The Diagnostic Challenge of Psychiatric Symptoms in Neurodegenerative Disease: Rates of and Risk Factors for Prior Psychiatric Diagnosis in Patients With Early Neurodegenerative Disease

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Objective: To identify rates of and risk factors for psychiatric diagnosis preceding the diagnosis of neurodegenerative disease.

Method: Systematic, retrospective, blinded chart review was performed of 252 patients with a neurodegenerative disease diagnosis seen in our specialty clinic between 1999 and 2008. Neurodegenerative disease diagnoses included behavioral-variant frontotemporal dementia (n = 69), semantic dementia (n = 41), and progressive nonfluent aphasia (n = 17) (all meeting Neary research criteria); Alzheimer's disease (n = 65) (National Institute of Neurologic and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association research criteria); corticobasal degeneration (n = 25) (Boxer research criteria); progressive supranuclear palsy (n = 15) (Litvan research criteria); and amyotrophic lateral sclerosis (n = 20) (El Escorial research criteria). Reviewers remained blinded to each patient's final neurodegenerative disease diagnosis while reviewing charts. Extensive caregiver interviews were conducted to ensure accurate and reliable diagnostic histories. For each patient, we recorded history of psychiatric diagnosis, family psychiatric and neurologic history, age at symptom onset, and demographic information.

Results: A total of 28.2% of patients with a neurodegenerative disease received a prior psychiatric diagnosis. Depression was the most common psychiatric diagnosis in all groups. Behavioral-variant frontotemporal dementia patients received a prior psychiatric diagnosis significantly more often (50.7%; *P* < .001) than patients with Alzheimer's disease (23.1%), semantic dementia (24.4%), or progressive nonfluent aphasia (11.8%) and were more likely to receive diagnoses of bipolar disorder or schizophrenia than were patients with other neurodegenerative diseases (*P* < .001). Younger age (*P* < .001), higher education (*P* < .05), and a family history of psychiatric illness (*P* < .05) increased the rate of prior psychiatric diagnosis in patients with behavioral-variant frontotemporal dementia. Cognitive, behavioral, and emotional characteristics did not distinguish patients who did or did not receive a prior psychiatric diagnosis.

Conclusions: Neurodegenerative disease is often misclassified as psychiatric disease, with behavioral-variant frontotemporal dementia patients at highest risk. While this study cannot rule out the possibility that psychiatric disease is an independent risk factor for neurodegenerative disease, when patients with neurodegenerative disease are initially classified with psychiatric disease, the patient may receive delayed, inappropriate treatment and be subject to increased distress. Physicians should consider referring mid- to late-life patients with new-onset neuropsychiatric symptoms for neurodegenerative disease evaluation.

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Patients with a neurodegenerative disease often receive psychiatric diagnoses either because their neurodegenerative disease has a psychiatric prodrome or because neuropsychiatric symptoms of the neurodegenerative disease are mistaken for those of a primary psychiatric disorder. Both patterns are seen in Alzheimer's disease, which has a poorly understood relationship with depression,[1] but psychiatric misclassification appears to be particularly common in frontotemporal dementia (FTD). This non–Alzheimer-type neurodegenerative disease consists of several clinical syndromes including behavioral (frontal-variant) frontotemporal dementia (behavioral-variant FTD), semantic dementia (temporal-variant FTD), and progressive nonfluent aphasia.[2] Behavioral-variant FTD is characterized by progressive changes in behavior, mood, and personality.[1] Behavioral changes may include disinhibition, compulsions, loss of insight, social inappropriateness, excessive jocularity, and gluttonous overeating.[2,3] Patients make impaired moral decisions[4] and often exhibit antisocial behaviors such as indecent exposure, erratic driving, and petty theft.[5] Mood disturbances including apathy, euphoria, and irritability are common,[2] while personality changes include loss of interpersonal warmth, empathy, assertiveness, and extraversion.[2] Due to these symptoms, patients with behavioral-variant FTD often initially receive diagnoses of major depressive disorder (MDD), bipolar disorder, or schizophrenia.[6–17] Semantic dementia is characterized by loss of semantic elements of language with preserved grammar and motor speech.[2] Little is known about the psychiatric misclassification of patients with semantic dementia; however, these patients exhibit social and behavioral symptoms that overlap with those of psychiatric disorders.[18] Patients with progressive nonfluent aphasia, who demonstrate agrammatism and motor speech impairment with spared semantic knowledge and single word memory,[2] do not typically develop a significant behavioral syndrome.

