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Nongenetic Factors as Modifiers of the Age of Onset of Familial Alzheimer's Disease

SILVIA MEJÍA, MARGARITA GIRALDO, DAVID PINEDA, ALFREDO ARDILA, AND FRANCISCO LOPERA

ABSTRACT. *Objective:* The purpose of this research was to identify environmental and personal factors that could be related to the variability in the age of onset of familial Alzheimer's disease (FAD) (36-62 years). *Methods:* A sample was taken of 49 subjects with FAD and with the mutation E280A in the presenilin-1 gene on chromosome 14; the sample was divided into two subgroups: 27 individuals with age of onset of the disease between 36 and 46 years (early onset) and 22 individuals whose disease began between 47 and 62 years (late onset). Information on environmental and personal factors was collected by means of a questionnaire answered by the patients if their clinical condition allowed it, or by their relatives; such information was organized in a categorical way. Comparisons between the two groups for each categorical variable were done by means of the chi-square test. Noncollinear variables that showed statistical significance were included as independent variables in a logistic regression analysis to predict their association with early onset of the disease. *Results:* Only 5 of the 140 studied variables were different between the two groups in univariate analysis: education, surgical history, type of stressful event, depression, and affective losses. The logistic regression model was constituted by education, depression, and affective losses. High-level education had approximately 15 times more probability of association with an early onset of the disease; both the history of affective losses and depressive symptoms had 4 times more probability of a similar association. *Conclusions:* The association of high-level education and early onset of the disease could be related to an earlier detection of symptoms, in turn determined by greater intellectual and environmental demands. The occurrence of depression and affective losses has been considered a prodromic manifestation of the disease. Our findings are evidence of high clinical heterogeneity even in a genetically homogeneous group.

KEYWORDS: Alzheimer's disease; age of onset; educational level; depression

From the Neurosciences Group, Faculty of Medicine, University of Antioquia, Medellín, Colombia (S. Mejía; M. Giraldo; D. Pineda; and F. Lopera), Neuropsychology and Conduct Disorder Group, Faculty of Psychology, Master's Program of Neuropsychology, University of San Buenaventura, Medellín, Colombia (D. Pineda), Florida International University, Miami, Florida, US (A. Ardila), and Doctoral Program of Psychology, Universidad Nacional Autónoma de México, México D.F., Mexico (S. Mejía).

Offprints. Requests for offprints should be directed to Francisco Lopera, Coordinador Grupo de Neurociencias, Universidad de Antioquia, Calle 62 No. 52-72, PO Box 5923, Medellín, Colombia. email: flopera@epm.net.co

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The clinical heterogeneity of Alzheimer's disease (AD) that is evident in the deterioration profile, the neuropsychological performance, the neuropathological evolution, the etiopathogenesis, and the age of onset has led to the proposal of the existence of different subtypes of this form of dementia (Alberca, 1998). For a better understanding of such heterogeneity, the role of genetic and nongenetic variables has been studied (Lendon et al., 1997; Rosselli et al., 2000; Velez-Pardo et al., 1998). Some of the nongenetic variables correspond to demographic factors such as age, gender, and socioeconomic level (Mejía et al., 1999) whereas others like occupational and educational achievements refer to different aspects of the subject's life (Letenneur et al., 2000; Stern et al., 1999). Likewise, some aspects of medical and neurological history as well as precedent mental disorders and psychological factors such as stress have been analyzed as possible protective or risk factors for AD (Rao et al., 1995).

It is generally accepted that familial AD (FAD) appears before the age of 65 years (early onset) whereas the sporadic form begins after that age (late onset). Different results have been reported in these two groups. A frequently studied variable is educational level; it has usually been managed in a dichotomous form (low-high) setting the cutoff point around 7 or 8 years of schooling (Caramelli et al., 1997; Stern et al., 1999). It has been proposed that a low level of education is a risk factor for sporadic AD (Evans et al., 1997; Stern et al., 1994) and it has been reported that individuals with a low schooling level (fewer than 8 years) exhibit a homogeneous deterioration pattern (Caramelli et al., 1997). In contrast, a high level of schooling has been related to a rapid and heterogeneous deterioration pattern with relative preservation of the cognitive area; this fact has been interpreted as evidence of a greater ability to compensate for neuronal damage in subjects with high educational level (Caramelli et al., 1997).

