Clinical, Genetic and Neuropathological Features of Frontotemporal Dementia: An Update and Guide

Aspetos Clínicos, Genéticos e Neuropatológicos da Demência Frontotemporal: Atualização e Guia

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ABSTRACT

Introduction: Frontotemporal Lobar Degeneration encompasses a group of heterogeneous disorders with shared behavioural and cognitive symptoms, as well as gross pathological features. The genetic underpinnings and histopathological aspects are quite diverse and form the basis of molecular classification, which is not easy to correlate with clinical findings and syndromes. Scientific research has brought to light an array of knowledge, often not easy to keep up with, especially in the last few years with regard to genetics and histopathology.

Material and Methods: The authors have searched the published literature on this topic, chose relevant references, and extracted and systematized the data.

Results and Conclusion: this manuscript presents an updated review of clinical, genetic and histopathological findings in Frontotemporal Lobar Degeneration, with special focus on behavioural variant Frontotemporal Dementia, the most common disorder. Current management is also reviewed, and genetic testing strategies are proposed by the authors for use in clinical practice. Public awareness on this group of disorders should be raised.

Keywords: Frontotemporal Lobar Degeneration/genetics; Frontotemporal Lobar Degeneration/pathology.

RESUMO

Introdução: A Degenerescência Lobar Frontotemporal engloba um conjunto de situações heterogéneas que partilham sintomas cognitivos e comportamentais, bem como características patológicas macroscópicas. As bases genéticas e características histopatológicas são bastante diversas e formam a base da classificação molecular das várias doenças, sendo difícil fazer uma correlação com os achados clínicos e síndromas. A investigação científica trouxe um conjunto vasto de conhecimentos, nem sempre fáceis de acompanhar, especialmente nos últimos anos em relação à genética e histopatologia.

Material e Métodos: Os autores fizeram uma pesquisa de literatura neste tema, escolheram referências relevantes, extraíram e sistematizaram os dados.

Resultados e Conclusão: o texto apresenta uma revisão atualizada dos aspetos clínicos, genéticos e histopatológicos da Degenerescência Lobar Frontotemporal, com ênfase especial na Demência Frontotemporal, a doença mais comum. O tratamento é também revisto e são propostas pelos autores estratégias relativamente à escolha dos testes genéticos na prática clínica. Deveriam ser promovidos a atenção e conhecimento públicos sobre este grupo de doenças.

Palavras-chave: Degenerescência Lobar Frontotemporal/genética; Degenerescência Lobar Frontotemporal/patologia.

INTRODUCTION

A 52-year-old man comes with his wife to the neurology clinic referred by the psychiatrist. He does not have a clue of why he comes in and declares that, apart from mild lower back pain, nothing is wrong with him. His desperate wife, however, reports the changes that came about for the previous year. Her husband had always been a very sober-minded, polite and working man but had unexpectedly become lazy and at times he did not even show up at work, putting off any questions by smiling and saying 'why should I anyway?'. He has been on sick leave for the past 3 months now. Moreover, he now repeatedly utters unacceptable sexual comments about other women and their way of dressing, including in their presence and his wife's. He had gradually developed a sweet tooth, with a special preference for jelly beans. He is now very rigid, demanding for example that his wife cooks only a very limited menu. During meals he stuffs his mouth with food almost up to the point of choking and always tries to steal some more from other people's plates. His father had died at the age of 56 after a few years of a behavioural disorder similar to this one. The patient has 2 children, aged 23 (single) and 28 years (married, without any children so far). After thorough clinical exploration, and analysing the blood tests and brain magnetic resonance imaging, the neurologist concludes that the patient suffers from Frontotemporal Dementia.

The neurodegenerative dementias are clinically characterized by cognitive and functional decline, ensuing from gradual loss of nervous cells in particular topographic locations and neural systems (i.e. disease-specific neural tropism). The relatively selective destruction of neural populations at the frontal and anterior temporal lobes, together with a relative preservation of posterior brain regions, has been associated with a heterogeneous group of disorders joined under the umbrella clinicopathological term Frontotemporal Lobar Degeneration (FTLD), at times clinically referred to as Frontotemporal Dementia (FTD),[1] however,