Previous case series have lacked adequate power to investigate the extent to which patients receive psychiatric diagnoses prior to a final neurodegenerative disease diagnosis. Furthermore, risk factors for prior psychiatric diagnosis in neurodegenerative disease remain poorly understood. To quantify and characterize rates of psychiatric diagnosis in

patients with various forms of neurodegenerative disease, we performed a systematic, retrospective, blinded chart review of a large sample of patients at a tertiary memory disorders clinic.

METHOD

Subjects

We analyzed charts of 252 consecutive patients seen at our specialty clinic over the last decade (1999–2008): 69 with behavioral-variant FTD, 41 with semantic dementia, and 17 with progressive nonfluent aphasia (all meeting Neary research criteria[19]); 65 with Alzheimer's disease (meeting National Institute of Neurologic and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association research criteria[20]); 25 with corticobasal degeneration (meeting Boxer research criteria[21]); 15 with progressive supranuclear palsy (meeting Litvan research criteria[22,23]); and 20 with amyotrophic lateral sclerosis (meeting El Escorial research criteria[24]). We reviewed clinical histories of patients diagnosed with both amyotrophic lateral sclerosis and another neurodegenerative disease to determine which symptoms developed first. If the earliest symptoms were motor deficits, the patient was placed in the amyotrophic lateral sclerosis group for analysis; otherwise, the patient was placed in the respective neurodegenerative disease group (usually behavioral-variant FTD) for analysis. Reviewers remained blinded to each patient's final neurodegenerative disease diagnosis while reviewing charts. At our clinic, patients were evaluated by a multidisciplinary team who performed behavioral, neurological, and neuropsychological assessments. Extensive caregiver interviews were conducted to ensure accurate and reliable diagnostic histories. All patients signed an institutional review board–approved research consent form.

Assessment of Psychiatric and Neurologic History

For each patient, we recorded history of psychiatric diagnosis, family psychiatric and neurologic history, age at symptom onset, and demographic information. A psychiatric diagnosis was recorded if (1) a psychiatric diagnosis was found in the chart and (2) the psychiatric diagnosis was within 10 years of the eventual neurodegenerative disease diagnosis. Charts, which typically included past medical records, were reviewed to qualitatively determine which symptoms led to the psychiatric diagnosis.

The time interval between psychiatric diagnosis and neurodegenerative disease diagnosis in our clinic was determined. Age at neurodegenerative disease onset was calculated as the age at first verified symptoms attributable to a neurodegenerative disease. One patient was excluded because her psychiatric diagnosis was attributable to a situational factor (MDD diagnosed 1 week after death of a family member). A new team of blinded evaluators reviewed 6 chart passages deemed ambiguous by initial evaluators. Genetic counselors prospectively determined family history information. A family history of psychiatric or neurologic

illness was recorded if the patient had at least 1 affected blood relative.

During their evaluation, patients underwent a series of cognitive, neuropsychiatric, and functional evaluations including the Mini-Mental State Examination,[25] the Clinical Dementia Rating scale,[26,27] the Neuropsychiatric Inventory,[28] and the Geriatric Depression Scale.[29] The Mini-Mental State Examination measures cognitive decline, the Clinical Dementia Rating scale measures neurodegenerative disease severity, and the Neuropsychiatric Inventory is a caregiver interview that measures neuropsychiatric and behavioral disturbances. The Geriatric Depression Scale is a 30-item self-report questionnaire that screens for depression.

Statistics

χ^2 analyses were conducted to determine differences in rates and types of psychiatric diagnoses across neurodegenerative disease groups and to determine differences in family history of psychiatric and neurologic illnesses across neurodegenerative disease groups. General linear models (SAS Proc GLM; SAS Institute Inc, Cary, North Carolina) were used to test differences in age at onset between patients who received a psychiatric diagnosis and patients who did not, as well as to compare cognitive testing scores within neurodegenerative disease groups, using gender and age as covariates in all analyses. Main findings for the general linear model tests are presented as means (standard deviations) and medians (interquartile ranges).

RESULTS

Demographic Data

Overall, there were more men than women with behavioral-variant FTD (2:1 men:women), Alzheimer's disease (1.4:1.0), semantic dementia (1.3:1.0), amyotrophic lateral sclerosis (3:1), and progressive supranuclear palsy (1.5:1.0), but not progressive nonfluent aphasia (0.3:1.0) and corticobasal degeneration (0.8:1.0), in our sample. A detailed summary of demographic information organized by psychiatric diagnosis history and neurodegenerative disease group is provided in Table 1. Patients were predominantly white (>95%).

