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Cognitive and Noncognitive Neurological Features of Young-Onset Dementia

Brendan J. Kelley Bradley F. Boeve Keith A. Josephs

Department of Neurology, Mayo Clinic, Rochester, Minn., USA

Key Words

Young-onset dementia · Cognitive decline, age of onset · Presenile dementia, clinical features

Abstract

Background: The rarity of young-onset dementia (YOD), the broad differential diagnosis and unusual clinical presentations present unique challenges to correctly recognize the condition and establish an accurate diagnosis. Limited data exist regarding clinical features associated with dementia prior to the age of 45. ***Methods:*** We retrospectively assessed cognitive and noncognitive neurological characteristics of 235 patients who presented for evaluation of YOD to investigate the clinical characteristics of YOD compared to later-onset dementias and to identify clinical features associated with specific etiologies that may aid in the evaluation of YOD. ***Results:*** Multiple cognitive domains were affected in most patients, and no significant differences in affected domains existed between groups. Early psychiatric and behavioral features occurred at very high frequencies. Nearly 80% of this YOD cohort had additional noncognitive symptoms or signs as a feature of their disease. Chorea was strongly associated with Huntington disease. Parkinsonism was not seen in patients having an autoimmune/inflammatory etiology. ***Conclusions:*** The rarity of YOD and the high frequency of early psychiatric features led to frequent misdiagnosis early in the clinical course. The high frequency of noncognitive symptoms and signs may aid clinicians in distinguishing patients requiring a more extensive evaluation for YOD.

Introduction

Young-onset dementia (YOD) defines the population that has developed progressive cognitive and/or behavioral decline between the ages of 17 and 45 years [1]. Etiologies of YOD differ from those causing early-onset dementia (EOD), typically defined as dementia occurring before the age of 65, and from etiologies causing late-onset dementia (patients >65 years old).

Studies of early-onset Alzheimer's disease (AD) have reported differences in verbal fluency and motor-executive functions compared to late-onset AD [2]. Similarly, age-dependent clinical characteristics have been reported for Creutzfeldt-Jakob disease (CJD) [3, 4]. Few studies have investigated clinical characteristics of the more broadly defined EOD, and clinical characteristics of YOD have only been reported in the context of case reports or small case series of specific diseases. Inferences are often made regarding the clinical features of this younger population based upon an imprecise amalgam of these scattered case reports and case series, as well as the collective clinical experience with dementia in older individuals. A more systematic overview of the clinical features associated with YOD is lacking.

We recently reported the demographic and etiological characteristics of a very large cohort of patients who fulfill criteria for YOD [1]. In this study we set out to determine the clinical characteristics of this cohort and to investigate whether certain clinical features are associated with specific etiologies and may have utility for guiding the diagnostic evaluation of YOD.

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Brendan J. Kelley, MD
Department of Neurology, University of Cincinnati
260 Stetson Street, Suite 2300
Cincinnati, OH 45267 (USA)
Tel. +1 513 558 5501, Fax +1 513 558 4305, E-Mail kelleyb3@uc.edu

Subjects and Methods

Our Institutional Review Board approved this retrospective single-cohort investigation. Informed consent was deemed unnecessary for this chart review.

Patient Identification

Search of the electronic medical record from 1996 to 2006 was performed using the Hospital International Classification of Diseases Adapted codes for patients with a diagnosis of dementia or neurodegenerative disorders which may present with onset of dementia between the ages of 17 and 45. This search was limited to outpatients seen at the Mayo Clinic, Rochester, Minn., USA. Medical records were reviewed, and relevant clinical data were extracted and tabulated.

Inclusion Criteria

Included patients had onset after the age of 17 of progressive cognitive and behavioral decline which impaired their ability to function independently. All were referred with clinically recognized cognitive and/or behavioral decline. We required documented evidence of previously normal cognitive functioning until the age of 17. For most patients, completion of high school without requiring special educational assistance was taken as sufficient documentation. For the few individuals not completing high school, evidence of sustained normal cognitive functioning and gainful employment prior to developing progressive cognitive decline was accepted.

