



The Quality of Life and Mental Health in Children with Primary Immunodeficiency

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ABSTRACT

Primary immunodeficiency disorders (PIDs) are characterized by recurrent and numerous infections, autoimmune disorders, and malignancies. These diseases are a heterogeneous group that contains many disorders caused by the disruption of the immune system. Despite being seen rarely, PIDs lead to serious morbidity and mortality. Children and adolescents with PIDs are expected to have a higher prevalence of psychopathologies and a lower level of the health quality of life. In this text, we aim to review and summarize the current literature.

Keywords: Primary immunodeficiency, psychiatry, quality of life, children, adolescent

Introduction

Although primary immunodeficiencies (PIDs), which may be fatal in the childhood period, can be recognized early and appropriate treatment modalities can be applied, they can lead to chronic diseases later in life. The improvements in intravenous immunoglobulin (IVIG) therapy have led to improved survival, so that psychosocial, school, academic difficulties and health quality of life (HR-QOL) have become a current issue nowadays.

In this text; the effects that the widespread use of IVIG to treat the physical health of PID children and adolescents has on daily life adaptations, comorbid psychiatric problems and quality of life have been reviewed and summarized.

Definition and characteristics of primer immunodeficiency: PID is a heterogeneous group of rare

hereditary diseases of the immune system (1) PIDs have clinical importance due to having high mortality and morbidity rates (2). Among the classic clinical findings of immunodeficiencies are infections poorly responsive to treatment or having complications besides being susceptible to infections of low virulence microorganisms. PIDs can also occur with autoimmunity, autoinflammatory or hemophagocytosis syndromes (3).

Congenital diseases usually start in early childhood and lead to morbidity and mortality. For this reason, early diagnosis of these diseases may be life-saving and increase the quality of life in the long term. Considering PIDs more frequently in the differential diagnosis and evaluating patients immunologically makes it possible for these patients to be diagnosed at an early stage to reach early treatment opportunities and protective measures (2).

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It is estimated that over 300 genetic disorders have an effect on the immune system. These diseases, especially the autosomal recessive ones, are more commonly seen in Turkey due to higher the prevalence of consanguineous marriages (4).

PIDs are categorized on the basis of their disruptive mechanisms. The most common immunodeficiencies in these five groups are humoral immunodeficiencies (50-60%), predominantly selective IG A deficiencies. This is followed by cellular deficiencies (10-15%), combined deficiencies (15-30%), phagocyte defects (10-15%) and complex defects (1-3%) (5). Humoral deficiencies are also the most common in Turkey (2).

The treatment in primary immunodeficiency: As a result of disrupted immune system function, frequent and multiple infections, autoimmune disorders and malignancies are commonly seen in patients with PIDs. Untreated or under-treated PID can lead to life-threatening infections, chronic organ damage, or a marked reduction in life expectancy (6). However, early diagnosis and replacement therapy allow long and better life conditions for patients. The approaches used in the treatment of patients with PIDs include prophylactic treatments which significantly reduce the risk of infections. IVIG therapy is used to prevent recurrent infections and limits the progression of complications. Furthermore, if this therapy is given early and appropriately, it prevents tissue damage from infections and inflammations. It generally takes 4 to 6 hours and is administered at monthly intervals in hospital (7).

Individuals with PIDs may frequently experience infections secondary to their disease affecting their physical and psychological well-being (8). The prognosis of PIDs varies from benign conditions, such as respiratory tract infections, to complex conditions, such as malignancies with lethal outcome (9). Some patients need lifelong IVIG treatment and/or frequent courses of antibiotics as a treatment and/or prophylaxis. Especially patients with PIDs have a higher incidence of autoimmune diseases and experience long-term complications of infections and/or treatment (10). As a result of advances in PIDs treatment, mainly related to IVIG therapy, morbidity and mortality rates have improved remarkably in recent years, and the majority of children with PIDs can survive into adulthood (7).

Although long-term IVIG infusion is shown to be effective, there are some disadvantages. Firstly, the most common side effects of IVIG infusion in the first 30 minutes are lower back pain, nausea, chills, low body temperature, and vomiting. In the later hours of the infusion, headache,

myalgia and syncope can be seen. Secondly, IVIG requires patients to be treated in inpatient clinics, regular visits to hospital resulting in a loss of school and family time, and a high cost of health care. That is to say, although IVIG treatment has enhanced the life-expectancy of such a chronic disease, it has caused secondary problems for children with PIDs and their families (11).

