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Nonamnesic Presentations of Early-Onset Alzheimer's Disease

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Abstract

Early-onset Alzheimer's disease (EOAD) beginning before the age of 65 may differ from late-onset AD (LOAD) in clinical course and frequency of nonamnesic presentations. In a 10-year retrospective review, 125 patients with EOAD, diagnosed clinically and verified by functional neuroimaging, were compared with 56 patients with LOAD and further classified depending on predominant cognitive difficulty on presentation. Eighty (64%) of the patients with EOAD had a nonamnesic presentation, compared with only 7 (12.5%) of the patients with LOAD. Compared with LOAD, the patients with EOAD had a shorter duration with lower Mini-Mental State Examination scores. The neuroimaging reports among the patients with EOAD showed more hippocampal atrophy with an amnesic presentation, more left parietal changes with impaired language presentations, and more right parietal and occipital changes with impaired visuospatial presentations. These findings indicate that EOAD differs from LOAD in a more aggressive course and in having predominantly nonamnesic presentations that vary in neuropathological location.

Keywords

Alzheimer's disease; early-onset; aphasia; posterior cortical atrophy; apraxia

Introduction

In 1907, Alois Alzheimer described a 51-year-old patient who developed dementia with predominant language and behavioral changes.¹ This patient, Auguste Deter, proved to have the amyloid plaques and neurofibrillary tangles that define the neuropathology of Alzheimer's disease (AD). For the next 70 years, early-onset dementia was the embodiment of AD, with the much more common late-onset AD (LOAD), with onset after age 65, considered "senile dementia" from normal aging. However, in 1968, Blessed and colleagues showed that the brains of patients with senile dementia had plaques and tangles that were qualitatively the same as early-onset forms.² From this point on, many clinicians and

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investigators came to view early-onset AD (EOAD) as just a younger version of the progressive amnesic presentation evident in most patients with LOAD.

Although the most common impairment is still in declarative episodic memory.³ The AD occurring in EOAD is more heterogeneous than LOAD.⁴⁻⁸ The EOAD contains a number of subtypes whose most prominent symptoms are disturbances in language,⁹⁻¹² visuospatial functions,¹³ executive functions,^{14,15} or another nonmemory cognitive domain such as limb apraxia.^{9,10,13,14,16-18} Some of these patients have early parietal involvement and are referred to as parietal or biparietal variant.¹⁶ Despite increasing appreciation for these nonamnesic subtypes of EOAD, it is unclear whether there is distinct cognitive variation from the earliest onset, before memory and other cognitive deficits accumulate.^{10,17,19} The early presenting impairments may reflect differences in the initiation of the underlying pathophysiology and provide clues to the mechanisms of AD.

This study aims to examine the clinical features of nonamnesic presentations of AD that occur at a young age. This study evaluates the presenting clinical features of a large sample of patients with EOAD, seen over a 10-year period, compared to those with LOAD. No prior studies have evaluated EOAD versus LOAD based primarily on the predominant presenting cognitive complaint. Furthermore, in order to overcome the traditional restriction of memory impairment for the diagnosis of AD, this study applies the proposed National Institute on Aging-Alzheimer's Association (NIA-AA) criteria, which include nonamnesic presentations for this disorder.²⁰ This proposal hypothesizes that the nonamnesic presentations of AD are common and distinct, possibly reflecting the differences in pathophysiological processes.

Methods

Participants

This was a retrospective cohort study of all patients who received a diagnosis of EOAD after presenting to a university clinic, whose focus is early-onset cognitive impairments, between the years 2002 and 2011. This study identified patients who, after a diagnostic evaluation, had an age of onset less than 65 years, and who, on retrospective review, met NIA-AA criteria for "probable AD dementia with intermediate evidence of AD pathophysiological process" (with the limb apraxia exception described below).²⁰ The family histories of these patients were extensively reviewed in order to exclude patients with an early-onset dementia among first-degree relatives (prior review identified only 1 individual who proved to have a presenilin 1 mutation). For comparison, this study included an additional cohort of established and well-diagnosed patients with LOAD from our larger AD program. These patients were a convenience sample of recently well-characterized patients with LOAD who were enrolled in our programs and who were similar in sex and education as the patients with EOAD. This study received institutional review board (IRB) approval for retrospective analysis of EOAD clinical records and additional IRB for the LOAD comparison group.

