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Research Article

Examination of the Neuroplastic Biomarker Levels in Attention Deficit Hyperactivity Disorder

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Abstract

Background and Objective: Attention Deficit Hyperactivity Disorder (ADHD) possesses lots of dysfunctions in biochemical component of brain. Some researchers proposed that examination of glial function require in ADHD. In this study, it is aimed to determine the serum levels of Glial Fibrillar Acidic Protein (GFAP) and Nogo-A which were not investigated previously in children with ADHD. **Methodology:** Twenty eight children, aged 6-10, diagnosed with attention deficit hyperactivity disorder according to DSM-IV criteria and 28 healthy children matching in age and gender were included in the study. Children were assessed via Kiddie-Sads-Present and Lifetime Version, Turgay DSM-IV based child and adolescent behavior disorders screening and rating scale and Stroop test. Serum GFAP and Nogo-A levels were determined by enzyme-linked immunosorbent assay. **Results:** The GFAP and Nogo-A serum levels of children with ADHD were found to be significantly higher than those of controls. Moreover, serum Nogo-A levels showed a significantly positive correlation with Stroop interference in children with ADHD. **Conclusion:** These findings may provide evidence for neuroplasticity, microglial and astroglial changes in children with ADHD. It is recommended that investigation of cerebrospinal fluid and brain levels of GFAP and Nogo-A may contribute to the clarification of the pathophysiology of ADHD.

Key words: ADHD, GFAP, Nogo-A, biomarker, neuroplasticity, stroop test, microglia, astroglial changes

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The pathophysiology of the Attention Deficit Hyperactivity Disorder (ADHD) remains unresolved due to complex interaction of genetic, environmental and neurophysiological factors¹. It was proposed that pathophysiology and neurobehavioural deficits of ADHD are in close connection with microstructural abnormalities of the brain white matter²⁻⁴, apoptotic neurodegeneration⁵, cytokine-related neurotrophin reflecting glial integrity (S100B)⁶, neurotrophic growth factor systems encapsulating brain-derived neurotrophic factor⁷ and microglial activation^{8,9}. It is also offered that markers of glial function and neurodegeneration ought to be studied in patients with ADHD^{5,6}. Yet, many molecules such as glial fibrillary acidic protein and Nogo-A, which are associated with glial cell function or involved in neurodegeneration are not looked into sufficiently in the clientele suffering from ADHD.

Myelin is an important constituent of white matter and reductions in volumes of white matter have been reported in ADHD^{10,11}. Myelin contains several proteins such as Nogo-A, which inhibits nerve fiber growth¹²⁻¹⁵. Nogo-A is originally displayed in the central nervous system of adults and it is primarily explained by oligodendrocytes and myelin and by sub-populations of neurons¹³⁻¹⁶. That Nogo-A is at the same time present in neurons¹⁵ has aroused curiosity in its relevance in producing common attitude, too. If truth be told, in a prevalent analysis, the rats with deficient of Nogo-A displayed several behavioral deficits, for instance impairments in short-term memory, reduced pre-pulse inhibition of the acoustic frighten reaction and behavioral inflexibility. Similar to Nogo-A deficient rats, some researchers were able to pointed out behavioral changes in Nogo-A knockout mice^{17,18}. Moreover, some uttered social attitude changes were found¹⁹.

Many neural models for the pathophysiology of ADHD have been based on the prefrontal cortex and its interconnections with the subcortical structures and striatum²⁰. It is estimated that astroglial (astrocytes) cells are the most abundant cell types in brain and they are indispensable for proper brain development, which have very crucial roles in preservation ion, water, energy homeostasis, modulate neuronal signaling and neurotransmitter²¹⁻²³. It was expressed that astrocytes are characterized by the presence of a unique structural protein, Glial Fibrillar Acidic Protein (GFAP)²⁴. In astrocytes, one of three important kinds of central nervous system neuroglia²⁵, GFAP immunoreactivity is adjusted via activation of adrenergic and serotonergic receptors²⁶ that are taken into consideration to act a significant role in the pathophysiology of mood disorders including ADHD²⁷⁻²⁹.

Taking into account the literature briefly, we can claim that the two molecules appear to be associated with ADHD. In this connection, we assume that ADHD may be affected by neuroplastic changes, glial cell function, serum GFAP and Nogo-A levels may change in ADHD and it is probable these molecules be utilized to comprehend the pathological operating principles of ADHD disorder.