Conclusion

Psychological impact and quality of life in primer immunodeficiencies: Taking into account the studies on children and adolescents with PID, it is seen that psychosocial characteristics and HR-QOL are related and have been evaluated together in the literature (Table I). It is noteworthy that these studies are usually cross-sectional and descriptive (10,12-14). Except for a few studies, psychiatric examinations of children and adolescents have not been performed and they have been generally evaluated with scales (15-19). One of these studies that was conducted in Turkey evaluated PIDs with psychiatric interviews and a modified version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version. The study was carried out on patients with JIA and healthy children selected as a control group. Although patients with PIDs were differentiated from healthy controls in terms of psychiatric diagnoses, there were no differences between JIA and PID (20). Similarly, the QOL scores were found to be similar in both JIA and PID, and both groups of chronic disease had lower scores compared to healthy controls (21).

Although healthy children frequently have been taken as a control group, in some studies, children with various chronic diseases, mostly children with juvenile rheumatoid arthritis (JRA) have been selected as a control group because healthy children as a control group would not be sufficient to determine the differences between PIDs and other chronic diseases (7,14,22).

Some studies have suggested that children with chronic disorders may be at risk of school absenteeism, participation in school and sporting activities, and the development of behavior and emotional disorders (23,24). Taking into consideration such challenges and the chronic nature of the disease, it is expected that the psychosocial development of children with PIDs, such as self-perception, self-esteem, interpersonal relationships and social activities are affected as with other pediatric situations and adults with PIDs (10,25,26). Consequently, there is evidence that patients with PIDs should be evaluated not only with simple clinical/disease parameters, but

Table I. The general characteristics of the studies related to the subject are given

Author, year	Methodology	Patients	Controls	Instrument	Findings
Cole, 2013 (18) but require lifelong treatment with immunoglobulin replacement. Some carry risks of inflammatory complications even with optimal treatment. Quality of life (QoL)	Cross sectional quantitative survey	47 Chronic Granulomatous Disease	0	PedsQL (HR-QOL), strength and difficulties questionnaire (emotional and behavioral difficulties)	Parent and self-reported QoL for non-transplanted children were significantly lower than HC. Parents reported increased emotional difficulties compared to published norms. PedsQL and SDQ scores for transplanted children were not significantly different from healthy norms
Kuburovic et al. (14)	Cross sectional quantitative survey	25 Mixed PID	139 50 JIA ¹ 89 HC ²	PedsQL ³ (HR-QOL), SCARED ⁴ (anxiety), Mood and Feeling Questionnaire (depression)	Children with PIDs had significantly lower HRQOL total score compared to children with JIA and healthy children on child rated and parent-rated assessments. Specifically, they had significantly lower emotional functioning compared to children with JIA, and social functioning compared to both children with JIA and healthy children. Only parent-rated school functioning scores were significantly lower among children with PIDs. For parent-rated assessments, six of 25 children with PIDs reported significant anxiety symptoms, and five had significant depressive symptoms
Zebracki et al. (7),	Cross sectional quantitative survey	36 Mixed PID	63 36 JIA 36 HC	CHQ-PF50 ⁵ (HR-QOL)	Compared with children with JIA, children with PIDs were similar in many aspects of their HR-QOL. However, parents of children with PIDs reported greater limitations in their personal time, poorer general health of their children, greater limitations in their children's physical functioning and family activities, and less bodily pain than children with JIA. In contrast, children with PIDs scored lower on most HR-QOL domains compared with HC
Soresina et al. (22),	Cross-sectional quantitative case control survey	25 X-linked agammaglobulinemia	311 80 HC 231 rheumatic disease	PedsQL (HR-QOL)	The agammaglobulinemia subjects perceived a lower global quality of life than the healthy subjects, but significantly higher than the rheumatic diseases controls.
Abolhassani et al. (15),	Cross sectional quantitative survey	26 Mixed PID	0	Causes of anxiety (study specific)	Most significant causes of anxiety include long duration of disease, lack of cure, and side effects and complications from treatment
Mozaffari et al. (12),	Cross-sectional quantitative case control survey	50 Mixed PID	100 HC	PedsQL (HR-QOL)	Patients with PID had great limitations in physical functioning and psychological well-being compared with children without a chronic health condition. Patients had lower QoL scores in all age groups compared with normal sample. Long duration of disease significantly correlated with low psychological score