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the latter designation should be reserved for a specific syndrome which is the main object of this text, also known as behavioural variant FTD (bvFTD). Arnold Pick first reported this condition in 1892, when the prototype of the current FTD concept has been forged, as he focused on a clinicopathological study that examined post-mortem the brain of patients with dementia or progressive aphasia, and described marked frontal and temporal atrophy.[1] In 1911, Alois Alzheimer identified 'Pick bodies' as neuronal argyrophilic inclusions in the brains of such patients.[2]

The prevalence of FTLD has been variably documented in several studies, estimated between 2.7-15.1 per 100000 individuals up to 65 years old.[1,3] It is the third most common neurodegenerative dementia in developed countries, following Alzheimer's disease (AD) and Dementia with Lewy bodies (DLB), with an incidence of 9.7-12% among all dementias.[4] Symptoms typically emerge between 50 and 60 years old.[3,5] Gender distribution is somewhat balanced, although certain variants show higher frequency in males, particularly semantic dementia (SD) and bvFTD.

This field has seen remarkable developments in the past few years, and it is a hot topic in clinical neuroscience.[6] Nevertheless, it has been challenging to keep up with the amount of research and novelties, as well as the correlations between phenotype, genetics and neuropathological findings. This review aims to bring a pragmatic and updated guide for clinicians and researchers, integrating the latest developments in the clinical, genetic and neuropathological fields.

METHODS

PubMed has been searched for manuscripts published until November 2012, written in English, Portuguese, Spanish and French. Search expressions included 'frontotemporal dementia', 'frontotemporal lobar degeneration', 'progressive nonfluent aphasia', 'semantic dementia', 'genetics', 'histopathology', and 'treatment'. Both authors have inspected and selected relevant references by consensus. Data have been extracted and structured in order to provide the readership with an updated and practical text. The authors also provide one specific case report and brain images deriving from their own clinical practice, in order to better illustrate manuscript contents.

RESULTS AND DISCUSSION

A) Clinical Features

FTLD is a unifying term for clinical, genetic and pathological perspectives, comprising various dementing disorders wherein the pathological changes mainly occur in the frontal and anterior temporal lobes. It has been classically accepted from a cognitive perspective that the right frontal lobe is involved in social cognition and emotions, whereas the left plays a nuclear role in linguistic abilities.[5] Furthermore, the frontal lobe may also be split into three major areas in a postero-anterior way: motor, premotor and prefrontal cortices. The latter comprises three divisions: frontomedial, mainly involved in motivational processes; orbitofrontal, that coordinates higher-order cognitive skills with regard to social behaviour, attention and emotions; and dorsolateral, involved in cognitive control and the so-called executive functions, such as organization, planning, learning and behavioural adjustment.[7] Whenever diseased (e.g. in FTLD), neural systems will become affected, thus resulting in the disruption of behaviour and the emergence of symptoms ascribable to each of the locations/neural systems involved.

Clinically, two major groups of disorders have been described:[6,8] the first, largely represented by a continuous but progressive impairment of personality and social behaviour, named bvFTD, correlates to prefrontal and anterior temporal lobe dysfunction, generally symmetrical or mostly right sided; and the second, with an insidious decrease of linguistic capabilities, named primary progressive aphasia (PPA), has been associated with essentially left-sided dysfunction and can be subdivided into three clinical subtypes, based on key symptoms: semantic dementia (SD), progressive nonfluent aphasia (PNFA) and logopenic variant of PPA (LPA).[9] Figure 1 depicts some of the typical neuroimaging findings related to these patterns of atrophy.

FTLD, mostly bvFTD, may also overlap with motor neuron disease in 10% of patients.[10] Other conditions presenting prominent symptoms related to disordered basal