Clinical Evaluation

On initial presentation, the patients have detailed evaluations that include clinical history, neurological examination, and neuropsychological mental status tests. All patients had routine laboratory tests and magnetic resonance imaging (MRI) of the brain. All the patients with EOAD underwent functional neuroimaging, either positron emission tomography (PET) or single photon emission tomography (SPECT). Because these were clinical evaluations, many patients presented to our program with their MRI, PET, or SPECT scans already having been completed elsewhere.

As part of their initial clinical evaluation, the patients with EOAD underwent a Mini-Mental State Examination (MMSE) and the neuropsychological mental status tests used in our program and based on the Consortium to Establish a Registry in AD (CERAD) and the Neurobehavioral Cognitive Status Examination (NCSE).^{21,22} These tests included digit span forward, digit span backward, verbal fluency for “F” words and for animal names, the 15-item mini-Boston Naming Test (BNT), and the CERAD verbal memory test rendering scores for the third learning repetition (trial 3), 5-minute delayed recall, and a subsequent recognition score (accurate Yes answers on true–false recognition). The construction test evaluated copies of a circle, rhombus, overlapping rectangles, and a cube for figure closure for 3-dimensionality, parallel opposite sides, correct internal lines, and frontal face orientation for a maximum score of 12. Limb praxis involved the ability to perform 4 transitive and 4 intransitive ideomotor tasks each in the right and left upper extremities. Speech fluency, verbal repetition, and auditory comprehension scores were modified from the Western Aphasia Battery,²³ and the calculation test was modified from the NCSE. Four common proverbs were included for abstraction ability and scored on the ability to interpret beyond the actual words. Finally, the Frontal Assessment Battery (FAB),²⁴ which comprises 6 items aimed at assessing executive abilities, was included in this battery.

Inclusion Criteria

In addition to retrospectively meeting NIA-AA criteria with evidence of neuronal degeneration on functional neuroimaging, inclusion criteria specifically included: (1) a predominant presenting complaint from a primary caregiver and (2) evidence of a salient impairment in the same cognitive domain on neuropsychological mental status testing.

The problem of meeting the criterion of “memory impairment” as a requisite to the diagnosis of AD is overcome through the retrospective application of the new proposed criteria for probable AD.²⁰ These NIA-AA criteria are used here, instead of the former research criteria,²⁵ because they take into account the developments that have occurred over the last 28 years, including consideration of the broad clinical spectrum of AD and nonamnestic presentations. All patients who met criteria for “probable AD” by former research criteria met NIA-AA criteria for probable AD dementia.²⁰

The predominant presenting cognitive impairment was the chief complaint, difficulty, symptom, or impairment communicated by the primary caregiver on initial presentation (more than one chief complaint was recorded if there was more than one equally prominent cognitive difficulty on presentation). As outlined in the modified NIA-AA criteria for probable AD, in addition to memory: “The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories: language, visuospatial, executive.” Accordingly, the nonamnestic presentations were categorized into language, visuospatial, and executive deficits with one exception or modification. This review found patients whose most prominent initial presentation was limb apraxia, associated with clinical evaluation and course consistent with EOAD rather than alternative diagnoses such as corticobasal syndrome (ie, absence of motor signs or symptoms). Presentation with limb apraxia might be consistent with NIA-AA “possible AD, atypical presentation”; however, this study included these patients under the probable AD “nonamnestic” category.

The NIA-AA criteria also indicated that the initial and most prominent cognitive deficits must also be evident on examination.²⁰ Hence, this study included patients with EOAD who had presenting cognitive deficits that were corroborated by the intake neuropsychological mental status tests. The patients included here had a “predominant” presentation further evident as a salient impairment in the same cognitive domain on testing.

