Characterization of patients with early vs. late-onset Alzheimer´s dementia

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Abstract

Introduction: Alzheimer´s dementia (AD) has an early and a late onset. More information is needed regarding risk factors according to the age of onset of AD. The objective is to characterize the sociodemographic, anthropometric, laboratory and genetic variables as well as the history of patients with a *de novo* diagnosis of AD, by age of onset, at the Hospital Universitario C.A.R.I.´s mental health site over a period of two years.

Methods: a cross-sectional descriptive study of 39 patients with a *de novo* diagnosis of AD. A questionnaire was completed, paraclinical studies were ordered and a blood sample was obtained for APOE genotyping. The IBM SPSS 21 software was used for analysis.

Results: 82.05% had late-onset and 17.95% had early-onset AD. Of those with early-onset AD, 57.14% were females, as were 71.90% of those with late-onset AD. 71.44% of those with early-onset AD were married and 53.12% with late-onset AD were widowed. Only 14.29% with early-onset and 18.75% with late-onset AD had optimal LDL levels. Altogether, 79.49% of the population was heterozygous for the ε4 allele. 71.43% of those with early-onset AD had a family history of dementia.

Discussion: age is the main factor associated with AD and females were more frequent in both groups. Social relationships play a role in early detection of symptoms. Lipid profile abnormalities were seen in both groups. Having at least one ε4 allele is a frequent finding in AD. Having a first-degree relative with dementia and/or Alzheimer´s was more frequent in early-onset AD. **(Acta Med Colomb 2020; 45. DOI: https://doi.org/10.36104/amc.2020.1316).**

Key Words: *APOE, dementia; Alzheimer´s disease, early onset; Alzheimer´s disease, late onset.*

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Introduction

Alzheimer's disease (AD) is a degenerative disease characterized by multiple cognitive deficits and deterioration of the overall intellectual capacity, interfering with the individual's occupational and social functioning (1). Disease progression is divided into three stages; however, in principle, two types of AD were recognized: senile and presenile, based on whether the symptoms began before or after age 65 (2). Before age 65, about 10% of patients present the familial or early-onset form, which has been associated with an autosomal dominant inheritance pattern and mutations on various genes. After age 65, Alzheimer's-type dementia (ATD) presents in the sporadic or late-onset form, influenced by susceptibility factors which interact with environmental factors (1).

Alzheimer´s disease is a global public health problem, as it is estimated that more than 50 million people live with dementia (3). In Colombia, the prevalence of dementia is 1.8-3.4% in people over the age of 65-75, respectively (4). A total of 2,018 patients were evaluated in a Bogotá clinic, of whom 49.56% were diagnosed by consensus as having AD (4). Strategies and more national studies are needed, especially in the Caribbean region, aimed at obtaining more knowledge of the risk factors, which will allow an adequate and early treatment approach to improve the patients' quality of life (5-7). The objective of this study was to characterize the sociodemographic, anthropometric, laboratory, genetic and historical variables of patients with a *de novo* diagnosis of ATD, as well as age of onset, at the mental health branch of the Hospital Universitario C.A.R.I., over a period of two years.

Materials and methods

A descriptive cross-sectional study was carried out using consecutive convenience nonrandom sampling of patients with a *de novo* diagnosis of ATD at the mental

health branch of the Hospital Universitario C.A.R.I. in Barranquilla, Colombia from 2014-2016. The Ethics Committee of the Universidad del Norte approved the performance of the study.

Initially, probable AD was diagnosed according to the patient's symptoms and clinical presentation, using the *National Institute on Aging, Alzheimer's Association* (8) and ICD-10 (9) criteria. Between 10 and 15 days after the initial consult, a diagnosis of possible AD was made according to the *Alzheimer's Association* (8) criteria, based on the neuropsychological assessment, and imaging and paraclinical test results. A definitive diagnosis of AD was not made as no *post-mortem* biopsies were performed during the course of the study. Patients under the age of 65 were classified as early-onset ATD and those over the age of 65 as late-onset ATD (10). The study inclusion criteria were: age over 45 years, a *de novo diagnosis of ATD by neuropsychological assessment and the diagnostic criteria of the National Institute on Aging, Alzheimer's Association* and ICD-10, a patient in the neurology outpatient department of the Hospital Universitario C.A.R.I mental health branch, a lifelong resident of the Atlántico Department, a signed consent form and having an adult companion. Patients with brain structure anomalies or other causes of their symptoms such as mixed, vascular, or frontotemporal dementias, tumors and vitamin B12 deficiency, among others, were excluded.

