

Psychosocial Functionality in Adolescents with Inborn Errors of Immunity During the COVID-19 Pandemic

COVID-19 Salgını Sırasında Doğuştan Bağışıklık Yetersizliği Olan Ergenlerde Psikososyal İşlevsellik

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ABSTRACT

Objective: We aimed to determine the impact of COVID-19 on the psychosocial functioning of adolescents with inborn errors of immunity (IEI).

Material and Methods: Thirty-six patients with IEI (18 mild, 18 severe) and 18 healthy controls aged between 10 and 17 were included in this study. Adolescents and their caregivers completed the Revised Child Anxiety and Depression Scale (RCADS) to measure symptoms of anxiety and depression and the Strengths and Difficulties Questionnaire (SDQ) to assess prosocial behaviors and emotional/behavioral problems. Additionally, the COVID-19 Phobia Scale (C19P-S) was answered by adolescents to assess the level of coronavirus phobia.

Results: According to SDQ, emotional scores of the adolescents in the control group are higher than the mild/severe patient group. Emotional scores of the severe patient group are higher than the mild group. The RCADS parent- and adolescent-reported depression scores and parent-reported social phobia scores of the control group were significantly higher than the mild group. There were no statistically significant differences between the groups according to COVID-19 Phobia Scale.

Conclusion: The healthy adolescents had higher psychiatric symptom scores, especially than the adolescents with mild IEI. We suggest that being exposed to health-related challenges even before the pandemics in adolescents with IEI helped them develop psychological resilience. Longitudinal and larger studies are needed to evaluate the long-term effects of the pandemic on the mental health of this vulnerable adolescent population.

Key Words: Adolescents, COVID-19 Pandemic, Primary immunodeficiency, Mental health

ÖZ

Amaç: Bu çalışma, doğuştan bağışıklık yetersizliği olan ergenlerin psikososyal işlevleri üzerinde COVID-19'un etkisini belirlemeyi amaçlamıştır.

Gereç ve Yöntemler: Bu çalışmaya 36 doğuştan bağışıklık yetersizlik hastası (18 hafif, 18 şiddetli) ve yaşları 10-17 arasında 18 sağlıklı kontrol dahil edildi. Ergenler ve onların ebeveynleri, kaygı ve depresyon semptomlarını ölçmek için Gözden Geçirilmiş Çocuk Kaygısı ve Depresyon Ölçeği'ni (RCADS) ve sosyal davranışları ve duygusal/davranışsal sorunları



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değerlendirmek için Güçler Güçlükler Anketi'ni doldurdu. Ek olarak, ergenler tarafından koronavirüs fobisinin düzeyini değerlendirmek amacıyla COVID-19 Fobi Ölçeği (C19P-S) yanıtlandı.

Bulgular: Güçler Güçlükler Anketi'ne göre kontrol grubundaki ergenlerin duygusal puanları hafif/ağır hasta grubuna göre daha yüksekti. Ağır hasta grubunun emosyonel puanları hafif gruba göre daha yüksekti. RCADS ebeveyn ve ergen skorlarına göre, kontrol grubunun depresyon puanları ve ebeveynlerin sosyal fobi puanları hafif gruba göre anlamlı derecede yüksekti.

Sonuç: Bu çalışma sonuçlarına göre sağlıklı ergenlerin psikiyatrik belirti skorları, özellikle hafif doğuştan bağışıklık yetersizliği olan ergenlere göre daha yüksekti. Doğuştan bağışıklık yetersizlikleri ergenlerin pandemiden önceki dönemde sağlıklı ilgili zorluklara maruz kalmalarının dayanıklılık geliştirmelerine yardımcı olduğunu düşünüyoruz. Pandeminin bu savunmasız ergen popülasyonunun ruh sağlığı üzerindeki uzun vadeli etkilerini değerlendirmek için uzun vadeli ve daha büyük çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Ergenler, COVID-19, Primer immün yetmezlik, Ruh sağlığı

