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ARTICLE

Neurotrophic Growth Factors (Vegf, Bdnf, Pdgf and Igf) Are Significantly Lower In Mothers of Autistic Children

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1 | INTRODUCTION

Autism spectrum disorders (ASDs) are pervasive developmental disorders that frequently involve deficits in social skills, communication and language. For the underlying neurobiology of these symptoms, disturbances in neuronal development and synaptic plasticity have been discussed. The physiological development, regulation and survival of specific neuronal populations shaping neuronal plasticity require the so-called 'neurotrophic factors' (NTFs). These regulate cellular proliferation, migration, differentiation and integrity, which are also affected in ASD. Therefore, NTFs have gained increasing attention in ASD research. The expression level of some growth-factor correlates with the clinical manifestations of ASD (1).

During development, BDNF and its receptors TrkB not only promote survival and differentiation of neurons but also are involved in neural plasticity in adulthood (2). Brain-derived neurotrophic factor serum levels are significantly increased in autism (3) and high expression of BDNF is also found in a model of autism [valproic acid (VPA)-treated rat offspring] (4). Epidermal growth factor (EGF). EGF strongly promotes cell proliferation and differentiation via MAPK, PKC, and Akt pathways in neural progenitor cells (5) and EGF and its receptor protein (EGFR) have been proposed as biomarkers of schizophrenia, depression, and bipolar disorder (6). Adult patients with high-functioning ASD show a significant reduction in serum levels of EGF as compared with controls (7) and our lab showed similar findings in children with ASD where EGF levels correlated with severity of symptoms (8).

Vascular Endothelial growth factor (VEGF) is a signal protein produced by many cells that stimulates the formation of blood vessels involved in both vasculogenesis and angiogenesis (9). VEGF has an important role in brain development and repair (10). VEGF levels in patients with ASD have been found to be lower than that of healthy controls (11). Studies have provided inconsistent data for insulin-like growth factors (IGF-1 and

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IGF-2) levels with respect to their association with ASD. IGF-1 is important for the survival of Purkinje cells of the cerebellum. Low concentrations of CSF IGF-1 (but not IGF-2) at an early age might be linked with the pathogenesis in autism (12). Platelet-derived growth factor (PDGF) are a family of molecules released from platelets which help to heal wounds and to repair damage to blood vessel walls. They also help blood vessels grow (13). The levels of PDGF have been found to be significantly higher in autistic children (14).

Mental disorders have, for most cases, an unknown etiology, but several studies indicate that neurodevelopmental changes happen in utero or early after birth. In a nested case–control study of the relation between blood levels of neuro-developmental (including BDNF, and VEGF-A) in autistic children, decreased levels of all the neurotropic markers was noted (15). This supports our findings that these markers are also significantly lower in mothers of autistic children. We have found several Neurotropic growth factors (VEGF, BDNF, PDGF and IGF) are significantly lower in mothers of autistic children (16-19) and suggest that continued analysis of these factors in mothers of autistic children will lead to better predictive, diagnostic and therapeutic modalities.

2 | METHODS

Subjects

Plasma VEGF, BDNF, PDGF and IGF were measured in 15 mothers of autistic children and 12 age and gender similar neurotypical controls. Subject plasmas were obtained from the Autism Genetic Resource Exchange (AGRE) **. This study was approved by the IRB of the Health Research Institute.

Plasma

All plasma was received frozen and immediately placed at -70C before Immunoassay analysis.

Immuno-array Assays

Immuno-array assays, as previously described (12), were performed by RayBiotech, Inc, Peachtree Corners, GA. 30092.

Statistics

Statistical analysis was done using T-tests with 95% confidence levels.

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3 | RESULTS

We found that BDNF levels significantly lower in mothers of autistic individuals compared to controls.

