Interleukin-1 α , interleukin-1 β and tumor necrosis factor- α genetic variants and risk of dementia in the very old: evidence from the “Monzino 80-plus” prospective study

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Abstract The association among single nucleotide polymorphisms in inflammatory genes as interleukin-1 alpha (*IL-1 α*), interleukin-1 beta (*IL-1 β*) or tumor necrosis factor alpha (*TNF- α*) and dementia has been explored mostly in Alzheimer’s disease, while few data addressing their association with dementia in very old people are available. We performed a prospective, door-to-door population-based study of 80 years or older residents in eight municipalities of Varese province, Italy (the “Monzino 80-plus” study). No difference was found by a cross-sectional approach

comparing *IL-1 α* *rs1800587*, *IL-1 β* *rs3087258* and *TNF- α* *rs1799724* genotypic and allelic frequencies between those affected and not affected by dementia. After a 5-year follow-up, the elderly carriers of T-allele of *TNF- α* *rs1799724* were at an increased risk of dementia ($p=0.03$). This association was no more significant adjusting for the apolipoprotein E epsilon-4 allele (*APOE- ϵ 4*, $p=0.26$), which was an independent predictor of dementia onset ($p=0.0002$). In short, in this Italian population of oldest olds, dementia was associated to the *APOE- ϵ 4* allele only.

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Introduction

Inflammation has a positive role in successful aging, as an effective inflammatory response is basic to cope with pathogen infections. However, a chronic inflammatory state or an overproduction of inflammatory factors might contribute to age-associated diseases like neurodegenerative disorders, autoimmunity and cancer (Caruso et al. 2004; Van Bodegom et al. 2007). The brain can activate an inflammatory reaction involving the production of proinflammatory cytokines (IL-1 β , TNF- α and IL-6) in response to a peripheral immune challenge (Tonelli and Postolache 2005). Dementia and cognitive decline are paralleled by an increased peripheral cytokines production (Weaver et al. 2002; Bruunsgaard et al. 1999; Holmes et al. 2003; van Exel et al. 2003; Dik et al. 2005) that can be interpreted as a consequence of the neurodegenerative process, creating a detrimental feedback loop that further sustains neuronal damage. Moreover, brain inflammatory cytokines can be increased by several different pathological conditions associated with dementia, like cerebrovascular injury (Paganelli et al. 2002), type-2 diabetes (Rizzo et al. 2008) and virus infection (Brabers and Nottet 2006).

Genes coding for the proinflammatory cytokines interleukin-1 alpha (IL1- α , GeneID: 3552), interleukin-1 beta (IL1- β , GeneID: 3553) and tumor necrosis factor alpha (TNF- α , GeneID: 7124) have single nucleotide genetic variants (single nucleotide polymorphism—SNP) in the promoter region that may change the transcription rate and consequently the cytokine production (Dominici et al. 2002; Wen et al. 2006; Prasad et al. 2010). Three of these SNPs, *rs1800587* (C/T) for IL-1 α , *rs3087258* (C/T) for IL-1 β and *rs1799724* (C/T) for TNF- α , have been evaluated also in the field of Alzheimer's disease (AD). In this context, their role as a susceptibility factor has been assessed mostly by case-control association studies focused on people aged between 70 and 80 years, with controversial results (Ehl et al. 2003; Sciacca et al. 2003; Wang et al. 2005; Ravaglia et al. 2006; Wehr et al. 2006; Perry et al. 2001; Culpan et al. 2003; Licastro et al. 2007). This

scenario holds true for many other AD susceptibility genetic loci, apart from the epsilon-4 allele of the gene coding for the apolipoprotein E (*APOE- ϵ 4*) located on chromosome 19, that have been consistently reported to be a risk factor (Saunders et al. 1993; Strittmatter et al. 1993; Bertram et al. 2010). Many less investigations are available on the role of *IL-1 α rs1800587*, *IL-1 β rs3087258* and *TNF- α rs1799724* as dementia risk modulators in the very old (>85 years), an age bracket where some of these polymorphisms have been explored in relation to survival (Cavallone et al. 2007). This is an important gap, as most dementia sufferers are 80 years or older. We decided to investigate the association of *IL-1 α rs1800587*, *IL-1 β rs3087258* and *TNF- α rs1799724* with dementia in a prospective door-to-door population-based study (the “Monzino 80-plus” study) enrolling elderly people residing in eight municipalities of Varese province (Italy).

