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Early-Onset Dementia: Frequency and Causes Compared to Late-Onset Dementia

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Key Words
Dementia, early onset, late onset · Alzheimer's disease

Abstract
Background: Research on the epidemiology of dementia has focused on the elderly. Few investigations have studied differences in etiologic frequencies between early-onset dementia (EOD), with onset at an age of less than 65 years old, and the more common late-onset disorder. ***Objectives:*** To determine relative frequencies and characteristics of EOD versus late-onset dementia (LOD; age of onset ≥65 years) diagnosed in a large memory disorders program over a 4-year period. ***Methods:*** We reviewed medical records, including an extensive neurobehavioral and neurological evaluation, of all patients seen at a large Veteran's Affairs Medical Center Memory Disorders clinic between 2001 and 2004 and assessed demographic variables, final diagnoses, presence of dementia, and differential diagnosis of dementing illnesses. ***Results:*** Among 1,683 patients presenting for evaluation of an acquired decline in memory or cognition, 948 (56%) met established clinical criteria for a dementing illness. About 30% (n = 278) of these had an age of onset of <65 years, compared to 670 with LOD. Patients were predominantly male (98%). Compared to the late-onset group, the EOD patients were less severely impaired on presentation, but they did not differ in gender distribution or educational background. The EOD group had significantly more dementia attributed to traumatic brain injury, alcohol, human immunodeficiency virus (HIV), and frontotemporal lobar degeneration compared to the LOD patients. In contrast, the LOD group had significantly more Alzheimer's disease compared to the EOD group. ***Conclusions:*** This study, conducted at a Veterans Affairs Hospital, is the largest series to date on EOD, and found a previously unexpectedly large number of patients below the age of 65 with cognitive deficits and impaired functioning consequent to head trauma, alcohol abuse, and HIV. These findings highlight the differential distribution and importance of preventable causes of dementia in the young.

Introduction

Early-onset dementia (EOD), with onset in those younger than 65 years, is a potentially devastating problem. These patients are often actively involved in holding jobs, providing for families, and caring for children when the disease strikes. Clinicians need to have greater famil-

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iarity and understanding of EOD and the range of different diseases and conditions that can cause dementia in a young person [1].

Despite its importance, investigators have paid relatively little attention to EOD, as compared to dementia with age of onset of 65 or older. Focusing only on the impact of dementia in older populations may substantially underestimate the frequency and importance of dementia in younger patients. Moreover, the differential diagnosis of EOD can be especially difficult early in its course. Patients with EOD are more likely than those with late-onset dementia (LOD) to be misdiagnosed, have dementias other than Alzheimer's disease (AD), or have a potentially treatable or preventable etiology [1, 2]. Current work on mild cognitive impairment as a prelude to AD further highlights the importance of early diagnosis of dementing illnesses [3], and this is especially important at a young age.

This study investigated the frequency and causes of EOD, as compared to LOD, among patients evaluated in a memory disorders program. Based in a Department of Veteran's Affairs medical center, this program is dedicated to the assessment of memory and other cognitive impairments and their impact and has evaluated large numbers of patients over the 4 years of this study.

Methods

This study reviewed the records of all patients presenting to the V.A. Greater Los Angeles Healthcare Center Neurobehavior Unit over the 4-year calendar period from January 1, 2001 through December 31, 2004. All patients in this study presented with memory or other related cognitive complaint. Behavioral neurologists and geriatric psychiatrists were in charge of evaluating these patients with comprehensive neurobehavioral tests of major areas of cognition, neurological examinations, laboratory assessments, and magnetic resonance imaging (MRI). Follow-up clinic visits were routinely scheduled for long-term monitoring and management.

The presence of dementia was diagnosed if patients had deficits in two or more domains of cognition sufficient to cause significant impairment in social or occupational functioning and representing a significant decline from a previous level of functioning [4, 5]. Diagnosis of dementia etiologies was made by neurology and psychiatry physicians using established guidelines and practices [5, 6]. Most subjects had a clear and predominant etiology, and for the few who did not, the single most probable etiology was taken. This was done for simplicity and to facilitate comparison between etiologic categories. The age of onset was determined for patients meeting criteria for dementia. Age of onset indicated the approximate beginning of the symptom and was specifically defined as the age at which the earliest conclusive dementia symptom was noticed by the caregiver or patient, or documented in the medical notes and other correspondence. Patients were included in the early-onset group if the onset of symptoms was prior to the age of 65 years, and in the late-onset group if the onset of symptoms was at or greater than the age of 65 years. The traditional age of 65 years was used to divide early- from late-onset subjects to allow comparison with previous studies. All patients underwent structural imaging with MRI (T_1, T_2, and FLAIR sequences) read on the day of acquisition by radiology physicians certified by the American Board of Nuclear Medicine. Neurology and psychiatry physicians used the MRI results in the process of arriving at the clinical diagnosis. The study compared demographic and dementia variables between these EOD and LOD groups. Continuous variables were compared between groups using two-tailed t tests, assuming a normal distribution. Categorical variables were compared between groups using χ^2 analysis.

