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Prognostic Factors for Improvement of Attention Deficit Hyperactivity Disorder (ADHD)

Hoda Shirafkan[1], Akbar Fotouhi[2], Javad Mahmoudi-Gharaei[3], Seyyed Ali Mozaffarpur[4], *Mostafa Hoseini[5], *Mehdi Yaseri[6]

[1]PhD Student of Biostatistics, Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran. [2]Professor/MD PhD, Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran. [3]Professor/MD, Psychiatry and Psychology Research Center, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran. [4]Associate Professor/MD, PhD, Traditional Medicine and History of Medical Sciences Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran. [5]Professor/PhD, Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran. [6]Associate Professor/PhD, Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.

Abstract

Background

Attention-deficit/hyperactivity disorder (ADHD) is usually accompanied with other comorbidities that make treatment suboptimal and results in inadequate outcomes. Investigating the factors having an effect on improvement of ADHD can lead to better outcomes and a higher adherence to medication.

Materials and Methods

This historical cohort study was carried out on records of 6 to 13 year old patients with ADHD during the years 2008 to 2015 in the Children's Medical Center in Tehran, Iran. Baseline characteristics of patients such as gender, birth weight, the age of the first diagnosis, weight, severity of ADHD at the baseline, time duration of receiving the Methylphenidate, types of comorbidity, and dosage of Methylphenidate were extracted from hospital records. The Generalized Estimating Equation (GEE) was used to develop a multivariable model. This model is based on a stepwise procedure.

Results

One hundred and thirty-nine children (75.5% boys, mean age of 97.8±26.8 months) were assessed. Time duration of receiving Methylphenidate (OR=1.06; p< 0.001), severity of ADHD at the baseline (OR=0.94; p< 0.001), and dosage of Methylphenidate (OR=2.34; p< 0.001) had a significant relationship with improvement. In this study any relationship between improvement of ADHD and other factors was not found.

Conclusion

In this study, the clinical severity of ADHD at baseline, logarithm of dosage of Methylphenidate, and time duration of receiving the Methylphenidate were associated with improvement of ADHD.

Key Words: Attention-deficit/hyperactivity disorder, Children, Methylphenidate, Prognosis.

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Corresponding Author:

Mehdi Yaseri, Department of Epidemiology and Biostatistics, Tehran University of Medical Sciences, Tehran, Iran; Email: m.yaseri@gmail.com
Mostafa Hoseini, Department of Epidemiology and Biostatistics, Tehran University of Medical Sciences, Tehran, Iran, Email: mhossein110@yahoo.com.

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1- INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) with estimated prevalence of 5–7% in school-aged children worldwide (1), is the most common neurobehavioral disorder in children (2). Hyperactivity, impulsiveness, and an increasing lack of attention are characteristics of ADHD that cause school-aged children to have low self-esteem, significant risk of long term social and academic problems (3), high level of emotional conduct, and peer problems. Also, these children are more likely to have difficulties with home life, friendships, classroom learning and recreational activities (4). ADHD is often accompanied with other behavioral, emotional, language, and learning disorders. Some factors such as the age and sex of the children, the geographic area, and the diagnostic criteria of ADHD can affect the prevalence of this disorder (5). Also, various combinations of genetic (6), and environmental risk factors such as prenatal maternal smoking, exposure to alcohol or lead, prematurity, low birth weight and pregnancy complications factors (7) can cause ADHD, too.

Although stimulant drugs including methylphenidate are considered as the first line therapy for ADHD, they can cause side effects including abdominal pain, loss of appetite, nervousness, insomnia, and compulsive behaviors (8). It is proposed that the adherence to stimulant medication ranges from 35% to 87% and even 11.3-16.7% in some areas (9); this low adherence results in suboptimal treatment and inadequate outcomes (10). The engagement of the patient and family and treatment adherence are positive predictors of treatment outcomes (11-14). Also, the result of medication and its side effects have important effects on adherence of management. Therefore, investigating the factors having effect on improvement can lead to better outcomes and a higher adherence to medication in future. Although a few studies have been carried out on the relation of additional symptoms/behaviors and/or comorbidities with the outcomes of medication (15, 16), the results are inconsistent (10). Therefore, this study evaluates the possible relationship between improvement (not meeting the criteria of ADHD), and important factors affecting ADHD in school-aged children.

