

HOMOCYSTEINE, PYRIDOXINE, FOLATE AND VITAMIN B12 LEVELS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER

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SUMMARY

Background: In our study, we aimed to evaluate the serum homocysteine levels, pyridoxine, folate and vitamin B12 levels in children with attention deficit hyperactivity disorders (ADHD).

Subjects and methods: This study included 30 newly diagnosed drug-naïve children with ADHD (23 males and 7 female, mean age 9.3±1.8 years) and 30 sex- and age-matched healthy controls. The diagnosis of ADHD was made according to DSM-V criteria. Children and adolescents were administered the Schedule for Affective Disorders and Schizophrenia for School Aged Children, Present and Lifetime Version, the Conners' Parent Rating Scale-Revised, Long Form, the Conners' Teacher Rating Scale and the Wechsler Intelligence Scale for Children Revised (WISC-R) for all participants. Homocysteine, pyridoxine, folate and vitamin B12 levels were measured with enzyme-linked immunosorbent assay.

Results: Homocysteine, pyridoxine, folate and vitamin B12 levels were significantly lower in children with ADHD compared with their controls ($p < 0.05$). A positive significant correlation was observed between the all WISC-R scores and vitamin B12 level in patients ($r = 0.408$, $p = 0.025$).

Conclusions: The results obtained in this study showed that reduced homocysteine, pyridoxine, folate and vitamin B12 levels could be a risk factor in the etiology of ADHD.

Key words: homocysteine – pyridoxine – folate - vitamin B12 - attention deficit hyperactivity disorders - children

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INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a widespread childhood neurobehavioural disorder, characterised by symptoms of inattention, impulsivity and hyperactivity, which can affect the academic, social and emotional life of a child in many aspects. ADHD has a pooled prevalence rate of 7.2% in the child and adolescent population (Association 2013, Hodgkins et al. 2013, Thomas et al. 2015). The etiology of ADHD is complex and not yet fully understood but the findings support the hypotheses that it is multifactorial. Neurochemical, neuroanatomic, genetic and environmental factors are thought to play a role in the etiology (Sciberras et al. 2017, Swanson et al. 2007).

Homocysteine is an essential amino acid produced during the metabolism of methionine, which has several important roles in human physiology. Homocysteine metabolism is associated with pyridoxine, folate and vitamin B12 levels (Brosnan et al. 2004). Under normal conditions, there is a strict balance between homocysteine production and metabolism. Homocysteine in the body, is metabolised using either the trans-sulfuration pathways which requires pyridoxine as a cofactor, or the remethylation pathways which requires folate and Vita-

min B12 together as a cofactor. Pyridoxine, folate and vitamin B12 deficiencies, and mutations in genes coding for methylenetetrahydrofolate reductase (MTHFR), cystathionine β -synthase (CBS) and methionine synthase enzymes cause homocysteine metabolic disorders and an increase in homocysteine in human tissues, known as hyperhomocysteinemia (Kałużna-Czaplińska et al. 2013, Malinowska et al. 2012, Perła-Kaján et al. 2007). Some studies have shown a relationship between folate, vitamin B12 and homocysteine and various psychiatric diseases such as cognitive disorders, neurodegenerative diseases, autism spectrum disorder, schizophrenia, affective disorder and depression (Bottiglieri et al. 2000, Ezzaher et al. 2011, Kale et al. 2010, Kałużna-Czaplińska et al. 2011, Kim & Lee 2014, Mikkelsen et al. 2016, Stanger et al. 2009).

These observations can be explained by the important role of pyridoxine, folate, vitamin B12, and homocysteine in the carbon transfer metabolism that is necessary for the production of serotonin, other monoamine neurotransmitters and catecholamines (Bottiglieri 1996). Previous studies have shown that through various molecular mechanisms, hyperhomocysteinemia is toxic for the brain (Beard et al. 2011, Ho et al. 2002, Kruman et al. 2000). However, these mechanisms are still a matter of debate.

To the best of our knowledge, there has been no study which has shown a potential relationship between serum homocysteine, pyridoxine, folate and vitamin B12 levels and ADHD in children. In a previous study, homocysteine and oxidative stress were evaluated in adult ADHD patients and it was reported that compared to the control group, homocysteine levels were low, the folate level was high and Vitamin B12 level was normal in the adult ADHD patients (Karababa et al. 2017).

The aim of the current study was to evaluate whether or not there was a relationship between homocysteine, pyridoxine, folate and vitamin B12 levels and ADHD in children.

