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Psychiatric Comorbidities in Children with Primary Immunodeficiency: A Randomized-Controlled Study

Primer İmmün Yetmezlikli Hastalarda Psikiyatrik Komorbiditeler: Randomize Kontrollü Çalışma

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ABSTRACT Objective: Primary immunodeficiency disorder (PID) comprises a broad, divergent group of disorders which emerge from defects in the development and functioning of the immune system. Our objective was to evaluate and compare emotional and behavioural problems in children and adolescents with PID. **Material and Methods:** The study involved 97 patients with PIDs following Bursa Uludağ University, Department of Pediatric Immunology from 2021 to 2022 and 82 healthy control. The Strengths and Difficulties Questionnaire, The Revised Child Anxiety and Depression Scale, and SNAP-IV Inattention and Hyperactivity/Impulsivity questionnaire were made to patients with PID and their caregivers regarding their concerns living with PID and to detect concurrent mental health. **Results:** Of 97 patients, 60 (61.2%) were female and 31 (38.8%) were male. The mean age of patients was 12.23±6.06 years. Common variable immunodeficiency (n=36, 37.6%) and Di George syndrome (n=23, 23.5%) were the most prevalent PIDs in the study, respectively. The children stated higher separation anxiety (p<0.01) panic disorder (<0.01). The parents disclosed statistically higher behavioral problems (p<0.01), social phobia (p<0.01) and depression (p<0.01). **Conclusion:** This study proved that living with PID negatively impacts children's and adolescents' mental health. Psychological co-morbidities are extremely common amongst those with chronic illnesses. Improvements in health and disease education are required to ensure a high quality of life. To relieve the psychological strain on children and also their caregivers, therapeutic options should be placed, including various support groups and counseling options.

Keywords: Psychology; depression; child; anxiety, seperation; common variable immunodeficiency

ÖZET Amaç: Primer immün yetmezlik bozukluğu [primary immunodeficiency disorder (PID)], bağışıklık sisteminin gelişimi ve işleyişindeki kusurlardan kaynaklanan geniş ve farklı bir grup hastalıktan oluşur. Amacımız PID'li çocuk ve ergenlerde duygusal ve davranışsal sorunları değerlendirmek ve karşılaştırmaktır. **Gereç ve Yöntemler:** Çalışmaya 2021-2022 yılları arasında Bursa Uludağ Üniversitesi Çocuk İmmünoloji Ana Bilim Dalında takip edilen 97 PID hastası ve 82 sağlıklı kontrol dâhil edildi. Güçlü Yönler ve Zorluklar Anketi, Gözden Geçirilmiş Çocuk Anksiyete ve Depresyon Ölçeği ve SNAP-IV Dikkat Eksikliği ve Hiperaktivite/Dürtüsellik anketi, PID'li hastalara ve bakım verenlerine PID ile yaşama kaygılarına ilişkin ve eş zamanlı zihinsel bozuklukları tespit etmek için uygulandı. **Bulgular:** 97 hastanın 60'ı (%61,2) kadın, 31'i (%38,8) erkekti. Hastaların yaş ortalaması 12,23±6,06 yıldı. Çalışmada en sık görülen PID'ler sırasıyla yaygın değişken immün yetmezlik (n=36, %37,6) ve Di George sendromu (n=23, %23,5) idi. Çocuklarda ayrılık anksiyetesi (p<0,01) ve panik bozukluğu (<0,01) daha yüksek bulundu. Ebeveynler istatistiksel olarak davranış sorunlarının (p<0,01), sosyal fobinin (p<0,01) ve depresyonun (p<0,01) daha yüksek olduğunu bildirdiler. **Sonuç:** Bu çalışma, PID ile yaşamanın çocuk ve ergenlerin ruh sağlığını olumsuz etkilediğini kanıtlamıştır. Kronik hastalığı olanlarda psikolojik rahatsızlıklar oldukça yaygındır. Yüksek yaşam kalitesini sağlamak için sağlık ve hastalık eğitiminde iyileştirmeler yapılması gerekmektedir. Çocuklar ve aynı zamanda onlara bakan kişiler üzerindeki psikolojik baskıyı hafifletmek için çeşitli destek grupları ve danışmanlık seçenekleri göz önünde bulundurulmalıdır.

