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RESEARCH ARTICLE

Emotional regulation and attachment style in previously untreated adolescents with attention deficit and hyperactivity disorder

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ABSTRACT

Objective: The aim of our study was to evaluate adolescents who have been diagnosed with attention deficit hyperactivity disorder (ADHD) for the first time, in terms of difficulties in emotion regulation and attachment characteristics and to compare them with healthy controls.

Method: The study is a cross-sectional with a healthy control group. A total of forty eight untreated adolescents with ADHD and 51 healthy subjects participated in the study. To determine the psychiatric disorders, all adolescents were assessed with a structural interview. All participants were assessed by WISC-R intellegence test. Emotion regulation and attachment characteristics were assessed by Difficulties in Emotion Regulation Scale and the Experiences in Close Relationships Scale. The ADHD symptoms of case group were evaluated by Conners' Parent Rating Scale which was competed by parents.

Results: Adolescents with ADHD displayed worse performance in emotion regulation. The avoidant attachment score was also higher in these adolescents. Furthermore, emotional regulation difficulties and attachment scores correlated with the severity of ADHD.

Conclusion: It has been shown that difficulty in emotion regulation and insecure–avoidant attachment styles have been more common in untreated adolescents with ADHD. The findings of our study support the view that ADHD is a heterogeneous condition and insecure attachment style and emotional regulation should be considered in the assessment and treatment of ADHD.

Keywords: Attention deficit hyperactivity disorder, attachment, emotional regulation

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in childhood with heterogeneous clinical symptoms, such as inattention, hyperactivity, and impulsivity (1). The core symptoms of ADHD are associated with significant impairments across youth's social, cognitive, behavioral, and family functioning (2,3). While executive functioning impairments have been central to cognitive theories of ADHD, recent studies has suggested to focus other psychological factors such as emotional regulation and attachment.

Studies have shown that these children have difficulty in social, emotional, and behavioral areas aside from the core symptoms of ADHD (4,5).

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Furthermore, children with ADHD show greater emotional reactivity (6), higher levels of negative affect (7), and lower levels of emotional awareness than those without (8). Emotional regulation is the ability of individuals to evaluate and change their emotional reactions and be aware of their emotions to achieve a goal. Impairments that can occur in this ability can lead to emotional dysregulation and impairment of children's adaptive skills. Although emotion dysregulation is not among the cardinal symptoms in the current classification system, it was defined in DSM III as a symptom associated with the disease (9). Despite not being included in the diagnostic criteria, emotional regulation is an important point that needs to be considered in the ADHD assessment process because of its effect on the psychosocial, physical, and social areas (8). Epidemiological studies have also focused on emotional dysregulation. In a study conducted on 5,326 adolescents, mood liability was found to be 38%, which is 10 times higher than that of the normal population, in children with ADHD (10). This rate was also found to be high in children with ADHD with no other comorbid psychiatric disorders (10). In another study conducted on 1,500 children, emotional problems had more impact on quality of life and self-esteem than hyperactivity and attention deficit (11). Children with ADHD and emotional regulation problems exhibit more impairment in peer relationships, family life, and academic performance than those with ADHD alone (4). In summary, emotional dysregulation is a clinical condition that can be common in children with ADHD and leads to adverse consequences.

From the perspective of attachment, a relationship exists between insecure attachment and ADHD, and attachment problems may contribute to the development of ADHD (12-14). Some authors stated that early attachment relationships may operate as organizers of the regulatory system, including the attentional system (15). The parent-child attachment may constitute a factor related to general psychopathology and ADHD symptoms, perhaps through its influence on self-regulation ability (16). Moreover, the attachment style may have an effect on the clinical characteristics and course of ADHD and may be a precursor for future ADHD development (17). Children with ADHD have relationship problems with parents, and they are more exposed to childhood trauma and parental loss or separation (18,19). Furthermore, secure attachment is based on the proper interaction between the parent and child, and the presence of behaviors, such as inattention, hyperactivity, and impulsivity, in the first years of life may prevent parents from receiving signals from their children and may cause the attachment development to be adversely affected. Moreover, individuals with insecure attachment are more prone to developing behavioral and emotional regulation problems (20). It is also important to note that especially behavioral problems related to attachment pattern may also be influenced by other variables such as child characteristics and environmental factors. Secure attachment has a positive effect on the problematic areas of children with ADHD (12). The finding that 60% of children have a secure attachment competency in the normal population and that less than 10% of children with ADHD have a secure attachment competency (21,22) supports converse relationship between ADHD and attachment. In a review investigating the relationship between ADHD and attachment, emotional dysregulation was found to be an important characteristic of both ADHD and reactive attachment disorder (23). Although biological factors are more emphasized in the etiology of ADHD, attachment that begins in childhood and continue throughout life can be an important factor affecting the clinical course of ADHD, as in many psychiatric disorders. However, very few studies have examined attachment in relation to ADHD and impact on the nature of disorder.

