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Brain-derived neurotrophic factor levels under chronic natalizumab treatment in multiple sclerosis. A preliminary report

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ABSTRACT

Aim of the study: Our main purpose was to investigate if the chronic treatment with the disease-modifying drug natalizumab shows quantifiable effect on BDNF levels in multiple sclerosis patients.
Materials and Methods: BDNF plasma concentration was evaluated using enzyme-linked immunosorbent assay in healthy individuals, not treated multiple sclerosis patients and patients treated with natalizumab.
Results: Multiple sclerosis patients have a significantly lower amount of peripheral BDNF than healthy individuals. Patients treated with natalizumab have significantly higher BDNF levels than not treated patients.
Conclusions: Chronic natalizumab treatment is associated with significantly increased plasma BDNF concentration in multiple sclerosis.
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1. Introduction

Multiple sclerosis (MS) is the most frequent demyelinating disease of the central nervous system (CNS), inducing a considerable disability in sufferers and having an important social impact [1].

The most widely accepted theory regarding the pathophysiology involves an immune attack against the myelin [2]. Following an initial, insufficiently identified trigger, the activated T lymphocites are orchestrating an inflammatory cascade of cytokines [3], disturbing the integrity of the blood–brain barrier (BBB). Further on, disease development requires probably a molecular mimicry-like behavior, a crossed autoreactive injury of the myelin sheath, involving other cytokines and macrophage activation [4]. The aforementioned attack triggers and accompanies neurodegeneration, expressed clinically by progressive brain atrophy [5]. The latter is a good marker for disability progression also [6].

After the attack takes place, several defense pathways are activated [7]. As an effect, migrating oligodendrocytes partially substitute the lost myelin [8]. The mentioned pathways are

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activated, among other means, by the production and release of neurotrophic growth factors [9]. They have several beneficial effects in the central nervous system (CNS): stimulating cell differentiation – glia and neuronal cells, neurite growth and plasticity, etc. [10]. Neurotrophins also modulate immune response through activated auto-reactive T-cells [11]. Thus, a neuroprotective treatment, potentially influencing also immune attack, might represent a valuable approach [12].

Available treatment is unsatisfactory to this point. High doses of glucocorticosteroids target relapses, frequently obtaining remission. The problematic part is the disease-modifying therapy, which fails to offer a symptom-free improvement; it only reduces the frequency of relapses, and eventually the severity of individual attacks [13]. Progression is slower, but never stops. For this purpose interferons, glatiramer acetate, natalizumab and other disease modifying drugs are available [14]. We focus here on natalizumab.

Natalizumab is a monoclonal antibody used for the treatment of relapsing-remitting multiple sclerosis (RRMS), proposed already even as first line approach [15] and under evaluation with promising results for secondary progressive multiple sclerosis (SPMS) [16], showing an impact on both progression and relapse frequency [17].

The drug targets the α4 subunit of integrins [18], surface molecules of T lymphocytes, or the integrin very late antigen (VLA-4) [19]. Integrins are playing a role when coupling with vascular endothelial receptors, like the vascular cellular adhesion molecule VCAM-1. The coupling facilitates adhesion of lymphocytes to vessel walls and crossing through the blood–brain barrier (BBB). If the adhesion is interfered, crossing the attack into the CNS compartment is also diminished [20].

A possible proof for the effect, contributing to the overall outcome, is that natalizumab probably induces through a co-stimulatory signaling pathway an increase of effector memory T-cells in the blood, but with no elevation of myelin-reactive cells: a sequestration outside the CNS [21]. Furthermore, natalizumab not only reduces the migration by blocking the integrins, but seemingly also by down-regulation of vascular cell adhesion molecule 1 (VCAM-1) expression [22].

Activated immune cells are capable of producing neurotrophic factors [23]. Early intervention in the cascade of inflammation might have an impact also on neurotrophic factor production [24]. Thus, reducing BBB crossing might have a dual impact.

One of the extensively investigated growth factors is the brain-derived neurotrophic factor (BDNF) [25], a representative of the neurotrophin gene family, along with NGF, NT3 and NT 4/5 [26]. It is produced by several cells, mainly astrocytes, but also immune cells, as it was mentioned before, and acts in both a pro-neurotrophin form, and a mature form [27], both presenting different functional aspects. Even the coupling differs: the immature form binds with the p75 receptor, with low affinity, showing pro-apoptotic effects on neurons, and overall inhibitory effect on regeneration [28]. On the other hand, the tyrosine receptor kinase B, or BDNF/NT-3 growth factors receptor (TrkB) coupling of the mature form induces neuroprotective mechanisms as plasticity, or survival mechanisms [29]. TrkB receptors are expressed on oligodendrocytes and oligodendrocyte progenitor cells [30], influencing myelinization-linked processes. In vitro, for example, BDNF enhances the number of the oligodendrocytes with topographic selectivity in the basal forebrain, not in the cortex [31]. Animal studies reveal similar observations, BDNF knock-out mice showing decrease in myelin proteins in the optic nerve and spinal cord in early development, with recovery during aging [32], and without recovery in the basal forebrain [33]. The effect on myelinization is even more expressed in case of previous injuries producing demyelinization [34].

Growing evidences are available regarding BDNF involvement in different CNS diseases. Among others, schizophrenia [35], Huntington's disease [36] and even Alzheimer's dementia [37] seems to involve alterations in BDNF homeostasis at a pathophysiological level.

Several studies investigated already the expression and different roles of BDNF in MS: on one hand from the point of view of genetic variations, with insufficient proof for association [38], on the other hand regarding the effect during disease course [39]. There are studies presenting that peripheral plasma concentration of BDNF is lowered [40], excepting perhaps transitory elevations during relapses [41]. These observations seem to be applicable for different clinical presentations, like RRMS and SPMS [42]. As presented in the in vitro and preclinical studies, if demyelinization occurs, BDNF has an important role in repair processes. Human studies on this effect reveal that BDNF expression increases around MS lesions and in perivascular spaces, its secretion being assured by microglia, astrocytes, but also by infiltrating immune cells [43].

In relation with the applied treatment, most studies were conducted on glatiramer acetate treated patients [44], results being heterogeneous, some reported increases (Azoulay et al., 2005)[40], and some decreased or no significant effect on plasma concentration [45]. There are also available data regarding BDNF levels under novel treatments, like laquinimod [46].

Our goal was to investigate the possible impact of natalizumab on BDNF plasma concentration, for which, to our knowledge, there are no similar available investigations.

2. Materials and method

Patients with confirmed RRMS were recruited, in accordance with the revised McDonalds criteria. SPMS group was formed from RRMS patients under natalizumab treatment, confirmed at inclusion as having already SPMS, the two diagnostic instances forming a continuum. Even if natalizumab is not an accepted treatment option for SPMS, they formed a new group, as they were already on this treatment. For comparison we have selected an age- and sex-matched group of normal subjects. The study was approved by the ethics committee of our university, being in accordance with the Helsinki principles for biomedical research. All participants signed an informed consent.

We have formed four groups: the control group (CTRL) with 20 healthy age and sex matched individuals, a group of 11 newly diagnosed patients with RRMS, non-treated, (NT), a group of 11 natalizumab-treated RRMS patients (Nat-RRMS) and a group of 9 SPMS (Nat-SPMS), previously RRMS, restaged at inclusion as SPMS, based on EDSS score increase without a

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