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Research / Araştırma

Factors Related to Methylphenidate Response in Children with Attention Deficit/ Hyperactivity Disorder: a Retrospective Study

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ABSTRACT

Factors related to methylphenidate response in children with attention deficit/ hyperactivity disorder: a retrospective study

Objective: We aimed to explore the predictive value of clinical features and self-concept on methylphenidate (MPH) response in children with attention deficit/hyperactivity disorder (ADHD).

Methods: The study had a naturalistic design where the results were analyzed retrospectively. ADHD and comorbidity were diagnosed by Schedule for Affective Disorders and Schizophrenia for School-Age Children Present Lifetime Version (K-SADS-PL). At the baseline assessment, parents completed Turgay DSM-IV Disruptive Disorders Rating Scale (T-DSM-IV-S) and Child Behavior Check List (CBCL); teachers were given T-DSM-IV-S, CBCL. The children completed Piers-Harris Children's Self-Concept Scale (PHSCS), Children's Depression Inventory (CDI), and Screen for Child Anxiety Related Emotional Disorders (SCARED). Following 4-8 weeks of MPH treatment, the parents completed T-DSM-IV-S and the clinician completed Clinical Global Impression-Improvement scale (CGI-I). This study included 54 children (18 girls, 36 boys; mean age 9.32±0.21 years old). The sample was divided in "good responders" (GR) and "poor responders" (PR) regarding the response criteria defined by authors.

Results: The PR group had significantly higher rates of anxiety disorders, higher internalizing scores and lower PHSCS scores compared to GR. Comorbid anxiety disorders, elimination disorders and negative self-concept were found to predict poor MPH response by multiple regression analysis.

Conclusions: The results point to the need for additional interventions in the presence of comorbid anxiety, incontinence or poor self-concept in children with ADHD.

Keywords: ADHD, anxiety, enuresis, methylphenidate, self-concept

ÖZET

Dikkat eksikliği/ hiperaktivite bozukluğu olan çocuklarda metilfenidat yanıtı ile ilişkili faktörler: Retrospektif bir çalışma

Amaç: Bu çalışmada dikkat eksikliği ve hiperaktivite bozukluğu olan çocuklarda (DEHB) klinik özelliklerin ve öz-kavramının metilfenidat (MTF) yanıtı üzerine etkilerinin araştırılması amaçlanmıştır.

Yöntem: Çalışma naturalistik desende yapılmış olup sonuçlar geriye dönük olarak değerlendirilmiştir. DEHB ve komorbid bozuklukların tanısı Okul Çağı Çocukları İçin Duygulanım Bozuklukları ve Şizofreni Görüşme Çizelgesi Şimdi ve Yaşam Boyu Şekli-Türkçe Uyarlaması (ÇGDBŞÖ-ŞY) ile konulmuştur. İlk görüşmede ebeveynlere Turgay DSM-IV'e dayalı Yıkıcı Davranış Bozukluklarını Tarama ve Değerlendirme Ölçeği (T-DSM-IV-YDDÖ) ve Çocuk ve Gençler için Davranış Değerlendirme Ölçeği (ÇDDÖ) uygulanmıştır. Öğretmenler T-DSM-IV-YDDÖ ve ÇDDÖ'ni doldurmuşlardır. Çocuklar ise Piers-Harris'in Çocuklarda Öz-kavramı Ölçeği (PHÇÖÖ), Çocuklarda Depresyon Ölçeği (ÇDÖ) ve Çocuklarda Anksiyete Tarama Ölçeği (ÇATÖ) ile değerlendirilmişlerdir. MTF tedavisini takiben ebeveynlere tekrar T-DSM-IV-YDDÖ uygulanmıştır. DEHB belirtilerindeki düzelme klinisyen tarafından Klinik Global İzlenim-İyileşme ölçeği ile değerlendirilmiştir. Çalışmaya toplam 54 çocuk (18 kız, 36 erkek; yaş ortalaması 9.32±0.21 yıl) dahil edilmiştir. Örneklem yazarlar tarafından belirlenen kriterlere göre "iyi yanıt verenler" (İY) ve "yetersiz yanıt verenler" (YY) olarak iki gruba bölünerek karşılaştırılmıştır.

