A Comparative Study of Cognitive Decline: Frontotemporal Dementia versus Alzheimer's Disease

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Introduction

Frontotemporal Dementia (FTD) is a common neurodegenerative dementia[1] . FTD accounts for roughly 10-20% of all dementia cases globally, equating to an incidence of 2.7–4.1/100,000 patients[2]. Symptoms can vary between patients but include changes in behavior, communication, and daily function. There is an increase in inappropriate behavior with slurred speech and a decrease in sensitivity to pain in patients with FTD. Memory deficits in patients are common as well. FTD often presents in patients under 65 years old in contrast to some other forms of dementia and is more common in males than females. The life expectancy of those with FTD is 6-8 years after symptoms begin[3]. Patients often succumb to life-threatening pneumonia associated with a lack of hygiene and airway clearance as the disease progresses.

There is no known cause of FTD, however, a family history of dementia is seen in 10-20% of cases. Additionally, some patients present with genetic mutations most commonly seen include C9orf72, MAPT, and GRN with unique geographic distributions[1]. FTD is typically diagnosed through comprehensive blood work, neuropsychological testing, and brain imaging. The disease is progressive and currently, there are no approved disease-modifying drugs available for the treatment of frontotemporal dementia. There are a few symptom management options for patients which include cognitive exercise and physical/occupational therapy.

Due to the lack of definitive diagnostic testing and similarity in symptoms, FTD can be very challenging to differentiate from the various other types of dementia. However, in this review, we will discuss key clinical and patient characteristics and diagnostic testing options to differentiate FTD from Alzheimer's, the most common form of dementia. We will also briefly discuss potential FTD-specific disease-modifying therapies currently being researched.

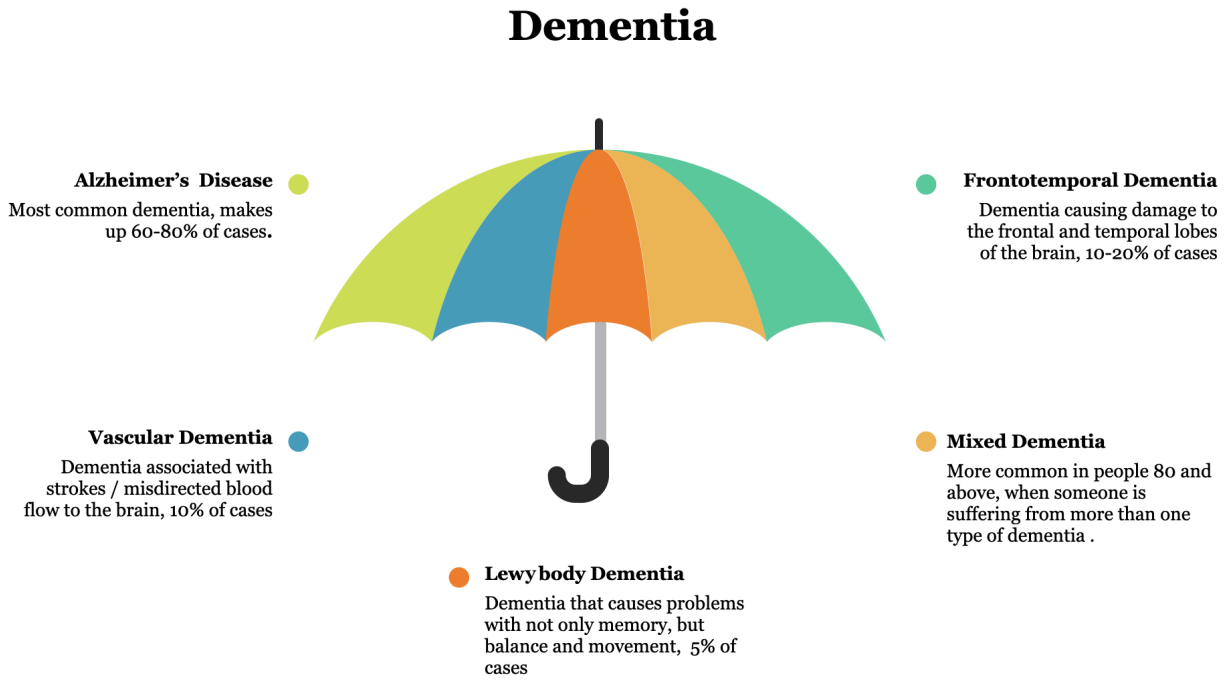

Figure 1: Overview of the types of dementias.