The patients with EOAD (but not the patients with LOAD) had PET or SPECT as part of their evaluation. This functional imaging was used to support the diagnosis of AD, which is particularly important given the presence of atypical, nonamnesic presentations. Per the new criteria, these patients had probable AD dementia with the addition of PET or SPECT findings of neuronal degeneration as evidence of an AD pathophysiological process.²⁰ In the absence of a positive amyloid biomarker, the PET and SPECT findings were only “intermediate” biomarker evidence for AD. The PET and SPECT scan reports described a continuum of parietal and parietotemporal involvement supportive of AD, and, hence, these were tallied as “PT/P” (parietotemporal and/or parietal involvement). The clinical reports on this functional imaging did not consistently comment on the presence or absence of changes in the posterior cingulate and precuneus; therefore, this study could not reliably assess changes in these regions.

Additional Procedures

The study compared demographics data (age of onset, age at initial visit, ethnicity, handedness, and education) and presenting symptoms between patients with EOAD and LOAD and across EOAD groups with different presentations. Age of onset was the best estimate from the main caregiver of the emergence of the presenting cognitive impairment as a sustained change from the patients’ premorbid state. As noted, neuroimaging reports were evaluated rather than the scans themselves. The scans were frequently not available for review, either because they were taken up to 10 years in the past, in the earliest EOAD patients, or they were done at other institutions on a range of scanners. The presence of regional changes or laterality was based on whether it was reported by the neuroradiologists who read the brain images. A number of patients died and had autopsy results are included here.

Statistical Analysis

Statistical Package for the Social Sciences version 19v (SPSS, Chicago, Illinois) was used for group comparisons. Chi-square analyses were performed on categorical data and t tests or analysis of variance for parametric comparisons. Post hoc comparisons are reported for individual group differences. For the 16 neurocognitive tests, a Bonferroni significance level was set at $P < .003$.

Results

The study identified 125 patients with EOAD who met inclusion criteria. These 125 patients with EOAD were initially compared with 56 patients with LOAD who were similarly reviewed for presenting cognitive complaints and then categorized and contrasted by presenting deficits.

The EOAD Versus LOAD

When patients with EOAD and LOAD were compared, the patients with EOAD had a shorter duration on presentation by about 1 year, yet their mean MMSE scores were lower (Table 1). The EOAD and LOAD groups did not differ significantly on percentage male or female, percentage left-handed, years of education, and percentage with family history of first-degree relative with dementia. Almost all the patients were Caucasian and non-Latino. The majority of the patients with EOAD were seen once or twice for diagnosis and then sent back to their primary physicians. The patients with EOAD had follow-up periods of :S1 year (71; 57%), 1 to 2 years (12; 10%), or 2 years (46; 37%).

The largest number of patients in either EOAD or LOAD groups presented with memory impairment; however, the patients with EOAD were more likely to have nonamnesic

presentations. Eighty (64%) of 125 patients with EOAD had a nonamnestic presentation (33 language, 35 visuospatial, and 12 limb praxis impairments) compared with only 7 (12.5%) of the 56 patients with LOAD.

The EOAD Subgroups

The amnestic versus combined nonamnestic group comparisons are described in text, and the specific subgroup comparisons are reported in Tables 2 to 4. When patients with EOAD were compared with each other, the typical amnestics were younger (55.61 ± 5.34) than the combined nonamnestics (60.13 ± 5.52 ; $t \frac{1}{4} 4.45$, $P < .001$) and had a correspondingly earlier age of onset (52.52 ± 5.76 vs 56.21 ± 5.22 ; $t \frac{1}{4} 3.64$, $P < .001$). The subgroup comparisons reveal a younger age of onset for amnestic compared to language and visuospatial subgroups (Table 2). The amnestic and combined nonamnestic patients did not differ significantly on duration in years (3.16 ± 2.01 vs 4.01 ± 2.61 ; $t \frac{1}{4} 1.89$), percentage left-handed or ambidextrous (2.22% vs 6.25.0%; $w^2 \frac{1}{4} 0.33$), percentage female (53.33% vs 48.75%; $w^2 \frac{1}{4} 0.09$), years of education (14.44 ± 4.21 vs 15.01 ± 4.22 ; $t \frac{1}{4} 0.77$), mean MMSE scores (22.18 ± 6.02 vs 20.24 ± 6.44 ; $t \frac{1}{4} 1.69$), and percentage with family history of first-degree relative with dementia (28.9% vs 42.5%; $w^2 \frac{1}{4} 1.73$).

