



Interleukin-8-251T > A, Interleukin-1 α -889C > T and Apolipoprotein E polymorphisms in Alzheimer's disease

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Abstract

An inflammatory process has been involved in numerous neurodegenerative disorders such as Parkinson's disease, stroke and Alzheimer's disease (AD). In AD, the inflammatory response is mainly located in the vicinity of amyloid plaques. Cytokines, such as interleukin-8 (IL-8) and interleukin-1 α (IL-1 α), have been clearly involved in this inflammatory process. Polymorphisms of several interleukin genes have been correlated to the risk of developing AD. The present study investigated the association of AD with polymorphisms *IL-8*-251T > A (rs4073) and *IL-1 α* -889C > T (rs1800587) and the interactive effect of both, adjusted by the Apolipoprotein E genotype. 199 blood samples from patients with AD, 146 healthy elderly controls and 95 healthy young controls were obtained. DNA samples were isolated from blood cells, and the PCR-RFLP method was used for genotyping. The genotype distributions of polymorphisms *IL-8*, *IL-1 α* and *APOE* were as expected under Hardy-Weinberg equilibrium. The allele frequencies did not differ significantly among the three groups tested. As expected, the *APOE4* allele was strongly associated with AD ($p < 0.001$). No association of AD with either the *IL-1 α* or the *IL-8* polymorphism was observed, nor was any interactive effect between both polymorphisms. These results confirm previous studies in other populations, in which polymorphisms *IL-8*-251T > A and *IL-1 α* -889C > T were not found to be risk factors for AD.

Key words: IL-8, IL-1 α , Alzheimer's Disease, APOE, inflammatory response.

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Introduction

Alzheimer disease (AD) is a progressive neurodegenerative disorder that causes loss of memory, mental confusion and several cognitive disturbances. It frequently occurs at around 60 years of age, but may also have an early onset at 40 years (Khachaturian, 1985). Dementia is an increasingly common diagnosis in the aging population, and the numbers are expected to rise exponentially in coming years. AD alone affects 5 million people in the US, while millions more are currently affected by vascular dementia,

Lewy body disease and frontotemporal dementia (Grossman *et al.*, 2006).

Two neuropathological features characterize the AD brain: amyloid plaques and neurofibrillary tangles. Plaques are mostly characterized by extracellular deposits of amyloid- β peptide (A β), which is derived from the processing of the amyloid precursor protein (APP). Neurofibrillary tangles correspond to intracellular accumulation of fibrils called paired helical filaments (Cacquevel *et al.*, 2004). In this sense, the neurological implications of AD come from the coexistence of two degenerative processes, tau protein aggregation and A β deposition, that affect polymodal association brain areas, a feature never observed in non-human primates and difficult to model (Delacourte, 2006).

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Familial early-onset AD is associated with mutations in the APP and presenilin genes, whereas only a polymorphic variation at the apolipoprotein E (APOE) locus, the $\epsilon 4$ allelic form has so far been firmly established as a genetic risk factor for late-onset familial and sporadic AD. However, these genetic risk factors only account for about 30-50 percent of all cases of AD. Thus, an interaction between genetic, biological and environmental factors might account for most AD cases, by promoting inflammatory reactions, particularly those mediated by the release of interleukin-1 α (IL-1 α) from microglial cells of the brain (Hayes *et al.*, 2004).

Infection or injury of the body results in inflammation. A hallmark of this response is the recruitment of neutrophils from the blood to the injured tissue. This process could be directed by chemotactic polypeptides, the so-called chemokines (Zlotnik and Yoshie, 2000). Chemokines are low-molecular-weight chemotactic cytokines that have been shown to play an important role in early inflammatory events (Baggiolini *et al.*, 1994). So far, microglial cells were shown to display an increased migratory response to β chemokines, including monocyte chemotactic protein 1 (MCP-1), suggesting that these molecules may play an important role in the trafficking of mononuclear phagocytes within the brain (Peterson *et al.*, 1997). It is widely accepted that chronic inflammatory reaction plays an important role in the pathogenesis of AD, and a variety of inflammatory factors, including cytokines and chemokines, have been detected in and around plaques and tangles (Galimberti *et al.*, 2006; Pomponi *et al.*, 2008). Moreover, elevated levels of chemokines are demonstrable in the brain in neurodegenerative diseases, such as AD, whereas in healthy brains they are detected at low levels (Galimberti *et al.*, 2006). Thirumangalakudi *et al.* (2008) made an immunohistochemical analysis of activated microglia and astrocytes as neuroinflammation markers, cytokines expression and cognitive alteration in C57/BL6 and low-density lipoprotein receptor (LDLR) (-/-)-deficient mice fed a fat/cholesterol-rich diet. Their findings link hypercholesterolemia with cognitive dysfunction potentially mediated by increased neuroinflammation and APP processing in a non-transgenic mouse model.

