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Chapter 6

Frontotemporal Lobar Degeneration

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Abstract

Frontotemporal lobar degeneration (FTLD) is an umbrella term covering a heterogeneous set of neurodegenerative disorders whose clinical presentation may be cognitive, behavioural., motor, or mixed. These syndromes frequently combine during the course of the disease. FTLD syndromes show considerable phenotypic overlap and variable histopathological and genetic correlations. Current neuropathological classification is based on specific types of protein deposits and their related genes.

Although infrequent in the general population, FTLD is nearly as common as Alzheimer's disease in patients below 65 years of age. Its scope extends from sporadic (60%) to familial forms (40%), some of the latter having an autosomal dominant inheritance pattern. Numerous mutations of several implicated genes have been described.

FTLD represents a diagnostic challenge owing to its mixed features. Implementation of various methods is required and consists of a clinical assessment, neuropsychological testing, structural or functional neuroimaging and, sometimes, genetic analysis looking for mutations. Additional CSF and blood biomarkers, some of them still under study, may provide information about FTLD genetic risk factors or exclude other diseases. To date, only an autopsy allows a definite diagnosis.

No therapies are currently available to cure or alter the evolution of FTLD disorders. Management strategies include pharmacological treatment of the signs and symptoms and non-pharmacological interventions for the patients, for instance skill-based compensation methods, environmental modifications or activity groups. Caregivers should be integrated in the process and offered support when needed (educational programmes, psychological follow-up, respite facilities, etc.). Genetic counselling may prove useful.

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Research aims at a better understanding of the biochemical pathways of the proteinopathies which will potentially lead to more efficient diagnosis tools and innovative drug strategies.

Introduction

More than a century ago, the Czech neuropsychiatrist Arnold Pick portrayed the clinical picture of several demented patients who presented with an atrophy of the frontal and temporal lobes. A few years later, Alois Alzheimer described the typical neuropathological lesions which he named Pick bodies. For several decades, both Pick's and Alzheimer's diseases have been the representatives of the degenerative dementias. The first international conference on frontotemporal dementia, in 1986, and the subsequent ones have promoted scientific exchange and generated important research activity [1]. This work has given birth to two distinct classifications, one clinical., the other one pathological., highlighting complementary aspects of the FTLD spectrum.

The term FTLD is based on the macroscopically predominant atrophy of the frontal and temporal lobes. It is also an umbrella term covering a heterogeneous group of neurodegenerative disorders. Indeed, clinical presentation may either be neuropsychiatric, i.e., behavioural variant frontotemporal dementia (bvFTD), progressive non fluent aphasia (PNFA) and semantic dementia (SD), or motor, i.e., corticobasal degeneration (CBD), progressive supranuclear palsy (PSP) and motor neuron disease (MND). Co-occurrence or a sequence of these syndromes is frequent during the course of the disease. In addition to this considerable clinical overlap, histopathological and genetic correlations prove to be inconstant. Each specific tissue pathology may cause several phenotypes and, conversely, each phenotype may be underpinned by various histopathological features. Current neuropathological classification is based on the various types of protein deposits grouped into three major categories: FTLD-tau, FTLD-TDP (transactive response DNA-binding protein 43) and FTLD-FUS (fused in sarcoma).

Research constantly redefines these issues. Novel diagnostic criteria attempt to better delineate the domain, additional genes are found to play a role. In short, recent classifications describe a growing complexity. This review chapter presents current knowledge and new insights in the FTLD spectrum (Figure 1).

Epidemiology

Estimation of FTLD prevalence and incidence is difficult to determine due to several factors. First, diagnosis is challenging, implying a risk of under- and over-diagnosis and misclassification [2]. Second, the rarity of FTLD in the population requires large-scale surveys which are seldom available. Third, the design of the studies (community-based, memory centre cohorts, autopsy series, etc.) inevitably induces biases and variable results.

FTLD prevalence estimates range from 2/100'000 to 35/100'000 persons in the general population [3, 4]. Overall incidence data are scarce and rates vary between 14/100'000 and 18/100'000 person-year [5, 6]. Age at presentation is around 50-60 years. This positions the

disease among the young-onset dementias although its incipience can vary widely from the third to the ninth decade of life [7-10]. FTLD duration extends from one to fourteen years with a median survival estimated at 6-11 years from symptom onset and 3-4 years from diagnosis [10-16]. Age at onset, gender, education, family history and neuropsychiatric profile do not affect survival rates in FTLD [11, 13]. Most studies report a male preponderance in bvFTD and SD, and a female preponderance in PNFA [4, 8-10, 13].

Compared to Alzheimer's disease (AD), FTLD survival rate is lower, and cognitive and functional decline is more rapid [11, 12]. In living individuals over 65 years of age, FTLD ranks between the second or third most common causes of dementia [17, 18]. Its rank drops to the fourth or fifth in autopsy series [19, 20]. When considering early-onset dementia, most studies indicate AD as the main aetiology, followed by FTLD or vascular dementia [21]. In the age group 45- to 64-years, FTLD may be as frequent as AD [8].