2- MATERIALS AND METHODS

2-1. Study design

This historical cohort study was carried out on the records of the school-aged patients with ADHD who were visited in the Children's Medical Center in Tehran as one of the most important pediatric hospitals in Iran. Children who were admitted to the psychiatric clinic of the center during the years 2008 to 2015 with diagnosis of ADHD were included in the study. This study was approved by the Ethics Committee of the Tehran University of Medical Sciences.

2-2. Participants

Inclusion criteria were the age range of 6 to 13 years old with the primary diagnosis of ADHD [based on Diagnostic and Statistical Manual of Mental Disorders (DSM), 4th edition, Text Revision (DSM-IVTR) (17), and DSM fifth edition (18)], and having at least one follow-up meeting and correct completion of the questionnaire by the parents. Children without any follow-up (with only one visit), unacceptable completion of Conners' Parent Rating Scale-revised: Short Form (CPRS-R: S), or the use of other drugs instead of methylphenidate were excluded from the study. Using the PASS software (version 11.0) with the power of 0.80 and the confidence level (CI) of 0.95 and the odds ratio of 2.75 for boys to girls, the sample size of the logistic was 139. Samples were randomly selected from existing files. If the record met

eligibility criteria, it was entered to the study.

2-3. Measurements

The basic characteristics of the patients such as [sex, birth weight (kilogram), the age of the first diagnosis (month), weight per visit (kilogram), severity of ADHD at baseline, times of repeated visits (in month compared with the first visit), dosage of Methylphenidate (milligram per day), and type of comorbidity (if present) including affective disorder (mood and bipolar disorders), Anxiety disorder (generalized anxiety disorder (GAD), Social anxiety disorder (SAD), Obsessive compulsive disorder (OCD), Phobia, and Anxiety disorder), oppositional defiant disorder (ODD), other comorbidities (mental retardation (MR), learning disorder (LD), stutter, Tic, and major depressive disorder (MDD)], were recorded.

2-4. Outcome

The outcome variable was considered to be improvement (not meeting the Conners' criteria) labeled as "1" and opposed to meeting the criteria labeled as "0". Conners' Parent Rating Scale-revised: Short Form (CPRS-R: S) was used for measuring the severity of ADHD. The Conners' Rating Scales (CRS) have been widely used for screening and measuring outcomes in treating children with ADHD (19). The CRS includes short and long versions. CPRS-R:S with 27-item is the most recent short version of the CRS that is widely used (20). The calculated reliability of CPRS-R: S is equal to 0.73 (21). Each item in CPRS-R:S is rated on a scale of 0 to 3: "0" for not true at all (never), "1" for just a little true (occasionally), "2" for pretty much true (often), and "3" for very much true (very often) (22). Children with a mean score of at least 1.5 (i.e. crude score greater than 41) were considered as ADHD. At each visit the form was completed by one parent. According to the score, being diagnosed as having ADHD was identified and considered as a binary dependent variable [0=diagnosis of ADHD (score>40), 1=exiting from the diagnosis of ADHD (score≤ 40)]. Dosage of Methylphenidate was recorded based on milligram (each tablet contained 10 milligrams of the Methylphenidate).

2-5. Statistical analysis

The baseline characteristics of the children were summarized by mean (±standard deviation) for quantitative variables, and by frequency (percentage) for qualitative variables. The associations between the explanatory variables between the two sexes were assessed with t-test and nonparametric test of Mann-Whitney U (for quantitative variables); and Chi-squared and Fisher exact tests was used for qualitative variables. Generalized estimating equation (GEE) model with logit link function and exchangeable correlation matrix was used to evaluate the relationship between improvement of ADHD and the dosage of methylphenidate, adjusted for other covariates that were significantly associated with improvement in bivariate tests. The adjusted odds-ratio and its confidence interval was calculated for the final selected model. The significance level was set to 5% for all tests. The statistical analysis was carried out using STATA version 14.0.