INTRODUCTION

The clinical course of COVID-19 infection in healthy children and adolescents has been reported to be milder than adults (1) and rarely progresses to acute respiratory distress syndrome, multiorgan system dysfunction and death (2). However, in the children and adolescents with inborn errors of immunity (IEI), the clinical course of COVID-19 differs from mild illness to death, which largely varies with the patient's age and the presence of immunosuppressive comorbidities (3). International studies show that more than 30% of patients with IEI have had mild COVID-19 infection and the 10% case-fatality rate was similar to the global data of the general population (4). On the other hand, in a Turkish study the COVID-19 infection mortality rate was reported as 7.6% among patients with IEI, which is eight times higher than the infection mortality rate (0.97%) of Turkey's general population (5). This wide range of mortality rates in different studies may be explained by the disease heterogeneity and concomitant comorbidities, as well as the differences in reporting systems in various countries.

Although adolescents' physical health was a less concern compared to other age groups, COVID-19-related mental health issues such as emotional reactions including concern, fear, and anxiety about being infected by the virus and depression, obsessive-compulsive symptoms, somatization, and behavioral issues have been found to be higher in young healthy individuals in most studies (6). However, there is limited data about the psychosocial effects of the pandemic on adolescents with chronic conditions (7). There are rare pre-pandemic studies about the behavioral, emotional and psychological well-being of adolescents with IEI and their parents. In these studies, it was reported that adolescents with IEI had significantly lower quality of life scores in adolescent and parent-rated questionnaires compared to healthy controls. In addition to this, higher rates of emotional, peer-relationship difficulties, anxiety and depressive scores were also reported in patients with IEI when compared to healthy controls (8,9). Psychosocial functionality in adolescents with IEI has not yet been the subject of extensive COVID-19 related psychological studies.

The management of a chronic illness during adolescence poses a significant burden not only for the adolescent but also for the

parents, caregivers, and the health care providers (10). Recurrent and chronic infections, concomitant medical problems, regular hospital visits, the need for frequent hospitalization, and long-term treatment with immunoglobulin replacement therapy and immunomodulatory drugs add to the burdens imposed on patients with IEI and their families. Some studies reported that the parents of adolescents with chronic conditions experienced higher levels of anxiety and post-traumatic stress than controls during the pandemic (11,12).

We hypothesized that adolescents with IEI may have greater levels of behavioral, depressive, and anxiety symptoms than their healthy peers. The aim of this study was to investigate how COVID-19 affected the psychological, emotional, and behavioral well-being of adolescents with IEI.

MATERIAL and METHODS

Participants

This study was conducted by the divisions of Adolescent Medicine, Pediatric Immunology and Child and Adolescent Psychiatry of the Hacettepe University. This study took place between April and July 2021, during which pandemic curfews imposed on weekdays and weekends, school closures and intercity travel bans continued in Turkey. Between the ages 10 and 17 years, healthy adolescents who visited the Adolescent Medicine clinic formed the control group and adolescents with IEI who were followed up by the division of Pediatric Immunology formed the study group. The groups were age and gender-matched. The IEI group was further classified as mild and severe subgroups. Thirty-six patients with IEI (18 mild, 18 severe) and 18 healthy controls aged between 10 and 17 from a single children's hospital were included in this study.

All IEI patients were clinically diagnosed before the COVID-19 pandemic. The clinical diagnoses were made according to the European Society of Immunodeficiencies (ESID) guidelines (13). Since there is not any standardized form for the assessment of IEI severity, we modified a previously used scale to determine the IEI severity of the adolescent patients included. A severity score was calculated for each patient using the following: T-cell levels less than 500 cells/ μ l were assigned 8 points, for each immunoglobulin class impacted 1 point was assigned

(maximum of 4), receiving immunoglobulin replacement therapy was 4 points, and immunosuppressant/immunomodulatory therapy usage was 3 points. These points were tailed and the child was assigned to a severity group (mild 0-5, moderate >6). During the study period, no patients were diagnosed with COVID-19. None of the participants were vaccinated against COVID-19 at the time of the study since vaccination for that age group in the country had not yet started.

