BDNF Plasma level in ADHD Children; Correlation to Different Symptomatology

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ABSTRACT

Background: Attention-deficit/hyperactivity disorder (ADHD) is a common psychiatric disorder with a large genetic component. Several lines of evidence suggest that Brain-derived neurotrophic factor (BDNF) plays a role in the etiology of ADHD. BDNF is a neurotrophin expressed in the brain throughout life and serves as a neurotransmitter modulator, and participates in mechanisms of neuronal plasticity, such as long- term potentiation and learning. A decreased midbrain BDNF activity may cause midbrain dopaminergic dysfunction, and therefore, resulting in ADHD. **Subjects and methods:** Twenty one cases of ADHD were selected and underwent IQ test (WISC), Conner's test to assess severity of different symptoms, 3 ml blood sample before the morning dose of treatment were collected to measure plasma level of BDNF. After full assessment patients were categorized into 3 diagnostic categories (hyperactive type, inattentive type, and combined type). Control group consisted of 20 normal volunteer children, with no psychiatric or neurological disorder. 3ml morning non clotted blood samples were collected from them. **Results:** There was no significant difference between ADHD children and control group regarding the BDNF plasma level. There was no gender difference in BDNF plama level. There was no significant difference between ADHD children either before treatment or after starting methyl phenidate (Ritalin). There was significant statistical difference regarding BDNF plasma level between the hyperactive type of ADHD patients, and inattentive type. There was highly significant statistical difference between the inattentive type of ADHD and control group regarding BDNF serum level. It is much lower in inattentive type (8466.67) than that of the control group (28689). Significant positive correlation was found between BDNF plasma level and performance IQ, hyperactivity, and hyperactivity- impulsivity. **Conclusion:** Plasma BDNF level is decreased in inattentive type of ADHD, and may be drugs acting on enhancement of BDNF activity will help in improvement of ADHD not on symptomatic bases, but on neurodevelopmental level.

Key words: Attention-deficit/hyperactivity disorder, BDNF, Egypt.

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INTRODUCTION

Attention deficit-hyperactivity disorder (ADHD) is one of the most common and pervasive childhood disorders with prevalence between 3% and 6% of school-aged children[1]. ADHD is a common psychiatric disorder with a large genetic

component. Brain-derived neurotrophic factor (BDNF) is a neurotrophin expressed in the brain throughout life and is involved in survival, differentiation, and synaptic plasticity of several neuronal systems including dopaminergic pathways[2].

Recent reports have suggested a pathophysiological role of BDNF in ADHD[3]. BDNF, a member of the neurotrophin family of trophic factors, and the most abundant neurotrophin in the brain exerts its effects by binding to the tropomyosin-related kinase B (TrkB) receptor[4]. It enhances the growth and maintenance of several neuronal systems, serves as a neurotransmitter modulator, and participates in mechanisms of neuronal plasticity, such as long- term potentiation and learning[5]. Several lines of evidence suggest that BDNF plays a role in the etiology of ADHD. First, earlier studies demonstrated that BDNF plays a key role in the survival and differentiation of midbrain dopaminergic neurons invivo[6] and in vitro[7]. Since dysfunction in the midbrain system is crucial in ADHD pathogenesis[8], a decreased midbrain BDNF activity may cause midbrain dopaminergic dysfunction, and therefore, resulting in ADHD. Second, psychostimulants such as methylphenidate are the agents commonly used in the treatment of ADHD. The classical action mechanism of psychostimulants involves enhancement of the release of dopamine and norepinephrine in the midbrain. BDNF has been shown tomodulate the release of dopamine through activation of TrkB (tropomyosin-related kinase B) receptors[9], and has also been implicated in the release of dopamine as well as in dopamine-related behaviors induced by psychostimulant, methamphetamine[10]. Furthermore, psychostimulants and antidepressants are the agents commonly used for the treatment of ADHD, and both have been found to elevate central BDNF[11]. From the above findings, it is highly likely that elevation of central BDNF activity is important in the treatment of ADHD.