As required by the inclusion criteria, the EOAD presentation subgroups had corresponding impairments on the initial neuropsychological mental status examination (Table 3). The amnestic patients had worse scores on the main memory measure, the CERAD delayed recall, compared to the combined nonamnestic patients (1.11 ± 1.71 vs 2.73 ± 2.47 ; $t \frac{1}{4} 10.9$, $P < .001$). In contrast, the amnestic patients did better than the combined nonamnestics on forward digit span (5.86 ± 1.08 vs 4.98 ± 1.35 ; $t \frac{1}{4} 12.58$, $P < .001$), mini-BNT (13.34 ± 2.67 vs 10.51 ± 4.38 ; $t \frac{1}{4} 12.62$, $P < .001$), speech fluency (7.76 ± 0.71 vs 6.55 ± 1.51 ; $t \frac{1}{4} 25.41$, $P < .001$), verbal repetition (7.8 ± 0.63 vs 7.11 ± 1.13 ; $t \frac{1}{4} 14.6$, $P < .001$), constructions (9.27 ± 2.38 vs 6.64 ± 3.52 ; $t \frac{1}{4} 19.9$, $P < .001$), and limb praxis (15.89 ± 0.38 vs 14.48 ± 2.33 ; $t \frac{1}{4} 16.2$, $P < .001$). The amnestic and combined nonamnestic groups did not differ significantly on backward digit span (2.97 ± 1.05 vs 2.71 ± 0.97 ; $t \frac{1}{4} 1.0$), "F" word fluency (8.54 ± 6.24 vs 6.88 ± 4.22 ; $t \frac{1}{4} 2.1$), animal fluency (12.58 ± 5.86 vs 11.83 ± 4.92 ; $t \frac{1}{4} 0.35$), CERAD trial 3 registration (4.46 ± 2.21 vs 4.32 ± 2.07 ; $t \frac{1}{4} 0.09$), CERAD recognition (7.5 ± 2.42 vs 8.35 ± 2.08 ; $t \frac{1}{4} 2.50$), auditory comprehension (19.60 ± 1.29 vs 18.79 ± 1.91 ; $t \frac{1}{4} 6.40$), calculations (6.23 ± 2.04 vs 5.41 ± 1.96 ; $t \frac{1}{4} 4.51$), proverbs (3.11 ± 1.23 vs 3.52 ± 0.80 ; $t \frac{1}{4} 5.0$), and the FAB (13.91 ± 2.04 vs 13.85 ± 1.46 ; $t \frac{1}{4} 0.03$).

Neuroimaging Reports

By definition, all patients had a PET or SPECT evidence of AD defined as P/PT hypometabolism or hypoperfusion. On MRI reports, 11 amnestic patients had hippocampal atrophy on MRI compared with only 2 of the combined nonamnestic patients ($w^2 \frac{1}{4} 12.62$, $P < .001$). The subgroup comparisons revealed that the amnestic subgroup had more hippocampal atrophy than the visuospatial subgroup on MRI (Table 4). In contrast, only 2 of the amnestic patients had P/PT atrophy on MRI compared with 28 of the combined nonamnestic patients ($w^2 \frac{1}{4} 13.11$, $P < .001$). The language subgroup had significantly more left-sided asymmetric P/PT involvement than the amnestic group on both MRI and PET. The visuospatial subgroup had significantly more right-sided P/PT involvement (on PET) and occipital changes (on MRI and PET) than amnestic and language subgroups (Table 4).

Autopsy Results

Among the 125 patients with EOAD, there were 16 known deaths and 7 autopsies. All the autopsies confirmed widespread AD with Braak and Braak stage VI involving neocortex. There were no other complicating neuropathological changes in these patients with EOAD.

Three were described as “tangle predominant” including 1 language and 2 visuospatial presentation patients.

Discussion

This study found differences between patients with EOAD and LOAD and among EOAD subgroups. The EOAD was more aggressive than the usual LOAD and included a larger percentage of patients whose earliest impairments were nonamnesic. Among patients with EOAD, those with an amnesic presentation had the youngest age of onset and more hippocampal atrophy and those with nonamnesic presentations had more P/PT involvement. Furthermore, the P/PT involvement was more left-sided with a language presentation and more right-sided with a visuospatial presentation. Occipital changes were also evident among many with a visuospatial presentation. These findings suggest that AD is not one disorder but includes EOAD subgroups with variations in AD pathophysiology from the very onset of their disease.

