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Major Depression and Onset of Frontotemporal Dementia

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Purpose: Frontotemporal dementia (FTD) is still a clinical challenge with the highest rate of misdiagnosis and poor outcome. The pathogenetic relationship between depression and neurodegeneration remains unclear. This study evaluated depression prevalence before FTD diagnosis.

Patients and Methods: The aim was to assess the prevalence and impact of depression on FTD diagnostic process. The clinical characteristics of 72 patients hospitalized in Department of Affective and Psychotic Disorders Medical University of Lodz between 2010 and 2020 with final diagnosis FTD were analyzed. The data referring to first psychiatric diagnosis, time from first psychopathological symptoms to clarification of FTD diagnosis were collected. The patients who did not undergo full neuropsychiatric verification were excluded from the analysis.

Results: About 69% of patients had other concomitant diagnosis of mental disorders which was made prior to FTD diagnosis. Among this subsample, 71% revealed depression diagnosis with at least moderate severity. The patients whose first diagnosis was psychotic depression revealed the longest period from the appearance of the first psychopathological symptoms to the diagnosis of FTD in comparison to the subsample with other psychiatric diagnosis (p=0.034; mean 4.33±3.28 years vs mean 2.68±1.39 years).

Conclusion: The severe depressive symptoms in older age may reflect the development of neurodegeneration before full-blown frontotemporal dementia symptomatology. We hypothesized that psychotic depression is a predictor of FTD. Further investigations in this field are required.

Keywords: affective disorders, psychosis, neurodegeneration, cognitive disorders, frontotemporal dementia

Introduction

Frontotemporal dementia (FTD) is both a symptomatically and pathologically heterogeneous disease which develops and accounts for 20–50% of dementia in patients under the age of 65.[1] Approximately 20% have autosomal-dominant genetic mutation,[2,3] the other cases are sporadic. There are currently four clinical variants:[4]

- behavioral variant (bvFTD) with predominant early behavioral and personality changes which is the most common form of FTD umbrella diseases,
- semantic variant of primary progressive aphasia (sv-PPA),
- non-fluent/agrammatic variant of primary progressive aphasia (nfv-PPA),
- logopenic variant of primary progressive aphasia (lv-PPA).

It is known that psychiatric disorders might be a part of dementia phenotype, however, they also might foreshadow the development of the neurodegenerative process. Depression is the most prevalent coexisting noncognitive feature that occurs along with cognitive deficits and is associated with neurodegenerative disorders and cognitive decline.[5] Severe symptoms are especially associated with increased risk of dementia in later age.[6] It is well known that depressive symptoms occur commonly among patients with Alzheimer's disease (AD) (20–40%) and those with vascular dementia (VD) (20%).[7,8] Less is known about the relationship between depression and frontotemporal lobe degeneration. There are

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potentially many etiopathogenic factors associated with depression and neurodegeneration. Depression and dementia are two of the predisposing factors of neuroinflammation. Meanwhile, healthy aging is associated with chronic inflammation, which contributes to increased vulnerability to anxiety and depression.[9] Structural brain changes have been described in both depression and neurodegenerative diseases. Some structural alterations are involved in the etiology of the disease, while others may result from the disease. Reduced overall gray matter volumes, reduced orbitofrontal cortex and gyrus rectus volumes in patients with depression may result in executive function impairment. Moreover, temporal lobe abnormalities like reduced volumes of the hippocampus, right precentral gyrus, left temporal gyrus, right postcentral gyrus, left paracentral gyrus, and left posterior cingulate were found. As a result, abnormal emotional responses and sensory input dysfunction are observed.[10] Additionally, patients with depression also revealed distinct functional alterations of the frontal lobe like reduced activity in the dorsomedial prefrontal cortex, dorsomedial thalamus, supragenual anterior cingulate cortex, and precuneus during self-referential processing of positive stimuli.[11] Recent studies also provide neuropsychological approach to the role of frontal dysfunction in memory, learning, and emotional judgment of patients.[12,13] Meanwhile, cognitive disturbances like attention, short-term memory, psychomotor speed, and executive function are often observed among depressive patients. It seems well established that depression can be the first symptom of dementia, but the time between a depressive episode and the occurrence of dementia is very variable depending on authors. The time from symptom onset to making a diagnosis is significantly longer in individuals with young-onset dementia than among those with late-onset dementia.[14] Patients suffering from neurodegenerative diseases are diagnosed too late, when neurological symptoms are actually noticeable and the disease is already in very advanced stages. However, studies have shown that some of them like, eg, AD probably begins many years before the first symptoms appear. Moreover, among people diagnosed with depression at an old age, the presence of β-amyloid plaques and accumulation of tau protein in the brain years before the presentation of dementia, have been verified.[15] We hypothesize that depression with severe course, especially with psychotic features, is a potential predictor of early frontotemporal neurodegeneration which is usually not diagnosed as dementia in the routine clinical manner.

