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Early cognitive impairment along with decreased stress-induced BDNF in male and female patients with newly diagnosed multiple sclerosis

Barbora Prokopova [a,e,1], Natasa Hlavacova [a,1], Miroslav Vlcek [b], Adela Penesova [b], Lucia Grunnerova [c], Alexandra Garafova [d], Peter Turcani [c], Branislav Kollar [c], Daniela Jezova [a,*]

[a] Institute of Experimental Endocrinology, Biomedical Research Center, Slovak Academy of Sciences, Bratislava, Slovakia
[b] Institute of Clinical and Translational Research, Biomedical Research Center, Slovak Academy of Sciences, Bratislava, Slovakia
[c] 1st Department of Neurology, Faculty of Medicine, Comenius University Bratislava, Bratislava, Slovakia
[d] University Hospital and Slovak Medical University, Bratislava, Slovakia
[e] Department of Pharmacology and Toxicology, Faculty of Pharmacy, Comenius University Bratislava, Bratislava, Slovakia

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ABSTRACT

The aim of this study was to evaluate neuroendocrine activation during stress in patients with recently diagnosed multiple sclerosis before starting the immunomodulatory therapy (EDSS score ≤ 2.0). We verified the hypothesis that certain cognitive and affective dysfunction is present already at this early stage of the disease. The sample consisted of 38 subjects, which involved patients who were recently diagnosed multiple sclerosis and age- and sex-matched healthy volunteers. Stroop test served as mental stress model enabling measurement of cognitive performance. Present results showed increased state anxiety, depression scores and poorer performance in the Stroop test in the group of patients compared to healthy subjects. The cognitive dysfunction was particularly evident in male patients with simultaneously decreased concentrations of the brain-derived neurotrophic factor (BDNF) in plasma. The patients at this stage of the disease have not yet developed the hyperactivity of the hypothalamic-pituitary-adrenocortical axis. They showed normal levels of plasma copeptin and reduced aldosterone response to mental stress test in women only. Concentrations of plasma copeptin were higher in men compared to women. Very early stages of multiple sclerosis are accompanied by disturbances in psychological well-being, mild cognitive dysfunction and decreased plasma concentrations of BDNF, particularly in male patients.

1. Introduction

Multiple sclerosis is a chronic demyelinating disease which is the most common neurological condition in adults of working age. Morphologically, the disease is manifested by inflammation, demyelination and axonal loss. The disease affects twice as many women than men and is associated with an increased degree of disability (Karussis, 2014; Grigoriadis and van Pesch, 2015). A characteristic feature of the disease is damage to different areas of the central nervous system associated with various neurological symptoms.

During the course of multiple sclerosis, stressful life events are recognized as possible trigger of the relapses. The disclosure to the patient of the diagnosis of multiple sclerosis, the commencement of immunomodulatory therapy, and the unpredictability and vagaries of the disease progression are all sources of stress (Schumann et al., 2012). Most of the clinical studies support a hyperactivity of HPA (hypothalamic–pituitary–adrenal) axis in patients with multiple sclerosis, which is one of the main stress systems (Heesen et al., 2007). That is manifested by elevated basal plasma levels of adrenocorticotropic hormone (ACTH) and cortisol (Michelson et al., 1994) and enlarged adrenal glands in patients with multiple sclerosis (Reder et al., 1994). Neuroendocrine disturbances in multiple sclerosis are further supported by high incidence of active lesions in hypothalamus observed in the brains of patients post mortem (Huitinga et al., 2004).

Multiple sclerosis is a disease which influences every-day life of the patient. The patient needs to deal with a diagnosis of an incurable lifetime disease. In more advanced stages, the disease interferes with common daily activities and gradually reduces quality of life (Janssens et al., 2003). Therefore it is not surprising that in addition to neurological symptoms that characterize multiple sclerosis, wide range of psychiatric disturbances can appear during the course of the disease. In more advanced stages of multiple sclerosis, mainly affective disorders are present, e.g. anxiety, bipolar disorder or depression (Vattakatuchery et al., 2011). The impact of the disease on psychological well-being of newly diagnosed patients with multiple sclerosis is not clear.

* Corresponding author at: Institute of Experimental Endocrinology, Biomedical Research Center, Slovak Academy of Sciences, Dubravska cesta 9, 845 05 Bratislava, Slovakia.
E-mail address: daniela.jezova@savba.sk (D. Jezova).
[1] Equally contributed.

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One of the frequent symptoms of multiple sclerosis is cognitive deficit. The features of cognitive impairment in multiple sclerosis are not uniform and they may depend on the lesion localization (Amato et al., 2008). It has been demonstrated that memory, attention, information processing speed, executive functions, and visual spatial perception are frequently impaired with the disease progression (Savettieri et al., 2004; Bobholz and Rao, 2003). Studies with recently diagnosed patients with multiple sclerosis have detected cognitive impairment at the onset of the disease (López-Góngora et al., 2015), but none of them described participants at the very beginning of the disease, after the first episode of symptoms suggesting multiple sclerosis and with values of Expanded Disability Status Scale (EDSS) <2.0.

Brain-derived neurotrophic factor (BDNF) is the most abundant growth factor (neurotrophin) in the brain. It is important for survival, neuronal differentiation, synaptic plasticity and repair processes in the central nervous system (Benarroch, 2015). Not surprisingly, BDNF plays an important role in the etiology of multiple sclerosis, particularly in improving the clinical symptoms of the disease (remission phase) (Sarchielli et al., 2002). It is hypothesized that abnormalities in the biosynthesis of BDNF may be related to cognitive changes in a number of psychiatric and neurological disorders, including multiple sclerosis (Lühder et al., 2013). Data concerning levels of BDNF in patients with multiple sclerosis are inconsistent. Some authors describe reduced levels of BDNF in patients in a stable phase of relapsing-remitting multiple sclerosis compared to healthy volunteers (Azoulay et al., 2005; Frota et al., 2009), while others point to its increased levels during the relapse (Sarchielli et al., 2002).

