

# Possible Role of Brain-Derived Neurotrophic Factor (BDNF) in Autism Spectrum Disorder: Current Status

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## ABSTRACT

Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family of survival-promoting molecules, plays a vital role in the growth, development, maintenance, and function of several neuronal systems. The purpose of this review is to document the support for the involvement of this molecule in the maintenance of normal cognitive, emotional functioning, and to outline recent developments in the content of Autism spectrum disorder (ASD). Current and future treatment development can be guided by developing understanding of this molecule's actions in the brain and the ways the expression of BDNF can be planned. Over the years, research findings suggested a critical role played by BDNF in the development of autism including increased serum concentrations of BDNF in children with autism and identification of different forms of BDNF in families of autistic individuals.

**Key Words:** *Brain-derived neurotrophic factor. Autism spectrum disorder. Treatment.*

## INTRODUCTION

Autism is a neurodevelopmental disorder that develops within the first three years of life and is characterized by deficits in social interaction, impaired communication and restricted and stereotyped behaviours.<sup>1</sup> Although there is no known unique cause of autism or no laboratory test,<sup>2</sup> there is growing evidence that autism may be influenced by genetic, neurological, environmental and immunological factors, however its exact pathophysiology is unknown.<sup>3,4</sup>

The prevalence of Autism Spectrum Disorder (ASD) has increased worldwide dramatically by over 600% in the past few decades.<sup>5</sup> In the last 20 years, there has been an increase in the incidence of autism in the third world countries which cannot be explained by increase awareness only.<sup>3,6</sup> In South Asian developing countries, including Pakistan, the prevalence of ASD is unknown.<sup>7</sup> This may be due to the lack of existing research infrastructure and availability of well-trained and experienced human resources for conducting autism surveillance and research. Medications have not been proven to correct the core deficits of ASD and are not the primary treatment. Educational interventions, including behavioural strategies and rehabilitative therapies, are extremely important for management of ASD.<sup>8</sup>

It is now well documented that neurotrophic factors (NTFs) such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), and insulin-like growth factor (IGF), are important regulators of neuronal growth, differentiation, and survival during early brain development.<sup>9,10</sup>

The purpose of the current review, therefore, was to overview whether serum levels of BDNF are altered in autistic children and could be used as early marker in ASD.

**Role of BDNF in Autism:** BDNF is a member of the "neurotrophin" family of growth factors, which are related to the canonical NGF. Neurotrophic factors are found in the brain and the periphery.<sup>11</sup> Multiple lines of evidence directly or indirectly suggest an involvement of BDNF in autism, which plays a key role in the development and plasticity of the brain. BDNF has a trophic effect for specific neuronal populations during development and in the mature brain, influencing neuronal survival, morphology, differentiation and synaptic strength.<sup>12</sup> Direct evidence supporting an involvement of the BDNF in autism comes from several studies (Table I) showing that BDNF levels in the blood, serum and brain are increased in autistic children compared with normal controls.<sup>13-15</sup> A strong and as yet unexamined candidate gene for modulating brain anatomy in ASD is BDNF which also plays an important role in neurogenesis, cortical lamination, synaptic plasticity, and neuron survival.<sup>12</sup>

BDNF is active in the hippocampus, cortex, and basal forebrain areas vital to learning, memory, and higher thinking. It helps to support the survival of existing neurons, and encourages the growth and differentiation of new neurons and synapses and itself is an important

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*Received: April 11, 2013; Accepted: October 08, 2013.*

for long-term memory.<sup>16</sup> Deviations in BDNF levels have been linked to deficits in serotonin, which is associated with mood disorders. In at least a subset of autism, altered serotonin levels are among one of the few consistent research findings.<sup>17</sup> BDNF is trophic for serotonergic neurons, and abnormalities in serotonin levels are the most common biochemical findings in autism.<sup>18</sup> Animal studies suggest that concentrations of BDNF in the central nervous system (CNS) and serum are closely correlated,<sup>19</sup> offering the possibility that concentrations in peripheral blood may be useful as a possible biologic marker for autism.