Exclusion Criteria

Patients with long-standing static encephalopathy or diagnosed mental retardation were excluded. Patients requiring special education during their academic career were excluded. Those with cognitive deficits referable to a specific incident (e.g. traumatic brain injury, stroke, subarachnoid hemorrhage, ruptured aneurysm) were excluded.

Clinical Data

Age at onset was recorded as the age at which cognitive changes were apparent to the patients, their families or their close associates. Onset was characterized as acute (sudden onset occurring over the course of days), subacute (onset occurring over the course of weeks) or gradual (onset occurring over more than 6 weeks). Clinical course was characterized as progressive, relapsing-remitting or relapsing-progressive. Individuals who progressed from their baseline cognition to severe dementia within 18 months of onset were characterized as rapidly progressive.

Cognitive and behavioral symptoms were reported by the patient, family members and close associates. Physician observations and bedside cognitive tests recorded in the medical record were used to corroborate these reported symptoms. When available, neuropsychological testing was reviewed to further corroborate reported cognitive symptoms. Cognitive and behavioral disturbances were classified by cognitive domain. Symptoms present within the first year after onset were denoted as 'early' and those evident at the time of presentation 'at presentation'. The presence of psychiatric symptoms was recorded for patients who had received psychiatric diagnoses. Although the first clinical diagnoses may not have been readily apparent, the referring diagnosis was recorded for all patients.

Episodic clinical features (such as seizure, nocturnal behaviors or hallucinations) were recorded based upon clinical report. Every patient underwent a thorough neurological examination performed by a member of the neurology department at the Mayo Clinic [5]. The results of these examinations were recorded and reviewed.

Final diagnosis was determined by the evaluating physician's review of all available laboratory, electrophysiological, neuroimaging and pathological data at the last patient contact. Diagnoses were grouped by etiological category (e.g. neurodegenerative, vascular), as in our previous work [1].

Statistical Analysis

Statistical analyses were performed utilizing the JMP computer software (JMP Software, version 6.0.0; SAS Institute Inc., Cary, N.C., USA) with α set at 0.05. Gender ratios and other binomial data (e.g. presence of family history) were compared across groups with the χ^2 test. The Kruskal-Wallis test was used to compare continuous data across groups. The Bonferroni correction was used to account for multiple comparisons.

Results

Application of the inclusion and exclusion criteria to the search results identified 235 individuals appropriate for this study.

Demographic Data

A summary of the basic demographic and etiological data is presented in table 1. Table 2 lists the major etiologies which were identified, grouped by etiological category. Further details regarding the demographics and the composition of these etiological groups have been previously reported [1]. At the time of referral, 29 patients (12.3%) had psychiatric disorders listed as the working diagnosis.

Tempo of Onset and Clinical Course

Significant differences were found between the etiological groups in both tempo of onset ($p < 0.0001$) and in clinical course ($p < 0.0001$). Those having autoimmune or vascular etiologies were more likely to have an acute or subacute onset of symptoms than other etiological groups. Those having a rapidly progressive course were more likely to have had an infectious etiology, although infectious etiologies accounted for only 36% of the rapidly progressive patients [6].

Cognitive and Behavioral Features

Table 3 summarizes these symptoms. Neuropsychological testing was available for 117 individuals. At the group level, memory, attention and executive dysfunc-

Table 1. Demographic data

Female gender	116 (49.4)
Caucasian race	212 (90.2), unknown n = 12
Education, years	13.9 ± 2.4, unknown n = 4
Family history of neurological illness	60 (26), adopted n = 5
Age at onset, years	34.7 ± 7.9
Age at presentation, years	36.7 ± 7.8
Years from onset to presentation	2.0 ± 2.2
Short test of mental status score at presentation (maximum 38)	26.4 ± 8.1 (n = 155, range 3–38), unable n = 48, not recorded n = 32
Onset of cognitive decline	
Gradual	181 (77.0)
Subacute	47 (20.0)
Acute	7 (3.0)
Course of cognitive decline	
Progressive	217 (92.3), rapid n = 22 (9.4)
Relapsing-progressive	14 (6.0)
Relapsing-remitting	4 (1.7)
Etiologies	
Neurodegenerative	73 (31)
Autoimmune/inflammatory	50 (21)
Vascular	14 (6)
Metabolic	25 (11)
Infectious	11 (5)
Other	18 (8)
Unknown	44 (19)

Figures in parentheses are percentages.