In light of the above-mentioned information, the objective of this study was to assess adolescents diagnosed with ADHD for the first time and who have not been treated previously and then to compare them with healthy controls. Furthermore, the attachment characteristics of the adolescents with ADHD and the possible correlation of emotion dysregulation with ADHD symptoms were investigated. Based on the current literature, the following hypotheses were tested; (1) Adolescents with ADHD would represent more avoidant and anxious attachment style; (2) Adolescent with ADHD would experience more emotional regulation difficulties compared to healthy adolescents; (3) Attachment and emotional regulation scores would correlate with ADHD severity in case group. Although studies were previously conducted on various neuropsychological deficits, studies examining the relationship between emotional regulation and attachment with ADHD are limited. The current study contributes to the literature of the association between attachment pattern, emotional regulation and ADHD.

METHOD

Participants and Procedure

The study is a cross-sectional study with a healthy control group. The subjects of ADHD group were recruited at Mardin Public Hospital Child and Adolescent Psychiatry outpatient clinic based on incidental sampling. The sample included 48 adolescents aged 12–17 years (M=14.7, SD=1.7) and diagnosed with ADHD according to the DSM IV-TR criteria. ADHD subjects were selected from adolescents who had never received any previous medical and psychological treatments. A total of 69 subjects were planned to participate; however, 18 of the subjects were excluded for having at least one comorbid disorder except ODD and 3 of the subjects were excluded for having an estimated IQ below 80. Due to high comorbidity with ADHD and Oppositional Defiant Disorder (ODD), ODD were not defined as an excluding criteria. The inclusion criteria for the case group were as follows: (1) meet diagnostic criteria for at least one subtype of ADHD according to the DSM IV-TR, (2) demonstrate an IQ 80 or above on the Wechsler Intelligence Scale for Children (WISC-R), (3) no chronic medical illness requiring treatment. The exclusion criteria were as follows: (1) an estimated IQ below 80 and (2) the presence of any of the following comorbidities: mental retardation, anxiety disorder, mood disorder, conduct disorder, psychotic disorders, alcohol and substance use. As the control group, 51 adolescents aged 12–17 years (M=15.2, SD=1.3) who scheduled an appointment with the pediatrician, had never received any psychiatric disorders, estimated IQ score of 80 or higher, had no chronic medical illness, and agreed to participate in the study with their parents were included in the study. Nine adolescent were excluded from control group due to having at least one psychiatric disorder.

All families and children signed an informed consent form that was specifically designed for the current study. An interview was conducted using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version to determine the psychiatric disorders that could be present in the all children by licensed two child and adolescent psychiatrist. The WISC-R intelligence test was applied to determine the intelligence levels of all children. Furthermore, the participants completed the Difficulties in Emotion Regulation Scale and the Experiences in Close Relationships Scale. In addition, parents of the case group completed the Conners' Parent Rating Scale to assess ADHD severity. Ethical approval was obtained from Diyarbakir Gazi Yasargil Research and Training Hospital (Turkey).

Measures

Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL): The K-SADS-PL is a semi-structured interview form developed to determine the previous and present psychopathologies of children and adolescents according to the DSM-III-R and DSM-IV diagnostic criteria (24). Translation to Turkish and validity and reliability studies of the K-SADS-PL were performed (25).

Conners' Parent Rating Scale (CPRS-48): The Conners' Rating Scale is used as a reviewing instrument to determine behavioral problems observed in children and as an additional criterion for the diagnosis and for monitoring and grading the treatment (26). The CPRS short form includes additional items for psychosomatic problems and anxiety as well as items related to hyperactivity and learning and behavioral problems. The Turkish validity and reliability studies were conducted and the Cronbach's alpha value of the scale was determined as 0.90 (27).