Table 1. Patient characteristics for EOD vs. LOD

	EOD	LOD
Patients	278	670
Sex (M/F)	270/8	658/12
Handedness (R/L/AMBI/U)	170/28/3/77	427/35/7/201
Ethnic data[1]		
Caucasian	156	372
African-American	84	197
Age of onset[2], years	51.52 ± 10.75	75.22 ± 5.64
Age of presentation[3], years	56.54 ± 9.81	77.69 ± 5.54
Duration of follow-up, months	11.63 ± 16.59	13.40 ± 16.97
Education, years	13.66 ± 2.48	12.90 ± 3.64
Mini Mental State Examination score[4]	23.57 ± 6.09	21.38 ± 6.85

[1] The rest included: 21 Latino, 6 Asian, 11 unknown for EOD; 39 Latino, 17 Asian, 2 Native American, 43 unknown for LOD.
[2] $t = 40.70$, $p < 0.001$.
[3] $t = 36.57$, $p = < 0.001$.
[4] $t = 5.02$, $p < 0.01$.

Results

A total of 1,683 patients were seen and evaluated for memory and related cognitive complaints from 2001 to 2004. Of these, 948 met criteria for dementia (56.3%). Among these dementia patients, 278 (29.3%) had an age of onset of <65 years (mean = 51.52 ± 10.75), and 670 (70.7%) had an age of onset of 65 years or older (mean = 75.22 ± 5.64). There were no significant differences between the EOD and LOD patients in gender distribution, years of education, and duration of follow-up (table 1). At the time of presentation, however, the patients with EOD were less impaired on the Mini-Mental State Examination compared to the patients with LOD ($t = 5.02$, $p \leq 0.009$) [7].

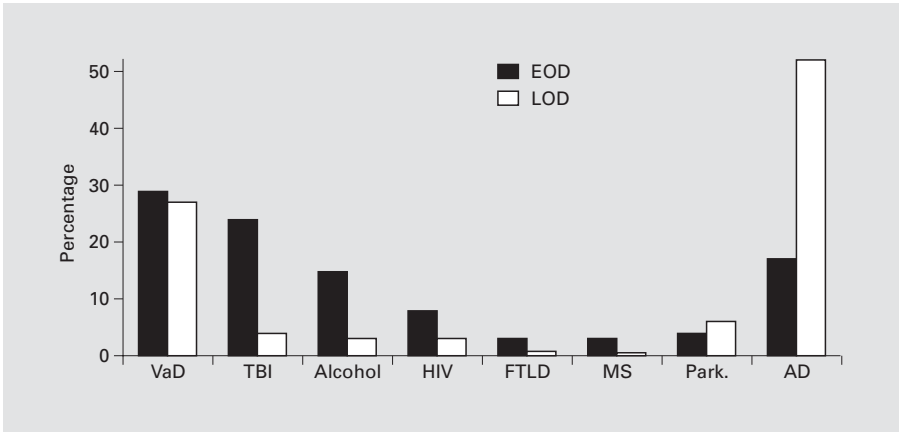

Fig. 1. Relative proportions of significantly different dementia etiologies. MS = Multiple sclerosis; Park. = parkinsonism with dementia. Categories with <3% or miscellaneous are not included.

Table 2. Common diagnostic groups and percentages

Diagnosis	EOD	LOD	χ^2	Significance
AD	48 (17)	348 (52)	89.70	<0.001
VaD	80 (29)	184 (27)	n.s.	
Parkinsonian disorders with dementia[1]	11 (4)	43 (6)	n.s.	
TBI	67 (24)	30 (4)	71.60	<0.001
Alcohol-related	15 (5)	17 (3)	4.05	<0.05
HIV-associated	22 (8)	17 (3)	6.89	<0.01
NPH	6 (2)	7 (1)	n.s.	
FTLD	7 (3)	5 (<1)	4.74	<0.05
Huntington's disease	4 (1)	2 (<1)	n.s.	
Multiple sclerosis	8 (3)	3 (<1)	n.s.	
Dementia NOS	2 (<1)	10 (1)	n.s.	
Miscellaneous[2]	8 (3)	4 (<1)	n.s.	
Total (n = 948)	278 (100)	670 (100)		

NPH = Normal pressure hydrocephalus; dementia NOS = dementia not otherwise specified. Figures in parentheses indicate percentages.

