

## THE ACCURATE DIAGNOSIS OF EARLY-ONSET DEMENTIA

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### ABSTRACT

Early-onset dementia (EOD, <65 years at onset) is a relatively common and frequently misdiagnosed condition. One reason for misdiagnosis is that EOD has a more varied differential diagnosis than late-onset dementia (LOD). For example, Alzheimer's disease (AD), the preponderant LOD, makes up only about one-third of EODs; the rest are due to vascular dementias, frontotemporal lobar degenerations, traumatic head injury, alcohol-related dementia, and a great many other conditions. Another reason for misdiagnosis is that early-onset AD may have predominant cognitive deficits other than memory loss and a potential familial inheritance with spastic paraparesis, seizures, or myoclonus. A third reason is that EOD often presents with neuropsychiatric features out-of-proportion to any cognitive deficits. Despite these obstacles, it is important to accurately diagnose EODs, particularly because they differ in management and course. Clinicians can successfully diagnose most EODs with careful cognitive and family histories, mental status and neurological examinations, and neuroimaging.

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**Key Words:** dementia, Alzheimer's disease, vascular dementia, frontotemporal dementia, traumatic brain injury

## INTRODUCTION

Early-onset dementia (EOD) is an important and poorly understood diagnostic category. Investigators, however, have relatively ignored EOD while focusing on late-onset dementia (LOD) [1, 2]. This is unfortunate because EOD can have particularly devastating psychosocial consequences as it afflicts people who are often in their most productive years and supporting families [1-4]. Moreover, EOD is more of a problem and more common than previously realized. Recent clinical reports indicate a significant proportion of EOD patients compared to LOD patients [1, 4, 5]. Among 948 U.S. veterans, 278 (30%) had EOD [1], and, among 619 patients in England, the proportion of patients with EOD was 28.6% [4]. In another report of 311 patients in Brazil, the proportion of patients with EOD was a high of 46.6% [5]. These studies indicate that there are significant proportions of patients with EOD at least among select populations.

EOD is a somewhat arbitrary and poorly understood category of dementia. The definition of EOD is based on a traditional and historical cut-off of dementia with age of onset of less than 65 years [1, 2]. Although this separation is artificial, it is still used in discussing patients with dementia. For example, the World Health Organization continues to distinguish between “dementia in Alzheimer’s disease with early onset before age of 65” vs. “dementia in Alzheimer’s disease with late onset” [6]. The overall prevalence of EOD is low compared to LOD, but still considerable [5, 7-9]. The prevalence of EOD is about 67 to 81 per 100,000 persons in the 45 to 65 year old age group with exponential increases beginning at age 35 [4, 10-13]. The incidence of EOD is about 8.3 new cases per year per 100,000 persons in the 50–64 age range [14].

## THE MISDIAGNOSIS OF EOD

Despite the importance, clinicians misdiagnose many if not most patients with EOD early in their course [2, 5, 10, 15-17]. Although clinical criteria exist for the most common EODs, misdiagnosis is common even at tertiary centers [2]. Clinicopathologic studies report a wide range (0-71%) of clinical accuracy for diagnosing VaD and FTD [13, 15, 18, 19]. During the first few years of their disease, these patients may see many different doctors and undergo extensive medical evaluations with significant delays in diagnosis of 3-4 years or more [17, 18]. Yet, the accurate diagnosis of EODs has management consequences [2, 20]. For example, patients with early-onset AD may respond to acetylcholinesterase inhibitors; however, those with frontotemporal dementia (FTD) may worsen with these medications [21]. A range of specific drugs continue to be tried for VaD including nimodipine, propentofylline, vinpocetine, and pentoxifylline [22]. Infectious and toxic-metabolic causes of EOD have their own treatments. Furthermore, EODs may require different attention to potential genetic factors or additional diagnostic measures, such as a search for rarer vasculopathies (see Figure 1).