SUBJECTS AND METHODS

Participants

The study included 30 newly diagnosed drug-naive children with ADHD aged 6-15 years and a control group of 30 age and gender-matched healthy children. The ADHD diagnosis of the patients was made according to the DSM-V criteria. The Turkish version of the Schedule for Affective Disorders and Schizophrenia for School Aged Children, Present and Lifetime Version (K-SADS-PL) was applied to all the children by one of the researchers. The K-SADS-PL is a semi-structured interview form which is used to determine present and lifetime psychopathologies in children and adolescents (Kaufman et al. 1997). The K-SADS-PL was applied taking into account the DSM-IV diagnostic criteria. Validity and reliability studies of the scale have been conducted for a Turkish population (Gökler et al. 2004). The parents of the children completed the Conners' Parent Rating Scale-Revised, Long Form and teachers completed the Conners Teacher Rating Scale. The validity of these forms was tested by Dereboy et al. (2006). Parents and teachers also completed the Turgay DSM-IV-based Child and Adolescent Behavior Disorders Screening and Rating Scale. The reliability and validity testing of the scale was made by Ercan et al. (2001). The Wechsler Intelligence Scale for Children-Revised (WISC-R) was used for evaluation of the IQ of patients. Exclusion criteria were any concomitant psychiatric disease, chronic metabolic, endocrine, gastroenterological or neurological disease, malnutrition and obesity, the presence of infection, those taking vitamin or mineral support, any medication such as steroids or anti-epileptic drugs, or those with any substance addiction.

The control group was formed of the children of healthcare personnel at the hospital where the study was conducted or of patients presenting at the hospital for routine health examinations. The families were given information about the study and children who were willing to participate and were age and gender-matched to the study group were included. A psychiatric examination was made of the control group subjects and the K-SADS-PL, the Conners' Parent Rating Scale-Revised, Long Form and teachers completed the Conners Teacher

Rating Scale, the Turgay DSM-IV-based Child and Adolescent Behavior Disorders Screening and Rating Scale and WISC-R were administered. Children were excluded from the control group if they had any psychiatric disorders, chronic medical disease, malnutrition and obesity, were taking any medication, vitamin-mineral support or substances, or if any emotional disorder diagnosis was made with the semi-structured diagnosis interview. The study was approved by the scientific research ethical committee of Sutcu Imam University, Medical Faculty, Kahramanmaraş (no:12, dated 19/10/2015), Turkey and a detailed signed informed consent was obtained from the parent of each child included in the study.

Biochemical parameter measurement

Blood sampling

Blood samples were taken from the study participants between 08.00 and 11.00. After separation from the serum, the samples were stored at -20°C in the Biochemistry Dept until analysis. In our study, the serum levels of homocysteine, pyridoxine, folate and vitamin B 12 were measured by a quantitative sandwich enzyme immunoassay technique (ELISA) using a commercial kit (AX51301 IBL International, Hamburg, Germany, CEA916Ge Cloud-Clone Corp., Houston, USA, CEA610Ge Cloud-Clone Corp., Houston, USA, CEA924Ge Cloud-Clone Corp., Houston, USA, respectively) according to the manufacturer's instructions.

Statistical Analysis

Data obtained in the study were analysed with Windows SPSS 22 software. The study data were summarised using descriptive statistics (number, percentage). The patient and control groups were compared using the chi-square test for categorical variables and the Student's t-test for continuous data. Correlations between the clinical variables were analysed with the Pearson's correlation test. A value of $p < 0.05$ was accepted as statistically significant.

RESULTS

The study group of children with ADHD comprised 23 males and 7 females with a mean age of 9.33 ± 1.8 . The control group comprised 21 males and 9 females with a mean age of 9.46 ± 1.87 years (range, 6-15 years). No statistically significant difference was determined between the groups in respect of age, gender, all WISC-R scores ($p > 0.05$ for all). (Table 1).

The mean serum homocysteine level of the ADHD patients was found to be statistically significantly lower compared to that of the control group (5.29 ± 0.73 and 6.54 ± 2.17 ($\mu\text{mol/L}$) (mean \pm sd), respectively $p = 0.004$). The levels of pyridoxine, folate and vitamin B12 were determined to be statistically significantly lower in the ADHD group compared to the levels of the control group

Table 1. Characteristics of patients and healthy controls

	ADHD (n=30)	Controls (n=30)	p
Gender (male/female)	23/7	21/9	0.559
Age, years, (mean±sd)	9.33±1.84	9.46±1.87	0.782
WISC-R scores			
Verbal	100.03±6.24	101.36±8.23	0.483
Performance	99.66±6.81	103.66±9.39	0.079
Total	99.93±5.94	102.20±7.52	0.201