Endogenous BDNF may be critical for normal development and function of central serotonergic neurons[12], and hence, impulse regulation. BDNF is known to act as a growth and survival factor for dopamine [6] and serotonin neurons during brain development[13]. BDNF is also thought to prevent neuronal death. Studies on genetically modified BDNF deficient mice showed the thickness of the cerebral cortex was reduced relative to controls, and a deficit in central nervous system myelination. Moreover, BDNF has subtle effects on neuronal structure and function, for example, as molecular mediators of synaptic and morphological plasticity[14].

Psychostimulants and antidepressants are the agents commonly used for the treatment of ADHD and were also found to elevate central BDNF. It is proposed that BDNF may play a role in the therapeutic action and pathogenesis of ADHD. This hypothesis may provide a new direction for the treatment and the pathogenesis of ADHD[14].

BDNF is found in both human serum and plasma[15]. Serum levels of BDNF have been found to be 200-fold higher than plasma levels[16]. Human platelets contain a large amount of BDNF[15], therefore, the difference between serum and plasma levels of BDNF could reflect the amount of BDNF stored in circulating platelets. Since BDNF is known to cross the blood–brain barrier in both directions, circulating BDNF might originate from neurons and glial cells of the brain. Accordingly, plasma BDNF

may reflect circulating levels rather than the levels stored in platelets[3].

In the present study, therefore, we examined the plasma levels of BDNF in children with ADHD and in normal controls. We then explored for any correlations between plasma BDNF levels and clinical characteristics of ADHD symptoms

SUBJECT AND METHODS

ADHD cases were collected conveniently from the outpatient clinic, Institute of Psychiatry, Ain Shams University. Inclusion Criteria were: Children with ADHD, both sexes included, age from 5-14, before treatment or after starting Ritalin. Exclusion criteria were: mentally retarded, other comorbidity (conduct, depression, psychosis, epilepsy, any other neurological disorder). 21 Cases were diagnosed after history taking, clinical interview, then selected cases underwent IQ test (Wechsler intelligence scale for children), Conner's test to assess severity of different symptoms, 3ml blood sample before the morning dose of treatment. After full assessment patients were categorized into 3 diagnostic categories (hyperactive type, inattentive type, and combined type). Control group consisted of 20 normal volunteer children, with no psychiatric or neurological disorder. Morning blood samples of 3ml were collected from them. For ADHD patients and normal controls, unclotted blood samples were drawn from the subjects' antecubital veins between 8 a.m. and noon. This was done to exclude the circadian effect of BDNF levels (17).

All collected blood samples were centrifuged, plasma was separated, stored in -80 degree till all samples were collected, then measurement of serum level of BDNF was done using specific kits for its assessment (Quantikine Human BDNF immunoassay). Assessment of BDNF plasma level was done in the medical research institute in Ain Shams University Hospitals

Statistical methods:

SPSS statistical software package (V.17, Echo soft Corp., USA, 2008) was used for data analysis. Data were expressed as Mean ±SD for quantitative measures.

The following tests were done:

1. Comparison between two independent mean groups for parametric data using Student T test.

2. Comparison between two independent groups for non-parametric data using Wilcoxon Rank Sum test.

3. Comparison between more than 2 patient groups for parametric data using Analysis of Variance (ANOVA).

The multiple comparisons (Post-hoc test or least significant difference, LSD) were also followed to investigate the possible statistical significance between each 2 groups.

4. Pearson correlation test to study the possible association between each two variables among each group for parametric data.

The probability of error at 0.05 was considered significant while at 0.01 and 0.001 are highly significant

RESULTS

Descriptive statistics:

For control children BDNF plasma level was (mean=28689pg/ml, SD+/-12705) and for patients the mean age of children was 7.26±2.07, the mean IQ was 99.62±8.58

and the mean BDNF level 27171.4±25368.5. There was no significant difference between ADHD children and control group regarding the BDNF plasma level as shown in (table 1).