The influence of schooling on the age of onset of AD has also been studied by comparing the familial (early) and sporadic (late) forms of the disease. Specifically, a delay has been found in the age of onset in subjects with high-level education (Callahan et al., 1996; Letenneur et al., 1999, 2000); according to Katzman (1993), education delays 4 to 5 years the onset of symptoms, which led him to propose the hypothesis of *functional brain reserve.* Katzman stated that people with more years of education have a higher cognitive reserve, which enables them to sustain brain damage for longer periods before symptoms manifest; in contrast, subjects with low cognitive reserve exhibit symptoms with lesser brain damage.

However, the relationship between education and age of onset reported in other studies does not support Katzman's hypothesis. Moritz and Petitti (1993) reported that in subjects with lower level of education the disease began later; lower educational level nevertheless was associated with greater severity of the disease at the time of diagnosis. These authors concluded that a lower level of education may lead to delayed detection of the disease and consequently belated referral to clinical centers.

Likewise, in other studies the possibility has been considered that a high level of education may be responsible for the failure to clinically detect symptoms and consequently may be associated with a

later age of onset of the disease (Stern et al., 1994). In order to understand these results it is crucial to define the age of onset. Some authors define it starting with the clinical diagnosis (Stern et al., 1994) whereas others consider two different criteria: appearance of mild cognitive symptoms or first clear evidence of dementia (Breitner & Magruder-Habib, 1989; Brooks, 1995).

It is difficult to accurately determine the age of onset of AD due to its characteristic variations such as insidious beginning and gradually progressive course. Mild symptoms may be present for a considerable period of time before the family can detect them and inform the clinician about the behavioral and/or neuropsychological changes. That is, a preclinical threshold can exist for several years during which there are characteristic pathologic changes without clinical manifestations (Cummings et al., 1998).

Other studies do not support the hypothesis of functional brain reserve but point to the need for considering the relationship between education and cognitive deterioration as a complex one in which many factors participate (Ardila et al., 2000). Recently, Harwood and colleagues (1999) analyzed ethnic differences in risk factors for AD; they found that low educational level is a risk factor in White, non-Hispanic subjects but not in White Hispanic individuals because of the presence of other risk factors that can be associated with AD in this group. Cobb and colleagues (1995) also found that a low educational level was a risk factor for other dementias but not for AD. This association may be due to the presence of noxious habits and other risk factors for stroke in the less educated population; Cobb and colleagues concluded that formal education does not postpone the development of symptoms of serious cerebral diseases.

We have analyzed the effect of education, occupation, and gender on the age of onset in a group of individuals with FAD. Higher educational and occupational levels were not found to delay the appearance of symptoms because in the early-onset group a significantly greater proportion of subjects with high education levels and more highly qualified occupations was found (Mejía et al., 1999).

In a multicenter study directed by Gatz (Gatz et al., 2000), completion of 6 years of schooling was found to protect against the development of AD. However, when subjects with dementia were paired with their twins without dementia, the effect of education became not significant. Partial information on their younger years revealed an additional protective effect associated with participation in intellectual activities such as reading or attending cultural events.

Depression and other psychosocial factors have also been related to the development of AD. Stressful events can be either a risk factor if they are chronic or a protective factor if they are infrequent or acute. By means of a meta-analysis with 5 case-control studies and 10 prospective studies, Jorm (2000) recently found an increased incidence of dementia in individuals with a history of depression.

A widely accepted hypothesis considers depression a prodromic manifestation of AD. In a study of twins discordant for this type of dementia, Wetherell and colleagues (1999) found that depression 10 years before the onset of dementia was associated with a higher risk of AD;

this finding was interpreted by the authors as a prodromic phase of dementia.

Geerlings and colleagues (2000) found that the association between depression and higher risk of AD was present only in subjects with high educational level; they considered such a finding as evidence of the role of depression as an early manifestation of AD previous to the cognitive deterioration. Jorm and colleagues (1991) found that depression was associated with late-onset AD (more than 70 years) only if depressive symptoms had appeared 10 years before the beginning of dementia. However, depression that had begun more than 10 years before dementia was associated with the onset of AD at any age. That is, the risk of developing AD decreases as the interval between depression and dementia increases. For these authors the finding that subjects with late depression, who also frequently have cognitive deficits, develop dementia some years after the appearance of depression suggests that late depression is a prodromic symptom of dementia.