Psychiatric Diagnosis, Age, Gender, and Education

Seventy-one of 252 patients (28.2%) had a prior psychiatric diagnosis, of which MDD and bipolar disorder were the most frequent (Table 2). No patients were diagnosed with personality or obsessive-compulsive disorders, although some patients did demonstrate obsessive-compulsive behaviors. Significantly more patients with behavioral-variant FTD had a prior psychiatric diagnosis than other groups ($\chi^2 = 18.9$, $P < .001$) (Table 2). Rates of prior psychiatric diagnosis ranged from 50.7% in behavioral-variant FTD (35 of 69 patients), 24.4% in semantic dementia (10 of 41 patients), and 23.1% in Alzheimer's disease (15 of 65 patients) to <12% in the other neurodegenerative disease groups. Patients with behavioral-variant FTD who received a psychiatric diagnosis

Table 1. Demographic and Family History Data and Cognitive Test Scores (total sample = 252)

Psychiatric Diagnosis Status by Neurodegenerative Disease Diagnosis Group	N (number of patients missing family history)	Gender Ratio, Male/Female	Age at Symptom Onset, Mean (SD), y	Education, Mean (SD), y	Patients With Family History, n (%)		MMSE Score, Mean (SD)	CDR Score, Mean (SD)	GDS Score, Mean (SD)
					Neurodegenerative Disease History	Psychiatric History			
Behavioral-variant frontotemporal dementia									
With psychiatric diagnosis	36 (1)	0.57	51.1 (10.0)[a]	16.1 (3.1)[b]	12 (33.3)	17 (47.2)[c]	22.2 (8.8)	1.4 (0.8)	9.3 (6.2)
Without psychiatric diagnosis	33 (4)	0.76	56.8 (7.1)	14.9 (3.1)	13 (39.4)	6 (18.2)	23.1 (6.7)	1.2 (0.7)	5.8 (6.6)
Alzheimer's disease									
With psychiatric diagnosis	15 (0)	0.67	55.1 (7.9)	14.7 (2.7)	5 (33.3)	4 (26.7)	18.7 (7.0)	0.9 (0.6)	5.8 (4.2)
Without psychiatric diagnosis	50 (1)	0.56	57.5 (9.0)	15.8 (3.2)	25 (50.0)	11 (22.0)	21.6 (6.6)	0.9 (0.5)	7.7 (5.1)
Semantic dementia									
With psychiatric diagnosis	10 (2)	0.50	54.6 (5.3)	16.4 (2.4)	4 (40.0)	1 (10.0)	20.9 (10.1)	1.1 (0.9)	7.7 (7.2)
Without psychiatric diagnosis	31 (1)	0.58	59.7 (7.4)	15.7 (3.1)	9 (29.0)	6 (19.4)	21.4 (7.2)	0.8 (0.5)	6.9 (3.7)
Progressive nonfluent aphasia									
With psychiatric diagnosis	2 (0)	0.50	55.0 (7.1)	18.0 (0.0)	0 (0)	0 (0)	17.0 (0.0)	0.5 (0.0)	2.0 (0.0)
Without psychiatric diagnosis	15 (1)	0.20	62.8 (8.6)	15.1 (3.3)	5 (33.3)	4 (26.7)	25.4 (3.9)	0.4 (0.3)	7.8 (5.9)
Amyotrophic lateral sclerosis									
With psychiatric diagnosis	2 (2)	1.00	55.5 (0.7)	15.0 (0.0)	...	...	28.0 (1.4)	1.5 (0.7)	11.5 (7.8)
Without psychiatric diagnosis	18 (0)	0.72	55.4 (10.2)	16.1 (2.2)	11 (61.1)	5 (27.8)	24.9 (7.6)	0.9 (0.7)	8.5 (4.6)
Corticobasal degeneration									
With psychiatric diagnosis	2 (2)	1.00	62.0 (12.7)	19.0 (0.0)	...	...	27.0 (1.4)	0.8 (0.4)	2.5 (0.7)
Without psychiatric diagnosis	23 (0)	0.39	59.4 (8.0)	15.1 (2.3)	7 (30.4)	4 (17.4)	20.7 (6.9)	0.9 (0.7)	8.5 (5.7)
Progressive supranuclear palsy									
With psychiatric diagnosis	4 (4)	0.50	59.0 (6.7)	17.5 (5.0)	...	...	27.4 (2.9)	0.8 (0.3)	11.2 (3.4)
Without psychiatric diagnosis	11 (2)	0.64	63.4 (7.0)	16.7 (3.4)	7 (63.6)	0 (0)	27.3 (2.1)	0.6 (0.3)	12.5 (7.6)