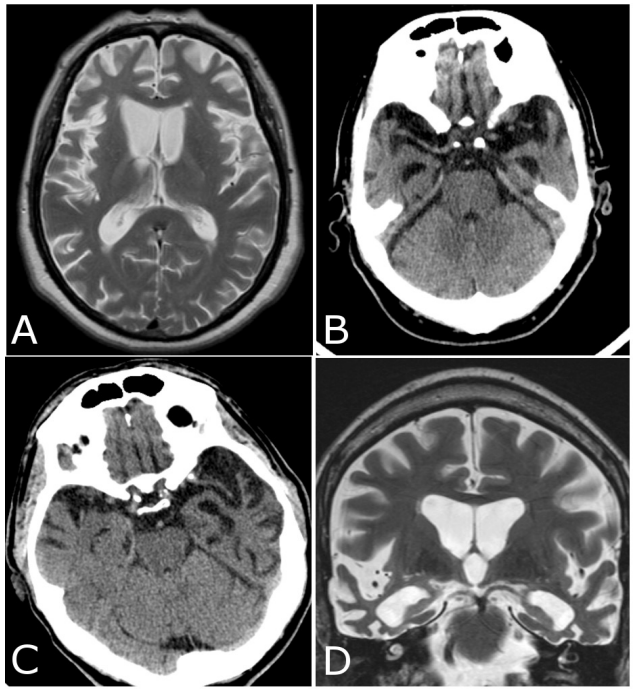

Figure 1 – Neuroimaging findings in FTLD.
A (MRI, axial T2): bilateral frontal lobe atrophy, more so on the right side (left side of image) in bvFTD; B (CT scan): bilateral anterior temporal lobe atrophy in bvFTD; C (CT scan): left sided temporal lobe atrophy, around the perisylvian area, in a patient with PNFA whose symptoms had surfaced ten years before. Rostral slices (not shown here) disclose atrophy of left frontal lobe around anterior language centres; D (MRI, coronal T2): bilateral temporal lobe atrophy, including lateral neocortex and medial structures, predominantly on the right side, in a patient with SD (right-sided variant) whose symptoms had been noticed 7 years before.

ganglia circuits, such as progressive supranuclear palsy (PSP) and the corticobasal syndrome (CBS) have been associated with FTLD.[6,10]

Behavioural variant FTD

This is the most prevalent clinical presentation within the FTLD category. Symptom onset is insidious, followed by gradually worsening course, where cognitive deficits are most recognizable with regard to executive functions, personality and social decorum, with a relative maintenance of visuo-perceptive skills, at least until later stages.[11] Nonetheless, exceptions have been described, especially in association with progranulin gene mutations.[12] The diagnosis may be hard to establish as these symptoms may also be found in other dementias, yet the most pronounced in bvFTD are personality changes along with apathy or disinhibition, which tend to be quite less pronounced in other disorders in early stages. Apathy is expressed by reduced motivation concerning work or prior hobbies and gradual social isolation, which can be misdiagnosed as pathological depression.[13] Throughout disease course, patients may disregard their personal hygiene and even lose sphincter control.[14] Behavioural disinhibition is characterized by impulsivity or misjudgement leading to overspending, inappropriate interpersonal remarks and numerous embarrassing or antisocial attitudes, like breaking legal rules or embarking on physical threats, incongruent with premorbid personality and behaviour.[14] Recurrent inappropriate sexual comments can be noted but patients do not usually exhibit hypersexuality, but rather a decreased libido.[1,13] The clinical picture is not uncommonly mistaken with a psychiatric disorder.

Patients with bvFTD show a variable decrease of their insight and commonly display stereotyped behaviours, which range from an exaggerated use of recurrent verbal sayings, to collecting and counting rituals.[15] Often, they modify their eating patterns, overeating sweets and consuming alcohol excessively and, during disease course, some may take in non-food items.[16] Social emotions often become affected, as patients show an egocentric, apathetic behaviour towards others, including close relatives who display remarkable concerns about their health status (i.e. affective blunting).[17] Besides, they become inflexible when adapting to circumstances and daily routines or distinct perspectives.[18] Some might demonstrate distractibility, perseverant attitudes, concrete thinking, slowed speech or echolalia.[19] They may also display non-fluent aphasia, characterized by a shortage of word production and poverty of speech content.[14,20]

Overall cognitive decline of these patients can be less severe as compared to behavioural changes, and cognitive assessment commonly fails to recognize significant episodic memory deficits.[14] Among the several symptoms, social disinhibition, stereotyped actions and odd dietary changes are those most notably distinct from the clinical picture of AD.[10]

Imaging techniques usually disclose a pattern of frontal hypometabolism, hypoperfusion and atrophy (see Fig. 1), but topographical involvement might depend on the leading symptoms observed: frontomedial with apathy, orbitofrontal with disinhibition and dorsolateral with executive dysfunction.[13,21]

Primary Progressive Aphasia (PPA)

The term refers to a group of conditions typically featuring atrophy of the left frontal and temporal regions, bound to an insidious linguistic decline that lasts for at least two years, without compromising additional cognitive skills.[22] The core presenting symptom is aphasia, and its variants are classified based on the type of specific language deficits.[23-25] Nonetheless, the classification of PPA has been revised recently, so that the terminology may still not be uniformized.

