Review

Biological Psychiatry

Psychiatric Symptoms in Frontotemporal Dementia: Epidemiology, Phenotypes, and Differential Diagnosis

Daniela Galimberti, Bernardo Dell'Osso, A. Carlo Altamura, and Elio Scarpini

ABSTRACT

Frontotemporal dementia (FTD) is the most frequently occurring dementia in the presenile population. Despite epidemiologic data showing that patients with FTD may have experienced previous psychiatric disorders and that patients with psychotic disorders may develop dementia more often than expected in the nonaffected population, the overlap between these two conditions has been underestimated. Nevertheless, the identification in recent years of several genetic causes of FTD associated with heterogeneous and atypical presentations, including pure psychiatric symptoms, has shifted scientific interest back to obtaining a better understanding of common mechanisms between FTD and psychotic disorders. We review the current knowledge of the FTD spectrum and common features shared by FTD and some psychiatric diseases, starting from Pick's clinical description of the disease, moving toward pathogenic aspects of the disease and genetic causes and associated phenotypes, and finishing with analysis of crossing borders between FTD and psychiatric disorders (mainly represented by schizophrenia and bipolar spectrum disorders) in clinical practice in terms of overlapping symptoms, differential diagnosis, comorbidity, and treatment issues.

Keywords: Bipolar disorder (BD), Frontotemporal dementia (FTD), Frontotemporal lobar degeneration (FTLD), Pick dementia, Psychosis, Schizophrenia (SZ)

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> "Dementia praecox consists of a series of states, the common characteristic of which is a peculiar destruction of the internal connections of the psychic personality. The effects of this injury predominate in the emotional and volitional spheres of mental life."
>
> —E. Kraepelin, 1919

Although the concept of "dementia praecox" as a frontotemporal disorder characterized by psychotic symptoms and dementia in young people was proposed by Kraepelin decades ago (1), few studies investigated the neuropathology of the so-called organic psychoses or secondary schizophrenia (SZ). The first description of a case that would be defined today under the umbrella of frontotemporal dementia (FTD), reported by Pick in 1892 (2), was actually not prototypical. Pick described a 71-year-old woman ("Auguste H.") with marked language disorder, severe comprehension deficit, and semantic and phonemic paraphasias, but with relatively preserved repetition. In addition, she had bouts of aggressiveness. The patient died soon after presenting to Pick, as a result of a febrile disease. Autopsy revealed brain atrophy, more pronounced in the left hemisphere and particularly in the left temporal lobe. This case was cited as the first description of primary progressive aphasia (PPA) (3). Pick described the first case ("Anna H.," 41 years old) of the most common clinical presentation of the disease 12 years later, consisting of behavioral abnormalities, including stereotypy and flattening of affect, now referred as behavioral variant frontotemporal dementia (bvFTD).

FROM PICK'S DISEASE TO FTD

Pick's case descriptions did not include results of microscopic histopathologic examination, which was carried out later by Alzheimer (5), who described argyrophilic intracytoplasmic inclusions and ballooned neurons, which he named Pick bodies and Pick cells, realizing that the changes observed were distinct from changes found in the form of cerebral degeneration later associated with his name. The clinical descriptions and pathologic findings were put together later to form the nosologic entity called Pick's disease (4,6,7). The concept that Pick bodies and Pick cells are not always present in patients with FTD has been recognized for a long time (8) but substantially ignored, along with the observation that no Pick pathology may be present in patients with a clinical presentation consisting of FTD associated with motor neuron disease (MND) (9).

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Research on FTD started in the 1980s, when two groups from Lund, Sweden, and Manchester, United Kingdom, respectively, tried to define this entity better. The two groups agreed on the following: 1) FTD is more than Pick disease, 2) FTD and PPA (with two subtypes, progressive nonfluent aphasia [PNFA] and semantic dementia [SD]) have overlapping pathogenic bases, and 3) many cases show autosomal dominant inheritance (often with an early onset). Clinical criteria were defined for the diagnosis of FTD (10), which were later refined (11), including three clinical syndromes: bvFTD, PNFA, and SD.

The most common clinical presentation, bvFTD, is characterized by behavioral changes and progressive deterioration of personality. Patients may show a wide spectrum of symptoms, including behavioral alterations, such as disinhibition, overeating, and impulsiveness, and impairment of cognitive functions, with relative sparing of memory. Changes in social behavior, loss of empathy, and impairment of social insight are early and consistent symptoms of bvFTD. Patients perform poorly on laboratory-based tasks, including recognizing emotions, attending to salient information that guides social behavior, representing social knowledge, comprehending mental states of others, and maintaining insight to their own difficulties (12). Reviews of clinical features (13–17), clinical criteria (11), and behavioral rating tools for FTD (17) did not include psychotic and other psychiatric symptoms, possibly because of the divergence that occurred in the middle of the 20th century between neurology, which became mainly associated with organic causes, and psychiatry, which focused instead on psychodynamic issues (18).

