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Research report

Serum neurotrophic factors in adolescent depression: Gender difference and correlation with clinical severity

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ABSTRACT

Background: Brain derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3) and glial cell line derived neurotrophic factor (GDNF) play critical role in growth, differentiation, maintenance and synaptic plasticity in neuronal systems which is more relevant in adolescence. The present study was undertaken to verify the 'neurotrophin hypothesis' in adolescent depression by (i) comparing serum concentrations of neurotrophic factors in depression patients and healthy control, and (ii) analyzing correlations between clinical severity and serum neurotrophin levels.

Methods: Eighty four adolescent (aged 13–18 years) depressed patients (56 males; 60 medication free/naive) and 64 healthy controls (39 males) were recruited. Severity of depression was measured by Beck's depression inventory, and anxiety by state-trait anxiety inventory. Measurement of serum neurotrophins was done by ELISA.

Results: Adolescents with depression had significantly lower levels of BDNF: mean diff. (95% C.I.): 2093.9 (1074.0, 3113.9), NGF: 813.3 (343.1, 1283.6) and GDNF: 158.8 (77.2, 240.4) compared to controls. On gender based analysis female controls had significantly increased trait anxiety scores [−1.1 (−1.8, −0.1)], as compared to control males. In the patient group, female patients had far lower level of NGF: 919.6 (210.9, 1628.3) and NT-3: 1288.8 (145.4, 2432.3) compared to male. BDI-II score showed a statistically significant ($p<0.01$) negative correlation with all four neurotrophins in male patients while in female patients such negative correlation was observed only with NGF and GDNF ($p<0.01$).

Limitations: The study is cross-sectional from a tertiary care hospital.

Conclusion: The novelty of the study lies in its large number of exclusively adolescent depression patients showing significant reduction of BDNF, NGF and GDNF serum levels as compared to controls. A gender bias with much reduction in female has also been recorded.

1. Introduction

Adolescent depression is a chronic and serious illness which can result in marked functional impairment of the human biological system. It has also been shown that depression in adults has its roots in adolescence and childhood (Weissman et al., 1999; Danese et al., 2008; Birmaher et al., 1996). The pediatric mood disorders in Indian population have a unique clinical presentation, especially in adolescent age group (Sagar et al., 2012). Recently, there have been many studies on understanding the role of different laboratory parameters to elucidate the underlying pathophysiology of depression in adults and elderly population (Yoshida et al., 2012; Diniz et al., 2010). However similar studies in depressed adolescent population are very few (Gabbay et al., 2009; Högberg et al., 2012; Mamalakis et al., 2006).

Neurotrophic factors are the regulators of neurogenesis, neuronal growth, differentiation, plasticity of neuronal networks and cell death and are also associated with inflammation and autoimmune demyelination (Sendtner et al., 2000; Linker et al., 2009; Lee and Son, 2009). This regulation of networking in the brain by neurotrophic factors is of paramount importance during transformation in adolescence which is obviously related to neuroplasticity. The neuroplasticity hypothesis of depression proposes that a dysfunction of neural plasticity is relevant in

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etiopathogenesis of depression since plasticity orders the base-line neurosynaptic support for various mood and depressive disorders (Pittenger and Duman, 2008). Many studies are in accord with the neurotrophin hypothesis of depression which states that depression is a result of stress-induced decrease in BDNF expression and that antidepressants increase BDNF expression (Duman and Monteggia, 2006; Duman et al., 1997). Several studies have shown reduction in the level of circulating BDNF in depressed patients as compared to that of healthy controls across various age groups (Sen et al., 2008; Bocchio-Chiavetto et al., 2010). Very few studies are there on neurotrophin profile in adolescents. Study by Sasaki et al. (2011) has observed low serum BDNF levels in male pediatric depression patients with mean age 13 years . Another study by Dmitrzak-Weglarz et al. (2013) in polish adolescent girls with anorexia nervosa, reported low serum Neurotrophin-4 and significant association of BDNF, GDNF serum levels with patient personality dimensions as measured by Temperament and Character Inventory (TCI) and executive function as measured by the Wisconsin Card Sorting Test (WCST). Neurotrophic cascades have also been made as a target for therapeutical interventions since many drugs currently used to treat these depressive disorders increase the concentration of these factors (Sen et al., 2008; Wolkowitz et al., 2011; Brunoni et al., 2008).

BDNF is so far the most extensively studied member of this family, being predominantly assessed as a possible biomarker of several mood disorders (Hashimoto, 2010; Fernandes et al., 2011). NGF, another member of neurotrophin family has a relevant role in neurogenesis, neuronal plasticity and signaling of different cells of the human immune system (Berry et al., 2012). Studies have shown lower serum BDNF and NGF concentrations in many affective disorders including bipolar disorder (Lin, 2009; Barbosa et al., 2011a), major depressive disorder (Brunoni et al., 2008), manic depression (Tramontina et al., 2009) and obsessive compulsive disorder (Maina et al., 2010). In most of the studies serum concentrations of these neurotrophins have been shown to correlate negatively with severity of the disease (Satomura et al., 2011; Teixeira et al., 2010). From the above findings, BDNF and NGF have been suggested to represent a probable biological state marker for depression (Sen et al., 2008).

