frontotemporal dementia and primary progressive aphasia. The neuropathology underlying the clinical syndromes is also heterogeneous. A common feature is the accumulation of certain neuronal proteins. Of these, the microtubule-associated protein tau (MAPT), the transactive response DNA-binding protein, and the fused in sarcoma protein are most important. Approximately 10% to 30% of FTLD shows an autosomal dominant pattern of inheritance, with mutations in the genes for *MAPT*, progranulin (*GRN*), and in the chromosome 9 open reading frame 72 (*C9orf72*) accounting for more than 80% of familial cases. Although significant advances have been made in recent years regarding diagnostic criteria, clinical assessment instruments, neuropsychological tests, cerebrospinal fluid biomarkers, and brain imaging techniques, the clinical diagnosis remains a challenge. To date, there is no specific pharmacological treatment for FTLD. Some evidence has been provided for serotonin reuptake inhibitors to reduce behavioral disturbances. No large-scale or high-quality studies have been conducted to determine the efficacy of non-pharmacological treatment approaches in FTLD. In view of the limited treatment options, caregiver education and support is currently the most important component of the clinical management.

Keywords: review, frontotemporal dementia, frontotemporal lobar degeneration

Introduction

The term frontotemporal lobar degeneration (FTLD) refers to a group of progressive brain diseases, which are heterogeneous with regard to etiology and neuropathology, but share atrophy of the frontal and/or temporal cortex as a morphological feature. The clinical syndromes of FTLD are characterized by progressive deterioration of either behavior or language. The first patient was described in 1892 by Arnold Pick, a neurologist in Prague,¹ and FTLD was named Pick's disease for more than a century. Today, this term is used only for a small subgroup of FTLD with specific histopathological features. The nomenclature of FTLD has remained inconsistent. In the present review, FTLD is used as an overarching term for a clinicopathological complex, which includes two clinical syndromes and three major underlying neuropathological subtypes.

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The clinical syndromes – behavioral-variant frontotemporal dementia (bvFTD) and primary progressive aphasia (PPA) – are distinguished by the early and predominant symptoms. The neuropathological subtypes are characterized by an abnormal accumulation of proteins, microtubule-associated protein tau (MAPT), transactive response DNA-binding protein with molecular weight 43 kDa (TDP-43), and fused in sarcoma protein (FUS).

Clinical subtypes

bvFTD

The most common clinical syndrome of FTLT is bvFTD. Atrophy predominantly of the mesiofrontal, orbitofrontal, and anterior insular cortex regions of the frontal lobes leads to progressive personality changes and behavioral disturbances.²⁻⁴

Since 1994, four sets of diagnostic criteria have been published,⁵⁻⁸ which reflect the evolving understanding of the disorder.⁹ The most recent criteria, proposed by The International bvFTD Criteria Consortium,⁷ define three levels of diagnostic certainty and refer to six behavioral and cognitive symptom clusters (Table 1).

According to these criteria, bvFTD is characterized by early decline in social behavior and personal conduct, as indicated by early disinhibition, apathy, loss of sympathy, perseverative and stereotyped behaviors, and hyperorality.

Behavioral disinhibition is a frequent symptom of bvFTD. It has multiple appearances; eg, a lack of etiquette, with patients making offensive jokes, often with sexual reference, or exhibiting childish behavior. Patients may approach strangers in an aggressive manner or may touch them inappropriately. They may exhibit impulsive or risky behaviors such as gambling, or may fall for financial scams; eg, doorstep selling. In a recent study of pathologically confirmed bvFTD cases, 76% of patients showed behavioral disinhibition or impulsivity.⁷

Over 85% of patients in this study exhibited apathy and inertia as an early symptom.⁷ Inertia refers to a decreased action generating ability. Apathy corresponds to general passivity. Both result in a lack of motivation to pursue activities and hobbies, so patients may need assistance to initiate or continue those activities.

Human empathy relies on the ability to share emotions as well as the ability to understand other's thoughts, desires, and feelings.¹⁰ The loss of sympathy in patients with bvFTD results in a cold and indifferent attitude. There is converging evidence from neuroimaging studies that the

neurodegeneration in anterior regions of the medial frontal cortex is linked to the patients' deficits in their ability to attribute mental states to one's self and to others.¹¹

Patients may perform repetitive, stereotyped actions such as scratching, lip smacking, or clapping hands. Some may repeat phrases or stories. Rituals involving fixed wandering routes, hoarding, or object counting are also observed. These inappropriate repetitive behaviors are linked to a dysfunction of a circuit involving the orbitofrontal and anterior cingulate cortices, the basal ganglia, and the thalamus.¹²

Altered food preferences with craving for sweets, or rigid preference of particular foods are frequently observed.¹³ Some patients show binge eating, sometimes even with negative health consequences (eg, diabetes mellitus). There has been discussion about the involvement of the orbitofrontal–insular–striatal brain network and the hypothalamus.¹⁴

While behavioral changes dominate the initial presentation of bvFTD, cognitive deficits appear as the disease progresses. The neuropsychological profile of bvFTD is characterized by executive deficits and by relative sparing of memory and visuospatial functions.

