Review

Fronto temporal dementias

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Abstract

Frontotemporal dementias (FTD) are a heterogenous group of neurocognitive disorders which varies with regard to their clinical presentation, radiological characteristics, pathology and genetics. The core FTD clinical syndromes are behavioural variant FTD (bvFTD), semantic variant primary progressive aphasia (svPPA) and nonfluent/agrammatic variant of primary progressive aphasia (nfvPPA). FTD related syndromes include frontotemporal dementia with motor neuron disease (FTD-MND), progressive supranuclear palsy syndrome (PSP-S) and corticobasal syndrome (CBS). This article discusses the clinical presentation, diagnosis, neuropathology, neurogenetics and therapeutics of FTDs.

Key words: frontotemporal dementia, primary progressive aphasia, behavioural variant frontotemporal dementia, semantic variant primary progressive aphasia, nonfluent/agrammatic variant primary progressive aphasia, motor neurone disease, progressive supranuclear palsy, corticobasal syndrome

Introduction

Frontotemporal dementias (FTD) are a diverse group of neurocognitive disorders which varies according to their clinical presentation, neuroradiological features, neuropathology and neurogenetics. The current understanding of this spectrum of disorders encompasses three core clinical syndromes; behavioural variant FTD (bvFTD), nonfluent/agrammatic variant primary progressive aphasia (nfvPPA), and semantic variant PPA (svPPA). In addition, there are disorders such as frontotemporal dementia associated with motor neurone disease (FTD-MND), corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP-S), which are categorised as FTD related disorders. In this review, it is also discussed the various pathologies which are categorised under Fronto Temporal Lobar Degeneration (FTLD), genetics and therapeutics.

In 1892, Arnold Pick described a patient with progressive language dysfunction with temporal lobe atrophy in autopsy studies. In the pre brain imaging era, this is the first reported case of FTD[1]. In Pick's cases, Alois Alzheimer demonstrated interneuronal silver staining argyrophilic cytoplasmic inclusions in 1911[2]. They were later known as Pick Bodies. Further developments in clinical understanding, pathology and genetics over a century and especially the last three decades, lead to characterise our current understanding of the FTDs.

Epidemiology

While Alzheimer Disease is the most common type of dementia, FTD is the second most common cause in below 65 years[3]. In the USA, FTD prevalence ranges from 15-22 per 100,000 in the 45-65 years age group, with incidence ranges from 2.7-4.1 per 100,000[4]. This may be underestimating the actual figures, mostly due to under recognition of the condition or attributing it to other clinical conditions mostly as psychiatric disorders.

Behavioural Variant Frontotemporal Dementia

bvFTD is the commonest FTD, which characterises by the initial clinical presentations such as behavioural, emotional, personality and executive dysfunction[5]. They may develop symptoms such as disinhibition, apathy, lack of empathy and dietary changes[6]. These presentations are very likely to mistaken for a psychiatric illness. There are key six categories of symptoms (disinhibition, apathy, lack of empathy, compulsions, hyperorality and executive dysfunction) in diagnosing bvFTD. At least three should be present in order to make a possible bvFTD diagnosis[5] (Table 1).

Disinhibition could manifest as inappropriate behaviour such as overfamiliarity with strangers, inappropriate touching, and disrespecting interpersonal space. They may show impulsive behaviours like new onset gambling or excessive online shopping. Loss of manners or social decorum such as inappropriate comments or jokes to strangers, using rude language without embarrassment are commonly seen[6]. Behavioural disinhibition is linked to degeneration of the right orbitofrontal cortex[7].

Apathy or inertia could manifest as lack of involvement in family or social interactions, reduce drive to move, reduce social conversation or required frequent prompting from others. This could be easily misdiagnosed as depression[6]. Apathy in bvFTD has been correlated with degeneration of the medial prefrontal lobes and anterior cingulate cortex[8].

