DOI: 10.1590/0004-282X20150137

ARTICLE

Genetic predisposition to higher production of interleukin-6 through -174 G > C polymorphism predicts global cognitive decline in oldest-old with cognitive impairment no dementia

Predisposição genética à maior produção de interleucina-6 por meio do polimorfismo -174 G > C prediz declínio cognitivo global em idosos muito idosos com comprometimento cognitivo não demência

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ABSTRACT

Interleukin 6 (IL-6) is a pro-inflammatory cytokine upregulated in neurodegenerative contexts. The polymorphism IL-6 -174 G > C influences release levels of this cytokine. We aimed to evaluate the influence of IL-6 -174 G > C on global cognitive score of a group with cognitive impairment no dementia in one year of follow-up. **Methods:** The subjects were categorized in two groups: short-term decline in global cognitive score and those with short-term stability or improvement. IL-6 174 G > C information were compared among these groups. **Results:** We observed that individuals with cognitive impairment no dementia with GG^{lower} genotype were more frequent among global cognitive score non-decliners while carriers of at least one C^{higher} allele were more frequent in the group with global cognitive score decliners (p = 0.012; RR = 3.095 $IC_{95\%}$ = 1.087-8.812). **Conclusion:** These results suggest that the higher expression of IL-6 gene may be an independent risk factor for cognitive decline among individuals with cognitive impairment no dementia.

Keywords: IL-6, polymorphism, cognitive impairment no dementia, cognition.

RESUMO

Interleucina 6 (IL-6) é uma citocina pró-inflamatória cuja produção acentua-se em contextos neurodegenerativos. O polimorfismo IL-6 -174 G > C influencia os níveis secretados deste mediador inflamatório. Nós objetivamos avaliar a influência de IL-6 -174 G > C sobre o escore cognitivo global de um grupo com comprometimento cognitivo não demência em um ano de seguimento. **Métodos:** Os participantes foram categorizados em dois grupos: com declínio em escore cognitivo global em curto prazo e aqueles com melhora ou estabilidade do escore cognitivo global. **Resultados:** Nós observamos que indivíduos com comprometimento cognitivo não demência carreadores do genótipo GG^{baixa} foram mais frequentes entre pacientes com escore cognitivo global não declinante, enquanto carreadores de no mínimo um alelo C^{alta} foram mais frequentes no grupo que apresentou declínio no escore cognitivo global (p = 0,012; RR = 3,095 $IC_{95\%}$ = 1,087-8,812). **Conclusão:** Estes resultados sugerem que a alta expressão do gene IL-6 pode ser um fator de risco independente para declínio cognitivo entre pacientes com comprometimento cognitivo não demência.

Palavras-chave: IL-6, polimorfismo, comprometimento cognitivo não demência, cognição.

Cognitive impairment no dementia (CIND) is a clinical state characterized by impairment in memory and/or other cognitive domains which is not severe enough to establishment of a dementia diagnostic[1]. CIND occurrence may to be related to many conditions including neurological, psychiatric and vascular changes[1]. Frequently referred to as a transition phase between healthy aging and dementia, CIND is, however, a complex entity which can evolve different outcomes.

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Conflict of interest: There is no conflict of interest to declare.
Support: FAPEMIG and CNPq. ALT, MGC, PC and KBG are grateful to CNPq Research Fellowship (PQ).
Received 09 July 2015; Accepted 29 July 2015.

In population-based settings, and especially in oldest-old individuals, where multiple factors and pathological findings contribute to brain disorder[2], CIND may be a valuable concept, in opposition to mild cognitive impairment, which loosely predicts the pathological background that underpins cognitive deficits in the elderly[3]. Although subjects with cognitive impairment can display increased risk of dementia conversion[4], some individuals may remain stable or even show remission of cognitive deficits[5]. The pathophysiological mechanisms that mediate the transition between CIND and dementia remain poorly understood. Since inflammation is implicated in several neurodegenerative disorders, irrespective of the specific pathological background[6], it seems reasonable to investigate inflammatory pathways and its influence in CIND outcomes.

Interleukin-6 (IL-6) is a pleiotropic proinflammatory cytokine, which has been considered the major cytokine in central nervous system[7]. It participates in several brain processes, such as neurogenesis, synaptic plasticity, and inflammatory and neurotrophic pathways[7,8,9]. Imbalances between IL-6 concentrations in serum and cerebrospinal fluid are observed in CIND and dementia[10,11]. The increase of IL-6 production has been associated with disease progression and severity of symptoms in Alzheimer's disease[12,13].

The polymorphism -174 G > C (rs1800795) in IL-6 gene may affect its expression. The C allele is associated with increased transcriptional activity and higher IL-6 serum levels compared with G allele[14,15,16]. In this study, we evaluated the influence of this polymorphism on short-term global cognitive decline in a sample of Brazilian oldest-old categorized as CIND. To the best of our knowledge, this is the first study to address this issue.

METHOD

Study design

This prospective investigation was conducted with a subset of participants from the Pietà Study, a Brazilian population-based study on brain aging in subjects aged 75+ years, initiated in 2007, in Caeté (Minas Gerais state), Brazil. Diagnostic criteria, methods and baseline characteristics were previous reported[17].