Despite abundant scientific information on the nongenetic factors associated with AD, no studies that analyze the relationship between nongenetic variables and the age of onset of FAD have been found. There exists in Colombia the largest population in the world with a familial form of AD transmitted in an autosomal dominant way; all these subjects carry a mutation on Codon 280 of the presenilin-1 gene on Chromosome 14 (Lopera et al., 1997). Despite its uniform genetic basis, there is great variability in the age of onset of the disease as defined from the moment in which the first complaints of memory loss appear. Mean age of onset is 46.8 with a range between 34 and 62 years. The present research was carried out to study the nongenetic factors that may be related to the variability in the age of onset of FAD.

METHODS

Participants

A group of 49 subjects with the diagnosis of FAD and the mutation E280A in the presenilin-1 gene on Chromosome 14 was studied. The age of onset was defined as the moment of appearance of the first cognitive complaints that affected occupational, familial, or social life, according to information provided by the patient or his/her family. Mean age of onset was 46.8 ± 5.5 with a range between 34 and 62 years. Age of onset tended to cluster around the mean in a fairly even way. A histogram chart of age of onset can be observed in Figure 1. The group was divided into two subgroups according to age of onset: early (36-46, mean = 42.4 ± 2.7) and late (47-62, mean = 51.1 ± 4.0). Some characteristics of the two age subgroups can be observed in Table 1.

Instruments

The questionnaire of individual differences consisted of a total of 140 questions that grouped variables corresponding to six areas: (a) medical and neurological history; (b) history of smoking (1 pack/day), alcoholism (>2 drinks/day), and psychoactive drug consumption (daily basis); (c) psychological (conduct disorder in childhood; affective losses, i.e., disengagements, unattachments, separations, and bereavement events in couple history; and stressful life events, classified into two categories: death

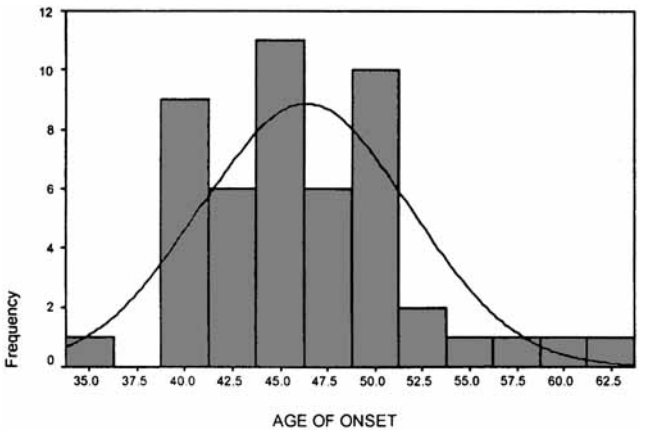

Figure 1. Age-of-onset histogram.

TABLE 1. General Characteristics of Early- and Late-Onset Groups

Characteristics	Early Age of Onset (36–46)	Late Age of Onset (47–62)
Number	27	22
Age	42.4 (2.7)	51.1 (4)
Gender, M/F	13/14	11/11
Education, years	5.4 (4.0)	3.2 (2.4)
Marital status, married/single	24/3	20/2
Socioeconomic stratum, 1-3/4-6/rural	22/3/2	15/2/5
Laterality, right-handed/left-handed	25/2	22/0
Height, cm	158.5 (3.1)	158.3 (2.8)
Weight, kg	58.3 (4.5)	54 (6.9)
Head circumference, cm	53.9 (0.4)	53.6 (0.5)

Note. Numbers in parentheses indicate standard deviation.

[referring to the death of someone significant] and health, social, and affective events [referring to illness, losing job, divorce, going to jail, etc.] and psychiatric history [depression, anxiety, and psychosis screening items]); (d) occupational achievements (primary occupation was recorded and classified as mid-high, middle, and low based on the cognitive demands the occupation required); (e) educational achievements (years of schooling); (f) leisure activities (participation in four types of activities on a daily basis: reading, watching TV, physical activities [e.g., exercising] and manual activities [e.g., knitting]). The questionnaire was answered either by patients if their clinical condition allowed it, or by their relatives. Information obtained from the patient was confirmed by a relative (wife/husband or brother/sister). The questionnaire was answered either at St. Vincent's University Hospital, at the Neurosciences Group premises, or during a domiciliary visit, if necessary. All information was categorized for further analysis.

Procedure

Questionnaires of individual differences were administered after an informed consent document for Investigation No. 1115-04-007-99 of Colciencias, the Colombian institution for scientific research, was signed.