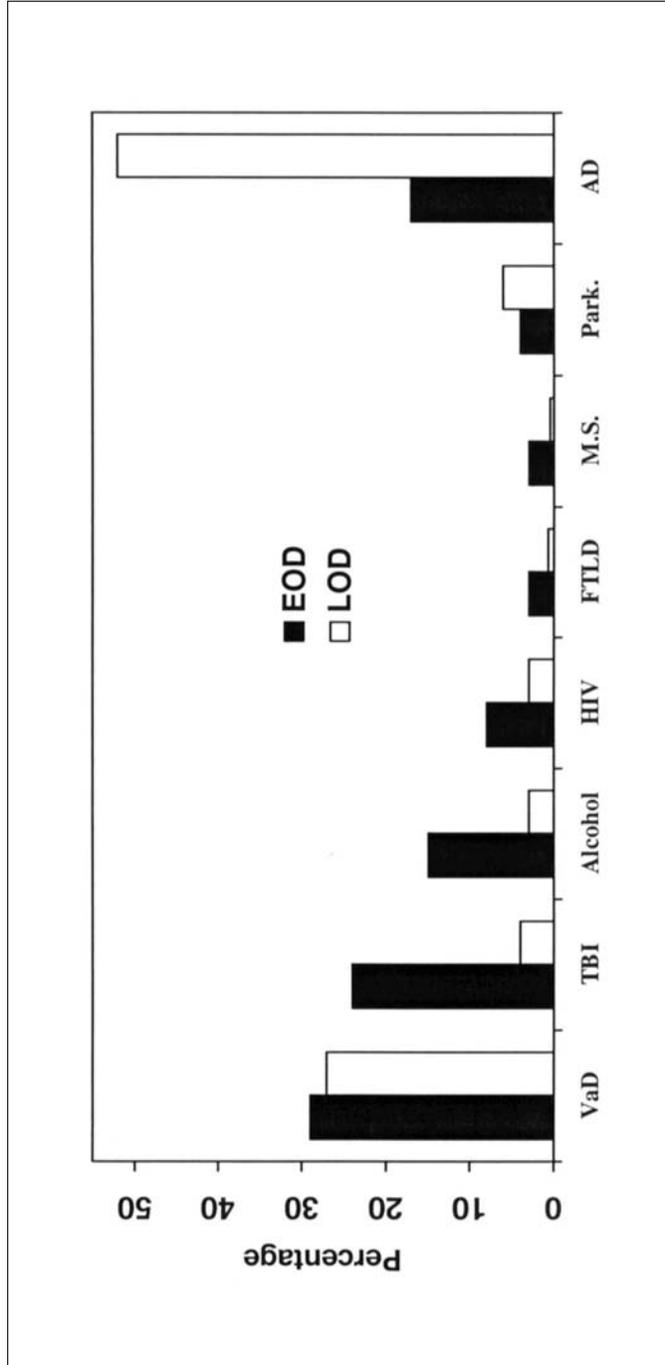


Figure 1. Dementia etiologies in VA dementia program.  
 EOD = early-onset dementia,  $n = 278$ ; LOD = late-onset dementia,  $n = 670$   
 VaD = vascular dementia; TBI = traumatic brain injury; FTLD = frontotemporal lobar degeneration;  
 M.S. = multiple sclerosis; Park. = dementia with Parkinsonism; AD = Alzheimer's disease  
 (Reproduced in part from McMurtry et al. 2006 [1], with permission.)

### **Clinical Case Example of Misdiagnosis**

A 42-year-old woman presented for neurological assessment because of a 3-year history of personality change [23]. She had become detached and disengaged from her work, family, and usual activities. Her personal hygiene had declined, and she followed exactly the same routines every day. The patient began eating more and gained a significant amount of weight. When asked, she stated that nothing was really wrong with her but that certain people were trying to hurt her. Her psychiatrist diagnosed her with major depression with paranoid features until it became clear that she was progressively worsening.

On examination, she had little spontaneous behavior or emotional expression. Mental status assessment revealed deficits in memory, visuospatial skills, and frontal-executive functions. Her neurological examination and routine laboratory data was otherwise normal, and her MRI revealing generalized cerebral atrophy. This time the patient was misdiagnosed as having FTD [24]. After yet another year of continued decline, a positron emission tomography (PET) study showed significant hypometabolism in prefrontal, parietal, and temporal cortex bilaterally and genetic testing revealed the presence of a presenilin-1 mutation for autosomal dominant AD. The patient did not have a known family history for this disorder but information on her father was lacking. Once correctly diagnosed, appropriate management was initiated including a further investigation of her family history and genetic counseling.

