NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

RESEARCH ARTICLE

Arch Neuropsychiatry 2021;58:128–132
https://doi.org/10.29399/npa.27274

Serum Brain-Derived Neurotrophic Factor, Glial-Derived Neurotrophic Factor, Nerve Growth Factor and Neurotrophin-3 Levels in Preschool Children with Language Disorder

Ayhan BİLGİÇ[1], Hurşit FERAHKAYA[1], İbrahim KILINÇ[2], Vesile Meltem ENERGİN[3]

[1]Department of Child and Adolescent Psychiatry, Meram School of Medicine, Necmettin Erbakan University, Konya, Turkey
[2]Department of Biochemistry, Meram School of Medicine, Necmettin Erbakan University, Konya, Turkey
[3]Department of Pediatrics, Meram School of Medicine, Necmettin Erbakan University, Konya, Turkey

ABSTRACT

Introduction: Accumulating studies demonstrate that neurotrophins may play a crucial role in a variety of neurodevelopmental disorders. However, little data are available regarding the potential role of neurotrophins in language disorder (LD). This study aimed to investigate serum brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GDNF), nerve growth factor (NGF) and neurotrophin-3 (NTF3) levels in preschool children with LD.

Methods: A total of 43 cases with LD and 43 healthy controls aged 18 to 60 months were enrolled in the study. The development levels and psychiatric symptoms of the children were determined by the Ankara Developmental Screening Inventory and Child Behavior Checklist 1.5–5, respectively. Serum neurotrophin levels were assessed by enzyme-linked immunosorbent assay kits.

Results: Serum GDNF and NGF levels were significantly higher, serum BDNF and NTF3 levels were significantly lower in the LD group than in the control group. However, with logistic regression analyses, only negative relationship of BDNF and NTF3 levels with the presence of LD remained significant after accounting for the confounders including development level and coexisting psychiatric symptoms.

Conclusions: These results suggest that low BDNF and NTF3 levels have independent negative relationships with LD, which could be contribute to etiopathogenesis of the disorder.

Keywords: Language disorder, preschool children, brain-derived neurotrophic factor, glial-derived neurotrophic factor, nerve growth factor, neurotrophin-3

Cite this article as: Bilgiç A, Ferahkaya H, Kılınç İ, Energin VM. Serum Brain-Derived Neurotrophic Factor, Glial-Derived Neurotrophic Factor, Nerve Growth Factor and Neurotrophin-3 Levels in Preschool Children with Language Disorder. Arch Neuropsychiatry 2021;58:128-132.

INTRODUCTION

Language disorder (LD) is a neurodevelopmental condition characterized by marked difficulties in the language acquisition and usage in consequence of deficits in the comprehension or production of vocabulary, grammar, semantics, and discourse without explanatory factors such as intellectual disability, autism spectrum disorder (ASD), or a sensorimotor impairment. It affects about 10% of all children and causes crucial impairment in the social and academic performance of a child in everyday life (1). Although LD is a prevalent disorder, its etiopathogenesis has received relatively little research interest compared to other frequent neurodevelopmental conditions such as ASD, intellectual disability and attention deficit hyperactivity disorder (ADHD).

Cause of LD remains poorly understood, but studies are intensifying into genetic and neural contributions. Though none clearly linked to causation, a number of candidate genes, such as *FOXP2* and *CNTNAP2* and rare copy number variants have been found to be related to the disorder (2–4). Neuroimaging studies also provided evidence about the pathogenezis of LD. For instance, structural and functional anomalies in the left supramarginal gyrus and decreases in right superior occipital gray matter, right postcentral parietal gyri and bilateral medial occipital gyri volume have been shown in patients with LD (5). Changes in white matter volumes and efficiency of white matter connections for language ability have been also reported in these patients (6). However, research about the role of other neurobiological parameters including neurotrophins in LD is very limited (7).

Neurotrophins are a polypeptide growth factor family that extensively expressed in the brain. They play crucial roles for the differentiation of neural pathways, survival of neurons, synaptic connectivity and regulation of brain plasticity. They are also related to the attentional systems, learning processes, cognitive functions, and memory (8). A variety of neurotrophins such as brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GDNF), nerve growth factor (NGF) and neurotrophin-3 (NTF3) have been reported to be associated with neurodevelopmental conditions such as ASD, intellectual disability and ADHD (9–19). These substances are also candidate substances involved in the pathogenesis of LD. To our knowledge, only one previous study scrutinised the potential role of BDNF in LD and observed a trend toward association between the BDNF gene and LD (7). However, no studies have so far examined the potential role of other neurotrophins in the disorder.