Data Analysis

The Spanish version of statistical program SPSS 10.0 was used. Frequency analyses for each categorical variable were made in the two age-of-onset groups. To establish the existence of association between the two groups and each of the studied variables, a cross-tabulation analysis (2 x 2) was carried out with the early- and late-onset groups as dependent variables and the remaining variables as independent ones. Because of the small number of the sample, chi-square with Yates's correction was used to define the level of significance (p). Odds ratio (OR) was calculated to determine the degree of association between two dichotomous variables. Later, a logistic regression analysis was performed in order to establish which of the variables with $p < .05$ in univariate analysis entered the regression model. Differences between means for continuous variables were analyzed through one-way variance analysis.

RESULTS

The following results were found by analyzing the different areas included in the questionnaire of individual differences:

No significant differences in behavioral history, alcoholism, or psychoactive drug consumption were found between the early- and late-onset groups. The number of surgical interventions was the only variable in the medical and neurological history that showed a significant difference between the two groups. Although the proportion of subjects in the total sample with a history of surgical interventions was small (12 of 49; 24.5%), 75% of them (9 of 12) had a late age of onset of AD. This does not mean that subjects with an early age of onset of AD had had a significantly lower number of serious diseases, because the difference between the two groups was very small: 30% vs. 36% for individuals with early and late onset, respectively (Table 2).

Analysis of leisure activities did not reveal differences between the early- and late-onset groups either; however, some tendencies could be observed. Reading was more frequent in the early-onset group (44% vs. 27%); radio listening and television watching were more frequent in the late-onset group (68% vs. 56%); manual activities were equally frequent in both groups (11% vs. 18%); and physical activities (sports) were more frequent in the early-onset group (18% vs. 5%).

Psychological and psychiatric histories revealed some significant differences. An important affective loss before the beginning of AD was reported by 22 individuals of the total group (44.9%); out of them, 16 (72.7%) had early-onset disease (Table 2). The age at which the affective loss occurred was similar in both groups: early onset (31 ± 12) and late onset (38.3 ± 12.8). No significant precedent anxiety disorder was found in the psychiatric history. Nevertheless, 21 individuals of the total group (42.8%) reported having had depressive symptoms before the beginning of AD. Out of this subgroup, 15 (71.4%) had early-onset disease (Table 2).

TABLE 2. Cross-Tabulation Analysis and Chi-Square of Significantly Different Variables Between Early- and Late-Onset Groups

Variables	Age of Onset		Chi-Square Yates Correction	p	OR	95% CI	
	Early	Late				Inferior	Superior
Surgical interventions							
Present	3	9	5.9	.015	2.5	1	7.1
Absent	24	13					
Affective losses							
Present	16	6	5.8	.016	4.2	1.2	14.5
Absent	11	16					
History of depression							
Present	15	6	4.0	.044	3.3	1	11.1
Absent	12	16					
Stressful events[a]							
Social-health-affective	15	7	4.2	.040	3.9	1	14.9
Death	6	11					
Education							
Low	17	20	5.5	.018	5.8	1.1	30.6
High	10	2					

Note. CI = confidence interval; OR = odds ratio.
[a]Information not available in 10 individuals.

No differences were found between the two groups in the number of stressful events, but they were detected in the type of event (social-health-affective vs. death) that was reported as the first one to happen (Table 2): A social-health-affective event had been the first one in 15 of 21 individuals with early-onset disease (71.4%) but only in 7 of 18 of those with late-onset disease (38.9%). In the remaining 10 individuals this information was not available.

In regard to educational achievement, the distribution between low and high educational levels was 37 (75.5%) and 12 (24.5%) individuals, respectively; the former individuals were equally distributed between the early- (17 of 37; 46%) and late-onset (20 of 37; 54%) groups whereas most of the latter individuals (10 of 12; 83.3%) belonged to the early-onset group (Table 2). No differences were found as regards the place of schooling (rural, urban, both) but the proportion of individuals with high educational levels who studied in an urban setting was higher.

Stepwise logistic regression analysis was carried out with the variables described in Table 2. The final regression model consisted of the variables "Education," "Affective loss," and "Depression" (Nagelkerke R^2 = 44.8). In such a model, the probabilities of association with early-onset disease were as follows (Table 3): 14.8 times for having a high education level (OR = 15.8, 95% confidence interval [CI] 1.2-200, $p < .05$); 4.4 times for having had an affective loss (OR = 5.4, 95% CI 1-28.3, $p < .05$); and 4.2 times for having a history of depressive symptoms (OR = 5.2, 95% CI 1-27.7, $p < .05$).

No significant differences were found between the early- and late-onset groups in regard to the following variables: having a medium- to high-level occupation, study in an urban school, and the habit of reading; however, in the three variables there was predominance of early-onset disease (Table 4).