IL-8 enhances the survival of hippocampal neurons *in vitro* and increases the proliferation of glial cells (Araujo and Cotman, 1993). Strong immunoreactivity for CXCR2 (chemokine (C-X-C motif) receptor 2), the IL-8-related receptor, has been demonstrated in both AD and age-matched subjects with non-inflammatory affections of the nervous system. In particular, CXCR2 expression in AD is close to neuritic plaques, surrounding A β deposits (Galimberti *et al.*, 2003, 2006). Increased IL-1 expression, in the form of higher tissue concentrations of the IL-1 protein and increased numbers of IL-1 immunoreactive astrocytes, has been demonstrated in the brains of patients with AD and in those elderly individuals with Down syndrome who show

AD-type pathology in their brains (Griffin *et al.*, 1989). Polymorphisms located in the promoter regions of the *IL-1 α* and *IL-8* genes have been widely studied as risk factors for AD. For instance, the *IL-1 α* -889C > T polymorphism was strongly associated with late-onset AD in samples from two different centers: Indianapolis, IN, USA, and Munich, Germany (Du *et al.*, 2000). However, other studies conducted in different populations did not show this association (Kuo *et al.*, 2003; Tang *et al.*, 2004; Zhou *et al.*, 2006; Dursun *et al.*, 2009; Hu *et al.*, 2009). In addition, Infante *et al.* (2004) reported that neither the presence of the *IL-1 α* -889 T allele nor the presence of the *IL-8* -251T > A polymorphism TT genotype was associated with AD in Caucasians originating from a homogeneous population in a limited geographical area in Northern Spain. However, subjects carrying both the *IL-1A* allele T and the *IL-8* TT genotype had about twice the risk of developing AD than subjects without these genotypes.

In the present study, we characterized the *IL-8* -251T > A and *IL-1 α* -889C > T polymorphisms in AD patients, healthy young and elderly control groups. We also investigated a possible interactive effect between these polymorphisms in the developing of AD, as proposed by Infante *et al.* (2004)

Materials and Methods

Patients and controls

Peripheral blood samples were obtained from 440 Brazilian individuals: 199 AD patients, 146 healthy elderly controls (EC) and 95 healthy young controls (YC).

The sample of AD patients was composed of 87.44% subjects of European origin, 6.80% of Japanese origin and 5.76% of African origin; the sample of elderly controls was composed of 89.78% subjects of European origin, 5.84% of Japanese origin and 4.38% of African origin; and the sample of young controls was composed of 87.65% subjects of European origin, 6.8% of Japanese origin and 4.75% of African origin. Thus, there was no difference in the ethnic distribution of the three groups. The mean age and standard deviation of the samples was: 73.81 \pm 7.95 years in the AD group, composed of 68 men and 131 women; 71.25 \pm 9.02 years in the EC group, composed of 53 men and 93 women; and 20.56 \pm 1.64 years in the YC group, composed of 31 men and 64 women. The AD patients were selected according to the NINCDS-ADRDA criteria for probable AD (McKhann *et al.*, 1984). Vascular dementia was excluded by a Hachinski score of 5 or higher and by neuro-imaging (Hachinski *et al.*, 1975). Patients as well as controls were from São Paulo City, and all subjects gave informed consent for participation in this study, which was approved by the USC (Universidade do Sagrado Coração de Bauru) ethics committee (Protocol number 0110/2004). The control groups were composed of relatives (spouse or children) or

friends of the patients. For these groups, exclusion criteria were a history and examination findings suggestive of neurological (seizure, brain trauma with loss of consciousness longer than 15 min, stroke, Parkinson's disease) or psychiatric disease (depression and substance abuse, including alcohol), and evidence of functional decline as shown by a structured questionnaire. All experiments were conducted in accordance with the Declaration of Helsinki.

Laboratory analysis

Total genomic DNA was extracted from blood samples using a Qiagen extraction kit, according to the manufacturer's instructions.

IL-8 -251T > A genotyping: *IL-8 -251T > A* genotypes were determined using the polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) method. A 349 bp fragment was amplified from genomic DNA using the forward and reverse oligonucleotides IL-8F1 5'-CAT GAT AGC ATC TGT AAT TAA CTG-3' and IL-8R2 5'-CTC ATC TTT TCA TTA TGT CAG AG-3', respectively, as described previously (Hamajima *et al.*, 2003). PCR conditions involved an initial denaturation step of 94 °C/5 min, followed by 30 cycles of 94 °C for 45 s, 52 °C for 45 s, 72 °C for 1 min, and a final extension step of 72 °C for 7 min. The amplification products were digested with *MunI* restriction enzyme (Fermentas, Ottawa, ON, Canada), subjected to electrophoresis on a 3% agarose gel, stained with ethidium bromide and analyzed on an Alpha Imager 2200 (Alpha Innotech Corporation, San Leandro, CA, USA). After digestion, three different band combinations were found, viz. a 349 bp fragment (TT genotype), 202 and 147 bp fragments (AA genotype); and 349, 202 and 147 bp fragments (TA genotype).

