Association of IL-1β, IL-1α and IL-10 single nucleotide polymorphisms with Mini-Mental State Examination and event-related potentials

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DOI: 10.21203/rs.2.18551/v1

SUBJECT AREAS
  Neurobiology of Disease
KEYWORDS

Neuroinflammation, Alzheimer’s disease, genetics, polymorphisms, MMSE, event-related potentials, IL-10, IL-1
Abstract
Background: Neuroinflammation is enhanced in Alzheimer’s disease (AD) brain. Its association with both amyloid and tau pathology is well documented. Activated microglia in the AD brain release pro-inflammatory cytokines that can damage neurons, while anti-inflammatory cytokines are also released to oppose this process. Association of IL-1β -1473C/G, IL-1α -889C/T and IL-10 -1082G/A polymorphisms with AD has been amply documented previously. In this study we assessed whether people carrying certain genotypes in these polymorphisms were more prone to disease progression as tested by the Mini-Mental State Examination (MMSE) scores and event-related potentials (ERP).

Methods: After blood collection, isolation of DNA and determination of polymorphisms, 226 subjects were tested neuropsychologically using MMSE (including AD patients, mild cognitive impairment patients, patients with other causes of dementia, and healthy controls). ERP were measured by electroencephalography (EEG) in this cohort.

Results: MMSE scores were significantly lower in patients carrying the G allele in the IL-1β -1473, T allele in the IL-1α -889, and A allele in the IL-10 -1082 polymorphism. The P300 latency was significantly prolonged in patients carrying the G allele in the IL-1β -1473 polymorphism.

Conclusions: Patients carrying risk genotypes in IL-1β -1473, IL-1α -889 and IL-10 -1082 polymorphisms may be susceptible to faster disease progression. Additionally, IL-1β -1473 polymorphism may represent a strong genetic biomarker of AD.

Background
In addition to amyloid β protein and tau pathology, neuroinflammation plays a key role in the development of Alzheimer’s disease (AD) [1–4]. During sustained neuroinflammation in AD brain, pro-inflammatory cytokines released from microglia, such as interleukin (IL)-1α, IL-1β, IL-6 and tumor necrosis factor α (TNFα), lead to neuron damage [5,6], while anti-inflammatory cytokines (like IL-10) are also released to maintain homeostasis [7]. Association of IL-1β -1473C/G, IL-1α -889C/T and IL-10 -1082G/A single nucleotide polymorphisms (SNPs) with AD has been shown in many studies [8–25]. These polymorphisms could affect the amount of produced mRNA and proteins [26–30]. Thus, patients carrying certain genotypes in IL-1β -1473C/G, IL-1α -889C/T and IL-10 -1082G/A
polymorphisms may present with increased amount of pro-inflammatory cytokines (IL-1β and IL-1α) and decreased amount of anti-inflammatory cytokines (IL-10) and consequently be more vulnerable to inflammatory mechanisms that could lead to AD [3,31]. Because event-related potentials (ERP) measured by electroencephalography (EEG) and Mini-Mental State Examination (MMSE) scores show potential in early and differential diagnosis of AD [32,33], we assessed whether MMSE scores and evoked potentials differed among patients carrying particular IL-1β -1473C/G, IL-1α -889C/T and IL-10 -1082G/A genotypes, which would in turn indicate a genetic predisposition to develop AD or for being prone to faster disease progression.

Methods

Subjects

A cohort of 226 patients hospitalized at Clinical Hospital Center Zagreb participated in this study. They gave informed consent for participation in the study. Of them, 113 suffered from AD, 53 from mild cognitive impairment (MCI), 52 from other causes of dementia (22 from frontotemporal dementia [FTD], 2 from Parkinson’s disease [PD], 14 from vascular dementia [VaD], 7 from dementia with Lewy bodies [DLB], 3 from mixed dementia [AD+VaD], 1 from corticobasal syndrome [CBS], and 3 from nonspecific dementia [ND]), and 8 were healthy controls (HC) (Table 1). They all underwent neuropsychological testing using the Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-Cog), the Montreal Cognitive Assessment (MoCA) and the MMSE. Also, neurological examination and full blood tests (serology for Lyme’s disease and syphilis, thyroid function test, levels of folic acid and vitamin B12) were done. Diagnosis of AD was established by the criteria of the National Institutes on Aging – Alzheimer’s Association (NIA-AA) [34], MCI by the criteria of Albert et al. [35] and Petersen et al. [36], FTD by the criteria of Neary et al. [37], while VaD was diagnosed using Hachinski Ischemic Score (HIS) [38] and the criteria of the National Institute for Neurological Disorders and Stroke—Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINCDS-AIREN) [39]. All procedures were performed in accord with the Helsinki Declaration [40] and were approved by the Ethical Committee of the Clinical Hospital Center Zagreb (case no. 02/21 AG, class 8.1-18/82-2 from April 24, 2018) and by the Central Ethical Committee of the University of


