RESEARCH ARTICLE

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Serum Brain-Derived Neurotrophic Factor (BDNF) Level in Children with Specific Learning Disabilities

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SUMMARY

Objective: Specific learning disorder (SLD) is a neurodevelopmental disorder frequently seen in childhood with deficits in many areas of functioning. Although the etiology of SLD is known to be multifactorial, research findings are limited. In this study, we aimed to compare the serum levels of brain-derived neurotrophic factor (BDNF) in children with SLD to healthy children to find out whether BDNF has a role in the pathophysiology of SLD.

Method: The study included 30 children between the ages of 7-12, diagnosed with SLD and 30 age and gender matched healthy controls. The groups were tested on the Affective Disorders and Schizophrenia Interview Schedule for School-age Children–Now and Lifetime Form (K-SADS-PL), the Wechsler Intelligence Scale for Children-revised form (WISC-R), the Teacher Information Form (TIF) and the Specific Learning Difficulty Battery (SLDB).

Results: No difference the serum BDNF levels in children with SLD and the healthy controls. BDNF levels did not correlate with the WISC-R scores and reading rate in the SLD group.

Conclusion: An association was not determined between SLD and and serum BDNF levels. Our study was the first to investigate this relationship and provided preliminary data on this topic. There is a need for further studies with large patient groups of phenotypic homogeneity.

Keywords: Brain-derived neurotrophic factor, learning, child

INTRODUCTION

Brain-derived Neurotrophic Factor (BDNF) is a protein that plays role in many processes such as the development of synaptic connections and continuation of neuronal life, also partaking in the regulation of neural circuit development, such as differentiation of neural stem cells, axonal growth and guidance, and synapse formation and maturation (Yeom et al. 2016).

BDNF plays an essential role in learning, memory, attention, and cognitive functions (Yeom et al. 2016, Yamada et al. 2002). The role of BDNF in learning and memory has been investigated in animal models. The results of performance tests on rats for cognitive assessment were found to correlate with BDNF levels, such that a single intrahippocampal BDNF administration produced a better cognitive performance and a BDNF antibody introduced into the lateral ventricle worsened cognitive performance (Cirulli et al. 2004, Mu et al. 1999).

However, it was aslo reported that trangenic mice overexpressing BDNF in the forebrain including the striatum, hippocampus, frontal cortex, parietal cortex and the occipital cortex under αCaMKII promoter control showed impaired learning and short-term memory (Cunha

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et al. 2009). BDNF is present in the entire central nervous systemwith the highest levels found in the frontal cortex amygdala and the hippocampus in which the long-term memory formation, was affected by increased endogenous or infused BDNF (Cunha et al. 2010). BDNF has also been shown to have an important role in memory processing in the prefrontal cortex (Galloway et al. 2008).

So far, studies in humans have mostly investigated the BDNF gene expression and peripheral levels of the protein in cases of neurological and psychiatric disorders including schizophrenia, bipolar disorder, major depressive disorder, anxiety disorder, and Alzheimer's disease which share common etiopathogenetic mechanisms affecting the neurocognitive functions. (Cattaneo 2016). There are also studies on BDNF in various neurodevelopmental disorders of childhood, including attention deficit hyperactivity disorder (ADHD), autism, and intellectual disability (ID). Hence, a large body of evidence indicates that BDNF plays an important role in the pathophysiology of various psychiatric disorders despite the inconsistentcy in results on the peripheral BDNF levels, such that the same psychopathology has been associatied with increased or decreased levels of BDNF (Zhang et al. 2016, Zheng et al. 2016, Sargın et al. 2012, Bilgic et al. 2017, Nelson et al. 2001, Miyazaki et al. 2004). The inconsistencies in research results have been attributed to the limited number as well as the heterogeneity of the patients populations with respect to sociodemographic variables, chronic conditions, psychiatric comorbidities, smoking and alcohol use, exercise, food intake before blood sampling, using serum or plasma samples and the storage of blood sample that could affect the estimations on peripheral BDNF levels (Cattaneo et al. 2016). Alongside peripheral BDNF measurement, polymorphism of the Val66Met allele in the BDNF gene has also been investigated in psychiatric disorders and the observed social and cognitive dysfunctions have been associated with molecular, cellular and structural alterations in the brain (Dincheva et al. 2012, Lamb et al. 2015). The Val66Met polymorphism impairs BDNF transport to dendrites, reduces dendritic branching and BDNF release by the hippocampal neurons and disrupts synaptic plasticity in cerebral regions including the infralimbic medial prefrontal cortex, hippocampus, and central amygdala (Baj et al. 2013, Jing et al. 2017, Tsai 2018). There also exist inconsistent data on the Val66Met polymorphism in the BDNF gene in neuropsychiatric disorders. This is believed to result from multiple factors such as age, gender, ethnicity, environmental factors and gene-gene interaction that may act as confounding variables (Tsai 2018).