3- RESULTS

Of the 139 children enrolled in the study, 105 (75.54%) were male and 34 (24.46%) were female. The overall mean (±standard deviation) age at the beginning of the study is 97.79 (± 26.8) months. In this study, 4 children had attention deficit disorder (ADD) (2 girls and 2 boys), and 80 children had comorbidities with ADHD (34 anxiety disorders, 27 ODD, 5 Mood disorders, and 25 had other comorbidities). The baseline characteristics of these individuals are shown in **Table.1**. The overall improvement rate among all

follow-ups was 61.33%, which was 60.58% among boys, and 63.98% among girls, which does not show a significant difference (P = 0.21). In univariate analysis five variables (weight of the patients in each follow up, severity of ADHD at the baseline, time duration of receiving the Methylphenidate, the existence of ODD as comorbidity, and dosage of Methylphenidate) had a significant relation with improvement (not meeting diagnostic criteria of ADHD). These variables were entered into a multivariable GEE model using stepwise procedure. Based on this model, three variables (except weight and ODD) were found independent predictors of improvement (**Table.2**).

Table-1: The basic characteristics of children with ADHD.

Variables	Overall (n=139)	Girl (n=34)	Boy (n=105)	P-value
Age at baseline (month)	97.79±26.8	100.76±22.52	96.83±20.28	0.340
Mean ±SD	3.11±0.54	3. 19±0.40	3.09±0.58	0.351
Birth weight (kg) (Mean ±SD)	12(8.63%)	1(2.94%)	11(10.48%)	0.173
Low birth weight, number (%)	24.88±7.29	24.97±8.11	24.84±7.04	0.932
Weight at baseline(kg)	22.95±14.43	19.64±13.28	24.02±14.69	0.124
Mean ±SD	51.61±11.08	50.20±10.24	52.06±11.35	0.396
Times of repeated visits (month) Mean ±SD	4.97±2.87	4.76±2.47	5.04±2.99	0.631
Severity at baseline				
Mean ±SD	4(2.87%)	2(5.88%)	2(1.90%)	0.227
Number of follow-up	1(0.72%)	0	1(0.95%)	--
Accompanied affective disorder				
Mood (%)	21(15.11%)	8(23.52%)	13(12.38%)	0.114
Bipolar (%)	9(6.47%)	4(11.76%)	5(4.76%)	0.149
Accompanied Anxiety disorder	6(4.31%)	3(8.82%)	3(2.86%)	0.136
GAD (%)	7(5.04%)	4(11.76%)	3(2.86%)	0.039*
SAD (%)	5(3.60%)	1(2.94%)	4(3.81%)	0.813
Phobia (%)				
OCD (%)	4(2.87%)	2(5.88%)	2(1.90%)	0.227
Anxiety (%)	19(13.67%)	1(2.94%)	18(17.14%)	0.036*
Accompanied other comorbidities	9(6.47%)	3(8.82%)	8(7.62%)	0.821
Mental retardation (%)	1(0.72%)	1(2.94%)	0	--
Learning disorder (%)	27(19.42%)	4(11.76%)	23(21.90%)	0.194

[a] Children with a birth weight of less than 2,500 grams were considered as low birth weight. ADHD: attention-deficit hyperactivity disorder; GAD: generalized anxiety disorder; SAD: Social anxiety disorder; OCD: obsessive compulsive disorder; ODD: oppositional defiant disorder; MDD: major depressive disorder; SD: standard deviation. * Significant at 0.05.

Table-2: Association between explanatory variables and improvement of ADHD.

Variables	Univariate Analysis		Multivariable Analysis	
Covariates	OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Gender (male)	0.84 (0.53,1.33)	0.465	--	--
Age (month)	1.003 (0.99,1.01)	0.469	--	--
Weight (kg)	1.04(1.02,1.07)	< 0.001*	--	--
Birth weight (kg)	0.99 (0.9994, 1.0001)	0.291	--	--
Time (month)	1.07 (1.05,1.09)	< 0.001*	1.06(1.04,1.08)	< 0.001 *
Severity at baseline	0.96 (0.94,0.98)	< 0.001*	0.94(0.92,0.97)	< 0.001 *
Log Dose Methylphenidate, (mg)	2.95 (1.99,4.37)	< 0.001*	2.34(1.50,3.64)	< 0.001 *
Accompanied ODD	0.62(0.39,0.98)	0.042*	--	--
Accompanied affective disorder [a]	1.01 (0.78,1.31)	0.920	--	--
Accompanied anxiety disorder [b]	1.05 (0.67,1.65)	0.832	--	--
Accompanied other comorbidities [c]	0.88 (0.71,1.09)	0.241	--	--