The exclusion criteria for IEI group were having a diagnosis of a psychiatric disorder and intellectual disability before pandemic. There were no patients with a previous psychiatric disorder or intellectual disability in the patient group. Having a previous chronic, systemic or psychiatric disorder and/or intellectual disability before pandemic period were also the exclusion criteria for the control group. All adolescents in the healthy control group were interviewed by HEEADSSS (home, eating, education, activities, drugs, sexuality, suicide, safety) psychosocial assessment which is a part of the standard care routine of the Adolescent Medicine clinic and offers a framework for gathering detailed data about the young person's strengths and risky behaviors. At the end of this interview, adolescents who were determined not to have any psychiatric disease were included in the control group. Eight adolescents in the control group were excluded according to exclusion criteria. This study was approved by the Ethics Committee of the Hacettepe University (Decision number: 2021/368) and the Turkish Ministry of Health. Written informed consent were obtained from both adolescents and their parents.

Measures

Sociodemographic Information Form

This form was designed by the authors and included the parents' age and gender, the participants' age and gender, school grade, the number of children in the family, family structure (core, separated, large etc.), settlement (village, town, city), family income, parents' educational and employment status, family history of psychiatric disorders, and family history of COVID-19 infection.

Revised Child Anxiety and Depression Scale (RCADS)

The RCADS consists of 47 items developed to measure DSM-IV based symptoms of anxiety disorders and depression in children and adolescents. The subscales correspond to separation anxiety disorder (SAD) (7 items), social phobia (SP) (9 items), generalized anxiety disorder (GAD) (6 items), panic disorder (PD) (9 items), obsessions/compulsions (6 items) and major depressive disorder (MDD) (10 items). RCADS provides two summary scales: 1. Total anxiety and depression (total internalizing score), 2. Total anxiety and six subscales (14). In all instances, a higher score reflects a greater degree of symptom severity. Turkish reliability and validity study of the RCADS was provided by Gormez et al. (15) in children aged 8-17 years old. Inter-scale reliability is strong/excellent with a Cronbach's α of

0.95 and coefficients for the RCADS subscales ranging from 0.75 to 0.86 demonstrating good internal consistency. RCADS was administered face to face to both the participant and one of the parents.

Strengths and Difficulties Questionnaire (SDQ)

The SDQ is a brief behavioural screening questionnaire designed to assess prosocial behaviors and emotional/behavioral problems of children. It contains five subscales, 25 questions (positive/negative). Subscales are inattention/hyperactivity, emotional problems, conduct problems, peer problems and prosocial behaviour. The scores related for inattention/hyperactivity, emotional problems, conduct problems, and peer problems can be summed to form a total difficulties score ranging from 0-40. The prosocial score is not included in the total score and is rated as positive behavior while others are rated as negative (16). High scores indicate greater clinical psychopathologies. The Turkish reliability and validity study was provided by Güvenir et al. (17) in children aged between 4-18. The Turkish SDQ was observed to be stable and reliable. SDQ was administered face to face to both the participant and one of the parents.

COVID-19 Phobia Scale (C19P-S)

C19P-S is a self-report five-point Likert-type scale which aims to assess the levels of coronavirus phobia developed by Arpacı et al. (18) in Turkey. The total score ranges from 20-100. It includes 20 items, 4 subscales (psychological factors, psychosomatic factors, economic factors, social factors). High scores indicate a greater phobia. C19P-S was administered face to face to the adolescents in both groups. The validity and reliability study of this scale was conducted between the ages of 12 and 92 (18).

Statistical Analyses

Statistical analyses were performed with the IBM SPSS Statistics for windows version 23. (IBM Corp., Armonk, NY) software. Frequencies and percentage for qualitative variables, mean \pm standard deviation or median (min-max) for numerical variables were used as descriptive statistics. The Shapiro-Wilk test was used to determine if the numerical variables were normally distributed or not. Chi-square test was used to determine whether there was a difference in terms of qualitative variables among three groups. When numerical variables were normally distributed one-way ANOVA was used and pairwise comparisons were performed using the Tukey test; otherwise the Kruskal-Wallis test was used and pairwise comparisons were performed using Dunn's test. A statistically significant P value of 0.050 was used.