SLD, in being a neurodevelopmental disorder, is characterized by impaired acquisition or utilization of one or more neurodevelopmental skills, including listening, speaking, reading, writing, reasoning, and performance in mathematics (Karaman 2012). The prevalence of SLD among school children is between 5-15%, with a male/female ratio of about 2-3/1 (APA 2013).

SLD is a disorder of biological origin arising from the interactions of genetic, epigenetic and environmental factors. Familial and twin studies have indicated that the genetic component has a strong role with a heritability index greater than 0.6, in the development of SLD. But aspecific pattern for genetic transmission has not yet been shown (APA 2013). Some genome studies, however, indicate signs of the roles played by the KIAA0319, DYX1C1, DCD2 and ROBO1 genes in regulating axonal growth and connections as well as neural cell migration; and autopsy studies onalterations of cerebral structures in SLD showed signs of anomalous neural migration (Guidi et al. 2018). Brain imaging, on the other hand, suggested that reading disability is related to the fusiform gyrus, temporoparietal cortex, and the inferior frontal cortex, while disability in mathematics is related to the right intraparietal sulcus (Ashkenazi et al. 2013). The difficulties in central executive functions such as working memory, visual spatial domain, short-term memory, phonological awareness and verbal abilities like naming fluency are the common findings of the reported studies on children with SLD (Taur et al. 2014, Faedda et al. 2019, Moura et al. 2017, Kohli et al. 2005).

Although BDNF levels have been studied in other neurodevelopmental disorders of childhood, information on the relationship between peripheral BDNF levels and SLD as characterized by attention, memory and other neurocognitive dysfunctions has not been found in the literature.

In this study it was aimed to assess serum BDNF levels among children with SDL who did not have any medical or psychiatric comorbidity. It was hypothesized that the BDNF levels in SLD dif fered in comparison to healthy controls.

METHOD

Participants

A total of 450 children aged 7-12 years, diagnosed with SLD on the basis of the DSM-5 criteria, at Ankara Pediatric Hematology, Oncology Training and Research Hospital, Child and Adolescent Psychiatry Clinics, between January 2018 and June 2018, were accepted as the participants of the study and referred to the study team after clinical interview, family interview and assessment of skills in reading, writing, and mathematics appropriate for age and class at school by means of psychiatric examination and a teacher information form. The child and adolescent psychiatrists in

the study team re-evaluated the referred patients for SLD and any psychiatric comorbidity by detailed history taking, clinical interview, psychiatric examination and examining the teacher information form.

The exclusion criteria of the study comprised having any psychiatric disorder, chronic neurological and medical disorder, history of head trauma, and mental retardationas assessed by the Wechsler Intelligence Scale for Children-Revised form (WISC-R) on verbal IQ, performance IQ and/or having a total score of < 80 (Savasir and Sahin 1995). Comorbid psychiatric disorders were excluded since BDNF is thought to play a role in various different psychiatric disorders. After being tested by the study team on the (WISC-R) for mental level assessment, the Specific Learning Disability Extended Neuro-psychometry Battery (Karakas et al. 2017) and the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (Gökler et al. 2004), the first 30 children with confirmed SLD diagnosis, who met the inclusion and exclusion criteria and agreed to participate in the study formed the participants of the study. The control group consisted of 30 age and gender matched children referred by Yenimahalle Training and Research Hospital Well Child Outpatient Clinic and included in the studyafter following the same evaluation as for the patient group. The exclusion criteria for the control group included having any psychiatric disorder, chronic neurological or medical disorder, history of head trauma, and the results on verbal IQ, performance IQ and/or having a total score of <80 on the WISC-R. A sociodemographic information form prepared by the researcher was completed by all participants.

After being informed about the study design, all patients gave written informed consent. The study was approved by Ankara Pediatric Hematology Oncology Training and Research Hospital Ethics Committee (No 2018-156).

Biochemical Analysis

Serum BDNF measurement was carried out by collecting 5 ml fasting venous blood samples from the patient and control groups between 08:00-09:00 a.m. After 120 minutes of waiting for clotting, the samples were centrifuged at 3000 rpm for 20 minutes and the sera were stored -80°C until biochemical analysis using the ELISA technique in compliance with the manufacturer's instructions (Cloud-CloneCorp.).