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Table 1. Diagnostic Criteria for behavioural variant FTD

(Adopted from Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011)[5]

I	Neurodegenerative disease	
	A	Shows progressive deterioration of cognition/behaviour by observation or history
II	Possible bvFTD: 3 of 6 must be present	
	1	Behavioural disinhibition
	2	Apathy/inertia
	3	Loss of sympathy or empathy
	4	Perseverative, stereotyped or compulsive/ritualistic behaviour
	5	Hyperorality and dietary changes
	6	Executive dysfunction with relative sparing of episodic memory and visuospatial function
III	Probable bvFTD; All (A-C) must be present	
	A	Meets criteria for possible bvFTD
	B	Exhibits significant functional decline
	C	Imaging results consistent with bvFTD
IV	Behavioural variant FTD with definite FTLD Pathology	

Lack of empathy or sympathy is common in bvFTD. These symptoms may especially be noticeable in the sorrowful events of the loved ones. Another aspect of bvFTD may be that the patient may not be concern of the impact and consequences of their diagnosis of bvFTD to others (frontal anosodiaphoria)[9]. Lack of empathy has been correlated with degeneration of subcallosal gyrus in bvFTD and right temporal lobe in svPPA[10].

Perseveration or stereotypies could be simple repetitive actions like tapping, lip smacking or more complex actions like collecting usually uninterested things which otherwise would end up in trash bin, walking repeatedly in same routes or counting rituals. Perseveration and stereotypies in bvFTD reported to be associate with degeneration in several brain areas[6].

Hyperorality and dietary habits could manifest as developing a sweet tooth, overeating and weight gain. Later in bvFTD, hyperorality may complicate with oral exploration which may end up with eating inedible things. Hyperorality has been strongly correlated with orbital frontal cortex, striatum and right insular cortex[11].

Executive dysfunction in bvFTD should be differentiated from Alzheimer disease. Presence of episodic memory and visuospatial function are useful markers in favour of bvFTD. Executive dysfunction in bvFTD could manifest as poor performances in jobs, unsuccessful investments or poor planning. Dysexecutive syndrome is strongly related to dysfunction of dorsolateral prefrontal cortex[12].

Neurocognitive assessment of bvFTD could initially be normal and a strong index of suspicion is required. Mostly the initial clues to the diagnosis would be gathered from the informant's history or by observation. Atrophy of the frontal and/or anterior temporal lobes in MRI/CT or hypometabolism in PET/SPECT would support a probable diagnosis of bvFTD[5].

Primary Progressive Aphasias

In PPAs the language dysfunction is the first symptom to be noticeable. Ninety years after Arnold Pick described the language dysfunction with temporal degeneration, Mesulam coined the term "slowly progressive aphasia" in 1982[13]. He renamed the disorder as primary progressive aphasia later in 1987[14]. There after PPAs were categorised as semantic dementias and progressive non fluent aphasias (PNFA) with some incomplete fitting for "fluent speech disorders with frequent word finding pauses" for nearly two decades until, Gorno-Tempini et al introduced the logopenic variant primary progressive aphasia (lvPPA)[15,16]. Since lvPPA is primarily associated with AD pathology[17], a detailed discussion is not intended in this review (See Table 3).

Semantic Variant Primary Progressive Aphasia

Temporal variants of the FTD spectrum of disorders expands our understanding of the language, behaviour and their neuroanatomical lateralisation. Semantic variant primary progressive aphasia (svPPA) presents with initial symptoms predominantly related to deficits of semantic knowledge. svPPA is about one fourth of FTDs[18]. About 70% of the patients who have predominant left temporal lobe involvement do usually present with semantic deficits. The remaining 30% which have right temporal lobe involvement presents with more behavioural symptoms[19]. Eventually both temporal lobes would get affected and result in an overlap syndrome.

The classic left temporal svPPA is also called as semantic dementia, presents with anomia and problems with single world comprehension[16]. While anomia is not specific for semantic dementia, it is more commonly seen in this variant. Word comprehension problems are initially common for low frequency words (giraffe) than frequently used words (dog). With disease progression, svPPA patients use categorical words (animal instead of dog, vegetable instead of carrot) and later may use very non-specific words (thing/place) more frequently. Semantic dementia patients find it difficult to read and write irregularly spelled words due to the loss of knowledge of that word. They may write "*det*" for debt and pronounce debt as "*deBt*". This phenomenon is named as surface dysgraphia and surface dyslexia respectively[16] (see Table 2).