There was highly significant statistical difference between the inattentive type of ADHD and control group regarding BDNF plasma level. It is much lower in inattentive type (8466.67) than that of the control group (28689) as shown in (table 2). There was no significant difference between ADHD children either being males or females regarding all variables assessed in this study including BDNF plasma level

As shown in (table 5), there were significant statistical differences between different diagnostic subtypes of ADHD patients regarding:

Severity of cognitive problems with the combined type being the highest (82.45), and the hyperactive type was the lowest in severity of cognitive problems (70.75).

Liability was highest in the combined type (71.27), followed by the hyperactive type (63.25), and was least in the inattentive type (50.17).

Hyperactivity-impulsivity was highest in the combined type (79.27) followed by the hyperactive type (78), and was least in the inattentive type of ADHD (50.33). There was no significant statistical difference between different diagnostic subtypes regarding BDNF plasma level.

There was no significant difference between ADHD children regarding all variables measured, either before treatment or after starting methyl phenidate (Ritalin) as shown in (table 4). There was significant statistical difference regarding BDNF serum level between the hyperactive type of ADHD patients (42750), and inattentive type (8466.67). BDNF plasma level is much lower in the inattentive type, than that of the hyperactive type as shown in (table 6).

There were no significant statistical difference between the hyperactive and combined subtypes of ADHD regarding BDNF plasma level and all other variables except the inattention which is higher in the combined type (76.55), than that of the hyperactive type (49) as shown in (table 7).

There were no significant statistical difference between the inattentive and combined subtypes of ADHD regarding BDNF plasma level and all other variables except the liability and hyperactivity–impulsivity variables which were higher in the combined type, than that of the inattentive type as shown in (table 8).

Correlation studies:

Significant positive correlation between:

Verbal IQ and total IQ (r=0.837, p=0). Inattention and cognitive problem (r=0.578, p=0.006). Liability and total IQ (r=0.446, p=0.043). Liability and hyperactivity (r=0.559, p=0.008). Hyperactivity–impulsivity and hyperactivity (r=0.799, p=0). Hyperactivity–impulsivity and liability (r=0.779, p=0). BDNF plasma level and performance IQ (r=0.49, p=0.024). BDNF plasma level and hyperactivity (r=0.526, p=0.014). BDNF plasma level and hyperactivity-impulsivity (r=0.565, p=0.008).

Significant negative correlation between: Hyperactivity and age (r=-0.696, p=0). Liability and age (r=-0.436, p=0.048); Hyperactivity–impulsivity and age (r=-0.758, p= 0).

Non Significant positive correlation between: BDNF serum level and total IQ (r=0.307, p=0.175), BDNF plasma level and verbal IQ (r=0.079, p=0.733), BDNF

plasma level and lability (r=0.371, p=0.097).

Non Significant negative correlation between: BDNF plasma level and age (r=-0.25, p=0.275), BDNF plasma level and cognitive problem (r=-0.156, p=0.499). BDNF plasma level and inattention (r=0.219, p=0.34).

Table (1): Comparing BDNF level in patients & control group using Wilcoxon Rank Sum Test:

Sample	BDNF level		z	P value	significance
	Mean	SD			
Patients	27171.4	25368.5	-1.357	0.175	NS
Control	28689	12705			

Table (2): Comparison between BDNF plasma level in different diagnostic categories of ADHD, and BDNF level in control group

Control group		Combined type		Inattentive type		Hyperactive type		
SD	Mean	SD	Mean	SD	Mean	SD	Mean	
12705	28689	27361.9	31709.09	4129.245	8466.67	25837.63	42750	BDNF plasma level
		-0.454		-3.47		-1.24		Z
		0.649		0.001		0.215		P value
		NS		HS		NS		significance

Table (3): Comparison between patients regarding gender (males & females)

variables	Males n=13		Females n=8		t	P value	Signif.
	Mean	SD	Mean	SD			
Age	7.538	2.331	6.81	1.60	0.844	0.409	NS
WISC:							
Total IQ	100	9.6	99	7.211	0.271	0.789	NS
Verbal IQ	102.15	10.908	99	12.961	0.574	0.576	NS
Performance IQ	91.77	9.748	90.13	6.534	0.462	0.649	NS
Conner's test							
Cognitive problem	80.77	5.761	77.13	11.294	0.847	0.418	NS
Hyperactivity	74.54	17.952	73.63	16.509	0.119	0.907	NS
Inattention	71.31	11.665	72.5	15.156	-0.19	0.852	NS
Liability	62.23	15.653	66.13	10.869	-0.672	0.51	NS
Hyperactivity-impulsivity	68.92	16.444	73.75	16.968	-0.641	0.532	NS
Wilcoxon Rank Sum Test					z	p	Signif.
BDNF plasma level	25123.08	26983.15	30500	23877.55	-0.545	0.585	NS