Materials and methods

Study sample and clinical evaluation

The Monzino 80-plus study is an ongoing, prospective, door-to-door population-based survey among all 80 years or older residents in eight neighbouring municipalities in the province of Varese, Italy, and has been fully described elsewhere (Tettamanti et al. 2006). Briefly, details about the participants' lifestyle, habits, medical history and health status were collected by trained psychologists from both the subject and a family member. The participants were administered a set of neuropsychological tests including CERAD battery (Morris et al. 1989), Mini-Mental State Examination (Folstein et al. 1975), Instrumental Activities of Daily Living (Lawton and Brody 1969), Spontaneous Behavior Interview-bADL (Lucca et al. 1996) and Geriatric Depression Scale (ten-item version) (D'Ath et al. 1994). The diagnosis of dementia was made according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders IV.

Standard protocol approvals, registrations and patient consents

The study procedures were in accordance with the principles outlined in the Declaration of Helsinki of

1964 and the following amendments. The study protocol was submitted to and approved by the Local Research Ethics Committee (Azienda Sanitaria Locale of Varese Province, Varese, Italy). Separate written informed consents for data and blood sample collections were obtained from all participants.

DNA analysis

Blood samples (3 mL) were collected by venipuncture. One aliquot of blood was used to extract genomic DNA (gDNA) using a semi-automated vacuum-based nucleic acids extractor (AB6100, Applied Biosystems). From the subjects who gave their consent for genetic testing ($n=609$), gDNA was extracted and genotyped for *IL-1 α rs1800587*, *IL-1 β rs3087258* and *TNF- α rs1799724*. To reduce false genotyping rate, each SNP was assessed in duplicate and only unambiguous results were considered. *IL-1 α* , *IL-1 β* and *TNF- α* genotyping was performed by restriction fragment length polymorphisms using the following primers: *IL-1 α* –889 C/T (*rs1800587*) F 5'-AAG CTT GTT CTA CCA CCT GAA CTA GGC-3' and R 5'-TTA CAT ATG AGC CTT CCA TG-3'; *IL-1 β* –511 C/T (*rs3087258*) F 5'-TGG CAT TGA TCT GGT TCA TC-3' and R 5'-GTT TAG GAA TCT TCC CAC TT-3' and *TNF- α* –850 C/T (*rs1799724*) F 5'-AAG TCG AGT ATG GGG ACC CCC CGT TAA-3 and R 5'-CCC CAG TGT GGT GCC ATA TCT TCT T-3' and the restriction enzymes NcoI, AvaI and HindII, respectively (Promega, Madison, WI, USA). The apolipoprotein E (*APOE*) genotype was assessed as previously described (Albani et al. 2007).

Statistical analysis

The univariate relationship of genotypic or allelic frequency was analysed using χ^2 tests, in case of nominal variables (e.g. sex), and t tests or analyses of variance, in case of continuous variables (e.g. age).

The logistic regressions were used to study the relationship between the genotypic frequency and the severity of dementia adjusting for age, sex and education level. The association between the genetic trait and the subsequent incidence of dementia was plotted using a Kaplan–Meier survival curve. p values were calculated by means of Cox proportional hazard regression models, adjusting for age, sex, education level and *APOE* genotype. Our study had 80% power to detect a variation of around 10–12% of the minor allele of *IL-1 α rs1800587*, *IL-1 β rs3087258* or *TNF- α rs1799724* ($\alpha=0.05$, effect size small-to-medium). The limit of significance was set at $p=0.05$.

Results

Association between *IL-1 α rs1800587*, *IL-1 β rs3087258*, *TNF- α rs1799724* and dementia: cross-sectional analysis

The main demographic and cognitive features of the population from the Monzino 80-plus study included for the genetic study are reported in Table 1. The population was divided into participants with dementia ($n=229$, 37.6%) and participants without dementia ($n=380$, 62.4%) in order to compare genotypic and allelic frequencies in the two groups. The results are shown in Table 2. The genotypic distributions respected Hardy–Weinberg equilibrium ($p>0.05$) for all SNPs (both for demented and non-demented). We found no association, either at genotypic or allelic level among the genetic variants considered and dementia presence. The same results were found when we tried to stratify the population according to sex (data not shown) or when the presence of the SNPs *rs1800587*, *rs3087258* or *rs1799724* was related to baseline severity of dementia (Table 3). In this case, a possible sex contribution was not taken into account due to limited sample size.