To study the relationship between the age of onset of dementia and that at which the affective loss took place, both ages were compared in each group (Table 5). In the group with early-onset dementia (42.4 ± 2.7), the age of the affective loss (31 ± 12) was significantly lower ($t = 3.5$, $p < .01$). Likewise, in the group with late-onset dementia (51.4 ± 4), the age of the affective loss (38.3 ± 12.8) was significantly lower ($t = 3.4$, $p < .05$). Affective loss occurred an average of 21 ± 5 years before the beginning of disease in the early-onset group, and 18.4 ± 9.5 years before in the late-onset group. No differences were found between the groups in this respect.

DISCUSSION

Our results show that variability in the age of onset of FAD is associated only with some of the variables considered in the literature. No differences were found in variables for which effects on AD have been reported: smoking (Fratiglioni & Wang, 2000), alcoholism (Harwood et al., 1999; Rao et al., 1995), gender (Rocca et al., 1986), and head circumference (Graves et al., 1996).

Most studies on the age of onset of AD have compared groups with the sporadic (late-onset) and familial (early-onset) forms of the disease. In the present study, all individuals had the familial form with onset before 65 years; however, we divided them into two subgroups: early (36-46 years) and late onset (47-62 years). Also, in our sample no subjects were found with some of the characteristics analyzed in other studies; for instance, no individual had been exposed to toxic substances during his/her occupational life.

The only variables with a clear role were education, depression, and affective losses, which entered the logistic regression model and jointly predicted 44.8% of the variance. This indicates that variables belonging to different areas of the subject's life, such as educational achievement and psychological history, show an association with the age of onset of genetically determined AD.

In regard to educational achievement, 83% of individuals with high-level schooling (7-14 years) were found to have had an early onset of their disease. Other tendencies related to education were

TABLE 3. Logistic Regression Model of the Variables Depression, Education, and Affective Losses

		95% CI		
Variable	OR	Inferior	Superior	*p*
Education	15.8	1.2	200	.03
Affective loss	5.4	1.0	28.3	.04
Depression	5.2	1.0	27.7	.05

Note. CI = confidence interval; OR = odds ratio.

TABLE 4. Relationship Between Some Variables and the Age of Onset of Alzheimer's Disease

Variable	Age of Onset of AD	
	Early (%)	Late (%)
Medium- to high-level occupation (n = 14)	71.4	28.6
Urban school (n = 22)	68.2	31.8
Reading habit (n = 18)	66.7	33.3

Note. AD = Alzheimer's disease.

TABLE 5. Relationship Between the Age of Onset of Alzheimer's Disease (Early vs. Late) and the Age of Affective Loss

	Early Age of Onset	Late Age of Onset	F	p
Age of onset	42.4 ± 2.7	51.1 ± 4	80.1	<.01
Age at affective loss	31 ± 12	38.3 ± 12.8	1.4	*ns*
Difference between age of onset and age at affective loss	21 ± 5	18.4 ± 9.5	0.4	*ns*

observed in this group and allowed more thorough analysis. Besides the greater number of educational years, there was a higher proportion of individuals with medium to high occupational level who had attended urban schools and used to read as a leisure activity before the onset of the disease. These data indicate that in the family of subjects with genetically determined AD who possess similar characteristics of low schooling level, geographic origin in a rural area distant from the city, and dedication to farm or domestic jobs, there exists a subgroup of persons whose symptoms begin early (36-46 years) and in whom different conditions come together: higher educational level (7-14 years of schooling), wider academic opportunities due to their urban education, greater stimulation of labor skills related to urban-type jobs (bar manager, mechanic, clothes manufacturer, salesperson, etc.), and more stimulation of intellectual ability by devoting more time to reading. The rest of the sample is made up of individuals clearly disadvantaged with respect to the former ones: low educational levels, rural place of study, low-level occupation, and no reading habit before symptoms. In addition, there may be other factors not considered in this study that can interact with the aforementioned ones and create more negative conditions (Cobb et al., 1995).