The variables included were: sociodemographic characteristics (age, sex, marital status), anthropometric measurements (BMI), laboratory measurements (fasting blood sugar, total cholesterol, LDL, HDL and triglycerides), genetic measurements (*APOE) and personal, family, disease and toxicological history (history of smoking, arterial hypertension, diabetes mellitus, hyperlipidemia, a relative with dementia and a relative with Alzheimer's) in patients with a de novo diagnosis of ATD. The history information was obtained from self-reported data on a structured questionnaire; laboratory measurements from results obtained from each patient's insurance company, and genotyping of the APOE gene from analysis of a blood sample drawn by the researchers. A calibrated scale and stadiometer were employed to obtain the body mass index (BMI). The cut-off points for total cholesterol, LDL, HDL and triglycerides were categorized according to the Adult Treatment Panel III* (11) guidelines. The intermediate HDL cholesterol category corresponds to levels between 41 mg/dL and 59 mg/dL. The cut-off points for fasting blood sugar were categorized according to the *Standards of Medical Care in Diabetes* (12).

Genotyping of the APOE gene

The samples were processed and analyzed at the Genetics Laboratory of the Universidad del Norte. A 5 mL sample of peripheral blood was obtained from each patient in a vacutainer containing EDTA. The genomic DNA was obtained using the commercial UltraClean TM Blood DNA Isolation Kit® (*Mo Bio Laboratories, Inc*.). In order to identify the various alleles, a region of exon 4 of the *APOE gene was amplified. This region contains polymorphic sites 112 and 158 and is where the nucleotide substitutions occur which give rise to the various APOE isoforms. The specific primers* F4 5´.- ACAGAATTCGCCCCGGCCTGGTACAC-3´ forward and F6 5´.-TAAGCTTGGCACGGCTGTCCA AGGA-3´ backward (*Invitrogen Life Technologies, USA*), were used for the amplification, as described by Hixson and Vernier (13), through which an amplified product of 244 bp was obtained.

Amplification was performed using ICycler® (BioRad) equipment under the following conditions: an initial denaturing at 95°C for three minutes, followed by 30 denaturing cycles at 95°C for 45 seconds, hybridization at 62°C for 30 seconds, extension at 72°C for 30 seconds and a final elongation at 72°C for seven minutes. Then the samples were digested with five units of *HhaI restriction endonuclease* (Gibco-BRL, Rockville, MD, USA) for 16 hours at 37°C. The fragments obtained were separated by 8% polyacrylamide gel electrophoresis for four hours at 60 volts, and the various characteristic bands of each genotype were observed. Finally, real-time PCR was performed with TaqMan (Applied Biosystems) allelic discrimination, using assay ID C_3084793_20 (rs429358) for position 112 and assay ID C_904973_10 (rs7412) for position 158 on a 7500 *Real Time PCR System machine. The results were seen as amplification curves recognized by the tagging for each probe (VIC/FAM), on* 7500 v2.0.1 software.

Statistical analysis

A univariate analysis with descriptive statistics was carried out which expressed the absolute and relative frequencies of qualitative variables, and measures of central tendency and dispersion for quantitative variables. Allelic and genotypic frequencies were obtained by direct count.

Patients were divided into two groups by age of onset, the first with early-onset ATD (less than 65 years) and the second with late-onset ATD (equal to or greater than 65 years), to subsequently determine the presence of the sociodemographic, anthropometric, laboratory, genetic and history variables. *IBM SPSS Statistics* version 21 software was used.