PPA

The language variants of FTLT, semantic variant PPA (svPPA; also referred to as semantic dementia or temporal variant frontotemporal dementia) and nonfluent variant PPA (nfvPPA; also referred to as progressive nonfluent aphasia) are summarized under the term PPA.

svPPA is caused by marked, often asymmetric (left > right) anterior and inferior temporal atrophy.^{15,16} As the disease progresses, posterior temporal regions are also involved, as well as the orbitofrontal lobe, insula and anterior cingulate, and homologous regions in the opposite hemisphere.^{17,18} Speech is fluent, and syntax, prosody, and motor speech are intact. However, patients gradually lose their semantic memory – the knowledge about words, objects, and concepts. Speech becomes empty and ultimately meaningless. Semantic paraphasias are frequent, and surface dyslexia and dysgraphia occur. In advanced disease stages, semantic knowledge is impaired beyond language, and the patients develop features of multimodal agnosia. During the course of svPPA many patients present behavioral disturbances similar to bvFTD.¹⁹ Personality changes are frequently among the first symptoms in patients who exhibit a marked atrophy of the right temporal lobe.²⁰ In these patients, language deficits are less prominent than prosopagnosia and associative agnosia.²¹

nfvPPA is caused by a predominant left posterior fronto-insular atrophy. Patients with nfvPPA present with

Table I International consensus criteria for bvFTD**I. Neurodegenerative disease**

The following symptom must be present to meet criteria for bvFTD

A. Shows progressive deterioration of behavior and/or cognition by observation or history (as provided by a knowledgeable informant)

II. Possible bvFTD

Three of the following behavioral/cognitive symptoms [A–F] must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events

A. Early* behavioral disinhibition (one of the following symptoms [A.1–A.3] must be present):

A.1. Socially inappropriate behavior

A.2. Loss of manners or decorum

A.3. Impulsive, rash, or careless actions

B. Early apathy or inertia (one of the following symptoms [B.1–B.2] must be present):

B.1. Apathy

B.2. Inertia

C. Early loss of sympathy or empathy (one of the following symptoms [C.1–C.2] must be present):

C.1. Diminished response to other people's needs and feelings

C.2. Diminished social interest, interrelatedness, or personal warmth

D. Early perseverative, stereotyped, or compulsive/ritualistic behavior (one of the following symptoms [D.1–D.3] must be present):

D.1. Simple repetitive movements

D.2. Complex, compulsive, or ritualistic behaviors

D.3. Stereotypy of speech

E. Hyperorality and dietary changes (one of the following symptoms [E.1–E.3] must be present):

E.1. Altered food preferences

E.2. Binge eating, increased consumption of alcohol or cigarettes

E.3. Oral exploration or consumption of inedible objects

F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions (all of the following symptoms [F.1–F.3] must be present):

F.1. Deficits in executive tasks

F.2. Relative sparing of episodic memory

F.3. Relative sparing of visuospatial skills

III. Probable bvFTD

All of the following symptoms [A–C] must be present to meet criteria

A. Meets criteria for possible bvFTD

B. Exhibits significant functional decline (by caregiver report or as evidenced by CDR or FAQ scores)

C. Imaging results consistent with bvFTD (one of the following [C.1–C.2] must be present):

C.1. Frontal and/or anterior temporal atrophy on MRI or CT

C.2. Frontal hypoperfusion or hypometabolism on PET or SPECT

IV. bvFTD with definite FTLN pathology

Criterion A and either Criterion B or C must be present to meet criteria

A. Meets criteria for possible or probable bvFTD

B. Histopathological evidence of FTLN on biopsy or at postmortem

C. Presence of a known pathogenic mutation

V. Exclusionary criteria for bvFTD

Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD

A. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders

B. Behavioral disturbance is better accounted for by a psychiatric diagnosis

C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process

Notes: *As a general guideline, "early" refers to symptom presentation within the first 3 years. Reproduced from Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134(Pt 9):2456–2477, by permission of Oxford University Press.⁷

Abbreviations: bvFTD, behavioural-variant frontotemporal dementia; CDR, clinical dementia rating scale; FAQ, functional activities questionnaire scores; CT, computed tomography; FTLN, frontotemporal lobar degeneration; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

a nonfluent, effortful, halting speech that is dominated by obvious word-finding difficulties and agrammatism. Language production is simplified, phonemic paraphasias are frequent. Oral apraxia is observed in most patients, dysarthria occurs less frequently. In contrast to svPPA, object knowledge and single word comprehension are spared, while comprehension

of syntactically complex sentences is impaired. In the late disease stages, the patients become mute.^{16,22}

Recent diagnostic criteria suggest a third subtype of PPA that does not fit the criteria for svPPA or nfvPPA and has been termed logopenic variant of progressive aphasia (lvPPA).¹⁶ In lvPPA, atrophy is most prominent in the posterior cortical

region with asymmetrical (left > right) temporo–parietal atrophy. Patients present phonological disorders as well as impaired word retrieval and sentence repetition. On the other hand, motor speech, grammar, and comprehension are relatively intact. A recently published study examined the clinicopathological correlations within the PPA variants.²³ Fifty-two patients were included. From the 30 patients meeting the basic PPA criteria, all the svPPA patients (four) and 75% of the nfvPPA patients had frontotemporal lobar degeneration spectrum pathology. In the group of patients who met the logopenic variant PPA, the underlying pathology was heterogenous (46% Alzheimer's disease [AD], 8% AD mixed with dementia with Lewy bodies, 23% frontotemporal lobar degeneration, and 23% others). It is obvious that this causes great difficulty in diagnosing an aphasic syndrome.