Understanding of the neurobiology of FTD and its relationship with clinical manifestations of the disease has dramatically increased in recent years, with the discovery of multiple autosomal dominant genetic causes of FTD. Numerous genetic cases with co-occurrence of typical FTD symptoms and psychosis have been described, speeding up the research on common altered mechanisms between FTD and major psychoses, including SZ and bipolar disorder (BD). The focus of this review is on current knowledge of these disorders, in terms of clinical diagnostic criteria, genetic causes, phenotype heterogeneity, and overlapping pathogenic mechanisms.

CURRENT DIAGNOSTIC CRITERIA FOR FTD

In 2011, new criteria for bvFTD were proposed (19) together with a new classification of language presentations (20). According to these criteria, the main feature of bvFTD is the progressive deterioration of behavior or cognition or both based on observation or history (provided by a knowledgeable informant). If this criterion is satisfied, there are three further levels of certainty for bvFTD: possible, probable, or definite. “Possible” bvFTD requires three of six clinically discriminating features. “Probable” bvFTD meets the criteria of “possible” bvFTD with imaging results consistent with bvFTD (i.e., frontal or anterior temporal atrophy on magnetic resonance imaging or hypometabolism on positron emission tomography). “Definite” bvFTD includes histopathologic evidence of FTD hallmarks (postmortem) or the presence of a known pathogenic mutation. These new criteria have a flexible structure to account for the high heterogeneity at initial presentation.

Concerning language presentations, according to new criteria (20), PPA encompasses three presentations: nonfluent/agrammatic variant PPA (previously known as PNFA), semantic variant PPA (previously known as SD), and logopenic variant PPA. Progressive loss of speech, with hesitant, nonfluent speech output with phonetic/phonologic errors and distortions or agrammatism is typical of nonfluent/agrammatic variant PPA (21), whereas loss of knowledge about words and objects, anomia, and single-word comprehension deficits are core features of semantic variant PPA. Logopenic variant PPA is characterized by phonologic disorders, defective word retrieval, and sentence repetition deficits and seems to be associated in most cases with underlying Alzheimer’s disease (AD) pathology (20). Patients with logopenic variant PPA and nonfluent/agrammatic variant PPA have some deficits recognizing emotional prosody, whereas patients with semantic variant PPA show more widespread deficits in social comprehension (21).

Other phenotypes, such as progressive supranuclear palsy syndrome, corticobasal syndrome, and FTD with MND, are part of the clinical manifestations within the FTD spectrum. Considering the heterogeneity of the pathology at the basis of clinical symptoms, the term frontotemporal lobar degeneration (FTLD) (22) is currently used to designate pathologic features of the disease, including three major subtypes, defined by inclusions containing the proteins tau, FTLD-Tau (22); TAR DNA-binding protein (TDP)-43, FTLD-TDP; and fused in sarcoma (FUS), FTLD-FUS (23,24).

GENETICS: AUTOSOMAL DOMINANT MUTATIONS AND ASSOCIATED PHENOTYPES

Although most cases of FTD are sporadic, numerous cases are associated with familial aggregation and are inherited in an autosomal dominant fashion, suggesting a genetic cause (25–27). Up to 40% of patients have a family history, with FTD present or suggested to be present in at least one family member (26,28), with autosomal dominant cases accounting for 13.4% of total cases of FTD (27).

At the present time, three major genes have been associated with the FTD: microtubule-associated tau protein (*MAPT*) (29,30), progranulin (*GRN*) (31,32), and a hexanucleotide expansion in chromosome 9 (*C9ORF72*) (33,34). Valosin-containing protein (*VCP*) (35), charged multivesicular body protein 2B (*CHMP2B*) (36), TAR DNA-binding protein (*TARDBP*) (37), fused RNA binding protein (*FUS*) (38), and sequestosome 1 (*SQSTM1*) (39) are rare causes of familial FTD.

MAPT

The first evidence of a genetic cause for familial FTD came from the demonstration of a linkage with chromosome 17q21.2 in a form of bvFTD with parkinsonism with autosomal dominant inheritance (29), named FTDP-17, characterized pathologically by the presence of Pick bodies. The gene responsible for this association, *MAPT*, was discovered a few years later (30). *MAPT* encodes the microtubule-associated protein Tau, which is involved in microtubule stabilization and assembly. The H1 haplotype in this gene