Determination of polymorphisms
Venous blood was collected in plastic syringes with 1 ml of acid citrate dextrose as an anticoagulant. Salting-out method [41] was used for isolation of DNA from peripheral blood. SNPs were determined by ABI Prism 7300 Real Time PCR System apparatus (Applied Biosystems, Foster City, CA), using following TaqMan SNP Genotyping Assays (Applied Biosystems); *IL-1*α -889C/T (rs1800587), *IL-1*β -1473G/C (rs1143623) and *IL-10* -1082G/A (rs1800896).

Measurement of event-related potentials
ERP (P300 and N200) were measured using EEG in the Laboratory for Cognitive and Experimental Neurophysiology at the University Hospital Centre, Zagreb. For ERP measurement, 32 electrodes were placed on the head of patients according to the international 10/20 system. Overall 54 subjects (31 AD, 19 MCI patients and 4 HC) were tested by an auditory oddball paradigm. During the testing, participants were sitting in an auditory sound-proof chamber with headphones on. They had to count all target auditory tones among non-target and interfering tones. Some subjects participated in the auditory oddball paradigm with two frequencies, while the others participated in the auditory oddball paradigm with three frequencies. In the first paradigm, ERP were measured while subjects tried to differentiate target from non-target tone, whereas in the second paradigm, participants tried to differentiate target tone from non-target and interfering tones, as described previously [32].

Statistical analysis
Statistical analysis was performed with SPSS 19.0.1 (SPSS, Chicago, IL, USA), with the level of statistical significance set at $\alpha = 0.05$. We tested data normality using the Kolmogorov-Smirnov test.
However, non-parametric statistics were mostly used due to the small number of subjects in some groups. MMSE scores and ERP latencies were compared among groups using the non-parametric Kruskal-Wallis test. A post-hoc non-parametric test to correct $p$ values was used for pairwise comparisons.

Results

**IL-1β rs1143623, IL-1α -889C/T, IL-10 -1082G/A genotype and MMSE**

MMSE scores were significantly lower when all subjects ($U=5132; Z=-1.965; p=0.049$), or AD, MCI and HC subjects ($U=3001; Z=-2.013; p=0.044$), or only AD and MCI patients were grouped together ($U=2573; Z=-2.405; p=0.016$) for CG and GG compared to CC IL-1β rs1143623 genotypes (Figure 1). MMSE scores were significantly lower in all subjects with TT and TC compared to CC IL-1α -889C/T genotypes ($U=5265; Z=-2.072; p=0.038$; Figure 2). MMSE scores were significantly lower in MCI patients with AA and AG compared to GG IL-10 -1082G/A genotypes ($U=107.5; Z=-2.167; p=0.030$; Figure 3).

**IL-1β rs1143623, IL-1α -889C/T, IL-10 -1082G/A genotype and event-related potentials**

P300 latency was significantly prolonged in patients with CG and GG compared to CC IL-1β rs1143623 genotypes ($t = -2.142, df = 52, p = 0.037$; Figure 4). There was no significant difference in N200 latency in patients with different IL-1β rs1143623, IL-1α -889C/T and IL-10 -1082G/A genotypes. Also, P300 latency did not differ among patients with different IL-1α -889C/T and IL-10 -1082G/A genotypes.

Discussion

The goal of this study was to test whether polymorphisms in genes for IL-1β, IL-1α and IL-10 are associated with MMSE scores and ERP. Polymorphisms in IL-1β, IL-1α and IL-10 genes could lead to different transcription products and consequently influence the amount of the produced proteins [26-30]. Increase in production of pro-inflammatory cytokines (IL-1β and IL-1α) and decrease in production of anti-inflammatory cytokines (IL-10) would result in increased inflammation that favours development of AD [1,2,31]. We show that MMSE scores are significantly lower in carriers of a G allele.
in *IL-1β* –1473, T allele in *IL-1α* –889, and A allele in *IL-10* –1082 polymorphisms, while P300 latency is significantly prolonged in carriers of a G allele in *IL-1β* –1473 polymorphism.

Pro-inflammatory cytokine IL-1β contributes to inflammation-mediated cognitive decline [42].