Statistical Analysis

SPSS 21.0 (NY IBM Corp.,2012) software package was used for statistical analysis. Categoric variables were expressed numerically (n) and by percentage (%). Continuous variables were tested with the Kolmogorov-Simirnov test for normality of distribution, and expressed as the arithmetic mean, standard deviation, median, minimum, and the maximum. Paired comparisons of continuous variables were performed with the Student-t and Mann-Whitney U tests; and comparisons involving three or more groups were carried out with ANOVA and ANCOVA. Categoric variables were compared using the Pearson χ^2 and Fisher's exact tests. Correlations between BDNF levels and age, gender, the WISC-R scores, and reading speed were tested with the Spearman correlation analysis. A p value of <0.05 was considered statistically significant.

RESULTS

This study included a total of 30 children with SLD and 30 healthy children. The children with SLD had a median age of 8.7 (min-max=7-11.5) years and the healthy controls had a median age of 8.5 (min-max=7-11.5) years. The SLD group included 13 girls (43.3%) and 17 boys (56.7%). There were not any statistically significant differences between the study groups with respect to median age and sexual distribution. Also, significant differences were not found between the two groups with respect to parental age, parental educational level, and parental occupational status, either (Table 1).

Eight children with SLD had dyslexia (difficulty in reading) and dysgraphia (written expression) and 22 children had dyslexia, dysgraphia and dyscalculia (difficulty in mathematics,). All children in the control group and only 1 patient in the SLD group had acquired reading and writing skills at the appropriate time, whereas 24 (80%) patients were delayed in doing so; and the remaining 5 (16.7%) patients in the SLD group did not have reading and writing skills. The difference on the time to acquire reading and writing skills was statistically significant between the two subgroups. Also, the WISC-R mean verbal, performance, and the total scores of the SLD group were significantly lower as compared to the control group. When the children in the SLD group who could not progress to the reading test were excluded, the mean reading speed (word/minute) was found to be significantly lower in the SLD group [43.8 vs. 92.9; t(58)=7.092; p<0.001] (Table 1).

Comparison of the serum BDNF levels of the SLD subgroups with the healthy control group did not show significant differences [F(2)=0.206, p=0.814] (Table 2). When these comparisons were repeated by ANCOVA with controlled total intelligence scores, the distributions of BDNF levels were similar in the SLD subgroups and the control group [F(2)=0.489, p=0.616].

Table 1. Demographic and Clinical Properties of the SLD and Healthy Control Groups

	Total	SLD	Control	Statistics t, z or χ^2	p value
Age (years)[a]	8.5 (7-11.5)	8.7 (7-11.5)	8.5 (7-11.5)	-0.097	0.923
Sex, n (%)				.000	1.00
Girls	26 (43.3)	13 (43.3)	13 (43.3)		
Boys	34 (56.7)	17 (56.7)	17 (56.7)		
Maternal age (years)[b]	34.8 (4.7)	35.0 (5.2)	34.7 (4.3)	-0.243	0.809
Paternal age (years)[b]	38.6 (3.9)	39.2 (4.3)	38.0 (3.4)	-1.155	0.253
Maternal education, (years)[a]	5 (0-15)	5 (0-15)	5 (5-15)	-1.482	0.138
Paternal education, (years)[a]	8 (5-15)	5 (5-15)	8 (5-15)	-1.246	0.213
Maternal occupation, n (%)				1.661*	0.745
Housewife	39 (65.0)	21 (70.0)	18 (60.0)		
Worker	17 (28.3)	8 (26.7)	9 (30.0)		
Government employee	3 (5.0)	1 (3.3)	2 (6.7)		
Self-employed	1 (1.7)	0	1 (3.3)		
Paternal occupation, n (%)				3.588*	0.268
Unemployed	1 (1.7)	1 (3.3)	0		
Worker	38 (63.3)	21 (70.0)	17 (56.7)		
Government employee	11 (18.3)	3 (10.0)	8 (26.7)		
Self-employed	10 (16.7)	5 (16.7)	5 (16.7)		
SLD types, n (%)					
Reading-writing	8 (13.3)	8 (26.7)	-		
Combined type**	22 (36.7)	22 (73.3)	-		
No SLD	30 (50.0)	-	30 (100.0)		
Reading-writing, n (%)				63.219*	<0.001
In time	31 (51.7)	1 (3.3)	30 (100.0)		
2. semester of the 1.class	12 (20.0)	12 (40.0)	0		
2.class	9 (15.0)	9 (30.0)	0		
3.class	3 (5.0)	3 (10.0)	0		
Illiterate	5 (8.3)	5 (16.7)	0		
Reading speed (word/min)	68.4 (36.3)	43.8 (29.9)	92.9 (23.2)	7.092	<0.001
WISC-R scores[b]					
Verbal score	96.0 (11.8)	89.1 (10.1)	103.0 (9.0)	5.564	<0.001
Performance score	102.0 (10.0)	98.1 (9.1)	106.0 (9.5)	3.265	0.002
Total score	98.9 (11.0)	92.6 (9.1)	105.3 (9.0)	5.382	<0.001
Laboratory					
BDNF (pg/dL)[b]	664.8 (96.6)	669.4 (85.0)	660.2(108.4)	-0.181	0.857