Table 2. Etiological data

Group	Major etiologies	n
Neurodegenerative		73
	Frontotemporal dementia	31
	Huntington's disease	18
	AD	4
Autoimmune/inflammatory		50
	Multiple sclerosis	26
	Autoimmune encephalopathy[a]	11
	Neuropsychiatric lupus	10
Vascular		14
	Vasculitis	7
Metabolic		25
	Mitochondrial	13
	Storage disorders	11
Infectious		11
	Prion disease	6
	HIV dementia	3
Other		18
Unknown		44

Etiological groups were mutually exclusive.
[a] Includes Hashimoto encephalopathy.

tion were commonly evident at the time of presentation. Attention was impaired in 166 (71%) and was an early feature in 148 (63%). Executive dysfunction was an early feature in 162 (69%) and evident at presentation in 179 (76%). Taken together, 207 (88%) patients presented with attentional and/or executive deficit, and one or both of these was an early feature in 198 patients (84%). There was no significant difference between etiological groups (p = 0.42).

Personality change was commonly reported and was the most commonly noted early feature, closely followed by behavioral abnormalities (e.g. abnormal eating behaviors). Personality change was reported in 158 (67%) individuals at the time of presentation and was an early feature in 157 (67%). Psychiatric symptoms were reported as an early feature in 114 (49%) and were evident by the time of presentation in 119 (51%). In order of decreasing frequency, psychiatric diagnoses were depression, anxiety, bipolar disorder and psychosis. Behavioral abnormalities were evident at presentation in 123 (52%) and an early feature in 116 (49%). Behavioral abnormalities and/or psychiatric symptoms were present in 164 (70%) and were an early feature in 199 (68%). There was no significant difference in the frequency of these symptoms between etiological groups (p = 0.44).

Language impairment was uncommon, although 55% of the infectious etiology group demonstrated early language impairment, 5 of whom had CJD and 1 of whom had progressive multifocal leukoencephalopathy.

Visuospatial dysfunction was present in 47 (20%) individuals at presentation and was accompanied by visual hallucinations in 9 (19%) of these patients.

Other Neurological Features

Additional neurological symptoms and/or signs were present in 186 patients (79%) at the time of presentation. The details of these abnormalities are outlined in table 4. In 3 individuals, the only abnormality identified was hyperreflexia. After Bonferroni correction, significant between-group differences were identified for parkinsonism (less common in the autoimmune/inflammatory etiologies), chorea (more common in neurodegenerative etiologies), myoclonus (more common in infectious etiologies), seizure (less common in the neurodegenerative etiologies and more common in the metabolic etiologies), optic neuritis (more common in autoimmune/inflammatory etiolo-

Table 3. Cognitive and behavioral features of the entire cohort and each etiological class