Age

FTD symptoms begin to show between the ages of 40 and 65 with initial findings of changes in behavior and impaired ability to perform daily functions[4]. As the name implies, FTD begins in the frontal and temporal lobes of the brain. The frontal lobe is located at the front of the skull and is generally responsible for cognitive function, emotion control, and motor movement. The temporal lobes are located on both sides of the skull and are involved in processing and storing memories.

On the other hand, Alzheimer's symptoms onset at an average age of 80. Most often, memory loss is the primary complaint. Alzheimer's first affects the entorhinal cortex and the hippocampus which are involved in learning and memory. The entorhinal cortex is found in the medial temporal lobe and the hippocampus is embedded within that lobe. In the advanced stages of FTD, brain damage expands to these areas also, with the symptoms frequently mimicking Alzheimer's.

Both FTD and Alzheimer's are cognitive impairment diseases that cause major disruption in a person's life, but at different stages. *Alzheimer's symptoms display around the age of 80 when people are retired and may not be receiving sufficient activity daily.* As both diseases progress, the symptoms correspond, making initial symptoms the most crucial information for diagnosis.

Since FTD symptoms typically become apparent during middle age, people may be forced to leave their jobs due to their inability to perform efficiently. Since FTD symptoms begin around middle age when people still have daily occupations, symptoms of FTD can impact their jobs. FTD can cause irregular character such as outbursts and hypersexuality which can lead to inappropriate workplace activity and adverse consequences. An early on set preventative measure that can be taken for FTD is avoiding head injuries.

Genetics

While the cause of FTD remains unknown, family history of dementia accounts for 10-20% of cases. The most common genetic mutations include C9orf72, MAPT, and GRN. Genetic mutations that rarely cause FTD are TARDBP, VCP, CHMP2B, SQSTM1, UBQLN1, and TBK1[5]. This section will cover the major genetic drivers of FTD and discuss their pathophysiology and inheritance patterns.

The most commonly mutated gene is C9orf72 which accounts for about 25% of familial cases of FTD. The normal function of C9orf72 is the regulation of autophagy, a mechanism by which cells remove dysfunctional molecules and vesicular trafficking. Hexanucleotide repeat expansion of six nucleotides (GGGGCC) is the most common type of C9orf72 mutation[6,7,8]. The hexanucleotide is repeated normally less than 17 times in healthy patients however in FTD this expansion occurs more than 30 times and potentially even thousands. There are several current theories regarding the deleterious effects of the expansion however the prevailing thought is that it leads to haploinsufficiency. This idea leads to impaired autophagy and vesicle trafficking which increases neuronal damage and impairs microglia and macrophage functions[9]. Hexanucleotide repeat expansion of C9orf72 is also seen in Amyotrophic lateral sclerosis(ALS). Genetic testing of C9orf72 is often conducted for ALS however patients with a family history of FTD are encouraged to get genetic testing and counseling.

MAPT gene mutations account for 5-20% of FTD familial cases. The standard function of MAPT is to provide instructions for production of tau, a protein found in the nervous system. The V337M MAPT mutation[10,11] is correlated with FTD. MAPT mutations are linked to the *accumulation of hyperphosphorylated* tau protein in both neurons and glial cells. V337M mutations increase the composition of tau into filaments. V337M mutations cause an exchange of valine for methionine at position 337 of TAU. Genetic testing for V337M mutation is not customary.

GRN gene mutations are involved in 5-20% of FTD inherited cases. GRN is involved in making progranulin, a protein found that assists in the conservation of neurons and microglia. Arg493Ter[12], or R493, is the most common GRN gene mutation and stops the customary production of progranulin and cuts the production in half. The inheritance pattern of Arg493 is incomplete, autosomal dominant. Diseases associated with this Arg493Ter also include CLN11

disease, a condition focused on continuous seizures, balance problems, and vision impairment. One altered allele of GRN is associated with FTD, but two copies are associated with CLN11. Testing for Arg493Ter is infrequent.