Bulgular: YY grubunda İY grubuna göre anksiyete bozuklukları sıklığı ve ortalama içevurum skorları anlamlı olarak daha yüksek, öz-kavramı skoru ise anlamlı olarak daha düşük bulunmuştur. Çoklu regresyon analizinde eşlik eden anksiyete bozukluğu, eşlik eden dışa atım bozukluğu varlığı ve olumsuz öz-kavramı düşük MTF yanıtının öngörücüleri olarak bulunmuştur.

Sonuç: Bu çalışmanın sonuçları DEHB'ye eşlik eden anksiyete bozukluğu, inkontinans veya olumsuz öz-kavramı varlığında MTF tedavisine ek tedavi seçeneklerine ihtiyaç olduğunu göstermektedir.

Anahtar kelimeler: DEHB, anksiyete, enürezis, metilfenidat, öz-kavramı

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurobehavioral disorders of childhood associated with psychiatric comorbidity and impairments in adaptive functioning (1,2). The American Academy of Pediatrics (3), an international consensus statement (4), and the Texas Children's Medication Project (5) have recommended stimulants as the first line of treatment for ADHD. Methylphenidate (MPH) is the only stimulant available in Turkey in immediate-release and long-acting forms.

Despite the effectiveness of MPH, a significant proportion of children in treatment present partial response to medication and negative outcomes (6). In this sense, the identification of clinical predictors of poor response to MPH has implications for effective treatment.

Children with ADHD and their families are at risk for several comorbid clinical conditions that may be associated with poorer outcomes. Children with ADHD frequently present comorbid disorders, such as conduct disorder (CD), oppositional defiant disorder (ODD), or mood and anxiety disorders (7).

The ADHD literature has revealed that the most consistent predictors of a positive response to stimulants include higher levels of attention deficiency (8-11), higher levels of hyperactivity (10,12,13), younger age (8,11), and higher intellectual functioning (8,14,15). The most consistent predictor of a negative stimulant medication response is comorbidity of internalizing psychopathology (8,13,16,17). The literature is inconsistent regarding the predictive value of comorbid externalizing problems (17,18). Demographic factors including gender, years of education, and socioeconomic status have generally not been predictive of medication response (13,22). In the Multimodal Treatment Study of Children with ADHD (MTA study), four moderators of treatment response were identified in school-aged children with ADHD: 1) co-morbid anxiety disorder in the child, 2) initial severity of the child's ADHD, 3) child's intelligence quotient (IQ), and 4) presence of high depressive symptoms in parents (20,21).

Children with ADHD may be challenged in many aspects of life, displaying a predisposition for academic under-achievement, lower self-concept and disruption in relations with peers, teachers and parents (22,23). Findings of previous studies concerning the relationship between ADHD and self-concept are inconsistent, with some studies indicating that self-concept scores are higher in children with ADHD than in those without ADHD (2), others reporting that scores are lower in children with ADHD (24), and some reporting no difference between children with or without ADHD (23). Although there is evidence that MPH has a promoting effect on self-concept of children with ADHD (24), further research is needed to understand the effect of self-concept on treatment outcome.

To our knowledge, the roles of clinical features, comorbid disorders and self-concept of children with ADHD as predictors of treatment response have not been conjointly evaluated in a naturalistic setting until now. The accurate identification of factors that influence MPH response may assist mental health professionals in developing more effective treatment strategies involving additional pharmacological and/or behavioral interventions. Therefore, we aimed to evaluate the effect of clinical factors (severity and subtype of ADHD, comorbid diagnoses, internalizing and externalizing problems) and self-concept on MPH response in a naturalistic sample of children and adolescents with ADHD. The main hypotheses of this study were comorbidity or low self-concept may be associated with poor response to MPH in children with ADHD.