SD patients display a fluent form of PPA. The hallmark of SD is a reduced efficiency on actions that rely on intact semantics. This way, besides fluent speech, they can either show anomia or comprehension decrement that end up in greater difficulties when recognizing objects and people.[26] Some also suffer from variable degrees of dyslexia and dysgraphia, particularly noted while using unfamiliar or less frequent words, switching the ideal designations to broader terms or superordinate categories (e.g. 'lion' is identified as 'cat' or 'animal').[27] Furthermore, subtle behavioural changes similar to bvFTD are often found, especially as disease progresses,[28] though they do not dominate the clinical picture. They exhibit degraded social functioning with depression, apathy or irritability, coupled with emotional coldness and loss of empathy. Behavioural rigidity, compulsive or repetitive behaviours and peculiar food choices are also frequent.[9,28] Imaging studies show a pattern of anterior temporal atrophy which is often more pronounced on the left side but can later spread to other temporal regions.[29]

In contrast, PNFA presents with an increasingly hesitating and less fluent speech, eventually coupled to apraxia of speech, with phonological errors, shorter and simpler phrases, agrammatism and aprosodia, and mutism might eventually ensue as disease progresses. This impairment is clearly influenced by the complexity of sentences, meaning that single-word comprehension and object knowledge are usually spared, helping differentiate PNFA from other PPA variants.[24,30,31] Social conduct, memory and visuo-perceptive skills of these patients are usually normal, at least in early stages.[32] Cortical atrophy in PNFA mainly involves the left anterior perisylvian region, extending to the left dorsolateral prefrontal cortex as the disease progresses, which is in accordance with the regions responsible for sentence processing.[24]

LPA is defined by a speech output that is spontaneous but slow, but usually no discernible grammar errors or motor control. However, unlike PNFA, these patients do not improve if the speech is simpler and normally show episodic memory deficits. The imaging pattern shows posterior perisylvian cortex atrophy, typically on the left hemisphere, and Alzheimer's disease is usually the pathological underpinning, unlike the previous forms.[9,24]

Table 1 – Genes involved in hereditary FTLD and related disorders.

	Locus	Function	Mutation effects (frequency)	Associated phenotypes
MAPT	17q21.31	Encodes microtubule-associated protein, responsible for microtubule stabilization, promoting their binding with tubulin in order to enhance the protein-mediated transport of vesicles and organelles.[62, 63]	Increases the number of toxic aggregates of tau protein (< 25%)[62, 64, 65]	bvFTD PSP CBS bvFTD with parkinsonism bvFTD-ALS[64]
GRN	17q21.32	Encodes progranulin, a growth factor involved in cell cycle and motility control, as well as on oncogenesis and inflammatory cellular mechanisms.[34, 66]	Blocks progranulin translation through haploinsufficiency (5 - 25%)[34, 67]	bvFTD bvFTD with parkinsonism PNFA PSP CBS[66, 68]
C9ORF72	9p21.2	Still uncharacterized protein, with unknown function.[69]	Hexanucleotide expansion that leads to toxic RNA accumulation which loses its function (6 - 37%)[69-71]	bvFTD FTD-ALS PSP CBS[71]
CHMP2B	3p11.2	It is part of an endosomal complex (ESCRT) that controls endocytic pathways of protein transport, autophagy and cytokinesis.[72]	Leads to the production of non-functional proteins (< 1%)[64,73]	bvFTD (later during course with parkinsonism, dystonia, myoclonus, upper motor neuron features)[73]
VCP	9p13.3	Valosin containing protein is a structural protein involved in the vesicle transport pathways and the control of cellular processes like mitosis and proteasomal protein degradation.[33,74]	Decreases proteasomal activity and increases protein aggregation (< 1%)[34,74]	bvFTD IBMPFD[64,74]

Legend: CHMP2B – chromatin-modifying 2B protein; C9ORF72 – chromosome 9 open reading frame 72; ESCRT – endosomal sorting complex required for transport; FTD-ALS – frontotemporal dementia associated to amyotrophic lateral sclerosis; GRN – progranulin gene; IBMPFD – inclusion body myositis, Paget's disease of bone and Frontotemporal Dementia; MAPT – microtubule-associated protein tau gene; VCP – valosin-containing protein.

Table 2 – Neuropathological findings and phenotypical correlations in FTLD-TDP.

