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Increased plasma levels of brain derived neurotrophic factor (BDNF) after multiple sclerosis relapse

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ABSTRACT

Brain derived neurotrophic factor (BDNF) has been related to neuroprotection in a series of central nervous system diseases, although its role in multiple sclerosis (MS) was only partially investigated. In this work, we aimed to evaluate the plasma levels of BDNF from 29 MS patients and 24 control subjects. MS patients had decreased levels of BDNF in comparison with healthy controls. BDNF levels increased significantly after MS relapse. Our results provide some evidence for the involvement of BDNF in the pathogenesis of MS and suggest a role for this neurotrophin during the recovery of acute demyelinating inflammatory lesion.

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Multiple sclerosis (MS) is the most common inflammatory disease of the central nervous system (CNS). Demyelination and axonal damage caused by inflammatory lesions determine a wide spectrum of clinical symptoms [7]. In general MS begins at third or fourth decade of life and affects more women than men [15]. MS patients may present different forms of clinical evolution. Relapsing-remitting MS (RR-MS) is the form presented by approximately 80% of patients at disease onset. RR-MS patients evolve with relapses marked by acute demyelinating lesions and related clinical symptoms followed by a variable period of remission, in which symptoms are not present or are stable [12]. MS etiopathogenesis is unknown, but strong evidence points to polygenic susceptibility and multiple environmental triggering factors [17].

Although the complex pathogenesis of this disease is not understood, an immune reaction against myelin sheath is suggested to be the primer event. Auto-reactive T lymphocytes are activated at lymph nodes and entry into the CNS triggering a series of mechanisms responsible for myelin damage. $CD4^+$ and $CD8^+$ T cells, macrophages, antibodies and complement, pro-inflammatory cytokines such as interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) are definitely involved in the mechanism of myelin disruption, oligodendrocyte damage and axonal degeneration [3,8,13].

Nevertheless, the immune system is not always detrimental for the CNS, and it seems to play a role in the clinical improvement during resolution of inflammation [4]. Anti-inflammatory cytokines such as interleukin 10 (IL-10), transforming growth factor beta (TGF-β), regulatory T cells and B cells could contribute to decrease or to control the inflammatory process [3,12,13].

Neurotrophins are a group of proteins expressed in the CNS and peripheral nervous system of vertebrates that play an essential role in the development, maintenance and repair of nervous system [18]. They include brain derived neurotrophic factor (BDNF), neuronal growth factor (NGF), Neurotrophins (NT) 3 and 4. BDNF is a homodimeric protein released in the synapses and presents a widespread distribution in the CNS. One class of BDNF receptors is the tropo-myosin related kinases (TRK) family, and their interaction is essential in a series of cognitive functions, such as learning and memory, and seems to play a role in the synaptic plasticity [9,17]. Neurons are the major source of BDNF. Immune cells can also produce BDNF, but its role in autoimmune diseases has just begun to be understood [10].

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The aim of the present study was to measure plasma BDNF levels of RR-MS patients and healthy controls, investigating their correlation with relapses and clinical parameters.

Twenty-nine patients (M/F, 7/22; mean ± SD age years, 33 ± 10, median 33, range 19–54) with definitely RR-MS, according to the McDonald criteria [14], were recruited for this study. These patients were followed for 1 year and blood samples were collected at the beginning and at the end of the study. Patients who relapsed in this 1-year period had more blood samples collected at the onset of relapse and 2 weeks later. Relapses were defined as an acute new symptom or worsening of old symptom topographically related to a white matter lesion in the CNS that lasted over 24 h [14]. Kurtzke Expanded Disability Status Scale (EDSS) was used to assess neurological compromise. EDSS ranges from 0, normal neurological examination, to 10, death due to MS [11].

For comparison, 24 healthy subjects matched for age (M/F, 9/15; mean ± SD age years, 33 ± 9, median 33, range 18–52) were also invited to participate.

All blood samples were collected in the morning, and the plasma was separated and frozen at −70° until BDNF assessment. BDNF was measured by sandwich ELISA according to the protocol provided by the manufacturer (R&D Systems, USA). Non-parametric analysis was performed using the Mann–Whitney test or the Wilcoxon test for comparison of unpaired and paired data, respectively. The p value was set at 0.05.

All MS patients had less than 10 years of disease (mean ± SD disease duration years, 5 ± 3, median 5, range 0.2–10). The mean ± SD EDSS was 1.8 3 ± 0.7, median 1.5, range 1–3.5.

BDNF levels were decreased in MS patients (median [range] pg/ml, 1160 [352.6–2640]) in comparison with control subjects (median [range] pg/ml, 1640 [632.4–4268]; $p = 0.03$) (Fig. 1). Women tended to have higher BDNF levels than men, but this difference did not reach statistical significance ($p = 0.06$ for patients and 0.08 for controls).