Table (4): Comparison between ADHD patients regarding initiation of treatment

	Patients before starting methyl phenidate n=15		**Patients already on methyl phenidate n=6**		**t**	**P value**	**Sign**
	Mean	SD	Mean	SD			
Age	7.06	2.05	7.75	2.230	-0.649	0.533	NS
WISC:							
Total IQ	98.066	7.401	103.5	10.784	-1.132	0.295	NS
Verbal IQ	98.533	8.450	107	16.407	-1.202	0.274	NS
Performance IQ	90.533	9.642	92.67	5.125	-0.656	0.521	NS
Conner's test							
Cognitive problem	78.466	9.372	81.67	4.082	-1.089	0.29	NS
Hyperactivity	75.66	16.757	70.5	18.62	0.591	0.57	NS
Inattention	71.6	12.965	72.17	13.363	-0.089	0.931	NS
Lability	62.6	13.79	66.5	14.91	-0.553	0.594	NS
Hyperactivity-impulsivity	70.866	16.03	70.5	18.855	0.042	0.968	NS
Wilcoxon Rank Sum Test					z	p	Sign
BDNF plasma level	29666.6	29257.2	20933.3	10588.04	-0.195	0.845	NS

Table (5): Comparison between different subtypes of ADHD using Analysis of variance

	Hyperactive type n=4		Inattentive type n=6		Combined type n=11		f	P value	Mean
		SD	Mean	SD	Mean	SD			
WISC:									
Total IQ	97	4.967	95.33	6.377	102.91	9.7	1.896	0.179	NS
Verbal IQ	97.75	5.5	100.5	8.961	102.36	14.479	0.223	0.802	NS
Performance IQ	89.25	13.745	90	2.757	92.45	8.982	0.262	0.772	NS
Conner's test									
Cognitive problem	70.75	13.301	79.5	4.183	82.45	5.803	3.788	0.042	S
Hyperactivity	85.75	5.679	49.5	5.683	83.45	6.203	71.894	0	HS
Inattention	49	1.155	78.17	6.432	76.55	6.832	34.14	0	HS
Liability	63.25	14.033	50.17	7.111	71.27	11.261	7.375	0.005	HS
Hyperactivity-impulsivity	78	4.69	50.33	5.317	79.27	12.877	16.935	0	HS
BDNF plasma level	42750	25837.63	8466.7	4129.25	31709.09	27361.9	3.099	0.07	NS

Table (6): Comparison between hyperactive and inattentive subtypes of ADHD using least significant difference (LSD)

	Hyperactive type n=4		Inattentive type n=6		Mean difference	P value	Signif.
	Mean	SD	Mean	SD			
WISC:							
Total IQ	97	4.967	95.33	6.377	1.67	0.757	NS
Verbal IQ	97.75	5.5	100.5	8.961	-2.75	0.727	NS
Performance IQ	89.25	13.745	90	2.757	-0.75	0.897	NS
Conner's test							
Cognitive problem	70.75	13.301	79.5	4.183	-8.75	0.079	NS
Hyperactivity	85.75	5.679	49.5	5.683	36.25	0	HS
Inattention	49	1.155	78.17	6.432	-29.17	0	HS
Liability	63.25	14.033	50.17	7.111	13.08	0.078	NS
Hyperactivity-impulsivity	78	4.69	50.33	5.317	27.67	0.001	HS
BDNF plasma level	42750	25837.63	8466.67	4129.245	34283.33	0.033	S

Table (7): Comparison between hyperactive and combined subtypes of ADHD using LSD:

	Hyperactive type n=4		Combined type n=11		Mean difference	P value	Significance
	Mean	SD	Mean	SD			
WISC:							
Total IQ	97	4.967	102.91	9.7	-5.91	0.234	NS
Verbal IQ	97.75	5.5	102.36	14.479	-4.61	0.518	NS
Performance IQ	89.25	13.745	92.45	8.982	-3.2	0.543	NS
Conner's test							
Cognitive problem	70.75	13.301	82.45	5.803	-11.7	0.013	S
Hyperactivity	85.75	5.679	83.45	6.203	2.3	0.519	NS
Inattention	49	1.155	76.55	6.832	-27.55	0	HS
Liability	63.25	14.033	71.27	11.261	-8.02	0.221	NS
Hyperactivity- impulsivity	78	4.69	79.27	12.877	-1.27	0.833	NS
BDNF plasma level	42750	25837.63	31709.09	27361.92	11040.91	0.423	NS

Table (8): Comparison between inattentive and combined subtypes of ADHD using LSD:

	Inattentive type n=6		Combined type n=11		Mean difference	P value	Significance
	Mean	SD	Mean	SD			
WISC:							
Total IQ	95.33	6.377	102.91	9.7	-7.58	0.086	NS
Verbal IQ	100.5	8.961	102.36	14.479	-1.86	0.763	NS
Performance IQ	90	2.757	92.45	8.982	-2.45	0.592	NS
Conner's test							
Cognitive problem	79.5	4.183	82.45	5.803	-2.95	0.435	NS
Hyperactivity	49.5	5.683	83.45	6.203	-33.95	0.435	NS
Inattention	78.17	6.432	76.55	6.832	1.62	0.609	NS
Liability	50.17	7.111	71.27	11.261	-21.11	0.001	HS
Hyperactivity-impulsivity	50.33	5.317	79.27	12.877	-28.94	0	HS
BDNF plasma level	8466.67	4129.245	31709.09	27361.92	-23242.4	0.063	NS

DISCUSSION

There was no significant difference between ADHD children and control group regarding the BDNF plasma level as shown in (table 1). Our results were disconcordant with findings of Shim and his colleagues; they found that the mean plasma BDNF levels in ADHD patients were 833.8±371.0 pg/ml, whereas 578.5±304.0 pg/ml in normal controls, thus showing significantly higher mean plasma BDNF levels in ADHD patients than in normal controls[3].

BDNF level in the inattentive type of ADHD is much lower (8466.67) than that of the control group (28689) as shown in (table 2).

There was no significant gender difference between ADHD children regarding all variables assessed in this study including BDNF plasma level. This was concordant with results of Shim et al. as there was no significant difference observed in the plasma levels of BDNF between both sexes (825.2±361.4pg/ml vs. 864.4±425.4pg/ml, t=−0.276, df=39, p=0.784 in ADHD patients[3].

Although Tsai suggested that decreased central BDNF activity, especially in the midbrain region, may play a role in the pathogenesis of ADHD[18], one recent study suggests that this hyperactivity is gender-specific; male BDNF conditional knockouts exhibit hyperactivity, whereas female BDNF conditional knockouts display normal loco motor activity, with a prominent increase in depression-like behaviors[19].

There was no significant difference between ADHD children regarding all variables measured, either before treatment or after starting methyl phenidate (Ritalin) as shown in (table 4).

This may be explained by the fact that we withdraw blood sample in the morning before the morning dose of Ritalin. Ritalin act only for 4-6 hours so its effect on BDNF here may be hidden.

On other hand; other authers found that there is an increase of plasma BDNF levels in untreated ADHD patients[20].

Recent animal study found that repeated injections of amphetamine were accompanied by an elevated BDNF mRNA and BDNF immunoreactivity in the basolateral amygdala, rostral piriform cortex and paraventricular nucleus of the hypothalamus[11].

There was no significant statistical difference between different diagnostic subtypes regarding BDNF plasma level.