Association of *IL-1β* polymorphisms with AD was reported before by numerous studies [43–46]. *IL-1β* +3953, *IL-1β* –31 and *IL-1β* –511 polymorphisms were mainly tested [43–46], although the results of our previous study [18] showed that levels of various cerebrospinal fluid (CSF) biomarkers (amyloid β₁₋₄₂, total tau, phosphorylated tau isoforms and visinin-like protein 1) were pathological in patients carrying a G allele in the *IL-1β* –1473 polymorphism. The results of the present study are further strengthening the association of *IL-1β* –1473 polymorphism with AD, as MMSE scores were lower and P300 latencies increased in patients carrying a G allele in the *IL-1β* –1473 polymorphism. Distribution of *IL-1β* –1473 genotypes between AD patients and HC was assessed in only two studies that reported no differences [47,48]. Our results disagree with these results as well as those of Lee and collaborators [28] showing that presence of the G allele in *IL-1β* –1473 polymorphism leads to weaker promoter activity and consequently lower levels of IL-1β protein. Thus, further analyses on the distribution of *IL-1β* –1473 genotypes between AD patients and HC and the influence of *IL-1β* –1473 polymorphism on the amount of produced IL-1β protein should be conducted.

The association of SNPs in genes for other pro-inflammatory cytokines and vulnerability of AD was also tested. Pro-inflammatory *IL-1α* cytokine is overexpressed in AD brain [49]. As presence of a T allele in the *IL-1α* –889 polymorphism leads to increase in transcriptional activity of the *IL-1α* gene [29,30], this could explain why carriers of a T allele in the *IL-1α* –889 polymorphism have higher risk for AD [8–17]. Our recent study showed that there is no association between CSF AD biomarkers and *IL-1α* –889 genotypes [18]. However, the present study indicates that although the *IL-1α* –889 polymorphism is not suitable as an early genetic biomarker of AD, it could be an index of disease severity as patients carrying the T allele in *IL-1α* –889 polymorphism have significantly lower MMSE scores. According to these results, T allele carriers could be more vulnerable to disease progression. Our results agree with previous studies showing increased risk of AD in carriers of a T allele in the *IL-1α* –889 polymorphism [8–17,46,50–52]. However, due to the facts that many studies did not reveal
an association of the *IL-1α* –889 polymorphism and AD [53–75] and that our recent study failed to detect an association of this polymorphism with CSF AD biomarkers [18], these results should be validated in larger cohorts.

Polymorphisms in the anti-inflammatory cytokine IL-10 gene are also associated with AD. Production of IL-10 is significantly decreased in carriers of A allele in *IL-10* –1082 polymorphism [26,27]. Also, carriers of an A allele in *IL-10* –1082 polymorphism have an increased risk for AD [19–25,76–78]. Our results support these studies as MMSE scores were significantly lower in MCI patients with the *IL-10* –1082 A genotype. Additionally, these results are in accord with our recent study showing that CSF p-tau_{181} levels are pathological in patients carrying the AA *IL-10* –1082 genotype [18]. However, it should kept in mind that other studies failed to detect an association between the *IL-10* –1082 polymorphism and AD [46,72,79–86] or showed opposite results (association of the G allele in *IL-10* –1082 polymorphism with increased risk for AD) [71,74].

**Conclusion**

In conclusion, our study shows that patients with the *IL-1β* –1473 G, *IL-1α* –889 T and *IL-10* –1082 A genotypes have significantly lower MMSE scores. Additionally, patients carrying a G allele in the *IL-1β* –1473 polymorphism have prolonged P300 latencies. These results indicate that these risk genotypes could represent genetic biomarkers of disease progression [87] and as such should be further correlated with neuroimaging and genetic biomarkers of AD. The most important finding of this study is the association of the *IL-1β* –1473 polymorphism with MMSE scores and P300 ERP. This finding together with our previous results [18] indicates that the *IL-1β* –1473 polymorphism could be strong genetic biomarker of AD.

**List Of Abbreviations**

AD, Alzheimer’s disease; ADAS-Cog, Alzheimer’s Disease Assessment Scale-cognitive subscale; CBS, corticobasal syndrome; CSF, cerebrospinal fluid; DLB, dementia with Lewy bodies; EEG, electroencephalography; ERP, event-related potentials; FTD, frontotemporal dementia; HC, healthy control; HIS, Hachinski Ischemic Score; IL, interleukin; K-W, Kruskal-Wallis; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; ND,
nonspecific dementia; NINCDS-AIREN, National Institute for Neurological Disorders and Stroke - Association Internationale pour la Recherche et l'Enseignement en Neurosciences; PD, Parkinson’s disease; p-tau\textsubscript{181}, tau phosphorylated at Thr 181; SNP, single nucleotide polymorphisms; TNFα, tumor necrosis factor α; VaD, vascular dementia.