Experiences in Close Relationships Scale (ECRS): The scale developed by Brennan and Shaver and measures anxiety and avoidance which are two main dimensions of attachment (28). The scale consists of 36 items, and each dimension is measured with 18 items. Participants assess how much each item describes them by using 7-point Likert-type scales (1=does not describe me at all, 7=fully describes me). The Turkish version of the scale was validated (29). The Cronbach's alpha value of avoidant and anxious domain were determined as 0.90 and 0.94, respectively (29).

Difficulties in Emotion Regulation Scale (DERS): The scale developed by Gratz and Roemer and consists of the sub-dimensions of awareness, clarity, non-accept, strategies, impulse, and goals and contains 36 items (30). In completing this self-report scale, adolescents are asked to read the items and to mark the closest expression based on the frequency that suits them (1=almost never, 5=almost always). Although a cut-off score is not determined for the scale, high scores point to the presence of more severe difficulties in emotional regulation. The Turkish validity and reliability studies of the scale were conducted and cronbah's alpha value of scale was determined as 0.94 (31).

Data Analysis

Data analyses were performed using the Statistical Package for Social Science (SPSS 22.0 for windows). The measured variables were presented as the mean±standard deviation and the categorical variables as percentage and number. The Kolmogorov–Smirnov test and histograms were used to evaluate the distribution of the numeric variables. Student's t-test was used to compare the numerical variables with the normal distribution, and the Mann–Whitney U test, a nonparametric test, was used for those with a non-normal distribution. The categorical variables were assessed by Pearson's chi-square test and Fisher's exact test. To determine the direction and the level of correlation between the numerical variables, Pearson's correlation test was used for those exhibiting a normal distribution and Spearman's correlation test for the non-normally distributed numerical variables. A multivariate analysis of covariance (MANCOVA) was used to identify effect of covariates such as age and sex on the results. For the MANCOVA's, the Wilk's Lambda test is reported in results section. Logistic regression analyses were conducted to assess the possilbe effect of ADHD on independent variables. Odds ratios and 95% confidence intervals (95% CIs) were computed. Value of statistical significance was determined as $p<0.05$.

RESULTS

The mean age of the case group was 14.7±1.7 years and that of the control group was 15.2±1.3 years. In terms of gender, 85.4% (n=41) of the case group consisted of males and 14.6% (n=7) of females; 52.9% (n=27) of the control group consisted of males and 47.1% (n=24) of females. As expected, the number of males in the case group was higher than that in the control group. A significant difference was found between the two groups in terms of gender (chi-square test, $\chi^2=12.1$ df=1, $p<0.001$). The academic achievement of the adolescents with ADHD was significantly lower than that of the control group (chi-square test, $\chi^2=37$, df=4, $p<0.001$).

About 35.4% (n=17) of the adolescents with ADHD and 13.7% of the control group were smoking. A statistically significant difference was found between the two groups in terms of smoking (chi-square test, $\chi^2=6.3$ df=1, $p=0.012$). Five adolescents in the case group did not attend school, compared to one in the control group. No significant differences were observed between the groups in terms of sociodemographic characteristics, such as age, number of siblings, parental status, parental age, and family income ($p>0.05$).

Among the adolescents in the case group, 81.3% (n=39) had mixed-type ADHD, 14.6% (n=7) had predominant attention deficit-type ADHD, and 4.2% (n=2) had predominant hyperactivity-type ADHD. Additionally, 8 of adolescents (16.6 %) in case group had ODD comorbidity. The mean score of the CPRS of the case group was 52.2±17.7.

The total WISC-R score of the case group was 95±4 and that of the control group was 97±2. No significant difference was found between the groups in terms of the intelligence levels ($p>0.05$).

The case and the control groups were compared by the Mann–Whitney U test because the ECRS subscale and total scores did not exhibit a normal distribution. Higher scores of scales indicating more disturbed attachment pattern in ECRS. The ECRS avoidance and the total attachment scores of ADHD adolescents were higher than those of the control group (Table 1). No significant difference was found between the two groups in terms of the anxious attachment scores.