[a]Significant compared to patients without a psychiatric diagnosis in the same neurodegenerative disease group, $P < .001$.
[b]Significant compared to patients without a psychiatric diagnosis in the same neurodegenerative disease group, $P < .05$.
[c]Significant compared to patients who did not have behavioral-variant frontotemporal dementia and received a psychiatric diagnosis, $P < .01$.
Abbreviations: CDR = Clinical Dementia Rating scale, GDS = Geriatric Depression Scale, MMSE = Mini-Mental State Examination.
Symbol: ... = missing data for subgroup.

were younger (mean age, 51.1 [10.0] years vs 56.8 [7.1] years; median age, 52 [45.50–57.00] years vs 56 [52.25–60.75] years; $F_2 = 8.84$; $P < .001$) and more educated (mean education, 16.1 [3.1] years vs 14.9 [3.1] years; median education, 16 [15.5–18.0] years vs 16 [12.0–16.0] years; $P < .05$) than those who did not receive a psychiatric diagnosis (Table 1). Women with behavioral-variant FTD received a psychiatric diagnosis more often than men with behavioral-variant FTD ($P < .05$) (Figure 1).

Neuropsychiatric Symptoms

Patients with behavioral-variant FTD given a prior psychiatric diagnosis scored lower on the Neuropsychiatric Inventory delusions subscale when compared to behavioral-variant FTD patients who were not given a psychiatric diagnosis ($P < .05$). Patients with semantic dementia given a prior psychiatric diagnosis scored lower on the irritability subscale than patients with semantic dementia who were not given a psychiatric diagnosis ($P < .05$). There were no differences in other Neuropsychiatric Inventory subscales (data not shown for Neuropsychiatric Inventory) or in Mini-Mental State Examination, Geriatric Depression Scale, or Clinical Dementia Rating scale scores in patients with and without psychiatric diagnoses across neurodegenerative disease groups (Table 1). Initial symptoms leading to prior psychiatric diagnoses are documented in Table 3.

Family History

Patients with behavioral-variant FTD were more likely to have a family history of psychiatric illness compared to those with other neurodegenerative diseases ($\chi^2 = 22.3$, $P < .01$), and patients with behavioral-variant FTD who were given a psychiatric diagnosis had higher rates of family history of psychiatric illness than behavioral-variant FTD patients who had not received a psychiatric diagnosis ($\chi^2 = 5.1$, $P < .05$) (Table 1).

Referral Period

The mean delay between receiving psychiatric and neurodegenerative disease diagnoses was 33.3 (3.4) months. For patients previously diagnosed with MDD, the delay was 33.9 (4.6) months, while with bipolar disorder there was a delay of 32.2 (7.9) months. One behavioral-variant FTD patient diagnosed with schizophrenia had a delay of 81 months and the other a delay of 2 months.

Table 2. Characterization of the Psychiatric Diagnoses Within Each Neurodegenerative Disease[a,b]

| Psychiatric Diagnosis	Behavioral-Variant Frontotemporal Dementia		Alzheimer's Disease		Semantic Dementia		Progressive Nonfluent Aphasia		Total
	Men (n=20), n (%)	Women (n=16), n (%)	Men (n=10), n (%)	Women (n=5), n (%)	Men (n=5), n (%)	Women (n=5), n (%)	Men (n=1), n (%)	Women (n=1), n (%)	Total (N=63), n (%)
Major depressive disorder	13 (65)*	8 (50)*	4 (40)	4 (80)	3 (60)	3 (60)	1 (100)	1 (100)	37 (59)
Bipolar disorder	4 (20)*	4 (25)*	…	1 (20)	…	2 (40)	…	…	11 (17)
Schizophrenia	1 (5)	1 (6)	…	…	…	…	…	…	2 (3)
Anxiety disorder	…	1 (6)	1 (10)	…	1 (20)	…	…	…	3 (5)
Adjustment disorder	…	…	3 (30)	…	…	…	…	…	3 (5)
Other	2 (10)	2 (13)	2 (20)	…	1 (20)	…	…	…	7 (11)

[a]Frequency of psychiatric diagnoses is separated by the eventual neurodegenerative disease diagnosis and gender. The "other" category includes conversion disorder, normal aging, inattention, and pseudodementia.
[b]Patients with amyotrophic lateral sclerosis, progressive supranuclear palsy, progressive nonfluent aphasia, and corticobasal degeneration were excluded from this table for clarity.
*$P<.001$.
Symbol: … = value of zero.