Bias control

The questionnaire was designed using simple and understandable vocabulary. The information was provided by the patient and/or his/her companion. For each laboratory sample, the reported value was assessed, taking into account the normality range established by each laboratory for each test. A nonsignificant lacunar infarct was found in one patient on brain imaging follow up. However, he was not excluded from the study since the ATD diagnosis was made by prior neuropsychological assessment with initial imaging showing no vascular disorders.

Results

The population consisted of 39 patients. Altogether, 82.05% of the patients had late-onset ATD, while 17.95% had an early onset. The average age of onset for the early-onset ATD group was 60.85 ± 3.48 years (median 62, IQR 57-64). In the late-onset group it was 78.87 ± 5.39 years (median 78, IQR 76-83). Females made up 57.14-71.90% of the population with early-onset and late-onset ATD, respectively. A total of 71.44% of those with early-onset ATD were married, while 53.12% of those with late-onset ATD were widowed. Altogether, 57.14% of those with early-onset ATD were overweight, while 40.63% of those with late-onset ATD were overweight (Table 1).

Altered glucose and hyperglycemia were seen in 9.37-6.25% of patients with late onset. On the lipid profile, 42.86% with early onset and 25% with late onset had borderline high total cholesterol, while only 18.75% of those with late-onset ATD had high levels. In terms of HDL cholesterol, 42.86% of the early onset group had an intermediate level and 28.75% a low level. In the late onset group, 62.5% had intermediate levels and 12.5% had low levels of HDL cholesterol. Only 14.29% of early-onset ATD had optimal LDL levels, similar to the late-onset group with 18.75%. With triglycerides, 14.29% of early-onset ATD were categorized at both the upper limit of normal and high, while for those with late onset, 15.63% were at the upper limit of normal and 9.37% were high (Table 2).

For *APOE* gene polymorphism, 79.49% of the general population with ATD were heterozygous for the ε4 allele, of whom 64.10% had ε3/ε4 and 15.39% had ε2/ε4. A total of 12.82% of the ATD population were homozygous for the ε3 allele and 2.56% were homozygous for the ε2 allele; 5.13% were ε2/ε3. No homozygotes for the ε4 allele were found. Altogether, 71.44% of the patients with early-onset ATD had allelic heterozygosity for *APOE* ε4, with 57.16% being ε3/ε4 and 14.28% ε2/ε4. A total of 81.24% of those with late-onset ATD had at least one *APOE* ε4 allele, with 65.62%

Table 1. *Description of the sociodemographic and anthropometric variables of patients with a de novo diagnosis of ATD, by age of onset, at the mental health branch of the Hospital Universitario C.A.R.I over a period of two years.*

Variable	Type of AD onset			
	Early (n=7)		Late (n=32)	
	Number	(%)	Number	(%)
Sex				
Female	4	57.14	23	71.90
Male	3	42.86	9	28.10
Marital status				
Single	1	14.28	2	6.25
Married	5	71.44	11	34.37
Common law	0	0.00	1	3.13
Divorced	0	0.00	1	3.13
Widowed	1	14.28	17	53.12
BMI				
Underweight	0	0.00	3	9.37
Normal	3	42.86	15	46.88
Overweight	4	57.14	13	40.63
Grade I obesity	0	0.00	1	3.12

Table 2. *Description of laboratory variables in patients with a de novo diagnosis of ATD, by age of onset, at the mental health branch of the Hospital Universitario C.A.R.I over a period of two years.*

Variable	Type of AD onset			
	Early (n=7)		Late (n=32)	
	Number	(%)	Number	(%)
Fasting blood sugar				
Normal	7	100.00	27	84.38
Altered glucose	0	0.00	3	9.37
Hyperglycemia	0	0.00	2	6.25
Total cholesterol level				
Desirable	4	57.14	18	56.25
Borderline high	3	42.86	8	25.00
High	0	0.00	6	18.75
HDL cholesterol level				
Low	2	28.57	4	12.50
Intermediate	3	42.86	20	62.50
High	2	28.57	8	25.00
LDL cholesterol level				
Optimal	1	14.29	6	18.75
Almost optimal	4	57.13	17	53.12
Borderline high	1	14.29	4	12.50
High	1	14.29	4	12.50
Very high	0	0.00	1	3.13
Triglyceride level				
Normal	5	71.42	24	75.00
Upper limit of normal	1	14.29	5	15.63
Elevated	1	14.29	3	9.37

having ε3/ε4 and 15.62% having ε2/ε4. There was allelic homozygosity for *APOE* ε3 in 14.28% of the early onsets, while in the late-onset group there were 12.5% with ε3/ε3 and 3.13% with allelic homozygosity for *APOE* ε2 (Table 3).