There was no correlation between BDNF levels and age ($p = 0.13$), age of onset ($p = 0.09$), length of disease ($p = 0.50$) and EDSS scores ($p = 0.1816$).

Twelve patients had relapses during the study. BDNF was significantly increased in MS patients after relapse (median [range] pg/ml, 2392 [1093–3122]) when compared with levels in the beginning of the experiment (median [range] pg/ml, 1399 [591.3–2028]; $p = 0.0086$) (Fig. 2).

Our results showed lower BDNF levels in MS patients and increased levels of this neurotrophin after MS relapse. This result is in line with previous studies that demonstrated lower serum levels of BDNF in MS patients in comparison with healthy subjects [2,5]. Indeed there is a growing body of evidence implicating a role for BDNF in MS. For instance, BDNF was found to be present in immune and CNS cells of demyelinating lesions. TRK B, one of the receptors of BDNF, was expressed in neurons around active lesions of MS [21]. Interestingly, supernatants of peripheral blood mononuclear cell cultures presented higher levels of BDNF during relapse in RR-MS patients when compared to remission [1]. This is in accordance with our result of higher circulating levels of BDNF after MS relapse. Moreover, Weinstock-Guttman *et al.* [22] found that BDNF was positively correlated with higher inflammatory activity in the white matter of MS patients. Together these results may indicate a role for BDNF in stimulating CNS recovery after an acute inflammatory lesion. Further studies are warranted to confirm this hypothesis.

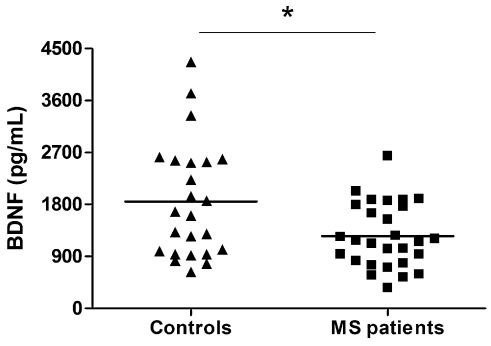


Fig. 1. Initial BNDF levels from healthy controls and MS patients. Plasma from control subjects ($n = 24$) and MS patients ($n = 28$) was collected and BDNF levels were measured by ELISA. Bars represent median values. MS patients had a significant decrease in BDNF levels (median [range] pg/ml, 1160 [352.6–2640]) when compared to healthy controls (1640 [632.4–4268]; $p = 0.03$) (Mann–Whitney, $p < 0.05$).

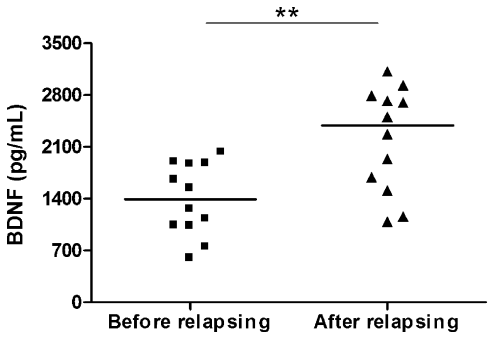


Fig. 2. BDNF levels before and after relapsing from MS patients. Plasma from 12 MS patients was collected at study entry (median [range] pg/ml, 1399 [591.3–2028]) and just after the relapse and BDNF levels were measured by ELISA. BDNF levels were increased in MS patients (2392 [1093–3122]) after the relapsing episode (Mann–Whitney, $p < 0.01$).

We did not find any association between BDNF levels and clinical parameters. By contrast, Sarchielli *et al.* found an inverse correlation between BDNF circulating level and EDSS scores [19]. This discrepant result may be due to the small size of our cohort and the small range of EDSS scores in 1 year. Despite being the most used scale to measure disability in MS, the EDSS score correlates poorly with clinical impairment determined by multiple subtle signs and symptoms. Moreover, EDSS does not always correlate with lesions on magnetic resonance imaging [6]. Thus, disease progression may be misjudged by the EDSS.

Current MS therapies have been also correlated with BDNF production [20,16]. For instance, mononuclear cells of MS patients in use of glatiramer acetate (GA) presented higher levels of BDNF than the cells from patients treated with other immunomodulatory drugs [20]. Among our patients, 17 were treated with interferon beta, 5 started GA during follow-up. However, we did not find any correlation between BDNF levels and drug treatment in the present study.

In conclusion, we presented data showing an association of BDNF and MS, which supports data from previous works. Furthermore, we found an association between BDNF levels and clinical recovery from relapsing, which could point to a neuroprotective role for BDNF in MS.

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References

[1] D. Azoulay, N. Urshansky, A. Karni, Low and dysregulated BDNF secretion from immune cells of MS patients is related to reduced neuroprotection, J. Neuroimmunol. 195 (2008) 186–193.