Figure 1. Rates of Psychiatric Diagnosis Within Each Neurodegenerative Disease[a]
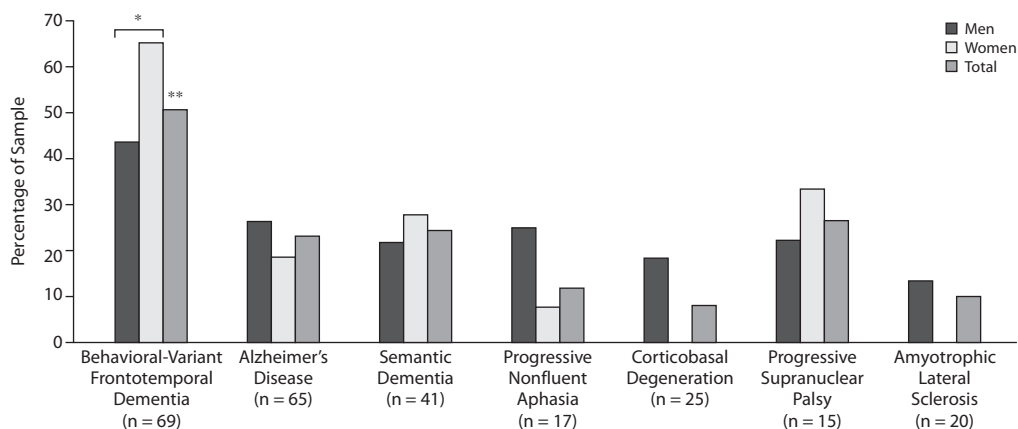
[a]Percentage of patients given a psychiatric diagnosis for symptoms that eventually led to a neurodegenerative disease diagnosis, separated by gender.
*$P<.05$ for comparison of rates of psychiatric diagnosis in men versus women with behavioral-variant frontotemporal dementia.
**$P<.01$ for rates of psychiatric diagnosis in patients with behavioral-variant frontotemporal dementia compared to patients with other forms of neurodegenerative disease.

DISCUSSION

In 252 patients with various forms of neurodegenerative disease, 28.2% received a psychiatric diagnosis prior to neurodegenerative disease diagnosis. Rates of prior psychiatric diagnosis ranged from <12% in patients with progressive nonfluent aphasia, corticobasal degeneration, or amyotrophic lateral sclerosis (disorders with prominent speech, language, or motor impairments) to 24.4% in semantic dementia, 23.1% in Alzheimer's disease, and 50.7% in behavioral-variant FTD (disorders with predominantly cognitive or behavioral symptoms). Across groups, the most commonly observed prior psychiatric diagnosis was MDD, but diagnoses of bipolar disorder and schizophrenia also occurred. While symptom type and severity upon our evaluation were unrelated to psychiatric diagnosis, younger age at symptom onset was associated with increased rates of prior psychiatric diagnosis in behavioral-variant FTD. Most patients (59.1% [42 of 71]) were diagnosed with a psychiatric disorder within 3 years of neurodegenerative disease diagnosis, but 1 patient waited 81 months before her diagnosis

was revised from schizophrenia to behavioral-variant FTD. These high rates of psychiatric diagnosis were driven by several factors including significant symptom overlap between psychiatric disorders and neurodegenerative disease, particularly with behavioral-variant FTD.

Overlap in Symptoms

Early neurodegenerative disease symptoms may mimic psychiatric symptoms, leading to psychiatric misclassification of patients. Apathetic symptoms such as low social engagement, fatigue, and lack of initiation are common in both neurodegenerative disease[2] and MDD and therefore lead to diagnostic confusion.[8] Loss of empathy and emotional blunting are common in behavioral-variant FTD and semantic dementia[2] and may be mistaken for MDD symptoms of social withdrawal or anhedonia. Importantly, behavioral-variant FTD patients rarely complain of subjective sadness,[30] a hallmark symptom of MDD. Furthermore, the profound loss of empathy that characterizes behavioral-variant FTD patients and some semantic dementia patients is unusual with late-life psychiatric disorders. In fact, geriatric

Table 3. Initial Symptoms Leading to Preliminary Psychiatric Diagnosis[a]

