

Effect of Methylphenidate and Folic Acid on ADHD Symptoms and Quality of Life and Aggression: A Randomized Double Blind Placebo Controlled Clinical Trial

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Objective: This clinical trial examines the effect of augmentation of methylphenidate (MPH) with folic acid to improve quality of life, and to treat aggression and ADHD symptoms .

Method: Participants of this eight week randomized double blind placebo controlled clinical trial were 49 children with ADHD. They were randomly assigned into one of the two groups: the first group receiving methylphenidate (10 to 20mg/day) plus folic (5mg/day), and the second group receiving methylphenidate plus placebo. Parent-reported ADHD symptoms and Overt Aggression Scale score were the outcome measures. Quality of life was assessed as well. Assessments were performed at pre-intervention, and at one month and two months after starting the interventions using repeated measure analysis .

Results: The mean age of children was 9.6(2.7) years. Age and gender were not associated with the groups. ADHD symptoms significantly decreased in both groups during the trial. However, no difference was observed between the groups. Moreover, aggression non-significantly decreased in both groups. Meanwhile, there was no difference between the two groups in efficacy for treating different types of aggressive behaviors including: verbal aggression, physical aggression against people, physical aggression against properties or objects, and aggression against self (self-injurious behavior). While methylphenidate improved quality of life of children with ADHD, folic acid did not improve it more than placebo. Both medications were well tolerated.

Conclusion: considering the marked limitations of this trial, this primarily report suggests that methylphenidate may improve ADHD symptoms and the quality of life of children with ADHD. Current evidence does not support that folic acid as an adjuvant is effective for treating ADHD symptoms or aggression, or the improving quality of life of children with ADHD.

Key words: Attention deficit hyperactivity disorder, child, Aggression, methylphenidate, folic acid, clinical trial, quality of life, therapeutics

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Attention deficit hyperactivity disorder (ADHD) is a common long life disorder with serious consequences including difficulties in family relationships, educational and occupational problems, and legal issues. Most of inmate adolescents with aggressive behaviors suffer from ADHD (1, 2). There is an elevated level of subcortical aggression in ADHD subjects in comparison to healthy controls (3). In addition, the symptom of impulsivity is found in many children with ADHD (4). The reason of high rate of aggression in ADHD is not known (5). Aggression can be classified into two groups: overt aggression, such as physical aggression and covert aggression, such as lying (6).

Hyperactivity is associated with physical aggression leading to poorer peer functioning (7). Moreover, aggression in children with ADHD is associated with both overall ADHD symptom severity and the hyperactive-impulsive ADHD symptoms (8). While a review article reported that the first choice of medication for treating aggression in ADHD is the medication used for treating ADHD (6), a recently published clinical trial reported that it needs to be examined whether treating the core symptoms of ADHD decreases the associated emotional and behavioral symptoms in children and adolescents with ADHD (8). Meanwhile, both articles emphasized that more research is needed to investigate treating aggression in ADHD .

Folic acid is normally found in many foods such as spinach, beans and liver. It is a B vitamin. There are no serious side effects after taking folate. Some of the side effects of taking folic acid are: nausea, decrease of appetite, irritability, and boating. These adverse effects are usually self-limited and can be managed easily by modulation of its dosage. The therapeutic dosage for treating folic acid deficiency in children is 1 mg per day which can be taken orally, intramuscularly, subcutaneously or intravenously. The therapeutic dosage of folic acid for maintenance therapy is about 0.5 mg/day .

ADHD, especially inattentive type is strongly associated with lower level of folate (9). This association is independent of age and gender (9). Moreover, higher hyperactivity and peers relations problem in offspring are associated with lower maternal folate red blood cell and total folate in early pregnancy (10). In addition, folic acid improves restless leg syndrome which is very common in children with ADHD (11) .

Folate administration is suggested for managing aggression (12). Folate deficiency is associated with aggression (13). Since, no clinical trial study was found in this regard, conducting a clinical trial on this matter is recommended (12).