### **High Proportion of Non-AD Dementias**

There are several reasons for the misdiagnosis of EOD. One reason is that patients with EOD are more likely than those with LOD to have dementias other than AD (see Figure 1) [2, 14, 20]. Although AD is the most frequent etiology of dementia [2], it accounts for only about one third of all those with an early age onset, compared to about two thirds (50-75%) of LODs [4, 9, 25-27]. The other common EODs are vascular dementia (VaD), FTD and related disorders, sequelae from traumatic brain injury (TBI), and alcohol-related dementia [1, 4, 5, 14, 20]. VaD is more common in EOD than in late-onset disease [4, 25, 28], and, in a few reports, VaD is the most prevalent EOD [1, 5, 26]. Similarly, FTD is much more common in EOD than in late onset disease [28], and, in a few reports, FTD is as prevalent as AD among EODs [13, 28]. TBI and alcohol are common causes of dementia in the young but vary with specific population groups (see Table 1).

In several series [1, 5, 26], VaD was the most important and common cause of dementia in the presenium. There are problems in the diagnosis of clinical VaD. The major clinical criteria for VaD and other vascular dementias overlap in <50% of cases [22, 29], and patients with VaD often lack a history of stroke, an abrupt or stepwise decline in cognition, focal neurological signs, or a clear relationship of magnetic resonance imaging (MRI) changes to cognition [22, 30]. In contrast, a plurality, if not the majority, of patients with VaD have subcortical ischemic

Table 1. Comparison of Percentages of EOD in Different Studies

Diagnosis	England <i>n</i> = 185 [4]	Australia <i>n</i> = 150 [18]	Scotland <i>n</i> = 114 [17]	Brazil <i>n</i> = 141 [5]	Japan <i>n</i> = 34 [20]	United States <i>n</i> = 278 [1]
AD <sup>a</sup>	65 (35.1%)	32 (21.%)	60 (52.6%)	30 (21.3%)	15 (44.1%)	48 (17%)
VaD (1°SIVD)	34 (18.4%)	38 (25%)	13 (11.4%)	52 (36.9%)	8 (23.5%)	80 (29%)
FTLD (1°FTD)	23 (12.4%)	36 (24%)	NR	7 (5%)	5 (14.7%)	11 (4%) <sup>c</sup>
Parkinsonian <sup>b</sup>	16 (8.5%)	NR	NR	5 (3.5%)	1 (2.9%)	9 (3.2%)
Huntington's	9 (4.9%)	NR	NR	NR	0	4 (1%)
TBI	NR	NR	NR	13 (9.2%)	3 (8.8%)	67 (24%)
Alcohol-related	19 (10.3%)	3 (2%)	14 (12.3%)	7 (5%)	0	15 (5%)
Other <sup>d</sup>	19 (10.2%)	41 (27%)	27 (23.7%)	27 (19.1%)	2 (5.9%)	44 (15.8%)

<sup>a</sup>Probable and possible AD. <sup>b</sup>Parkinsonism disorders include dementia with Lewy bodies.

<sup>c</sup>Numbers include a few patients reclassified from original paper. FTD artificially low because of mental health clinic presentation, rather than to "memory" clinics. NR = Not Reported.

<sup>d</sup>Other: Infections, toxic-medical conditions, normal pressure hydrocephalus, multiple sclerosis.

disease composed of pre-infarction white matter changes (leukoaraiosis) and lacunar strokes on MRI [28, 29, 31, 32]. These changes can be associated with an insidious and gradually progressive dementia as the ischemic burden accumulates [29-31]. Structural imaging with MRI can be helpful; however, the presence of subcortical ischemic vascular changes may not be the cause of the clinical dementia; many of these patients have mixed Alzheimer-vascular dementia [29, 33-36]. In sum, the most common form of VaD has at least two strategically placed subcortical lacunes plus at least a moderate amount of leukoaraiosis on MRI.

FTD is the third most common EOD in most series, and one that typically presents in the fifties or earlier. Like AD, FTD is an insidious and progressive neurodegenerative dementia without overt neurological signs. The early diagnosis of FTD is difficult and relies on the detection of alterations in social interpersonal behavior, abnormalities in personal regulation, emotional blunting, and loss of insight [24]. Many of these patients have subtle behavioral changes of a socio-emotional nature which can dominate the cognitive examination and obscure the diagnosis of an EOD [15, 24, 37]. Routine clinical MRI usually does not distinguish AD from FTD [24], and investigators have not established a reliable biological marker that can help discriminate between these dementias. Patients with FTD, however, have frontal, anterior temporal, or frontotemporal hypometabolism or hypoperfusion on functional neuroimaging and usually meet diagnostic criteria after a period of follow-up.