METHOD

The study had a naturalistic design and the results were analyzed retrospectively. All participants were recruited among the outpatient referrals to Ondokuz Mayis University, Faculty of Medicine, Department of Child and Adolescent Psychiatry in Samsun, Turkey. We reviewed medical records of patients diagnosed with ADHD between 2007 and 2008. Inclusion criteria for the study were the following: 1) a diagnosis of ADHD according to DSM-IV criteria, 2) chronological age between 7 and 18 years, 3) no previous/current ADHD

treatment at referral, 4) having completed at least 4 weeks of MPH treatment, 5) having completed pre/post-treatment visits and assessment scales. Psychotic disorder, bipolar disorder, mental retardation, and pervasive developmental disorders were accepted as exclusion criteria. Additionally, patients with neurological disorders or significant medical problems were also excluded.

Baseline Assessment

Before beginning the treatment, all outpatients underwent a comprehensive clinical assessment including sociodemographic data, medical history and psychiatric examination routinely. After psychiatric examination and ADHD diagnosis, the patients and their parents completed the following rating scales.

Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): ADHD and comorbid psychiatric disorders were diagnosed by clinical examination using KSADS-PL. This scale was developed by Kaufman et al. (26) and Gokler et al. (27) reported that the Turkish version of the scale was valid and reliable for use in the Turkish population.

Turgay DSM-IV-Based Disruptive Behavioral Disorders Screening and Rating Scale (T-DSM-IV-S): The severity of baseline ADHD, ODD and CD were evaluated by T-DSM-IV-S completed by parents and teachers. The Scale was developed by Turgay (1995) and translated and adapted to Turkish by Ercan et al. (28) The scale is based on DSM-IV diagnostic criteria and evaluates inattention (IA: 9 items), hyperactivity-impulsivity (HI: 9 items), opposition defiance (OD: 8 items), and CD: 15 items. Greater scores reflect increase in severity. Symptoms are scored by assigning a severity estimate for each symptom on a 4-point Likert-type scale (0=not at all, 1=just a little, 2=quite a bit, and 3=very much).

Child Behavior Checklist (CBCL): Internalizing and externalizing problems were evaluated by CBCL completed by parents and teachers. The CBCL is a 118-item questionnaire that assesses the emotional and behavioral symptoms of a child (29,30). The parents scored each problem item as 0=not true, 1=somewhat/sometimes true, or 2=very/often true. The items consisted of eight syndrome scales: withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention problems, delinquent behavior, and aggressive behavior. The scores of these eight scales, as well as scores for total behavior, internalizing, and externalizing problems were derived.

Piers-Harris Children's Self Concept Scale (PHSCS): The PHSCS is an 80-item, self-report instrument designed to assess the self-concept in children and adolescents aged 6 to 18 years (31). Yes or no responses determine the scores for each item in either a negative or positive direction. Higher scores reflect a more positive self-concept.

Children's Depression Inventory (CDI): CDI is a self-report questionnaire used to evaluate depression in children aged 6-17 years. It was reported that the Turkish version of the scale was valid and reliable for use in the Turkish population (32).

Screen for Child Anxiety-Related Emotional Disorders (SCARED): Children are asked to mark the most appropriate response to each item for evaluation of anxiety. The original scale was developed by Birmaher et al. (33), and Karaceylan (34) reported that the Turkish version of the scale was valid and reliable for use in the Turkish population.

Assessment of Treatment Response to Methylphenidate

Response to MPH treatment and clinical improvement were assessed at the end of 4-8 weeks of medication using the following tools.

1-T-DSM-IV-S was completed again by parents.

2-Clinical Global Impression Scale- Improvement subscale (CGI-I) score was given by the clinician according to clinical interview with patients and their

parents. Clinical improvement was rated on a scale of 1-7. Lower scores reflect reduced psychopathology and greater therapeutic effectiveness. CGI-I score 1 means very much improved and 7 means very much worse (35).

There were two criteria defining good response to MPH treatment: 1) more than 30% decrease in T-DSM-IV-S inattention and/or hyperactivity-impulsivity scores rated by parents, 2) CGI-I score of 1 or 2 rated by clinician. The participants were accepted as "good responders" (GR) to MPH if at least one of these criteria was present following the treatment. The remainder of the sample was accepted as "poor responders" (PR).