Correspondence Address: Ayhan Bilgiç, Department of Child and Adolescent Psychiatry, Meram School of Medicine, Necmettin Erbakan University, Konya, Turkey • **E-mail:** bilgicayhan@yahoo.com
Received: 12.06.2020 , **Accepted:** 25.11.2020, **Available Online Date:** 03.06.2021

Neurotrophins cross the blood-brain barrier and their blood levels are closely related to the levels in the central nervous system. As explained before, no data have been available regarding the link between circulating neurotrophin levels and LD. Therefore, there is a necessity to assess circulating neurotrophins in LD in order to fulfil this research gap. The present study aimed to investigate whether serum levels of BDNF, GDNF, NGF and NTF3 in preschool children with LD differ from healthy controls. Although LD is considered as an isolated disorder, it shows high comorbidity with both internalizing (e.g., depression, anxiety disorders) and externalizing (e.g., ADHD, oppositional-defiant disorder) disorders, delayed motor development and even low IQ (20, 21), and changes in neurotrophin levels were reported in these conditions (12, 14–16, 18, 19, 22). Thus, this study also took into account the potential impact of internalizing and externalizing behavioural problems and development levels on the link among circulating neurotrophins and LD. We hypothesized that, compared with healthy controls, children with LD would have significantly altered serum neurotrophin levels, and that LD would have relationships with serum neurotrophin levels independent from potential confounders.

METHOD

Subjects

Patients were recruited from the Outpatient Clinic for Child and Adolescent Psychiatry at the Meram School of Medicine, Necmettin Erbakan University. Patients with a diagnosis of the LD and healthy controls were enrolled in this study. All participants were monolingual Turkish-speaking and all of them had hearing measured within normal limits. Children in the patient group had diagnoses of LD as described by DSM-5 criteria. Exclusion criteria included the existence of a major physical illness (e.g., cancer, cerebral palsy, etc.), intellectual disability, ASD, tic disorder, or head trauma. Children who had a history of be on psychotropics were also excluded. The control group comprised volunteers who applied to pediatric outpatient clinic and did not have a psychiatric disorder or a major physical illness. This study was assessed and approved by the Necmettin Erbakan University. Local Ethics Committee. The research protocol has been illuminated to the parents and they provided a written informed consent.

Instruments

Ankara Developmental Screening Inventory (ADSI): It assesses developmental levels of Turkish children within 0–6 years old (23). It has a total of 154 questions for the caregiver and the questions are related to the distinct aspects of development. The inventory has four different categories as cognitive language, fine motor ability, gross motor ability, and social and self-care skills. The scores of these four categories also gives a general developmental score.

Child Behavior Checklist 1.5-5 (CBCL/1.5-5): Behavior and emotional problems of children were assessed by parent-rated CBCL/1.5-5. This questionnaire contains 99 items with three response options. Children's behavioral problems could be evaluated into 7 categories in the scale, as emotionally reactive, anxiousness/depression, aggressive behavior, attention problems, somatic complaints, withdrawn symptom and sleep problems. The behavioral problems could also be investigated as two broad-band problems, as internalizing and externalizing problems. A higher score on the scale represents a higher severity. The reliability and validity of the CBCL/1.5-5 have been established for the Turkish population (24).

Diagnostic and Symptom Assessment

The diagnoses of LD were made in accordance with the DSM-5 criteria with psychiatric interview and one-way mirror observation of mother-child interaction. The first author A.B., who have an extensive experience in neurodevelopmental disorders, reviewed all the information and confirmed the diagnoses of LD. The ADSI was administered by psychologists who had training and experience about its administration. Patients who had the ADSI total score/normative data score below 0.70 were excluded to rule out intellectual disability. To address the internalizing and externalizing symptoms of children, parents completed the CBCL/1.5–5.

Blood samples

Blood samples of the participants were drawn from an antecubital vein. These samples were centrifuged and the obtained serum was frozen at -80°C till assayed. Serum BDNF, GDNF, NGF and NTF3 levels were measured with commercial enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturers' protocols (MyBioSource, CA, USA). The samples patient and control groups were run together in the same plates.