IL-1 α -889C > T genotyping: *IL-1 α -889C > T* genotypes were also determined using PCR-RFLP. A 194 bp fragment was amplified from genomic DNA using the forward and reverse oligonucleotides IL-1AF1 5'-GCA TGC CAT CAC ACC TAG TT-3' and IL-1AR1 5'-TTA CAT ATG AGC CTT CCA TG-3', respectively, as described previously (Tanriverdi *et al.*, 2006). The PCR conditions included an initial denaturation step of 94 °C for 5 min, followed by 40 cycles of 94 °C for 30 s, 55 °C for 30 s, 72 °C for 30 s, and a final extension step of 72 °C for 7 min. The amplification products were digested with *NcoI* (Fermentas, Ottawa, ON, Canada), subjected to electrophoresis on a 3% agarose gel, stained with ethidium bromide and analyzed on an Alpha Imager 2200 (Alpha Innotech Corporation, San Leandro, CA, USA). After digestion, again three different results were found: a 194 bp fragment (TT genotype); 174 and 20 bp fragments (CC genotype); and 194, 174 and 20 bp fragments (TC genotype). The 20 bp fragments could not be visualized in the agarose gel.

APOE genotyping: The *APOE* genotypes were determined by PCR-RFLP using the oligonucleotides and reaction conditions described by Hixson and Vernier (1990).

The amplification products were digested with *HhaI* (Fermentas, Ottawa, ON, Canada), subjected to electrophoresis on a 4% NuSieve[®] GTG[®] agarose gel (Cambrex, Rockland, ME, USA), stained with ethidium bromide and analyzed on an Alpha Imager 2000 (Alpha Innotech Corporation, San Leandro, CA, USA).

Statistical analysis

The chi-square test was used to compare categorical variables and to test the deviation from the Hardy-Weinberg equilibrium for each polymorphism. A value of $p < 0.05$ was considered statistically significant, and all tests were two-tailed. Logistic regression was used to investigate the individual relationships and interactive effect between independent variables (carriers versus non-carriers of the *IL-1 α* T allele, and carriers versus non-carriers of the *IL-8* TT genotype). This approach was based on the findings of Infante *et al.* (2004), who suggested an interactive effect of the *IL-1A* allele and the *IL-8* TT genotype. For this analysis, we considered both polymorphisms as dependent variables, and gender, age and *APOE* genotype groups as co-variables in the model. The crude odds ratio (OR) was calculated considering the AD group genotypes in relation to the genotypes of the elderly and of the young control groups, using gender and age as co-variables. The adjusted odds ratio (OR) by *APOE* genotype considered three groups of *APOE* genotypes: 1) E2E2 with E2E3; 2) E3E3; and 3) E3E4 with E4E4, as well as gender and age as co-variables. Ninety-five percent confidence intervals were calculated. The statistical analyses were performed using the SPSS 16.0 package.

Results

Table 1 presents the *IL-8 -251T > A* and *IL-1 α -889C > T* genotype distributions in the AD, EC and YC subject groups. The *APOE* genotype distributions among the three subject groups are also shown in Table 1. There were no statistically significant differences concerning gender among the subject groups ($p = 0.22$; data not shown).

The genotype distributions concerning the *IL-8 -251T > A* and the *IL-1 α -889C > T* polymorphism were in Hardy-Weinberg equilibrium in all three subject groups. The *APOE* genotype distribution was also in Hardy-Weinberg equilibrium in the three subject groups. The comparison of the genotype frequency distribution in the AD patients and the EC group did not show any significant difference for either *IL-8 -251T > A* ($p = 0.05$) or *IL-1 α -889C > T* ($p = 0.23$). Similarly, no significant difference was found in the comparison between AD patients and the YC group (Table 1).

Logistic regression analysis did not detect an association of AD with any of the polymorphisms individually. An interactive effect of both polymorphisms in our tri-hybrid Brazilian population was not detected (Tables 1 and 2). As expected, logistic regression analysis revealed a strong as-

Table 1 - Absolute and relative genotype frequencies of the *IL-8* and *IL-1 α* polymorphisms and *APOE* genotypes in an Alzheimer's disease patient group (AD) and in an elderly (EC) and a young (YC) healthy control groups.