RESULTS

Demographic features of the participants are listed in Table I. There were no statistically significant differences between the

Table I: Demographic Features of the Groups

	Severe (n=18)	Mild (n=18)	Control (n=18)	F /X ²	p
Participant age (mean±SD)	14.4 ± 2.1	14.0 ± 2.3	14.3 ± 1.57	0.176	0.839
Participant gender*					
Girl	6 (33.6)	6 (33.3)	6 (33.3)	0.000	1.000
Boy	12 (66.7)	12 (66.7)	12 (66.7)		
Parent's gender*					
Mother	13 (72.2)	12 (66.7)	13 (72.2)	0.178	0.915
Father	5 (27.8)	6 (33.3)	5 (27.8)		
Mother's age*					
<29	1 (5.6)	1 (5.6)	0 (0.0)	7.422	0.217
30-39	4 (22.2)	8 (44.4)	5 (27.8)		
40-49	12 (66.7)	9 (50)	9 (50)		
≥50	1 (5.6)	0 (0.0)	4 (22.2)		
Father's age*					
<29	0 (0.0)	1 (5.6)	0 (0.0)	9.720	0.08
30-39	2 (11.1)	4 (22.2)	1 (5.6)		
40-49	14 (77.8)	11 (61.1)	9 (50.0)		
≥50	2 (11.1)	2 (11.1)	8 (44.4)		
Mother's grade at school*					
Illiterate	0 (0.0)	1 (5.6)	0 (0.0)	8.433	0.596
Literate	0 (0.0)	0 (0.0)	2 (11.1)		
Primary-middle school	7 (38.9)	5 (27.8)	6 (33.3)		
High school	7 (38.9)	10 (55.6)	6 (33.3)		
Graduate	4 (22.2)	2 (11.1)	3 (16.7)		
Postgraduate	0 (0.0)	0 (0.0)	1 (5.6)		
Father's grade at school*					
Illiterate	0 (0.0)	1 (5.6)	0 (0.0)	7.355	0.466
Literate	0 (0.0)	0 (0.0)	1 (5.6)		
Primary-middle school	9 (50)	8 (44.4)	4 (22.2)		
High school	5 (27.8)	5 (27.8)	9 (50.0)		
Graduate	4 (22.2)	4 (22.2)	4 (22.2)		
Postgraduate	0 (0.0)	0 (0.0)	0 (0.0)		
Mother's employment status*					
Not working	14 (77.8)	14 (77.8)	15 (83.3)	0.336	1.000
Working	4 (22.2)	4 (22.2)	3 (16.7)		
Father's employment status*					
Not working	3 (16.7)	2 (11.1)	4 (22.2)	0.857	0.898
Working	15 (83.3)	16 (88.9)	14 (77.8)		
Family Structure*					
Core	16 (88.9)	16 (88.9)	16 (88.9)	2.405	1.000
Large	1 (5.6)	2 (11.1)	2 (11.1)		
Other (divorced etc.)	1 (5.6)	0 (0.0)	0 (0.0)		
Living place*					
Village	0 (0)	0 (0)	0 (0.0)	3.060	0.349
Town	2 (11.1)	3 (16.7)	0 (0.0)		
City	16 (88.9)	15 (83.3)	18 (100)		
Family history of psychiatric disorders*					
No	15 (83.3)	14 (77.8)	14 (82.4)	0.316	1.000
Family work impact status from Covid*					
No	10 (55.6)	9 (50.0)	11 (61.1)	0.450	0.799
Family history of Covid*					
No	14 (77.8)	14 (77.8)	8 (44.4)	6.000	0.05

*n (%)

three groups according to the parents' and the participants' age and gender, school grade, the number of children in the family, family structure, settlement, family income, parent's educational and employment status, family history of psychiatric disorders, and family history of COVID-19 infection.