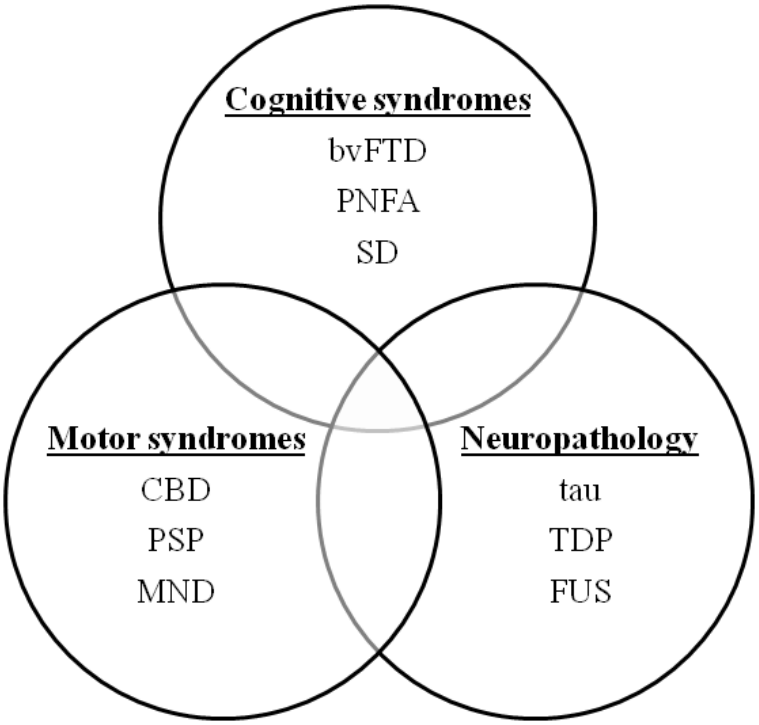

Figure 1. FTLD spectrum: bvFTD behavioural-variant frontotemporal dementia, PNFA progressive non-fluent aphasia, SD semantic dementia, CBD corticobasal degeneration, PSP progressive supranuclear palsy, MND motor neuron disease, TDP transactive response DNA-binding protein, FUS fused in sarcoma.

Clinical Aspects

From a clinical point of view, FTLD comprises various syndromes according to their presenting features. Ongoing debate prompted the revision of the former 1998 criteria [22]. New diagnostic criteria for FTLD cognitive and behavioural variants have been proposed in 2011 in order to improve diagnostic accuracy and sensitivity (Tables 1-4) [23, 24].

Table 1. Summary of bvFTD diagnostic criteria (adapted from Rascovsky, 2011)

Criteria	Rating
I. Progressive cognitive and/or behavioural deterioration	Compulsory
II. Possible bvFTD	≥ 3 symptoms (A-F) compulsory
A. early behavioural disinhibition	
B. early apathy	
C. early loss of empathy	
D. early repetitive, stereotyped or compulsive behaviour	
E. hyperorality and dietary changes	
F. specific neuropsychological profile	
III. Probable bvFTD	All symptoms (A-C) compulsory
A. meets criteria for II	
B. functional decline	
C. compatible imaging	
IV. bvFTD with definite FTLD pathology	≥ 2 symptoms compulsory
A. meets criteria for II or III	(A + either B or C)
B. histopathological evidence	
C. known genetic mutation	
V. Exclusionary criteria	A and/or B exclusionary
A. other non-degenerative nervous system or medical disorders	C admissible for II, exclusionary for III
B. psychiatric disorders	
C. incompatible biomarkers	

"Early" refers to symptom presentation within the first 3 years.

Table 2. Summary of PNFA diagnostic criteria (adapted from Gorno-Tempini, 2011)

Criteria	Rating
I. Clinically diagnosed PNFA	≥ 1 criterion (a-b)
a. agrammatism	AND
b. effortful speech with distorsions	≥ 2 criteria (c-e)
c. impaired comprehension of complex sentences	
d. spared comprehension of simple words	
e. spared object knowledge	
II. Imaging-supported PNFA	criteria (a) AND (b) compulsory
a. meets criteria for I	
b. supportive imaging	
III. PNFA with definite pathology	criterion (a) compulsory
a. meets criteria for I	AND
b. histopathological evidence	≥ 1 criterion (b-c)
c. known genetic mutation	

Table 3. Summary of SD diagnostic criteria (adapted from Gorno-Tempini, 2011)

Criteria	Rating
I. Clinically diagnosed SD	criteria (a) AND (b) compulsory
a. impaired confrontation naming	AND
b. impaired single-word comprehension	≥ 3 criteria (c-f)
c. impaired object knowledge	
d. surface dyslexia or dysgraphia	
e. spared repetition	
f. spared speech production	
II. Imaging-supported SD	criteria (a) AND (b) compulsory
a. meets criteria for I	
b. supportive imaging	
III. SD with definite pathology	criterion (a) compulsory
a. meets criteria for I	AND
b. histopathological evidence	≥ 1 criterion (b-c)
c. known genetic mutation	

A number of diagnostic issues, some of them addressed below, remain controversial and may indicate future perspectives:

- Whereas early episodic memory impairment has been reported in bvFTD cases, and therefore removed from the new definition, it remains an exclusion criterion for the primary progressive aphasias (PPA) [23, 25, 26]. The terminology itself ("aphasia") indicates overemphasis on language at the expense of other cognitive functions. Growing evidence questions the overly restrictive diagnostic criteria for PNFA and SD, such as the absence of early episodic memory impairment, or the preserved calculation and spatial orientation [27-31]. More flexible definitions and a reduced distinction between core and supportive features would better accommodate the variations of the clinical presentation.
- A second or benign form of bvFTD, called "phenocopy syndrome", has been described in patients who progress slowly or not at all, and do not show atrophy on MRI [32-34]. Although the aetiology of these phenocopies is unknown, some of them could reflect a mid-life decompensation of a psychiatric disorder. Personality disorders, autism spectrum disorders and chronic low-grade mood disorders are hypothetical candidates [34, 35]. Intriguingly, some unrelated patients display the same pathogenic mutation on chromosome 9 [36]. The precise nature of this entity still needs to be determined.
- A third type of PPA, the logopenic variant, has been coined by Gorno-Tempini in 2004 and added to her classification in 2011 [24]. Two recent studies, though, failed to support the reliability of its diagnostic criteria [37, 38]. Additionally, AD seems to be the most common underlying pathology [24]. This syndrome remains somewhat elusive.
- Current FTLD definitions leave little to no room to the overlapping syndromes. PSP, CBD and MND are not even mentioned in spite of a common neuropathological

classification and entangled clinical course [39-41]. While some patients reach enough criteria to deserve several diagnoses within the FTLD spectrum, in other cases, intermingled clinical features may alter the clinical and neuropsychological picture, making diagnosis difficult. This considerable overlap has given birth to the notion of a single nosographic category called "Pick complex" [42, 43].

Table 4. Additional criteria for the diagnosis of primary progressive aphasias (PNFA and SD), Gorno-Tempini et al. (2011)

Criteria	Rating
Inclusion criteria: 1. Most prominent clinical feature is difficulty with language. 2. These deficits are the principal cause of impaired daily living activities. 3. Aphasia should be the most prominent deficit at symptom onset and for the initial phases of the disease.	Criteria 1-3 compulsory
Exclusion criteria: 1. Pattern of deficits is better accounted for by other nondegenerative nervous system or medical disorders. 2. Cognitive disturbance is better accounted for by a psychiatric diagnosis. 3. Prominent initial episodic memory, visual memory, and visuoperceptual impairments 4. Prominent initial behavioural disturbance	Criteria 1-4 must be answered negatively

FTLD motor syndromes are not devoid of cognitive and behavioural features of their own, which may present even in non-demented patients and before the onset of the motor symptoms.