Overlap of FTLD with corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), and motor neuron disease

There is considerable clinical and histopathological overlap of FTLD with the atypical parkinsonian disorders CBD and PSP, and with motor neuron disease (Table 2). Patients with PSP

show vertical gaze palsy and parkinsonian symptoms such as bradykinesia, axial rigidity, and postural instability, which poorly respond to levodopa treatment. Rapid eye movement sleep behavior disorder is observed in Parkinson's disease, but not in PSP.²⁴ Difficulties in swallowing and aspiration occur in the later disease stages. CBD is characterized by an insidious onset and slow disease progression, lack of response to levodopa therapy, akinetic rigidity, limb apraxia, and speech and language impairment.²⁵ Myoclonus, asymmetric dystonia, alien limb phenomenon, frontal executive dysfunction, and visuospatial deficits are secondary criteria. Episodic memory is relatively preserved as hippocampi and temporal cortices are unaffected.²⁶ Patients with PSP or CBD may develop behavioral disturbances similar to bvFTD or PPA. Vice versa, patients with bvFTD or nfvPPA may develop neurological symptoms which are characteristic for later-stage PSP or CBD.²⁷

Amyotrophic lateral sclerosis (ALS), as the most common form of motor neuron disease, presents with atrophic paresis, fasciculations, and muscular cramps as signs of involvement of the spinal motor neurons, and brisk reflexes, pyramidal signs, and increased muscular tonus indicating affection of cortical motor neurons. Weakness of the respiratory muscles and breathing insufficiency are the main cause of death.

Table 2 Molecular classification of FTLD with genetic and clinical correlations

Molecular class	Pathological subtype*	Associated genes	Clinical phenotypes				
			bvFTD	nfvPPA	svPPA	Park	MND
FTLD-tau		• <i>MAPT</i>	+	(+)	(+)	+	ALS, PLS
	• PiD		+	+	(+)		
	• CBD		+	+		+	PLS
	• PSP		+	+		+	PLS
	• AGD			+			
	• NFT-dementia			+			
FTLD-TDP	• MSTD		+			+	PLS
		• (<i>TARDBP</i>)	(+)			+	ALS
	• Type A	• <i>GRN</i>	+	+		+	
	• Type B	• <i>C9orf72</i>	+	+	(+)	+	ALS
	• Type C		+		+		
FTLD-FUS	• Type D	• <i>VCP</i>	+			(+)	ALS
		• (<i>FUS</i>)	(+)				ALS
	• aFTLD-U		+				
	• NIFID		+			+	PLS
FTLD-UPS	• BIBD		+			+	ALS
	• FTD-3	• <i>CHMP2B</i>	+			(+)	(ALS)

Notes: *Indicates the characteristic pattern of pathology, not the clinical syndrome. (+) Rare cause or unusual phenotype.

Abbreviations: aFTLD-U, atypical frontotemporal lobar degeneration with ubiquitinated inclusions; AGD, argyrophilic grain disease; ALS, amyotrophic lateral sclerosis; BIBD, basophilic inclusion body disease; bvFTD, behavioral-variant FTD; *C9orf72*, chromosome 9 open reading frame 72; CBD, corticobasal degeneration; *CHMP2B*, charged multivesicular body protein 2B; FTD, frontotemporal dementia; FTD-3, FTD linked to chromosome 3; FTLT, frontotemporal lobar degeneration; FUS, fused in sarcoma; *GRN*, progranulin gene; *MAPT*, microtubule-associated protein tau; MND, motor neuron disease; MSTD, multiple system tauopathy with dementia; NFT-dementia, neurofibrillary tangle predominant dementia; nfvPPA, nonfluent variant primary progressive aphasia; NIFID, neuronal intermediate filament inclusion disease; Park, parkinsonism; PiD, Pick's disease; PLS, primary lateral sclerosis; PSP, progressive supranuclear palsy; svPPA, semantic variant primary progressive aphasia; *TARDBP*, transactive response DNA-binding protein; TDP, transactive response DNA-binding protein with molecular weight 43 kDa; UPS, ubiquitin proteasome system; *VCP*, valosin-containing protein.

Up to 15% of patients with FTLD also show symptoms of ALS. About 5% of patients with ALS develop the full clinical phenotype of bvFTD, svPPA, or nvPPA.^{28,29}

Epidemiology

Only a few studies have attempted to determine the epidemiology of FTLD. It is difficult to obtain reliable estimates of prevalence and incidence because the concept and nomenclature of FTLD are changing and clinical diagnosis can be challenging. In the population as a whole, FTLD is relatively rare³⁰ and has been included in the list of “orphan diseases” (Orpha number ORPHA282 of <http://www.orpha.net>). Among people below the age of 65 years, however, the prevalence of FTLD is comparable to that of AD. It has been estimated at 15 per 100,000 patients between 45 and 65 years of age.³¹ Population-based studies have shown that male and female persons are equally affected.^{30–32} The mean age of onset is approximately 58 years,³² but patients with an onset in their thirties have been described.³³ Prognosis is poor, and FTLD leads to death within 3 to 10 years after diagnosis, with survival in svPPA being longer than in nvPPA and bvFTD.^{34,35} Main causes of death are pneumonia, circulatory system failure, and cachexia.³⁵

Diagnosis and differential diagnosis

Medical history and neuropsychology

The diagnostic latency between the symptom onset and the correct diagnosis ranges from 3 (nvPPA) to 4 (bvFTD and svPPA) years,³⁶ reflecting the challenge of diagnosis despite recent advances in the clinical characterization of FTLD.⁹ The majority of patients with bvFTD do not complain of any symptoms.³⁷ Behavioral changes reported by relatives are often unspecific, and may suggest a psychiatric, rather than a neurodegenerative, disorder. Moreover, patients may perform within normal ranges on neuropsychological tests of memory and language, and structural imaging abnormalities may be subtle and confounded by age-dependent changes.