MATERIALS AND METHODS

Study design, participants and diagnostic assessment:

Scientific Research Projects Unit of Batman University has supported the study in question. On 27 February, 2015, the research protocol was affirmed by Batman University Ethics Committee of Medical Ethics with decision number of 167. The investigation was performed in line with the Helsinki Convention principles on Human Rights and decent clinical application.

Prior to treatment, the study group consisting of 28 children aged 6-10, diagnosed with ADHD as to 4th edition criteria of Mental Disorders Diagnostic and Statistical Manual (DSM-IV-TR, 2000) stood ready at Dicle University Child Psychiatry Department in Diyarbakır, Turkey. The children with ADHD, suffering from oppositional disorder and behavioural disorder were also accepted to the investigation. Twenty eight children, who did not have any psychiatric disorders and medical illnesses matched for age and gender were selected as healthy control group. Children's parents filled up a consent form and a questionnaire asking about demographic information.

Kiddie-Sads-Present and Lifetime Version (K-SADS-PL) were administered by interviewing the parents of the children and finally achieving summary ratings including all sources of information. The test, created by Gokler *et al.*³⁰ was transcribed for children and adolescents living in Turkey.

The K-SADS-PL is a semi-structured diagnostic interview designed to assess present and previous stages of psychopathology in children and adolescents in line with DSM-III-R and DSM-IV criteria³¹.

Turgay DSM-IV based child and adolescent behavior disorders screening and rating scale (T-DSM-IV-S) was singly utilized after K-SADS-PL. This scale was developed by Turgay according to DSM-IV criteria, consisting of 41 items. It is an individually administered test including 9 items (questioning the lack of attention), 6 items (questioning of hyperactivity), 3 items (questioning the impulsivity), 8 items (questioning the oppositional defiant disorder), 15 items (questioning the behavioral disorders)³².

Stroop test, which reflects the frontal area of operations, was administered after T-DSM-IV-S. In the Stroop test,

processing speed and resistance to interference were gauged by requesting the subject to focus his/her attention meticulously on the task-related stimulus, react to this stimulus and inhibit a racing automatic response³³. The timing, mistake numbers and the proofs were evaluated. Children diagnosed with psychiatric and neurological disorders such as mental retardation, history of seizures, history of encephalitis, pervasive developmental disorder, chronic systemic disease, pervasive improvement disorder and intelligence scores lower than about 70 were not included into the survey³⁴.

Biochemical measurements: The followings are some the requirements of the steps to take prior to performing of specimen collection. Blood samples were taken into a vacutainer without anticoagulant between 08:00 and 11:00 am. They were routinely centrifuged at the speed of 2000-3000 rpm for 20 min after clotting for 30 min. Hence, blood cells and all great particles in blood samples were precipitated. Then, both hemolyzed and lipemic blood samples were taken out. Yellow and clear serum samples were picked up for the investigation. The aliquots of serum samples were preserved at -70°C for computation of GFAP and Nogo-A concentrations.

Afterwards, aliquots of serum samples were stored at -70°C. Serum level measurements of GFAP and Nogo-A were determined with enzyme linked immunosorbent assay (ELISA) method (SHANGHAI Yehua Biological Technology; catalog number is YHB1327Hu for GFAP, catalog number is THB0304Hu for Nogo-A) in accordance with the producer's instructions. These kits use a double-antibody sandwich ELISA to assay the level of GFAP and Nogo-A in samples. Briefly, samples were put into wells, pre-coated with monoclonal antibody and incubated; later, antibodies tagged with biotin were added and joined with streptavidin-HRP to create immune complex; after this incubation and washing were performed. Afterwards, chromogen solutions were put on them and under the influence of stop solution, the color eventually changed into yellow. The Optical Density (OD) of each well was computed under 450 nm wave-lengths within 10 min just after having added stop solution. As to standard concentrations and matching OD values, the linear regression equation of the standard curve was computed and as a result, we found out GFAP and Nogo-A concentration of samples. Assay ranges were 5-2000 pg mL⁻¹ for GFAP and 1-300 pg mL⁻¹ for Nogo-A.

Statistical analysis: Statistical analyses were conducted making use of statistics programs with IBM SPSS Statistics 22.0 package program (IBM Corp., Armonk, New York, USA). The

commonness of the data was evaluated through the Shapiro Wilk normality test and Q-Q graphs. Data were stated in numbers for categorical variables and Mean±SD or median (25-75th percentile) for perpetual variables. Age, GFAP and Nogo-A matchings between groups were conducted by utilizing the Mann-Whitney U test. Gender comparison was carried out with the exact method of the chi-square test.