[a]: Median (minimum-maximum), [b]: Arithmetic mean (standard deviation),
*: Fisher's exact test, **: Reading-writing plus mathematics learning disorder

Table 2. Comparison of BDNF Levels Between SLD Subtypes and Control Groups

	SLD group				
	Reading-writing	Combined	Control	Statistics	
	n=8	n=22	n=30	F	p value
Laboratory					
BDNF (pg/dL)[b]	705.8 (60.6)	656.0 (92.7)	660.2 (108.4)	0.206	0.814

b: Arithmetic mean (standard deviation)

Table 3. Correlation Analysis of the BDNF Levels of the SLD and Control Groups with Age, Intelligence, and Reading Speed with Pearson Correlation Analysis

			Age (years)	WISC-R Verbal	WISC-R Performance	WISC-R Total	Reading Speed
BDNF	SLD	rho	-0.386*	0.193	0.004	0.061	0.072
		p	0.035	0.307	0.981	0.747	0.704
	Control	rho	0.122	0.399*	-0.044	0.188	0.269
		p	0.521	0.029	0.817	0.320	0.151

Correlation Analyses

Correlation analyses between BDNF levels and the variables of age, WISC-R scores, and the number of words read per minute in the SLD group (n=30) demonstrated a moderate negative correlation between age and BDNF level (Pearson rho = -0.386, p = 0.035). Significant correlations were not determined between the other variables and BDNF levels. Similarly, the BDNF levels of the control group (n=30) did not show significant correlations with age, WISC-R score, and number of words read per minute (for all, p>0.05). (Table 3)

DISCUSSION

In the present study, serum BDNF levels were compared between children with SLD and age and gender matched healthy controls. To the best of our knowledge, our study is the first to analyse serum BDNF levels in children with SLD.

Given the reports on neural development problems, and observation of attention, memory, and other neurocognitive dysfunction in SLD, it was hypothesised that BDNF may play a role in the aetiology of these problems. However, this hypothesis was not confirmed since our study failed to detect any difference between the serum BDNF levels of children with SLD and the healthy controls. Performance results on the Rey auditory-verbal learning test and the serum BDNF levels of 150 healthy adults aged 18-60 years were also reported not to correlate (Wilkosc et al. 2016).

A study with 38 young adults aged 22-27 years failed to show any impact of Val66Met polymorphism in the BDNF gene on short-term implicit motor learning and associative word learning abilities (Freundlieb et al. 2012). Our results are similar to those of the studies which did not confirm a relationship between BDNF and learning. However, many studies have shown a positive relationship between BDNF level and verbal memory and cognitive functions in healthy adults (Gunstad et al. 2008, Komulainen et al. 2008 Li et al. 2009, Erickson et al. 2010). Jasinska et al. (2016) in their study with results contradicting ours, analysed the BDNF gene Val66Met allele polymorphism and neural activation patterns using functional Magnetic Resonance Imaging (fMRI) during the task of reading on 81 healthy children aged 6-10 years. The Met carriers showed a worse performance in tasks such as reading comprehension and phonological memory. In agreement with this finding, they had a greater activation during reading in the cerebral regions including fusiform gyrus, left inferior frontal gyrus, left superior temporal gyrus, and hippocampus associated with the task. Thus, it is unclear whether these findings in healthy individuals and different age groups would show parallelism in children with SLD.

Whereas meta-analyses of the studies on schizophrenia, bipolar disorder, anxiety disorders, and Alzheimer's disease reported lower peripheral BDNF levels in affected individuals compared with the controls, the meta-analysis on autism spectrum disorders provided evidence of higher BDNF levels in patients than in the controls (Zhang et al. 2016, Zheng et al. 2016). Some studies reported increased BDNF levels while others reported reduced BDNF levels in ADHD patients in comparison to controls. There are also studies that did nor determine any difference between BDNF levels of the ADHD and control groups (Sargın et al. 2012, Bilgic et al. 2017). However, in smilarity to the findings of our study, a recent meta-analysis by Zhang et al. (2018) reported not observing any significant difference in the peripheral BDNF levels of patients with ADHD and control groups. Among studies investigating the relationship between BDNF and ID in childhood, higher neonatal BDNF levels were found in children with ID (Nelson et al. 2001) and in school children with ID and a mean age of 11 years (Miyazaki et al. 2004) as compared with controls. Both sets of results suggested that higher BDNF levels may be associated with an abnormal neuronal development in prenatal or postnatal period, and proposed that BDNF irregularity may be used as a biomarker for ID.

