Frontotemporal Dementia

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KEYWORDS

• Frontotemporal dementia (FTD) • Primary progressive aphasia • Nonfluent PPA • Semantic PPA • Motor neuron disease • Progressive supranuclear palsy (PSP) • Corticobasal syndrome (CBS)

KEY POINTS

- The core frontotemporal dementia (FTD) spectrum disorders include behavioral variant FTD, nonfluent/agrammatic variant primary progressive aphasia, and semantic variant PPA.
- Related FTD disorders include frontotemporal dementia with motor neuron disease, progressive supranuclear palsy, and corticobasal syndrome.
- The most common neuropathologic substrates of frontotemporal lobar degeneration (FTLD) are FTLD-tau, FTLD-TDP, and FTLD-FET.
- The 3 genes most commonly associated with FTD are *C9ORF72*, *MAPT*, and *GRN.*
- There are currently no US Food and Drug Administration -approved treatments for FTD.

INTRODUCTION

Frontotemporal dementia (FTD) has undergone numerous changes in nomenclature and categorization schemes since it was first described by Pick in 1892. Presently, FTD encompasses clinical disorders that include changes in behavior, language, executive control, and motor symptoms. Here, the term is used to characterize the core FTD spectrum disorders: behavioral variant FTD (bvFTD), nonfluent/agrammatic variant primary progressive aphasia (nfvPPA), and semantic variant PPA (svPPA). Related FTD disorders discussed include frontotemporal dementia with motor neuron disease (FTD-MND), progressive supranuclear palsy syndrome (PSP-S), and corticobasal syndrome (CBS). The term frontotemporal lobar degeneration (FTLD) is used for pathologic conditions that cause degeneration of frontal and temporal lobes. FTD is a heterogeneous disorder with distinct clinical phenotypes associated with multiple neuropathologic substrates.

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A BRIEF HISTORY OF FRONTOTEMPORAL DEMENTIA

In 1892, Pick,[1] a Czech neurologist, provided the first known description of a patient with FTD. He depicted a patient with progressive deterioration of language associated with left temporal lobe atrophy, a process that would presently be classified as svPPA.[2] Histologic analysis of Pick's clinical cases, performed by Alois Alzheimer in 1911, showed silver staining argyrophilic cytoplasmic inclusions within neurons.[3] In 1923, Gans described "Pick's atrophy" to characterize unique cases with atrophy in the frontal and temporal lobes.[4] By 1926, Pick's students Onari and Spatz expanded on Alzheimer's pathologic description by delineating Pick's bodies from Pick's cells identifying "Pick's disease" as a neuropathologic entity.[4,5]

There was then a dearth of research into dementia until the 1970s. During this period, most clinical, anatomic, and pathologic patterns gleaned by these early pioneers was largely overlooked.[6] Until the late 1950s to early 1960s, a vascular cause was the accepted cause of "senility," purportedly emanating from decreased cerebral blood flow and miniature infarctions and deemed "arteriosclerotic dementia."[7,8] Only a few groups continued Pick's work during this time, using accurate clinical descriptions correlated with neuroanatomical and pathologic analysis. The perseverance of these researchers would not be appreciated until decades afterward. Marginal progress in FTD research was made until Delay, Brion and Escourolle, a French group of researchers, published their seminal paper emphasizing the clinical and neuropathologic differences between (AD) and Pick's disease. Pick's disease was described to feature frontotemporal atrophy with sparing of the posterior lobes with histology revealing ballooned cells and cortical-subcortical gliosis.[4] The clinical syndrome of Pick's disease showed increased behavioral alterations, lack of insight, and relative freedom from apraxia and agnosia.[4] In contrast, AD featured more diffuse cerebral atrophy and on histology showed neurofibrillary tangles and senile plaques. Clinically, Alzheimer patients had symptoms of agnosia, apraxia, and problems with spatial orientation. In 1974, Constantinidis and colleagues[9] divided Pick's disease into 3 subtypes. Only one of the 3 subtypes had classic Pick bodies, suggesting that Pick bodies were not required for a diagnosis of Pick's disease.

By the 1970s, there was a major shift in reasoning: arteriosclerotic dementia was no longer considered the underlying abnormality for senility, and the concept of dementia became associated with Alzheimer neuropathology.[8,10] In 1976, Katzman[11] wrote about an Alzheimer epidemic, suggesting that in the United States 880,000 to 1,200,000 people over the age of 65 may have AD. During this period, the phrase, "don't pick Pick's disease" was often repeated to young researchers looking for careers in neurology, based on the misconception that Pick's disease was both very rare and indistinguishable from AD during life.[6] Although most dementia research in the United States was focused on AD, 2 groups in Europe started following large cohorts of persons with non-Alzheimer dementias. In Lund, Sweden, Ingvar, Gustafson, and Brun found clinical correlation of frontal lobe atrophy with hypoperfusion in the frontal lobes, and only 20% of cases had classic Pick bodies on autopsy.[12,13] In Manchester, England, Neary, Snowden, and Mann described a large cohort of patients with dementia of the frontal type and found clinical correlations with neuroimaging (single-photon emission computed tomography, SPECT), neuropsychiatric testing, and neuropathology.[5] Around the same time, Mesulam[14] described patients with nonfluent and fluent aphasia without Alzheimer abnormality.[5] Mesulam eventually coined the term primary progressive aphasia (PPA).[15] In 1989, Snowden and colleagues[16] suggested the term "semantic dementia" to describe the patient with predominant left temporal atrophy and aphasia that Pick originally described,