RESULTS

Behavior disorders screening and rating scale results of children with ADHD were shown in Table 1. Interference effects of ADHD, obtained by applying the Stroop test were 23.85±9.70. The average focusing score of participants with ADHD as to parents was 17.6±4.4 points and as to teachers 16.5±5.1 points. The average hyperactivity-impulsivity score of children with ADHD as to parents was found to be 12.6±8.7 points and as to teachers 13.5±5.6 points. The average opposition defiance score of children with ADHD as to parents was 9.5±7.5 points and as to teachers 10.1±7.3 points (Table 1).

Our study included 28 children with ADHD (14 female and 14 male) and 28 controls (13 female and 15 male). The average age of the controls was 8.34±1.48 and mean age of children with ADHD was 8.92±2.22 ($p = 0.371$, Table 2).

The GFAP levels (median = 629.0 and min-max = 371.5-1724.0 pg mL⁻¹) of children with ADHD were determined to be significantly higher than those (median = 428.50 and min-max = 175.0-708.5 pg mL⁻¹) of controls ($p < 0.001$, Fig. 1, Table 2).

The Nogo-A levels (median = 64.0 and min-max = 13.5-120 pg mL⁻¹) of children with ADHD were computed to be significantly higher than those (median = 47.5 and min-max = 10.5-71.4 pg mL⁻¹) of controls ($p = 0.041$, Fig. 2, Table 2). The GFAP and Nogo-A concentration did not show any statistical difference according to age and gender in study groups ($p > 0.05$).

Serum Nogo-A levels displayed a significantly positive correlation with interference effects of Stroop test in children with ADHD (Fig. 3) once correlation analyses were conducted.

Table 1: T-DSM-IV-S and Stroop test scores of ADHD children

Parameters	Children with ADHD (n = 28)	
Interference effect	23.85±9.70	
	According to parents	According to teachers
Attention	17.6±4.4	16.5±5.1
Hyperactivity-impulsivity	12.6±8.7	13.5±5.6
Opposition defiance	9.5±7.5	10.1±7.3

T-DSM-IV-S: Turgay DSM-IV based child and adolescent behavior disorders screening and rating scale. Data are stated as Mean±SD for perpetual variables

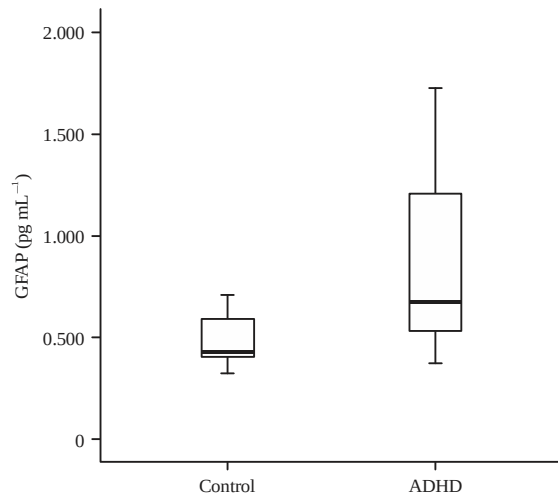


Fig. 1: Tukey box plots illustrating the results of the categorical comparison between control and patients in terms of serum GFAP levels