In order to detect behavioral alterations, the diagnostic procedure should include a careful medical history, which needs to be obtained not only from the patient, but also from a close relative or friend. Standardized caregiver questionnaires (ie, the Frontal Behavioral Inventory³⁸ or the Frontal Systems Behavioral Scale³⁹) have been developed to assess bvFTD.

Detailed neuropsychological examination involving tests of memory, language, visuoconstruction, and executive tasks may identify cognitive deficits that are not apparent in everyday life. The cognitive profile might also help to discriminate FTLD from other causes of dementia, particularly from AD.

The cognitive profile in bvFTD is usually characterized by executive and generation deficits in the context of relatively preserved memory and visuospatial functions.⁷ However, unimpaired performance in neuropsychological tasks, even in measures of executive functions, does not exclude a diagnosis of bvFTD. Language deficits in PPA can be detected by careful analysis of spontaneous speech and by using standardized language tasks.

One of the most frequent misdiagnoses of bvFTD is major depression, which frequently is suggested by relatives who interpret the patients' apathy, loss of interest, and social withdrawal as indicating a mood disorder. Therefore, a detailed psychiatric examination is also required – most patients with bvFTD do not complain at all about depressive symptoms such as sadness, self-doubts, or suicidal ideation. Further psychiatric diseases that sometimes mimic bvFTD are bipolar affective disorders or schizophrenia, as well as substance abuse.

Laboratory tests, neuroimaging, and cerebrospinal fluid analysis

Laboratory tests, neuroimaging, and cerebrospinal fluid analysis are needed to exclude vascular, infectious, inflammatory, neoplastic or paraneoplastic, and metabolic diseases, some of which may be amenable to treatment.

In bvFTD, structural imaging studies revealed grey matter atrophy in the frontal and temporal lobes, the anterior cingulate, anterior insula, and in subcortical structures.^{40,41} However, in early stages, changes may be very subtle. Visual rating scales are available to detect and quantify bvFTD-specific atrophy patterns (eg, Kipps et al⁴²). Atrophy of the amygdala can help to discriminate between bvFTD and AD,⁴³ while atrophy of the hippocampus⁴⁴ does not differentiate between bvFTD and AD.^{43,45} In svPPA, marked anterior and inferior temporal atrophy is observed, whereas in nvPPA, the size of the inferior frontal gyrus, the insula, and the premotor and supplementary motor area of the left hemisphere is reduced.^{46–48} Cerebral fluorodeoxyglucose positron emission tomography typically reveals glucose hypometabolism in the corresponding regions and may provide additional information in cases with borderline findings. Amyloid positron emission tomography imaging can be employed to exclude the presence of AD pathology in patients with FTLD.^{49,50}

So far there are no cerebrospinal fluid biomarkers that can positively identify FTLD. Phospho-tau and β -Amyloid appear to be helpful for discriminating FTLD from AD, with high cerebrospinal fluid p-tau and low ratios of $A\beta(1-42)/A\beta(1-40)$ and $A\beta(1-42)/A\beta(1-38)$ being specific for AD.⁵¹

Genetics of FTLD

Approximately 40% of FTLD patients have a history that is suggestive of familial transmission, but only 10%–30% of family pedigrees show an autosomal dominant inheritance pattern. To date, mutations in five genes have been identified which are displayed in Table 3. Mutations of *chromosome 9 open reading frame 72 (C9orf72)*, *microtubule-associated protein tau (MAPT)*, and *progranulin (GRN)* explain over 80% of cases in FTLD families with a strong autosomal dominant family history.

MAPT

Up to 40 different mutations have been found in *MAPT*, accounting for 50% of familial cases of FTLD. These cases show a considerable variability of the clinical presentation.^{52,53} Mutations of *MAPT* lead to impaired microtubule assembly, impaired axonal transport, and promote pathological tau filament aggregation.⁵⁴ Very early age at onset (<50 years), parkinsonism, and oculomotor dysfunction are suggestive of *MAPT* mutations.⁵⁵

GRN

Mutations in the *GRN* gene account for 3% to 26% of familial cases.^{56,57} GRN is a growth factor that is expressed by many cell types, including neurons. The role of GRN for neuronal survival and function is still unclear/under debate. Null mutations cause disease via haploinsufficiency. As a result, reduced levels of GRN protein are observed in bodily fluids. The corticobasal syndrome and nfvPPA were related to *GRN* mutations.⁵⁸

C9orf72

Only recently, an abnormal expansion of a hexanucleotide repeat in the *C9orf72* gene was found to be a relatively common genetic cause of FTLD, accounting for 20% of familial cases.^{59,60} So far, the function of *C9orf72* is unknown.