Type	Cortical inclusions			Clinico-genetic associations
	NCI	NII	DN	
A	+++	+	++	bvFTD, PNFA, CBS *(GRN and C9ORF72 mutations)*
B	++	0	+	FTD-ALS, bvFTD *(C9ORF72 mutations)*
C	+	0	+++	SD, bvFTD
D	+	+++	+++	bvFTD, IBMPFD (*VCP* mutations)

Legend: bvFTD – behavioural variant of frontotemporal dementia; C9ORF72 – chromosome 9 open reading frame 72; CBS – corticobasal syndrome; FTD-ALS – frontotemporal dementia associated to amyotrophic lateral sclerosis; GRN – progranulin gene; IBMPFD – inclusion body myositis, Paget's disease of bone and frontotemporal dementia; PNFA – progressive nonfluent aphasia; SD – semantic dementia; VCP – valosin-containing protein.

B) Genetics

A positive family history of FTLD is present in 25-50% of cases,[33,34] and the transmission is usually autosomal dominant.[35] A few genes have been associated with FTLD (Table 1).

C) Neuropathology

Apart from those instances where a genetic defect is recognized, post-mortem neuropathological brain examination is essential so that the entity underlying FTLD can be identified. Also, dissimilar pathologies are often co-identified.[4] Linking phenotypical features and molecular pathology has been a huge challenge along the history of neuroscience research, and FTLD is probably the most paradigmatic case. The core pathological features of FTLD are the selective atrophy of frontotemporal cortex, associated with neuronal loss, gliosis and spongiosis of cortical superficial layers.[1,5] Histochemically, FTLD can be categorized according to the major component of the cellular inclusions deposited in the brain (tau, TDP-43 and FUS), thus designating FTLD-tau, FTLD-TDP and FTLD-FUS, correspondingly.[36]

FTLD-tau

Microtubule-associated protein tau (MAPT) is a phosphoprotein present mostly in neurons, enhancing microtubule polymerization, assortment and also stabilization, primarily in axons. This happens due to a binding interaction with the 3 or 4 microtubule-binding domains at its C-terminus (3R or 4R tau, respectively), relying on RNA splicing.[37] Identical proportions of 3R and 4R tau can be found in the normal brain, whilst there may be preferential deposits of 3R or 4R in different tauopathies, thus offering a biochemical subclassification.[5] FTLD-tau cluster includes disorders such as Pick's disease (PiD), PSP and Corticobasal Degeneration (CBD), as well as other entities such as Argyrophilic Grain Disease (AGD) or Multiple System Tauopathy with Dementia (MSTD).[36,38] Fundamentally, tau mutations are prone to considerably impair the binding to microtubules, via hyperphosphorylation mechanisms which have inhibitory outcomes resulting from abnormal tau aggregation.[37,39]

PiD is the prototype of FTLD and is a 3R tauopathy displaying Pick bodies, that are solitary, circular, argyrophilic inclusions located in neuronal cytoplasm. They can be usually seen in the dentate gyrus of the hippocampus, amygdala and frontotemporal neocortex, mainly in layers II and III.[40] On the other hand, PSP and CBD are both 4R tauopathies and they are more common than PiD.[4,40] PSP is characterized by bigger neuronal inclusions named globose neurofibrillary tangles and also glial inclusions termed tufted astrocytes on the basal ganglia, subthalamic nucleus and substantia nigra.[41] CBD is distinguished by astrocytic plaques in basal ganglia, thalamus and brainstem, that are not found in any other pathology.[4,40] Notwithstanding, in both these entities significant cortical involvement might also be found.[5]

FTLD-TDP

TAR DNA-binding protein 43 (TDP-43) is a ubiquitously expressed RNA-binding protein most often located in the nucleus that can shuttle between the nucleus and cytoplasm. It is a global regulator of transcription and other multiple aspects of RNA processing and functioning.[42] TDP-43 controls its own expression by a feedback system, ensuring that intracellular level is tightly controlled, which is imperative since it acts in multiprotein/RNA complexes, wherein a suitable structure needs a specified ratio between TDP-43 and its RNA partners.[43] In a disease scenario (e.g. FTLD-TDP), cellular conditions contribute to TDP-43 aggregation. This may trigger a decrease in the pool of TDP-43 that could be integrated into the complexes, hence decreasing their activity and causing neurodegeneration.[44] Pathological classification is based on three types of TDP-43 immunoreactive inclusions: neuronal cytoplasmatic inclusions (NCI), neuronal intranuclear inclusions (NII) and dystrophic neurites (DN). The first two classifications emerged in 2006 by Sampathu et al[45] and Mackenzie et al[46] the first using monoclonal antibodies and the latter using clinicopathological correlations. Both were based on the fact that the inclusions were immunoreactive to ubiquitin but not tau, thus the designation FTLD-U.[14] Later, this has been changed to FTLD-TDP, when TDP-43 was identified as the main component, leading to a new classification centred on the relative frequency of four pathological subtypes summarized in Table 2, where a correlation with the main clinical phenotypes is also established.[47,48]