Moreover, stimulants are commonly administered for treating ADHD. Emotional problems, sleep problems, decreased appetite, and irritability are among common adverse effects of stimulants (14, 15). It is supposed that stimulants affect through dopamine system. Folic acid increases monoamines such as dopamine in animal models (16) .

According to a recently published review article, while aggressive behavior in ADHD is commonly reported, its reason or neurobiology is not clearly known (5). Stimulants and behavior therapy decrease aggression in about half of the children with ADHD (17). However, many of these children do not respond to stimulants (15). In addition, the investigation of treatment for management of aggression in ADHD is highly recommended (5) .

Current randomized placebo controlled clinical trial examines the effect and safety of folic acid as an adjuvant for treating aggression and the core symptoms of ADHD in children with ADHD.

Material and Methods

The participants of this study were a clinical sample of children and adolescents with ADHD diagnosed according to Diagnostic and Statistical Manual of Mental Disorders- Fourth edition (DSM-IV) diagnostic criteria. Assessment interviews were conducted by a board certified child and adolescent psychiatrist .

To examine the effect of folic acid on treating aggression, it was estimated that a sample of 28 participants (14 children in each group) was needed to provide 90% power to detect a difference in aggression score of 5 and SD=4 with a P-value less than 0.05.

The children and adolescents were randomly assigned in a 1:1 ratio to folic acid (5mg/day) or placebo group, and were assessed 3 times. The first assessment was conducted at baseline for consenting and screening. The follow up assessments were conducted on day 30 and day 60. Follow up phone calls were done for those subjects who were not visited in the clinic until the end of the study. All the patients in both groups took methylphenidate 10 mg/day for children less than 25 kg, and 20 mg for children over than 24 kg, which was administered in two divided doses .

Inclusive criteria were: being identified as a case with ADHD according to DSM-IV diagnostic criteria; children with the age range of 5 or 16 years; children and parents who provided informed assent/consent .

The exclusion criteria were: self-reported allergic reaction to folic acid; kidney disease; estimated mental retardation and mild pervasive developmental disorder; being on dialysis, infection; anemia; being alcoholic; epilepsy; taking medications such as phenytoin, methotrexate, nitrofurantoin, tetracycline; barbiturates such as phenobarbital; and anti-epileptic medication such as phenytoin or primidone; a diagnosed psychotic disorder and mood disorder; other conditions that preclude participation (or increase risk) in the clinical trial (Type 1 diabetes mellitus; metabolic diseases, gastro-intestinal disorders affecting nutrient absorption, cancer); extensive use of nutritional folic acid supplements within the previous 3 months; and behavior therapy or any other psychotherapy in the last three months or during this study .

The primary scale for impulsivity was the Persian version of DSM-IV based parents' ADHD rating questionnaire (18) which consisted of three questions. The answers were scored from 0 to 3, with higher score showing a worse condition .

The modified Overt Aggression Scale (OAS) was used to measure aggression (19). This scale assesses four types of aggression including: verbal aggression, physical aggression against people, physical aggression against property or objects, and aggression against self (self-injurious behavior). This scale also considers duration and starting and finishing times of aggression. The severity of aggression was also assessed. A weighted score was assigned to the most severe form of aggressive behavior in each subscale. Then, the weighted scores were summed up to provide a total score .

Persian version of the 23-item PedsQL™ 4.0 Generic Core Scales was used to measure the quality of life children (20). We assessed the two aspects of emotional functioning and social functioning; in this scale higher score represents worse condition of quality of life .

Children and the rater were blind to the treatment group. The study was conducted with the approval of the Shiraz University of Medical Sciences Ethics Committee. Written informed consent was obtained from the parents and children .

Statistical Analysis

Statistical analysis was performed using SPSS for Windows. Mann-Whitney U test was used to compare age, the difference of mean total inattentiveness score during the trial, and the difference of mean total hyperactivity/impulsivity score during the trial between the two groups. Gender ratio was compared between the groups using Fisher's exact test. Repeated measures ANOVA were used to examine the effect of interventions on impulsivity, and aggression. The variables of hyperactivity and inattentiveness were considered as covariates. A significance level of .05 was set.