ADHD - Attention deficit hyperactivity disorder; sd - standard deviation; WISC-R - Wechsler intelligence scale for children-revised; statistically significant at p<0.05

Table 2. Laboratory results of patients and healthy controls

	ADHD (n=30) mean±sd	Controls (n=30) mean±sd	p
Homocysteine (µmol/ L)	5.29±0.73*	6.54±2.17	0.004
Piridoxine (ng/mL)	45.41±5.64*	53.87±8.50	<0.001
Folate (pg/mL)	158.90±20.22*	169.13±16.98	0.038
Vitamin B12 (pg/mL)	259.75±44.40*	388.64±73.11	<0.001

ADHD - Attention deficit hyperactivity disorder; sd - standard deviation; statistically significant at p<0.05;

* Lower than those of controls

Table 3. Correlations of homocysteine, piridoxine, folate and vitamin B12 results with age and WISC-R scores of ADHD patients

	Homocysteine	Piridoxine	Folate	Vitamin B12
Age				
r	-0.237	0.017	0.005	-0.145
p	0.208	0.929	0.981	0.446
WISC-R Verbal				
r	0.259	-0.017	-0.008	0.409*
p	0.167	0.931	0.968	0.025
WISC-R Performance				
r	0.015	0.214	0.056	0.396*
p	0.936	0.257	0.767	0.030
WISC-R Total				
r	0.124	0.126	-0.007	0.408*
P	0.514	0.505	0.969	0.025

Pearson correlations, ADHD - Attention deficit hyperactivity disorder; WISC- R, Wechsler intelligence scale for children-revised

(45.41±5.64 (ng/mL) vs 53.87±8.50 (ng/mL), (p<0.001); 158.90±20.22 (pg/mL) vs 169.13±16.98 (pg/mL), (p=0.038); 259.75±44.40 (pg/mL) vs 388.64±73.11 (pg/mL) (mean±sd), (p<0.001), respectively) (Table 2).

According to the Pearson Correlation analysis, a positive correlation was determined between the all WISC-R scores and vitamin B12 in ADHD patients. No correlation was determined between age and homocysteine, pyridoxine, folate, Vitamin B12 levels in children with ADHD (Table 3). No correlation was also determined between the points of the Connors Parent and Connors Teacher Rating Scale and homocysteine, pyridoxine, folate and Vitamin B12 levels in ADHD (p>0.05 for all).

DISCUSSION

In this study, the serum homocysteine level of ADHD children was found to be statistically significantly lower than that of the control group. To the best

of our knowledge, this is the first study to have evaluated the relationship between the serum homocysteine level and ADHD in children.

Although the mechanism of homocysteine in the development of psychiatric disease is not fully known, it is thought that a high homocysteine concentration causes excitotoxicity by activating N-methyl-D-aspartate receptors and increases oxidative stress, thereby causing psychiatric diseases (Beard et al. 2011, Ho et al. 2002, Kruman et al. 2000). Previous studies have reported that a high homocysteine level has a role in several neurodegenerative diseases, cognitive disorders and psychiatric diseases (Bottiglieri et al. 2000, Kałużna-Czaplińska et al. 2011, Kim & Lee 2014, Mattson & Shea 2003, Stanger et al. 2009). Although studies have reported a high level of homocysteine in schizophrenia, there are also studies that do not support this finding (Kale et al. 2010, Miodownik et al. 2007, Muntjewerff et al. 2003). Karababa et al. evaluated homocysteine levels in adult

ADHD patients and it was reported that compared to the control group, homocysteine levels were low, the folate level was high and vitamin B12 level was normal in the ADHD patients (Karababa et al. 2017). Similarly in the current study, the homocysteine level was seen to be low in children with ADHD. Although a high homocysteine level is thought to be related to several diseases, a low homocysteine level has been reported to create a risk for some diseases. For example, a strong relationship has been shown between low homocysteine and peripheral neuropathy (Cullen et al. 2012). Moreover, a low homocysteine level could be an indicator of excessive transformation to cystatin in the trans-sulfuration pathways for glutathione, taurin and sulphate production. For example, in individuals with Down's syndrome, as there is greater transformation of homocysteine to cysteine associated with excessive activation in the CBS enzyme which functions in the tran-sulphuration pathway, the serum homocysteine level has been reported to be low (Gane & Bhat 2014). Homocysteine is thought to be a storage molecule for sulphur and a transfer molecule for methyl metabolism. As homocysteine is a normal mediating substance for the transformation of methionine to cysteine and thereby has a role in glutathione, taurin and sulphate production, hypohomocysteine creates a risk for the body because hypohomocysteine causes a reduction in cysteine. Reduced cysteine limits the production of sulphate, taurin and glutathione (necessary for the glutathione mechanism which is an important antioxidant system of the body). Individuals with low homocysteine have a limited capacity to respond to oxidative stress and exposure to certain toxins (Vitvitsky et al. 2003). It was shown that a reduction in glutathione is related to diseases that affect almost all large organ systems (Lang et al. 2000, Lord & Fitzgerald 2006). In addition, any condition which increases oxidative stress in body has the tendency to increase the demand for hepatic glutathione production. Thus, oxidative stress leads to homocysteine glutathione synthesis causing a fall in plasma homocysteine levels which are critical for the potential total body glutathione status. This means that a low homocysteine level could restrict the amount of glutathione which could be produced as a response to oxidative stress (Pizzorno 2014). Therefore, low levels of homocysteine levels caused by increases oxidative stress can be important in the etiology of children with ADHD. In line with this finding, although a high homocysteine level has been reported to be a risk factor in neurodegenerative diseases and psychiatric diseases such as schizophrenia, ASD, it is also thought that a low homocysteine level could be a risk factor for ADHD. However, the mechanism of this is not clear. As this is the first study to have shown a reduced homocysteine level in children with ADHD, there is a need for further studies to support this finding.