	Memory	Language	Praxis	Executive	Attention	Visuo-spatial	Behavioral disinhibition	Psychiatric	Personality change
Early									
Entire cohort	126 (54)	39 (17)	n.a.	162 (69)	148 (63)	41 (17)	116 (49)	114 (49)	157 (67)
Degenerative	31 (42)	9 (12)	n.a.	44 (60)	43 (59)	8 (11)	37 (51)	37 (51)	51 (70)
Autoimmune/ inflammatory	31 (62)	9 (18)	n.a.	34 (68)	31 (62)	10 (20)	24 (48)	22 (44)	32 (64)
Vascular	9 (64)	3 (21)	n.a.	11 (79)	11 (79)	3 (21)	7 (50)	6 (43)	9 (64)
Metabolic	12 (48)	3 (12)	n.a.	18 (72)	18 (72)	5 (20)	14 (56)	15 (60)	17 (68)
Infectious	5 (45)	6 (55)	n.a.	10 (91)	6 (55)	4 (36)	5 (45)	4 (36)	6 (55)
Other	8 (44)	1 (5.6)	n.a.	15 (83)	10 (56)	3 (17)	6 (33)	5 (28)	10 (56)
Unknown	30 (68)	8 (18)	n.a.	30 (68)	29 (66)	8 (18)	23 (52)	25 (57)	32 (73)
p	0.09	0.06	n.a.	0.22	0.69	0.53	0.85	0.31	0.81
At presentation									
Entire cohort	165 (70)	67 (29)	28 (12)	179 (76)	166 (71)	47 (20)	123 (52)	119 (51)	158 (67)
Degenerative	49 (67)	21 (29)	5 (6.8)	53 (73)	54 (74)	10 (14)	40 (55)	40 (54)	51 (70)
Autoimmune/ inflammatory	39 (78)	11 (22)	4 (8.0)	36 (72)	35 (70)	11 (22)	24 (48)	24 (48)	33 (66)
Vascular	9 (64)	5 (36)	2 (14)	11 (79)	11 (79)	4 (29)	7 (50)	6 (43)	9 (64)
Metabolic	16 (64)	7 (28)	5 (20)	22 (88)	21 (84)	5 (20)	14 (56)	15 (60)	17 (68)
Infectious	5 (45)	6 (55)	3 (27)	10 (91)	6 (55)	4 (36)	6 (55)	4 (36)	6 (55)
Other	12 (67)	4 (22)	5 (28)	15 (83)	10 (56)	4 (22)	6 (33)	5 (28)	10 (56)
Unknown	35 (80)	13 (30)	4 (9.1)	32 (73)	29 (66)	9 (20)	26 (59)	25 (57)	32 (73)
p	0.22	0.55	0.13	0.46	0.33	0.63	0.65	0.34	0.95

Data are presented as the number of patients followed by the percentage of the relevant etiological group in parentheses.
n.a. = Data not available.

gies), the presence of visual symptoms (more common in vascular, infectious and metabolic etiologies) and cerebellar dysfunction (more common in autoimmune/inflammatory and infectious etiologies). No between-group differences were found for motor or sensory symptoms.

Five patients were deaf, 1 having a degenerative etiology, 2 having mitochondrial disorders, 1 with Susac syndrome and 1 with an unknown etiology. Six patients had autonomic dysfunction at the time of presentation: 1 with an autoimmune etiology, 1 with a metabolic etiology and 4 with unknown etiology.

Table 5 presents the most common etiologies within these groups that were associated with key clinical features.

Discussion

Cohort as a Whole

Most patients in this large cohort of YOD presented with additional neurological symptoms or signs accompanying their progressive cognitive decline. These symptoms and signs occurred at a much higher frequency than would generally be expected in early-onset AD or other early-onset dementias [7], although few cohorts have reported these data directly. Taken as a whole, our population demonstrates significant heterogeneity, encompassing individuals presenting with a broad range of neurological features in association with progressive cognitive decline. When sorted by etiology, some generalizations become apparent.

Cognitive Domains

As might be expected within a cohort of mixed dementias, dysfunction of multiple cognitive domains was evident at the time of presentation. This was also true of symptoms present within 1 year of onset. No significant differences between etiological categories were found. Although language dysfunction was more commonly reported as an early feature within the infectious group (55 vs. 17% in the overall cohort), this difference did not reach statistical significance. This trend may be due to

Table 4. Additional neurological features of the entire cohort and each etiological class