In this study, EOAD had shorter duration and more impaired presentation than LOAD, consistent with a more rapid or aggressive course and with several prior studies.^{26,27} A few other studies report a longer duration in EOAD than in LOAD,^{19,28} possibly because of misdiagnoses of their patients with EOAD with atypical presentations.¹⁹ One of these reports included all early-onset dementias²⁸; hence, their longer duration likely resulted from the presence of rare dementias requiring a high index of suspicion.

The EOAD is much more heterogeneous than LOAD and includes a higher percentage of nonamnesic cognitive syndromes.^{5,6,10,19,29} These cognitive syndromes can differ from typical AD in clinical and cognitive features,¹⁷⁻¹⁹ a higher mortality,³⁰ potentially different predisposing factors,³¹ and neuropathological involvement.³² Although episodic memory impairment is the usual predominant symptom in AD, 22% to 33% of those with EOAD can have predominant cognitive syndromes involving language, visuospatial abilities, behavioral/executive functions, and limb praxis.^{4,5,7,9,10,13,14,16-19,29} These prior studies have focused on the predominant cognitive syndrome rather than the actual first and most prominent symptom or impairment. Using this approach, and the new diagnostic criteria for AD, this study found that nearly two-thirds of patients with EOAD begin as a nonamnesic impairment compared to only one-eighth of patients with LOAD.

Similar to Alois Alzheimer’s original patient, a common nonamnesic presentation is with language impairment,¹⁸ possibly with logopenic aphasia.³³ Alzheimer’s first patient had a severe language impairment and limb apraxia, which may have been worse than her memory impairment.¹ The logopenic variant of primary progressive aphasia is most often due to AD.^{9-12,18} This aphasia is characterized by anomia with word-finding difficulty and some effortful or halting speech, phonemic paraphasic errors, and decreased sentence repetition.¹¹ Among the patients with EOAD in this study, language impairment was the second most common nonamnesic presentation, and it was primarily characterized by effortful and halting speech, word-finding difficulty, or both.

Among the patients with EOAD in this study, visuospatial impairment was the most common nonamnesic presentation. These patients developed problems with spatial processing, including localization, environmental orientation, or dressing difficulty (dressing apraxia). Many had nonspecific complaints in “seeing” or visual perception. Other investigators have described the syndrome of “apraxia/visuospatial dysfunction” or a “biparietal” variant as roughly comparable to these patients¹⁹; however, it is unclear whether the “apraxia” is primarily limb apraxia of the ideomotor type or primarily involves spatial abilities such as dressing apraxia and oculomotor apraxia. The related cognitive syndrome of

PCA also affects visual perception, may involve basic visual processing, extends into the occipital lobes, and usually has AD on pathology.^{13,16,34,35} Some investigators include the “biparietal” variant as PCA and describe temporo-occipital forms and a basic visual variant.¹⁸ It appears from the literature on these different syndromes that nonamnestic EOAD subgroups overlap and may best be differentiated by focusing on the initial, presenting cognitive impairment.

Limb apraxia was a third nonamnestic presentation among the patients with EOAD in this study. Twelve patients with EOAD presented with the complaints of deterioration in writing which was mechanical and not linguistic or with problems with manual dexterity particularly related to specific complex motor activities, such as manipulating objects. Several of these patients included acalculia as a prominent presenting feature, and there was much overlap with the language-impaired patients. These last patients may correspond to an “aphasic–apraxic–agnosic” syndrome described in some patients with EOAD.¹⁹

A further nonamnestic presentation of EOAD is with executive function disturbances.¹⁷ Executive dysfunction develops as AD progresses but appears rare or, perhaps, difficult to recognize as the predominant presenting symptom. Paradoxically, executive function difficulty, primarily manifest as impaired problem-solving or decision-making, was present among the patients with LOAD rather than the patients with EOAD. This suggests that executive function difficulty may be a characteristic of LOAD as compared to EOAD.⁵