Anahtar Kelimeler: Psikoloji; depresyon; çocuk; anksiyete, ayrılık; yaygın değişken immün yetmezlik

Primary immunodeficient disorders (PID) constitute a diversified group of immune system disorders and contain a group of more than 450 hereditary diseases.[1] The clinical aspects of PID vary widely, and different parts of the immune system and other organ systems can be implicated. Due to immune system deficiency, patients with PID have an increased rate of recurrent infections, immune dysregulation, auto-immune disease, and malignancy.[1] The chronic course of the disease, severe infections, recurrent hos-

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pitalizations, life-long treatments, progressive or fatal nature of PIDs, the risk of multi-organ failure and poor prognosis, residual physical impairment, and shortened life expectancy make susceptible the patients to some psychiatric problems.

It is increasingly evident that being immunocompromised can cause some psychiatric disorders through various mechanisms, such as altered neurodevelopment stages, blood-brain barrier disruption, post-infectious micro-glia, or microbial dysbiosis.[2] The brain and immune system act similarly; that is, they consistently and accurately recognize between "threatening" and "non-threatening" to the individual.[3] Selective immunoglobulin A deficiency has been associated with an increase in lymphoid tissue infections associated with the mucous membrane (MALT), which is an important defensive barrier. It has been suggested that conditions within MALT can be associated with some forms of psychopathology in children, specifically obsessive-compulsive disorder and chronic tic disorders.[4] In a broad population-based study, patients with primary humoral immunodeficiency showed suicidal behaviour, particularly among women.[5] The accumulation of evidence suggests that immune system dysfunction is linked to autism disorders in a specific subset of children. An autoimmune process triggered by an infection in immunocompromised patients may cause neuroinflammation and autism spectrum disorders in the uterus and after birth.[6]

The purpose of this study was to evaluate the emotional and behavioural problems of children and adolescents suffering from PID. It is also essential to interpret parents' approach when assessing the severity and course of mental disorders of children with PID.

MATERIAL AND METHODS

STUDY POPULATION

Our study population included PID patients, followed by the department of pediatric immunology at between 2021 and 2022. The age spectrum varied from 5 to 18 years. This study was conducted with a total of 97 patients with PID and 82 age-paired healthy controls Patients with PID older than 12 years old and controls answered the questions themselves, while patients with PID aged 5-12 years answered under parental supervision. The median follow-up time was 86 months (minimum=12, maximum=262). Data from patients under 12 years of age with neurological or mental disorders did not include comparisons. Patients filled out a data form with questions on sociodemographic and clinical characteristics. The Strengths and Difficulties Questionnaire (SDQ), The Revised Child Anxiety and Depression Scale (RCADS), SNAP-IV Inattention and Hyperactivity/Impulsivity questionnaire were completed by the participants.[7]

Demographic data, patient diagnosis classifications, and a total score of psychiatric conditions were evaluated for each patient. Written informed consent was obtained from patients or their parents, and healthy controls and, ethical approval (date: February 21, 2023, no: 2023-3/26) was obtained through the Bursa Uludağ University Clinical Research and Ethics Committee. This study was conducted in accordance with the principles of the Declaration of Helsinki.

PSYCHIATRIC ASSESSMENT MEASURES

The SDQ,

SDQ the SDQ is a 25-item screening questionnaire. The items are categorized into five subgroups of each, creating scores for emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and prosocial behaviors.

The RCADS,

The revised Anxiety and Depression Scale for Children has an applicability advantage compared to other self-reported questiones for anxiety and depression in children and adolescents. Items are counted on a four-point Likert scale: 0 (ever), 1 (sometimes), 2 (often) and 3 (always).

SNAP-IV Inattention and Hyperactivity/Impulsivity Questionnaire

SNAP-IV is used to obtain parental scores. The 26 compoonents of the SNAP-IV comprises the 18 ADHD symptoms (9 for inattentive, 9 for hyperactive/impulsive) and 8 ODD symptoms defined in the Diagnostic and Statistical Manual of Mental Disor-

ders-IV. Items were marked on a 4-point scale from (0) not at all to many.

Sociodemographic İnformation Form

This form has been designed to collect the following data: age; level of education; gender; marital status of parents; socio-economic status.

STATISTICAL ANALYSIS

The statistical analysis was completed by SPSS version 28.0 (IBM, Armonk, New York, United States). $p<0.05$ is regarded as significant. Descriptive statistical methodologies were used to analyze participants' socio-demographic characteristics. The normal distribution of the variables was determined using probabilistic graphs and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). The scores were analysed through the independent t-test.

RESULTS

The study consists of 97 children and adolescents, those 37 (54.9%) female and 59 (60.8%) male. The mean age of patients was 12.10±3.888 years. The median follow-up time was 86 months (minimum=12, maximum=262). Eighty-two age-matched healthy control were included in the study. The scores of RCADS, SDQ, and SNAP-4 compared with the control group. The blank forms (if there is any empty answer form accepted as blank) were excluded from the study. The demographic status of the study and control group is listed in Table 1.