[1] EOD: includes corticobasal degeneration (n = 1), multisystem atrophy (n = 2); LOD: includes corticobasal degeneration (n = 1), multisystem atrophy (n = 1).

[2] EOD: medical conditions (n = 3), sleep apnea (n = 4), Creutzfeldt-Jakob (n = 1), neurosyphilis (n = 2); LOD: medical conditions (n = 3), sleep apnea (n = 2), neurosyphilis (n = 1).

The final dementia diagnoses for EOD and LOD groups are included in table 2. There were significant differences between some of the most frequent diagnoses (see figure 1). Compared to the LOD group, the EOD group had significantly more cognitive impairment from traumatic brain injury (TBI), alcohol abuse, human immunodeficiency virus (HIV), and frontotemporal lobar degenerations (FTLD; primarily frontotemporal dementia). Compared to the EOD group, the LOD group had significantly more AD. Vascular dementia (VaD) was the most frequent EOD, but there were no differences between groups; both had high percentages of this disorder. Although not statistically significant, the LOD group had greater numbers of patients with a parkinsonian disorder with dementia. This latter group primarily included dementia with Lewy bodies and Parkinson's disease with dementia, two entities often difficult to distinguish by clinical criteria. This category also included small numbers of patients with corticobasal degeneration and multisystem atrophy.

Table 3. Comparison of percentages of EOD in different studies

Diagnosis	England [1, 2] (n = 185)	Scotland [18] (n = 114)	Australia [16] (n = 150)	Brazil [15] (n = 141)
AD	65 (35.1)	60 (52.6)	32 (21)	30 (21.3)
VaD	34 (18.4)	13 (11.4)	38 (25)	52 (36.9)
PD	16 (8.6)	NR	NR	5 (3.5)
TBI	NR	NR	NR	13 (9.2)
Alcohol-related	19 (10.3)	14 (12.3)	3 (2)	7 (5)
HIV-associated	NR	NR	NR	NR
NPH	NR	NR	NR	6 (4.2)
FTLD	23 (12.4)	NR	36 (24)	7 (5)
Huntington's disease	9 (4.9)	NR	NR	NR
Multiple sclerosis	8 (4.3)	NR	NR	2 (1.4)
Dementia NOS	NR	NR	NR	NR
Miscellaneous	11 (5.9)	27 (23.7)	41 (27)	19 (13.5)

Some diagnostic categories have been reassigned to facilitate comparison. PD = Parkinsonian disorders with dementia; NPH = normal pressure hydrocephalus; dementia NOS = dementia not otherwise specified; NR = not reported. Figures in parentheses indicate percentages.

Discussion

EOD is a significantly underrecognized subgroup of patients with dementia [2, 5]. This 4-year investigation of all patients presenting to a memory disorders program found that nearly 30% of patients with dementia had an age of onset of less than 65 years. When compared with similar patients with late-onset disease, these EOD patients had more treatable or preventable conditions and less AD. The particular population studied is skewed towards inner city male veterans of lower socioeconomic status. This is distinct from the usual population seen in university clinics, which may be skewed in a different way. Like any study of this nature, the population to which it is generalizable is unclear, but does represent a significant portion of the American population. Given the devastating nature of a dementia beginning at an early age, these findings emphasize the need to aggressively evaluate EOD patients for preventable and manageable causes of their disorder [1].

There are surprisingly few studies of the epidemiology of EOD compared to the many studies for LOD (table 3) [1, 2, 8–10]. The prevalence rate of EOD may range between 67 and 81 per 100,000 in the 45- to 65-year-old age group and increases exponentially from the age of 35 on [2, 11–13]. Among dementia patients, the proportion of those with EOD seems to vary widely. In one report of 619 patients in England, the proportion of patients with EOD was 28.6% [14] and in another report of 311 patients in Brazil, the proportion of patients with EOD was 46.6% [15]. These studies along with the findings reported here are consistent, however, in indicating a high proportion of patients with EOD.