Procedures

The research was approved by the Ethics Committee of the Faculty of Medicine, Ondokuz Mayis University. All assessments were done as part of a routine clinical work-up for the patients seen in the outpatient clinic. The study was comprised of two visits. The first visit consisted of baseline assessment. The purpose of the first visit was diagnostic assessment, completing baseline-rating scales and prescribing MPH. ADHD and comorbid disorders were diagnosed by clinical examination using K-SADS-PL. Subtype of ADHD was evaluated according to DSM-IV. During the first visit, parents completed T-DSM-IV-S and CBCL. Teachers were also given T-DSM-IV-S and CBCL and completed them before MPH treatment began. The children completed PHSCS, CDI, and SCARED during the first visit. Following these assessments, MPH was prescribed. Medication choice (short or long-acting MPH), dosage and the date for the second visit were determined on an individual basis. The general principal was to start with a low dosage, as is recommended in product monographs. The second visit consisted of MPH response assessment. The purpose of the second visit was to assess any changes in ADHD symptomatology. It took place 4 to 8 weeks after the recommended treatment began. The parents were given T-DSM-IV-S again. The clinician evaluated the clinical improvement of ADHD symptoms by using CGI-I scale in the second visit.

Statistical Analysis

Data were analyzed using SPSS for Windows version 16 (SPSS Inc, Chicago, IL). We calculated descriptive statistics for the overall sample. Then, the sample was divided into two groups named GR and PR. Mann-Whitney U test and Chi-square test were used for comparing two groups. For 2x2 tables, Fischer's exact test was used if the table had a cell with an expected frequency of less than five. The predictors of response were assessed with logistic regression analysis; predictors included age, gender, parents' age/ education level, MPH type/dose, duration of treatment, ADHD subtype, presence of comorbid disorders, severity of baseline ADHD/ ODD/CD symptoms, depression and anxiety scores, self-concept scores and CBCL scores. All values were reported as either percentages or mean±standard deviation. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

The sample of this study was composed of 54 children and adolescents with ADHD diagnosis aged between 7-13 years (mean age 9.32±0.21 years). Eighteen (33.0%) of them were girls and 36 (67.0%) were boys. Among these 54 children, 26.0% were diagnosed as inattentive subtype (ADHD/I) and the other 74.0% as combined subtype (ADHD/C). Comorbid psychiatric diagnoses were present in 69.0% of subjects. ODD was the most common comorbidity with a rate of 35.0%, and 15.0% of the patients had CD, 25.0% anxiety disorder, 11.0% depressive disorder, 7.5% tic disorder, and 9.5% had elimination disorder. Long-acting MPH was prescribed in 72.2% of patients while 27.8% were prescribed the short-acting form. The dosage of daily prescribed MPH ranged between 10 and 36mg (mean dosage 22.00±6.61mg/day). The mean duration of MPH use (time passed from first visit to second visit) was 6.87±1.46 weeks (range 4-8 weeks). Forty-five percent of subjects met the MPH response criteria and were inserted in the GR group.

Comparison of Good and Poor Responders

The whole sample was divided into two groups according to treatment response. The GR (n=24) and PR groups (n=30) did not show any significant differences in terms of age, gender, parents' age/education level, MPH type/dose, duration of treatment, ADHD subtype and baseline T-DSM-IV-S scores. The PR group showed significantly higher CDI scores and lower PHSCS scores. CBCL anxious/depressed subscale scores rated by parents and CBCL Internalizing scores rated by teachers were also significantly higher in PR than the GR group. Mean scores of scales and group comparisons according to treatment response are shown in Table 1.

The rate of psychiatric comorbidity was 93.3% in the PR and 37.5% in the GR group, respectively, and the difference between groups was statistically significant. Among comorbid psychiatric disorders, the two groups showed statistically significant difference only in anxiety disorders rates. Comorbidity rates and comparisons of groups according to treatment response are summarized in Table 2.