Common variable immunodeficiency (CVID) (n=36, 36.7%) and Di George syndrome (DGS) (n=23, 23.5%) were the most common PIDs in our study, respectively. The distribution of the diagnosis of the PID group is given in Figure 1. The emotional and behavioral problems perceived by parents were statistically higher in PID groups in terms of behavioral issues ($p<0.01$), social phobia ($p<0.01$), and depression ($p<0.01$) (Table 2).

The emotional and behavioral problems perceived by children and adolescents were statistically higher in PID groups in terms of separation anxiety ($p<0.01$), panic disorder (<0.01), and depression (<0.01) (Table 3).

DISCUSSION

In this study, we assessed the psychiatric comorbidities in children with PID. We found that statistically significant emotional and peer relation problems, panic disorder, depression, and attention deficiency, were noted by parents, and separation anxiety and depression by children. These results showed that mood problems for a long duration of disease in children and adolescents are the most critical stressor for parents. However, parents' first reaction at diagnosing their children with PID may often comprise acute fear and anxiety related to the possible fatal course of the disease, refusal of the diagnosis, the sorrow of losing their child, and self-blame.[8] Parents of patients with PID have difficulty coping with their children's disease progression and psychiatric problems. Approving a child's illness and its impact on family members is essential to supporting the child's healthy personality development.[9] Kayan Ocakoglu et al. screened anxiety-related emotional disorders in patients with PID and Juvenile idiopathic atrhtitis (JIA) by questionnaire.[10] The rate of mood disorders and other psy-

TABLE 1: Comparison of the sample according to sociodemographic features.

		Patients with primary immunodeficient disorder 97		Controls 82		
		n	%	n	%	p value
Gender	Male	59	60.8	45	54.9	0.71
	Female	37	54.9	38	45.1	
Age		12.10±3.888		12.94±2.411		0.93
Psychiatric disease in the family	No	81	83.5	70	85.4	0.837
	Yes	16	16.5	12	14.6	
Physical disease in the family	No	60	61.9	14	73.7	0.239
	Yes	37	38.1	5	11.9	

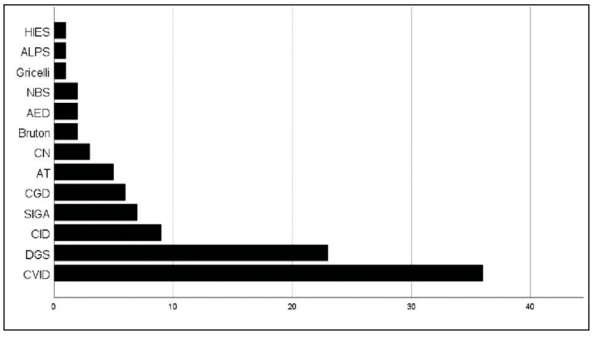

FIGURE 1: The distribution of the diagnoses of patients with primary immunodeficiency disorder.
HIES: Hyper immunoglobulin E syndrome; ALPS: Autoimmun lymphopriliferative syndrome; NBS: Nijmegen breakage syndrome; AED: Anhidrotic ectodermal dysplasia; CN: Congenital neutropenia; AT: Ataxia telengectasia; CGD: Chronic, granulomatosis disease; SIGA: Selective Ig A deficiency; CID: Combined immunodeficiency; DGS: Di George syndrome; CVID: Common variable immunodeficiency.

chopathologies was similar in patients with PID and JIA and higher than in the controls. Depression was a remarkable finding in patients receiving regular intravenous immunoglobulin (IVIG) treatment. On the contrary, no relationship was found between IVIG treatment and depression in our study. It can be explained that families and health workers support and give good care to children receiving IVIG treatment.

There are a few studies concerning PID patients' mental health. Previous research on pediatric PID indicates that patients are at increased risk of school absenteeism, limited participation in social and physical activities, and symptoms of anxiety and depression. The other study disclosed that pediatric PID patients developed psychosocial problems, e.g., peer relationship difficulties and hyperactivity.[11] In our study, children reported separation anxiety and emotional issues, which may affect school attendance and mood status.

TABLE 2: Comparison of emotional and behavioral problems perceived by parents.