Subjects

A total de 27 individuals participants of Pietà study and diagnosed with CIND in accordance with standard criteria[18] and consensus discussion among clinical investigators were included in this study. All participants or their legal representatives signed the written informed consent and the study protocol was approved by the Ethics Committee of the Universidade Federal de Minas Gerais.

Cognitive evaluation

The cognitive performance of the 27 oldest-old individuals with CIND [median age (IQ) = 81[9] years] was evaluated with brief cognitive tests, consisting of the mini-mental state examination (MMSE), animal category fluency test (CF) and picture drawings memory test (PDMT) with learning and delayed recall tasks. All cognitive tests were applied twice, with a one-year interval, and were normalized by schooling level (Z score). The Z scores derived from each cognitive test were used to calculate a global cognitive score (GCS). According to the numeric difference between GCS score obtained in 2008 and in 2009, the subjects were then categorized in two distinct groups: decliners, who showed short-term cognitive or functional decline expressed by a negative difference between GCS measures on the follow-up; and non-decliners, those who demonstrated short-term stability or even improvement in cognitive abilities expressed by a null or positive difference between GCS measures on the follow-up evaluation.

Molecular analyses

Venous blood samples were collected after fasting for 12 h in tubes with EDTA (Vacuette™). Whole blood samples were used for DNA extraction using the kit Biopur (Biometrix™). Genotyping of the SNP IL-6 -174G > C was made using PCR multiplex system kit Cytokine genotyping Tray (One Lambda™), followed by agarose gel electrophoresis 2.5%.

RESULTS

We observed on follow-up that 51.8% of CIND subjects evolved to decline in GCS, while 48.2% remained stable or improved.

Individuals with GG^{lower} genotypes for IL-6 -174 G > C were less frequent among GCS decliners and more found among GCS non-decliners (Table). CIND carriers of at least one C^{higher} allele were more frequent in the group with short-term global cognitive decline (Table). These subjects showed a 3-fold higher risk of decline than individuals with GG^{lower} genotype (RR = 3.095 $CI_{95\%}$ = 1.087-8.812). These findings were independent of gender, age and ApoE ε4 carrier status in a logistic regression model (all p > 0.05).

Table. Short-term cognitive outcome in CIND participants according to IL-6 -174 G > C genotype.

SNP IL-6 -174 G > C	Decliners (n = 14)	Non-decliners (n = 13)	p-value*
GG	4 (28.6)$^{+}$	10 (76.9)$^{++}$	
GC	5 (35.7)	2 (15.4)	0.039*
CC	5 (35.7)	1 (7.7)	
GG	4 (28.6)	10 (76.9)	0.012*
C carriers	10 (71.4)	3 (23.1)	
CC	5 (35.7)	1 (7.7)	
G carriers	9 (64.3)	12(92.3)	0.080

CIND: cognitive impairment no dementia; IL-6: interleukin 6; SNP: Single Nucleotide Polymorphism. Variables expressed in n (%). * significant, $\chi 2$ test. $^{+}$ less frequent $^{++}$ more frequent. C carriers: genotype GC + CC; G carriers: genotype GG + GC.

DISCUSSION

Several evidences indicate inflammatory pathways involvement in brain disorders frequently accompanied of neurodegenerative process as Alzheimer disease and CIN[6, 10,11]. Pro-inflammatory cytokines such as IL-6 are related to apoptosis, excitotoxicity, cytotoxicity and enhancer of immune activation leading neurodegeneration progression in many diseases[19].

Our results indicate that a genetic predisposition to higher production of IL-6 is an independent risk factor for cognitive decline among CIND individuals. Supporting our findings, Saykin et al.[20] showed that carriers of CC^{higher} genotype for IL-6 -174 G > C, among elderly with cognitive impairment, exhibited the most pronounced gray matter reduction in medial temporal lobe, mainly in left hippocampus. Economos et al.[21] demonstrated that increased serum levels of IL-6 were associated with cognitive decline in a cohort of elderly participants with diverse ethnical backgrounds[21]. Further, Zhao et al.[22] observed a weak but significant association between higher serum levels of IL-6 and worse cognitive performance in a group of Chinese individuals with amnestic mild cognitive impairment.

In addition to the proposed role of IL-6 in cognitive processes, there are growing evidences pointing to the involvement of this cytokine in age-associated functional performance. IL-6 serum concentrations were also associated with a slower gait speed in a community-based cohort of older adults, and predicted risk of gait speed decline[23]. Additionally, Adriansen et al.[24] studied global functional decline in a population-based cohort of Belgium oldest-old using an extensive panel of inflammatory markers According to their findings, IL-6 was the only inflammatory marker with an independent association with functional decline, in a dose-dependent manner[24].

Event thought there are conflicting results regarding the role of IL-6 levels and age-associated cognitive and functional performance[25,26], our findings stand in accordance with a growing set of studies that reinforce the association between this cytokine and age-related outcomes.

Our data suggest that the higher expression of IL-6 gene is an independent risk factor for cognitive decline among CIND individuals. Some methodological limitations are found in this study, such as the absence of IL-6 levels data and the small sample size. However, we could not find another similar study that approached the influence of IL-6 -174 G > C on cognitive decline in CIND. Therefore, we considered this investigation an initial and preliminary study that indicates the need for further research in this direction.

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