Neurodegenerative Disease	Psychiatric Diagnosis	Initial Symptoms
Behavioral variant frontotemporal dementia	Bipolar disorder	Social withdrawal and lack of empathy
	Bipolar disorder	Euphoria, alternating mood, dietary changes, lack of judgment
	Bipolar disorder	Euphoria, disinhibition, impulsivity, alternating mood, compulsive behaviors
	Bipolar disorder	Lack of judgment, disinhibition, compulsive behaviors, euphoria
	Bipolar disorder	Euphoria and hobby changes
	Bipolar disorder	Disinhibition, impulsivity, mental rigidity
	Schizophrenia	Sexual disinhibition, impulsivity, stealing, repetitive speech
	Schizophrenia	Apathy, social withdrawal, poor hygiene, compulsive behaviors
	Major depressive disorder	Heavy drinking
	Major depressive disorder	Profound apathy
	Major depressive disorder	No empathy for wife's breast cancer
	Major depressive disorder	Apathy and lack of empathy
	Major depressive disorder	Apathy and social withdrawal
	Major depressive disorder	Lack of empathy and apathy
	Major depressive disorder	Lack of empathy and lack of insight
	Major depressive disorder	Profound apathy
	Major depressive disorder	Apathy, anhedonia, and social withdrawal
	Major depressive disorder	Lack of empathy, dietary changes, anhedonia, poor hygiene
	Major depressive disorder	Apathy, social withdrawal, and anhedonia
	Major depressive disorder	Lack of judgment and compulsive behaviors
	Major depressive disorder	Cognitive problems
Semantic dementia	Bipolar disorder	Disinhibition, compulsive behaviors, impulsivity
	Major depressive disorder	Apathy, emotional distance, loss of sexual interest
	Major depressive disorder	Memory deficits, dietary changes, insomnia
	Major depressive disorder	Severe lack of empathy
	Major depressive disorder	Memory deficits
Alzheimer's disease	Bipolar disorder	Slight disinhibition and anxiety
	Major depressive disorder	Memory difficulties and mood disturbance
	Major depressive disorder	Reduced speech and movement
	Major depressive disorder	Memory difficulties and mood disturbance
	Major depressive disorder	Memory deficits and stealing
	Major depressive disorder	Memory deficits and disorientation

[a]Categorization of initial symptoms leading to a preliminary psychiatric diagnosis for 32 patients whose medical charts contained appropriate documentation.

patients diagnosed with a psychiatric disorder show increased social anxiety and are more attentive to clinician expectations than either healthy older adults or neurodegenerative disease patients.[30] Patients with behavioral-variant FTD and semantic dementia often display dramatic dietary changes including ritualistic food selection or compulsive overeating, which sometimes results in weight gain,[3] whereas decreased appetite and weight loss are common in Alzheimer's disease.[31] While these dietary changes overlap with symptoms of MDD, compulsive or ritualistic eating and either dramatic weight gain or loss (seen with behavioral-variant FTD with comorbid amyotrophic lateral sclerosis) are more typical of behavioral-variant FTD. Variations on these emotional and eating symptoms were frequently cited as reasons for MDD diagnosis in our sample, suggesting that neurodegenerative disease symptoms were confused with symptoms of primary psychiatric disorders.

Patients with Alzheimer's disease have high levels of subjective sadness,[32] which may lead to high rates of MDD diagnosis; however, in our study, subjective sadness was not often cited as a symptom that led to prior diagnosis of MDD in patients with Alzheimer's disease. In contrast, memory loss was a common reason for patients with Alzheimer's disease or semantic dementia to receive a diagnosis of MDD. Although late-life depression may cause some cognitive impairment (ie, "pseudodementia"), up to 70% of patients with pseudodementia will eventually develop neurodegenerative disease leading to doubts regarding the diagnostic utility of pseudodementia.[33] Personality changes are typical in early Alzheimer's disease, particularly loss of extraversion and social assertiveness,[34] which may be mistaken for MDD-related social withdrawal. Given the high symptom overlap between neurodegenerative disease and MDD, physicians should have a high index of suspicion for neurodegenerative disease in middle-age to late-age patients with new-onset depressive or cognitive symptoms and should refer such patients for specialist consultation to rule out neurodegenerative disease. This has been emphasized by others.[8]