Disorder	Group	n	$\bar{X}$±SD	p value
Attention deficit hyperactivity	Study	97	4.3093±2.40815	0.6
	Control	37	4.108102±28259	
Behavioral problems	Study	97	3.2268±1.71090	**<0.01**
	Control	37	1.9189±1.46018	
Emotional problems	Study	97	3.5155±2.35458	0.154
	Control	37	2.8649±2.32334	
Peer relation problems	Study	97	3.5773±2.00434	0.306
	Control	37	3.1892±1.80797	
Prosocial skills	Study	97	7.6186±2.24278	0.49
	Control	37	7.3243±2.26144	
Social phobia	Study	97	7.5361±4.81115	**<0.01**
	Control	82	4.0366±5.58314	
Panic disorder	Study	97	6.3814±3.30544	**<0.01**
	Control	82	1.2439±2.01575	
Depression	Study	97	9.2165±4.88242	**<0.01**
	Control	82	2.42683±4.24854	
Separation anxiety	Study	97	6.8247±3.44604	**<0.01**
	Control	82	1.5000±2.64458	
Generalized anxiety disorder	Study	97	5.5258±3.16588	**<0.01**
	Control	82	2.2561±3.73773	
Obsessive compulsive disorder	Study	97	5.0000±2.89396	**<0.01**
	Control	82	1.6341±2.46713	
SNAP4 attention deficiency	Study	97	9.1340±6.31075	**<0.01**
	Control	63	3.6825±5.08580	
SNAP4 hyperactivity deficiency	Study	97	8.8660±5.91014	**<0.01**
	Control	63	2.5079±3.35469	

SD: Standard deviation.

TABLE 3: Comparison of anxiety and depressive symptoms perceived by child and adolescents.

Disorder	Group	n	$\bar{X}$±SD	p value
Social phobia	Study	97	7.2577±5.29402	0.009
	Control	63	4.7302±6.83257	
Panic disorder	Study	97	5.4227±4.45308	**<0.01**
	Control	61	2.8852±4.74727	
Depression	Study	97	6.9794±5.93011	**<0.01**
	Control	63	3.8571±5.24514	
Separation anxiety	Study	97	5.4021±3.77674	**<0.01**
	Control	62	1.7742±2.57618	
Generalized anxiety disorder	Study	97	5.0619±4.04355	**<0.01**
	Control	62	3.3387±4.55186	
Obsessive compulsive disorder	Study	97	3.9794±3.62278	**0.015**
	Control	62	2.5323±3.65171	

SD: Standard deviation.

A study evaluating patients with DGS revealed learning impairments, mild to moderate mental retardation, and attention deficit hyperactivity (ADHD).[12] 22q11.2 Deletion syndrome is a disease that includes congenital malformations and neuropsychiatric disorders caused by alterations of meiotic chromosomes. One of the genes responsible for the deletion region, catechol-O-methyltransferase (COMT) in the DGS phenotype, has been studied extensively.[13] Haploinsufficiency of the COMT gene gives rise to an increased dopamine level, which inhibits prefrontal cognitive functioning and may lead to a high rate of psychosis and other psychiatric disorders.[14]

A meta-analysis of health-related quality of life in patients with PID found that children and young adults with PID have a lower quality of life than healthy controls. Patients and their parents were assigned the lowest scores for emotional measurements.[15] To evaluate psychiatric support in PID patients, an individual review of the psychological effects and ultimate emotional, intellectual, and social outcomes in these patients is required.

Our study has many limitations. First, our results mirror our sample groups. It would be appropriate to replicate our findings in a larger population. Also, even if we used validated questionnaires, evaluating patients through a clinical interview would be better. In addition, the wider age distribution can be considered a limitation. Our study group includes patients with different immune deficiencies, and not being evaluated according to the severity of the disease is an another limitation.

Beyond these limits, our study has many strong points:

1. Our findings reflect the psychological well-being of children suffering from PID.

2. To our knowledge, this is the largest study evaluating psychiatric problems in children with PID.

3. Our study focuses on the psychological health of patients with PID.

CONCLUSION

As a result, new research is needed to determine the main stress factors and to continue psychological counseling in order to increase the quality of life of patients with PID, both mentally and physically. Psychiatrists and immunologists should pay attention to the critical role of psychiatric outcomes in the long treatment period of PID patients.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that pro-

vides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Sara Şebnem Kılıç;* ***Design:*** *Sara Şebnem Kılıç, Hülya Köse;* ***Control/Supervision:*** *Sara Şebnem Kılıç;* ***Data Collection and/or Processing:*** *Hülya Köse, Şafak Eray;* ***Analysis and/or Interpretation:*** *Şafak Eray, Serkan Turan;* ***Literature Review:*** *Hülya Köse;* ***Writing the Article:*** *Hülya Köse, Şafak Eray, Serkan Turan;* ***Critical Review:*** *Sara Şebnem Kılıç;* ***References and Fundings:*** *Hülya Köse;* ***Materials:*** *Hülya Köse.*

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