The median (min-max) values of the SDQ subgroup scores in the parent and adolescent groups are presented in Table III. The highest emotional symptom scores of adolescents were observed in the control group, the lowest were observed in the mild IEL group. Emotional scores of the control group

Table II: Diagnostic Subgroups of Adolescents with IEI

IEI Groups	n (%)	Severe /Mild (n)
Innate immune system defect	5 (14)	1/4
Immune deficiency with immune dysregulation	7 (20)	4/3
Primary antibody deficiency	4 (12)	3/1
Combined immune deficiency	10 (27)	10/0
Autoinflammatory disease	1 (3)	0/1
Other antibody deficiency	9 (24)	0/9

Table III: Parental and Adolescents' Scores of the SDQ

SDQ Subgroup	Severe (n=18) Median (min-max)	Mild (n=18) Median (min-max)	Control (n=18) Median (min-max)	Kruskal -Wallis H	p
Emotional Symptoms					
Parent	2.0 (0-6)	1.0 (0-6)	2.0 (0-6)	0.471	0.790
Adolescent	2.0 (0-7) ^a	1.0 (0-3) ^{a,b}	2.0 (0-10) ^b	8.300	0.016
Conduct Problems					
Parent	0.0 (0-3)	1.0 (0-5)	1.0 (0-4)	4.394	0.111
Adolescent	1.0 (0-5)	2.0 (0-5)	2.0 (1-6)	1.966	0.374
Inattention/ Hyperactivity					
Parent	3.0 (0-9)	3.0 (0-8)	4.0 (2-7)	3.004	0.223
Adolescent	3.0 (0-10)	3.0 (0-6)	3.5 (0-9)	0.704	0.798
Peer Problems					
Parent	4.0 (1-6)	2.0 (0-6)	3.5 (0-6)	2.895	0.235
Adolescent	3.0 (0-4)	3.0 (0-5)	3.0 (0-9)	0.451	0.796
Prosocial Behaviour					
Parent	8.0 (4-10)	7.5 (4-10)	7.0 (2-10)	1.830	0.400
Adolescent	8.0 (4-10)	8.0 (4-10)	8.0 (3-10)	0.933	0.627
Total Deviance/ Difficulties					
Parent	9.5 (2-18)	7.5 (2-23)	9.5 (6-19)	3.090	0.213
Adolescent	10.5(5-20)	8.5 (4-15)	11 (3-31)	3.722	0.155

SDQ: Strength and Difficulties Questionnaire, **a, b:** There was a statistically significant difference between the groups indicated with the same letter ($p < 0.050$).

Table IV: Scores of the COVID-19 Phobia Scale in Adolescents

C19P-S Subgroup	Severe (n=18) Median (min-max)	Mild (n=18) Median (min-max)	Control (n=18) Median (min-max)	Kruskal -Wallis H	p
Psychological factors	20.5 (6-30)	14.0 (7-28)	14.0 (6-27)	0.867	0.648
Psycho-somatic factors	8.0 (5-20)	5.5 (5-17)	7.0 (5-15)	1.794	0.408
Social factors	13.0 (5-24)	9.0 (5-25)	11.5 (5-18)	2.639	0.267
Economic factors	7.0 (4-17)	6.5 (4-16)	6.0 (4-17)	1.872	0.392
Total score	35.5 (15-65)	27.5 (16-59)	29.0 (17-46)	1.606	0.448

were statistically higher than the severe and mild IEI groups ($p < 0.050$). Also, the emotional scores of adolescents were statistically different between the severe-mild IEI and mild IEI-control groups ($p = 0.016$). There were no statistically significant differences between the groups according to parent scores ($p = 0.790$). The subgroup scores of C19P-S are presented in Table IV.

There were no statistically significant differences between the groups according to COVID-19 Phobia Scale. However, the depression and social phobia subgroup scores of parents in the control group were statistically higher than the mild IEI group in RCADS questionnaire ($p = 0.001$ and $p = 0.031$). The depression

scores of adolescents in the control group were significantly higher than the mild group ($p = 0.006$). Parental and adolescent scores in the severe group were higher than the mild group but lower than the control group, but the difference was not statistically significant (Table V). All adolescents with high scores were referred for further psychiatric evaluation.