Investigators have concluded that EOAD and LOAD can be separate syndromes based on greater cortical deficits in EOAD, particularly affecting the parietal lobes.³⁶ Consistent with this hypothesis, both neuroimaging and neuropathological studies suggest more severe deficits in P/PT areas and less hippocampal atrophy in EOAD compared with LOAD.^{37–40} Voxel-based morphometry studies of EOAD have showed more widespread cortical atrophy than in LOAD and less atrophy in anterior hippocampus and amygdalae,^{41,42} and PET studies of EOAD show greater regional hypometabolism than those with LOAD.^{40,38} There are bilaterally overlapping areas of parietal and posterior temporal involvement in logopenic aphasia and in PCA,⁴³ and the different nonamnestic syndromes appear to be overlapping syndromes that vary in their regional cortical involvement in early stages.^{17,43} In this study, there is more left parietotemporal involvement with a language presentation and more right parietotemporal (and occipital) with a visuospatial presentation. In a recent clinicopathological study comparing patients with an aphasic presentation of AD with an amnestic presentation of AD, there was left-sided tangle predominance and higher neocortical-to-entorhinal tangle ratio in the language predominant patients. Finally, recent neuropathological findings identify a “hippocampal sparing” subtype of AD that is younger at death and has higher than expected neurofibrillary tangles in inferior parietal, superior temporal, and middle frontal association cortices.³²

Patients with EOAD with nonamnestic presentations could be genetically predisposed to relatively greater regional vulnerability in P/PT neocortex rather than in the more typical entorhinal–hippocampal system. The occurrence of EOAD is affected by genetic risk factors such as the presence of an apolipoprotein E e4 allele, the possibility of undetected autosomal dominant mutations, or an autosomal recessive inheritance.⁴⁴ This suggests that, in nonamnestic presentations of EOAD, there may be unidentified genetic or inheritable risk factors that predispose to an initial neocortical focus of neurofibrillary tangles, as further suggested by the 3 “tangle-predominant” autopsies in this series.

There are several potential limitations to this study. First and most apparent is that it is a retrospective review. This methodology, however, allowed for the inclusion of a large number of patients with EOAD who had the same basic clinical and neurocognitive

assessment and who had their diagnosis supported by functional neuroimaging. Second, the clinician determined the most important or salient symptom/symptoms reported by caregivers on initial presentation and did not assess changes in initial diagnosis over time. This study, however, included only patients whose presenting symptoms were corroborated by neurocognitive examination. It did not detect a change in the diagnosis of AD in those patients followed in the program. Third, the referral nature of our clinic may have resulted in a larger proportion of nonamnestic presentations than evident in the community. This, however, was not reflected in our LOAD comparison group. Finally, this study analyzed the clinical neuroimaging reports rather than the scans themselves. This was made necessary by the multiple different sources of these scans and the fact that, given the 10-year period of review, many of these scans were no longer available. Although the reports lack sensitivity for the consistent detection of changes, it remains significant that diverse neuroradiologists reported regional or laterality differences between subgroups of patients with EOAD.

In conclusion, the findings of this large review of patients with EOAD, and their comparison with LOAD, indicate that EOAD is composed of not only the youngest distribution of the typical amnestic patients with AD but also nonamnestic variants. These patients with EOAD with nonamnestic presentations vary in initial neuropathological location and suggest variations in the expression of the pathophysiology of AD, particularly in the neocortical distribution of neurofibrillary tangles. These patients are a window to understanding variations in the pathophysiology of AD, and future work should focus on prospective, clinical, neuroimaging, and pathological investigations of subgroups of patients with EOAD.