Bipolar disorder was the second most common psychiatric diagnosis and usually occurred in behavioral-variant FTD. Patients ranged in age between 27 and 61 years when diagnosed with bipolar disorder and appear to have been erroneously diagnosed with bipolar disorder due to symptom overlap. Epidemiologic studies suggest that over 8% of new bipolar disorder cases occur in geriatric patients,[35] although even these studies may have inadvertently included patients who had bipolar symptoms due to a neurodegenerative disease. Symptoms of behavioral-variant FTD such as euphoria, disinhibition, impulsivity, poor decision-making, and compulsive behaviors[2] are similar to those seen in primary mania, which may lead to diagnostic confusion. In behavioral-variant FTD, euphoria presents as inappropriate

childlike jocularity (eg, repetitive phrases and jokes) rather than pressured speech and sustained emotional intensity. Disinhibition in behavioral-variant FTD presents as undue familiarity, carelessly voicing insulting observations, petty theft, sexual acting out, or poor financial decisions. However, unlike bipolar disorder patients, behavioral-variant FTD patients are unlikely to demonstrate remorse, even when confronted with the consequences of their behavior. Complex stereotyped movements, vocalizations, and other compulsions are frequent in behavioral-variant FTD and may resemble agitation seen in patients with bipolar disorder.[2] In behavioral-variant FTD patients, however, these symptoms typically have the appearance of mindless habits that are invariant for months, rather than occurring as variable, impulsive expressions of intense emotion, as seen in true mania. Useful symptoms to distinguish behavioral-variant FTD from bipolar disorder include insidious onset and progressive nature, stereotyped movement and speech, prominent disinhibition without remorse, profound loss of empathy and social sensitivity, overeating or compulsive eating fads, lack of insight and concern (ie, "la belle indifference"), and absence of symptom periodicity.

In our sample, 2 patients later found to have behavioral-variant FTD were diagnosed with schizophrenia at ages 33 and 34, late but not unprecedented ages for schizophrenia onset. Neither had psychotic symptoms, but both had behavioral disturbances such as social withdrawal, sexual disinhibition, impulsivity, stealing, hoarding, repetitive speech, and compulsive behaviors, which may have led to a psychiatric diagnosis. Both patients exhibited symptom progression typical of behavioral-variant FTD. Psychotic symptoms occur in approximately 10% of patients with FTD,[36] thus this symptom is not diagnostically definitive. Misdiagnosis of behavioral-variant FTD patients with schizophrenia is documented, and meta-analysis indicates that younger age at behavioral-variant FTD onset is associated with increased risk for schizophrenia diagnosis.[37] While some have argued that this association may be due to an interaction between brain development and neuropathology leading to psychotic symptoms,[37] it is more likely due to misdiagnosis of young patients presenting with personality change, amotivation, and bizarre behavior. It is unusual but not unheard of for patients in their 30s to develop neurodegenerative disease. Up to 50% of patients with FTD have a family history of neurodegenerative disease, often through an autosomal dominant pattern of inheritance,[38] which is rarely observed in schizophrenia. Thus, development of symptoms in the third decade of life or a family history of a highly penetrate illness should raise concern for an underlying neurodegenerative disease.

Shared Etiology Versus Independent Risk Factor

Psychiatric symptoms in patients who go on to develop neurodegenerative disease may represent a prodrome to the neurodegenerative disease or an independent risk factor for developing neurodegenerative disease. These 2 hypotheses are difficult to differentiate and are not mutually exclusive.

For example, MDD occurs in up to 30% of patients with Alzheimer's disease,[1] although the causal direction remains unclear.[1] Depressed patients with Alzheimer's disease have greater reductions in catecholamines (hormones implicated in affective disorders) than nondepressed Alzheimer's patients.[39] Also, MDD is associated with hypofunctioning frontostriatal and limbic circuits,[40] areas damaged in neurodegenerative diseases such as behavioral-variant FTD and semantic dementia,[41] suggesting that MDD may be a consequence of injury to the same regions affected in neurodegenerative disease. Similarly, more severe vascular damage to these circuits causes increasingly worse depressive symptoms in a dose-response relationship.[42] Alternatively, depression may increase the risk for developing Alzheimer's disease and cognitive impairment,[1] possibly through glucocorticoid-induced hippocampal damage in MDD.[1] Patients with Alzheimer's disease in our sample typically received an MDD diagnosis (often for memory loss) within 3 years of being diagnosed with Alzheimer's disease. Our study is not designed to unequivocally demonstrate cause-and-effect relationships, but this tight timeframe and symptom overlap suggest that either MDD can represent a prodrome to Alzheimer's disease or early Alzheimer's disease may be mistaken for MDD but that MDD is unlikely to play a causative role in Alzheimer's disease development.