PSP may be associated with bvFTD and PNFA [39, 41]. Its main cognitive features are due to fronto-subcortical dysfunction: apathy, slowness of information processing, impaired memory retrieval, decreased verbal fluency (letter greater than semantic), executive dysfunction (planning, attention shifting, abstraction, reasoning), utilization or imitation behaviour, frontal release signs (primitive reflexes), and other specific behavioural symptoms (disinhibition, irritability, stereotypy, rituals, gluttony, sweet tooth). Language disorders belong to the non-fluent type [44, 45].

CBD may also be associated with bvFTD and PNFA [39, 46]. Frontal lobe involvement predominates, especially in the early stage of the disease: decreased verbal fluency, concreteness in thinking, impaired reasoning, slowed information processing, lack of insight, poor information retrieval, impaired execution of sequential actions, frontal release signs. Personality changes may include apathy, lack of concern about personal behaviour or behaviour of others, disinhibition, perseveration, inattention. Other cognitive symptoms consist of motor speech disturbances (mainly non-fluent aphasia, apraxia of speech or global aphasia), variable episodic memory performance, acalculia, ideational (object use) apraxia, ideomotor (on command or imitation) apraxia, buccofacial apraxia, constructional (draw or copy) apraxia [45, 47, 48].

MND is a general term for a group of diseases whose most common form is amyotrophic lateral sclerosis (ALS). Up to 15% of FTLD patients and 30% of ALS patients present an overlap syndrome [49]. In the vast majority of cases, the mental symptoms precede the motor ones: they begin with changes in behaviour (apathy, stereotypies, greed, tendency to hoard things), cognition (impaired planning, memory deficits, mental rigidity, visuospatial dysfunction) and the emergence of psychiatric symptoms (depression, bipolar disorder, delusions, hallucinations, paranoid or catatonic psychosis). As the psychiatric symptoms tend to subside, the cognitive frontal-executive dysfunction becomes prominent. Patients show a behavioural syndrome (altered social conduct, emotional blunting, loss of insight, impaired emotional processing and recognition of facial emotions) and pronounced language disorders (reduced verbal fluency, verbal perseverations, echolalia, use of stereotypic expressions, impaired comprehension, selective semantic deficit in the knowledge of actions compared to objects, and in the production and comprehension of verbs, as opposed to nouns and adjectives) [50, 51].

Differential Diagnosis

Determination of the correct diagnosis is not only academically satisfying, but also of significant importance given its implications for management, prognosis and potential genetic counselling. The first step is to exclude any treatable or reversible condition which can mimic FTLD. This can be achieved by collecting the following information:

- past and present medical history: age at onset, course (acute, progressive, episodic), pace, cognitive domains involved and their chronology, behaviour, associated symptoms (neurological., psychiatric, others), degree of disability, assessment of co-morbidity.
- family history
- drugs: prescribed and over-the-counter, alcohol, other substances
- physical examination
- standard blood tests: complete blood cell count, C-reactive protein, renal and liver functions, folate, B12, TSH, electrolytes
- neuropsychological testing
- neuroimaging (preferably magnetic resonance imaging).

If these procedures prove non-diagnostic, further investigation is indicated according to the presumed diagnosis. A host of ancillary methods are available, such as lab tests (toxicology, infectiology, serum electrophoresis, autoantibodies, genetic analysis, urine analysis), lumbar puncture and CSF analysis, additional imaging (PET, SPECT, CT scan, DAT-scan, angiography, carotid duplex, cardiac echography, etc.), EEG, ENMG, specific tissue biopsy [52, 53]. The most frequent causes of dementia syndromes and their supportive tests are summarized in Table 5.

When any organic aetiology has been reasonably dismissed, a “functional” psychiatric diagnosis should be considered. Caution is warranted as a significant overlap blurs the distinction between FTLD and some other psychiatric disorders. Confounding biases include

a similar clinical presentation, neuropsychology (e.g., executive dysfunction) and, to a certain extent, imaging (e.g., frontal hypoperfusion). Moreover, shared genetic vulnerabilities have been demonstrated, for instance, in reported families with genetic mutations causing FTLD in some members and schizophrenia in others who carry the same mutation [54-56]. Part of the difficulty is also due to the prolonged latency, up to 20 years, between the emergence of psychiatric symptoms and neurocognitive decline [57, 58]. Early-stage FTLD patients may present features of a major depressive disorder, bipolar disorder, schizophrenia, anxiety disorder, or adjustment disorder [59]. Less frequent diagnoses or behaviours that may eventually prove to be due to FTLD are conversion, attention deficit, attempted suicide, substance abuse, obsessive-compulsive disorder, pathological gambling, and antisocial behaviour [59-64].

Several indicators should arouse suspicion of FTLD in psychiatric patients: cognitive impairment, lack of emotional distress, progressive treatment-resistant illness, unusual psychiatric presentation, new onset of a psychiatric disorder in middle-aged and older patients, positive family history of dementia and/or neurological symptoms [65]. Conversely, late-onset psychiatric disorders may be supported by a positive personal or family history of affective or psychotic disorder, a long-term clinical observation over one or more years (by health professionals, family or caregivers), and the presence of specific symptoms rarely seen in FTLD (for instance feelings of worthlessness and poor self-esteem in depression, euphoria and insomnia in mania, obsessions in OCD, complex delusions in schizophrenia) [65, 66]. A thorough history and a consultation with a trained psychiatrist are highly advisable.

Complementary Investigations

Once a possible FTLD syndrome is suspected, the next challenge is to further characterize it. The various instruments available constitute a body of evidence which may support diagnosis if positive, but fail to exclude it if negative or inconclusive. They also lack specificity in accurately predicting the underlying pathology (i.e., definite FTLD diagnosis), but may prove useful to monitor disease progression and therapeutic responses.