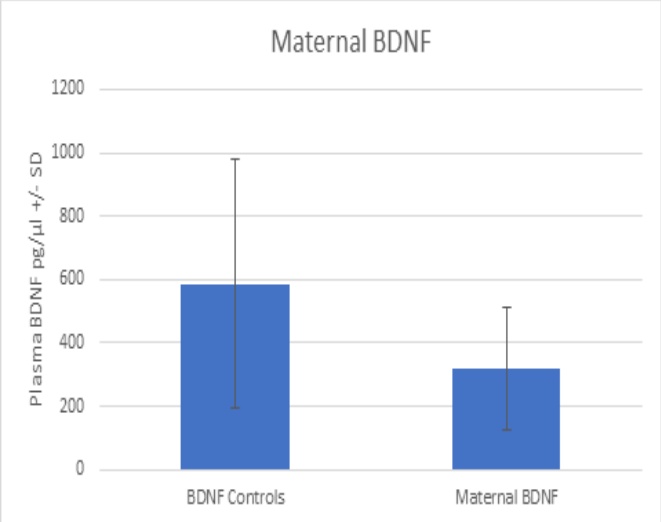

Figure 1. Maternal BDNF (319 +/- 195 pg/µl) of individuals with autism was significantly lower than in controls (586 +/- 393 pg/µl) (p=0.01)

We found that VEGF levels were significantly lower in the plasma of mothers of autistic children (Figure 2).

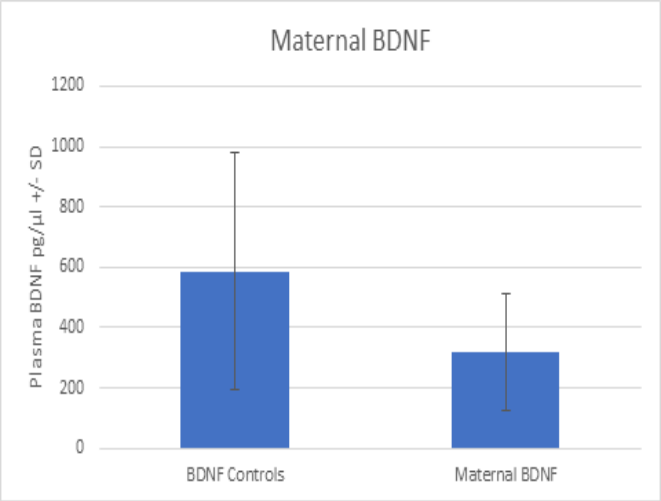

Figure 2. VEGF growth factor plasma levels of mothers of autistic children are significantly lower (58 +/- 25 pg/µl) than controls (132 +/- 58 pg/µl) (p=0.014)

We found that the matermal PDGF-AA levels (209.9 +/- 67 pg/µl) were significantly lower than the autistic (402.3 +/- 221.7 pg/µl) and control concentrations (394.3 +/- 164.5 pg/µl) (p=0.002) (Figure 3).

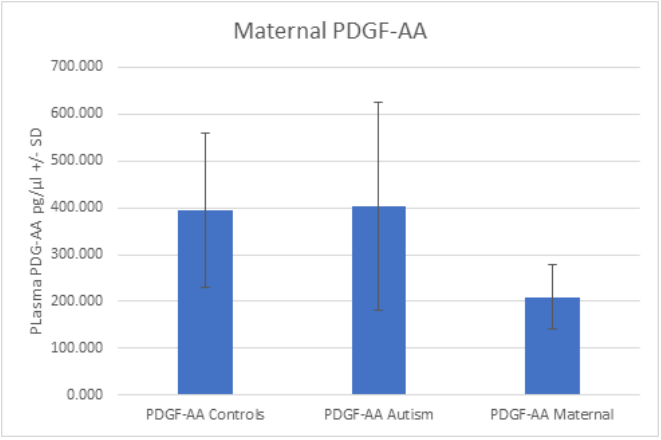

Figure 3 Maternal PDGF is significantly lower than autistic and control plasma concentrations.

We found that IGFBP-1levels were significantly lower in the plasma of mothers of autistic children (Figure 4).