Right temporal svPPA patients present with behavioural changes such as social isolation, irritability, compulsions[6,19]. They may fail to respond to social cues or facial expressions due to atrophy of right amygdala which is linked with the failure of recognizing the facial emotions[21]. With progression, they lose the ability of facial recognition (prosopagnosia) and eventually may fail to recognise themselves in front of the mirror.

It is interesting that svPPA patients may acquire new artistic abilities after development of their cognitive symptoms. Left temporal variant would develop new visual abilities like painting, while right temporal variant would acquire new writing abilities. But these skills would decline with the involvement of contralateral temporal lobe[6].

Table 2. Diagnosis of semantic dementia

(Adopted from Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology.* 2011)[16]

Clinical diagnosis of svPPA	
A. Both of the core features should be present	
	1. Impaired confrontational naming 2. Impaired single word comprehension
B. 3 of the following 4 should be present	
	1. Impaired object knowledge (esp. for low frequency words) 2. Surface dyslexia or dysgraphia 3. Spared repetition 4. Spared speech production (grammar and motor speech)
Imaging supported svPPA	
A. Clinical diagnosis of svPPA +	
B. Imaging confirmation of at least one of the following	
	1. Predominant anterior temporal lobe atrophy 2. Predominant anterior temporal hypoperfusion/hypometabolism on SPECT/PET
svPPA with definite pathology	
A. Clinical diagnosis of svPPA+	
B. With one of the following must be present	
	1. Histopathologic confirmation of specific pathology 2. Presence of a known pathologic genetic mutation

Table 3. Differentiation of primary progressive aphasias

	svPPA	*nfvPPA*	*lvPPA*
Single word comprehension	lost	intact	intact
Grammar	intact	+/- lost	intact
Fluency	intact	lost	+/-lost (word finding difficulty)
Repetition	intact	affected	affected
Praxis of speech	intact	affected	+/- affected (Phonologic paraphasic errors)

Nonfluent/agrammatic Primary Progressive Aphasia (nfvPPA)

These patients present with initial symptoms of effortful speech and word finding difficulties. With disease progression, the speech become slower and more effortful. They make inconsistent errors of phonation with insertions, deletions and distortions of sounds. This could be appreciated by asking to repeat a complex structured word (hippopotamus, catastrophe). Agrammatism may be absent or subtle initially and may affect in the later stages. Aphemia (significantly impaired speech func-tion with relative sparing of the written language) is a common phenomenon and patients tend to function with writing, typing and other electronic language devices in the initial stages[6,16]. The neuroanatomical correlate of nfvPPA is considered to be Broca's area (Broadman area 44/45)[15]. Apraxia of speech (difficulty produce normal phonation and prosody of speech) was originally described in nfvPPA[16]. However, studies on apraxia of speech are now shedding light on new understanding that initial predominant apraxia of speech is entirely a different entity called Primary Progressive Apraxia of Speech[22,23] while some are believing it is still a subtype of nfvPPA.

Frontotemporal Dementias Related Syndromes

Frontotemporal Dementia with Motor Neurone Disease

The association was noted first after the world war II, in the Guamanian Chamorros as "guam complex" (atypical parkinsonism, MND and FTD). Despite extensive international research, the cause of this association is still unclear and reduced prevalence of guam complex made it to assume that it is an environmental cause rather than genetic[24].

However current FTD-MND syndrome is characterised by coexisting criteria fullfilling FTD and Motor Neurone Disease (MND). FTD-MND patients are having lesser life expectancy than average FTDs. The association is much common with bvFTD than PPAs. The association is now more characterised after the establishment of its histopathological and genetic overlap. There are several genes described such as FUS, TDP-43, CHCHD10, UBQLN2, TBK1, VCP, SQSTM1 and most importantly C9orf72 associated with FTD-MND[25].

