Early- versus late-onset Alzheimer's disease: more than age alone

Chapter 3.1

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Abstract
Objective
Alzheimer's disease (AD) is the most common cause of dementia at older age. Although less prevalent before the age of 65 years, it is still the most frequent cause of early-onset dementia followed by frontotemporal dementia. The typical presentation of AD is memory dysfunction, however presentations with prominent cognitive impairment in other domains besides memory, like prominent apraxia, language problems or executive dysfunction may occur and are relatively more common in early-onset AD. In this retrospective descriptive study we determined the prevalence of non-memory presentations in a large sample of early-onset AD patients compared to late-onset AD.
Methods
The clinical files of 270 patients with AD starting before the age of 65 years and 90 patients with late-onset AD (≥ 65 years) were reviewed to assess clinical characteristics. Patients were classified as memory presentation and non-memory presentation according to their clinical presentation.
Results
The mean age of the early-onset group was 56 ± 5 years and 74 ± 6 years for the late-onset group. A third of the early-onset AD group presented with non-memory symptoms compared to only 6% in the late-onset group ($p < 0.001$). Within the group with non-memory presentations apraxia / visuospatial dysfunction was the most prevalent presenting symptom (12%).
Conclusion
Patients with early-onset AD often present with a non-memory phenotype, of which apraxia / visuospatial dysfunction is the most common presenting symptom. Atypical presentations of AD should be considered in the clinical differential diagnosis of early-onset dementia.

Introduction

In 1906 Alois Alzheimer presented the results of his post-mortem studies of a 51 year old patient, Auguste D, who developed dementia at a young age. She became the first patient who suffered from what was later called Alzheimer's disease (AD) [1]. The first symptom was jealousness towards her husband, soon afterwards she developed rapid loss of memory and disorientation in her own home. Alzheimer also described the presence of severe language disturbances and apraxia. She died four and half years after the disease onset and post-mortem examination revealed an atrophic brain with neurofibrillary pathology and unusual deposits in the cortex. Nowadays these features are recognized as typical for AD and this pathology can occur at younger and older age [2,3].

AD is the most common form of degenerative dementia at older and younger age (arbitrarily defined as first symptoms below 65 years of age) [4,5]. The most common and prominent presentation is impairment of anterograde episodic memory [6,7]. The inevitable progression of the disease over time leads to involvement of other cognitive domains [6]. However, there has been an increasing awareness that AD is not clinically homogeneous and patients can present with predominant impairment in other domains beside memory, including visuospatial function and praxis, language and executive skills [8-17]. It has been suggested that these non-memory presentations especially occur in patients with early-onset AD [18-22].

Only a few studies have investigated the prevalence of non-memory presentations of AD [13,14]. It remains unclear how common these atypical presentations are in a memory clinic population and whether their prevalence differs according to age at onset.

The aim of this retrospective study was therefore to investigate the prevalence of non-memory presenting symptoms among early-onset AD patients in comparison with a group of late-onset AD patients in a memory clinic setting. We hypothesized that especially younger patients present more often with prominent non-memory impairment and relatively preserved memory function.

Methods

Patients and clinical evaluation

We included 297 consecutive patients with early-onset AD who presented at the Alzheimer Center of the VU University Medical Center in Amsterdam from 1997 till 2007. For comparison we also included 90 patients with late-onset AD, randomly selected from the same time period. For the diagnostic procedure all patients underwent a standard battery of investigations including a patient and informant-based medical history, physical and neurological examination including mini-mental state examination (MMSE) [23], laboratory tests, neuropsychological assessment, EEG and MRI of the brain.

The diagnosis of probable AD was made according to the NINCDS-ADRDA criteria by a multidisciplinary team, including a neurologist, psychiatrist, neurophysiologist, neuropsychologist and specialized nurse [24]. When memory impairment was absent and other diagnoses were excluded, a diagnosis of possible AD was made. In all other cases a diagnosis of probable AD was made. In the majority of cases the diagnosis possible AD changed to probable AD, when memory impairment became present. Patients were followed up to confirm the clinical diagnosis for at least one year. All patients gave written informed consent for their clinical data to be used for research. The study was conducted in accordance with regional research regulations and conformed to the Declaration of Helsinki.

Post-mortem examinations were available from 7 patients. The diagnosis in another patient was confirmed by the presence of a *presenilin* 1 (PSEN 1) mutation.