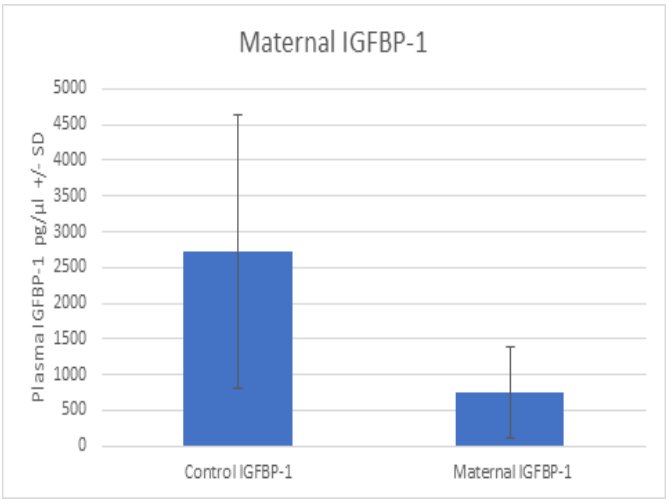

Figure 4. IGFBP=1 growth factor plasma levels of mothers of autistic children are significantly lower (745 +/- 636 pg/µl) than controls (2714 +/- 1913 pg/µl) (p=0.023).

4 | DISCUSSION

The physiological development, regulation and survival of specific neuronal populations shaping neuronal plasticity require neurotrophic factors. These regulate cellular proliferation, migration, differentiation, and integrity, which are also affected in ASD.

Clinical data on neurotrophic factor levels in children with ASD have yielded inconsistent results. One study showed that the serum BDNF levels of children with ASD were significantly higher than that of the control subjects (20), whereas Makkonen et al. (21) suggested that was no significant difference in serum BDNF concentrations between cases and controls, and another study showed that BDNF serum levels were significantly decreased in ASD children when compared with controls (22). For VEGF, results from Emanuele et al. showed that VEGF levels in patients with ASD were lower than that of healthy controls (23). In contrast, one study indicated that VEGF levels did not show significantly difference between children with ASD and healthy controls (24). Moreover, studies have demonstrated inconsistent data for IGF-1 and IGF-2 levels comparing ASD children and healthy controls (25, 26). A recent meta-analysis showed

Elevated peripheral blood BDNF, NGF and VEGF concentrations as a manifestation of children with ASD (27). Our data is among the first to find that mothers of autistic children may have altered concentrations of neurotrophic factors. If this data is confirmed it may lead to better diagnostic tools for ASD.

REFERENCES

1. Shim SH, Hwangbo Y, Yoon HJ, Kwon YJ, Lee HY, Hwang JA, et al. Increased levels of plasma glial-derived neurotrophic factor in children with attention deficit hyperactivity disorder. Nord J Psychiatry (2015) 69(7):546–51.
2. Jeong HI, Ji ES, Kim SH, Kim TW, Baek SB, Choi SW. Treadmill exercise improves spatial learning ability by enhancing brain-derived neurotrophic factor expression in the attention-deficit/hyperactivity disorder rats. J Exerc Rehabil (2014) 10(3):162–7.
3. Qin X, Feng J, Cao C, Wu H, Loh Y, Cheng Y. Association of peripheral blood levels of brain-derived neurotrophic factor with autism spectrum disorder in children: a systematic review and meta-analysis. JAMA Pediatr (2016) 170(11):1079–86.
4. Schuch V, Utsumi DA, Costa TVMM, Kulikowski LD, Muszkat M. Attention deficit hyperactivity disorder in the light of the epigenetic paradigm. Front Psychiatry (2015) 6(126):1–7.
5. Galvez-Contreras AY, Quinones-Hinojosa A, Gonzalez-Perez O. The role of EGFR and ErbB family related proteins in the oligodendrocyte specification in germinal niches of the adult mammalian brain. Front Cell Neurosci (2013) 7:258.
6. Galvez-Contreras AY, Campos-Ordonez T, Lopez-Virgen V, Gomez-Plascencia J, Ramos-Zuniga R, Gonzalez-Perez O. Growth factors as clinical biomarkers of prognosis and diagnosis in psychiatric disorders. Cytokine Growth Factor Rev (2016) 32:85–96.
7. Suzuki K, Hashimoto K, Iwata Y, Nakamura K, Tsujii M, Tsuchiya KJ, et al. Decreased serum levels of epidermal growth factor in adult subjects with high-functioning autism. Biol Psychiatry(2007) 62(3):267–9.
8. Russo AJ. Decreased epidermal growth factor (EGF) associated with HMGB1 and increased hyperactivity in children with autism. Biomark Insights (2013) 8:35–41.
9. Senger, D.; Galli, S.; Dvorak, A.; Perruzzi, C.; Harvey, V.; Dvorak, H. (25 February 1983). "Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid". Science. 219(4587): 983–985.
10. Jesmin S, Togashi H, Sakuma I, Mowa CN, Ueno K, Yamaguchi T, et al. Gonadal hormones and frontocortical expression of vascular endothelial growth factor in male stroke-prone, spontaneously hypertensive rats, a model for ADHD. Endocrinology (2004) 145(9):4330–43.
11. Emanuele E, et al. Serum levels of vascular endothelial growth factor and its receptors in patients with severe autism. Clin. Biochem. 2010;43:317–319.
12. Riikonen R, Makkonen I, Vanhala R, Turpeinen U, Kuikka J, Kokki H. Cerebrospinal fluid insulin-like growth factors IGF-1 and IGF-2 in infantile autism. Dev Med Child Neurol. 2006 Sep;48(9):751-5.
13. Hannink M, Donoghue DJ (1989). "Structure and function of platelet-derived growth factor (PDGF) and related proteins". Biochim. Biophys. Acta. 989 (1): 1–10.
14. Zakareia FA, Al-Ayadhi LY, Al-Drees AA. Study of dual angiogenic/neurogenic growth factors among Saudi autistic children and their correlation with the

