The Frontotemporal Dementias

Maria Landqvist Waldö, MD, PhD

KEYWORDS

• Frontotemporal dementia • FTD • Behavioral variant • Progressive aphasia
• Neuropsychiatric symptoms

KEY POINTS

- Frontotemporal dementia is a heterogeneous group of familial and sporadic neurodegenerative disorders primarily affecting the frontal and temporal lobes.
- Misdiagnoses for psychiatric disorders are common, especially in the behavioral variant, which manifests personality and behavioral changes.
- The diagnostics are based on the clinical picture, family history, brain imaging, and neuropsychological and laboratory evaluations, as well as clinical follow-up.
- Neuropathologic classification is based on the type and morphology of protein accumulation in the brain.
- The treatment should focus on managing behavioral symptoms, modifying the environment, and providing support for the families/caregivers.

INTRODUCTION

Frontotemporal dementia (FTD) is a clinical spectrum of neurodegenerative disorders affecting primarily the frontal and/or temporal lobes. Prominent symptoms include personality and behavioral changes as well as language disturbances. Frontotemporal lobar degeneration (FTLD) is the neuropathologic umbrella term for these genetically and neuropathologically heterogeneous disorders, which as a group constitute a common cause of dementia, particularly in younger individuals.

FTD was previously named Pick's disease after the neurologist Arnold Pick, who, around the turn of last century, published a series of cases in which he described the association between dementia with progressive aphasia, behavioral symptoms, and temporal/frontal atrophy.[1,2] Later, the term Pick's disease was used to define only a subset of patients with FTD with specific histopathologic features. In the 1980s, research groups in Lund, Sweden, and Manchester, United Kingdom, described patients with dementia who, on neuropathologic examination, showed frontotemporal degeneration lacking the most typical signs of Pick's disease.[3]

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Section of Geriatric Psychiatry, Department of Clinical Sciences, Lund University, Klinikgatan 22, Lund SE-221 85, Sweden
E-mail address: maria.landqvist@med.lu.se

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The clinical concept of FTD encompasses the behavioral variant FTD (bvFTD) as well as the progressive aphasias semantic dementia (SD) and progressive nonfluent aphasia (PNFA).[4] There is a strong association with amyotrophic lateral sclerosis (ALS), which is partly attributed to overlapping genetic factors.[3,5] Because corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) also overlap with FTD, both clinically and neuropathologically, they are often considered to be part of the FTD complex.[6]

The diagnostic complexity, with regard to clinical, neuropathologic, and genetic aspects, is reflected in the attempts to develop consistent and useful criteria. The nomenclature of FTD has been subject to repeated revisions, discussions, and controversies over the years. New clinical diagnostic criteria were suggested in 2011, both for bvFTD and primary progressive aphasia (PPA) (**Table 1**).[7,8] In 2009, neuropathologic consensus criteria based on protein pathology were introduced, with 3 major subgroups: tau, transactive protein 43 (TDP-43), and fused in sarcoma (FUS).[9]

EPIDEMIOLOGY

FTD is the second most common form of non-Alzheimer dementia, and in young-onset dementia (<65 years) it is almost as common as Alzheimer's disease (AD), representing up to 20%.[10] According to neuropathologic studies, FTD accounts for 5% to 10% of all dementia cases.[10] The disorder is considered to be a mainly young-onset dementia, with mean age at onset of about 58 years.[11] Onset as early as the age of 30 to 40 years, as well as onset after 80 years old, has been described.[10] There seem to be variations in age at onset between different subgroups, with younger onset in bvFTD and SD than in PNFA, in which mean onset is at more than 60 years.[11] Some neuropathologic studies indicate that there could be differences in age at onset between pathologic subgroups, with tau-positive cases being about 5 years older at the time of diagnosis.[12] Mean duration is about 6 to 10 years,[10] and mean survival from diagnosis is about 4 years.[13] However, it is difficult to predict the course of time for an individual patient and no reliable prognostic markers are available. The prevalence of FTD is estimated to be around 15 to 22 per 100,000 in the age group 45 to 65 years[14] and the incidence is 3 to 4 cases per 100,000 person-years.[15] However, diagnostic difficulties and the concept and nomenclature of FTD/FTLD changing over time, in combination with FTD being a relatively uncommon disease, make it difficult to obtain reliable estimates of prevalence and incidence. No convincing gender differences have been found.[6,16] The strongest identified risk factors for FTD are genetic, with FTD being familial in 30% to 50% of cases.[17,18] Other risk factors have not been shown, but a higher risk for FTD after head trauma and an association with thyroid disease have been suggested.[16,19]

BEHAVIORAL VARIANT FRONTOTEMPORAL DEMENTIA

The behavioral variant is the most common clinical syndrome of FTD and accounts for nearly 60% of cases.[16] The onset is gradual and insidious, resulting in a decline from premorbid functioning. The early stage is typically characterized by changes of personality and behavior, with signs of disinhibition, loss of personal and social awareness, and a lack of insight into the present condition. Neglect of personal hygiene, restlessness, distractibility, and mental rigidity are common. Disinhibition, lack of judgment, and loss of insight may lead to socially inappropriate behavior, shoplifting, and traffic incidents. Changes in eating and oral habits, such as overeating, craving sweets, gluttony, mouthing inedible objects, excessive consumption of cigarettes and alcohol, as well as stereotyped ritualistic behaviors, are often present. Echo