We performed the intent-to-treat (ITT) analysis using last-observation-carried-forward (LOCF) imputation method. The patients who completed one month of the trial and had at least one assessment after the baseline evaluation were included in ITT analysis.

Result

Out of 58 children with ADHD, 49 agreed to participate. They were randomly allocated to two groups. From 23 children in the MPH + Folic acid, 2 patients dropped out in the first month and only 8 patients completed the two months of the trial. Out of 26 children in the MPH + Placebo group, 4 dropped out in the first month and 13 completed the two months of the trial. Figure 1 displays the number of the patients assessed ADHD symptoms in the study groups, the number of patients who completed the study, and the rate and the reasons of withdrawal in each group.

The number of girls in the MPH + folic acid and MPH+ Placebo group was 4 and 3, respectively ($P=0.555$). The mean age of children in the MPH+ Folic acid and MPH+ Placebo group was 9.6 ($SD=2.8$) and 9.9 ($SD=2.5$), respectively ($P=0.941$). The mean difference of inattentive score during the trial was not different between the two group ($P=.558$). The mean difference of hyperactivity/impulsivity score during the trial was not different between the two group too ($P=.257$).

ANCOVA test showed no statistically significant difference between the two groups regarding the impulsivity score ($F(1, 39) =20.3, P=0.998$).

Moreover, no significant time effect was observed on impulsivity score ($F(2, 78) =1.2, P=0.296$) (Table 1).

ANCOVA test did not reveal a statistically significant difference between the two groups regarding the effect on inattentiveness score ($F(1, 41) =.45, P=0.505$). However, there was a significant time effect in both groups ($F(2, 82.)=9.8, P<0.001$).

While the total score of aggression non-significantly decreased in both groups, ANCOVA did not show any significant time effect (Time \times group) regarding the total score of aggression ($F(2, 78) =1.4, P=.240$). Moreover, there was no significant difference between the two groups regarding the total aggression score ($F(1, 39) =1.2, P=0.264$).

Furthermore, ANCOVA displayed no significant time and group interaction effect in both groups regarding the score of verbal aggression ($F(2, 78) =.25, P=.776$). There was no significant difference between the two groups regarding the effect on verbal aggression score ($F(1, 39) =0.94, P=0.338$).

Time and group interaction effect was not significant for the other three types of aggression including physical aggression against people, physical aggression against property or objects, and aggression against self (self-injurious behavior). In addition, the difference between the two groups was not significant regarding these three types of aggression.

There was a significant time effect on emotional functioning of quality of life ($F(2, 48) =13.5, P<0.001$) while the difference was not statistically significant between the two group ($P=0.795$).

Regarding social functioning, time effect was statistically significant ($F(2, 48) =3.9, P<0.026$). However, no difference was detected between the two groups ($F(1, 24) =1.1, P=0.298$).

Co-administration of folic acid and MPH was generally well tolerated. No serious adverse effects were reported in folic acid group. Four patients in the folic acid group dropped out due to adverse effect; the most common of which were nausea and vomiting ($n=2$), and decreased appetite ($n=2$). Meanwhile, three patients dropped out due to adverse effects in the placebo group including nausea and vomiting ($n=1$), decreased appetite ($n=1$), and nasal bleeding ($n=1$).

Table 1: The mean (SD) scores of impulsivity, inattentiveness, quality of life, and aggression in the groups