Clinical characteristics at presentation were retrospectively rated from the patient files by 3 raters (EK, VL and YP). Twenty-seven cases were excluded because detailed information about their presenting symptoms was lacking. Patients were categorized according to presenting symptoms in two main groups: memory and non-memory impairment. This way of subdividing was described earlier and does not exclude the presence of other cognitive deficits [25].

We further subdivided the non-memory presentations in the following groups:

(I) *apraxia / visuospatial dysfunction*: This group included patients with either difficulties in spatial orientation, resulting in getting lost or problems in praxis, for example dressing apraxia (in the literature often referred to as biparietal dysfunction [12]). (II) *Language dysfunction*: Language impairment, both of the fluent and non-fluent type, has been reported to be a predominant presenting feature of AD, additional slight memory impairment is usually present [10,14,26,27]. (III) *aphasic-apraxic-agnosic syndrome*: This syndrome was characterized by a combination of language impairment, problems in praxis and agnosia and often mild memory impairment. This syndrome exceeds the clinical presentation of apraxia / visuospatial dysfunction alone as aphasic symptoms are also present.

(IV) *posterior cortical atrophy (PCA)*: These patients presented with progressive disturbances of vision, problems in reading, visual agnosia or components of Balint syndrome (ocular apraxia, simultanagnosia, optic apraxia) [16].

(V) *dysexecutive syndrome*: This syndrome was characterized by prominent executive dysfunction with or without behavioural change [9,28].

When there was disagreement about the presenting symptom, consensus was reached between at least 2 raters. Disease duration was estimated as the reported duration of symptoms until a diagnosis was made. Post-mortem examination was available from 7 patients.

Statistical analysis

For statistical analysis SPSS version 14.0 was used. Basic demographic data were examined using Chi-squared test for categorical data and t-tests for continuous data. Statistical significance was set at $p < 0.05$.

Results

Table 1 shows the demographics, disease duration, presenting symptoms and MMSE score of the patient groups. The mean age of first symptoms was 56 ± 5 years for the young patients and 74 ± 6 years for the elderly patients. Patients with early-onset AD had a longer disease duration compared to patients with late-onset AD (time in years, 3.4 ± 2 vs. 2.5 ± 2, p = 0.001). There was no difference in MMSE score between the two groups (mean MMSE score 20 ± 6 vs. 21 ± 5, p = 0.1).

Table 1. Demographic and clinical characteristics by patient groups

	Early-onset Alzheimer's disease	Late-onset Alzheimer's disease
N total	270	90
Age (at first symptoms)	56 (5)	74 (6)
Females	143 (53%)	50 (56%)
Duration of symptoms (years)	3.4 (2)*	2.5 (2)
MMSE [a]	20 (6)	21 (5)
Memory-impairment	183 (68%)	85 (94%)
Non-memory impairment	87 (32 %) #	5 (6%)

Data are presented as mean (SD) and median or N (%)
* significant difference ($p < 0.05$) compared to late-onset AD
# significant difference ($p < 0.001$) compared to late-onset AD
[a] MMSE available for 309 subjects

One third of the patients with early-onset AD presented with non-memory impairment compared to only 6% in patients with late-onset AD ($p < 0.001$).

In table 2 the prevalence of the different non-memory presentations is shown. In patients with early-onset AD, apraxia / visuospatial dysfunction was the most frequent non-memory presentation(12%), followed by language impairment (9%) and an aphasic-apraxic-agnosic syndrome (8%), whereas executive dysfunction and PCA occurred less often (2% vs. 1 %). However, in patients with late-onset AD, 2% presented with an aphasic-apraxic-agnosic syndrome and 1 % with either apraxia / visuospatial dysfunction, language impairment or an executive dysfunction and none of the patients presented with PCA.