Table 3 FTLD – genes

Gene symbol	Chromosomal location	Gene name	Mutation frequency
<i>C9orf72</i>	9p21.2	Chromosome 9 open reading frame 21	14%–48%
<i>GRN</i>	17q21.32	Progranulin	3%–26%
<i>MAPT</i>	17q21.1	Microtubule-associated protein tau	0%–50%
<i>CHMP2B</i>	3p11.2	Charged multivesicular body protein 2B	<1%
<i>VCP</i>	9p13.3	Valosin-containing protein	<1%

Note: Data from Sieben et al.⁵⁷

Abbreviation: FTLD, frontotemporal lobar degeneration.

Fewer than 20 GGGGCC hexanucleotide repeats in the intronic region of the *C9orf72* gene are regarded as normal, the lower limit of the pathogenic range is considered as 65 repeats.⁶¹ Patients with *C9orf72* expansions appear to have a family history of ALS and FTLD. Psychotic symptoms occur in up to 38% of patients with *C9orf72* mutations.⁶²

Valosin-containing protein (VCP) and charged multivesicular body protein 2B (CHMP2B)

Mutations in two other genes, *VCP*⁶³ and *CHMP2B*,⁶⁴ leading to TDP-43-positive FTLD, account for a minority of familial cases.⁵⁷

Genetic counseling

Genetic testing of symptomatic persons is of high importance to confirm the diagnosis if one or more relatives are affected. With the advent of disease-modifying drugs tailored to the different neuropathological subtypes, results of genetic testing will probably influence therapeutic decisions. Frequently, unaffected relatives seek advice with regard to predictive genetic testing. Formal counseling by a geneticist or genetic counselor is recommended. While practice guidelines exist for numerous diseases, including AD,⁶⁵ international guidelines for genetic counseling in FTLD have not yet been developed.

Neuropathology of FTLD

Considering the variability in clinical features and molecular genetics, it is not surprising that the neuropathology associated with FTLD is heterogeneous as well.⁶⁶ A consistent feature is the relatively selective degeneration of the frontal and temporal cerebral lobes. In addition, most cases of FTLD have abnormal intracellular accumulation of some disease-specific protein, so it has become popular to classify FTLD into broad categories, based on the molecular defect thought to be most characteristic (Table 2).⁶⁷

Until recently, the best studied FTLD subgroups were those conditions characterized by the accumulation of hyperphosphorylated tau protein in neurons and glia (FTLD-tau). These cases represent ~40% of FTLD and include those with the neuropathology of Pick's disease, PSP, CBD, and cases of familial FTLD caused by mutations in *MAPT*. Although there is significant overlap in the morphology, and cellular and anatomical distribution of tau-positive pathology among the FTLD-tau subtypes, each condition is characterized by some specific type of inclusion that allows pathological diagnosis; Pick bodies in Pick's disease, tufted astrocytes

and numerous neurofibrillary tangles in subcortical nuclei in PSP, and astrocytic plaques and abundant thread pathology in CBD. In addition to these morphological differences, the biochemical form of tau that accumulates in the inclusions varies among the different conditions, with Pick bodies composed primarily of tau isoforms with three microtubule binding domains (3-repeat, 3R tau), while the inclusions of PSP and CBD contain 4R tau.

The majority of cases of tau-negative FTLN are characterized by neuronal cytoplasmic inclusions and dystrophic neurites in the superficial layers of the frontotemporal neocortex, and dentate granule cells of the hippocampus, that were originally recognized with ubiquitin immunohistochemistry (FTLD-U). In 2006, TDP-43 was identified as the ubiquitinated pathological protein in most cases of FTLN-U (subsequently renamed FTLN-TDP), as well as the vast majority of ALS.⁶⁸ This discovery provided strong evidence that FTLN and ALS are closely related conditions with overlapping molecular pathogenesis. The pathological form of TDP-43 that accumulates in FTLN and ALS is composed of abnormal C-terminal fragments that are ubiquitinated and hyperphosphorylated. Different patterns of FTLN-TDP are now recognized, based on the cortical distribution and relative abundance of cytoplasmic inclusions versus neurites, with each having fairly specific clinical and genetic correlations (Table 2).⁶⁹ In most series, FTLN-TDP represents the largest molecular FTLN subgroup, present in about half of all FTLN cases.

An important recent discovery has been the identification of abnormal expansion of a GGGGCC hexanucleotide repeat in a noncoding region of the *C9orf72* gene as the most common genetic cause of both FTLN and ALS.⁷⁰ The neuropathology of these cases is a combination of FTLN-TDP and classical ALS with TDP-positive inclusions. In addition, ubiquitin-positive, TDP-negative neuronal inclusions in the neocortex, hippocampus, and cerebellum are a consistent and unique pathological feature of cases with the *C9orf72* mutation. It has recently been shown that this TDP-negative pathology is the result of unconventional translation of the expanded GGGGCC repeat. Sense (and possibly antisense) translation in the three alternate reading frames results in the generation of several different peptides, each composed of repeating units of two amino acids (ie, glycine–alanine, glycine–proline, glycine–arginine).^{71,72} Novel antibodies against these various dipeptide repeats are proving to be a highly sensitive and specific tool for demonstrating this unique pathology. The relationship between the dipeptide repeats and TDP-43 mismetabolism and their relative roles in

the pathogenesis of disease in cases with the *C9orf72* mutation is currently an important area of investigation.