TBI is an important cause of EOD. In some series, dementia from TBI comprises 9-24% of EODs [1, 5, 28]. Since TBI is the most common cause of neurologic illness in young people, it is not surprising that it is a significant cause of chronic deficits in cognition. The vast majority of TBIs are non-penetrating and result from motor vehicle accidents (50%), falls (21%), violence (12%), and sports or recreational injuries (10%) [2]. Diffuse, non-penetrating TBI often results in permanent neurobehavioral deficits in information processing speed and motor slowing, attention and concentration, memory, and frontal-executive functions [2]. The most common and severe focal TBI effects result from bilateral injuries to the basolateral frontal cortex and the temporal lobes. Furthermore, TBI is a risk factor for the eventual development of AD [2].

EOD can be a consequence of chronic alcohol abuse [4, 20]. Alcohol-related dementia is more common in younger people than in old people [4, 38]. For example, alcohol-related dementia occurred in 12% of one series of EOD patients from England [4]. This entity is heterogeneous and includes disturbances in executive functions and autobiographical memory as well as the clinical features of vitamin deficiency states such as Wernicke-Korsakoff's syndrome [2]. Moreover, drug and alcohol abuse often occur together, and their effects may be difficult to disentangle. Clinicians should always evaluate the presence of alcohol or other drug abuse as potential etiological factors for a cognitive decline in young people.

The differential diagnosis of EOD also includes a range of other conditions (see Table 2). Most of these are infections, toxic-metabolic, or inheritable conditions. Infectious dementias include Creutzfeldt-Jakob Disease and other prion disorders, HIV-associated dementia, and the residual of encephalitides. Familial prion disorders may have a chronic progressive course, particularly if due to an insertional mutation. Toxic-metabolic disturbances, such as hepatic failure or sleep apnea, can have a chronic course and present with dementia. Inheritable disorders range from Huntington's disease (HD) to a number of inborn errors of metabolism that can occur in adulthood. The differential diagnosis of EOD includes a number of miscellaneous conditions such as normal pressure hydrocephalus (NPH), epilepsy, multiple sclerosis, and neoplastic-related conditions. Finally, additional neurodegenerative disorders should be considered. These include Parkinsonian disorders with dementia especially Parkinson's disease dementia, dementia with Lewy bodies, progressive supranuclear palsy, and corticobasal degeneration [4, 20, 39].

### **Differences between Early-Onset AD vs. Late-Onset AD**

Another reason for the misdiagnosis of EOD is the potential clinical differences between early-onset AD and late-onset AD [1, 4]. The traditional model of AD is the late-onset disorder characterized by prominent memory difficulty and word-finding problems. Early reports, however, considered sporadic early-onset

Table 2. Common Early-Onset Dementias

<b>Neurodegenerative Disorders</b>	<b>Toxic-Metabolic Disorders</b>
Alzheimer's disease and variants	Alcohol and other substance abuse
Frontotemporal dementia and variants	Heavy metals, organophosphates, toxins
Dementias with Parkinsonism	Sleep apnea
Huntington's and Wilson's disease	Anoxic and Hypoglycemia
Spinocerebellar Ataxias	Gastrointestinal, hepatic encephalopathy
Dementia with motor neuron or muscle disease	Renal failure and dialysis dementia
	B <sub>12</sub> , thiamine, folate, niacin deficiencies
	Thyroid, parathyroid, adrenal, pituitary
<b>Vascular Disorders</b>	<b>Adult Inborn Errors of Metabolism</b>
Strategic subcortical strokes ± leukoariosis	Leukodystrophies.
Binswanger's disease (severe leukoariosis)	Polioencephalopathies, e.g., Fabry, Kuf, etc.
Inherited vasculopathies	Porphyria
CNS vasculitides, e.g., Sneddon, Susac, etc.	
<b>Infectious Disorders</b>	<b>Miscellaneous</b>
HIV-associated dementia	Traumatic brain injury, dementia pugilistica
Creutzfeldt-Jakob disease and other prions	Normal pressure hydrocephalus
Neurosyphilis	Hashimoto's encephalopathy
Lyme disease	Epilepsy-related
Chronic fungal meningitis	Neoplastic or paraneoplastic
Whipple's disease	Multiple sclerosis
Post-encephalitis	CNS sarcoidosis
Subacute sclerosing panencephalitis	Psychiatric diseases especially depression
Progressive multifocal leukoencephalopathy	

