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Quality of life among children with Inborn Errors of Immunity at king Abdullah Specialized Children Hospital, Riyadh, Saudi Arabia: A Cross Sectional Study

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Abstract

Background: Inborn Errors of Immunity (IEI) include a vast array of immunity disorders that are diagnosed early in life and that are associated with a high disease burden. Studies on the burden of IEI on the quality of life in Saudi Arabia are scarce. The aim of this study was to assess quality of life of IEI patients at a major tertiary care hospital in Riyadh, Saudi Arabia.

Methods: This is a cross-sectional survey-based study of all IEI patients using the validated PedsQL, version 4 questionnaire that aims at assessing the quality of life of IEI patients as reported by patients or one of their parents. Data was analyzed using the Statistical Package for Social Sciences (SPSS) version 26.

Results: The study included 51 IEI patients, more than half of which were between 2-12 years of age (63%). Data was mostly collected from one of the parents (84%). The lowest score was reported for school functioning with a mean score of 72.7 (SD=31.4). Emotional functioning score were significantly lower among those older than 18 years and those between 6-12 years old (P=0.04). Residing in the capital, was also significantly associated with higher physical functioning and total scores (P=0.01 and 0.03 respectively). Furthermore, social score was significantly higher among those with an unemployed parent (P=0.03).

Conclusion: This study showed IEI patients suffer from a low quality of life score that influences both school and emotional functioning. Quality of life scores were significantly associated with parent's employment status and patients' age. Living in proximity to healthcare centers, was associated with higher physical functioning and total scores. Healthcare providers managing IEI patients in Saudi Arabia should evaluate their quality of life to ensure optimal school and emotional wellbeing of the child.

Keywords: Primary immunodeficiencies; Inborn Errors of Immunity; Quality of Life; Saudi Arabia.

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1. Introduction

Inborn Errors of Immunity (IEI) are a group of approximately 430 heterogeneous immunity disorders that are characterized by decreased immunity at the innate level involving disorders of phagocytosis and the complement system or at the adaptive level including B-cell, T-cell, or combined immunodeficiencies [1]. Another updated phenotypic classification of IEI suggested by the International Union of Immunological Societies (IUIS) in 2019, identifies 8 categories that include immunodeficiencies affecting cellular and humoral immunity (severe combined immunodeficiency: SCID or combined immunodeficiency), combined immunodeficiencies with associated or syndromic features (such as congenital thrombocytopenia, DNA repair defects, etc.), predominantly antibody deficiencies with recurrent bacterial infections (IgG, IgA, IgM deficiencies), diseases of immune dysregulation and autoinflammatory disorders [2]. The most common of these are the primary antibody deficiencies [3] which include common variable immunodeficiency, IgA, or IgG deficiency, X-linked agammaglobulinemia and other specific antibody deficiencies [1]. Severity of IEI also vary between asymptomatic as in the case of IgA deficiencies to life-threatening forms such as SCID (sever combined immunodeficiencies) [4]. Diagnosed IEI patients are more susceptible to acquiring infections, malignancies, autoimmunity, and lympho-proliferative disorders [5].

The prevalence of IEI varies according to the type of deficiency and geographical location but seems to be highly associated with consanguinity [6]. One study in the United States reported in 2014 a prevalence ranging between 41.1 and 50.5 per 100,000 [7]. On the other hand, European data provided by the European Society for Immunodeficiencies registry for the years 2004-2014 reveal a prevalence of 5 per 100,000 and varying by country [8]. In the Middle East, epidemiological studies done through national registries or referral centers report an overall prevalence ranging between 0.81 and 30.5 in 100,000 population [6] with the highest prevalence of 30.5 per 100,000 in Turkey [9] and 20.27 per 100,000 in Kuwait [10] and an incidence of 9.7/1 million/year in Iran [11]. In Saudi Arabia, a tertiary hospital experience in 2015 done over 3 years reported a prevalence of 7.2 in 100,000 children [12]. This prevalence is similar to the one reported in 2016 by an Omani study [13]. However, there are limited numbers of studies related to prevalence of IEI in the gulf or Arab countries.