FTLD-FUS

After the FTLD-U label has been carved, about 7-20% of the patients were clinically determined to have negative inclusions for TDP-43 pathology, thus the terminology 'atypical FTLD-U' (aFTLD-U). Subsequently, research has been carried out in order to better characterize those inclusions which resulted in the identification of the fused in sarcoma (FUS) protein as their main component. Similarly to TDP-43, it is a ubiquitously expressed DNA/RNA binding protein that regulates numerous cellular processes like cell proliferation, DNA repair and RNA splicing.[49] For most cell types, FUS can be found predominantly in the nucleus. Nonetheless, once mutated, FUS becomes anomalously distributed in the cytoplasm, where it forms insoluble aggregates that feature a toxic gain-of-function.[50] FUS inclusions are morphologically identical to the ones containing TDP-43, with a variable amount of distinct NCI along with thick filament NII.[51] These have been assigned to a few remote variants of FTLD, such as neuronal intermediate filament disease (NIFID) and basophilic inclusion body disease (BIBD).[38,51] Patients with FTD-FUS typically present with bvFTD symptoms without associated motor neuron disease, and some with parkinsonism,[49,52] yet an exclusive cognitive and behavioural outline can be found. Obsessions and rituals are typical, along with a social disengagement and executive impairments that present as perseveration and problematic mental shifting. Of note, cases with especially young age at

onset of symptoms have been described in association with FUS pathology.[53]

Clinical Management

General issues

FTLD is frequently unfamiliar to the common citizen and many physicians. Therefore, FTLD caregivers can be especially distressed while searching for medical advice, considering that FTLD is significantly less prevalent and understood than AD and there is a higher frequency of upsetting behavioural symptoms in these patients.[54] Medical management should start with thorough explanation of symptoms and the condition itself to the family and caregivers, as most of the time they will be uninformed, anxious, depressed and even burned out – from our experience there is commonly the belief by the family that the patient might be faking the symptoms or acting on purpose. This might contribute to better understanding of the situation and hopefully lower stress levels. Due to the remarkable behavioural modifications and compromised judgment abilities, safety tends to be problematic even in the early stages of FTLD (especially bvFTD), an issue that should be assessed and discussed with the caregiver.[55]

Genetic testing and counselling

Genetic counselling is a delicate issue requiring in-depth clinical and genetic knowledge with regard to disease features, allied with a degree of experience and sensitivity towards the subjects involved. As a rule of thumb, before embarking on any kind of testing, patients and families should be informed in detail about the complex genetics of FTLD, the potential consequences of carrying a mutation, and the possibility of not detecting any mutations at all. The starting point is to actively obtain an extensive family history, which should include no less than three generations, in order to increase sensitivity and define the pattern of transmission, whenever possible.[56] Should the classical autosomal dominant pattern be uncovered, each direct family member (e.g. siblings, sons) of the index case has a 50% chance of harbouring the genetic defect, whether it is identifiable or not through appropriate testing. If the family history is negative, the odds of finding a pathogenic mutation might decrease to about 3%.[57] Clinical presentation of the index case and affected family members should be thoroughly revised in order to define the phenotype and assist the clinician choosing the specific test, although phenotype-genotype correlation is far from perfect (Fig. 2) and phenotypic variability is common. The fact that incomplete and age-dependent