Not finding a correlation between serum BDNF level and SLD in our study may be attributed to various factors. The first factor may be the aetiopathogenic and phenotypic heterogeneity of SLD. Our participants with SLD did not have a single phenotypic feature such as dyslexia, dysgraphia, or dyscalculia, but rather showed these in different combinations. Secondly, the small number of SLD patients may well have affected our results. Hence, future studies on larger participant groups with homogenous phenotypic features may produce more accurate results for a possible relationship between SLD and BDNF. Moreover, serum BDNF levels may not reflect the central BDNF levels. It is

still debated whether BDNF crosses the blood brain barrier. Several studies have shown that BDNF is a large protein molecule that cannot effectively cross the blood brain barrier (Poduslo and Curran 1996, Zhang and Pardridge 2001, Pardridge 2007, Pilakka-Kanthikeel et al. 2013). However, other studies have shown a positive correlation between serum BDNF level and central BDNF level (Klein et al. 2011, Tsai 2017). Inter-species differences in this relationship have also been demonstrated (Klein et al. 2011) such that a parallelism between peripheral and central BDNF levels is far from clear.

The relationship between BDNF gene polymorphism and cognitive functions has also been a subject of research. Episodic memory, abnormal hippocampal activation and irregularity of BDNF release was demonstrated in the presence of Val66Met allele polymorphism in the BDNF gene (Egan et al. 2003) and serum BDNF level was found to be increased with polymorphism in adult humans (Lang et al. 2009). Aurelli et al. (2010) analysed Val66Met and 270C/T polymorphisms in the BDNF gene in children with ID and found a greater incidence of mutation in the Val66Met allele in children with ID. Although the functional importance of this change is not completely understood, it is considered to affect the morphology of the hippocampus and the prefrontal cortex with roles in learning and memory and where BDNF concentration is high. Furthermore, the effect of the BDNF gene on the Continuous Performance Test was shown in two separate studies (Cho et al. 2010 and 2011). Şimşek et al. (2016), however, could not demonstrate any correlation between peripheral BDNF levels and the Stroop test scores. Despite these conflicted observations, it is believed that BDNF may be related to many psychiatric disorders, warranting further studies in this field.

Our results did not show any sign of relationship between intelligence test scores and serum BDNF levels in the SLD group. Yeom et al. (2016) showed a negative relationship between serum BDNF level and WISC-R verbal and total scores of pre-school children who were not assessed for psychiatric diagnoses. Studies involving larger groups of children with various ages and psychiatric disorders should elucidate this relationship more accurately.

Whereas serum BDNF level and age are not correlated in healthy control groups, a negative correlation was found in SLD groups. Similarly to our results, correlations were not found between the ages and BDNF levels of 110 healthy children, adolescents, and adults (Lughetti 2011). Investigation of the change in serum BDNF levels with age showed that serum BDNF level increased in the first few years of life, then showing as mall decrease followed by steady increase to reach adult levels (Katoh-Semba 2007). We believe that whether the relationship between age and BDNF levels in individuals with SLD is unique to SLD should be further studied by large-scale studies involving different age groups.

Our study has some limitations. Our sample was both small and phenotypically non-homogeneous. Only the reading speed was used as an objective criterion for specific assessment of the severity of SLD. Also, potentially confounding factors such as diet, exercise, and body mass index were not controlled in BDNF measurement.

The strengths of our study include the assessment of the participants by a semi-structured psychiatric interview, exclusion of psychiatric and medical comorbidities, and using serum samples in being less sensitive than plasma to external factors such as heat, anticoagulant use, pre-centrifuge time, excluding of medical and/or psychiatric comorbidities (as well as smoking and alcohol use), using fasting blood samples and serum instead of plasma in order to avoid their implication in previously reported contradictory results on BDNF levels in psychiatric disorders.

In conclusion, although, contrary to our hypothesis, a correlation between SLD and serum BDNF level was not determined, this study has provided preliminary data in being the first to investigate that relationship. Large-scale studies involving participants with phenotypic homogeneity are needed to investigate the role of BDNF in the pathophysiology of SLD.

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