Table 2. Subdivision of non-memory symptoms by patient groups

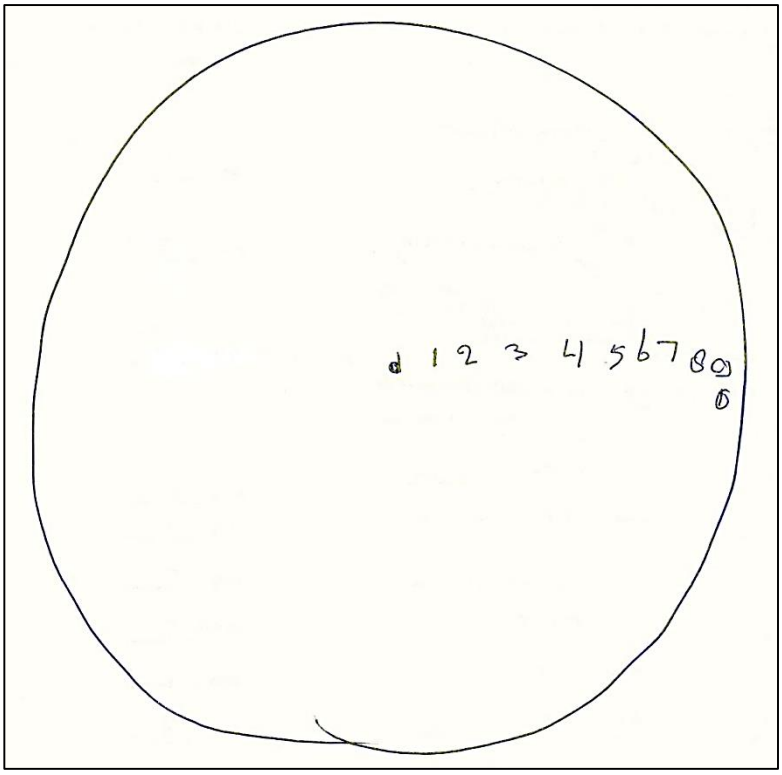
	Early-onset Alzheimer's disease	Late-onset Alzheimer's disease
Apraxia / visuospatial dysfunction	33 (12%)	1 (1%)
Language syndrome	25 (9%)	1 (1%)
Aphasic-apraxic-agnosic syndrome	22 (8%)	2 (2%)
Dysexecutive syndrome	4 (2%)	1 (1%)
Posterior Cortical Atrophy	3 (1%)	0 (0%)

Data are presented as N (%)

Post mortem examination was available from 7 patients: 3 patients with a non-memory presentation and 4 patients with a memory presentation. AD pathology was confirmed in all cases. There was no main difference in the distribution of AD pathology except for 2 patients. The first patient presented with apraxia / visuospatial dysfunction (case 1) and post-mortem examination showed AD pathology mainly in the parietal lobes. In the second patient, with a memory presentation, AD pathology was mostly found in the frontotemporal lobes. The patient with the PSEN 1 mutation presented with memory impairment.
Below we give case descriptions as an illustration of two different atypical presentations.

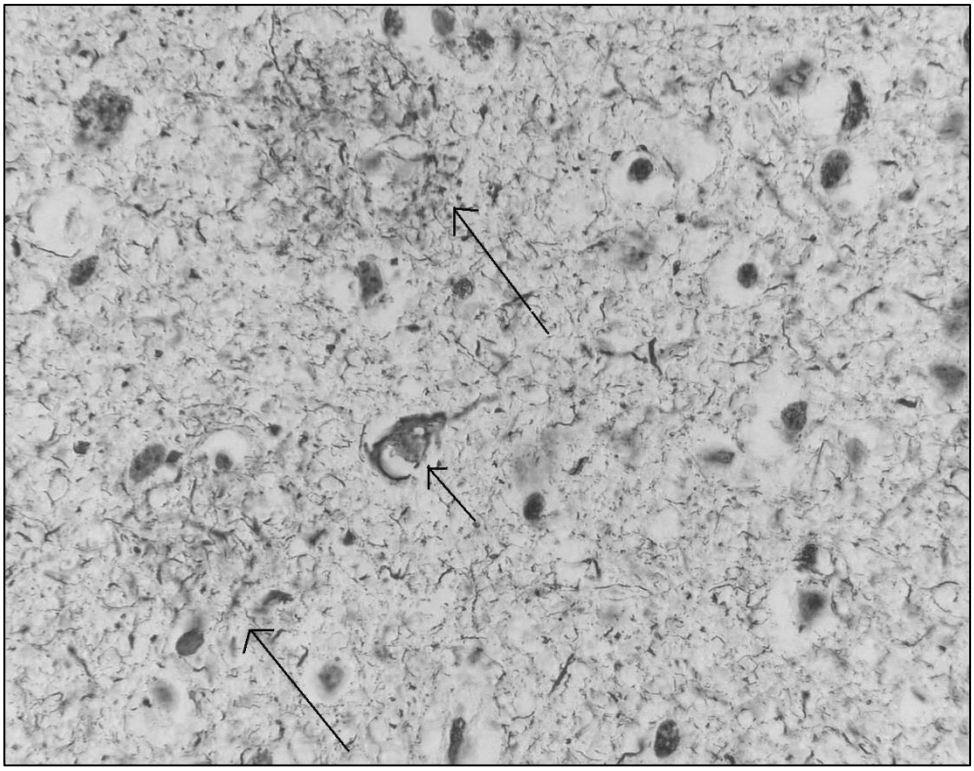
Case 1 apraxia /visuospatial dysfunction:
This 57 year old right-handed electrical mechanic presented at our memory clinic with a 3 year history of problems in activities in daily living and problems at work. He had troubles with writing, calculating and became more and more apractic. He was disorientated in place and at his work he had difficulties with making (routine) electrical connections. There were mild memory problems, that did not interfere with daily life activities and there was no change in behaviour. Neurological exam showed prominent apraxia and mild memory dysfunction. He was not able to imitate hand movements, copying of drawings and clock drawing was disturbed (see figure 1). Spontaneous speech was unremarkable. His MMSE score was 23/30. MRI of the brain showed mild to moderate parietal atrophy, without medial temporal lobe atrophy. A diagnosis of possible AD was made. During 6 years of follow up his language and visuospatial function deteriorated, he became severely apractic, but his memory remained relatively preserved. Repeated MRI showed progressive severe parietal atrophy and moderate medial temporal lobe atrophy. He died 10 years after the first symptoms. Post-mortem examination showed AD pathology, mainly located in the parietal lobes (see figure 2).