AD and late-onset AD to be separate diseases based on greater cortical deficits and greater parietal involvement in early-onset AD [40]. Some found a higher prevalence of language impairment and a faster progression in early-onset AD vs. late-onset AD [41-43], but others failed to find these differences [40, 41]. Extensive neuropsychological testing, however, has indicated that cortical visuospatial functions are more impaired in early-onset AD vs. late onset disease, including embedded figure perception, hand-eye coordination, block design, and visual reproduction [40, 44]. Consistent with these neuropsychological findings, positron emission tomography (PET) scans and neuropathology suggest more severe deficits in parietal areas in early-onset AD vs. late-onset AD [2, 45-47]. Furthermore, clinicians need to recognize patients with early-onset AD that might have an autosomal dominant frontal disorder as illustrated by the Clinical Case Example [23, 48]. Distinct from the usual sporadic early-onset AD, the rare patients with presenilin 1 or other mutations can develop paraparesis, seizures, and myoclonus, in addition to a frontally predominant disorder resembling FTD [23, 49]. It is important to recognize these genetic variants so that clinicians and families can consider genetic testing and counseling.

### **Presentation with Neuropsychiatric Symptoms**

A further source of misdiagnosis is the presentation of EOD with neuropsychiatric symptoms. Several EODs can present with a wide variety of subtle behavioral, cognitive, psychiatric, or neurological symptoms. FTD in particular, results in personality changes, including alterations in social-emotional behavior, insight, and personal regulation, changes in oral behavior, and repetitive, compulsive acts. Some of these patients have even presented with sociopathic acts [50]. Other neuropsychiatric presentations of EODs include apathy or abulia with VaD, intermittent explosive disorder and poor judgment with TBI, depression or disinhibition with HD, and psychosis or anxiety with Hashimoto's encephalopathy. The clinician needs a high index of suspicion for EOD when patients develop new onset psychiatric symptoms in mid-life.

### **THE EFFECTIVE DIAGNOSIS OF EODs**

Given these sources of misdiagnosis, what can clinicians do to effectively diagnose EODs? The accurate diagnosis of most of these disorders is possible with a series of systematic steps. First, obtain a good clinical history and course. Determine if there has been a change from a prior level of functioning and whether there are cognitive deficits, behavioral or neuropsychiatric features, or both. Second, evaluate for dementia risk factors. These include a history of TBI with coma or significant post-traumatic amnesia and a history of alcohol and drug abuse. Third, determine if there is a positive family history for dementia. In particular, evaluate for autosomal dominant disorders among first-degree

relatives. Fourth, perform a thorough neurological examination. The additional features of pyramidal, extrapyramidal, cerebellar, or peripheral nerve involvement are key diagnostic clues in this group and help to direct investigations. Fifth, obtain an MRI. The presence of white matter changes is particularly useful in evaluating for vascular disease or leukodystrophies. Finally, obtain special tests as needed. Useful studies are lumbar puncture for infectious processes, diffusion-weighted MRI for prion disease, and positron emission tomography for FTD. Together, these steps should facilitate the accurate diagnosis of most patients with EOD.

## CONCLUSIONS

Patients with EODs are not rare, and most psychiatrists and neurologists are likely to be faced with one of these patients. EODs have a broader differential diagnosis than LOD. AD, the preponderant dementia in late life, makes up only about a third of EODs and often differs in having more visuospatial deficits than memory loss and a greater risk of familial inheritance. Compared to LOD, a greater proportion of EODs have VaD, FTD and related syndromes, dementia due to TBI, alcohol-related dementia, and other conditions. Moreover, compared to LOD, EODs are more likely to present with neuropsychiatric features. Careful attention to cognitive and family history, mental status and neurological examinations, and neuroimaging can differentiate most EODs as long as clinicians have a high index of suspicion. More research needs to clarify methods to diagnose these entities because they have different managements and are increasingly likely to have targeted treatments in the future.

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