In 10%–20% of cases originally classified as FTLN-U (5%–10% of all FTLN), the cellular inclusions do not stain for either tau or TDP-43. The term “atypical” FTLN-U recognizes that these cases have a consistent and unique phenotype (sporadic, with very early onset severe psychobehavioral abnormalities in the absence of language or motor features), as well as novel pathological features (TDP-negative inclusions that include unusual vermiform neuronal intranuclear inclusions).³³ Following the discovery of mutations in *FUS* as a cause of ALS, it was recognized that most of the remaining tau/TDP-negative FTLN subtypes were characterized by inclusions that are immunoreactive for *FUS* as well as the other members of the FET family of proteins (Ewing sarcoma protein and TAF-15).⁷³ In addition to atypical FTLN-U, this FTLN-*FUS* group also includes two rare conditions in which FTLN usually coexists with pyramidal and/or extrapyramidal motor dysfunction; basophilic inclusion body disease and neuronal intermediate filament inclusion disease. As with the FTLN-tau subtypes, each of the conditions in the FTLN-*FUS* group have overlapping but distinct neuropathological features.

There remain very rare FTLN cases, such as the Danish family with autosomal dominant FTLN caused by a mutation in the *CHMP2B* gene, in which the pathological inclusions are only demonstrated with nonspecific markers of the ubiquitin proteasome system, and possibly some cases in which no inclusions can be detected. However, recent advances now make it possible to assign the vast majority of FTLN cases to one of three major molecular subgroups (FTLN-tau, FTLN-TDP, or FTLN-*FUS*).

Treatment

Pharmacological treatment

Compared with AD, the cholinergic system is relatively intact in FTLN.^{74,75} On the other hand there is strong evidence for abnormalities in the serotonergic system of FTLN patients, with a decrease in 5-HT1A and 5-HT2A receptors and neuronal loss in the raphe nuclei.⁷⁵ Furthermore, a disruption of the dopaminergic system has been demonstrated,⁷⁶ including low levels of dopamine metabolites and reduced presynaptic dopamine receptors in the putamen and caudate of FTLN patients.⁷⁷

Given the relative preservation of cholinergic neurons in brains of patients with FTLN, there is no reason to expect a benefit from cholinesterase inhibition as in AD. Nonetheless, a number of small trials have evaluated cholinesterase inhibitors in FTLN.^{115–118} These studies are summarized

in Table 4. In summary, cholinesterase inhibitors do not improve cognition or behavior in FTLD. This also applies to memantine, an N-methyl-D-aspartate-type glutamate receptor antagonist that is approved for the treatment of AD. Several recent studies failed to demonstrate a benefit of this compound in FTLD (Table 4).^{119–122} Nonetheless, about 30% to 40% of patients with FTLD currently receive treatment with cholinesterase inhibitors or memantine.^{78,79}

The effect of antidepressants, particularly of selective serotonin reuptake inhibitors on neuropsychiatric symptoms in FTLD has been studied in several trials (Table 5).^{85,123–128} There is some evidence that the serotonergic antidepressants have potential for reducing behavioral disturbances, in particular disinhibition, apathy, repetitive behaviors, sexually inappropriate behaviors, and hyperorality.^{75,80} The British Association for Psychopharmacology has recently assigned a B rating for the treatment of behavioral disturbances in FTLD with selective serotonin reuptake inhibitors, indicating good overall clinical evidence.⁸¹

A handful of small studies have been performed in patients with FTLD using dopaminergic agents (Table 6).^{119–121} Positive effects on behavior have been reported, but the results have not been replicated in larger studies.

Antipsychotics are commonly prescribed to treat disinhibition, agitation, and psychosis in dementia regardless of etiology.⁸² No controlled studies are available on antipsychotics in FTLD. Positive effects of risperidone, olanzapine, and aripiprazole have been described.^{83–85} However, it is important to keep in mind that patients with FTLD may be susceptible to extrapyramidal side effects of antipsychotics⁸⁶ and that the use of atypical antipsychotics for the treatment of behavioral disorders in elderly patients with dementia is associated with increased mortality.⁸⁷

Non-pharmacological interventions

As long as effective pharmacological therapies for symptom management and disease-modification are not available, it is important that a multidisciplinary team identifies non-pharmacological interventions that support the patients' engagement in activities and ensures an optimal quality of life.⁸⁸ Treatment strategies should be individually tailored because symptom pattern, rate of decline, needs, and available resources are highly variable. Where necessary, specific disciplines (neurologists, psychiatrists, neuropsychologists, social workers, speech–language pathologists, occupational therapists, physiotherapists, neurorehabilitation