The DERS subscale scores were also compared by the Mann–Whitney U test because they did not exhibit a normal distribution. Awareness, clarity, impulse, goals, and total scores among the DERS subscales of the case group were significantly higher. Higher scores in DERS adress the difficulty in emotional regulation. In addition, no difference was found between the two groups in the non-accept and strategies subscale scores (Table 1).

Correlations

In the present study, the correlation between the total score of the CPRS and emotional dysregulation and the attachment scores of the case group was examined to investigate the effect of the ADHD symptoms on attachment and emotional regulation. Significant correlation was found between the total score of the CPRS, the DERS total score, and the avoidant attachment score (Table 2). Additionally, there was a significant correlation between insecure attachment and emotional regulation scores (rho=0.614, $p<0.001$).

Analysis of Covariance

A MANCOVA was used to investigate the effect of age and gender in group comparisons. Attachment and emotional regulation scores selected as dependent variables, and sex and age were selected as a covarites in the model. We found that covariates of age (Wilks' Lambda=0.974, F=0.740, p=0.53, partial $\eta^2=0.02$) and sex (Wilks' Lambda=0.987, F=0.376, p=0.78, partial $\eta^2=0.01$)

Table 1: Comparison of the ECRS and DERS scores between the case and the control group

	Case group		Control group		
	M	SD	M	SD	p*
Anxious attachment score	66.2	20.5	62.5	21.5	0.234
Avoidant attachment score	67.6	16.4	53.9	12.5	<0.001
Total score	133.8	27.4	116.5	23.2	0.004
Awareness	15.3	4.7	12.4	3	0.001
Clarity	13.3	4.2	10.6	3.5	0.001
Non-accept	15	6.5	13.8	5.6	0.480
Strategies	21.8	7.8	19.1	6	0.072
Impulse	18.8	7.1	13.4	5.8	<0.001
Goals	18	5	15.7	4.5	0.020
Total DERS score	102.2	24.5	85	20	<0.001

*Mann–Whitney U Test, ECRS: Experiences in Close Relationships Scale, DERS: Difficulties in Emotion Regulation Scale, M=Mean, SD: Standard deviation

Table 2: The relationship between the ADHD severity and emotional dysregulation and attachment in the case group

			DERS		ECRS	
			Avoidant attachment		Anxious attachment	
	rho	p	rho	p	rho	p
Conners' Parent Rating Scale Score	0.481	0.001	0.361	0.036	0.238	0.16

Spearman's correlation analysis, DERS: Difficulties in Emotion Regulation Scale, ECRS: Experiences in Close Relationships Scale

had no effect in group differences. After controlling sex and age, there were still significance differences in insecure attachment and emotion regulation scores between case and control group (Table 3).

Logistic Regression Analyses

We assessed the effect of ADHD on measured variables by binary logistic regression analyses. In regression model, diagnosis of ADHD was added as a dependent variable. Attachment scores, emotional regulation scores and sociodemographics characteristics which were significant in our previous analyses were added to the model as an independent variables. As a result of analyses, diagnoss of ADHD was significantly related with increased risk of emotion dysregulation, insecure attachment and smoking (Table 4).

DISCUSSION

In this study, compared with healthy adolescents, untreated adolescents with ADHD were found to have worse emotional regulation skills and higher insecure–

Table 3: Results of MANCOVA for attachment and emotional regulation in the case and control group after controlling age and sex

	Type III sum of squares	df	F	p	Partial eta2
ECRS total score	6849.0	3	3.6	0.018	0.11
Avoidant attachment	4477.2	3	7.2	<0.001	0.20
Anxious attachment	305.0	3	0.2	0.88	0.008
DERS total score	7601.6	3	5.4	0.002	0.16
Awareness	251.7	3	6.0	0.001	0.17
Clarity	285.1	3	7.4	<0.001	0.2
Non-accept	74.9	3	0.7	0.57	0.02
Strategies	188.8	3	1.3	0.26	0.05
Impulse	837.8	3	6.8	<0.001	0.19
Goals	249.2	3	3.9	0.012	0.12

MANCOVA: multivariate analysis of variance, DERS: Difficulties in Emotion Regulation Scale, ECRS: Experiences in Close Relationships Scale