Neuropsychological Profile

An interesting meta-analysis sought to identify the cognitive tests that best discriminate between AD and FTLD [67]. None of them was found contributory due to substantial overlap in the scores. The most significant differences between groups were measured in orientation, memory, visuomotor function and general cognitive ability tests (persons with AD performed more poorly than those with FTLD), and in language tests (persons with AD did better than those with FTLD). Another recent meta-analysis investigated the ability of 18 neurobehavioral scales to distinguish between AD and FTLD [68]. Four of them allowed an excellent discrimination, surpassing the cognitive tests, namely, the Schedules for Clinical Assessment in Neuropsychiatry, the Scale for Emotional Blunting, the Middleheim Frontality Score and the Frontal Behavior Inventory. Neuropsychologists are sometimes in the difficult position of attempting to determine whether poor performance in a cognitive domain is

primary, or secondary to deficits in a different cognitive domain (e.g., executive dysfunction interfering with episodic memory), or due to behavioural abnormalities (e.g., reluctance to follow instructions) [69]. The cognitive tests and scores should therefore be used cautiously when considering differential diagnoses.

Table 5. Differential diagnosis of dementia

Type	Examples	Testing
Degenerative	AD, FTLD, Lewy bodies, Parkinson, Huntington, multiple system atrophy, prion disorders, CBD, PSP, MND	Medical history, physical examination, lab tests, imaging, EEG, ENMG, LP, neuropsychological testing
Inflammatory/Autoimmune/ Infectious	Systemic lupus erythematosus, Sjögren, Behçet, polyarteritis nodosa, sarcoidosis, celiac disease, Hashimoto's encephalitis, HSV, HIV, CMV, EBV, Lyme, syphilis, Whipple, tuberculosis, malaria, fungal meningitis	Lab tests, LP
Vascular	CNS vasculitis, macro/micro-infarcts, microangiopathic diseases, thrombotic thrombocytopenic purpura, hyperviscosity syndromes, chronic subdural hematoma	Lab tests, neuroimaging, carotid duplex, ECG, skin biopsy (CADASIL), muscle biopsy (vasculitis)
Neoplastic	Primary and secondary malignancies, paraneoplastic syndromes	Lab tests, LP, imaging
Toxic/ Metabolic	Uremia, hepatic encephalopathy, hypo/hyper-thyroidism, hyperPTH, hypo/hyper-corticism, porphyria, vitamin deficiencies, alcohol, drugs, heavy metal poisoning, Wilson	Lab tests, liver biopsy
Neurological	Hydrocephalus, epilepsy, multiple sclerosis	EEG, imaging
Psychiatric	Depression, schizophrenia, bipolar disorder, obsessive-compulsive disorder, conversion, etc.	Clinical assessment

AD Alzheimer's disease, CADASIL cerebral autosomal-dominant arteriopathy with subcortical infacts and leukoencephalopathy, CBD corticobasal degeneration, CMV cytomegalovirus, CNS central nervous system, EBV Epstein-Barr virus, ECG electrocardiogram, EEG electroencephalogram, ENMG electroneuromyogram, EBV Epstein-Barr virus, FTLD frontotemporal lobar degeneration, HIV human immunodeficiency virus, HSV herpes simplex virus, LP lumbar puncture, MND motor neuron disease, PSP progressive supranuclear palsy, PTH parathyroid hormone.

Screening tools are valuable in substantiating the clinical impression. They include the widely used Mini-Mental State Examination and the Montreal Cognitive Assessment, the latter being superior for bvFTD [70]. Frontal lobe functions can be assessed by bedside short scales, for instance the Frontal Assessment Battery [71]. Additional questionnaires are commonly used to check FTLD behavioural symptoms, e.g., the Neuropsychiatric Inventory

or the Frontal Behavior Inventory [68, 72]. Finally, assessment of everyday functioning is part of the diagnostic work-up and measures basic and higher order skills, as in ADL (activities of daily living) and IADL (instrumental activities of daily living) scales [73].

Typical neuropsychological patterns which correspond to FTLD clinical phenotypes are based on formal neuropsychological testing [73]. They are described as an executive dysfunction with relative sparing of memory and visuospatial functions for bvFTD, a prominent nonfluent aphasia in the absence of initial episodic memory, visual memory, and visuoperceptual impairments for PNFA, and a profound semantic loss, preserved phonology, syntax, elementary perceptual processing, spatial skills, and day-to-day memorizing for SD [22-24]. As stated before, a great individual variability in the neuropsychological profile emphasizes the need to combine cognitive assessment with other tests and measures [73, 74].

Imaging Techniques

Based on the current diagnostic criteria, standard structural magnetic resonance imaging (MRI) has become a requisite. It should be noted that frontal and temporal atrophy are supportive features for FTLD, but their absence does not exclude the diagnosis [73]. As usual in FTLD, there is no one-to-one correspondence between neuroimaging and the clinical syndromes, genetic mutations or underlying pathology [75, 76]. MRI-based studies nonetheless disclose patterns of atrophy which may help identify the type of FTLD syndrome or distinguish it from other neurodegenerative disorders. bvFTD is characterized by an atrophy of the frontal lobes, involving medial., dorsolateral and orbitofrontal regions, as well as the thalamus and the anterior temporal lobes [75, 76, 77]. In PNFA, the atrophy is observed primarily in the posterior frontal premotor cortex, involving Broca's area and the superior premotor regions, but it has also been reported in the superior temporal gyrus and the striatum [76]. SD is associated with an atrophy of the left (sometimes right) anterior temporal lobe, especially in the inferior regions, the orbitofrontal lobe, insula, caudate nucleus, thalamus and contralateral temporal pole [76].

Recent imaging techniques help to sort through the various neurodegenerative disorders, provide a diagnosis at an earlier stage, and give insight into disease progression. Some of these techniques are recommended in the evaluation of FTLD, while others are used in research settings. It is beyond the scope of this chapter to develop all of them in detail, so only the main principles of each technique will be addressed.