Corticobasal Degeneration

Corticobasal degeneration (CBD) was first described on autopsy studies in 1968, by Rebeiz. "Corticodentatonigral degeneration with neuronal achromasia" was the original description of the CBD pathology[26]. Corticobasal Syndrome (CBS) is used to describe the classic clinical syndrome associated with the CBD pathology. There are CBS cases not associated with CBD pathology and vice versa[6]. To diagnose probable CBS, patient should present with asymmetric presentation with two of the following motor symptoms (limb rigidity or akinesia, limb myoclonus, limb dystonia) and two of the following higher cortical functions (limb or orobuccal apraxia, cortical sensory impairment and alien limb phenomenon)[27]. Interestingly CBD is more likely to be symmetric than CBS, while asymmetric cases also do exist. CBD patients typically presents with initial behavioural, language or dysexecutive syndrome that may suggest bvFTD or nfvPPA and later develop motor symptoms such as parkinsonism with axial rigidity[28]. There are no specific biomarkers that predict CBD pathology to date.

Progressive Supranuclear Palsy

Progressive Supranuclear Palsy syndrome (PSP-S) was first described in 1964 by Steele, Richardson and Olszewski and known as the eponymous syndrome of the authors (Steele Richardson Olszewski Syndrome)[30]. There are several sub types of PSP has been described. Williamson in 2009, proposed the most widely used classification. He classified the classic Richardson syndrome as PSP-S. PSP-Parkinsonism (PSP-P) is the most common non-Richardson subtype which differentiate from PSP-S by having tremor and mild levodopa respon-

siveness. PSP-pure akinesia with gait freezing (PSP-PAGF) is a slowly progressive disease despite of severe atrophy in the globus pallidus, substantia nigra and subthalamic nuclei. In addition, PSP-Corticobasal Syndrome (PSP-CBS) and PSP-progressive nonfluent aphasia (PSP-PNFA) have been described[31].

While majority of patients with PSP-S presents with classic PSP syndrome, a minority with bvFTD or nfvPPA can later develop PSP-S or Initial presentation of PSP may eventually progressed to bvFTD or nfvPPA[32,33].

Neuropathology of FTDs

"Frontotemporal lobar degeneration" (FTLD) is a selective neurodegenerative process that results in neuronal loss and gliosis of the frontal and temporal lobes of the brain[34]. The term FTLD also loosely used to group the diverse array of pathological substrates that is associated with FTDs. Some of these pathologies are described with neurodegenerative processes other than the spectrum of FTDs as well.

FTLD-tau is discovered in 1975. In Pick's disease, pick bodies are mainly composed of 3 repeat tau (3R tau). 4 repeat tau (4R tau) is predominantly described in CBS, PSP, globular glial tauopathy (GGT) and argyrophilic grain disease (AGD)[6]. The latter two are rare FTDs and a detailed discussion is not intended in this review (see Figure 1).

TAR DNA- binding protein 43 (TDP-43) is the main neuropathology of FTLD-U (tau negative and Ubiquitin positive) and amyotrophic lateral sclerosis (ALS). There are 4 TDP-43 sub types (TDP-43 Type A, B, C and D). FUS (Fused in Sarcoma) is linked to FET protein family. FET consists of FUS and other RNA/DNA binding proteins of Ewing's sarcoma (EWS) and TATA-binding protein-associated factor 15 (TAF15)[6]. Neuronal intermediate filament inclusion disease (NIFID), Basophilic inclusion body disease (BIBD) are rarely encountered FTLD pathologies.

This diagram summarizes the overlap of FTD spectrum disorders with neuropathology.

A small portion of clinical syndromes being caused by AD pathology. lvPPA is highly correlated with AD pathology.