[a] Affective Disorder is comprised of mood and bipolar disorders. [b] Anxiety disorder is comprised of GAD, SAD, OCD, Phobia, and Anxiety disorder. [c] Other comorbidities include MR, LD, stutter, Tic, and MDD. ADHD: attention-deficit hyperactivity disorder; ODD: oppositional defiant disorder; 95% CI: 95% confidence interval. *Significant at 0.05.

4- DISCUSSION

In this study, the clinical severity at baseline, logarithm of dosage of Methylphenidate, and time duration of receiving the Methylphenidate were associated with improvement of ADHD.

Dosage of Methylphenidate had a meaningful association with improvement of ADHD, in which the chance of improvement increased 2.34 times as one unit addition in dosage of Methylphenidate in logarithm scale. Also, with one unit increase in severity, the chance of improvement decreased, and with one month increase in receiving Methylphenidate, the chance of improvement increased. As ADHD can cause social, emotional and economical failure and also increased mortality (23), pharmacological treatment in many cases is inevitable. To the best of our knowledge, there are not any studies investigating factors affecting improvement of ADHD with Methylphenidate, so it seems that this study can be the first one of its kind. Since the adherence to treatment of ADHD is not as desired most of the time (10), considering the factors that can affect the improvement of the disease can be effective in managing the treatment process. According to the results of this study, in patients with the same severity of disease, with increasing doses, the chance of improvement increases over time. Also, in patients with the same dosage of Methylphenidate, the chance of improvement decreases at the rate of 6% with increase in unit of each score of the severity of the ADHD (based on CPRS-R: S). If we focus on the time duration of receiving MPH (as the main variable), and considering the dose and severity of the disease as constant, the chance of improvement increases by 6% per every month of medication. In this study, the male to female ratio was 3.09:1 which was similar to other studies (24-26), but a

statistically significant relationship was now found between improvements of ADHD among sexes. The major subtype in our study was combined subtype which was consistent with findings of some studies (10), but in other studies inattentive subtype was the most predominant (27). Results revealed that the predominant psychiatric disorders accompanying ADHD were ODD (19.42%) followed by GAD (15.10%), which was more than what was reported in other studies (28).

It could be due to recording the samples from a referral center. Like other similar studies in this field (19, 22, 29-31), we used Conners' Rating Scales to evaluate ADHD. We used the CPRS-R:S version of it because the reliability and validity of its Persian version had already been evaluated (21). Being conducted with a diverse sample of children with main diagnosis of ADHD and the mean follow-up period of 22.42 months can be considered the strengths of this study. Although the participants were randomly recruited, since our hospital is a referral center, samples may not represent the community of patients. It is suggested that a multicenter study be done for better generalizability. In addition, full consideration of all factors that may have an impact on improvement of ADHD, such as those related to socio-economic status of family, and environmental factors like possible stressors that may be encountered by any patient, were outside the scope of this paper and hence these may represent confounding variables.

Factors associated with improvement of comorbidities were not assessed separately, because we did not find reliable data of valid questionnaires in these areas. Nevertheless, the results of this study showed three factors affecting improvement of ADHD. As Methylphenidate had the greatest impact on the improvement of these patients, conducting a study to find the optimal dose of methylphenidate can be suggested to have the best result with the fewest complications.

5- CONCLUSION

In this study, based on a multivariable Generalized estimating equation analysis some characteristics including the clinical severity at baseline, logarithm of dosage of Methylphenidate, and time duration of receiving the Methylphenidate were associated with improvement of ADHD.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGMENTS

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8- COMPLIANCE WITH ETHICS GUIDELINES

This study was approved by the Ethics Committee of the Tehran University of Medical Sciences. The researchers adhered to principles of the Helsinki Declaration.

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