In a retrospective study on blood obtained from full term neonates, Nelson *et al.* identified a nearly three-fold increase in BDNF levels in children later diagnosed with ASD compared with typically developing children.<sup>20</sup> This study is especially revealing since the results were obtained early, before symptoms appeared; although a later subsequent study by the same group failed to confirm this results.<sup>21</sup> Katoh-Semba *et al.* investigated the characteristics of serum BDNF as well as its age-related changes in healthy controls in comparison to autism cases.<sup>22</sup> In healthy controls, the serum BDNF concentration increased over the first several years, then slightly decreased after reaching the adult level. In the autism cases, mean levels were significantly lower in children 0 - 9 years old compared to teenagers or adults, or to age-matched healthy controls, indicating a delayed BDNF increase with development. In addition, BDNF

expression was shown to be increased three-fold in the forebrains of adults with autism when compared with brain specimens from control adults,<sup>23</sup> suggesting that alterations in BDNF expression in autism may be important throughout the life of the individual.

Early BDNF hyperactivity may play an etiological role in autism early in life. Furthermore, BDNF hyperactivity may be associated with early brain outgrowth, increased prevalence of seizures in autism. BDNF is produced by initiated immune microglial cells<sup>24</sup> and may directly act on astrocytes to modify neuronal transmission. Indeed, postmortem analysis of brain material from subjects with autism revealed not only marked activation of microglia but also astroglia.<sup>25</sup>

*In vitro* assays have demonstrated that BDNF stimulates neuronal outgrowth on neonatal astrocytes,<sup>26</sup> which may explain, in part, previous findings of larger neuronal cells in young subjects with autism.<sup>27</sup> Experimental evidence pointed out that pro-inflammatory activity in some autism subjects could lead to the aberrant production of BDNF from immune cells such as monocytes and B cells. To help elucidate the role of an immune challenge on BDNF production by immune cells, Enstrom *et al.* stimulated peripheral blood cells using various immune cell mitogens and found that plasma levels of BDNF levels are increased in children with autism, especially in early onset autism subjects.<sup>28</sup> In a trios-based association study, the SNP haplotype combinations showed significant associations in the autism group.<sup>29</sup> They also

**Table 1:** Summary of findings from different studies of BDNF levels in autism and control subjects.

| Reference No. | Method               | Material                  | ASD group: age and number of subjects | BDNF*   | Result  |
|---------------|----------------------|---------------------------|---------------------------------------|---|---|
| 11            | ELISA                | Serum                     | 3-9 years, A:44,C:40                  | 442 ± 20 (290 ± 90pg/ml),<br>323 ± 114 (290 ± 90) pg/ml | Increase in mild autism and no significant change in severe condition |
| 8             | ELISA                | Serum                     | Up to 12 years, A:46, C:53            | 353.2 ± 78 (540 ± 57) ng/ml                             | Decrease  |
| 33            | ELISA                | Platelets-rich plasma     | 2-15 years,A:146,C:50                 | 40.44 ± 13.87 ng/ml<br>(23.26 ± 12.34) ng/ml            | Increase  |
| 28            | Luminex              | Neonatal blood            | NB,A=84, C:159                        | 54.1± 40 (53.7± 47.7) pg/ml                             | No change   |
| 26            | Luminex              | Plasma                    | 2-6 years,A=37,C=42                   | 2512.103 ±327.79<br>(1463.07 ± 174.61) pg/ml            | Increase  |
| 34            | RT-qPCR              | Lymphocytes               | 20 years, A:11,C:13                   | 0.094 ± 0.1(0.034 ± 0.02)<br>BDN gene expression        | Increase  |
| 20            | Western blot         | Serum                     | 0-9 years,A:7,C:17                    | 174.1 ± 190.4 (400.6 ±148.8) pg/ml                      | Decrease  |
| 12            | ELISA                | Serum                     | 4-6 years,A:37,C:17                   | 32,279 (8,708 )pg/ml                                    | Increase  |
| 19            | Luminex              | Dried newborn blood spots | NB,A:27,C:20                          | 3404 (3299) pg/ml                                       | No change   |
| 17            | ELISA                | Serum                     | 18-26 years, A:18,C:18                | 25.6 ± 2.15<br>(61.6 ± 10.9) ng/ml                      | Decrease  |
| 16            | Post mortem          | Serum/Brain tissue        | -----                                 | -----   | Increase  |
| 13            | ELISA                | Serum                     | 3-27 years, A:18,C:16                 | 25.2 ± 2.5 (17.5 ± 2.0) ng/ml                           | Increase  |
| 18            | RIC                  | Dried newborn blood spots | NB, A:69,C:54                         | 37.4 ± 19.9 (13.3± 5.0) pg/ml                           | Increase  |
| 21            | Two-site immunoassay | Autopsy specimens         | Adults, A:5,C:5                       | 36.52 (11.44) pg/mg                                     | Increase  |
| 29            | -----                | Cerebellum \ Serum        | A:6,C:6                               | -----   | Decrease  |
| 31            | ELISA                | Serum                     | A:29,C:29                             | 791± 475.4 (351.4 ± 347.2) pg/ml                        | Increase  |
| 32            | ELISA                | Serum                     | 3-12 years, A:20, C:20                | 1252±773(1434±635) pg/ml                                | No change   |