	Parkinsonism	Chorea	Myoclonus	Seizure	ON	Visual impairment	Motor dysfunction	Hyperreflexia	Hyporeflexia	Sensory changes	Cerebellar dysfunction
Early											
Entire cohort	31 (13)	21 (8.9)	n.a.	44 (19)	14 (6)	24 (10)	47 (20)	n.a.	n.a.	24 (10)	75 (32)
Degenerative	11 (15)	19 (26)	n.a.	3 (4.1)	1 (1.4)	2 (2.7)	7 (9.6)	n.a.	n.a.	5 (6.8)	11 (15)
Autoimmune/ inflammatory	0	1 (2)	n.a.	8 (16)	10 (20)	7 (14)	11 (22)	n.a.	n.a.	6 (12)	25 (50)
Vascular	1 (7)	0	n.a.	2 (14)	1 (7.1)	5 (36)	6 (43)	n.a.	n.a.	1 (7.1)	3 (21)
Metabolic	1 (4)	0	n.a.	9 (36)	0	6 (24)	6 (24)	n.a.	n.a.	4 (16)	9 (36)
Infectious	2 (18)	0	n.a.	1 (9.1)	1 (9.1)	3 (27)	2 (18)	n.a.	n.a.	1 (9.1)	6 (54)
Other	5 (28)	0	n.a.	8 (44)	0	0	2 (11)	n.a.	n.a.	2 (11)	3 (17)
Unknown	11 (25)	1 (2.3)	n.a.	13 (30)	1 (2.3)	1 (2.3)	13 (30)	n.a.	n.a.	5 (11)	18 (41)
p	0.0004	<0.0001	n.a.	<0.0001	<0.0001	<0.0001	0.03	n.a.	n.a.	0.90	0.0003
At presentation											
Entire cohort	34 (14)	23 (10)	20 (8.5)	46 (20)	14 (6)	29 (12)	50 (21)	61 (26)	25 (11)	24 (10)	76 (32)
Degenerative	12 (17)	20 (27)	4 (5.5)	3 (4.1)	1 (1.4)	2 (2.7)	8 (11)	11 (15)	5 (6.9)	5 (6.8)	11 (15)
Autoimmune/ inflammatory	1 (2)	1 (2)	1 (2)	9 (18)	10 (20)	8 (16)	12 (24)	18 (36)	1 (2)	6 (12)	25 (50)
Vascular	1 (7)	0	0	2 (14)	1 (7.1)	6 (43)	6 (43)	8 (57)	1 (7.1)	1 (7.1)	4 (29)
Metabolic	1 (4)	0	2 (8)	9 (36)	0	8 (32)	6 (24)	4 (16)	4 (16)	4 (16)	9 (36)
Infectious	2 (18)	1 (9.1)	7 (64)	1 (9.1)	1 (1.9)	3 (27)	2 (18)	4 (36)	2 (18)	1 (9.1)	6 (54)
Other	5 (28)	0	2 (11)	8 (44)	0	0	2 (11)	3 (17)	2 (11)	2 (11)	3 (17)
Unknown	12 (27)	1 (2.3)	4 (9.1)	14 (32)	1 (2.3)	2 (4.6)	14 (32)	13 (30)	10 (23)	5 (11)	18 (41)
p	0.002	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.04	0.01	0.03	0.90	0.0003

Data are presented as the number of patients followed by the percentage of the relevant etiological group in parentheses.
n.a. = Data not available; ON = optic neuritis.

CJD commonly affecting language and to other infectious etiologies (e.g. progressive multifocal leukoencephalopathy or herpes simplex virus) causing focal damage which affects language functioning.