Table 4 Clinical drug trials in FTLD

Drug	Author	Method	n	Duration	Behavior	Cognition/ function
Rivastigmine (3–9 mg/d)	Moretti et al ¹¹⁵	Open-label, controlled	20	12 months	Improved (NPI)	Executive function: unchanged; MMSE: deterioration
Donepezil (5–10 mg/d)	Mendez et al ¹¹⁶	Randomized, open-label, controlled	24	6 months	Worsened (FTD inventory)	Global cognitive performance: unchanged; dementia severity: unchanged
Donepezil (10 mg/d) or rivastigmine (6–12 mg/d)	Lampl et al ¹¹⁷	Randomized comparison trial	9	6 months	Not evaluated	Improved (MMSE, clock drawing)
Galantamine (16 or 24 mg/d)	Kertesz et al ¹¹⁸	Open-label followed by randomized, double-blind, placebo-controlled	36	18 weeks open-label and 8 weeks randomized	No treatment effects (FBI)	Trend of efficacy in language subscores of PPA subgroup; no treatment effect on Clinical Global Impression of Severity and Improvement
Memantine (20 mg/d)	Diehl-Schmid et al ¹¹⁹	Open-label, uncontrolled	16	6 months	Unchanged (NPI, FBI)	Worsened (ADAScog)
Memantine (20 mg/d)	Vercelletto et al ¹²⁰	Double-blind, placebo-controlled	49	52 weeks	Treatment group slightly better compared to placebo group (FBI)	No treatment effects (CIBIC, MMSE, DAD, MDRS)
Memantine (20 mg/d)	Chow et al ¹²¹	Open-label, uncontrolled	16	7–8 weeks	Unchanged (FAB, FBI, SRI)	Unchanged (CDR)
Memantine (20 mg/d)	Boxer et al ¹²²	Multicenter, randomized, double-blind, placebo-controlled	76	26 weeks	No treatment effect (NPI)	No treatment effect (CGIC)

Abbreviations: FTLD, frontotemporal lobar degeneration; NPI, Neuropsychiatric Inventory; FTD, frontotemporal dementia; FBI, Frontal Behavioral Inventory; FAB, Frontal Assessment Battery; SRI, Stereotypy Rating Inventory; MMSE, Mini-Mental State Examination; PPA, primary progressive aphasia; ADAScog, Alzheimer's Disease Assessment Scale-cognitive subscale; CIBIC, Clinician Interview Based Impression of Change; DAD, Disability Assessment for Dementia; MDRS, Mattis Dementia Rating Scale; CDR, Clinical Dementia Rating; CGIC, Clinical Global Impression of Change; d, day.

Table 5 Serotonergic antidepressants

Drug	Author	Method	n	Duration	Behavior	Cognition/function
Paroxetine (20 mg/d) versus piracetam (1,200 mg/d)	Moretti et al ⁸⁵	Randomized, controlled	16	14 months	Improved in paroxetine group	Stable in paroxetine group
Paroxetine (40 mg/d)	Deakin et al ¹²³	Randomized, double-blind, placebo-controlled	10	6 weeks	No treatment effect (NPI, CBI)	Cognition (neuropsychological battery): unchanged/worsened
Sertraline (50–100 mg/d)	Mendez et al ¹²⁴	Open-label	8	6 months	Decreased stereotypical movements	Not evaluated
Trazodone (300 mg/d)	Lebert et al ¹²⁵	Randomized, double-blind, placebo-controlled, crossover	26	12 weeks	Improved (NPI)	No treatment effect (MMSE)
Fluvoxamine (50–150 mg/d)	Ikeda et al ¹²⁶	Open-label	15	12 weeks	Improved (NPI, SRI)	Unchanged (MMSE)
Citalopram (40 mg)	Herrmann et al ¹²⁷	Open-label	15	6 weeks	Improved (NPI, FBI)	Not evaluated
Moclobemide (300–600 mg/d)	Adler et al ¹²⁸	Open-label	6	4 weeks	Minor improvement of some BPSD (symptom list) in a few patients	Unchanged

Abbreviations: NPI, Neuropsychiatric Inventory; CBI, Cambridge Behavioral Inventory; SRI, Stereotypy Rating Inventory; FBI, Frontal Behavioral Inventory; BPSD, Behavioral and Psychological Symptoms in Dementia; d, day; MMSE, Mini-Mental State Examination.

professionals) should be consulted.⁸⁸ It is essential to assess and monitor the patient's responses to stimuli, to structure and modify the living environment, to take appropriate measures regarding safety, and to help caregivers develop strategies for managing behavioral disturbances. These tasks are very often the responsibilities of advanced practice nurses.^{89–91}

Large non-pharmacological intervention-studies with the aim to improve or maintain behavior, cognition, or language in people with FTLD have not yet been performed. In an uncontrolled study, the efficacy of a 4-week inpatient treatment program for patients with FTLD or AD and their caregivers was evaluated.⁹² The intervention consisted of a multimodal rehabilitation for patients in combination with an educational program for caregivers. The pre–post comparison showed that the treatment program was associated with an improvement of depression and other psychopathological symptoms in patients with FTLD and with reduced burden on their caregivers.

A few single-subject studies have investigated the efficacy of speech therapy on word-finding ability in patients

with PPA and demonstrated minor improvements of naming immediately following treatment completion.^{93–95} However, there is little evidence for sustainability and generalizability of these learning effects. To date, there is general consensus that the goal of speech therapy in PPA is not to regain lost language, but to maximize communication skills as long as possible. Interventions may include the development of skills for facilitating communication and teaching the use of communication tools.⁹⁶

Caregiver support

Given the lack of pharmacological or non-pharmacological treatments with proven efficacy, caregiver support is the mainstay of the management of FTLD.