	Group	Pre-intervention	One month	Two month	Between groups difference
Impulsivity score	MPH+ folic acid	5.3(2.9)	3.2(2.2)	4.0(2.3)	$F(1, 39)=20.3, P=0.998$
	MPH+ Placebo	5.5(2.5)	3.8(2.0)	3.7(2.2)	
Inattentiveness	MPH+ folic acid	16.4(3.9)	13.8(4.7)	14.0(5.1)	$F(1, 41)=.45, P=0.505$
	MPH+ Placebo	15.8(5.6)	13.5(4.7)	12.5(5.1)	
Total score of aggression	MPH+ folic acid	19.0(12.0)	8.6(9.8)	8.4(10.3)	$F(1, 39)=1.2, P=0.264$
	MPH+ Placebo	19.8(13.0)	14(10.8)	13.0(9.9)	
Verbal aggression	MPH+ folic acid	3.9(2.6)	2.4(2.4)	2.2(2.6)	$F(1, 39)=0.9, P=0.338$
	MPH+ Placebo	4.3(2.3)	3.4(2.6)	2.7(2.2)	
Emotional functioning	MPH+ folic acid	7.7(5.4)	4.0(4.1)	3.7(4.2)	$F(1, 24)=.1, P=0.795$
	MPH+ Placebo	6.6(3.8)	5.5(3.4)	4.3(2.8)	
Social functioning	MPH+ folic acid	6.1(4.8)	3.3(4.2)	3.1(5.4)	$(F(1, 24)=1.1, P=0.298)$
	MPH+ Placebo	3.0(4.1)	2.3(3.9)	2.2(3.6)	