DISCUSSIONS

In this study, emotional and behavioral problems and anxiety and depressive symptoms of adolescents with mild and severe

Table V: Parental and Adolescents' Scores of the RCADS

RCADS Subscores	Severe (n=18) Median (min-max)	Mild (n=18) Median (min-max)	Control (n=18) Median (min-max)	Kruskal -Wallis H	p
Separation anxiety					
Parent	2.5 (0-10)	2.0 (0-5)	2.0 (0-7)	2.048	0.359
Adolescent	2.0 (0-6)	1.5 (0-10)	1.0 (0-9)	0.234	0.890
Generalized anxiety					
Parent	4.9 (2-11)	4.4 (0-12)	5.0 (0-15)	1.019	0.601
Adolescent	6.0 (0-10)	6.0 (1-12)	7.0 (0-13)	0.137	0.934
Depression					
Parent	7.0 (2-15)	4.0 (1-15) ^a	9.0 (5-20) ^a	13.847	0.001
Adolescent	7.0 (0-21)	4.0 (1-19) ^b	10.5 (1-23) ^b	10.115	0.006
Panic disorder					
Parent	2.0 (0-14)	2.0 (0-6)	3.0 (0-9)	2.018	0.365
Adolescent	3.0 (0-10)	3.0 (0-15)	3.5 (0-18)	1.164	0.320
Social phobia					
Parent	5.5 (0-18)	5.2 (1-19) ^c	9.0 (0-19) ^c	6.976	0.031
Adolescent	7 (1-17)	5.8 (2-15)	9.0 (4-21)	4.148	0.126
Obsessions /compulsions					
Parent	3.5 (0-12)	2.0 (0-12)	2.5 (0-10)	0.365	0.833
Adolescent	5.0 (0-9)	4.0 (0-10)	5.0 (0-12)	2.815	0.245
Total anxiety					
Parent	20.0 (4-64)	16.0 (4-38)	27.5 (1-55)	3.396	0.183
Adolescent	23.0 (4-68)	21.3 (8-51)	28.5 (10-66)	2.252	0.324
Total anxiety & depression					
Parent	29.3 (7-76)	19.7 (5-45)	36.0 (9-75)	5.506	0.064
Adolescent	29.0 (4-59)	24.5 (10-70)	38.5 (11-86)	4.714	0.095

RCADS: Revised Child Anxiety and Depression Scale, ^{a, b, c}: There was a statistically significant difference between the groups indicated with the same letter ($p < 0.050$).

IEI were compared to healthy controls during the early stages of COVID-19 pandemic when isolation rules were strictly continued in Turkey. In contrast to our hypothesis, we found that healthy controls exhibited more emotional/depressive and social phobia symptoms than the adolescents with mild IEI. On the other hand, the severe IEI group had significantly higher emotional symptoms than the mild IEI group. The highest depressive symptoms were observed in the control group. The depressive symptoms of the severe IEI group were higher than the mild IEI group, but the only significant difference was between the control and the mild IEI group scores. In addition, coronaphobia levels and anxiety symptoms were not different between the three groups.

In contrast to our results demonstrating that the highest emotional symptoms were observed in the control group, P. Titman et al. (9) showed that children with primary antibody deficiency had significantly higher emotional scores of SDQ than the healthy controls. Their results were also consistent with studies designed in patients with different types of IEI and healthy children (19). Kuburovic, et al. (8) using different self and parent-rated assessments, found that children with IEI had significantly lower emotional functioning, higher anxiety and depressive symptoms than children with juvenile idiopathic arthritis (JIA) and healthy controls. In a different study designed by Ocaçoğlu, et al. (20) the rate of psychopathology was found similar in IEI and JIA patients, being higher than the healthy control group. Piazza-Waggoner, et al. (21) also observed that

as the severity of the disease increased, patients' psychosocial functioning deteriorated. However, all these studies showing that the psychosocial functioning of healthy children are higher than the IEI group, were conducted before the pandemic.

During the pandemic, the lockdowns, school closures, spending much more time at home, obligation to wear a mask, decreased social interaction, fear of getting infected had a negative impact on all adolescents. Some of these drastic changes occurred with the pandemic in the lives of healthy adolescents might have been already experienced before the pandemic at some level by the patients with IEI as a burden of their disease and related lifestyle. On the other hand, facing the risk of experiencing a serious health problem like the pandemic for the first time in the healthy control group may have increased their fear, anxiety and they may have failed to elicit a coping response. This might be the cause of our results contradicting the studies conducted prior to the pandemic. In addition, compared to the IEI group, higher family history of COVID-19 infection in the control group, although not statistically significant, may have affected their family functionality and this may have been reflected as emotional symptoms.