Table I. Continued					
Author, year	Methodology	Patients	Controls	Instrument	Findings
Titman et al. (16),	Cross sectional quantitative survey	43 Primary antibody deficiency syndromes	0	PedsQL SDQ ⁶ Illness severity scale (study specific)	Higher rates of psychological difficulties, particularly emotional and peer-relationship difficulties were found in children with PAD when compared with healthy controls. QoL was poorer than in HC, and also worse than in children affected by diabetes mellitus. Variations in QoL and the degree of psychological difficulties were found between specific diagnostic groups, with children affected by transient hypogammaglobulinemia of infancy being amongst those with the lowest scores of QoL.
Stephenson et al. (19)	Cross sectional quantitative survey	76 22q11 deletion syndrome/ DiGeorge syndrome	55 HC	MAS ⁷ CDI ⁸ BASC ⁹	The 22q11.2DS youth were more likely to be in anxiety, depressed or comorbid clusters than the typically developing youth. Children with 22q11.2DS comorbid for anxiety and depression exhibited the worst functional outcomes
Kayan Ocakoğlu et al. (20,21)	Cross-sectional quantitative case control survey	48 Mixed PIDs on IVIG treatment	64 34 JIA 30 HC	K-SADS-PL ¹¹ (psychiatric examination) PedsQL CDI SCARED	70.45% of the children with PIDs, 62.5% of those with JIA and 23.3% of HC have a psychiatric problem. There is no statistically difference between PIDs and JIA. The most frequent psychiatric diagnoses in PIDs and JIA groups were depressive disorders, anxiety disorders and disruptive behavior disorders. PIDs and JIA groups had lower quality of life scores than health controls. PIDs and JIA groups were not found statistically different from each other

¹Juvenile idiopathic arthritis, ²Healthy Control, ³Pediatric Quality of Life Inventory, ⁴Screen for Child Anxiety Related Emotional Disorders, ⁵Child Health Questionnaire, parent form, ⁶Strengths and Difficulties Questionnaire, ⁷Multidimensional Anxiety Scale for Children, ⁸Children's Depression Inventory, ⁹Behavioral Assessment Scales for Children, ¹⁰The Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version, ¹¹(Kayan Ocakoğlu B. et al., Intravenöz İmmünglobulin Tedavisi Alan Ağır İmmün Yetmezlikli Hastalarda Ruhsal Durum Özellikleri, Yaşam Kalitesi ve Aile Özellikleri Ocak, 2016'. Yayınlanmamış Uzmanlık Tezi. Ege Üniversitesi)
PID: Primary immunodeficiency, HR-QOL: Health quality of life, IVIG: Intravenous immunoglobulin,

also with patient-reported prognostic measures, how the child copes with his/her disease, and how the family perceives the effect of the disease across different life domains (14). Therefore, HR-QOL should be a part of the multidimensional evaluation and treatment in children with PIDs, because it provides direct information about disease and treatment. However, HR-QOL of children with PIDs have remained largely unstudied.

Whereas Kuburovic et al. (14) found that HR-QOL scores of children with JIA were higher than PIDs, the studies conducted by Zebracki et al. (7) stated that the quality of life scores in patients with PIDs were higher than those with rheumatologic disease (20).

Both the requirements of treatment and the complications of PID increase the burden on the family and the patient. However, since PIDs are seen rarely and contained a huge number of different disorders, the literature is not sufficient to determine emotional and behavioral problems in this group (14,15,17). The available research highlights those children with PIDs who have serious problems in different areas of life such as discontinuity in the educational system, limited participation in social and sport activities, and anxiety and depression symptoms (14). Other studies have also found that these children have emotional problems, difficulties in relationships with their friends and

hyperactivity (16,27). In addition, social and attention problems are found as the most common difficulties in children with 22q.11 deletion syndrome (17). As a result, these findings demonstrate that patients with PIDs tend to develop psychosocial problems.

With the advancements in treatment options in chronic diseases, the importance of psychosocial adjustment, quality of life and rehabilitation services has begun to rise. An appropriate care for these patients requires a team of psychiatrists, psychologists, social workers, and teachers working together to handle all the aspects that should be considered to improve these patients' life quality. Consequently, psychosocial disorders as well as psychiatric symptoms have increased in children with PIDs. For this reason, psychosocial problems should be taken into consideration and, if needed, a psychiatric assessment should be made.

As seen in this review, published literature in this area is very limited. Multi-centered, longitudinal research is needed to evaluate and monitor the child's emotional, social, family, and school functioning. The treatment of comorbid psychiatric illnesses and appropriate psychosocial interventions will help to improve the functioning and the quality of life in children with PIDs.

Ethics

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Authorship Contributions

Concept: S.E., N.E.K., G.A., Design: S.E., B.K.O., Data Collection or Processing: B.K.O., Analysis or Interpretation: S.E., N.E.K., G.A., B.K.O., Literature Search: B.K.O., Writing: B.K.O.

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