Table 4: Final model of logistic regression analyses

						95% CI for Exp (B)	
	B	SE	Wald	p	Odds ratio (OR)	Lower	Higher
Smoking	2.67	1.25	4.52	0.03	0.69	0.06	0.81
Avoidant attachment	0.97	0.30	10.40	0.001	0.91	0.85	0.96
Anxious attachment	0.55	0.36	2.20	0.14	1.06	0.98	1.13
Awarenes	0.29	0.18	6.33	0.012	0.74	0.59	0.94
Clarity	0.13	0.15	0.70	0.40	0.88	0.65	1.18
Non-accept	0.12	0.07	2.82	0.093	1.13	0.98	1.30
Strategies	0.14	0.85	2.58	0.10	1.14	0.97	1.35
Impulse	0.36	0.12	9.41	0.002	0.69	0.55	0.88
Goals	0.81	0.10	0.64	0.42	0.92	0.76	1.12
Constant	11.41	2.96	14.8	0.001	0.9		

B is the unstandardized B regression coefficient, SE is the standard error of the regression coefficient, Wald is the chi-square test value, Sig. is the p value of the Wald chi-square test, odds ratio is the exponential of the regression coefficient

avoidant attachment characteristics. Moreover, higher severity of ADHD was associated with more emotional dysregulation and attachment problems. The emotional regulation problems and attachment characteristics seems to have a great effect on functioning and are important points that should be considered in the evaluation of ADHD. These two conditions may also be factors that increase morbidity in children with untreated ADHD.

We found a significant difference in the awareness, clarity, impulse, and goals sub-scales and total scores of the DERS. Among the DERS sub-scales, awareness is expresses the lack of awareness of emotional reactions; clarity is the insufficient understanding of emotional reactions; impulse conveys the difficulties in controlling impulses while experiencing negative emotions; and goals expresses the difficulties in focusing while experiencing negative emotions (31). As observed from our findings using this scale, the adolescents with untreated ADHD were observed to have difficulties in understanding emotional situations, in impulse control, and in behavior regulation areas compared with their healthy peers in emotional situations. According to Barkley's model, compared with those without ADHD, the inhibitory deficit in ADHD individuals leads to more emotional reactivity or emotional dysregulation when emotional situations are encountered (32,33). Similarly, children and adolescents with ADHD are emotionally more reactive than the controls (6). In our study, consistent with previous studies, the presence of emotional dysregulation and emotional reactivity was found in these children. Moreover, the fact that these findings correlated with ADHD severity reveals how great the effect of ADHD is on children's lives. The exclusion of comorbid psychiatric conditions, primarily conduct disorder, suggests that emotional regulation difficulties can be more specific to ADHD. Emotional dysregulation is not unique to ADHD. However, the addition of this condition to ADHD increases the impairment in functioning (4), and the demonstration of the improvement effect of ADHD treatment on emotional regulation increases the importance of early treatment in ADHD. In support of this finding, a study conducted on 79 ADHD children with emotional dysregulation showed that comorbidity, social deficiency, and continuity of ADHD symptoms were greater in these children than in those with ADHD without emotional dysregulation after four years (34). Similar study showed that people with ADHD and emotional symptoms have significantly lower quality of life and worse social adjustment compared people with ADHD but no emotional symptoms (35). Studies have focused on psychiatric comorbidities, such as substance use disorder, in the adolescence period of children with untreated ADHD. However, emotional problems, which are known to have a great effect on quality of life and self-respect, have remained in the background. Moreover, in adolescence, which is an important period for the development of identity, children with ADHD are at risk of being excluded by their peers or being exposed to bullying because of behaviors associated with emotional regulation. From the etiological perspective, neurophysiological changes have been shown in emotional dysregulation and in ADHD. The demonstration of abnormalities in children with ADHD, especially abnormalities in parasympathetic mechanisms including emotional

regulation (36), shows that the emotion dysregulation seen in ADHD is also associated with neurochemical changes in brain. However, emotional regulation in ADHD is still not fully understood. Neuropsychological tests related to emotional control (impulsivity, self-regulation, and executive functioning in positive and negative emotions) also show that the processing of emotional stimulation is impaired in ADHD (37).

