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Increased plasma levels of BDNF and inflammatory markers in Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is the most common cause of dementia in the elderly. Neurotrophic factors and inflammatory markers may play considerable roles in AD. In this study we measured, through Enzyme-Linked Immunosorbent Assay, the plasma levels of brain derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF) and neuronal growth factor (NGF), as well as tumor necrosis factor-alpha soluble receptors, sTNFR1 and sTNFR2, and soluble intercellular adhesion molecule 1 (sICAM-1), in 50 AD patients, 37 patients with mild cognitive impairment (MCI) and 56 healthy elderly controls. BDNF levels, expressed as median and interquartile range, were higher for AD patients (2545.3, 1497.4–4153.4 pg/ml) compared to controls (1503.8, 802.3–2378.4 pg/ml), $P < 0.001$. sICAM-1 was also higher in AD patients. sTNFR1 levels were increased in AD when compared to controls and also to MCI. GDNF, NGF and sTNFR2 levels showed no significant differences among the studied groups. The increase in BDNF might reflect a compensatory mechanism against early neurodegeneration and seems to be related to inflammation. sTNFR1 appears to mark not only the inflammatory state but also differentiates between MCI and AD, which may be an additional tool for differentiating degrees of cognitive impairment.

1. Objectives of the study and background

AD is characterized by the presence of extracellular amyloid plaques, containing deposits of beta-amyloid protein (Aβ), intracellular neurofibrillary tangles and extensive neuronal and synaptic loss (Adlard and Cummings, 2004). The genetic background plays a considerable role in AD as polymorphisms in the gene of apolipoprotein E (APOE) affect the risk of the late-onset form of the disease, with the ε4 allele and the ε2 allele being respectively related to an increased and decreased risk for AD development (Leduc et al., 2010). Additionally, inflammatory processes follow Alzheimer's neuropathology (Papassotiropoulos et al., 2001). Activated microglia and astrocytes identified near amyloid plaques lead to increased levels of inflammatory cytokines as: interleukin-1 (IL-1), interleukin-3 (IL-3) and tumor necrosis factor α (TNF-α) (Akiyama et al., 2000; Song et al., 2009).

Levels of TNF-α soluble receptors (sTNFR1 and sTNFR2) have also been described as representatives of the inflammatory activity in AD patients and individuals with mild cognitive impairment (MCI) (Diniz et al., 2010). sTNFR1 and 2 are induced by TNF-α in

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humans, and are more stable than the cytokine itself. Therefore, these soluble receptors reflect the levels of TNF-α over a prolonged time (Buchhave et al., 2010). TNF-α can increase the expression of adhesion molecules such as the vascular cell adhesion protein 1 (VCAM-1) and the intercellular adhesion molecule 1 (ICAM-1) in the endothelium (Collins et al., 1995). These molecules are biomarkers of microvascular lesion and the plasma levels of their soluble forms are reported to be increased in AD (Breteler, 2000; Ewers et al., 2010).

Recent findings have highlighted changes in the levels of neurotrophic factors in *post-mortem* AD brain, where increased levels of neuronal growth factor (NGF) and decreased levels of brain derived neurotrophic factor (BDNF) were reported (Ferrer et al., 1999; Hellweg et al., 1998; Hock et al., 2000). BDNF was, however, strongly positive in damaged neurites surrounding amyloid plaques (Ferrer et al., 1999), suggesting a positive regulatory circuitry of this neurotrophic factor in damaged brain areas.

The ability of neurotrophic factors to provide support, growth and survival to neurons, brings the idea that a loss or dysfunction in their production might be related to the development of neurodegenerative disorders (Siegel and Chauhan, 2000). In effect, BDNF is able to decrease the amount of Aβ and generate peptides which have neurotrophic and neuroprotective roles (Rohe et al., 2009; Thornton et al., 2006).

Changes in peripheral levels of neurotrophic factors have, as well, been observed in the context of psychiatric or neurodegenerative diseases. Serum BDNF was found to be reduced (Forlenza et al., 2010; Lee et al., 2009) in AD and MCI patients, in contrast with its increase reported by Angelucci et al. (2010) and Laske et al. (2006). Schizophrenia (SZ) and bipolar disease (BD) patients also displayed elevated BDNF circulating levels (Gama et al., 2007; Barbosa et al., 2012). Measurements of glial cell-derived neurotrophic factor (GDNF) in blood showed its elevation in euthymic BD patients (Barbosa et al., 2011) and AD ones (Straten et al., 2009), while opposite findings have also been described for the latter subjects (Marksteiner et al., 2011). Regarding NGF, it was proposed that the pre-dementia stage that precedes AD is marked by a decrease in its serum levels (Schaub et al., 2002). Such decrease was also observed in Huntington and Parkinson disease patients (Lorigados Pedre et al., 2002; Tasset et al., 2012).