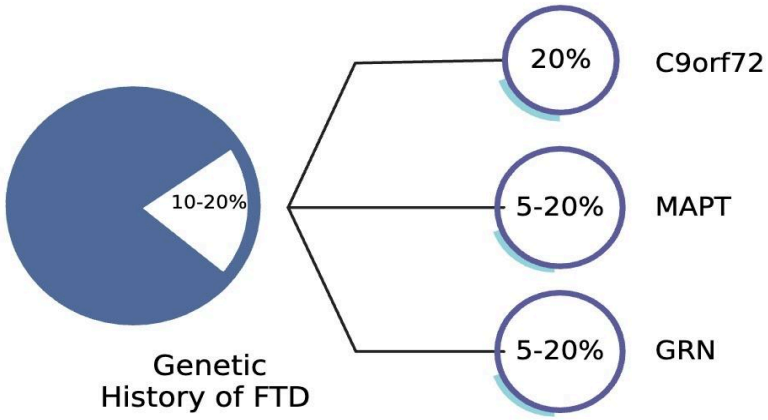

Figure 2: Percentage of genetic mutations within FTD patients.

Diagnosis

Due to similarities between FTD and Alzheimer's, the age of the patient is a key factor when diagnoses are made. Initial symptoms are important in the diagnosis as well. Alzheimer's patients have a diagnostic age of 65 and above. Hallucinations are a symptom associated with Alzheimer's patients more than those with FTD. Personality changes and difficulty with language are the initial symptoms of FTD patients[13].

FTD is diagnosed through meeting 3 of the 6 criteria[14,15] .

(1) early disinhibition, or to be unable to stop improper behavior. Ex. Loss of manners in social settings, rude comments and impulsivity.
(2) early inertia, or loss of ability to act in day to day life.
(3) early loss of sympathy or empathy, or no longer having compassion for others. Ex. unable to understand others feelings.
(4) preservative, stereotyped, or compulsive behavior, meaning to be fixated on a specific subject.
(5) hyperorality and dietary changes, usually referring to overeating and putting non-edible objects in your mouth.
(6) neuropsychological profile with executive dysfunction and relative preservation of episodic memory and visuospatial abilities. This refers to someone who has difficulty controlling their thoughts and actions while also still having the ability to recall past memories.

Table 1: FTD Diagnosis Criteria (need 3/6)
1. Early Disinhibition
2. Early Inertia
3. Early loss of sympathy or empathy
4. Preservative, stereotyped, or compulsive behavior
5. Hyperorality and dietary changes
6. Neuropsychological Profile Deficits

Cognitive assessment exams are also used to diagnose FTD such as The Frontal Assessment Battery[16]. FAB is a cognitive test that assesses the function of the frontal lobe. Patients must already be diagnosed with mild dementia in order to use the FAB[17]. A cutoff score of 12/18 on the FAB allows differentiation between FTD and mild Alzheimer's (sensitivity 77% and specificity 87%).

MRI imaging greatly assists in confirming FTD rather than diagnosing. MRI imaging can track FTD in the brain by following the destruction path of the disorder, beginning with the frontal and temporal lobes. Alzheimer's first damages the hippocampus and entorhinal cortex.

Conclusion

Frontotemporal Dementia is a neurodegenerative disease accounting for about 20% of all dementia cases with no known cause. Cognitive therapy is the most common treatment for managing FTD symptoms. Signs of FTD appear between ages 40 to 65 while Alzhiemer's symptoms begin around 80. Symptoms of FTD include inappropriate or irregular behavior as well as difficulty with communicating. Family history of dementia accounts for 10% to 20% of FTD cases. Genetic mutations that are most frequently seen in FTD patients are C9orf72, MAPT, and GRN. When diagnosing FTD personality changes and language issues are the usual indicators. Initial symptoms are also essential in diagnosis because of the similar pathways the diseases take as they progress. The biggest unmet need regarding FTD is the need for greater recognition of the condition in general, which can lead to earlier diagnosis and treatment that can improve the cognitive ability of patients rather than suppress the symptoms. Increasing awareness will assist in expanding research on FTD for future developments.

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