Personality changes were noted in 67% of the cohort and psychiatric symptoms were an early feature in 49% of the cohort. This is consistent with reports of the high rate of psychiatric symptoms in young-onset CJD cohorts [3, 4] and in EOD cohorts [8] when these have been compared to later-onset CJD and later-onset dementia, respectively. The cause for this high rate of behavioral symptoms in younger patients with dementia is unclear, particularly since they appear to be present early in the course of dementia (rather than as a consequence of longer-standing dementia) [8]. Psychiatric disorders may be more commonly diagnosed in younger individuals, possibly related to increased rates of atypical psychiatric presentations (and consequent underdiagnosis) in the elderly [9] or to increased physician suspicion of psychiatric disorders in younger patients. Dementias in which psychiatric features tend to appear later in the course of cognitive decline (such as AD) are distinctly uncommon etiologies of YOD. This observation is also supported by several epidemiological studies of EOD cohorts [7, 8, 10–15]. Although the relative infrequency of AD within these YOD and EOD populations may account for some of the observed increased frequency of early psychiatric and behavioral features, increased rates of neuropsychiatric features have been noted in early-onset AD populations as well [2, 16]. Further, the similar findings in young-onset CJD and in our YOD cohort suggest that other age-specific factors play an important role.

There may also be bias among neurologists to ascribe cognitive and behavioral symptoms in younger adults to psychiatric disorders. Incomplete recording of initial diagnoses precluded estimating the number of patients in this cohort who initially received a psychiatric diagnosis as the primary cause of their symptoms. Based upon the number who received a psychiatric diagnosis within the first year of symptom onset, one would expect the percentage to be high. At the time of presentation (average of 2 years after onset), the working diagnosis remained psy-

Table 5. Associations of clinical features and etiological groups

Feature	Etiological group	Diagnoses commonly identified	Etiological group less commonly identified
Early language disturbance	infectious	CJD	
Parkinsonism	other		autoimmune (0%)
Chorea	degenerative	Huntington's disease, familial CJD (n = 1)	
Myoclonus	infectious	CJD	
Seizure	metabolic, other		degenerative (4%)
Optic neuritis	autoimmune	multiple sclerosis	
Visual symptoms	vascular, infectious	CJD	
Hyperreflexia	vascular	PACNS	degenerative (15%), metabolic (16%), other (17%)
Cerebellar dysfunction	autoimmune, infectious	multiple sclerosis, CJD	

PACNS = Primary angiitis of the central nervous system.

chiatric in 12.3% of the cohort, despite a clinical course of progressive cognitive decline that had reached the severity of dementia.

Behavioral abnormalities were an early feature in 49% of our cohort. Taken together, early psychiatric symptoms, personality changes and behavioral abnormalities describe a group of symptoms that very commonly accompany progressive cognitive decline in YOD. This constellation of symptoms clearly presents a worrisome situation for the families of these patients, which may include young children. These families should be counseled accordingly. Further, the high rates of attentional and executive dysfunction raise important issues related to safety within the home (both for the patient and for family members), and families should be screened for concerns related to financial oversight, issues related to driving and other daily activities which may expose themselves or others to physical harm and/or exploitation.

Neurodegenerative Etiologies

Neurodegenerative etiologies accounted for 31% of patients in this cohort. Within this group, nearly all presented with gradual onset and progressive course. Chorea was significantly more common in this group, explained by the 18 patients with Huntington's disease within this group.

Frontotemporal dementia represented 13% of patients in our cohort. Only 3 individuals were diagnosed as having AD, and one of these presented with posterior cortical atrophy. Although the rarity of AD in this YOD cohort may account for the lack of early memory disturbance in the neurodegenerative etiological category in comparison to others, the pattern of cognitive decline in early-onset AD has been reported to differ substantially from that of late-onset AD [2, 16].

Autoimmune/Inflammatory Etiologies

Overall, this etiological category described 50 patients in the cohort, among whom 26 had multiple sclerosis and 11 had autoimmune encephalopathy. The construct of 'subcortical dementia' suggests that this etiological category should exhibit more difficulties with attention and executive function, more mood disturbances and fewer memory disturbances in comparison to other etiological categories. This was not, in fact, the case. Attention and executive dysfunction, memory impairment and psychiatric disturbance or early personality change occurred at rates similar to the other etiological categories.

The construct of 'white-matter dementia' [17] predicts that language function would be normal, but the observed frequency of language derangement was similar to that of the other etiological categories. This could be due in part to the inclusion of some patients with leukoencephalopathy in other etiological groups (such as metabolic or unknown).