FTLD-tau
3R (3 repeat tau),
4R (4 repeat tau),
FTLD-TDP(TAR DNA-binding protein 43)
FTLD-FET(fused in sarcoma, Ewing's sarcoma, TATA-binding protein-associated factor 15)
FTLD-UPS(ubiquitin-proteasome system)
aFTLD-U (atypical FTLD with ubiquitin inclusions
NIFID (Neuronal intermediate filament inclusion disease)
BIBD (Basophilic inclusion body disease)

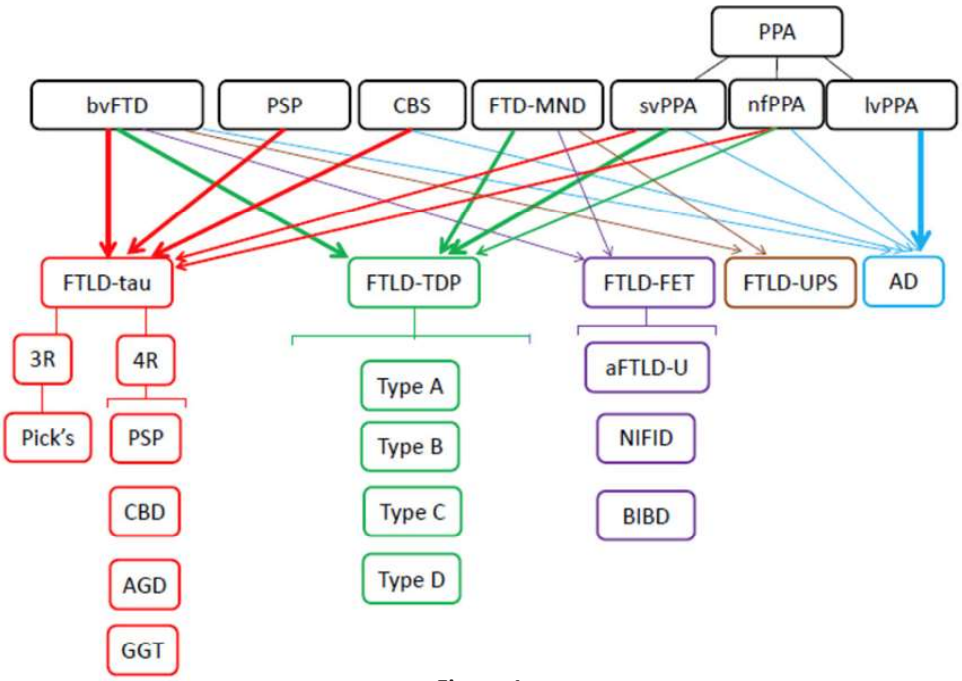

Figure 1.

(Reprinted from *Neurology Clinics* 2017; **35**(2): 339-374, Olney NT, Spina S, Miller BL. Frontotemporal Dementia, with permission from Elsevier.

FTD Genetics

Although majority of FTDs are sporadic, up to 40% can have a family history of dementia, psychiatric disorder or motor symptoms. At least 10% can have autosomal dominant pattern[35]. Genetics are mostly described in FTD-MND which is the most heritable category while svPPA is the group which is least heritable[36].

C9orf72, MAPT and GRN are the three most common genes associated with FTDs. There are several less common genes such as VCP, CHMP2B, TARDBP, FUS, EXT2, TBK1 and SQSTM1 that are associated with FTDs.

Treatment of FTDs

To date there are no FDA approved treatment for FTDs. However, clinicians who are managing patients with FTD, use off-label medication and behavioural therapy. Alzheimer disease treatment has not demonstrated to be useful in FTDs. Sometimes acetylcholine esterase inhibitors may aggravate FTD symptoms.

Off label use of selective serotonin uptake inhibitors (SSRIs) are acceptable for behavioural symptoms[38]. Behavioural symptoms of FTD could also be treated with atypical antipsychotics, but one should be cautious about the potential extrapyramidal side effects.

Nonpharmacological therapies are helpful when there's no specific pharmacological treatment available. Caregiver education and training about behavioural, environmental and physical techniques to redirect unwanted behaviours has been utilized in FTDs[39]. Physical exercise has been demonstrated to delay cognitive decline and should consider in all patients whenever it is safely administrable[40]. Primary progressive aphasia patients may benefit from regular speech and language therapy programme.

Although there is no FDA approved treatment, the expanding knowledge on pathology and neurogenetics has given hope for the researchers for development of several therapeutic targets and several clinical trials are currently underway. A molecular based FTD therapeutic is not hopefully far away.

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