Table 1 Main demographic features of the population considered for genetic testing

Number of subjects (M:F)	Age (years $\pm$ SD) [range]	MMSE (mean $\pm$ SD)	Education level (years $\pm$ SD)
Non-demented (105:275)	87.8 $\pm$ 4.4 [80–99]	25.9 $\pm$ 2.9	5.3 $\pm$ 2.4
Demented (32:197)	90.6 $\pm$ 4.1* [81–104]	13.1 $\pm$ 6.3**	4.6 $\pm$ 2.2*

M males, F females, MMSE Mini-Mental State Examination, SD standard deviation

* $p<0.0001$; ** $p=0.0006$, Student's t test vs. non-demented

Table 2 Genotypic and allelic distributions of *IL-1 α rs1800587*, *IL-1 β rs3087258* and *TNF- α rs1799724*

Diagnosis (no. subjects)	Genotype count (%)			χ^2	p	Allele count (%)		χ^2	p
	C/C	C/T	T/T			C	T		
<i>IL-1α rs1800587</i>									
Non-demented (348)	202 (58.1)	120 (34.5)	26 (7.4)			524 (75.3)	172 (24.7)		
Demented (210)	117 (55.7)	72 (34.3)	21 (10.0)			306 (72.8)	114 (27.2)		
Univariate				1.1	0.57 ^a			0.8	0.36 ^b
Adjusted				1.15	0.56 ^c				
<i>IL-1β rs3087258</i>									
Non-demented (363)	205 (56.5)	126 (34.7)	32 (8.8)			536 (73.8)	190 (26.2)		
Demented (223)	122 (54.7)	78 (34.9)	23 (10.4)			322 (72.2)	124 (27.8)		
Univariate				0.41	0.81 ^a			0.3	0.54 ^b
Adjusted				0.45	0.80 ^c				
<i>TNF-α rs1799724</i>									
Non-demented (356)	151 (42.4)	172 (48.3)	33 (9.3)			474 (66.6)	238 (33.4)		
Demented (215)	107 (49.8)	91 (42.3)	17 (7.9)			305 (70.9)	125 (29.1)		
Univariate				2.9	0.23 ^a			2.3	0.12 ^b
Adjusted				2.1	0.34 ^c				

^a Associated p value for genotypic frequency distribution comparison

^b Associated p value for allelic frequency distribution comparison

^c Associated p value for genotypic frequency distribution comparison after adjusting for age, sex and education level

Association between *IL-1 α rs1800587*, *IL-1 β rs3087258*, *TNF- α rs1799724* and dementia: longitudinal analysis

Taking advantage of the availability of a longitudinal follow-up of the participants to the Monzino 80-plus study, we decided to evaluate the association between

dementia onset over time and *IL-1 α rs1800587*, *IL-1 β rs3087258*, *TNF- α rs1799724* or *APOE* genotype, considering as a risk factor the presence of at least one T-allele or, in the case of the *APOE* genotype, assuming that the epsilon-4 (ϵ 4) allele should increase dementia incidence in comparison to ϵ 4-non-carriers. The curves are shown in Fig. 1, where the p values

Table 3 Assessment of the association between dementia severity at base-line and *IL-1 α rs1800587*, *IL-1 β rs3087258* or *TNF- α rs1799724* genotype

	Genotype count (%)			<i>F</i>	<i>p</i>
	C/C	C/T	T/T		

<i>MMSE</i> Mini-Mental State Examination, <i>SD</i> standard deviation	<i>IL-1α rs1800587</i>					
	No. of subjects	117	72	21	1.5	0.22
	Age (mean±SD)	89.9±4.2	90.8±3.6	90.8±4.7		
	MMSE (mean±SD)	13.1±5.5	11.4±6.0	12.5±6.0		
	<i>IL-1β rs3087258</i>					
	No. of subjects	122	75	26	1.0	0.36
	Age (mean±SD)	90.0±3.9	90.9±4.3	92.0±4.6		
	MMSE (mean±SD)	13.1±5.5	12.5±6.3	10.7±5.5		
	<i>TNF-α rs1799724</i>					
	No. of subjects	107	91	17	0.2	0.8
	Age (mean±SD)	90.8±3.9	90.0±4.3	88.8±3.4		
	MMSE (mean±SD)	12.2±6.3	12.8±5.1	11.9±6.2		

MMSE Mini-Mental State Examination, SD standard deviation

Fig. 1 Incident cases of dementia in the Monzino 80-plus study. Incident dementia cases were stratified according to the genetic variants of *APOE*, *IL-1 α* , *IL-1 β* and *TNF- α* . The participants to the study were followed up for 5 years, and the occurrence of dementia during this period was registered. In each plot, the comparison is made between the carriers of at least one risk allele (blue line, +) and non-carriers of the same allele (red line, -/-) according to a dominant model. **a** *APOE*.