Four additional MRI-based techniques are used in FTLD imaging [73, 75, 76]. *Voxel-based morphometry* converts structural MRI data in order to quantify changes of gray matter volume on a voxel-by-voxel basis. A voxel is a 3D pixel (*vo*lumetric pi*xel*). *Diffusion tensor imaging* (DTI) is part of an MRI protocol that measures the diffusion of water through brain tissue. Several parameters can be extracted such as mean and radial diffusivity and fractional anisotropy. DTI provides information on the integrity of white matter tracts. *Resting state functional MRI* (RS-fMRI) examines functional connectivity, namely the blood-oxygen-level dependent signals provided by the spontaneous neuronal activity in the brain at rest. It offers the advantage of not requiring active participation in specific tasks on the part of patients. RS-fMRI identifies increased or decreased activity in specific brain networks. *Arterial spin labelling perfusion MRI* (ASL) uses arterial blood as an endogenous tracer for perfusion. As perfusion and regional metabolism are coupled, ASL depicts functional deficiencies in a

similar way as PET or SPECT (see below), but it is non-invasive and free of exposure to ionizing radiation and intravenous contrast agents.

Positron emission tomography (PET) is a functional imaging technique which uses radioactive isotopes [73, 75, 77]. The most common is 18-F-fluorodeoxyglucose (FDG-PET). The labelled glucose is taken up by the metabolically active cells, thus measuring brain activity. New amyloid PET imaging uses ligands such as Pittsburgh compound B (PiB) or 18-F-florbetapir, which bind to cerebral amyloid deposits and detect AD pathology in vivo.

Single-photon emission computed tomography (SPECT) is another functional imaging modality. The radio-labelled 99m-Tc-hexamethylpropylene amine oxime (HMPAO) crosses the blood-brain barrier and is taken up by brain tissue in proportion to blood flow, hence tracking cerebral perfusion [75]. A special type of SPECT, using 123-I-fluoropropyl-carbomethoxy-iodophenylnortropane (FP-CIT), is also called a DAT (dopamine transporter) scan [78]. DAT is responsible for the reuptake of dopamine in the synaptic cleft. The ligand, a cocaine analogue, allows in vivo assessment of nigrostriatal nerve integrity. It is a sensitive tool for the early diagnosis of Parkinson's disease and atypical parkinsonism, and for the differentiation of Lewy body dementia from AD.

Genetics

A positive family history is observed in 25-30% of FTLD cases, and an additional 10-15% of cases are hereditary with an autosomal dominant inheritance [79, 80]. Importantly, as new genes and mutations will likely be identified in the future, not finding a mutation does not exclude a genetic cause [73]. While sporadic cases are unlikely to display pathological mutations, seven genes have been involved so far in familial FTLD [79, 81]:

MAPT (microtubule-associated protein tau), located on chromosome 17, encodes a protein implicated in the cytoskeleton. 44 different mutations have been reported.

GRN (progranulin) was the second FTLD-related gene to be discovered on chromosome 17. It encodes progranulin, a cellular growth factor precursor. 69 different mutations have been reported.

C9orf72 (chromosome 9 open reading frame 72) mutation is characterized by a large expansion of a non-coding hexanucleotide (GGGGCC) repeat. C9orf72 gene encodes a ubiquitously expressed protein of unknown function.

Mutations in C9orf72, GRN and MAPT are the most common ones and together explain up to 40% of the familial cases [79].

Less frequently implicated genes are:

VCP (valosin-containing protein) on chromosome 9 encodes a member of the family of the ATPases. 17 different mutations have been described.

CHMP2B (charged multivesicular body protein 2B, sometimes also referred to as chromatin-modifying protein 2B) on chromosome 3 encodes a component of the endosomal-lysosomal complex. Only 4 different mutations have been described [81].

TARDBP (transactive response DNA-binding protein 43) on chromosome 1 encodes a nuclear protein called TPD or TPD-43, involved in RNA regulation. Abnormal TDP accumulation in neuronal and glial cytoplasm has been found in sporadic and genetic forms with mutations in TARDBP, GRN, VCP and C9orf72, suggesting a final common mechanism leading to cell death [82].

FUS (fused in sarcoma) on chromosome 16 encodes a multifunctional nuclear DNA/RNA binding protein [82].

As for diagnosis, genetic testing has a great value in neuropathological studies, when oriented by immunohistochemistry. The benefit of genetic screening in clinical practice proves much more difficult to assess. Identification of the genetic signature of FTLD subtypes is complicated by the clinical heterogeneity, variable expression, misdiagnoses, premature death due to other causes, missing or incomplete medical records and lost family histories [83]. Several algorithms guiding genetic screening have been proposed [81, 84-87]. Current recommendations, though, indicate that genetic testing should only be undertaken in specialist centres with expertise in genetic counselling, in patients with appropriate phenotype or a family history of an autosomal-dominant dementia, and with consent [73]. The topic of predictive genetic testing for at-risk family members will be addressed in the Management Strategies section.

Other Biomarkers

- Routine cerebrospinal fluid (CSF) analysis may help to rule out certain infectious causes (e.g., neurosyphilis, HIV, neuroborreliosis) [73]. Besides, CSF ratio tau/amyloid beta 1-42 is significantly lower in FTLD than AD [73, 88]. A wide range of novel CSF biomarkers, some of them promising (e.g., interleukine-17, fas), still require further validation [88-91]. Indeed, in 2010, an in-depth exploration of human CSF unmasked 745 previously undetected proteins [90]. The growing number of potential biomarkers highlights the need for rigorous evaluation of their diagnostic accuracy.
- No blood biomarker is currently recommended for the diagnosis of FTLD, except DNA analysis for genetic testing [73]. The challenge is obvious: peripheral blood has no direct connection with the brain; blood contains a mixture of thousands of proteins and peptides; its constituents are subject to a huge intra- as well as inter-individual variability [90]. In the particular case of known GRN mutations, the dosage of plasma progranulin might be considered as carriers display decreased levels, unlike non-carriers [85, 86]. It has also been reported that plasma TDP level, when detected by a highly sensitive assay, may rise along with the extension of TDP brain lesions [89, 90].

Neuropathology

A detailed neuropathological examination is mandatory for a definite diagnosis and subtyping of FTLD (Table 6) [92]. The neuropathological diagnostic procedure requires sampling of numerous brain regions, application of a panel of antibodies and staining methods, and identification of specific lesions [93, 94]. Categorization depends on the major component of the neuronal inclusions, reported as FTLD-tau, FTLD-TDP, and FTLD-FUS. As might be expected, atypical variants and mixed neurodegenerative aetiologies do exist. To

date, Pick's disease is the sole FTLD cognitive syndrome with specific neuropathological hallmarks.

