Genetics of Frontotemporal Dementia

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ABBREVIATION: FTD = frontotemporal dementia

HISTORY OF FRONTOTEMPORAL DEMENTIA

In 1892, Arnold Pick, a neuropsychiatrist at the University of Prague, made the first description of frontotemporal dementia (FTD). In his case report, "On the relationship between senile atrophy of the brain and aphasia," he described a 71-year-old man who developed progressive aphasia and apraxia. Upon autopsy, the patient's brain showed asymmetric atrophy.[1]

Pathologically, FTD is associated with atrophy of the frontal and/or temporal lobes, gliosis, neuronal swelling, and eventual microvacuolation.[2,3] Pick bodies are hyperphosphorylated tau accumulations in the neuronal cytoplasm, which may be found with silver staining but are not pathognomonic for the disease.[4] TAR DNA–binding proteins are hyperphosphorylated, ubiquinated, cleaved proteins and are the most commonly found neuropathology in FTD.[5]

FTD is an uncommon disease compared with other neurodegenerative disorders such as Alzheimer disease. However, in presenile dementia, FTD incidence is similar to that of Alzheimer disease. In a study of 50–59-year-old patients in Rochester, Minnesota, incidence of FTD cases and Alzheimer cases were both found to be 3.3/100,000 person years.[6] In Cambridge, United Kingdom, FTD incidence was found to be 3.5/100,000 person years, whereas Alzheimer disease incidence was 4.2/100,000 person years.[7] Although FTD is considered a presenile dementia, 20%–25% of patients with FTD are older than 65 years. The median survival is 6 ± 1.1 years.[8,9]

WHAT ARE THE CLINICAL MANIFESTATIONS OF FRONTOTEMPORAL DEMENTIA?

FTD has 3 main clinical manifestation groups based on dominant symptoms at diagnosis. The first is the frontal variant or behavioral variant, which may represent 70% of FTD.[5] Frontal variant FTD results in alterations in interpersonal skills and behavior. Persons may show uninhibited behavior, disinhibition, apathy, or new obsessions or rituals, usually first noticed by a close contact of the patient.[2,10]

Progressive nonfluent aphasia variant is another manifestation group where patients present with word-finding difficulty. Speech can become nonfluent, but comprehension remains intact.[2,10]

Semantic dementia group is characterized by the loss of semantic memory. Patients may present with loss of word understanding and the inability to use or recall certain words. Instead, patients use less precise substitute terms and phrases. Speech remains fluent.[2,8,10]

In time, most manifestations of FTD converge and overlap, expressing multiple symptoms causing increased impairment.[5]

ARE THERE GENETIC TYPES OF FTD?

Approximately 20%–40% of FTD cases have a family history of disease, and 10% of FTD cases are inherited in an autosomal dominant fashion.[11] The most notable variants are found in *MAPT* (microtubule-associated protein tau), *C9ORF72*, and *PGRN* (progranulin).[8,10]

Mutations in the gene *MAPT* on chromosome 17 have been found to be associated with Pick bodies and FTD. *MAPT* mutations have been shown to be responsible for 11% of overall FTD cases.[12]

C9ORF72 mutations result in hexanucleotide repeat expansions; however, the mechanism behind this expansion is unclear, and the length of repeats has not been shown to correlate with severity. *C9ORF72* mutations have shown to result in 6% of overall FTD cases.[12]

PGRN gene mutations on chromosome 17 likely result in lysosomal impairment and cause ubiquitin-positive cytoplasmic and intranuclear inclusions. *PGRN* mutations have been found to result in 10% of total FTD cases and 22% of familial FTD cases.[13]

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IS THERE DIAGNOSTIC TESTING FOR FTD?

Currently, diagnosis of FTD is based on clinical characteristic signs of continual change in behavior and language with the exclusion of delirium and psychotic disorders. Imaging is used to confirm the diagnosis by visualizing atrophy at the frontal and/or temporal lobes and exclude other diagnoses, including tumor, stroke, or infection.

WHAT IS THE ROLE OF IMAGING IN FTD?

MR imaging is useful in excluding other diagnoses and can show atrophy of the frontal and/or temporal lobes with sparing of the posterior cortical areas to support the diagnosis of FTD.[14]

Other methods besides the standard T1 MR imaging have recently been used to evaluate FTD. Imaging of patients with frontal variant FTD has shown gray matter atrophy of the frontal and temporal lobes, with the right usually more affected than the left. Other affected structures include anterior cingulate, anterior insula, and subcortical structures. Patients with semantic FTD commonly present with atrophy of the temporal lobes, with the left more commonly affected than the right. Patients with progressive nonfluent aphasia FTD present initially with atrophy in the left inferior frontal lobe, insula, and premotor cortex.[14]

T2 and proton density–weighted MR imaging of FTD have shown increased white matter signal intensity in either the frontal or temporal lobes.[3]

DTI of frontal variant FTD has shown bilateral frontal and temporal lobe changes of the white matter. Semantic FTD has shown asymmetrical (left more than right) changes. Progressive nonfluent aphasia FTD has shown white matter changes in the dorsal language pathways.[14]

Resting-state fMRI has been used to analyze changes in FTD. However, results have been contradictory and inconclusive.[14]

Arterial spin-labeling perfusion MR imaging in frontal variant FTD has shown hypoperfusion in the frontal regions, anterior cingulate, and thalamus.[14]

SPECT and PET in FTD show hypometabolism in the frontal and temporal lobes, with progressive nonfluent aphasia variant showing more hypometabolism in the temporal lobes and frontal variant FTD showing more hypoperfusion in the frontal lobes. This technique may be useful and assist in diagnosis when MR does not show atrophy of frontal or temporal lobes.[2,14]

CONCLUSIONS

Diagnosis of FTD still rests on a characteristic clinical examination. Of the imaging modalities, SPECT and PET studies appear to be a sensitive diagnostic tool. Structural imaging is contributory when atrophy is present; however, characteristic signs of FTD may not be present early in the disease process. Genetic and idiopathic forms of FTD have similar imaging and genetic mutations, suggesting a common pathophysiology.

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