In this study, the pyridoxine, folate and Vitamin B12 levels of the ADHD group were found to be low compared to those of the control group. Optimal develop-

ment and functioning of the immature central nervous system (CNS) is dependent on a sufficient amount of pyridoxine (Bowling 2011, Georgieff et al. 2015). Maternal pyridoxine deficiency can cause motor and behavioural abnormalities such as hyperactivity, seizures, ataxia and neuropsychiatric disorders (Guilarte et al. 1991). The primary symptoms of pyridoxine deficiency are neurological such as depression, reduced cognition, dementia and autonomic dysfunction (Stover & Field 2015, Dakshinamurti & Dakshinamurti 2013). Furthermore, it is necessary for the synthesis and metabolism of neurotransmitters such as glutamate, noradrenalin, serotonin, gamma-aminobutyric acid (GABA) and dopamine in the CNS (Bowling 2011, Stover & Field 2015, Dakshinamurti & Dakshinamurti 2013). Therefore, because of the biochemical disorders (catecholamine and serotonin deficiency, glutamate/GABA imbalance and excessive plasma tryptophan) that emerge in ADHD, it has been reported that it could be a disease related to pyridoxine (Dolina et al. 2014). In addition, decreased methylation of dopamine receptors and membrane phospholipids could contribute to attention deficit disorder (Kuznetsova & Deth 2008). In the current study, the low pyridoxine level in the ADHD group suggests that there could be an effect in the formation of ADHD through the effect on neurotransmitters.

Folate have a role in important biochemical events such as primarily purine and pyrimidine and the metabolism of homocysteine and methionine amino acids. They also affect neural stem cell proliferation and differentiation, reduce apoptosis, and alter DNA biosynthesis. Therefore, folate is an essential substance in tissues in which DNA construction and destruction is rapid, such as in embryo development, gastrointestinal tract mucosa and hematopoietic tissues (Bailey 2007, Mattson & Shea 2003, Miller 2008). In addition, the effective functioning of the folate cycle is necessary for the synthesis and regeneration of tetrahydrobiopterin which is a cofactor necessary for enzymes that transforming amino acids to nitric oxide and monamine neurotransmitters (serotonin, melatonin, dopamine, noradrenalin, adrenalin) (Kennedy 2016). Previous studies have reported that folate deficiency has a role in the etiology of neurodegenerative diseases such as Alzheimer's and Parkinson's disease as it causes an increase in the homocysteine level (Mattson & Shea 2003). Studies conducted on the relationship between ADHD and folate and folate metabolism have focussed on symptoms of folate deficiency in the antenatal period which will be observed in childhood (Julvez et al. 2009, Schlotz et al. 2010). Developmental delays, cognitive impairment and reduced memory function have been shown to be related to cerebral folate deficiency of abnormal folate transfer to the fetal CNS (Mattson & Shea 2003, Moretti et al. 2008, Schlotz et al. 2010), and better cognitive performance (de Lau et al. 2007) has been related to higher plasma folate. Maternal folate deficiency in the gestational period has been related to hyperactivity in childhood (Schlotz et al. 2010). There