Another study from Turkey by Kılıç et al. (22) investigated the effects of COVID-19 pandemic on mental health of children with IEI found the depression scores significantly higher in patients with IEI than controls. However, they used only parent-reported scales and the study was performed at a different time period

during the pandemic with less limited social restrictions. A study evaluating the effect of pandemic on anxiety symptoms among Turkish adolescents with another chronic condition, cystic fibrosis (CF) found that COVID-19 had no effect on the anxiety of adolescents with CF (23). Similar to our results, healthy children had higher anxiety symptoms than patients with CF.

Although COVID-19 pandemic is expected to bring more stress for the immune compromised patients and their families, the lower emotional symptoms of mild IEI group than healthy control group in adolescents in our study may also be the result of both the patient's and parents' being exposed to the difficulties prior to the pandemic resulting from having a chronic condition, recurrent complicated medications and hospitalizations that leads to post-traumatic growth and resilience in the adolescents with mild IEI. Post-traumatic growth is defined as a significant positive change in an individual's life as an effect of exposure to a traumatic event which is a process that goes beyond the absence of symptoms or a return to baseline functioning following a trauma such as experiencing a serious pediatric illness (24,25). Eventually, these adolescents develop resilience as the ability to maintain healthy levels of functioning despite difficult experiences or returning to normal functioning when experiencing crisis and are more adaptive when responding (26,27). However, the adolescents with severe IEI having more difficulties in their disease management, poorer course of the disease with regard of disease activity and duration and more impaired quality of life may have caused higher emotional and depressive symptoms than the mild group.

In this study, adolescent-rated emotional symptoms scores of SDQ and parent-rated social phobia scores of RCADS were significantly different between three groups. Hence, adolescent and parent scores differed in terms of emotional symptoms and social phobia scores both in SDQ and RCADS scales, as with some other subscales. Similar to our study, parent-child agreement on reports of especially internalizing symptoms has been shown to be low in previous studies (29,30). Internalizing symptoms are generally better described by patients than parents (28).

This study has some limitations. First of all, it was conducted in a single center which limited reaching a larger sample of patients. To accurately analyze the effect of the pandemic, the data were collected before the COVID-19 restrictions were dropped in Turkey. Therefore, the limited number of participants is due to the restricted time between the onset of the study and the onset of the normalization period. Also, as this was a cross-sectional study, we could not analyze the premorbid characteristics and psychosocial functionality of the adolescents before the pandemic. We also could not conduct a formal interview with the IEI patients to identify psychosocial challenges because of the pandemic restrictions. However, participants in the IEI group had not been previously diagnosed with a psychiatric disorder. Despite these limitations, there are some strengths of this study. This is one of the first study evaluating the psychiatric

effects of COVID-19 pandemic on adolescents with IEIs. The assessments being performed both for the parent and the adolescent in a limited time frame is another strength of the study.

In conclusion, healthy adolescents had more psychiatric symptoms than the adolescents with mild IEI during the pandemic, and the adolescents with IEIs did not have higher coronaphobia than their healthy peers. We suggest that being exposed to health-related challenges even before the pandemics in adolescents with IEI helped them to develop psychological resilience. However, the emotional and behavioral symptoms in adolescents with severe IEI were higher than the ones with mild IEI both in parental and adolescent reports. This finding is most probably because of the awareness of the increased burden of the disease, significant morbidity and poorer course of severe IEI. Although there is no significant difference between the COVID-19 Phobia Scale scores, family history of COVID was seen more frequently, close to a significant level, in the control group than in the disease group. This may be a limitation that affected the results. This study points out that routine psychosocial screening is essential for all adolescents especially in risky conditions that poses a threat to their mental health and wellbeing. Healthcare providers should pay attention to disease characteristics and personal strengths while evaluating for psychosocial stressors in adolescents with IEI.

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