In most, but not all, studies the most frequent EOD is AD accounting for 20–34% of patients, followed by VaD and FTLD [1, 2, 9, 16–20]. Despite a plurality of AD, the proportion of EOD patients with AD is far less than for LOD. AD accounts for about two thirds of all dementias [5], but only about one third of all patients with an early age of onset. The large majority of patients with EOD do not have AD, and the differential diagnosis of EOD is wide. Moreover EOD from a non-AD dementia is often mistaken as AD [1, 5]. The lower than expected percentage of late-onset subjects diagnosed with AD most likely reflects the population from which the subjects were drawn. Our clinic is not strictly an AD clinic, but rather a broader dementia and memory disorders clinic, which affects the patient population.

VaD or multiple cognitive deficits from cerebrovascular disease was the most common EOD in this series, present in 28.8% of our EOD patients. A few other reports of EOD also found that VaD was at least as common if not more so than AD [9, 15, 18, 21]. Fujihara et al. [15] found a cerebrovascular etiology for dementia in 36.9% whereas AD was present in only 20.3%. Ferran et al. [22] reported that 17% of people under 65 years referred for the investigation of suspected dementia eventually received a diagnosis of VaD, while Delaney and Rosenvinge

[19] found that 17/27 patients with EOD in the Southampton area were suffering from this disorder. Clearly, depending on the population, VaD remains an important cause of acquired cognitive deficits in middle-aged adults.

The differential diagnosis of EOD also includes the consequences of head injuries, alcohol abuse, HIV infection, and a range of other conditions. As evident in this series, other dementias such as FTLD, Huntington's disease, multiple sclerosis, and Creutzfeldt-Jakob disease are also present in younger people. In contrast, parkinsonian disorders with dementia which are relatively common in the elderly, especially dementia with Lewy bodies, account for only a small proportion of those with EOD [1, 2, 27].

Early-onset, non-AD dementias also include FTLD as the second most common neurodegenerative dementia in the presenium [23, 24]. FTLD includes frontotemporal dementia and Pick's disease and comprises a group of disorders characterized by focal degeneration of frontal and temporal lobes with an age of onset of 45–60 (range 20–75 years) [5, 13]. In some series, FTLD may be as common as AD in young patients [13, 16]. Its prevalence varies with demographic characteristics of the population and may be more common among individuals of European ancestry [25]. This may explain its lower prevalence in this study, which had a heterogeneous ethnic population.

Alcohol-related dementia is more common in younger people than in old people [1, 2, 26]. For example, alcohol-related dementia occurred in 12% of one series of EOD patients [2]. Drugs and alcohol abuse often occur together, and there effects may be difficult to disentangle. The effects of alcohol are heterogeneous and include disturbances in executive function and autobiographical memory as well as the clinical features of vitamin deficiency states such as Wernicke-Korsakoff's syndrome [5]. Clinicians should always evaluate the presence of alcohol or other drug abuse as potential etiological factors for a cognitive decline in the presenium.

This study appears to have particularly high numbers of patients with TBI and alcohol abuse. In part, this reflects the population of this study, specifically the veteran and male predominant nature of the patients. Males are more likely than females to have had significant head injuries and alcohol abuse. Other studies with different populations, however, have also found high numbers of patients with TBI, alcohol abuse or both [1, 2, 15]. In general, however, there is a trend towards male predominance among patients with EOD [2, 15, 16]. These veterans are at an increased risk for development of AD due to higher frequencies of TBI and substance abuse, and because of this may require closer follow-up to identify symptoms of AD as early as possible.

This study has several strengths. First, this is the largest investigation of dementia etiologies in EOD. Prior reports have had relatively small sample sizes. Second, the patients had extensive evaluations, including mental status scales, neurobehavioral examination for deficits in the major cognitive domains, neurological examinations, and MRI. Patients were evaluated for established diagnostic criteria for dementing illnesses. Finally, this study directly compares the frequencies of etiologies between comparable patients with EOD and LOD.

Conversely, this study has several potential limitations. First, it is a veteran's population and not entirely generalizable to other populations. Second, these patients were seen in a medical center with high rates of referrals for potentially severer cognitive impairments. This, however, would not be expected to affect the differential distribution of disorders between those with EOD and those with LOD. Finally, this is a clinical study without pathological confirmation of dementia diagnoses.

Overall, the results of this report highlight the frequency and importance of EOD. Among patients less than 65 years of age at onset, many of the leading causes of dementia were either treatable or preventable. This is distinct from the causes of dementia in LOD and argues for greater, more aggressive evaluations and intervention, where possible. Future studies can profitably focus on the management of these patients with EOD.

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