A = autistic subjects; C = Control subjects; ELISA = Enzyme-linked immunosorbent assay; NB = Newborns; RIC = Recycling immunoaffinity chromatography; RT-qPCR = Real-time quantitative polymerase chain reaction. \*BDNF Concentration (Control values with standard deviation in parenthesis).

examined the expression of BDNF mRNA in the peripheral blood lymphocytes and this found to be significantly higher in drug-naïve autism patients than in control group. They suggested that BDNF has a possible role in the pathogenesis of autism through its neurotrophic effects on the serotonergic system.

Croen *et al.* investigated BDNF as a possible early biologic marker for autism.<sup>30</sup> They measured the level of BDNF in blood collected from women during pregnancy and from their babies at birth. They found that the BDNF concentrations in maternal mid-pregnancy and newborn blood specimens did not differentiate children with autism from control children. Reduced BDNF in the cerebellum may be an indicator of aberrant brain development and growth in autism.<sup>31</sup>

Abdallah *et al.* also examined levels of BDNF in dried blood spot samples of neonates diagnosed with ASD later in life with matched controls using Luminex technology.<sup>32</sup> Recently, Ricci *et al.* observed increase in serum BDNF levels as compared to healthy controls while Mansour *et al.* have reported no significant change in BDNF concentration in ASD subjects compared to controls.<sup>33,34</sup> Furthermore, patients below age of 6 years had significantly higher levels of BDNF than patients above age of 6 years.

An extensive literature search in the Pubmed, Google Scholar, Science Direct and The Cochran Library database was performed using text words 'Brain-derived neurotrophic factor and Autism'. The references of all included papers, reviews, were searched till May, 2013. Results of all studies are summarized in Table I.

## DISCUSSION

The present review of studies demonstrated the possible critical role played by BDNF in ASD. It has been proposed that early BDNF hyperactivity may be involved in autism early in life. BDNF has a possible role in the pathogenesis of autism through its neurotrophic effects on the serotonergic system. The pathophysiological correlation between BDNF and autism are not well explained yet.<sup>34</sup>

Regarding BDNF concentration values, there has been great debate in studying relationship between BDNF and autism. Some studies showed a higher level of BDNF among autistic patients compared to controls.<sup>14,15,28</sup> On the contrary other studies have reported significantly reduced BDNF in autistics than in normal controls.<sup>10,19,22</sup> However, some studies showed no statistically significant difference between patients and control groups regarding BDNF concentration values.<sup>21,30,34</sup>

The disagreement can be explained by many factors including difference in methodology, mean age between patients and controls and brain development and growth in autism.<sup>34</sup>

Connolly *et al.* showed that mean BDNF levels and both IgG and IgM autoantibodies to BDNF were elevated in children with ASD compared with controls.<sup>14</sup> In agreement with these results, Nelson *et al.* compared a set of neurotrophin and neuropeptide serum levels in a group of children with ASD and another group of children with mental retardation with healthy control group.<sup>20</sup> Results revealed that neonatal concentrations of vasoactive intestinal peptide, calcitonin gene-related peptide and NT-4/5, BDNF concentrations were higher in children with ASD and in those with mental retardation without ASD than in control children.

An overall increase of BDNF levels in autistic individuals was shown in a study by Miyazaki *et al.*<sup>15</sup> However, it is noticed that the age range was much larger in the autistic individuals (between 3 and 27 years) than in the control group (22 - 24 years).

Hashimoto *et al.* showed that in young autistic male adults (age  $21.1 \pm 2.1$  years), the BDNF concentration was significantly lower than in neurotypical controls (22.2 years).<sup>9</sup> The serum levels of BDNF in patients with autism were significantly lower than those of normal controls. Nevertheless, no correlations between BDNF levels and clinical variables in autistics were detected.