Most IEI are diagnosed at an early age but can present later in adulthood. Early detection and management are associated with better outcomes. Hence, screening [14-16] and employing a high level of suspicion is a key factor in improving detection rates of IEI [17]. Newborn screening for treatable and severe forms of IEI is now a common practice in many countries. As for management, the mainstay of treatment for most antibody deficiency is regular intravenous or subcutaneous immunoglobulin therapy

[18,19] and bone marrow transplantation for combined immunodeficiencies; these therapies are associated with an improved quality of life (QOL) [20,21].

The burden imposed by IEI on patients is huge and encompasses both physical and emotional consequences especially due to the severity and chronicity of the disorder. Children with IEI have lower health related quality of life (HRQOL) scores [22], and more limitations in physical and social functioning [23-26]. The literature also shows a high disease burden for IEI which includes a higher number of hospitalizations per year, emergency room visits, monthly visits to clinics as well as family monthly expenses related to the disease and absenteeism from school or work [27]. The most widely used tool for assessing HRQOL in pediatric IEI patients is the Pediatric Quality of Life Inventory (PedsQL) which measures 4 domains, which are physical, emotional, social, and school functioning as reported by either parent or child [28].

Several studies assess the QOL of pediatric IEI patients and reveal a poor quality of life that is associated with delayed diagnosis and type of disease. In the MENA region and Saudi Arabia, there is a paucity of literature on the QOL of pediatric and adult IEI patients, even though it is more common in these areas where consanguinity is a prevalent occurrence. Therefore, this study is the first to assess the QOL of pediatric IEI patients using the PedsQL questionnaire.

2. Subjects and Methods

2.1 Study design and setting

This is a cross sectional study utilizing phone call or face-to-face administered questionnaires answered by caregivers of IEI patients or by patients themselves visiting the Pediatric Daycare Unit (PDCU) at King Abdullah Specialist Children Hospital (KASCH) in Riyadh, Saudi Arabia.

2.2 Identification of study participants:

This study included a total of 51 patients of both genders of Saudis aged 2-37 years with IEI visiting PDCU at KASCH, Riyadh. Non-probability convenience sampling was used in selection of the subjects; (all Patients with IEI diagnosis receiving IV treatment were included) Those 18 years or older provided self-reported data, while for those younger than 18 years old, data was given by the patients themselves or by one of their parents/caregivers.

2.3 Study instruments and data collection process

Data was collected by the co-investigators using the Arabic version of PedsQL, version 4 was used [28]. The tool is composed of 23 items that cover the following domains: physical, emotional, social, and school functioning. Each item is on a 5-point Likert scale ranging between 0 and 4 (0= never, 1= almost never, 2= sometimes, 3= often, 4= almost always). Scores are linearly transformed to a 0- to 100- point

scale (4 = 0, 3 = 25, 2 = 50, 1 = 75, 0= 100) and higher scores reflect a better HRQOL. Scores are composed of averages for each of the four domains, and two summary scores of psychosocial health and physical health. The validity and reliability of the PedsQL has already been established [29].

2.4 Data analysis

Data was entered and analyzed using the Statistical Package for the Social Sciences (SPSS) version 26. Descriptive statistics were performed whereby categorical variables were presented as frequencies (percentages) and numerical data as mean ± standard deviation (SD). Inferential statistics was done using independent samples T test and one-way ANOVA to test the association between the scores of the different domains with several independent variables. Any test was declared significant at a p-value <0.05.

3. Results

This study included 51 IEI patients of both genders. The mean age of patients was 10.4 (SD=7.4) with a slightly higher percentage of females, 28 (54.9%). Most cases (62.8%) were between the ages of 2 and 12 years old. For most patients (84.3%), data was reported by one of the parents. More than a third of the cases (33.3%) were in kindergarten or in preschool and almost a third (31.4%) had no schooling. For most patients' families, they lived in an owned property (72.5%) and a villa (62.7%). Slightly more than half of the patients (52.9%) lived outside the capital, Riyadh. Characteristics of the study sample are summarized in Table 1.