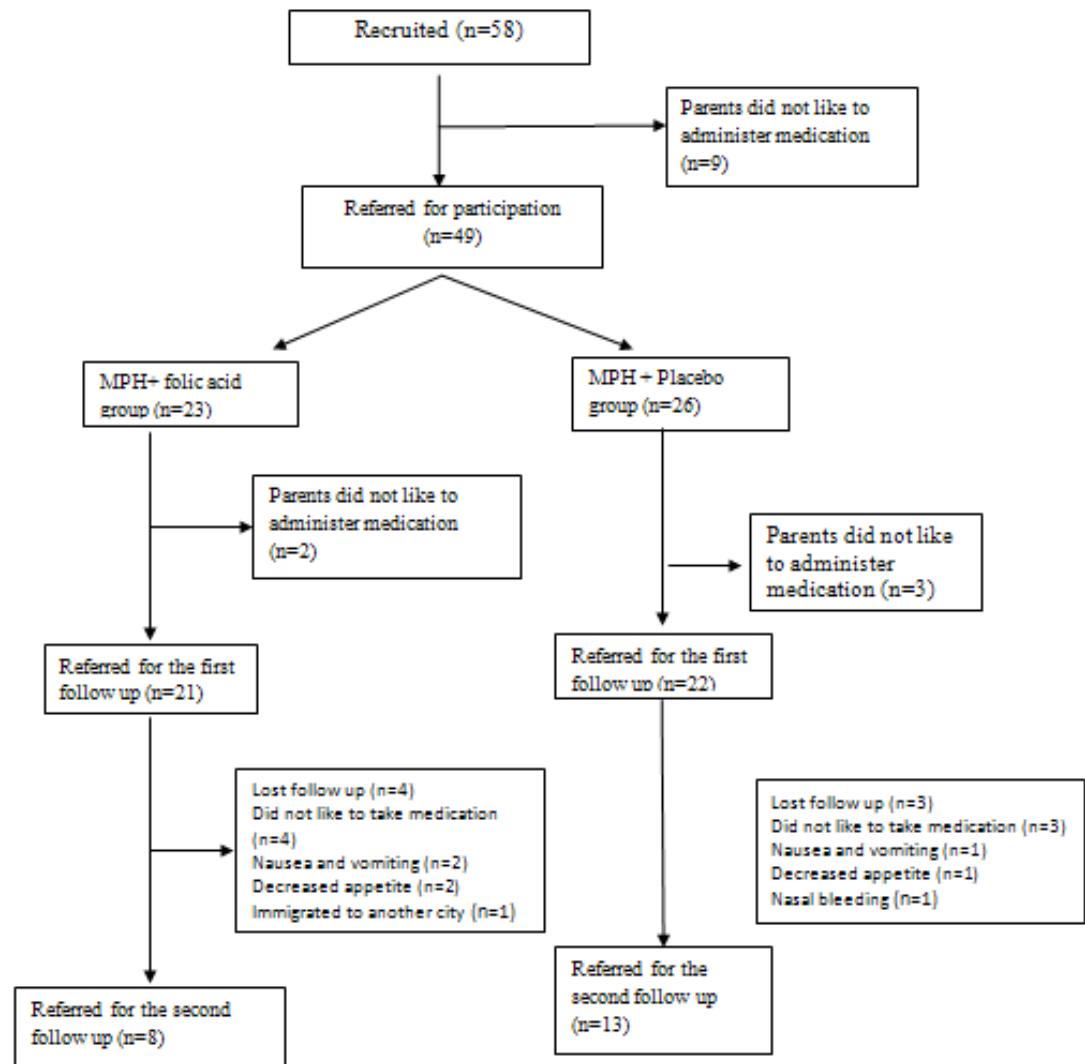


Figure 1: Flowchart for the clinical trial of folic acid group versus placebo group.

Discussion

Overall, this clinical trial showed that methylphenidate improves both inattentiveness and hyperactivity in children with ADHD, while it does not increase aggression. Verbal aggression decreased markedly in both groups. It means that there is no evidence for superior effect of folic acid over placebo in the treatment of ADHD symptoms and the different types of aggressive behaviors in children with ADHD. These results seem to be in line with review articles which concluded that ADHD medications should be administered for treating aggression in ADHD (6, 21).

In this study, quality of life, and emotional and social functioning were improved in both groups. However, current evidence does not support that administering folic acid improves the quality of life more than placebo.

The sample size of the current study was small and the results may be susceptible to sampling error or random effect. The rate of dropout was high. We are not sure if

the exacerbation of ADHD symptoms or aggression had been as a high rate of drop out. The trend toward efficacy for the total aggression score separates folic acid and placebo group. However, the trend of efficacy on the types of aggression was not markedly different. In addition, duration of the current study was relatively short, 8 weeks. Therefore, long-term safety was not guaranteed. Therefore, more time may be required to show folic efficacy. Another reason for negative results may be the low administered dose of MPH. In addition, current results were obtained from a single center. An approach to treat aggression in ADHD is to target comorbid disorders. However, in the current study, those children with bipolar disorder, psychotic disorder, and major depressive disorder were not included. The folic acid level of serum was not assessed. However, no other published trial was found on examining the efficacy of folic acid on ADHD and aggressive behavior.

It should be mention that folic acid was well tolerated. There was no markedly increase in the rate of adverse effect in the folic acid group .

In conclusion, this preliminary report suggests that MPH improves ADHD core symptoms. Moreover, current results suggest that MPH may non-significantly decrease aggression in children with ADHD. However, folic acid augmentation adds noting to MPH efficacy.