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Table 1

Early-Onset Alzheimer's Disease (EOAD) Versus Late-Onset Alzheimer's Disease (LOAD): Clinical and Demographic Characteristics

	EOAD, N = 125	LOAD, N = 56	Significance
Age of presentation	58.5 (5.86)	80.5 (9.19)	t = 19.40, P < .001
Age of onset	54.9 (5.67)	76.02 (5.60)	t = 23.25, P < .001
Duration, years	3.72 (2.44)	4.71 (3.20)	t = 2.28, P < .05
Sex, M/F	62/63	24/32	w ² = 0.46, NS
Handedness, R/L	119/6	49/7	w ² = 2.38, NS
Education, years	14.0 (4.2)	15.1 (3.24)	t = 1.74, NS
FHx	(47) 37.6%	26 (46.43%)	w ² = 0.91, NS
MMSE	21.01 (6.33)	23.41 (2.12)	t = 2.78, P < .01
Main cognitive impairment on presentation			
Memory	45 (36%)	49 (87.5%)	w ² = 41.05, P < .001
Language	33 (26.4%)	3 (5.4%)	w ² = 10.98, P < .001
Visuospatial	35 (28%)	1 (1.8%)	w ² = 15.03, P < .001
Executive ^a	0 (0%)	3 (5.4%)	w ² = 3.92, P < .05
Limb praxis	12 (9.6%)	0 (0%)	w ² = 4.31, P < .05

Abbreviations: M/F, male/female; R/L, right/left or ambidextrous; FHx, family history of first-degree relatives with dementia; MMSE, Mini-Mental State Examination; NS, not significant.

^aProblem-solving or decision-making.

Table 2

Early-Onset Alzheimer's Disease (EOAD) Presentation Subgroups: Clinical and Demographic Characteristics^a

	Amnestic, N ¼ 45	Language, N ¼ 33	Visuospatial, N ¼ 35	Limb praxis, N ¼ 12	Significance 4 groups
Age of presentation	55.6 (5.34)	59.73 (5.02)	60.91 (4.6)	58.92 (8.7)	F ¼ 7.07, P < .001 ^b
Age onset	52.52 (5.76)	55.91 (5.02)	56.82 (4.89)	55.83 (5.62)	F ¼ 4.99, P < .01 ^b
Duration	3.16 (2.01)	3.83 (2.2)	4.28 (3.05)	3.75 (2.41)	F ¼ 1.45, NS
Sex—M/F	21/24	17/16	19/16	5/7	w ² ¼ 0.81, NS
Hand—R/L	44/1	30/3	32/2	12/0	w ² ¼ 2.66, NS
Education	14.44 (4.21)	14.04 (5.21)	14.99 (3.52)	16.01 (3.12)	F ¼ 0.80, NS
FHx	13 (28.9%)	18 (54.5%)	12 (34.3%)	4 (33.3%)	w ² ¼ 7.18, NS
MMSE	22.18 (6.02)	18.36 (7.33)	21.22 (6.07)	22.1 (3.41)	F ¼ 2.64, NS
Main cognitive impairment on presentation	45 memory	16 fluency-effortful, halting, 13 word-finding, 8 reading or spelling, 2 auditory comprehension	16 localization, 9 general visual perception, 8 visual reading, 6 env. orientation, 4 dressing ability, 4 object recognition, 2 color appreciation, 2 driving ability	6 mechanics of writing, 2 manual dexterity, 4 specific complex motor activity (9 language) (2 acalculia)	

Abbreviations: M/F, male/female; R/L, right/left or ambidextrous; FHx, family history of first-degree relatives with dementia; MMSE, Mini-Mental State Examination; NS, not significant.

^aPost hoc comparisons using Bonferroni correction: Amnesia group has significantly lower ages of presentation and onset as compared to language and visuospatial groups.

Table 3 Early-Onset Alzheimer's Disease (EOAD) Presentation Subgroups: Neuropsychological Mental Status Tests^a