Table 6. Nomenclature for FTLD, adapted from Mackenzie et al., 2010

Molecular class	Neuropathological diagnosis	Associated genes
FTLD-tau	Pick's disease	MAPT
	Corticobasal degeneration	
	Progressive supranuclear palsy	
	Argyrophilic grain disease	
	Multiple system tauopathy with dementia	
	Neurofibrillary tangle predominant dementia	
	White matter tauopathy with globular glial inclusions	
	Unclassifiable	
FTLD-TDP	Type 1-4	GRN
	Unclassifiable	VCP
		C9orf72
		TARDBP
FTLD-FUS	Atypical FTLD with ubiquitinated inclusions	FUS
	Neuronal intermediate filament inclusion disease	
	Basophilic inclusion body disease	
FTLD-UPS	Frontotemporal dementia linked to chromosome 3	CHMP2B
FTLD-no inclusions		

CHMP2B charged multivesicular body protein 2B, C9orf72 chromosome 9 open reading frame 72, FUS fused in sarcoma, MAPT microtubule-associated protein tau, TARDBP transactive response DNA-binding protein, TDP transactive response DNA-binding protein 47, UPS ubiquitine-proteasome system, VCP valosin-containing protein.

Recent research activity indicates a trend to look for common traits and mechanisms which could unify these seemingly disparate disorders. Anatomically, the topographical distribution of the lesions seems to correlate better with clinical picture rather than the type of protein deposits [95]. At a molecular level, a theory develops the concept of a prion-like induction and spreading of the pathogenic proteins [96]. Other research demonstrates the role of the mammalian target of rapamycin (mTOR), a protein kinase which inhibits autophagy, in tau accumulation and aging [97]. Our understanding of neurodegenerative disorders is still limited and will require further research effort.

Risk Factors

Little is known about FTLD risk factors. Medical conditions include traumatic brain injury and, possibly, thyroid disease [98-100]. Exposure to environmental neurotoxins, e.g., manganese, could result in an increased risk for subsequent development of FTLD [4, 101]. Genetic risk factors, apart from known genetic mutations, are also involved. A positive family history of first- or second-degree relatives affected by Parkinson's disease, FTLD or another

dementia, especially if age at onset is before 65, provides a reasonably effective means of detecting those at risk for an inherited form of FTLD [81]. Furthermore, some psychiatric disorders (e.g., schizophrenia, bipolar disorder) may represent the prodrome of a neurodegenerative disease as well as an independent risk factor for it, in the same way as depression may increase the risk for developing AD [54-59]. These hypotheses are difficult to differentiate due to considerable phenotypic variability, possible misdiagnoses and shared genetic features. Finally, a genome-wide association (GWA) study found that variant alleles of TMEM106B on chromosome 7, encoding an uncharacterized transmembrane protein, contribute to the risk for FTLD-TDP [79, 102]. Other FTLD-related genes and molecular pathways are currently being investigated [80, 82].

Management Strategies

Pharmacological Treatment

To date, no treatment or lifestyle intervention has proven successful in preventing or delaying the development of non-AD dementias [73].

Current recommendations and recent studies discourage the use of cholinesterase inhibitors and memantine in the treatment of FTLD cognitive deficits [69, 73, 103, 104]. FTLD is not a hypocholinergic dementia, hence no gain is expected from cholinesterase inhibition. Memantine, a NMDA glutamate receptor antagonist, might even hasten cognitive decline. No medication of any type has been shown to improve cognition [73, 105, 106].

As for FTLD behavioural and psychological symptoms of dementia (BPSD), some medications may be used in clinical practice in spite of insufficient evidence [73]. Indeed, symptomatic therapy can enhance quality of life and provide relief to the patients and their caregivers. Most studies show a decrease of serotoninergic receptors in the frontotemporal regions and raphe nuclei [69]. Selective serotonin reuptake inhibitors are considered safe and effective in treating mood and behavioural symptoms [69, 73, 105-107]. Sertraline, paroxetine, fluvoxamine, fluoxetine, and citalopram have all demonstrated some effect on depressive symptoms, disinhibition, carbohydrate craving, compulsions, verbal and motor stereotypies, sexually inappropriate behaviours, apathy and hyperorality. In one study, however, paroxetine seemed to worsen cognition [108]. Trazodone has a 5HT1a-agonist and 5HT2c-antagonist effect, and a modest selective serotonin reuptake inhibitor effect. It improves BPSD, including delusions, aggression, anxiety, irritability, depression, disinhibition, agitation, and eating disorders. Conventional and atypical antipsychotic agents may be prescribed for aggression, psychosis and agitation [73, 109]. Their efficacy must be carefully weighed against their significant side effects, especially extrapyramidal symptoms, higher mortality due to cardiac-related events and infections, weight gain, stroke, and accelerated cognitive decline [69, 73, 106].

Innovative approaches with existing drugs are being explored. There is some evidence for reduced dopamine transport in the putamen and caudate of FTLD patients [69]. Recent studies on dopaminergic agonists, such as amphetamines, tolcapone, and bromocriptine, suggested a decrease in risk-taking behaviours and an improvement of apathy, slowing and perseveration [69, 103, 105-107]. Monoamine oxidase inhibitors might be useful, given

FTLD serotoninergic and dopaminergic deficits. Indeed, selegiline may reduce BPSD [103, 107]. Mood stabilizers are potential neuroprotective therapies. Lithium reduces tau phosphorylation and aggregation, whereas valproate reduces amyloid plaques in animal models. Unfortunately, no efficacy has been conclusively demonstrated in clinical trials [106, 110]. Two neuropeptides, oxytocin and vasopressin, are involved in social cognition, i.e., recognition of facial expressions, empathy and cooperative behaviour, which are frequently affected in FTLD patients [69, 111]. Oxytocin has been shown to improve social behaviour, while vasopressin antagonists have raised theoretical interest.