Figure 1.



Drawing of a clock by a patient presenting with apraxia and visuospatial dysfunction

Figure 2.



Results of neuropathological microscopical examination after autopsy, revealing the typical pathological findings in AD. The short arrow points at the neurofibrillary tangles and the large arrows point at the plaques. This patient presented with apraxia / visuospatial dysfunction and AD pathology was mainly found in the parietal lobes

Case 2 language dysfunction:

This 62 year old right-handed retired physiotherapist presented with a two year history of language problems. She had troubles finding the right words and expressing herself in the communication with others, but had no other complaints. She did not experience memory dysfunction. Her children noticed mild forgetfulness and had to take over her financial administration. There were no other problems in activities of daily living. Neurological exam revealed prominent language dysfunction, with a fluent speech with word finding problems and semantic and phonemic paraphasias, decreased understanding of sentences and difficulties in picture naming. There were also disturbances in categorical fluency. Her MMSE score was 21/30. MRI of the brain showed severe diffuse atrophy with medial temporal lobe atrophy on the left side more than on the right side, but no lateral or polar temporal atrophy. A diagnosis of possible AD was made.

During the 4 years of follow up she deteriorated and became completely dependent in activities of daily living. The diagnosis was changed into probable AD. There were no prominent behavioural disturbances. She was admitted to a nursing home four years after the first symptoms.

Discussion

It is well known that a presentation of progressive amnestic disorder with gradual involvement of language, visuospatial abilities and behaviour is likely to represent AD pathology [6,11]. However, there is a growing understanding that patients with AD may also present with marked disproportionate impairment in a single cognitive domain other than memory [8-17]. In this retrospectively collected large cohort we found that the prevalence of non-memory presentations in patients with early-onset AD is five times higher than in patients with late-onset AD. These presentations consisted most often of apraxia / visuospatial dysfunction, followed by language impairment and an aphasic-apraxic-agnosic syndrome, whereas only a small minority had prominent executive dysfunction or visual impairment.

Several studies have found that some patients present with predominant visuospatial problems or apraxia, which precede the memory loss usually seen in AD and underlying AD pathology in these patients has been confirmed in a number of studies [8,12,14-16,29,30]. Both the terms PCA and biparietal dysfunction are used to describe this syndrome. Whereas the former is mostly used for patients with predominant visual dysfunction, with atrophy particularly located in the posterior regions, the latter describes patients with particularly praxis - and visuospatial dysfunction with atrophy mainly in the parietal region [12,16]. In our study in early-onset AD, biparietal dysfunction occurred more often than predominant visual dysfunction (12% vs. 1%), whereas in the late-onset group only 1% reported biparietal dysfunction and none of the patients presented with prominent visual dysfunction. None of our patients with biparietal dysfunction or visual dysfunction fulfilled the clinical criteria for vascular dementia, dementia with Lewy bodies, corticobasal degeneration or Creutzfeld Jacob disease, forming the most relevant differential diagnosis of this clinical presentation.