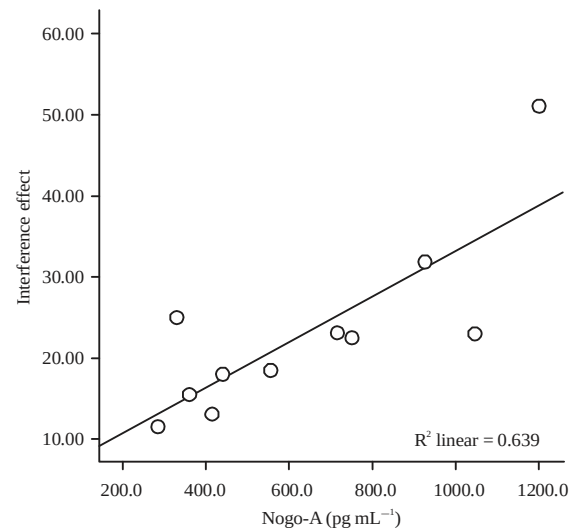


Fig. 3: Correlation between Nogo-A and interference effect in children with ADHD

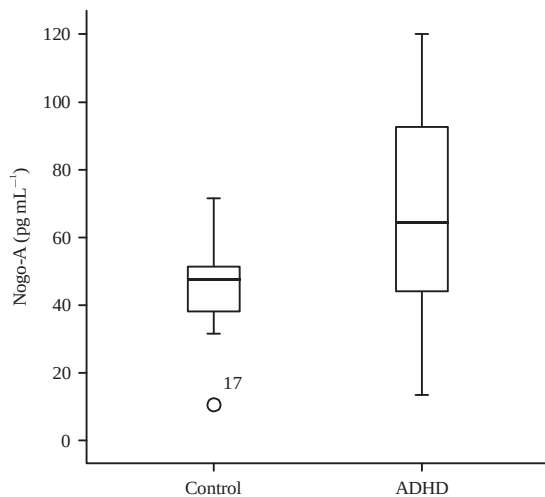


Fig. 2: Tukey box plots illustrating the results of the categorical comparison between control and patients in terms of serum Nogo-A levels

Table 2: Main characteristics and biochemical results of study groups

Parameters	Control (n=28)	ADHD (n=28)	p-value
Gender (F/M)	13/15	14/14	p = 0.891
Age (years)	8.34 ± 1.48	8.92 ± 2.22	p = 0.371
GFAP (pg mL ⁻¹)	428.50 (175.0-708.5)	629.0 (371.5-1724.0)	p < 0.001
Nogo-A (pg mL ⁻¹)	47.5 (9.85-71.4)	64.0 (13.5-120)	p = 0.041

Data are stated as No. for categorical variables and Mean ± SD or median (25-75th percentile) for perpetual variables. F: Female, M: Male

On the other hand, there were not any other significantly correlations between clinical and molecular parameters.

DISCUSSION

To our knowledge, this is the first study to assess serum levels of GFAP and Nogo-A in children with ADHD. The results indicate that GFAP and Nogo-A serum levels of children with ADHD were found to be significantly higher than those of controls.

It has been demonstrated that maintained microglial activation can have significant contribution to axon loss and loss of connectivity. Histopathologic studies of after death in mood disorders have uncovered substantial morphologic changes in glial cells in various parts of the prefrontal cortex^{35,36}. On the other hand, attention deficit hyperactivity disorder has been attributed to dysfunction of dopamine transporter in the prefrontal cortex^{37,38}. In respect to that point, there have been evidences to suggest microglial activation in ADHD^{8,9}. Therefore, we investigated the hypothesis that there might be differences in serum GFAP levels. These results show that indeed it is the case. It is found that the GFAP levels significantly higher in children with ADHD than those of controls.

Shim *et al.*⁷ showed that the median plasma glial cell line-derived neurotrophic factor levels in patients with ADHD were significantly higher than those of healthy controls. It is also found that plasma glial cell line-derived neurotrophic factor levels had a significantly positive correlation with inattention, hyperactivity-impulsivity and K-ARS total scores in patients with ADHD. Oades *et al.*⁶ hypothesized that changed serum levels of S100B, a putative biomarker of the

integrity of glial function, could mirror dysfunction and an impaired energy supply for neuronal activity in ADHD. It is found that S100B levels tended to be lower in ADHD. Oades *et al.*⁶ also suggested that other markers of glial function require examination in patients with ADHD. Both S100B and GFAP have been used as markers of astroglial plasticity, particularly in brain injury³⁹. Contrary to findings of the Oades *et al.*⁶, it is found that the GFAP levels significantly higher in ADHD children than those of controls. Although S100B and GFAP have been used as markers of astroglial plasticity, it has already been stated that they do not necessarily change at the same time, frame or direction³⁹.

Importantly, as GFAP is the crucial element liable for the assembly and extension of the intermediate filament inside the astrocytic processes, it is credited that GFAP induction is seriously significant for the constitution of the elaborated and thickened astrocytic processes seen in responding gliosis. It was showed that astroglial activation leads to the rapid synthesis of GFAP²². Thus, it may be suggested that microglial and astroglial activation lead to increased GFAP levels in ADHD group.

Numerous different inhibitors of axonal growth have been defined in myelin, including Nogo-A⁴⁰, myelin-related glycoprotein⁴¹ and oligodendrocyte myelin glycoprotein⁴². Additionally, the failure of axonal regeneration could at the same time emerge from the existence of a glial scar, which hinders neuronal regrowth. The GFAP, particularly stated in astrocytes, creates the basic element of the glial scar^{43,44}. Myelin is an important constituent of white matter and reductions in white matter volume have been reported in ADHD^{10,11}.