Materials and Methods

Participants

We analyzed 72 patients with diagnostic ICD-10 (*International Statistical Classification of Diseases and Related Health Problems*) code F02, who were treated in psychiatric wards in Department of Affective and Psychotic Disorders Medical University of Lodz between 2010 and 2020. The main inclusion criterion was final diagnosis of FTD at discharge from the hospital. Primarily, the patients were admitted to the hospital due to other psychiatric reasons. The diagnoses other than FTD were made based on clinical examination by senior psychiatrist according to ICD-10 diagnostic criteria. During hospitalization, the FTD diagnosis was made as the only diagnosis or as comorbidity. The diagnosis was made based on results from psychiatric and neurological exams, functional assessment, neuropsychological testing, and brain imaging. Neuroradiologists interpreted the neuroimaging. The following clinical data were collected: sociodemographic characteristics, psychiatric diagnosis preceding symptoms of FTD, the time since first psychopathological symptoms to diagnosis of FTD, clinical variant of FTD, concomitant somatic diseases, brain imaging, previous psychopharmacotherapy. Based on preliminary analysis of samples, patients who did not meet direct ICD-10 diagnostic criteria for FTD (F02.0) and whose diagnosis was made without brain magnetic resonance imaging (MRI), Single Photon Emission Computed Tomography scan (SPECT) or neuropsychological examination were excluded from the study. Finally, 45 patients' clinical data were investigated, 15 males, and 30 females. The mean age of the participants was 61.8 years. Among evaluated patients the following FTD variants were diagnosed: bvFTD = 34 (75.5%), nfvPPA= 6 (13.3%) and svPPA=5 (11.1%). Twenty five (55.5%) of all evaluated patients had at least one concomitant somatic illness like hypertension, diabetes, hyperlipidemia, thyroid disease. The study group was primarily divided into three subsamples: those with concomitant psychotic depression (F32.3 and F33.3) before FTD diagnosis (FTD1, n=9), those with concomitant other psychiatric diagnosis, ie, moderate and severe depression (F32.1, F32.2, F33.1, F33.2) without psychotic features, anxiety disorder (F41), delusional disorder (F22), bipolar disorder (F31) (FTD2, n=22), and FTD patients without previous psychiatric diagnosis (FTD3, n=14) (Table 1). The psychiatric disorders were diagnosed based on senior

Table 1 Study Groups' Characteristics

Characteristics Mean ± SD	FTD 1 (N= 9)	FTD 2 (N= 22)	FTD 3 (N= 14)
Age (years)	64.67 (±9.23) min=53; max=84	60.09 (±9.16) min=43; max=79	61.86 (±8.28) min=41; max=69
Sex; male:female	1:8	8:14	6:8
Time to diagnosed FTD (years)	4.33 (±3.28) min=2; max=12	2.68 (±1.39) min=1; max=6	1.93 (±1.38) min=0; max=5
	Kruskal–Wallis test: H (2 N=45) p=0.034		
Previous diagnosis (N)			
Depressive disorder/depressive episode	–	14	–
Depression with psychotic features	9	–	–
Bipolar disorder	–	2	–
Anxiety disorder	–	2	–
Delusional disorder	–	4	–
Chronic somatic disorder	5	15	5

Abbreviations: FTD 1, FTD + psychotic depression; FTD2, FTD + other psychiatric diagnosis; FTD3, FTD without previous psychiatric diagnosis.

psychiatrist's clinical assessment and according to ICD-10 criteria. The participants gave written informed consent for inclusion of their medical data into the study. The study was approved by the Ethics Committee of the Medical University of Lodz (RNN/53/18/KE). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013.

Statistical Analysis

The structural characteristics were calculated for the qualitative analysis and the arithmetic mean (x) and median (Me) were calculated for the quantitative characteristics to describe the studied group. To measure the dispersion, standard deviation (SD) was used. The range of the variables tested, ie, the minimum and maximum values were also calculated. Non-parametric tests, such as the Chi^2 Pearson's test, were used for non-measurable characteristics. For nonparametric features, a non-parametric equivalent of the Student's *t*-test was used, and the Mann–Whitney *U* test was applied for unrelated variables. A limit of statistical significance was set at $p<0.05$ for all the analyses. The statistical analysis was performed using the statistica 13th CSS program.