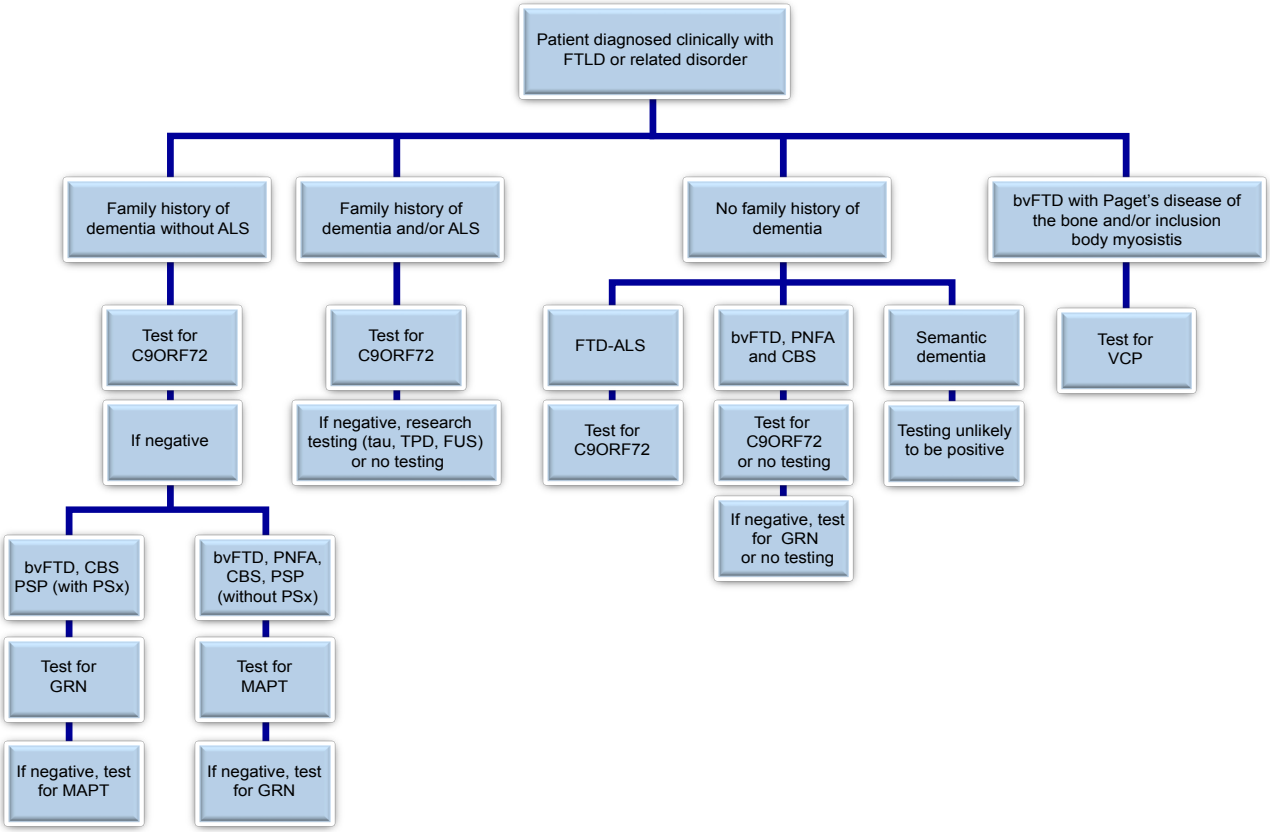

Figure 2 – Genetic testing algorithm: author proposal based on phenotypical correlations and estimated relative frequency of the several genetic causes. Legend: ALS – amyotrophic lateral sclerosis; bvFTD – behavioural variant of frontotemporal dementia; C9ORF72 – chromosome 9 open reading frame 72; CBS – corticobasal syndrome; FTD-ALS – frontotemporal dementia associated with amyotrophic lateral sclerosis; FTLD – frontotemporal lobar degeneration; FUS – fused in sarcoma protein; MAPT – microtubule-associated protein tau; GRN – progranulin; PNFA – progressive nonfluent aphasia; PSP – progressive supranuclear palsy; PSx – parietal symptoms; SD – semantic dementia; TDP – TAR-DNA binding protein; VCP – valosin-containing protein.

Table 3 – Current options for the pharmacological treatment of FTLD, based on published evidence and the authors' experience.