High significant positive correlation were found between BDNF plasma level & performance IQ (r=0.49, p=0.024); Hyperactivity (r=0.526, p=0.014); and hyperactivity- impulsivity (r=0.565, p=0.008). Our results were concordant with findings observed in other study that the severity of some symptoms in our ADHD patients was increased when plasma BDNF levels increased. However, the underlying mechanisms of how the differences in plasma BDNF levels are related to the severity of ADHD symptoms are not clear[20].

Significant negative correlation were found between age & hyperactivity (r=-0.696, p=0), & liability (r=-0.436, p=0.048); hyperactivity – impulsivity (r=-0.758, p=0).

Non Significant negative correlation were found between BDNF plasma level and age

(r=-0.25, p=0.275) & cognitive problem (r=-0.156, p=0.499) &inattention (r=-0.219, p=0.34).

Other studies demonstrate that there is a significant correlation between plasma BDNF levels and omission errors in ADS outcome-variable T-scores (pb0.001)[20].

Plasma BDNF levels had a significant positive correlation with the severity of inattention symptoms (20) finding suggests that changes in plasma BDNF levels could affect the severity of inattention symptoms (omission error). This finding is in the good agreement with the report that components of the regulated secretory machinery interact specifically with a signal in the BDNF prodomain, and that perturbations in BDNF trafficking may lead to selective impairment of CNS functions including learning and memory[22].

ADHD have evolved from simple one-cause theories to multi-factorial processes that reflect the confluence of many types of risk factors; including genetic, neurochemical, environmental and psychosocial factors[22].

It is suggest that decreased central BDNF activity, particularly in the midbrain region, may be implicated in the pathogenesis of ADHD. Several lines of evidence led to the formulation of this hypothesis. From the above findings it is likely that the elevation in central BDNF activity is important to the treatment of ADHD. This notion is also supported by the studies of zinc in ADHD. Numerous controlled studies have demonstrated reduced blood zinc levels in children with ADHD, compared to normal controls. Some studies have suggested that zinc monotherapy or zinc supplementation can yield significant benefits for patients with ADHD. Zinc treatment is known to induce cortical BDNF gene expression and activate TrkB signaling[20].

This hypothesis generates various clinical and therapeutic implications for ADHD. Molecular genetic studies show that ADHD is a common disorder, with significant multi-factorial genetic contributions[22].

BDNF exerts its influence on the brain chiefly through TrkB (tropmyosin related kinase B) receptors. Thus, any genetic factors that down-regulate the BDNF-TrkB signaling pathway may contribute to the pathogenesis of ADHD. Candidates for genetic studies (e.g., mutation analysis, micro-assay, or genetic association studies) relating to ADHD should therefore include genes that are related to the BDNF-TrkB signaling pathway[22].

Since decreased central BDNF activity may be implicated in the pathogenesis of ADHD, agents that can enhance central BDNF activity could be of potential use as treatments in ADHD. For example, cysteamine-related agents are known to elevate central BDNF levels in animals[24].

The decreased central BDNF hypothesis may complement the pre-existing ‘‘catecholamine hypothesis’’ of ADHD. This hypothesis may help to improve our understanding underpinning some clinical findings of ADHD, and provide new treatment strategies for this disorder[20].

CONCLUSION

Plasma level is decreased in inattentive type of ADHD, and may be drugs acting on enhancement of BDNF activity will help in improvement of ADHD not on symptomatic bases, but on neuro-developmental level.

LIMITATION OF THE STUDY

Different ranges of plasma BDNF of levels have previously been reported in healthy subjects, and these differences are most likely due to different assay methods used, such as the R&D ELISA kit or the Promega BDNF kit. Recently, Karege et al. showed that the stability of BDNF levels measured in whole blood, serum, and plasma varied among different laboratories (24). Different ELISA methods or different types of sampling tubes might lead to differences in measured BDNF levels. Another limitation of this study was that it did not consider the influence of physical activity on BDNF levels in ADHD patients and normal controls.

RECOMMENDATIONS

Further studies are required to elucidate the source and role of circulating BDNF in ADHD. Future studies are needed to establish the most reliable, accurate method for measurement of BDNF and to determine which source of BDNF platelets, plasma, serum, or whole blood provides the most reliable biological marker of ADHD.

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