A history of smoking was found in 57.14% of the early-onset group and 59.37% of the late-onset group. Both 75% of early-onset ATD (ex)smokers and 73.68% of late-onset (ex) smokers had smoked for more than five years. Of those with early-onset ATD, 42.85% were hypertensive and 28.57% had hyperlipidemia. Of those with late-onset ATD, 46.87% were hypertensive, 12.5% were diabetic and 25% had hyperlipidemia. Altogether, 71.43% of those with early-onset ATD had a family history of dementia, 100% of the cases being in first-degree relatives. Of the 59.37% of late-onset group members with a family history of dementia, 94.74% of the cases were in second-degree relatives. Likewise, 57.14% of the early-onset group had relatives with AD, these being first-degree relatives. Of the 43.75% of the late-onset group with a family history of AD, 92.86% were second-degree relatives (Table 4).

Table 3. *Description of genetic variables in patients with a de novo diagnosis of ATD, by age of onset, at the mental health branch of the Hospital Universitario C.A.R.I over a period of two years.*

Variable	Type of AD onset			
	Early (n=7)		Late (n=32)	
	Number	(%)	Number	(%)
APOE polymorphism				
ε2/ε2	0	0.00	1	3.13
ε2/ε3	1	14.28	1	3.13
ε2/ε4	1	14.28	5	15.62
ε3/ε3	1	14.28	4	12.50
ε3/ε4	4	57.16	21	65.62
ε4/ε4	0	0.00	0	0.00

Discussion

Alzheimer's disease is a primary, progressive, irreversible neurodegenerative central nervous system disease, and is the main cause of dementia (14). Age is the most significant

Table 4. *Description of personal, toxicological and family history variables in patients with a de novo diagnosis of ATD, by age of onset, at the mental health branch of the Hospital Universitario C.A.R.I over a period of two years.*

Variable	Type of AD onset			
	Early (n=7)		Late (n=32)	
	Number	(%)	Number	(%)
History of smoking				
Yes	4	57.14	19	59.37
No	3	42.86	13	40.63
Duration of smoking in smokers				
From 1 to 5 years	1	25.00	5	26.32
More than 5 years	3	75.00	14	73.68
History of hypertension				
Yes	3	42.85	15	46.87
No	4	57.15	17	53.13
History of diabetes mellitus				
Yes	0	0.00	4	12.50
No	7	100.00	28	87.50
History of hyperlipidemia				
Yes	2	28.57	8	25.00
No	5	71.43	24	75.00
History of a relative with dementia				
Yes	5	71.43	19	59.37
No	2	28.57	13	40.63
History of a first-degree relative with dementia				
Yes	5	100.00	7	36.84
No	0	0.00	12	63.16
History of a second-degree relative with dementia				
Yes	0	0.00	18	94.74
No	5	100.00	1	5.26
Family history of AD				
Si	4	57.14	14	43.75
No	3	42.86	18	56.25
History of a first-degree relative with AD				
Yes	4	100.00	3	21.43
No	0	0.00	11	78.57
History of a second-degree relative with AD				
Yes	0	0.00	13	92.86
No	4	100.00	1	7.14

risk factor for AD; specifically, being more than 65 years old. Thus, the greater the age the higher the prevalence and incidence of the disease (1, 15). In Colombia, the prevalence of dementia varies according to the study, age cut-off points and territory, with figures between 1.3% and 39.4% (16-20). The southwestern and eastern regions of Colombia have the highest prevalence of dementia in people 50 and 70 years old (4, 16).