are very few studies that have examined the relationship between folate and ADHD in children. It is shown that a low folate level, independent of attention deficit type, age and gender, is strongly related to ADHD (Krull et al. 2008). In a study investigating the role of the folate homocysteine metabolic pathway in the etiology of ADHD, it was also shown that folate homocysteine pathway gene variants could affect the etiology of ADHD through mild hyperhomocysteinemia and vitamin B12 deficiency (Saha et al. 2017). Due to the supplementary roles of folate and Vitamin B12 in folate and methionine cycles, they are inseparably associated with each other. In fact, Vitamin B12 deficiency causes a functional folate deficiency when folate is held in methyltetrahydrofolate form (Reynolds 2006). Vitamin B12 is necessary for brain development, neural myelination and cognitive function. Vitamin B12 deficiency in pregnancy and early childhood has been related to negative results in child health, primarily cognitive development disorders. However, the underlying mechanisms have not yet been clarified (Venkatramanan et al. 2016). In contrast, a review by Van de Rest et al. found a very limited number of studies that had examined the relationship between maternal vitamin B12 level and cognition and it was reported that as the results were inconsistent, there was thought to be a need for more research in this area (Van De Rest et al. 2012). Vitamin B12 is known to have a role in the prevention of disorders of CNS development, mood disorders and dementia disorders (Reynolds 2006). In a recent study is shown that children with ADHD compared to healthy controls have lower vitamin B12 level (Bala et al. 2016). In the current study, that the level of serum vitamin B12 was found to be low in the ADHD group compared to the control group support the findings of previous study.

Pyridoxine, folate and vitamin B12 are responsible for the acquisition of methyl groups, which are necessary for DNA and protein synthesis, and function as a cofactor in the one carbon metabolism formed from folate and methionine-homocysteine cycles. One carbon metabolism is very important in phospholipid synthesis, protein function, neurotransmitter synthesis and the regulation of DNA/RNA synthesis and metabolism. Therefore, pyridoxine, folate and vitamin B12 undertake significant functions in brain development, differentiation, maintenance and function (Mitchell et al. 2014, Reynolds 2006, Stover & Field 2015). In addition, it is known that one carbon metabolism affects epigenetic modifications which cause long-term changes affecting the brain memory, learning, cognition and behaviours (Schaevitz et al. 2014). A disruption in this metabolism has been shown in psychiatric diseases such as schizophrenia, bipolar disorder, ASD and depression (Sugden 2006). In the current study, it is thought that deficiency of pyridoxine, folate and B12 in children with ADHD may play a role in the etiology of ADHD through the impairment of the one carbon metabolism. However, further research is needed to clarify the pathogenesis of the relationship between one carbon metabolism and ADHD.

A genetic defect may be a reason for an impairment in pyridoxine, folate and Vitamin B12 metabolism or malnutrition of these vitamins may cause an impairment in homocysteine metabolism. However, in the current study, despite the reduction seen in pyridoxine, folate and vitamin B12 levels in the ADHD group, no increase was observed in the homocysteine level. This indicates that different mechanisms other than these vitamins could have a role in homocysteine metabolism.

In our study, there was no correlation between age, Conner's parent and teacher rating scale scores and intelligence level and pyridoxine, folate and vitamin B12 levels except positive correlations between intelligence level and vitamin B12. These results may indicate that vitamin B12 level may also be a possible risk factor for cognitive problems in children with ADHD.

To the best of our knowledge, this is the first study to have analysed the relationship between homocysteine, pyridoxine, folate and vitamin B12 in ADHD children. However, there were some limitations to this study, the most important of which were the small size of the sample and that there was no investigation of a possible genetic basis for the differences in the serum homocysteine and folate levels such as gene polymorphisms associated with MTHFR and other homocysteine metabolism.

CONCLUSION

Unlike other psychiatric diseases which are related to a high homocysteine level, a low homocysteine level could be considered a risk factor in the etiology of ADHD. Furthermore, the results obtained in this study showed that reduced pyridoxine, folate and vitamin B12 levels could be a risk factor for ADHD independent of the homocysteine levels. Pyridoxine, folate and vitamin B12 deficiency which is one of the preventable and treatable medical condition, could be given attention especially in ADHD patients. It can be useful to investigate pyridoxine, folate and vitamin B12 deficiency for patients with an ADHD diagnosis and treatment process. However, there is a need for further research verifying whether or not the compensation of folate, pyridoxine and vitamin B12 deficiencies in ADHD children will lead to behavioural and functional benefits and of the effects on homocysteine metabolism in ADHD.

Contribution of individual authors:

Hatice Altun: study design, data collection, analysis and interpretation of data, literature review, statistical analysis, manuscript preparation, approval of the final version;

Nilfer Şahin: study design, analysis and interpretation of data, statistical analysis, manuscript preparation, approval of the final version;

Ergül Belge Kurutaş: study design, analysis and interpretation of data, approval of the final version;

Olcay Güngör: data collection, analysis and interpretation of data, approval of the final version

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