New therapeutic targets could lead to the emergence of disease-modifying drugs. Protein-specific therapies include microtubule stabilizing agents and inhibition of enzymes which contribute to tau or TDP processing (phosphorylation, ubiquitination, expression, etc.) [103, 112, 113]. Many other molecules, e.g., neuroprotective peptides or antioxidants, are in pharmaceutical pipelines but have to face a number of limitations: compared with other therapeutic areas, CNS drugs have the lowest success rate in all phases of drug development; preclinical animal models have proven to be poor predictors when translated into clinical trials; in vivo diagnosis still awaits substantial improvement in the identification of the underlying proteinopathy, and in the measure of disease progression [103, 113, 114]. Finally, most neurodegenerative diseases are characterized by a long delay with neuropathological changes taking place before the presentation of clinical symptoms. Novel therapeutic strategies acknowledge the need for a better understanding and prevention of the degenerative cascades, for instance inflammation triggered by the pathogenic proteins [115, 116].

Non-pharmacological Treatment

Although a variety of interventions are used in different settings, there is insufficient evidence for recommending any of the non-pharmacological treatments addressing FTLD cognitive impairment and BPSD [73]. Since drug therapies for FTLD remain modestly effective and carry the risk of serious adverse effects, empirically-based strategies offer alternative options to relieve suffering and provide assistance to the patients and their families or caregivers. Each intervention should be individually tailored according to disease stage, symptoms pattern, needs, and available resources. Treatment is multidisciplinary and aims at improving daily functioning, managing symptoms and preserving quality of life.

Safety and Risk Management

Safety concerns are often associated with impaired cognitive functioning and impulsive behaviour. Environmental modifications may minimize risks and deleterious behaviour [117, 118]. They may include the removal of dangerous items (e.g., firearms), rearrangement of furniture to prevent falls or access to stairs, covering doorknobs to discourage elopement, installing door alarms to alert elopement attempts, locking the kitchen door to prevent binge-eating, etc. Evaluation by an occupational therapist may contribute to securing the patient's physical surroundings.

Financial problems may arise from neglected bills, impulsive or compulsive spending, or poor judgement (e.g., gifts to strangers) [65]. Limiting access to bank accounts and credit cards may prove necessary, as well as engaging in disability procedures. As FTLD frequently begins before 65, it may bring about a loss of income along with growing health care costs.

Families should be advised by a lawyer or social worker about financial planning. They should secure assets (e.g., life insurance) prior to genetic testing.

Assessment of driving ability should be made after diagnosis, with particular attention paid to visuospatial., visuoperceptual and executive abilities [73]. Referral to the local jurisdiction for a formal driving assessment helps to make the decision [65]. Cessation of driving will restrict the patient's autonomy, can undermine the patient-doctor relationship and cause conflicts between patient and family. The decision should therefore never be made lightly.

Behavioural Interventions

The objective of this approach is to target problematic behaviour identified by caregivers as most troublesome and to provide strategies to manage them effectively. BPSD may be conceptualized as a consequence of interacting factors which fall into three domains: patient (unmet needs, discomfort, incipient medical condition), caregiver (distress, communication style) and environment (clutter, hazards, general conditions) [119]. Potential triggers are identified and modified in order to improve well-being. For instance, adapting to the patient's abilities and simplifying daily tasks (e.g., clearing area of all items except those related to the present task) may alleviate excessive stress and concomitant agitation [117, 119, 120]. Improving caregiver communication skills reduces resistance to care among patients (e.g., informing patients about the upcoming task, or avoiding "elderspeak" such as "sweetie" or "good boy") [117]. Structuring the environment to facilitate participation may also prove useful (e.g., avoiding crowded or noisy places) [118].

Cognitive Interventions

Although no interventions can reverse the cognitive decline, it seems that a certain degree of improvement is possible in important skills such as memory or verbal communication, especially in progressive primary aphasia [117, 118]. For instance, structured oral reading of text enhances word production in PNFA [121]. Another study provides evidence that errorless learning ameliorates comprehension and naming deficits in SD [122]. Although maintenance of learning is variable, outcomes demonstrate that cognitive rehabilitation contributes to the treatment of neurodegenerative diseases.

Compensatory Devices and Interventions

Compensation means implementing new adaptive strategies when existing abilities are lost or insufficient for adequate functioning. The living environment should be simplified in order to promote self-reliance and a stable daily routine made of structured activities should be implemented [117, 118]. Physical interventions include exercise, assessment of swallowing and advice on dietary modifications, external aids for mobility and continence problems [117]. The learned dependency which occurs in the demented patients when the caregivers provide too much support is to be avoided. Whether by compassion or by irritation, caregivers may be tempted to do things for the patient instead of waiting for the patients to do them by themselves. These over-compensatory interactions lead to reduced activities of daily living [117, 118]. Caregiver's information and education promotes activity and preserves skills. Cognitive impairment may require external memory aids such as calendars, a diary, photo albums or electronic devices (e.g., tablets) [117, 118]. A wide array of communication

strategies and tools may prove useful for language deficits, for instance written messages, drawing charts, photographs, etc.[118, 123].

Community Services

Home-based interventions and visits are usually available in high-income countries. They consist of multidisciplinary teams with occupational therapists, nurses, social workers and household maids, who provide support to FTLD patients and their families.

Specialized day hospitals and recreational centres benefit patients while giving families respite [124]. Unfortunately, finding a facility which will admit FTLD patients may prove difficult due to their younger age, disruptive behaviour, physical strength and preserved mobility [125].

Respite facilities, for instance short-duration nursing home placement, are another way to support families. Hospitalization is reserved for cases which cannot be handled otherwise (e.g., violent behaviour). Residential care must be considered when care needs exceed the capacity of the carer [65]. Families and patients often need time and active assistance to accept change and prepare emotionally for separation, so that early conversations about this topic are useful [65].

Caregiver Support

Caregiver burden in FTLD is higher than in AD [124, 126]. Several patient-dependent variables contribute to carer burden: young age, impaired anterograde memory and emotion recognition, diagnosis (FTLD), low impulse control and behavioural disturbances [126, 127]. However, the patient's gender, performance on general measure of cognition, disease duration, language skills, and the type of relationship (i.e., spouse vs other) between the patient and the carer do not influence carer burden [127]. Regarding carer variables, young age, depression, social isolation, neglected personal needs, and inadequate coping style to problem behaviours are predictive of carer burden [124, 126, 127].