Patients with language problems can present with a wide range of clinical symptoms, due to a variety of underlying causes [31]. Primary progressive aphasia (PPA) is a clinical syndrome characterized by isolated decline in language functions due to neurodegeneration and covers the clinical subtypes progressive nonfluent aphasia (PNFA), semantic dementia (SD) and the logopenic variant (LPA) [26,32,33]. PNFA is characterized by effortful speech production, phonological and grammatical errors and word retrieval difficulties, whereas in SD there is an impairment in word and object meaning, leading to a fluent, empty but grammatically correct speech [33]. LPA is characterized by decreased spontaneous language production with frequent word finding pauses and phonemic paraphasias, whereas motor speech and grammar are preserved [26].

The pathology causing PPA is most often of the non-Alzheimer type, including Frontotemporal lobar degeneration (FTLD), although underlying AD pathology has also been reported [10,14,15,27,34]. In our patient group, no subjects fulfilled the clinical criteria for PNFA, SD or LPA. The language impairment we found was heterogeneous, including fluent but empty speech, phonemic and semantic paraphasias and difficulty in picture naming.
Although in our study a presentation with an aphasic-apraxic-agnosic syndrome was the third most common non-memory presentation, little is known about this particular syndrome. The patients in our group presented with apraxia, visual impairment and language problems and the clinical picture therefore exceeds that of biparietal syndrome or PCA alone. Memory was relatively spared. Only one study found anosognosia, severe visuospatial impairment, apraxia and fluent aphasia, with relative sparing of memory function in a patient with a known preseniline 2 mutation (M239V) [35]. More clinicopathological studies are necessary to determine whether this combination of symptoms represents a clinical subtype of AD or whether other underlying pathology is responsible for this syndrome.
Frontal impairment, like behavioural disturbances or a dysexecutive syndrome is a well-known symptom in frontotemporal dementia (FTD). In the differential diagnosis of FTD, AD is often mentioned. However, personality and behaviour change, characteristic for FTD, is relatively rare in AD. Apathy is the most prominent behaviour change in AD and its prevalence increases with increasing dementia severity [6]. Executive dysfunction is common in patients with established AD. Rarely, behaviour change or executive dysfunction is the most salient presenting symptom in AD. We found executive dysfunction rather than behavioural changes in a minority of our patient group. Therefore none of the patients fulfilled the criteria for FTD.

Little is known about what causes the atypical presentations and why they seem to occur more often in young patients. It has been suggested that the different clinical phenotypes of AD reflect the involvement of different genotypes. AD patients with a non-memory phenotype had a lower proportion of ApoE-ε4 alleles in comparison to AD patients with a memory phenotype [25]. Differences in genetic makeup or environmental influences could be responsible for the atypical presentations of AD especially seen in younger patients. Further clinicopathological studies are necessary to search for an explanation why young patients present more often with non-memory impairment and if there is a correlation between clinical symptoms and affected brain regions.
In this study young patients had a longer disease duration, defined as period between first symptoms and time of diagnosis, which has been found also by others [36]. This is probably due to the fact that younger patients are often misdiagnosed with for instance psychiatric disorders. Especially when patients present with atypical symptoms it is understandable that making a diagnosis takes more time [37]. It is important to consider atypical presentations of AD in the differential diagnosis of non-memory syndromes at a younger age.

To the best of our knowledge, this is the first study to determine the prevalence of atypical presentations in a large cohort of early-onset AD patients. A weakness of our study might be that pathological or genetic confirmation of the diagnosis AD was available in only 8 cases, 3 of which had a non-memory presentation and therefore we cannot fully exclude other or mixed underlying pathology.
Furthermore, in all patients an extensive clinical evaluation took place, the diagnosis was made in a multidisciplinary meeting and the patients were followed up to confirm the diagnosis. Moreover, MRI was often applied serially to exclude alternative disorders.
The relative high prevalence of non-memory presentations in early-onset AD might be attributable to the setting of our memory clinic, being a tertiary referral center, but this cannot fully explain the different clinical characteristics between the younger and older patients.
With this study we emphasize that early-onset AD is more variable in its clinical presentation than late-onset AD. This observation argues against the emphasis put on memory impairment as a core criterion in the newly proposed research criteria [38]. Our data may be of help when revising the NINCDS-ADRDA criteria.

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