The fact that high educational level was found to be associated with an early age of onset of AD contradicts the protective effect and the delay in the appearance of symptoms reported in different investigations (Callahan et al., 1996; Evans et al., 1997; Letenneur et al., 1999, 2000). However, in all those studies the age of onset was not under 55 years; also, the hypothesis of functional brain reserve was proposed by Katzman based

on the Shanghai study (Zhang et al., 1990) in which the prevalence of AD was found to be increased in illiterate or poorly educated subjects (1-6 years of schooling), mostly in those older than 75 years. Additionally, in his 1993 review, Katzman states that there exists in cases of genetic AD a latent period that can extend for very long between the appearance of initiating factors (formation of deposits of beta-amyloid) and that of the promoting ones associated with age. However, the protective effect of education does not act at that level but in a biologically different way by increasing brain reserve and delaying the beginning of symptoms; the effect is to lengthen the preclinical phase. Individuals included in this investigation had genetic AD and their mean age of onset was 46.3 ± 5.5 years; among them the group with early beginning of the disease (42.4 ± 2.7 years) had the highest level of schooling. This indicates that they constitute a group different from that whose results originated the hypothesis on the protective effect of education, and that reduction or increase of the latent period, according to Katzman, is not explained by schooling as a protective or risk factor.

Additionally it is necessary to discuss the role of education as a confounding variable. If the age of onset were defined by the moment at which the clinical diagnosis is established, it is feasible that a low educational level might give rise to false-positive diagnoses, advancing the age of onset in such individuals; in such cases, low schooling levels would appear as a risk factor. Contrariwise, a high level of schooling could serve to compensate, both cognitively and functionally, in the subject that is already having initial symptoms of AD (Christensen et al., 1997), giving rise to a false-negative diagnosis with delay in the appearance of symptoms; however, as severity of the disease progressed, compensation would no longer function. In this research the age of onset of the disease was not based on clinical diagnosis but on the time of appearance of the first symptoms as reported by the patient or by the family. However, with this approach, education may also act as a confounding variable, by modifying the time at which symptoms are detected and advancing the age of onset in those individuals with better academic preparation and greater occupational and nonoccupational demands (Gatz et al., 2000), as is the case of this research. It may be very likely that subjects with higher educational level and greater cognitive demands in their occupation are capable of earlier detection of their mistakes and difficulties; in contrast, individuals with low education levels and less cognitive occupational demands detect mistakes and difficulties later. This has been reported by some researchers (Moritz & Petitti, 1993; Stern et al., 1994) who found that the age of onset occurred later in individuals with lower educational level ($p < .0001$). However, less education was associated with greater severity of the disease at the time of diagnosis ($p < .008$), which suggests that less education may lead to delayed detection of the disease and belated referral to clinical centers (Moritz & Petitti, 1993).

Depression and affective losses were the two additional variables that entered the regression model to predict, together with education, 45% of variability. In the early-onset group, a higher proportion of individuals was found who reported having had depressive symptoms and having had an affective loss in their lives before the onset of AD.

A relationship between depression and AD has been reported in different studies (Jorm, 2000; Jorm et al., 1991; Wetherell et al., 1999). Depression has been considered a risk factor for dementia even if it occurs 10 years before the beginning of AD; this effect increases when depression happens in the middle of life (Agbayewa, 1986; Jorm et al., 1991); for that reason it has been stated that the risk of AD decreases as the interval between depression and dementia increases (Steffens et al., 1997). In the present research, an average of 20 years was found between affective loss and the onset of AD (the age of depressive symptoms was not recorded) in patients with early-onset AD. This interval has been considered more as evidence of the role of depression as a prodromic symptom in AD than as a true risk factor (Steffens et al., 1997); this coincides with the interpretation made by different investigators about the association between depression and AD (Jorm, 2000; Jorm et al., 1991; Wetherell et al., 1999).

On the other hand, it has been reported that such a relationship appears only in subjects with high educational levels (Geerlings et al., 2000). On this point our results were different: Only 40% of individuals with depression and early-onset AD had a high level of schooling; therefore, according to our data, the association between depression and AD cannot be explained by a higher number of schooling years.

The relationship between depression and Apo E4 has been repeatedly studied; some authors have found an association between depression and late-onset AD (Holmes et al., 1998) whereas others (Krishnan et al., 1996) have found a relationship with both early- and late-onset disease, and finally, no association has been found in other studies (Zubenko, 1996).

In conclusion, results of the present investigation indicate an association between the age of onset of symptoms in FAD and some individual variables; the evidence of two different subgroups in a genetically homogeneous sample suggests that another source of clinical heterogeneity can be individual differences. History of depression or affective losses and high educational level must be considered important variables in the subject's history that could change the timing in onset of symptoms of FAD. However, only results derived from longitudinal follow-up of healthy subjects with the mutation E280A in the presenilin-1 gene on Chromosome 14 will be considered conclusive in the future.

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