Age and Family History

Frontotemporal dementia typically occurs in the fifth or sixth decade of life, at which time it is equally prevalent with Alzheimer's disease (FTD: 3.5–4.8 and Alzheimer's disease: 4.2 per 100,000 people aged 45–64 years[43,44]). These rates are roughly 40 times smaller than new-onset MDD (190 per 100,000 people)[45] but similar to rates of new-onset bipolar disorder in this age group (11.3 per 100,000 people).[46] Thus, MDD may be frequently diagnosed in patients with neurodegenerative disease because MDD is more common in this age group.

Measures of depression, cognition, functional status, and neuropsychiatric symptoms did not distinguish neurodegenerative disease patients who received a psychiatric diagnosis, suggesting that no specific symptom clusters were associated with prior psychiatric diagnosis. Patients with behavioral-variant FTD who received a psychiatric diagnosis were significantly younger and more educated than their counterparts who had not received such a diagnosis, which may indicate that more educated individuals are held to different standards during initial evaluation. Patients with neurodegenerative disease who previously received a psychiatric diagnosis had higher rates of family history of psychiatric disorders, which may have biased physicians toward psychiatric etiologies rather than neurodegenerative diseases. Five of 8 behavioral-variant FTD patients diagnosed with bipolar disorder had family histories of bipolar disorder. Between 35% and 50% of patients with an FTD syndrome show a pattern of genetic inheritance,[13] thus these patients' family histories of bipolar disorder may actually represent history of familial FTD that was repeatedly misdiagnosed. Taken

together, these data suggest that youth, education, and a family history of psychiatric diagnosis predispose patients with a neurodegenerative disease to receive psychiatric diagnoses.

Limitations

Because all neurodegenerative disease groups were age-matched to patients with FTD, our sample includes many patients with atypical, early-onset neurodegenerative diseases. Such patients may be especially diagnostically challenging, possibly skewing our data toward higher rates of psychiatric diagnosis. Our study is not designed to determine cause-and-effect relationships (ie, whether a psychiatric disease causes development of neurodegenerative disease or whether the prodrome of a neurodegenerative disease resembles a psychiatric disease). Additionally, we cannot determine the proportion of patients with psychiatric disease in the general population who will develop neurodegenerative disease. Furthermore, our retrospective study design is susceptible to hidden confound bias as well as recall and selection biases. To mitigate against these biases, we included consecutive patients from our center, and reviewers remained blinded to neurodegenerative disease diagnoses. However, our data depend on the quality of physician notes, and we cannot exclude the possibility of systematic bias in documentation. Furthermore, only a subset of patients (63 of 252) had autopsy-confirmed neurodegenerative disease diagnosis, although all 63 autopsied patients were correctly diagnosed by our clinic premortem, testifying to our diagnostic accuracy.

Implications

Up to 18.5 million individuals worldwide will develop a neurodegenerative disease by 2050.[47] Accurate diagnosis of behavioral-variant FTD appears to present a particular diagnostic challenge. Misdiagnosis of neurodegenerative disease leads to ineffective and potentially harmful treatments, delays in organizing proper support, and increased family stress.[48] Accurate diagnosis allows families to begin to cope with their loved one's altered behavior and impaired cognition and allows time to plan for future care, receive counseling, and resolve legal matters. Furthermore, disease-modifying treatments for Alzheimer's disease and FTD are currently in clinical trials, underscoring the importance of early and accurate diagnosis. When patients with neurodegenerative disease are initially classified with a psychiatric disorder, it may cause them to lose precious treatment time during the initial phase of their disease. Physicians must be cognizant that there is significant symptom overlap between neurodegenerative disease and primary psychiatric disorders, that neurodegenerative diseases affecting social and emotional behaviors can begin in the third decade of life, and that new-onset psychiatric symptoms may actually be prodromal to neurodegenerative disease. Because of the importance of early, accurate diagnosis of neurodegenerative disease and the symptom overlap between psychiatric diseases and neurodegenerative diseases, physicians should consider referral to a specialist to rule out neurodegenerative disease in patients who present with new-onset behavioral, emotional, or cognitive changes after age 40. A detailed history, paying particular attention to evidence of insidious onset and progression or focal cognitive impairments, and a sophisticated clinical understanding of how neurodegenerative disease symptoms differ from those of psychiatric disorders are critical.

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