Copeptin is a molecule which has recently been found to play a role in affective, metabolic, cardiovascular and neurological disorders. It is a stable fragment of arginine vasopressin prohormone, and was found to reflect the stress level similarly as the activation of the HPA axis (Katan et al., 2008). In the literature, there is almost no work dealing with copeptin levels in patients with multiple sclerosis.

So far, neuroendocrine, cognitive and psychological characteristics of patients with multiple sclerosis have been investigated in advanced stages of the disease. Even studies with title words such as “early stages” (López-Góngora et al., 2015) or “recently diagnosed” (Janssens et al., 2003) included patients with multiple sclerosis at a mild level of disability reflected by values of EDSS higher than 2.0.

The aim of the present study was to evaluate the neuroendocrine activation during mental stress in patients with recently diagnosed multiple sclerosis before starting the immunomodulatory therapy. We also verified the hypothesis that certain cognitive and affective dysfunction is present already at this early stage of the disease.

2. Materials and methods

2.1. Subjects

The study was performed in 19 patients (10 female, 9 male), who were recently diagnosed multiple sclerosis based on McDonald's criteria (Polman et al., 2011). They were recruited from the registry of the 1st Department of Neurology, Faculty of Medicine, Comenius University, Bratislava, Slovakia. The patients were in the mean age of 30.58 ± 1.67 years, after the first episode of symptoms suggesting multiple sclerosis and had an EDSS (Kurtzke, 1983) score ≤ 2.0 at the time of diagnosis. The first episode was treated with the pulse, short-term glucocorticoid therapy using methylprednisolone (1000 mg per day intravenously for 3–5 days). The investigations were performed at least 2 months after the glucocorticoid treatment at the time patients were in remission and without any therapy. Participants with history of cardiovascular disease, hypertension, diabetes mellitus (type 1 and 2), thyroid disease, hepatic or renal disease, malignancy, acute or chronic infection were excluded from the study. No patient received any current medication and no steroid treatment during the evaluation. Nineteen healthy volunteers gender, age (±5 years) and BMI (±3 kg/m^2)—matched to patients served as a control group. Examinations were performed at the Institute of Experimental Endocrinology, Slovak Academy of Sciences, 9–12 weeks after the multiple sclerosis diagnosis was confirmed. All subjects gave written informed consent to participate and the protocol was approved by the Ethics Committee of Bratislava Self-Governing Region, Bratislava, Slovakia. The study was performed in accordance with the Declaration of Helsinki.

2.2. Stress procedure

A mental stress task, the Stroop test, was used as a mild stress model. Stroop test is based on the interference between the words and the colors, and it consists of four subtests as described previously (Garafova et al., 2014). The total duration of the mental stress procedure was 10 min.

2.3. Study design

The subjects were asked to restrain from stress and intensive physical activity 24 h before the study and to keep 12 h fasting. On the day of the investigation, subjects arrived at the examination room at 8:00 in the morning. The patient's socio-demographic and medical status was collected. The subject was asked to fill in psychological questionnaires. An intravenous catheter (Terumo Europe N.V., Leuven, Belgium) was placed in the cubital vein and blood samples for basal values were taken. The subject was asked to rest for 30 min in the sitting position to relieve stress from venipuncture. Following the 30 min stabilizing period, the stress procedure started. The blood samples were collected before (0 min), at the end of the Stroop test (10 min) and once again after 15 min of rest after the test was completed (25 min). Blood pressure (Dinamap Vital Sign Monitor, model 845 XT, Criticon X, Inc., Tampa, FL, USA) was measured on the left arm at the time of blood collections as well as during the rest.

2.4. Psychological characteristics

Slovak versions of several psychological questionnaires were administered at the time of initial screening examination.

State Trait Anxiety Inventory (STAI) (Mullner et al., 1980) was used for evaluation of state and trait anxiety. The questionnaire consists of two subscales specifically examining the state (STAI X1) and trait anxiety (STAI X1) dimensions. Both subscales contain 20 self-statements, to which participants must respond on a 1–4 scale yielding total scores of 20–80. For the trait subscale, the subjects are instructed to have their responses based on how they generally feel, while for the state subscale, they are asked to respond how they feel right now (Duncko et al., 2006).

Coping Inventory for Stressful Situations (CISS) (Endler and Parker, 1990) was used to determine the expression of stress coping strategies. Coping strategies identified by this inventory are task-oriented, emotion-oriented and avoidance-oriented strategy. Task-oriented strategy is supposed to consist of purposeful efforts aimed at the solution of a problem, while emotion-oriented strategy concentrates on regulation of distressing emotions and avoidance-oriented strategy is aimed on avoidance of the problem. The inventory contains 48 items with 16 items for each strategy and the subjects are asked to respond on a 5-point scale in accordance with how they do or feel generally (Duncko et al., 2006).

The shortened form of Beck Depression Inventory (BDI) questionnaire was used to assess depressive symptomatology. It is a 13-items self-report measure with 4 responses to each item scoring 0–3.

Eight State Questionnaire (8SQ) (Senka et al., 1994) is a tool for experimental assessment of eight specific personality categories (anxiety, stress, depression, regression, tiredness, feeling of guilt, extraversion and arousal). Subjects were asked to respond on a 4-point scale in accordance with their immediate feelings.