Class	Drug	Dose [mg/day]	Comments
Antidepressants The observation of impaired serotonergic activity in FTD implies biologic plausibility for the use of these drugs.	Paroxetine	10 - 20	Some trials have shown effective results on disinhibition, depressive symptoms, stereotypies and ritualistic behaviours, while others failed to show any improvement.[75-80]
	Sertraline	50 - 100	
	Fluvoxamine	50 - 100	
	Trazodone	50 - 300	Can be useful in anxiety and irritability, but without beneficial effects on cognition.[75,77-80]
Antipsychotics Have been commonly used, especially atypical drugs. Benefit to risk ratio must be thoroughly defined before prescription.	Risperidone	0.5 - 2	Used for troublesome agitation. Might worsen parkinsonian symptoms, increase risk of falls and the risk of vascular events.[75-80]
	Olanzapine	2.5 - 10	
	Aripiprazole	10 - 20	
Stimulants	Methylphenidate	20 - 40	Little evidence of efficacy. Could improve attention and executive functioning.[75-78]
Cholinesterase Inhibitors Many clinicians empirically use them, although cholinergic deficits do not seem important in FTLD.	Donepezil	5 - 10	Has been associated with behaviour worsening; benefits have been observed in global cognitive performance.[75-79]
	Galantamine	16 - 24	Data suggest it could improve language skills in PNFA and SD patients.[75,78,79]
	Rivastigmine	3 - 9	Small benefits have been seen both on behavioural symptoms and cognitive deficits.[76-79]
Glutamatergic NMDA Receptor Antagonists	Memantine	20	Some data suggest that agitation and anxiety could be significantly improved, as well as modest improvement on activities of daily living.[78,79,81] A recent randomized controlled trial did not show efficacy in FTLD.[82]
Mood Stabilizers	Carbamazepine	200 - 600	Mainly used to manage behavioural symptoms but no evidence of efficacy has been proven so far.[76,83]
	Valproic acid	500 -1000	
Benzodiazepines			Generally not recommended as they can induce paradoxical agitation or negative effects on cognition.[75]
Antiparkinsonian drugs	Levodopa	100 - 800	Typically there is no significant improvement of parkinsonian features, although some PSP patients might benefit.[84]
	Amantadine	100 - 300	

penetrance exists, especially with regard to GRN and C9orf72, brings additional difficulties to the process of genetic counselling.[58] Next-generation genomic sequencing techniques might render the process of genetic testing in FTLD much easier and quicker in the future.[59] Lastly, predictive genetic testing can be carried out in asymptomatic individuals who manifest such a wish, but only after a clearly pathogenic mutation has become evident in the index case. Of note, it has been found that both symptomatic and asymptomatic *GRN* mutation carriers display significantly decreased serum levels, unlike non-carriers. Such testing is a viable and currently much cheaper tool as compared to genetic testing that can be used for screening both symptomatic patients and at risk individuals.[60,61] As legally defined, predictive testing in Portugal must be performed exclusively in Medical Genetics specialized clinics, and testing is not allowed in asymptomatic individuals until they reach the age of 18 years.

We acknowledge that genetic testing and counselling is challenging. Clinicians ought to approach the process with exhaustive clarification of interpersonal matters, without ignoring the psychological frailty of the patients and families.

Pharmacological interventions

There is clear scarcity of evidence with regard to the pharmacological treatment of FTLD, with most data extracted from small trials, case series or isolated case reports. Therefore, drugs are used off label. There is no evidence that disease-modifying interventions have been made available so far, hence treatment remains purely symptomatic. Once behavioural symptoms emerge or become troublesome, clinicians must consider assessing pain, delirium or distress before embarking on potentially more aggressive pharmacological options. Also, adverse effects such as paradoxical responses, confusion, extrapyramidal effects or sedation are frequently seen, suggesting that minimal available dosage administration, gradual upward dose titration and regular clinical monitoring should be performed. Table 3 summarizes the currently available options.

CONCLUSIONS

FTLD refers to a group of disorders with heterogeneous clinical, molecular and pathological features. Disease consequences (e.g. individual, familiar, social, economic) can be devastating, especially since it generally affects younger individuals, as compared to AD or DLB. Current therapy is purely symptomatic and efficacy modest at most. Recent advances have been seen with regard to genetic causes, thus genetic counselling and testing is an important process during clinical management. FTLD is commonly seen in Neurology and Psychiatry clinics, although it remains largely unknown to many clinicians and the general public. Thereby, we propose a reinforcement of the public information about FTLD, along with the implementation of interventions focused on decreasing the burden of caregivers. Intervention by patient's associations would be most welcomed and should play a major role in this process. Future research should move the field to robust experimental designs, comprising adequate sample sizes and endpoints, as well as detailed analyses. This would maximize the amount and quality of research findings, thus contributing to enhance optimal care for these patients.

CONFLICT OF INTEREST AND FUNDING SOURCES

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