Results

Data analysis indicated that barely 31% (14/45) of participants had FTD solely, however 69% (31/45) of patients had concomitant diagnosis of a mental disorder according to ICD 10 criteria which was made prior to FTD diagnosis. Among this subsample, 71% (22/31) revealed depressive symptoms with at least moderate severity, 29% (9/31) had depression with psychotic features. We found no relationship between FTD variants and the type of previous psychiatric disorders (Ch^2 =1.09, p=0.296) as well as the time to diagnosis of dementia (p=0.616). Moreover, none of the FTD variants was associated with the coexistence of somatic illness.

Among the patients who were previously suffering from depressive symptoms, independent of severity, a tendency to longer time to diagnose FTD was observed in comparison to those with other psychiatric diagnosis (p = 0.089; mean 3.36 ±2.5

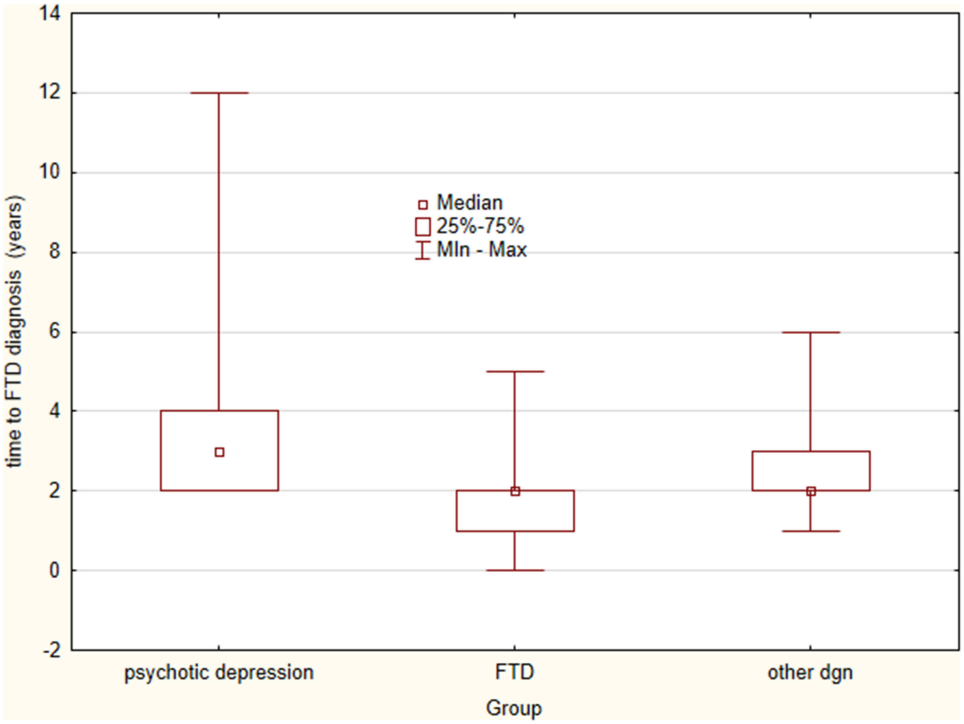

Figure 1 Time until diagnosing FTD in relation to type of previously diagnosed mental disorder.
Abbreviations: psychotic depression, patients previously diagnosed with psychotic depression; FTD group, patients diagnosed first with FTD; other dgn, patients previously diagnosed with other psychiatric disorders.

years vs mean 2.67 ±1.12 years). The subsamples FTD1, FTD2 and FTD3 did not differ according to gender (Ch^2=0.910; p=0.340) and age (F=0.85, p=0.433). The longest period from the appearance of the first psychopathological symptoms to the diagnosis of FTD was demonstrated in those patients whose first diagnosis was psychotic depression in comparison to the subsample with other psychiatric diagnosis (p=0.034; mean 4.33±3.28 years vs mean 2.68±1.39 years) Figure 1.

Discussion

The prevalence of depressive symptoms in FTD is significant. We also found a relatively high rate of major depression diagnosis prior to dementia diagnosis. However, in clinical practice, about 50% of patients with bvFTD is misdiagnosed with primary psychiatric disorder, mainly major depression, not with neurodegenerative disease.[9] Chakrabarty et al,[16] in a meta-analysis of 27 studies, found that 33% of patients with all subtypes of FTD revealed depressive symptoms. However, the prevalence of depressed mood solely was similar among patients with FTD and other dementias like AD, VD or Lewy body dementia, despite the fact that previously this symptom was primarily attributed to individuals with AD.