Hence, support services have been developed to meet the needs of this population. Group or individual information and education programmes are modestly successful in reducing stress and burden [126, 127]. Support groups for families, which may be internet-based, prove beneficial by providing mutual self-help and allowing verbalization of feelings [124, 126]. Mental health care professional counselling and case management also have positive effects on burden and satisfaction of caregivers [73]. In some instances, psychosocial support proves insufficient owing to high levels of carer distress. Referral to a mental health professional for psychotherapy should then be considered [65]. Practical issues, such as access to care facilities, disability procedures, financial advice and evaluation of needs should be addressed systematically. Integration of the caregivers and family members into a team surrounding the patient ensures that everyone has a proper understanding of the situation.

Genetic Counselling

Regarding FTLD genetic counselling, no internationally shared guidelines are available. In their absence, the approach is similar to that used for Huntington's disease and consists of a three-step programme [73, 128]. The pre-test session comprises general information on the disease, on the test, on possible alternatives (e.g., DNA bank, research), and on their consequences. Additional investigation, such as neurological and psychological examinations,

may be advisable, but should always be non-compulsory. A minimal interval of one month is necessary between the pre-test session and the decision to take the test in order to assimilate the information and make an informed decision. The result should be delivered as soon as possible after completion of the test. Follow-up sessions should be scheduled over two years in the post-disclosure period. These recommendations are intended to be individually tailored [128, 129].

Predictive testing is intended for at-risk family members of FTLD patients. Due to the complexity of FTLD genetics, it is highly recommended that the mutation be identified in an affected relative prior to pre-symptomatic testing of kindred [73, 84]. This requirement is sometimes extended to autosomal-dominant inheritance only, which may prove extremely difficult to establish and cause much frustration in families who fear that dementia in their family is genetic but have no way to prove it [83, 84]. As stated before, incomplete family history, misdiagnoses and psychiatric disorders may prevent exact determination of cases. Furthermore, mutations with incomplete or age-dependent penetrance contribute to the blurring of the picture [84].

If the index case cannot be tested or identified, the likelihood of a hereditary mutation is based primarily on a positive family history. A three-generation pedigree of family members with an FTLD disorder or another neurodegenerative disease must be collected [81]. Integration of several variables is required: family history, phenotype, age at onset, neuroimaging data and any other source of information (e.g., autopsy, progranulin plasma level, etc.). Should the family history be negative, the odds of finding a pathogenic mutation are less than 3% [84]. If the data point to a possible hereditary transmission of the disease, the next step is to decide which genes are the most likely candidates according to statistical probability. It is only at this point of the workup that adult family members are eligible for predictive testing [84-87].

Only a small proportion of those at risk requests testing [83, 129]. The most common reasons for testing are to further scientific research, to know if children are at risk, to plan for a medical and financial future, and to be relieved of anxiety [83]. The primary reasons of those who do not wish to pursue testing are to maintain hope, inability to cope with the stress of a positive result, and fear of knowing the future [83].

The impact of test results is difficult to predict and only slightly dependent on the outcome (positive or negative) [129]. Hence, support must be offered to carriers as well as non-carriers. Reactions depend on individual features such as baseline mood, ego strength, and coping strategies [129]. They range from relief, anxiety, depression or adjustment problems, to a decision not to procreate or divorce [83, 129].

End-of-life Issues

The scarcity of literature about end-of-life care in FTLD may translate the discomfort which many health professionals experience towards inevitable decline and death. Nevertheless, families and patients have to plan for their future and make decisions about the goals of care when there is still time and ability to discuss these matters [4]. The cognitive and physical progression of the signs and symptoms should be addressed pre-emptively during the follow-up sessions. The expressed will of the patients helps diminish the stress and guilt that some caregivers may feel about not doing enough or making the right decisions, for instance, about measures of comfort or referral to palliative care [65].

Anticipatory grief in dementia is equivalent in intensity and breadth to death-related grief [130]. However, the grief process is different for adult-child caregivers than for spouse caregivers, and depends upon the dementia stage [130]. Moreover, end-stage cognitive decline does not allow for patients and caregivers to grieve together. This experience of human condition may function as a starting point for clinical intervention [131, 132]. Support and guidance must therefore be adapted to fluctuating affective, intellectual and existential needs.

After the patient's death, contact with the family may address further issues, such as post-mortem brain examination, genetic implications of the disease and bereavement [65]. Anticipatory grief appears to alleviate post-death grief initially, but not in the long run, emphasizing the need for psychological follow-up to be offered upon request [130, 131].

Conclusion

Neurodegenerative disorders remain disconcerting and challenge our knowledge about their cause, their prevention and their treatment. The "airbag problem" theory may explain the lack of translational success despite the tremendous work and money invested in dementia research over the past thirty years. A recent and provocative paper describes it as an illustration of reverse causality [133].

The airbag theory questions beliefs about presumptive disease aetiology and suggests re-considering future research with an iconoclast state of mind. For instance, emerging evidence indicates that abnormal protein aggregation may not necessarily be the cause of neuronal toxicity and death [134]. This could partly explain why some individuals whose brain carries a heavy lesion burden remain cognitively healthy. Another part of the explanation could arise from the protective and adaptive mechanisms of the brain, such as neural genesis or neuroplasticity [135]. Obviously, a considerable amount of inter-individual variation exists.

Understanding why aging is the major risk factor for the development of neurodegenerative disorders may be a more promising approach than focusing on specific diseases, conditions or single aetiologies [136, 137]. Evolutionary theories provide valuable insight. Classical evolution theory predicts that genomes are inherently unstable because of the need for DNA variation as a substrate for evolution through natural selection [138]. Nonetheless, genetic control that drives aging is not optimized because evolutionary pressure decreases with age [138, 139]. Due to shorter life spans in the past, the antagonistic pleiotropy theory explains why some alleles, having a positive effect early in life and thus retained by selection, may accumulate in successive generations before uncovering their negative effects at an older age [139, 140]. These entangled concepts point to the need for interdisciplinary research in order to expand and nuance our knowledge of the aging processes, which might be the key to future treatments for those affected by these devastating diseases.

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