[2] D. Azoulay, V. Vachapova, B. Shihaman, A. Miler, A. Karni, Brain-derived neurotrophic factor in serum of relapsing remitting MS: reversal by glatiramer acetate, J. Neuroimmunol. 167 (2005) 215–218.
[3] A. Bar-Or, The immunology of multiple sclerosis, Semin. Neurol. 28 (2008) 29–45.
[4] W. Brück, The pathology of multiple sclerosis is the result of focal inflammatory demyelination with axonal damage, J. Neurol. 252 (Suppl. 5) (2005) 3–9.
[5] V. Castellano, L.J. White, Serum brain-derived neurotrophic factor response to aerobic exercise in multiple sclerosis, J. Neurol. Sci. 269 (2008) 85–91.
[6] M. D'Souza, L. Kappos, A. Czaplinsk, Reconsidering clinical outcomes in multiple sclerosis: relapses, impairment, disability and beyond, J. Neurol. Sci. 274 (2008) 76–79.
[7] G.C. Ebers, Natural history of multiple sclerosis, Neurol. Sci. 21 (Suppl. 2) (2000) 815–817.
[8] B. Hemmer, J. Archelos, H.P. Hartung, New concepts in the immunopathogenesis of multiple sclerosis, Nat. Rev. Immunol. 3 (2002) 291–303.
[9] R. Hohlfeld, M. Kerschensteiner, C. Stadelmann, H. Lassmann, H. Wekerle, The neuroprotective effect of inflammation: implications for the therapy of multiple sclerosis, J. Neuroimmunol. 24 (2000) 161–166.
[10] M. Kerschensteiner, C. Stadelmann, G. Dechant, H. Wekerle, R. Hohlfeld, Neurotrophic cross-talk between the nervous and immune systems: implications for neurological diseases, Ann. Neurol. 53 (2003) 292–304.
[11] J.F. Kurtzke, Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS), Neurology 33 (1983) 1444–1452.
[12] F.D. Lublin, S.C. Reingold, Defining the clinical course of multiple sclerosis: results of an international survey, Neurology 46 (1996) 907–911.
[13] R. Martin, M. Sospedra, The immunology of multiple sclerosis, Annu. Rev. Immunol. 23 (2005) 683–747.
[14] W.I. McDonald, A. Compston, G. Edan, D. Goodkin, H.P. Hartung, F.D. Lublin, H.F. McFarland, D.W. Paty, C.H. Polman, S.C. Reingold, M. Sandberg-Wollheim, W. Sibley, A. Thompson, S. van den Noort, B.Y. Weinshenker, J.S. Wolinsky, Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis, Neurology 5 (2001) 121–127.
[15] J.H. Noseworthy, C. Lucchinetti, M. Rodriguez, B.G. Weinshanker, Multiple sclerosis, N. Engl. J. Med. 343 (2000) 938–952.
[16] H.F. Petereit, H. Lindemann, S. Schoppe, Effect of immunomodulatory drugs on *in vitro* production of brain-derived neurotrophic factor, Mult. Scler. 9 (2003) 16–20.
[17] M.M. Poo, Neurotrophins as synaptic modulators, Nat. Rev. Neurosci. 2 (2001) 24–32.
[18] L.F. Reichardt, Neurotrophin-regulated signal pathways, Phil. Trans. R. Soc. B. 361 (2005) 1545–1564.
[19] P. Sarchielli, L. Greco, A. Stipa, A. Floridi, V. Gallai, Brain-derived neurotrophic factor in patients with multiple sclerosis, J. Neuroimmunol. 32 (2001) 180–188.
[20] P. Sarchielli, M. Zaffaroni, A. Floridi, L. Greco, A. Candeliere, A. Mattioni, S. Tenaglia, M. Di Filippo, P. Calabresi, Production of brain-derived neurotrophic factor by mononuclear cells of patients with multiple sclerosis treated with glatiramer acetate, interferon-beta 1a, and high doses of immunoglobulins, Mult. Scler. 13 (2007) 313–331.
[21] C. Stadelmann, M. Kerschensteiner, T. Misgeld, W. Brück, R. Hohlfeld, H. Lassmann, BDNF and gp145trkB in multiple sclerosis brain lesions: neuroprotective interactions between immune and neuronal cells? Brain 125 (2002) 75–85.
[22] B. Weinstock-Guttman, R. Zivadinov, M. Tamaño-Blanco, N. Abdelrahman, D. Badgett, J. Durfee, S. Hussein, J. Feichter, K. Patrick, R. Benedict, M. Ramanathan, Immune cell BDNF secretion is associated with white matter volume in multiple sclerosis, J. Neuroimmunol. 188 (2007) 167–174.