References

1. Matsuura N, Hashimoto T, Toichi M. The Characteristics of Ad/Hd Symptoms, Self-Esteem, and Aggression among Serious Juvenile Offenders in Japan. *Res Dev Disabil* 2010; 31: 1197-1203.
2. Ghanizadeh A, Nouri SZ, Nabi SS. Psychiatric problems and suicidal behaviour in incarcerated adolescents in the Islamic Republic of Iran. *Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit* 2012; 18: 311-7.
3. Keune PM, Schonenberg M, Wyckoff S, Mayer K, Riemann S, Hautzinger M, et al. Frontal Alpha-Asymmetry in Adults with Attention Deficit Hyperactivity Disorder: Replication and Specification. *Biological psychology* 2011; 87: 306-310.
4. Doerfler LA, Connor DF, Toscano PF, Jr. Aggression, Adhd Symptoms, and Dysphoria in Children and Adolescents Diagnosed with Bipolar Disorder and Adhd. *J Affect Disord* 2011; 131: 312-319.
5. King S, Waschbusch DA. Aggression in Children with Attention-Deficit/Hyperactivity Disorder. *Expert Rev Neurother* 2010; 10: 1581-1594.
6. List BA, Barzman DH. Evidence-Based Recommendations for the Treatment of Aggression in Pediatric Patients with Attention Deficit Hyperactivity Disorder. *The Psychiatr Q* 2011; 82: 33-42.
7. Tseng WL, Kawabata Y, Gau SS, Banny AM, Lingras KA, Crick NR. Relations of Inattention and Hyperactivity/Impulsivity to Preadolescent Peer Functioning: The Mediating Roles of Aggressive and Prosocial Behaviors. *J Clin Child Adolesc Psychol* 2012; 41: 275-287.
8. Connor DF, Ford JD. Comorbid Symptom Severity in Attention-Deficit/Hyperactivity Disorder: A Clinical Study. *J Clin Psychiatry* 2012; 73: 711-717.
9. Krull KR, Brouwers P, Jain N, Zhang L, Bomgaars L, Dreyer Z, et al. Folate Pathway Genetic Polymorphisms Are Related to Attention Disorders in Childhood Leukemia Survivors. *J Pediatr* 2008; 152: 101-105.
10. Schlotz W, Jones A, Phillips DI, Gale CR, Robinson SM and Godfrey KM. Lower Maternal Folate Status in Early Pregnancy Is Associated with Childhood Hyperactivity and Peer Problems in Offspring. *J Child Psychol Psychiatry* 2010; 51: 594-602.
11. Patrick LR. Restless Legs Syndrome: Pathophysiology and the Role of Iron and Folate. *Altern Med Rev* 2007; 12: 101-112.
12. Ghanizadeh A, Namazi MR. A Possible Research and Clinical Implication of Association of Homocysteine and Glutamate Levels in Brain for Management of Aggression. *Int J Dev Neurosci* 2010; 28: 125.
13. Chan A, Tchanchou F, Graves V, Rozen R, Shea TB. Dietary and Genetic Compromise in Folate Availability Reduces Acetylcholine, Cognitive Performance and Increases Aggression: Critical Role of S-Adenosyl Methionine. *The journal of nutrition, health & aging* 2008; 12: 252-261.
14. Wigal T, Greenhill L, Chuang S, McGough J, Vitiello B, Skrobala A, et al. Safety and Tolerability of Methylphenidate in Preschool Children with Adhd. *J Am Acad Child Adolesc Psychiatry* 2006; 45: 1294-1303.
15. Ghanizadeh A. A systematic review of the efficacy and safety of desipramine for treating ADHD. *Current drug safety*. 2013; 8: 69-74.
16. Ibrahim W, Tousson E, El-Masry T, Arafa N and Akela M. The Effect of Folic Acid as an Antioxidant on the Hypothalamic Monoamines in Experimentally Induced Hypothyroid Rat. *Toxicol Ind Health* 2012; 28: 253-261.
17. Blader JC, Pliszka SR, Jensen PS, Schooler NR, Kafantaris V. Stimulant-Responsive and Stimulant-Refractory Aggressive Behavior among Children with Adhd. *Pediatrics* 2010; 126: 796-806.
18. Ghanizadeh A, Jafari P. Cultural Structures of the Persian Parents' Ratings of Adhd. *Journal of attention disorders* 2010; 13: 369-373.
19. Yudofsky SC, Silver JM, Jackson W, Endicott J, Williams D. The Overt Aggression Scale for the Objective Rating of Verbal and Physical Aggression. *Am J Psychiatry* 1986; 143: 35-39.
20. Jafari P, Ghanizadeh A, Akhondzadeh S, Mohammadi MR. Health-Related Quality of Life of Iranian Children with Attention Deficit/Hyperactivity Disorder. *Qual Life Res* 2011; 20: 31-36.
21. Pappadopulos E, Woolston S, Chait A, Perkins M, Connor DF, Jensen PS. Pharmacotherapy of Aggression in Children and Adolescents: Efficacy and Effect Size. *Journal of the Canadian Academy of Child and Adolescent Psychiatry = Journal de l'Academie canadienne de psychiatrie de l'enfant et de l'adolescent* 2006; 15: 27-39.