Statistical Analysis

Statistical analyses were done with SPSS 23.0 statistical software (SPSS Inc., Chicago, IL, USA). The chi-square test was conducted to evaluate differences between groups in categorical variables. Kolmogorov-Smirnov one-sample tests were conducted to check the normality of the distribution of variables in the patient and control groups. The Student's t-test or Mann-Whitney U test was conducted to compare psychiatric tests score and biochemical variables between groups. Correlations analyses were made with the Spearman rank correlation coefficient. Logistic regression analyses were conducted to assess the independent adjusted relationships between the presence of LD and neurotrophin levels. Regression model contained the all neurotrophins and some clinical variables (such as the severities of developmental level defined by the ADSI, and internalizing and externalizing problems) showing significant difference between patient and control groups as independent variables. A value of $p<0.05$ (two-tailed) was considered to show significance.

RESULTS

A total of 59 children with LD were evaluated. Five of their parents did not accept to participate, and 11 of them were excluded due to the exclusion criteria. In the control group, 52 children were evaluated, 4 of their parents did not accept to participate and 5 were excluded. The final population of the study included 43 children with LD and 43 healthy controls. The demographic and clinical characteristics of the children with LD and controls are yielded in Table 1. No significant differences were found between two groups in respect for age and sex distributions. ADSI score/normative data scores in all four categories and ADSI total were lower in the LD group compared to controls. Anxious/depressed, sleep problems, attention problems, aggressive behavior, and internalizing and externalizing scores of children based on the CBCL/1.5-5 were higher in the LD group than in the controls (Table 1).

Serum GDNF (z=-2.844, p=0.004) and NGF (z=-4.084, p<0.001) levels were significantly higher, serum BDNF (z=-1.979, p=0.048) and NTF3 (z=-2.648, p=0.008) levels were significantly lower in the LD group than in the control group (Figure 1 and Table 2). To control confounding factors including the severities of developmental level defined by the ADSI, and internalizing and externalizing problems, the predictors for the presence of LD were tested using logistic regression analyses. The analyses showed that serum BDNF (β=-5.085, p=0.012) and NTF3 (β=-0.020, p=0.044) levels had a negative predictive effect for the presence of LD (Cox & Snell R^2=0.604). However, GDNF (β=4.268, p=0.332) and NGF (β=0.165, p=0.131) did not show significant relationship with LD.

The associations among serum levels of neurotrophins and age and sex were assessed in children with LD. Neurotrophin levels did not correlate

Table 1. Demographic and clinical characteristics of children with language disorder and unaffected comparison subjects

	Children With Language Disorder (n=43)	Controls (n=43)	$t/z/x^2$	p
Age, years	38.3±12.8	35.6±8.6	0.938[b]	0.348
Sex, Male/Female	27/16	27/16	0[c]	1
ADSI				
Total score/normative data (%)	0.89±0.12	1.08±0.16	6.158[a]	<0.001
Cognitive language score/normative data (%)	0.67±0.10	1.09±0.14	15.744[a]	<0.001
Fine motor score/normative data (%)	0.91±0.18	1.01±0.19	2.354[b]	0.019
Gross motor score/normative data (%)	1.01±0.20	1.15±0.27	2.649[a]	0.010
Social and Self Help score/normative data (%)	0.97±0.22	1.07±0.21	2.031[a]	0.045
CBCL/1.5–5				
Emotionally Reactive	3.00±2.92	2.72±2.48	0.004[b]	0.996
Anxious/Depressed	4.49±3.23	2.09±1.77	3.879[b]	<0.001
Somatic Complaints	2.47±2.56	1.70±1.98	1.359[b]	0.174
Withdrawn	3.26±3.32	1.65±1.63	1.939[b]	0.053
Sleep Problems	3.30±2.58	1.37±1.73	3.934[b]	<0.001
Attention Problems	3.37±2.00	1.14±1.41	5.171[b]	<0.001
Aggressive Behavior	12.44±6.75	5.86±4.22	5.232[b]	<0.001
Internalizing	13.21±10.41	8.16±6.92	2.232[b]	0.026
Externalizing	15.81±8.31	7.00±5.00	5.463[b]	<0.001

ADSI, Ankara Developmental Screening Inventory; CBCL/1.5-5, Child Behavioral Checklist 1.5-5
[a]Student T test, [b]Mann-Whitney U test, [c]Chi square test.