<i>IL-8</i> -251T > A*	AD	EC	YC
A/A	47 (23.62%)	28 (19.18%)	19 (20%)
T/A	101 (50.75%)	63 (43.15%)	49 (51.8%)
T/T	51 (25.63%)	55 (37.67%)	27 (28.42%)
<i>IL-1α</i> -889C > T**			
C/C	96 (48.24%)	78 (53.42%)	58 (61.05%)
T/C	84 (42.21%)	61 (41.78%)	30 (31.58%)
T/T	19 (9.55%)	7 (4.79%)	7 (7.37%)
<i>APOE</i> genotype			
E2/E2	0 (0%)	1 (0.68%)	1 (1.05%)
E2/E3	11 (5.53%)	11 (7.53%)	15 (15.79%)
E3/E3	85 (42.71%)	117 (80.14%)	55 (57.89%)
E2/E4	7 (3.52%)	2 (1.38%)	1 (1.05%)
E3/E4	78 (39.20%)	14 (9.59%)	20 (21.05%)
E4/E4	18 (9.04%)	1 (0.68%)	3 (3.17%)
Total	199 (100%)	146 (100%)	95 (100%)

*Chi-square test p value for AD x EC = 0.056; for AD x YC = 0.751.

**Chi-square test p value for AD x EC = 0.226; for AD x YC = 0.120.

sociation of the E4 allele in AD patients in relation to the EC (OR = 8.137, 95% CI = 4.569-14.489, $p < 0.001$) and YC (OR = 3.174, 95% CI = 1.850-5.446, $p < 0.001$) groups (data not shown).

Discussion

This study was the first one to investigate a potential association of polymorphisms *IL-8* -251T > A and *IL-1 α* -889C > T with AD in a Brazilian population. The genotype distributions of polymorphisms *IL-8*, *IL-1 α* and *APOE* in the three subject groups were in Hardy-Weinberg equilib-

rium. We did not observe an association of *IL-8* -251T > A and/or *IL-1 α* -889C > T with AD. The findings concerning *IL-8* -251T > A confirmed our previous study with a smaller sample (Vendramini *et al.*, 2007), which did not detect an association of this polymorphism with AD either. Infante *et al.* (2004) also observed a lack of association of polymorphisms *IL-1 α* -889C > T and *IL-8* -251T > A with AD. No association of the *IL1*-A polymorphism with AD was also reported in Chinese samples from Taiwan (Kuo *et al.*, 2003), from the Chengdu area (Tang *et al.*, 2004), and in a Han population (Hu *et al.*, 2009). Similarly, the *IL-1 α* -889C > T polymorphism was not associated with AD either in individuals from the Canary Islands, Spain (Deniz-Naranjo *et al.*, 2008) or in a homogeneous Caucasian population from northern Spain (Infante *et al.*, 2004).

No interactive effect of the *IL-1 α* -889T allele and the *IL-8* TT genotype concerning the AD group in relation to EC and YC was detected (Tables 1 and 2). However, our findings differed from those of Infante *et al.* (2004). This discrepancy may be due to the distinct ethnic composition of both populations. As it is well known, the Brazilian population is mainly composed of European, African and Amerindian descendants. Other variables, such as the AD age of onset or another undetectable stratification bias may also be involved.

Our findings concerning the lack of association of *IL8* and *IL1* with AD and of an interactive effect between them were consistent with the great majority of reports from different population samples. Hence, taking together our results with others from the literature, it appears that *IL-8* -251T > A and *IL-1 α* -889C > T do not play a major role in the pathogenesis of late-onset AD.

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Table 2 - Odds ratio (OR) - crude and adjusted by *APOE* genotype - and 95% confidence interval (CI) for interaction between *IL-1 α* T allele and *IL-8* TT genotype obtained from logistic regression analysis concerning Alzheimer's disease (AD) and elderly controls (EC), and Alzheimer's disease (AD) and young controls (YC).

<i>IL-1α</i> T allele	<i>IL-8</i> TT genotype	AD (%)	EC (%)	OR(95%CI)	p*	OR(95%CI)	p**
-	-	35.70	33.60	1 (reference)		1 (reference)	
-	+	12.60	19.90	0.595 (0.312-1.136)	0.12	0.542 (0.277-1.060)	0.07
+	-	38.70	28.80	1.265 (0.750-2.135)	0.38	1.110 (0.639-1.926)	0.71
+	+	13.10	17.80	0.690 (0.359-1.328)	0.27	0.553 (0.278-1.097)	0.09
<i>IL-1α</i> T allele	<i>IL-8</i> TT genotype	AD (%)	YC (%)	OR(95%CI)	p*	OR(95%CI)	p**
-	-	35.70	42.10	1 (reference)		1 (reference)	
-	+	12.60	18.90	0.782 (0.381-1.606)	0.50	0.666 (0.317-1.401)	0.28
+	-	38.70	29.50	1.549 (0.867-2.769)	0.14	1.345 (0.737-2.455)	0.33
+	+	13.10	9.50	1.628 (0.695-3.813)	0.26	1.174 (0.486-2.838)	0.72

*Crude OR. **Adjusted by *APOE* genotypes.

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