Declarations

Ethics approval and consent to participate

All procedures were approved by the Ethical Committee of the Clinical Hospital Center Zagreb (case no. 02/21 AG, class 8.1-18/82-2 from April 24, 2018) and by the Central Ethical Committee of the University of Zagreb Medical School (case no. 380-59-10106-18-111/126, class 641-01/18-02/01 from June 20, 2018). All patients gave informed consent for participation in this study.

Consent for publication

All patients gave consent for publication.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was funded by The Croatian Science Foundation grant IP-2019-04-3584 (“Role of blood-brain barrier, innate immunity, and tau protein oligomerization in the pathogenesis of Alzheimer’s disease”) to GŠ and by the Scientific Centre of Excellence for Basic, Clinical and Translational Neuroscience CoRE-NEURO (“Experimental and clinical research of hypoxic-ischemic damage in perinatal and adult brain”; GA KK01.1.1.01.0007 funded by the European Union through the European
Regional Development Fund), and in part by NIH grant P50 AG005138 to PRH.

Authors' contributions

GŠ conceived and directed the study. NK and FB performed the clinical assessments. MKS performed the measurement of evoked potentials. MNP, DŠŠ, MBL and NP determined IL-1β, IL-1α and IL-10 genotypes. MBL and GŠ completed statistical analysis. PRH substantially contributed to the interpretation of data and to manuscript preparation. All authors contributed to revising and editing the manuscript critically for important intellectual content. All authors read and approved the final version of the manuscript. All authors met the criteria for authorship, as defined by the International Committee of Medical Journal Editors.

Acknowledgments

Not applicable.

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Table

Table 1. Frequency of IL-1α -889C/T, IL-1β -1473C/G and IL-10 -1082G/A genotypes, and MMSE scores and ERP latencies in AD and MCI patients, HC, and in patients with other causes of dementia.
### Table

|       | IL-1α | IL-1β | IL-10 | MMSE | Age | Sex |
|-------|-------|-------|-------|------|-----|-----|
|       | TT    | CC    | TC    | CC   | GG  | GG  | AA | AG | Mean ± SD | Median (25–75th percentile) | F/M |
| AD    | 6     | 64    | 43    | 60   | 7   | 46  | 23 | 35 | 55 | 19.9 ± 4.5 | 73 (67-77) | 61/51 |
| MCI   | 5     | 30    | 18    | 40   | 1   | 12  | 9  | 24 | 20 | 25.1 ± 2.9 | 70 (59-74) | 27/2 |
| HC    | 7     | 1     | 3     | 2    | 2   | 3   | 1  | 3  | 4  | 27.8 ± 1.9 | 54 (41-60) | 5/3  |
| VaD   | 2     | 7     | 5     | 9    | 1   | 4   | 2  | 8  | 4  | 22.2 ± 5.0 | 71 (63-77) | 6/8  |
| FTD   | 14    | 8     | 14    | 2    | 6   | 4   | 7  | 11 | 11 | 16.7 ± 5.2 | 61 (56-64) | 11/11 |
| DLB   | 2     | 2     | 3     | 5    | 2   | 2   | 4  | 3  | 19.3 ± 3.9 | 70 (68-75) | 2/5  |
| AD + VaD | 1 | 2     | 2     | 1    | 2   | 1   | 1  | 2  | 19.3 ± 4.0 | 78 (68-75) | 0/3  |
| PD    | 1     | 1     | 1     | 1    | 1   | 2   | 2  | 10 | 22.5 ± 10.6 | 62 (63-77) | 1/1  |
| CBS   | 1     | 1     | 1     | 1    | 1   | 1   | 1  | 2  | 27 | 51 (48-54) | 1/0  |
| ND    | 1     | 2     | 3     | 1    | 2   | 2   | 1  | 2  | 20.7 ± 5.5 | 68 (63-77) | 2/1  |

AD: Alzheimer’s disease; AD + VaD: mixed dementia; CBS: corticobasal syndrome; DLB: dementia with Lewy bodies; F, female; FTD: frontotemporal dementia; HC: healthy control; IL: interleukin; M, male; MCI: mild cognitive impairment; ND: nonspecific dementia; PD: Parkinson’s disease; SD: standard deviation; VaD: vascular dementia.

### Figures

**Figure 1**

MMSE scores in A) all subjects, B) AD, MCI patients and HC grouped together, and C) AD and MCI patients grouped together, with different IL-1β rs1143623 genotypes. *p<0.05.
Figure 2

MMSE scores in all subjects with different IL-1α -889C/T genotypes. *p<0.05.
Figure 3

MMSE scores in MCI patients with different IL-10 -1082G/A genotypes. *p<0.05.
Figure 4

P300 latency in AD and MCI patients and HC with different IL-1β rs1143623 genotypes.

*p<0.05.