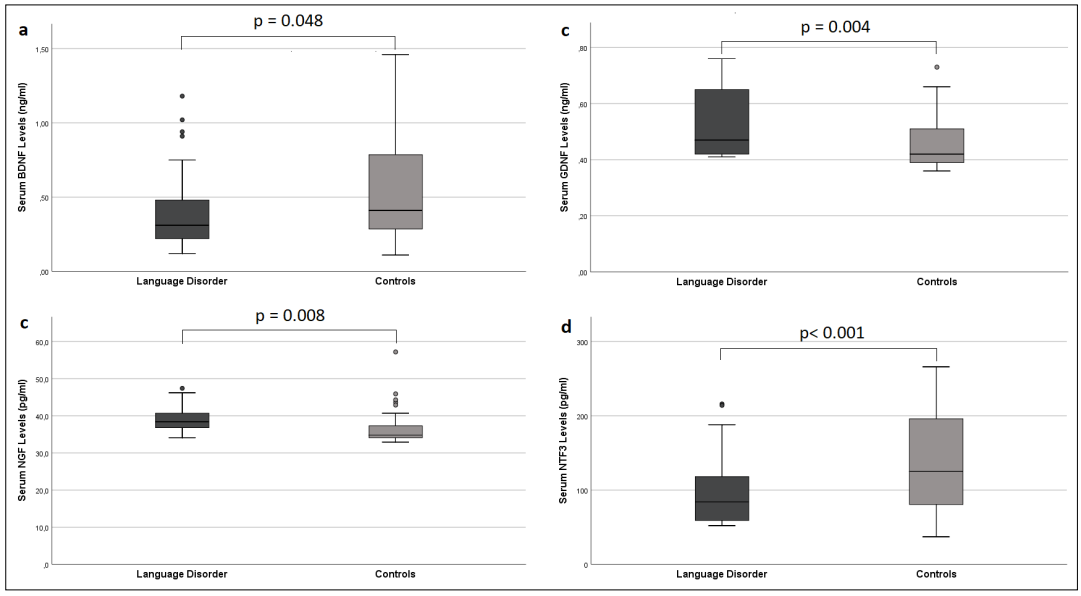

Figure 1. a–d. Box plots representing the distribution of serum BDNF **(a)**, GDNF **(b)**, NGF **(c)**, and NTF3 **(d)**. levels in children with LD and healthy controls. BDNF, brain-derived neurotrophic factor; GDNF, glial-derived neurotrophic factor; NGF, nerve growth factor; NTF3, neurotrophin-3; LD, language disorder. Mann-Whitney U test was used for comparisons between two groups.

Table 2. Serum neurotrophins levels of children with language disorder and unaffected controls

	Children with Language Disorder (n=43)	Controls (n=43)	z	p	r (Effect size)
BDNF (ng/ml)	0.38±0.25	0.54±0.39	-1.979[b]	0.048	0.21
GDNF (ng/ml)	0.53±0.13	0.46±0.10	2.844[b]	0.004	0.31
NGF (pg/ml)	39.1±3.3	36.8±4.51	2.648[b]	0.008	0.29
NTF3 (pg/ml)	98.4±46.7	135.7±66.7	-4.084[b]	<0.001	0.44

BDNF, brain-derived neurotrophic factor; GDNF, glial-derived neurotrophic factor; NGF, nerve growth factor; NTF3, neurotrophin 3.
Mann-Whitney U test was used for comparisons between two groups.

with age in the LD group. There was no difference between the two sexes for serum neurotrophin levels. The correlations among serum levels of neurotrophins were also evaluated in the LD group. GDNF was positively correlated with NGF levels (r_s=0.370, p=0.015). There was no another significant correlation among neurotrophin levels.

DISCUSSION

To our knowledge, this is the first study that scrutinized whether serum neurotrophin levels are related with LD. The results showed that preschool children with LD had higher serum levels of GDNF and NGF and lower serum levels of BDNF and NTF3 than healthy controls. Because circulating neurotrophin levels may be affected from the presence of comorbid psychiatric problems and may show relationships with each other, we also evaluated the independent adjusted associations of the abovementioned neurotrophins with LD. Analyses indicated an independent negative associations of serum BDNF and NTF3 levels with LD, while the relationships between GDNF and NGF with the disorder did not remain significant. Based on our results, it may be suggested that BDNF and NTF3 may play a role in the etiopathogenesis of LD.