Several studies have consistently shown that FTLD caregivers are heavily stressed and burdened as a result of their caregiving role. Family caregivers of patients with FTLD report higher levels of psychological distress and subjective burden than caregivers of patients with AD or other dementias.^{97–99} Specific problems of FTLD caregivers

Table 6 Dopaminergic drugs

Drug	Author	Method	n	Duration	Behavior	Cognition/function
Dextroamphetamine (20 mg/d) versus quetiapine (150 mg/d)	Huey et al ¹²⁹	Randomized, double-blind, crossover design	8	Two arms of 3 weeks	Improved with dextroamphetamine (NPI)	No treatment effect (RBANS)
Bromocriptine (22.5 mg/d)	Reed et al ¹³⁰	Double-blind, placebo-controlled, crossover	6, only PPA	Two arms of 7 weeks	Not evaluated	Slight slowing of language deterioration
Methylphenidate (40 mg/d; single dose)	Rahman et al ¹³¹	Randomized, double-blind, placebo controlled, crossover	8	Two test sessions, single dose	Decreased risk taking behavior on gambling task	Unchanged (cognitive test battery)

Abbreviations: NPI, Neuropsychiatric Inventory; PPA, primary progressive aphasia; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

include delayed diagnosis, uncertainty of diagnosis, young age of patients, behavioral problems, depression, lack of information, constraints regarding self-care, and lack of access to appropriate care facilities.¹⁰⁰ Most health and social care services do not meet the needs of younger patients with dementia and their caregivers because they are tailored to older adults and to patients with AD.¹⁰¹

A recent survey of FTLD caregiver needs showed that the most important needs and requests of the caregivers are detailed information about the disease, psychosocial support provided by experienced staff, appropriate financial support, and better education of health and social care professionals about the disease.¹⁰² Counseling of patients and caregivers, either in individual or group format, should include detailed information about the disease and the worsening of symptoms that may be expected, recommendations for the management of challenging behaviors, relevant caring issues, as well as legal and financial advice. Suggestions for caregivers' own well-being should also be offered. Caregivers should be motivated to participate in FTLD caregiver support groups or self-help groups, if available. Information about FTLD can also be found on the internet, for example on the webpage of the Association for FTLD (<http://www.theaftd.org>). In Canada, a regular biannual internet-based videoconferencing support group for FTLD spouses has been set up.¹⁰³

Future directions

In recent years, the accuracy of the clinical diagnosis of FTLD has been improved by detailed clinical descriptions, enlarged knowledge about the performance of the patients in neuropsychological tests, development of novel FTLD-specific assessment instruments including interviews and clinical rating scales, refined imaging techniques, and better understanding of cerebrospinal fluid biomarker changes, as well as revised diagnostic criteria. However, in the absence of specific and accurate biomarkers, diagnosis and differential diagnosis of FTLD is still challenging. There is a need for diagnostic interviews that enable a reliable assessment of behavioral disturbances and personality changes. Tests of social cognition and theory of mind need to be developed. The early clinical stages of bvFTD, svPPA, and nfvPPA that correspond to "mild cognitive impairment" in AD should be defined as part of a strategy aiming at timely diagnosis and treatment.

Recently, remarkable progress has been made regarding the understanding of the genetic causes, molecular basis, and neuropathological features of FTLD. Most common gene alterations that cause FTLD have been discovered and the major pathological proteins have been identified.

Nonetheless, there are plenty of future challenges. Some mutations underlying the proteinopathies await identification. Understanding the factors that modify the clinical expression of mutations will bring novel insights for the development of specific drug treatment. The contribution of susceptibility genes has yet to be explored.

A major goal of research is the identification of laboratory or imaging biomarkers that reliably identify pathological subtypes of FTLD: FTLD cases that are associated with tau and TDP-43 pathology represent potential targets for future therapies that aim at slowing or halting disease progression. Recently, an international multicenter Phase 3, 52-week study of methylene blue in bvFTD has been initiated (NCT01626378).¹⁰⁴ Methylene blue is a tau aggregation inhibitor that also appears to protect against TDP-43 toxicity in animal models.¹⁰⁵ This first clinical trial in bvFTD will most probably unveil potential difficulties with studies in bvFTD: the lack of appropriate outcome parameters; problems with recruitment; diminished patient compliance; behavioral disturbances that hamper the examinations, interviews, and neuroimaging; and concomitant psychiatric medication in high doses. A number of tau-based disease-modifying therapies have already been investigated in clinical trials:¹⁰⁶ the glyco-gen synthase kinase inhibitors lithium (NCT00703677)¹⁰⁷ and tideglusib (NCT01350362, NCT01049399);^{108,109} riluzole, a sodium channel blocker;¹¹⁰ coenzyme Q10, which improves mitochondrial function;¹¹¹ rasagiline, a monoamine oxidase inhibitor (NCT01187888);¹¹² and davunetide, a microtubule stabilizer (NCT01110720, NCT01056965).^{113,114} Beyond that, preclinical studies are under way that aim at the identification of agents with the potential to normalize GRN levels either by increased production or reduced clearance in FTLD-TDP cases that are caused by loss of function mutations in the *GRN* gene.¹⁰⁶ Given all these efforts, hopefully a causal treatment for FTLD will be available sooner or later.

Disclosure

The authors report no conflicts of interest in this work.

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