The findings of this study show that the adolescents with ADHD have more avoidant attachment characteristics. This insecure form of attachment can develop when the child's signals remain unanswered or are misinterpreted as a result of inappropriate behaviors or the late responses of the attachment figure. Children with insecure–avoidant attachment may not be fully capable of predicting the behavior of individuals compared with those with secure attachment. Furthermore, children with secure attachment are better at social competence, emotional regulation, and psychosocial well-being than children with insecure attachment, who are anxious, worried, or disorganized (38, 39). Moreover, insecure attachment is reported to be a risk factor that increases socio-emotional and behavioral maladjustment in adolescents with ADHD (40). Attachment affects the development of self-regulation skills. The finding of the present study suggests that in addition to their difficulties in emotion regulation, ADHD children may have difficulty in handling close relationships in the early period of life. Consequently, the quality of attachment that is expected to develop in a healthy way in early childhood can also be adversely affected. The fact that the attachment characteristics of children with ADHD are affected by the severity of the disorder also suggests the relationship of insecure–avoidant attachment with ADHD. The opposite of this can be considered: ADHD severity may increase by the higher impairment of attachment. Previous studies showed that this condition is associated with externalizing and behavioral problems in individuals with insecure attachment (41,42). In our study, the exclusion of disorders that could lead to externalizing problems except for ODD, increases the relationship between attachment and ADHD. But it should be keept in mind that ODD which is common comorbid condition with ADHD, may also be associated with attachment and emotional regulation. Due to nature of this disorder parent-child relationship can be affected by early age of life. However, one important point that should be noted is that defining the cause-and-effect relationship among the attachment pattern, emotional regulation, and ADHD is currently difficult. The relationship among these characteristics is probably bi-directional, and the presence of one of them poses a risk for another.

The limitations of the study should be considered during the assessment of the study findings. First of all, the present study was limited to cross-sectional relations, and causal effects need to be validated in future prospective designs. Self-report questionnaires were used. In particular, parental ratings which has been found to be less reliable than teacher ratings for externalizing behaviour problems, were used to assess the externalizing behaviours (43). This has also introduced the risk that there could be bias in data collected. Although the comorbid conditions were excluded from the study, ODD was not discounted. Children with ODD are known to have externalizing problems. The number of ODD sample may decrease the power of findings which then could be insufficient to make a generalization. The sample size also made difficult to have power to test diagnosis by subgroups of ADHD. However, it would be also interesting to examine the effect of comorbid conditions on attachment and emotional regulation. Parental psychopathology was based on their response and we did not conduct clinical interview with parents to detect possible disorders such as ADHD or other psychiatric conditions. Because parental psychopathology may have an influence on parent-child attachment. Future research using randomized design with larger sample size and using multiple informant report with structured interview would be valuable.

In conclusion, although the relationship of emotional regulation and attachment with ADHD is not yet fully understood, difficulties in emotional regulation and insecure–avoidant attachment style are determined to be more common in untreated ADHD adolescents and to affect the clinical course. While several factors may have an impact on emotional regulation and attachment, multivariate analaysis of covariance suggest that our findings display significant relationship with ADHD, regarless of age and gender. Emotional dysregulation, especially in response to negative situations and emotions, can lead to major problems in the social relations of these individuals. Our findings are also important in terms of demonstrating the effect of the attachment style on the life of adolescents. Secure attachment is protective in the prolongation of ADHD symptoms to the adulthood period, and the positive

effect of ADHD treatment, especially on emotional regulation, is important in assessing the findings of the present study. Owing to their symptoms, children with ADHD may be at risk of impairment of the mother–infant interaction. Therefore, this situation should be absolutely kept in mind by clinicians who evaluate childhood ADHD symptoms. Furthermore, developing appropriate behavioral intervention programs for this condition that may affect the attachment style may be an option. Another point is the relationship between emotional regulation and ADHD, which has the capacity to affect almost every aspect of life. In consideration of all of these, the effect of the lack of early intervention and treatment on the lives of children and adolescents with ADHD appears to be greater than expected. The treatment of this disorder will not only reduce the severity of illness but will also ensure improvement in many areas, especially quality of life, peer relations, and social life.

Ethics Committee Approval: Ethical approval was obtained from Diyarbakir Gazi Yasargil Research and Training Hospital (Turkey).

Informed Consent: Written informed consent obtained.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare that there is no conflict of interest.

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