BDNF is upregulated at the vicinity of Aβ plaques where an immune response is evoked by activated glial cells (Burbach et al., 2004; Ferrer et al., 1999). The implications of microglial activation and infiltrating cytokines in neuronal survival and memory processes in the context of neuronal damage illustrate the connection between the immune and nervous systems (Yirmiya and Goshen, 2011). Immune cells can produce the majority of neurotrophic factors and cytokines are able to influence such production (Kerschensteiner et al., 2003). Indeed, TNF-α and IL-6 enhanced the production of BDNF by cultured monocytes (Schulte-Herbrüggen et al., 2005) while a strong activation of the immune system was associated with a downregulation of BDNF mRNA expression (Lapchak et al., 1993). Reinforcing the cited modulatory circuitry, such downregulation was abrogated when cultured astrocytes were exposed to IL-4 (Derecki et al., 2010). Additionally, immune cells can express receptors for neurotrophic factors, which could be involved in the regulation of the inflammatory response (Nockher and Renz, 2006; Siegel and Chauhan, 2000). As the involvement of inflammation in AD pathology has been reported (Akiyama et al., 2000), the role of neurotrophic factors in the central nervous system along with their possible role in the inflammatory setting, makes them conceivable biomarkers for AD.

Heterogenous results concerning levels of neurotrophic factors have been reported so far, mainly due to differences in analyzed biological specimen (brain tissue, serum, plasma) and the disease stage in which it is sampled. As homogeneity between the studies is pursued, and similar evaluation protocols are applied to the subjects, more comparable results will be obtained enabling a better understanding of neurotrophic factors as biomarkers for AD.

The progressive and irreversible characteristics of AD have prompted researchers to look for useful biomarkers for either its early diagnosis or for understanding the course of the disease. In the past two decades, blood (serum, plasma or circulating cells) has been considered a potential source of biomarkers for the diagnosis of AD and for research purposes as it is easily obtained compared to cerebral spinal fluid (CSF) (Caramelli et al., 2011).

In the present study we measured the plasma levels of BDNF, GDNF, NGF as well as sTNFR1, sTNFR2 and sICAM-1 in order to evaluate the inflammatory and neurotrophic profile in AD and MCI patients in comparison with controls.

2. Methods

2.1. Subjects

This study evaluated 56 healthy controls, 37 patients with MCI and 50 AD patients, recruited from the outpatient clinic of Instituto Jenny de Andrade Faria, Universidade Federal de Minas Gerais (UFMG), Brazil. The groups were matched for age which ranged from 61 to 89 years old. None of the participants were in use of anti-inflammatories.

The diagnosis of AD and MCI was based on screening tests including the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) with cut-off limits adjusted according to the education level, CERAD Protocol (Morris et al., 1989), Activities of Daily Living Scale (Katz et al., 1963), Instrumental activities of daily living (Pfeffer et al., 1982) and Hachinski Ischemic Scale (<2) (Rosen et al., 1980). The diagnosis of probable AD was performed according to the DSM-IV and NINCDS-ADRDA criteria (McKhann et al., 2011).

No familial cases of AD were included in this study. The diagnosis of amnestic MCI followed the recommendation of Petersen (2004). The recruited patients underwent a thorough geriatric assessment, including medical history, physical and laboratorial screening tests, brain imaging exams and neuropsychological tests, when necessary.

The individuals enrolled in the control group were cognitively intact, with no personal and family (first degree relatives) history of neuropsychiatric diseases. They were submitted to clinical tests to exclude other psychiatric disorders.

In order to exclude patients or controls with acute inflammatory process, C-Reactive Protein (CRP) level was measured in all individuals through highly sensitive Near Infrared Particle Immunoassay rate methodology (IMMAGE® Immunochemistry systems, Beckman Coulter, Galway, Ireland). The elected participants had levels under 10 mg/L (Ansar and Ghosh, 2013). In effect, even when CRP is increased due to the time course of mild cognitive impairment, it does not reach values as high as 10 mg/L (Karim et al., 2013).

Demographic and clinical data of the participants were obtained retrospectively through medical record review or through interview during the collection of the blood samples.

AD patients were divided into two different groups according to their Clinical Dementia Rate (CDR) score (Morris, 1993). CDR1 corresponds to a mild stage of dementia, and 27 patients were found in this group. 16 patients were at a moderate stage of dementia and 4 were at a severe stage, they were listed together in the CDR2/CDR3 group.

This study was approved by the Ethics Committee of Universidade Federal de Minas Gerais, and the participants signed an