Extrapyramidal movement disorders would be expected to be an uncommon feature in these patients, and this was confirmed ($p = 0.002$). As would be expected due to the large number of multiple sclerosis patients in this

category, optic neuritis was more common ($p = 0.0001$) in the autoimmune/inflammatory group, and optic neuritis was found in only 4 patients outside of this group. As might be predicted, early cerebellar findings were more common in this group ($p = 0.0003$), with 50% of the group exhibiting cerebellar dysfunction. The only other etiological group with a comparable rate of cerebellar dysfunction was the infectious group, likely related to the substantial number of CJD cases in that group.

Deafness

One might expect deafness to be more common in the metabolic disorders category, as it may be associated with mitochondrial disorders [18]. This was not confirmed in our study. The presence of a patient with Susac syndrome in the vascular category and 1 patient with deafness in the degenerative category, combined with the small number of patients overall who presented with deafness, may account for this.

Associated Seizure Disorder

Seizures were much less commonly found in those having a neurodegenerative etiology, as expected. Patients having seizures as a part of their clinical presentation were found in a variety of etiological groups, but generally had etiologies commonly associated with seizure. Thus, the finding of seizure in the context of YOD may provide an important clue for narrowing the differential diagnosis by the negative association with neurodegenerative etiologies and an increased frequency in those with metabolic disorders. In our cohort, 96% of those manifesting seizures did so within the first year of symptom onset.

Misdiagnosis of EOD is common and can lead to significant delays in diagnosis [19]. This is speculated to be due to the broad differential diagnosis of EOD, the high proportion of non-AD dementias and clinical differences in cognitive, behavioral and other neurological features between EOD and later-onset dementia [20]. Our study underscores that these points are at least equally true of young-onset dementia. The mean time from onset to presentation was 2 years, and all patients had been previously evaluated by one or more neurologists prior to presentation at the Mayo Clinic. A wide variety of diagnoses were established in this cohort, spanning a varied spectrum of etiological groups. Despite exhaustive evaluation, an etiology was unable to be established in 19% of the cohort. Only 3 patients (1.4%) had AD. The high frequency of behavioral and psychiatric symptoms early in the course of disease is quite distinct from the clinical features of later-onset dementia and echoes the findings in young-onset CJD [3, 4] and in well-characterized EOD cohorts [8, 14, 21].

Progressive dementia having onset prior to the age of 45 is rare, and enrolling a large cohort prospectively would be problematic. Selection bias is inherent to single-center retrospective studies, and referral bias towards individuals physically and financially able and willing to travel for evaluation at our center is inherent to this study. However, YOD is an uncommonly encountered clinical circumstance, and such patients are very likely to be evaluated at regional tertiary referral centers to establish a diagnosis. Some conditions, such as HIV dementia and progressive multifocal leukoencephalopathy, are likely underrepresented in our cohort, as these diagnoses may have been established without referral. Thus, the impacts of selection bias are somewhat unclear. Subsequent multicenter regional (or national) studies would be required to address this bias.

Retrospective reporting of early cognitive and behavioral symptoms may be subject to recall bias, whereas neurological examination findings were ascertained through the thorough evaluation by trained neurologists and would not be expected to be liable to bias. By the time of evaluation, most patients had clinically evident impairment of multiple cognitive and behavioral domains, compatible with their diagnosis of dementia. This may in part account for the observation that early cognitive and behavioral symptoms did not distinguish between etiological groups, whereas examination findings did.

Our study explores the clinical spectrum of YOD by a review of 11 years of experience at a tertiary referral center. As such, this cohort provides a valuable window into the clinical spectrum associated with YOD. The significant overlap of clinical features between etiological groups challenges some of the conventional wisdom surrounding clinical features felt to occur (or not occur) in association with certain etiologies. We identified clinical features that may be helpful in guiding further diagnostic evaluations. Further study to better describe this population will aim towards an understanding of how best to approach patients having this challenging clinical presentation.

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