As BDNF was found to be frequently altered in ASD patients, one study focused on its usability as an early biological marker for autism.<sup>30</sup> BDNF concentrations were measured in archived mid-pregnancy and neonatal blood specimens using a highly sensitive bead-based assay. The concentration of BDNF in maternal mid pregnancy and neonatal specimens was similar across all three study groups, showing no connection between ASD pathogenesis and BDNF levels.

Further analysis using Luminex technology indicated that concentrations of a set of neurotrophins, neuropeptides and cytokines were analysed from archived neonatal blood of children with later-diagnosed autism.<sup>21</sup> Results showed inhibitory substances in eluates from archived bloodspots, especially marked for measurement of BDNF.

In the autism cases, mean levels were significantly lower in children 0 - 9 years old compared with teenagers or adults, or with age-matched healthy controls, indicating a delayed BDNF increase during development. No gender differences were reported.<sup>22</sup>

In contrast to the variety of studies on serum levels of NTFs, only few studies have examined cerebrospinal fluid (CSF) levels. The cause for altered neurotrophin serum and CSF levels in ASD patients remains yet to be clarified.<sup>11</sup>

Correia *et al.* examined the involvement of the BDNF signaling pathway in autism using various approaches.<sup>35</sup> The observed BDNF increase in 25% of autistic patients extended previous evidence for quantitative BDNF

anomalies in autism, obtained in smaller cohorts and in diverse tissues.<sup>14,19,22</sup>

A significant correlation with age was also detected and corroborated with previous studies which showed that serum or plasma BDNF levels in healthy human subjects are markedly altered by age.<sup>21,22</sup> A significant correlation of BDNF levels with medication was also observed.

An important connection between sonic hedgehog (SHH), BDNF pathways and oxidative stress was reported.<sup>13</sup> BDNF serum levels were found significantly higher in mild autistic children and on the other hand, not statistically significant in severe autism as compared to age and gender matched controls respectively.

Previous results obtained by authors showed that serum levels of BDNF in autistic children were significantly lower than those of normal controls.<sup>10</sup> Nevertheless, no correlations between BDNF levels and clinical variables in autistic patients were found. On the other hand, myelin basic protein (MBP) autoantibody serum levels in autistic were significantly higher than those of age matched healthy controls. Study suggested a highly possible pathophysiological role played by BDNF and MBP in autism spectrum disorders.

Regulation of BDNF in the cerebellum of autistic patients and controls was studied by Yip *et al.* measuring the protein level of BDNF in postmortem tissues.<sup>31</sup> The level of BDNF was significantly decreased in the autistic group compared to controls. Reduced BDNF in the cerebellum may be an indicator of aberrant brain development and growth in autism.

Elevated levels of BDNF were also found in postmortem brain tissue from adults with autism.<sup>23</sup> Concentrations different from those in controls have been found in peripheral blood of adults and children diagnosed with autism.<sup>14,15,28</sup>

The controversies between mentioned studies might point out BDNF as an important factor rather than being the only potential biological marker for autism. Since autism is a neurodevelopmental disorder that begins in childhood and BDNF is important in neurodevelopment, BDNF is suggestive of potential usefulness as sub-diagnostic biological marker of autism and that the investigation of this role may lead autism investigators in a new direction of research and the development of effective treatment modalities.<sup>37</sup>

## CONCLUSION

BDNF is one of major neurotrophins responsible for brain growth and development during pregnancy and early infancy. Due to the controversial results of BDNF in autistics in previous studies as well as due to observed wide variation in BDNF levels in both patients and control groups, the respective role of BDNF in ASD has been reviewed.

The emerging understanding of the role of BDNF in autism will most likely affect diagnostic and therapeutic processes. BDNF screening might become a new valid diagnostic tool for early identification of ASD patients.

Larger studies are strongly recommended to investigate the significant role played by BDNF in ASD phenotypes. The identification of biochemical markers related to autism would be beneficial for earlier clinical diagnosis and intervention not only in developed countries but could be very important in under-developed countries.

**Acknowledgement:** We thank Autism Research and Treatment Centre, Sheikh Al-Amoudi Autism research chair, King Abdul Aziz city for science and technology (KACST), and Health Research and Studies program at (NPST), Kind Saud University for sponsoring and financial support.

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