Previous studies have examined circulating BDNF levels in a variety of neurodevelopmental disorders, such as ASD, ADHD and intellectual disability (9–12, 17–19). Data are not universal (9–12, 17, 25), however, many studies indicated an alteration in BDNF levels in these disorders (9, 11, 12, 18, 19). Genetic studies also supported the involvement of BDNF in neurodevelopmental disorders (26, 27). Furthermore, animal studies pointed out the BDNF hypothesis through the display of certain common characteristics of neurodevelopmental disorders, such as learning deficiencies, memory impairments, aggressiveness, and food intake regulation in BDNF knockout mice (28). In line with our *a priori* hypothesis, findings demonstrated lower serum BDNF levels in children with LD than in healthy controls. Also, while taking into account the effects of confounding factors, the relationship between serum BDNF levels and LD remained significant. No previous studies showed a direct association between BDNF and LD, but a genetic study in a sample of 4 Canadian families found a link between single nucleotide polymorphisms in the BDNF gene and reading impairments which are related to an increase in the risk for LD (7). Additionally, verbal short term memory is an essential component of language processing and BDNF have been reported to be related to memory (8, 29). BDNF is well known for its positive effects on the differentiation and proliferation of embryonic neural stem/progenitor cells and impairments in its functions may contribute to the pathogenezis of LD through affecting the differentiation of neural pathways in developing brain.

Several lines of evidence from genetic, blood level and postmortem studies have suggested that NTF3 may be involved in the etiopathogenesis of neurodevelopmental disorders. For instance, Segura et al. reported low NTF3 mRNA expression in whole blood in patients with ASD (30). Cho et al. showed a relationship between a single-nucleotide polymorphism in NTF3 gene and selective attention deficits in ADHD subjects (31). Though negative findings were also available (25), several studies detected changes in circulating levels of NTF3 in patients with ASD and ADHD (9, 31, 32). A post-mortem study indicated an increase in NTF3 levels in the cerebellar hemisphere in patients with ASD (33). Our findings demonstrated a significant decrease in serum NTF3 levels in children with LD. Furthermore, the association between decreased serum NTF3 levels and LD was still significant after accounting the potential confounders. These findings suggested a decreased production and/or secretion of NTF3 in this disorder. NTF3 is extensively expressed in the brain and proposed to have important functions for axon outgrowth, synapse development, survival of neurons, plasticity and regulation of oxidative stress in the nervous system. Therefore, low levels of NTF3 are likely to contribute to the development of LD by affecting neurogenesis or exacerbating oxidative stress.

ADHD is one of the most investigated neurodevelopmental disorder for its potential relationships with GDNF and NGF (14–16, 32). Studies consistently reported higher circulating GDNF levels in cases with ADHD compared to controls (14, 15). However, the data about the link between circulating NGF and ADHD are not consistent. Guney et al. showed elevated serum NGF levels in children with ADHD than the controls (16). However, our previous report did not find a link between serum NGF levels and ADHD (32). There were also studies that showed a possible association between these neurotrophins and other neurodevelopmental disorders such as ASD (13). Our study showed significantly elevated serum levels of GDNF and NGF in children with LD compared to controls, but these relationships became non-significant after accounting for the confounders. Therefore, in spite of the fact that serum GDNF and NGF levels were higher in children with LD, this study did not provide evidence for a direct relationship among these neurotrophins and LD.

Accounting for the coexisting internalizing and externalizing symptoms and developmental levels is a strength of the present study. However, our study has some limitations. Since we did not measure the expressive and receptive language levels of participants, we couldn't evaluate the correlation between these parameters and neurotrophin levels. Another limitation is that the lack of a specific time window for the obtaining blood sample. Finally, although the most reliable method for measuring neurotrophins has so far not shown, measuring only the serum levels of these molecules can also be defined as a limitation.

In summary, we detected a negative relationship between serum BDNF and NTF3 levels and the presence of LD in preschool children. These findings provide some evidence that these neurotrophins may have a role in the pathogenesis of LD. Further studies consisting of a larger population and taking into account the defined limitations should be done for discovering the link between BDNF, NFT3 and LD.

Acknowledgments: *The authors wish to thank the patients and families who participated in this study.*

Ethics Committee Approval: This study was assessed and approved by the Necmettin Erbakan University Local Ethics Committee.

Informed Consent: The research protocol has been illuminated to the parents and they provided a written informed consent.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- AB, İK; Design- AB, İK, VME, HF; Supervision- AB; Resource- AB; Materials- İK, VME, HF; Data Collection and/or Processing- İK, HF; Analysis and/or Interpretation- İK, AB; Literature Search- HF, AB; Writing- AB, İK; Critical Reviews- VME, HF.

Conflict of Interest: No potential conflict of interest was reported by the authors.

Financial Disclosure: Funding for this study was provided by a grant from the Scientific and Technological Research Council of Turkey (TUBITAK) (Project no: 119S839).

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