Table 1: Mean scores of scales and group comparisons according to treatment response

Scale- subscale	Rater	GR n=24 Mean±SD	PR n=30 Mean±SD	z	p
T-DSM-IV-Attention	Parent	18.50±4.65	18.00±4.92	-0.358	0.720
	Teacher	16.29±5.19	16.97±5.41	-0.506	0.613
T-DSM-IV-Hyperactivity	Parent	15.83±6.50	13.67±5.65	-1.422	0.155
	Teacher	13.96±7.31	12.70±6.39	-0.715	0.475
T-DSM-IV-ODD	Parent	9.46±6.03	9.00±5.54	-0.280	0.780
	Teacher	8.42±6.00	8.72±6.72	-0.061	0.951
T-DSM-IV-CD	Parent	1.75±2.70	3.37±4.61	-1.073	0.283
	Teacher	1.79±2.85	3.47±4.79	-0.842	0.400
CBCL-Anxious/Depressed	Parent	2.50±1.86	4.03±2.74	-2.075	0.038*
	Teacher	2.50±1.88	3.93±2.81	-1.874	0.061
CBCL-Internalizing	Parent	11.29±5.71	14.47±7.19	-1.543	0.123
	Teacher	9.25±4.92	13.00±6.64	-2.164	0.030*
CBCL-Externalizing	Parent	15.29±9.42	17.23±12.61	-0.322	0.747
	Teacher	16.67±10.03	18.20±10.04	-0.506	0.613
CBCL-Total	Parent	47.83±20.27	54.87±21.18	-1.106	0.269
	Teacher	47.46±20.43	54.37±17.46	-1.524	0.128
PHSCS	Child	54.88±5.90	49.03±9.63	-2.404	0.016*
CDI	Child	6.92±3.18	10.97±6.21	-2.594	0.009*
SCARED	Child	18.62±9.24	25.13±13.68	-1.901	0.057

GR: Good responders, PR: Poor responders, S.D: standard deviations, T-DSM-IV: Turgay DSM-IV-Based Rating Scale, CBCL: Child Behavior Check List, PHSCS: Piers-Harris Children's Self Concept Scale, CDI: Children's Depression Inventory, SCARED: Screen for Child Anxiety-Related Emotional Disorders. *Statistically significant

Table 2: Rates of ADHD subtypes and comorbid disorders according to treatment response

	GR n=24		PR n=30			
	n	%	n	%	χ^2	p
ADHD Subtypes						
Inattentive	6	25.0	8	26.6	0.019	0.891
Combined	18	75.0	22	73.3		
Psychiatric comorbidity	9	37.5	28	93.3	16.76	<0.001*
Oppositional defiant disorder	5	20.8	14	46.6	2.85	0.091
Conduct disorder	1	4.1	7	23.3	-	0.063
Anxiety disorders	1	4.1	12	40.0	7.50	0.006*
Depressive disorders	1	4.1	5	16.6	-	0.210
Tic disorders	1	4.1	3	10.0	-	0.620
Elimination disorders	1	4.1	4	13.3	-	0.367

ADHD: Attention deficit/hyperactivity disorder, GR: Good responders, PR: Poor responders, *Statistically significant

Table 3: Predictors of MPH response

	OR	95% CI	p
PHSCS scores	1.12	1.00- 1.25	0.042*
Presence of comorbid disorders	24.98	4.23-147.43	<0.001*
Oppositional defiant disorder	3.98	0.59-26.58	0.153
Conduct disorder	4.72	0.30-74.40	0.270
Anxiety disorders	19.72	1.41-276.18	0.027*
Depressive disorders	3.20	0.20-49.67	0.405
Tic disorders	0.61	0.02-16.50	0.773
Elimination disorders	17.66	1.34-233.33	0.029*

OR: Odds Ratio, CI: Confidence Interval, MPH: Methylphenidate, PHSCS: Piers-Harris Children's Self Concept Scale, *Statistically significant

Predictors of Response to Methylphenidate

Logistic regression analysis was performed to determine the predictors of MPH response. Presence of comorbid psychiatric diagnosis and lower self-concept scores estimated by PHSCS were predictors of poor MPH response. Logistic regression analysis was applied again to subgroups of comorbid diagnosis to discriminate which comorbid disorders were predictive. Presence of comorbid anxiety disorders and elimination disorders predicted poor MPH response. Predictors of MPH response are summarized in Table 3.