However, as there is still not much information available from the adolescent age group, there is a need for the study to correlate the magnitude of depression and anxiety (state-trait scores) with serum BDNF concentrations in this age group. Further, as yet no study has been carried out to find out the variations in NGF levels in adolescent depression, little is known about whether the changes in the expression levels of these molecules are state- or trait-dependent in mood disorders?

NT-3, another important member of the neurotrophin family, couples to the same signal transduction pathways as BDNF through their respective receptors. NT-3 has been found to be highly expressed in developing CNS while BDNF was found to low in early embryonic stages of development (Bartkowska et al., 2010). There is paucity of studies about NT-3 level in peripheral serum and only one study shows that serum NT-3 level is increased during both manic and depressive episodes, but not in euthymia (Walz et al., 2007). To our knowledge, there is no report of serum NT-3 levels in adolescent depression patients.

GDNF is abundantly expressed in the CNS (Airaksinen and Saarma, 2002). Several studies report that circulating GDNF levels may be altered in bipolar disorder and major depressive disorder (Takebayashi et al., 2006; Barbosa et al., 2011b; Diniz et al., 2012). A recent study assessed peripheral GDNF levels in elderly subjects with major depression (Wang et al., 2011). However, no study to our knowledge addressed the role of GDNF in adolescent depression. Given the paucity of any streamlined data on all of peripheral BDNF, NGF, NT-3 and GDNF levels in adolescent depression, the present study was undertaken to compare serum levels of BDNF, NGF, NT-3 and GDNF levels in adolescent depression patients with their serum level in healthy controls of comparable age and also to find out their relation with clinical severity of depression and anxiety scores. Gender difference in serum neurotrophic factor levels also had been looked into in both control and patient groups. In spite of having a few ($n=24$) medicated patients, the effect of medication was analyzed by comparing serum neurotrophin levels in medicated and non-medicated/medication-naïve patients.

2. Materials and methods

2.1. Subjects

2.1.1. Cases

In this study 84 cases of adolescent depressed subjects were recruited from the Child-guidance-clinic and Walk-in-clinic of Department of Psychiatry, All India Institute of Medical Sciences, New Delhi during the period of November 2008–August 2011. The present study was approved by the institutional ethics committee of All India Institute of Medical Sciences. Participant information sheet having details about the study was made available to all participants. Written informed consent from parent/guardian/legally acceptable representative of the patient was taken before their entering in the study. None of our subjects was smoker.

Inclusion criteria for the depressed subjects were as follows: (1) age 13–18 years, (2) DSM-IV criteria for depression based on the Structured Clinical Interview for DSM Disorders—non-patient version (SCID-I/NP) (First et al., 2002), (3) 21 item Beck's Depression Inventory scores ≥7 on the Beck's Depression Rating Scale—(BDI-II), (4) otherwise medically healthy, with (5) normal laboratory findings regarding complete blood count, blood chemistry, renal, thyroid and liver function and negative urine toxicology test findings with unremarkable chest X-ray, ECG and EEG findings.

Exclusion criteria for the depressed subjects included: (1) medical illnesses (e.g. endocrine disorders, cancer, chronic infections, infection with HIV), autoimmune diseases, chronic fatigue syndrome, diabetes, any common infectious disease in the month prior to enrollment (including common cold or fever), any significant medical or neurological disorders or any history of medications with steroid, antibiotics, antioxidants, immune modifiers/modulators that could affect neurotrophin concentrations in serum (2) febrile illness (temperature >99 °F) within 4 weeks prior to blood collection, (3) immunizations within 4 weeks of initiation of the study, (4) in females, a positive urine pregnancy test, and (5) DSM-IV criteria or having history of psychotic disorders, mental retardation, post traumatic stress disorder, eating disorder, drug or alcohol abuse within the past 12 months.

The trained psychiatrist from the present group of authors interviewed all patient participants and their parents, using the Schedule for Affective Disorders and Schizophrenia—Present and Lifetime Version for Children (Kaufman et al., 1997), on the basis of a semi-structured interview. Based on the interview, the psychiatrist rated the severity of depression and anxiety on the BDI-II and the State and Trait Anxiety Inventory for Children (STAIC) (Spielberger et al., 1983). A local language (Hindi) version of the scales was used wherever applicable. Routine medical assessment and laboratory investigations (complete blood count, metabolic panel, liver function, thyroid function tests, and a urine toxicology test and pregnancy test) were done for all participants. Out of the total 84 patients in the study, 24 were on standard medication with Selective Serotonin Reuptake Inhibitor (SSRI).