The two forms of ATD are early onset and late onset. The familial or early-onset form appears before age 65, has a rapid progression and autosomal dominant inheritance and is related to mutations of the *amyloid precursor protein, presenilin 1 or presenilin 2* genes. The sporadic or late-onset form manifests with an age at onset over 65, is influenced by interaction between susceptibility and environmental factors and appears gradually with slow progression and a predominance of memory deterioration over intellectual disability (1, 2, 9, 21). In our study, the population with late-onset ATD was larger than that with early-onset, similar to what has been reported in the literature (21).

The results of this study showed that females were more frequent in the general population and by age of onset, similar to what has been reported in the literature, since women over the age of 55 have a double risk of having dementia due to a greater life expectancy and a higher incidence of dementia in older ages (6, 22). The gender differences may be due to biological or survival differences or to differences in the behavior and exposure of individuals (23), with the greatest effect occurring in *APOE ε4 carriers (24, 25)*.

In our study, most of the patients in the early-onset ATD group had regular company in their homes, while patients with late-onset ATD were more frequently widowed, which leads us to believe that the social environment may play a role in early diagnosis and timely treatment of the disease. Individuals with more social relationships have a lower incidence of dementia and early detection of symptoms, since a relative may note changes in the individual's cognitive function, behavior and functioning (26). In married early-onset ATD patients, the presence of a companion leads to diagnosis in the initial, early stages of the disease (27).

In this study, overweight was found to be more common in the early-onset ATD group than the late-onset group. Overweight has been associated with a lower age of onset of AD (28). Adiposity produces cognitive deterioration and neuronal degeneration, primarily in people with a high degree of inflammation (29). Likewise, obesity affects cognitive and motor functions (30, 31) due to altered insulin metabolism, whose receptors are densely expressed in the temporal and frontal regions and hippocampus, which are responsible for memory formation (32, 33). Blood sugar levels in this study were within normal limits for the entire early-onset group and most of the late-onset group, despite the fact that hyperglycemia causes tissue inflammation and increased oxidative stress and glycosylated products (34) in patients with AD compared to healthy individuals (32).

Within the laboratory measurements, LDL cholesterol levels outside of the optimal range and HDL cholesterol levels outside of the high range were frequent in both the early-onset and the late-onset groups. The relationship between early-onset ATD and elevated LDL cholesterol has been reported, even independently of *APOE* (35). High HDL levels are associated with a lower risk of dementia and both probable and possible AD (36), since its protective effect is based on reduced neuroinflammation and protection against memory deficits (37). In the current study, triglyceride levels were most frequently found within the normal range for both ATD groups, despite the fact that serum triglyceride levels have been found to be elevated in patients with AD, suggesting a potential risk factor for cognitive disorders (38). The apolipoprotein E gene (*APOE*) is the only gene which confers individual susceptibility to both sporadic and familial forms of ATD (2, 21). The *APOE* gene, located on the long arm of chromosome 19 (19q13.2), has three alleles (ε2, ε3 and ε4) which are co-dominantly transferred and code for three protein isoforms (E2, E3 and E4) which modify protein structure and affinity for the receptor, affecting lipid catabolism (39, 40). They differ in C/T nucleotide changes on exon 4 at positions 112 and 158 of the amino acid sequence (a change of arginine or cysteine) and result in six possible genotypes: ε2/ε2, ε3/ε3, ε2/ε3, ε3/ε4, ε2/ε4 and ε4/ε4 (41).

The most commonly reported genotype in the general population of Barranquilla, Medellín, Quindío, Bogotá and Valle del Cauca (Colombia) is ε3/ε3, generally followed by ε3/ε4, ε2/ε3 and ε2/ε4 (42). The presence of ε4/ε4 and ε2/ε2 genotypes in the general population varies by Colombian city (42). In this study, in both the ATD population as well as in the early-onset and late-onset groups, being heterozygous for the ε4 allele was the most frequent finding. In the ATD population, the most common genotype was ε3/ε4, followed by ε2/ε4, ε3/ε3, ε2/ε3 and, finally, ε2/ε2. In the early-onset ATD group, the most common genotype was ε3/ε4, followed equally by ε2/ε3, ε2/ε4 and ε3/ε3, while in the late-onset ATD group the most common genotype was ε3/ε4, followed by ε2/ε4, ε3/ε3 and, finally, an even split between ε2/ε2 and ε2/ε3.