	Amnestic, N = 45	Language, N = 33	Visuospatial, N = 35	Limb praxis, N = 12	Significance 4 groups
Forward digit span	5.86 (1.08)	4.54 (1.22)	5.22 (1.45)	5.44 (1.13)	F = 6.01, P < .001 ^b
Backward digit span	2.97 (1.05)	1.75 (1.16)	3.15 (0.59)	2.33 (0.58)	F = 4.81, NS
"F" word fluency	8.54 (6.24)	5.22 (3.28)	7.57 (4.69)	8.86 (3.72)	F = 1.82, NS
Animal fluency	12.58 (5.86)	10.53 (5.24)	13.02 (4.92)	11.29 (4.03)	F = 1.52, NS
Mini-BNT (15)	13.34 (2.67)	8.91 (4.67)	11.48 (4.09)	11.8 (3.58)	F = 6.7, P < .001 ^b
CERAD (10) trial 3	4.46 (2.21)	3.47 (2.22)	4.83 (1.65)	5.26 (1.98)	F = 1.9, NS
Delayed recall	1.11 (1.71)	2.88 (2.37)	2.53 (2.45)	2.86 (3.08)	F = 5.07, P = .002 ^c
Recognition	7.5 (2.42)	8.41 (2.29)	8.21 (1.63)	8.52 (2.74)	F = 1.43, NS
Constructions (12)	9.27 (2.38)	9.88 (2.04)	3.46 (1.52)	7.0 (2.45)	F = 68.98, P < .001 ^d
Limb praxis (16)	15.89 (0.38)	15.61 (0.75)	14.91 (1.52)	10.08 (2.19)	F = 87.39, P < .001 ^d
Speech fluency (8)	7.76 (0.71)	5.70 (1.29)	7.69 (0.63)	5.58 (1.72)	F = 40.4, P < .001 ^e
Verbal repetition (8)	7.8 (0.63)	6.45 (1.03)	7.74 (0.70)	7.02 (1.41)	F = 19.12, P < .001 ^e
Comprehension (20)	19.60 (1.29)	18.0 (2.09)	19.6 (1.19)	18.58 (2.27)	F = 7.9, P < .001 ^b
Calculations (8)	6.23 (2.04)	6.52 (1.42)	5.03 (1.92)	3.52 (1.51)	F = 10.87, P < .001 ^d
Proverbs (4)	3.11 (1.23)	3.36 (0.86)	3.71 (0.57)	3.36 (1.12)	F = 2.49, NS
FAB (18)	13.91 (2.04)	13.72 (1.49)	14.11 (1.57)	13.42 (1.16)	F = 0.06, NS

Abbreviations: NS, not significant; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; BNT, Boston Naming Test.

^aBonferroni significance level for 16 tests set at P < .003.^bThe language group had significantly lower scores as compared to the amnestic group.^cThe amnestic group had significantly lower scores than the language group.^dThe visuospatial and limb praxis groups had significantly lower scores than the amnestic group.^eThe language and limb praxis groups had significantly lower scores than the amnestic group.

Table4

Early-Onset Alzheimer's Disease (EOAD) Presentation Subgroups: Neuroimaging Reports

	Amnestic, N ¼ 45	Language, N ¼ 33	Visuospatial, N ¼ 35	Limb praxis, N ¼ 12	Significance
MRI	30 Normal-mild	25 Normal-mild	16 Normal-mild	10 Normal-mild	9.20, NS
Atrophy	2 PT/P	7 PT/P	19 PT/P	2 PT/P	18.61, P < .001 ^a
	0 Left > right	6 Left > right	0 Left > right	0 left > right	17.57, P < .001 ^b
	10 Right > left	0 Right > left	2 Right > left	0 right > left	5.23, NS
PET hypometabolism	11 Hippocampal	2 Hippocampal	10 Hippocampal	0 hippocampal	31.02, P < .001 ^c
	0 Occipital	0 Occipital	11 Occipital	0 occipital	15.65, P < .001 ^d
	40 PT/P	31 PT/P	33 PT/P	9 PT/P	
SPECT ^e	0 Left > right	7 Left > right	0 Left > right	2 Left > right	16.99, P < .001 ^b
	0 Right > left	0 Right > left	12 Right > left	0 Right > left	32.92, P < .001 ^d
	0 Occipital	0 Occipital	8 Occipital	0 Occipital	21.61, P < .001 ^d
	5 PT/P	2 PT/P	2 PT/P	3 PT/P	

Abbreviations: PT/P, parietotemporal and/or parietal involvement; SPECT, single photon emission tomography; NS, not significant; MRI, magnetic resonance imaging; PET, positron emission tomography.

^aVisuospatial group significantly more than amnestic group.

^bLanguage group significantly more than amnestic group.

^cAmnestic group significantly more than visuospatial group.

^dVisuospatial group significantly more than amnestic group and language group.

^eNo reported asymmetry inc SPECT hypoperfusion.