The *APOE*-epsilon 4 (*APOE*- $\epsilon 4$) allele was considered as risk allele. **b** *IL-1 α* -889 C/T (*rs1800587*). **c** *IL-1 β* -511 C/T (*rs3087258*). **d** *TNF- α* -850 C/T (*rs1799724*). For these three genetic variants, the minor T-allele was considered as the risk allele. Asterisk sign indicates the adjusted *p* value after correcting for age, sex and education. Number sign indicates the adjusted *p* value after correcting for age, sex, education and *APOE*- $\epsilon 4$ status

were corrected for age, sex and education level using Cox regression models. While for *IL-1 α* *rs1800587* and *IL-1 β* *rs3087258* no difference between C-carriers and T-carriers was detectable, for the *TNF- α* *rs1799724* T-allele carriers, an increased risk of developing dementia was present [OR (95%CI): 1.5 (1.03–2.2)]. The *APOE*- $\epsilon 4$ carriers were at an increased risk of dementia, with an OR (95%CI) of 2.96 (1.81–4.61). Finally, we verified whether the *TNF- α* *rs1799724* T-allele carriers had an increased risk of developing incident dementia independently from the *APOE* genotype. When we adjusted our multivariate analysis also for *APOE*- $\epsilon 4$

presence, the association was no longer significant [OR (95%CI): 1.2 (0.8–1.9), $p=0.26$].

Discussion

The neurodegenerative disorders affect the nervous system, and the neuroinflammation is a common trait that parallels the disease onset and progression. The role of inflammation as disease-triggering factor is controversial; however, in most cases, it contributes to worsen the pathology, while a chronic inflammatory response in the brain might predispose to dementia.

The individual genetic background might play a role in modulating the extent of neuroinflammation, in particular for genetic variants influencing the production of key proinflammatory cytokines like IL-1 α , IL-1 β and TNF- α . We have performed the genotyping of three SNPs located in the promoter region of the just cited genes in an Italian general population aged 80 years or older, in an attempt to evaluate an association between these genetic variants and dementia and to demonstrate whether the presence of these SNPs correlated with the severity of dementia. Our cross-sectional negative findings are not supportive of a major contribution of this genetic background to dementia status or severity, at least in our Italian population of the oldest old. Our results are in agreement with the others that have addressed the role of the examined SNPs in Alzheimer's disease in the Italian population, finding very limited or no association (Terreni et al. 2003; Licastro et al. 2007; Tedde et al. 2008; Serretti et al. 2009). However, positive associations have been reported, too (Bosco et al. 2004; Seripa et al. 2005; Grimaldi et al. 2000). A potential limitation of our analysis is the use of a diagnosis of dementia syndrome instead of the dementia type. However, while the great majority of the persons affected by dementia are 80 years or older, classification of dementias in the very old remains a big challenge even at autopsy stage, where an improvement of diagnostic criteria is a matter of investigation (Neuropathology Group: Medical Research Council Cognitive Function and Aging Study 2001; Sinka et al. 2010). The association between pathological features of Alzheimer's disease and dementia is stronger in younger old persons than in older persons (Savva et al. 2009), while mixed pathologies account for most dementia cases in very old persons (Jellinger and Attems 2010). Moreover, our study was able to detect only relatively high changes of the minor allele frequency of the three SNPs tested (10–12%), so we are not able to exclude that minor genetic variation from the explored SNPs can exist, even if in this case their contribution to a very frequent phenotype as dementia in the very old would be of limited impact.

When we analysed the same genetic data using the prospective approach, we found at first an association between the presence of *TNF- α rs1799724* T-allele and the development of dementia, with a small effect (OR: 1.5). Moreover, we confirmed a role as risk modulator for the *APOE- ϵ 4* allele that in our

longitudinal analysis clearly increased the risk for dementia development in the population (OR: 2.9). However, the *TNF- α rs1799724* T-allele effect was not independent from *APOE- ϵ 4* presence, and to better dissect its contribution to incident dementia, an increase in the sample size is probably required to have a sufficient number of T-allele carriers without the *APOE- ϵ 4* allele (that in our population were 38 subjects only). Ravaglia et al. analysed in a younger Italian population *IL-1 β rs3087258* and incident dementia (any type and AD), with a follow-up of 4 years, and they found no association (Ravaglia et al. 2006). Our negative results on *IL-1 β rs3087258* polymorphism are in agreement with this study and our contribution reinforces the finding by Ravaglia et al. but in an older population.

In summary, we did not find an association between dementia status or severity and *rs1800587*, *rs3087258* or *rs1799724* in a well-described population of Italian very old people, while the longitudinal approach gave evidence of the role of the *APOE- ϵ 4* allele as a risk factor for dementia syndrome development also in the oldest olds.

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