Increased GFAP and Nogo-A expressions have been reported in experimental injury in the peripheral nervous system and central nervous system in rodents⁴⁵⁻⁴⁷. Moreover, Liu *et al.*⁴⁸ showed that progesterone promotes neuroprotection following traumatic brain injury by inhibiting the expression of Nogo-A and GFAP. These data may suggest that GFAP and Nogo-A acted together or there is a potential synergism between GFAP and Nogo-A molecules. Therefore, it has been considered appropriate to examine both the GFAP and Nogo-A in children with ADHD. In accordance with previous studies with different patient groups, this study showed the increased levels of Nogo-A likewise GFAP in children with ADHD. The rats displaying lack of Nogo-A demonstrate behavioral abnormalities, for instance lowered pre-pulse inhibition of the acoustic fear reaction, behavioral inflexibility, short-term memory disturbances and deterioration in management of reference frames^{17,49,50}. Considering these aspects, it may be suggested that changes of serum Nogo-A levels in ADHD provide evidence of

relationship between Nogo-A and behavior abnormalities in children with ADHD. This suggestion is also supported with our other findings. Because, perhaps, one of the most important findings of our study is that there has been significantly positive correlation between serum Nogo-A levels and interference effects with Stroop Test in children with ADHD.

Stroop interference revealed a various hemodynamic reactions in the right dorsolateral prefrontal cortex in ADHD^{51,52}. Moser *et al.*⁵³, in their investigation, with sole photon emission, computerized tomography demonstrating an alleviation in regional cerebral blood flux during relaxation in the dorsolateral prefrontal cortex of participants with ADHD in relation with efficiency in Stroop task carried out separately. Most interestingly, Enkel *et al.*¹⁹ developed the behavioral profile of the Nogo-A deficient rat line in terms of prize sensitiveness and motivation and detected the concentrations of the monoamines dopamine and serotonin in the prefrontal cortex, dorsal striatum and nucleus accumbens. Permanent ADHD was featured by a subtle slenderizing of the medial prefrontal cortex, showing a role of the prefrontal cortex in the amelioration of ADHD symptoms^{54,55}. Considering the literature knowledge, it may be that prefrontal cortex is associated with both Nogo-A and Stroop interference. This knowledge may indicate a relationship between Nogo-A levels and Stroop interference effect in ADHD. Increased Nogo-A levels of children with ADHD indicate that it may be induced before the neuroplasticity process and the subsequent sprouting becomes manifest.

Finally, we desire to argue about the restrictions of this study. One may criticize that only serum GFAP and Nogo-A was gauged in this study while cerebrospinal fluid sample was absent. Secondly, we did not examine molecules in cellular level. On the other hand, there is a possibility that there may be peripheral sources of GFAP and Nogo-A that could be responsible for GFAP and Nogo-A existing in circulating cells; for instance, platelets and immune cells. Nonetheless, blood cells and all grand particles in blood samples were precipitated. Yellow and clear serum samples were picked up for the study in question. Both hemolyzed and lipemic blood samples were taken out. As a result, we consider that measured levels of GFAP and Nogo-A molecules can not be derived from the erythrocytes, platelets and immune cells. Lastly, the reduced sample size may have been limited to generalize these finding.

CONCLUSION

In conclusion, it may be suggested that the increase in GFAP levels may be the mirror of dysfunction or microglial and

astroglial changes in ADHD. Increased Nogo-A levels and their positive correlation with interference effect may indicate increased neuroplasticity process in children with ADHD. However, the lack of knowledge about GFAP and Nogo-A levels in cerebrospinal fluid remains unclear and deserves further investigation. It would be good to include more molecules to play a role in neuroplasticity and greater number clinical variables.

SIGNIFICANCE STATEMENTS

- Some researchers previously suggested that microglial activation is associated with pathophysiology and neurobehavioural deficits of ADHD
- Some researchers previously demonstrated behavioral alterations in Nogo-A knockout mice
- In this study, the serum GFAP levels of children with ADHD were found to be significantly higher than those of controls
- In this study, the serum Nogo-A levels of children with ADHD were found to be significantly higher than those of controls
- In this study, serum Nogo-A levels showed a significantly positive correlation with interference effects of Stroop test in children with ADHD

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