DISCUSSION

In this study, nearly half of the participants were evaluated as good responders to MPH treatment, while the remaining of the sample showed mild or no improvement and was classified as poor responders. The rate of MPH response estimated in our study was lower compared to results of previous studies. Barkley reported that approximately 75.0% of ''hyperkinetic'' children receiving stimulant medications respond favorably, while the remaining 25.0% are unchanged or made worse (36). Similar response rates were also reported in controlled clinical trials. For example, Efron et al. (37) found an MPH response rate of 72.0% and Greenhill et al. (38) found an MPH response rate of 77.0%. The inconsistency between response rates of our study and previous ones can be explained by the differences in sample characteristics and methodological diversity. The lower response rate to MPH in this study may be related to criteria that were used to define response. It was reported that the response rate can vary from 50% to 80% depending on how medication response is defined (8,9,13).

The results of the current study regarding rates of comorbid psychiatric disorders were similar to previous reports. Comorbid psychiatric diagnosis were present in 69.0% of subjects. ODD was the most common comorbidity with a rate of 35.0%, and 15.0% of them had CD, 25.0% anxiety disorder, 11.0% depressive disorder, 7.5% tic disorder, and 9.5% had elimination disorder in our study. It was reported that between 50.0% and 90.0% of children diagnosed with ADHD have comorbid psychiatric conditions at the time of diagnosis (39). Previous studies revealed that approximately 35.0% of children with ADHD also have anxiety (40); 4.0% have a comorbid mood disorder (41); 40.0% are diagnosed with ODD, and 14.0% with CD (42).

One of the major findings of the present study was that the presence of any comorbid psychiatric disorder predicted poor MPH response. Furthermore, among comorbid diagnoses, anxiety disorders and elimination disorders were found to be the predictors of poor MPH response in this study. Our result was consistent with most of the ADHD literature revealing that the presence of comorbid anxiety disorders in ADHD was predictive of a poorer response to MPH than was the case for non-anxious ADHD children (8,17). It is also known that there is an increased rate of elimination disorders in children with ADHD (43). Findings from this study showed that identification of anxiety and incontinence in children with ADHD is of great clinical relevance due to its relationship with poor MPH response. When one of these disorders co-exists with

ADHD, pharmacological and/or behavioral treatments are required for them in addition to MPH medication.

The results of this study were remarkable reporting negative self-concept as a predictor of poor MPH response in ADHD. Self-concept is the totality of the individual's cognitive image of him- or herself; it is the cognitive component of the self. A positive self-concept in children is associated with improved academic performance, healthy social relationships, and dynamic movement through successive developmental stages. The problems that children with ADHD experience in peer relationships and school performance are highly specific domains that can influence self-concept (44). These children are frequently criticized and disapproved by their parents, teachers and peers; therefore, they may develop perceptions of a poor self-concept. The result of this study points to the need to assess self-concept in children with ADHD for determining appropriate treatment strategy.

There were some limitations of the present study. First of all, this study had a naturalistic design and it was an open trial, where the results were collected retrospectively. Second, treatment response depended on the criteria that were determined by the authors. Although we used two different criteria, the results may vary with another type of definition. Third, dose increment was not applied to patients with poor response since this study included only one control visit. Treatment response could change in some patients when given higher doses. Finally, teachers could not complete rating scales after MPH treatment. For this reason, MPH response was assessed depending on ratings of parents and clinician.

To summarize, in our study, children who have comorbid anxiety or elimination disorders are less likely to respond to MPH. This study highlights the importance of considering comorbid disorders and the possible need for additional pharmacological and/or behavioral interventions in children with ADHD. Additionally, our results reveal the preliminary evidence of self-concept as a predictor of MPH response. Therefore, interventions aimed at improving self-concept – such as emphasizing personal strengths, determining attainable goals, helping to develop coping skills, and providing support of parents, peers and teachers – may be beneficial. Further longitudinal studies are needed for researching the effect of self-concept improvement on MPH response.

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