severity of this disorder. Neurosciences (Riyadh). 2012 Jul;17(3):213-8.

15. Skogstrand, K., Hagen, C.M., Borbye-Lorenzen, N. et al. Reduced neonatal brain-derived neurotrophic factor is associated with autism spectrum disorders. Transl Psychiatry 9, 252 (2019).
16. AJ Russo., Albert Mensah and Judith Bowman. "Platelet-Derived Growth Factor (PDGF)-AA Levels in Mothers of Autistic Children. EC Paediatrics 10.12 (2021).
17. A J Russo, Albert Mensah and Judith Bowman Endoglin Levels are Significantly Higher in Mothers of Autistic Individuals J Clin Stud Rev Rep, 2021 Volume 3(5): 1-
18. Russo AJ, Mensah A, Bowman J. BDNF Levels Significantly Lower in Mothers of Autistic Individuals. SOJ Pedia Clin Neonato. 2021; 1(3):1–2.
19. Russo A.J., PhD1,2*, Albert Mensah, MD2 and Judith Bowman, MD2 Lower VEGF Plasma Levels in Mothers of Autistic Children- Short Communication Recent Adv Clin Trials, 2022; 1: 1-3.
20. Meng WD, et al. Elevated serum brain-derived neurotrophic factor (BDNF) but not BDNF gene val66met polymorphism is associated with autism spectrum disorders. Mol. Neurobiol. 2017; 54:1167–1172.
21. Makkonen I, et al. Brain derived neurotrophic factor and serotonin transporter binding as markers of clinical response to fluoxetine therapy in children with autism. J. Pediatr. Neurol. 2011; 9:1–8.
22. Francis K, et al. Brain-derived neurotrophic factor (BDNF) in children with ASD and their parents: a 3-year follow-up. Acta Psychiatr. Scand. 2018; 137:433–441.
23. Emanuele E, et al. Serum levels of vascular endothelial growth factor and its receptors in patients with severe autism. Clin. Biochem. 2010;43:317–319.
24. Kajizuka M, et al. Serum levels of platelet-derived growth factor BB homodimers are increased in male children with autism. Prog. Neuropsychopharmacol. Biol. Psychiatry. 2010; 34:154–158.
25. Riikonen R, et al. Cerebrospinal fluid insulin-like growth factors IGF-1 and IGF-2 in infantile autism. Dev. Med. Child Neurol. 2006; 48:751–755.
26. Mills JL, et al. Elevated levels of growth-related hormones in autism and autism spectrum disorder. Clin. Endocrinol. (Oxf.) 2007; 67:230–237.
27. Liu SH, Shi XJ, Fan FC, Cheng Y. Peripheral blood neurotrophic factor levels in children with autism spectrum disorder: a meta-analysis. Sci Rep. 2021 Jan 8; 11(1):15.

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