The insidious onset of behavioral and personality changes is concomitant with the deterioration of executive function in bvFTD. The clashing of behavioral symptoms makes the differential diagnosis challenging, especially in the early stages of illness. Depression and FTD share common symptoms, including lack of interest, decreased motivation, low energy, and impaired concentration. Nevertheless, sustained depressive mood is not such a distinctive feature in patients with FTD. They mainly report apathy and sometimes mood changes, however, their descriptions tend to be shallow. Major depression can also present with anhedonia without pervasive sadness, which can be difficult to distinguish from apathy. It should be noted that often apathy is not experienced as distressing or accompanied by dysphoria.[17,18] Moreover, affected individuals are relatively young at disease onset which can diminish doctors' diagnostic alertness. Depression is the most common non-dementia disease in young adults diagnosed in memory disorder clinics (even 24% of patients).[19] The INSPIRED study[14] revealed that 46.4% of 88 participants with young onset dementia had a comorbid psychiatric diagnosis, however, depression was diagnosed in 30.7%. Interestingly, after the first specialist consultation hardly 5.4% of individuals were referred to a memory clinic. In contrast to our report, those participants were diagnosed mainly with Alzheimer's disease dementia

(53.4%) and FTD was found in merely 15.9% of patients. The latest meta-analysis found that individuals with previous history of depression or anxiety have a greater risk of all-causes dementia.[20] It remains unclear if the prevalence of depression differs between clinical subtypes of FTD. We did not find any relationship between primarily psychiatric diagnosis and FTD variants, however the studied subsamples are relatively too small to draw univocal conclusions.

In many studies the diagnosis of depression among patients with FTD is made based on caregiver reports and presence of depressed mood, which is not enough to determine the final diagnosis.[16] The diagnosis of depression in our study was made using ICD10 criteria, clinical and neuropsychological examination. In contrast to previous reports indicating a mild or moderate depression severity,[21] we found that a significant group of patients suffer from severe depression even with psychotic features. Furthermore, this subsample revealed the longest period before establishing FTD diagnosis. Patients with the most severe depression have dramatic declines in their interpersonal functioning, motivation and exhibit empathy deficits, apathy, and executive dysfunction. We hypothesized that such exacerbated depressive symptoms could confuse the diagnosis of the degenerative process but also diminish family awareness of this diagnosis. Therefore, such patients may reveal insufficient response to antidepressant treatment and may be perceived as having treatment resistant depression.

Depression appears to be linked with FTD, however, its impact is unclear. The following hypotheses should be considered in further research:[22,23]

- depression is a risk factor for FTD.
- Depression is a prodromal syndrome preceding full-blown FTD even for a few years.
- Depression is a strongly linked comorbid diagnosis to FTD, which is an early manifestation of the disease that will later cause dementia.
- Depression is a complication of FTD.

Limitations and Future Directions

Finally, our study covered a relatively small patient sample due to the exclusion of all cases with uncertain diagnosis of FTD. Furthermore, we analyzed clinical data retrospectively. Moreover, the analyzed population consisted of patients primarily hospitalized due to psychiatric disorders other than FTD. The final diagnoses were made ex post, and we included in the analysis only participants who had undergone SPECT. These factors additionally reduced the final study samples. Prospective observation could provide more information about deterioration of neurodegeneration process and its overlapping with depressive symptoms. No data about depression characteristics and potentially specific pattern of symptoms were available. It is known that psychotic symptoms in FTD are more prevalent among individuals with genetic cases with C9ORF72 mutation.[2,24] A significant percentage of investigated patients revealed psychotic symptoms, however they did not undergo any genetic assay in our research. However, for this reason we decided to distinguish patients with psychotic and nonpsychotic depression. Limitations of this study mean that our results are rather a "fishing expedition" and a proposal for further research. Studies exploring whether severe late onset depression is a clinical and biological predictor of frontotemporal degeneration, before full-blown dementia development, are needed.

Conclusion

Neurotransmission and other biological pathways and mechanisms involved in the association of cognitive deficits and major depression remain not clearly understood. It is essential to distinguish between depressive symptoms that can be the very first sign of a frontotemporal degeneration process and the ones which are not linked to neurodegenerative diseases. The prognosis and management is definitely different in FTD and primary psychiatric disorders, therefore early correct differential diagnosis is crucial. The first depressive episode, especially with significant severity, developed at later age but under age 65, should alert the physician to look for a potential neurodegenerative etiology specific for FTD. The identification of risk/prodromal factors becomes essential to prevent the disease and, especially, to prevent late detection/diagnosis of the disease. It seems that FTD, mainly in early stages, is significantly underdiagnosed. We propose the working hypothesis that depression, as one of the first clinical manifestations, can be effectively cured and in that way, at least partially, modifies the clinical course of FTD. Well conducted investigations in this unexplored area might be promising for further treatment outcome of FTD.

Disclosure

The authors report no conflicts of interest in this work.

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