Although homozygotes for ε4 were not found in both groups, there were homozygous patients for ε3, which is considered to be the most common allele in the general population. The ε4 allele is associated with low neurocognitive performance, particularly in episodic memory, and increases the risk of developing late-onset ATD (43). The ε4 allele is considered to be a risk variant compared to the ε3 allele (neutral) and ε2 (protective); thus, *APOE* ε4 is considered to be the greatest genetic risk factor for developing AD (44-46). Being a carrier of a ε4 allele increases the risk of AD three to ten times (1), decreases the age of onset for the late-onset ATD group (47) by one or two decades (48),

and may influence the increase in total cholesterol, LDL and triglyceride levels (49). A homozygous ε2 case, the rarest genotype in the general population, was found in the study in the late-onset ATD population. ε2 carriers have a lower risk and a delayed age of onset of AD, compared to ε3 homozygotes and ε4 carriers (41).

Within the personal history in our study, the habit of smoking, specifically for more than five years, was seen in most of the patients, both early as well as late-onset. Smoking doubles the risk of developing dementia and AD, as it accelerates cognitive function deterioration, induces synaptic changes and causes neurodegeneration in early stages (50). Smoking is associated with a thinner cortex in regions that show significant atrophy in early-onset ATD (51). In this study, not having a history of arterial hypertension was more frequent for both groups. Elevated blood pressure precedes AD by decades but decreases in the years prior to the onset of dementia (52).

In this study, a family history of dementia was more frequent for both groups, with first-degree relationships for the early-onset group and second-degree relationships for the late-onset group. In the early-onset group, a family history of AD was more frequent, all of whom were first-degree relatives. The heritability of AD is high (53), since the first-degree relatives (parents and children) of a person with AD have a 20% risk of developing the disease (54). Greater memory impairment and cortical thinning have been associated with a first-degree family history of AD (55). A family history of dementia is associated with decreased grey matter in the regions typically affected by AD (56). In the late-onset group in our study, a family history of AD was more frequent in second-degree relatives. When several individuals within one family have AD, the risk increases (54).

The limitations of this study include selection bias, given that it employed a consecutive convenience sample, since the data were obtained from a departmental hospital, which limits the generalization of the results to the population of the Caribbean region. Due to the sample size and descriptive methodology of the study, associations between the study factors and cognitive deterioration are not confirmed; however, knowledge is described, contributed and compared with what other statistical studies have shown. Schooling, length of work life and sedentary behavior were not included as variables in this study. Laboratory test variability was introduced since these studies were performed according to each patient´s health insurance.

Conclusions

This study was able to identify and describe risk factors in patients with ATD in a departmental hospital in Barranquilla, Colombia. Age is the main factor associated with the onset of ATD, and thus late-onset ATD was found more frequently than early-onset in the study population. Females were more frequent in both groups, just as has been reported. Social relationships play an important role in early recognition of symptoms, according to what was seen in this study. Overweight was more frequent in the early-onset ATD population and has been associated with a lowered age of onset of AD. The lipid disorders seen in both groups in this study have already been reported and associated with a risk of dementia and AD. The findings of the genetic study support the theory that having at least one ε4 allele of the *APOE* gene is a common finding in ATD, while the most frequent genotype in the general population is to be homozygous for the ε3 allele. Smoking, specifically for more than five years, was seen in both groups, which has been reported to be a risk factor for developing dementia and AD. Finally, a family history of dementia and Alzheimer›s in first-degree relatives was seen more frequently in the early-onset group than in the late-onset group. Thus, the study of *APOE* gene polymorphism along with knowledge of the demographic, sociocultural, laboratory and historical variables are useful tools for evaluating the presence of characteristics related to ATD, according to age of onset. More studies are needed in the Colombian Caribbean region to evaluate the relationship between risk factors and ATD according to age of onset. With this study, comparisons can be made with other studies which will allow healthcare professionals to achieve an appropriate and timely approach.

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