Table 1: Socio-demographic characteristics of the study sample (n=51)

Characteristic	N	%
Age, in years		
2-5	16	31.4
6-12	16	31.4
13-18	15	29.4
>18	4	7.8
Gender		
Male	23	45.1
Female	28	54.9
Residence		
Own property	37	72.5
Rented property	14	27.5
Type of residence		
Villa	32	62.7
Apartment	19	37.3
Area of residence		
Riyadh	24	47.1
Outside Riyadh	27	52.9
Respondent		
Father	27	52.9
Mother	16	31.4

Child	8	15.7
Parents' Education		
Illiterate	1	2.2
Read/Write	4	8.9
Intermediate	4	8.9
Highschool	30	66.7
University	6	13.3
Parent's employment		
Employed	34	66.7
Unemployed	17	33.3
Child education		
Preschool/Nursery	17	33.3
Elementary/Intermediate	13	25.5
Highschool	5	9.8
No schooling	16	31.4

The four domains of QOL revealed that physical health functioning had a mean score of 82.3 (SD=29.1), emotional functioning mean score of 80.8 (SD=28.8), social functioning mean score of 85.1 (SD=27.7), school functioning score of 72.7 (SD=31.4). As for the total PedsQL score, the mean score was 81.1 (SD=25.8). Mean scores of all PedsQL scores are summarized in Table 2.

Table 2: Mean scores for physical, emotional, social, and school functioning and total PedsQL scores (n=51)

PedsQL domain	Mean	SD*
Physical functioning	82.35	29.13
Emotional functioning	80.78	28.83
Social functioning	85.10	27.70
School functioning	72.66	31.42
Total score	81.09	25.76

*SD: standard deviation

The association between PedsQL scores and various predictors is shown in Table 3. Age was significantly associated with emotional functioning scores only (P=0.04), whereby lowest scores were in the older than 18 years and the 6 –12-year-olds. Although scores of all domains were lower when reported by one of the parents compared to self-reports of QOL, this difference was not statistically significant (P>0.05). Area of residence, specifically living in the capital, Riyadh was associated with higher mean scores in physical functioning (P=0.01) and the total score (P=0.03). On the other hand, area of residence was not associated with changes in the scores of the emotional, social, and school functioning domains. Finally, social score for PID patients was significantly higher among those with an unemployed parent (P=0.03).

Table 3: PedsQL score means across some predictors in IEI patients (n=51)

Variable	Physical score Mean(SD) P-value	Emotional score Mean(SD) P-value	Social score Mean(SD) P-value	School score Mean(SD) P-value	Total score Mean(SD) P-value
Age, in years					
2-5	92.2(9.7)	93.1(11.2)	87.5(18.3)	65.0(21.2)	90.6(10.3)
6-12	78.5(30.1)	76.9(27.9)	85.3(27.3)	81.2(19.1)	79.1(25.8)
13-18	79.2(36.0)	80.0(28.7)	85.0(31.8)	72.3(32.5)	78.0(28.9)
>18	70.3(47.7)	50.0(57.7)	75.0(50.0)	50.0(57.7)	62.5(47.9)
P-value	0.41	0.04*	0.89	0.38	0.21
Respondent					
Parent-report	82.0(28.5)	83.0(25.1)	84.7(26.5)	74.2(27.2)	81.7(24.0)
Self-report	84.0(34.5)	68.8(44.1)	87.5(35.4)	68.1(43.7)	78.0(35.8)
P-value	0.87	0.40	0.79	0.65	0.72
Area of residence					
Riyadh	93.0(12.0)	87.5(16.9)	91.5(15.2)	80.7(25.2)	89.2(11.7)
Outside Riyadh	72.9(36.2)	74.8(35.6)	79.4(34.7)	65.6(35.3)	73.9(32.2)
P-value	0.01*	0.12	0.11	0.18	0.03*
Parent's employment status					
Employed	85.4(29.0)	84.1(29.3)	80.6(32.4)	75.5(28.9)	81.9(28.3)
Unemployed	76.3(29.3)	74.1(27.5)	94.1(10.5)	66.5(37.3)	79.4(20.5)
P-value	0.30	0.25	0.03*	0.47	0.74

*Statistically significant at $p<0.05$

4. Discussion

IEI include a wide array of immunodeficiency disorders which make patients more prone to infection, autoimmunity, lymphoproliferation and malignancies [5]. The progressive and chronic nature of the disease as well as the associated comorbidities negatively affect the performance of IEI patients on the physical, emotional, social, and school functioning levels [21-24]. For this reason, QOL assessment is an important part of understanding the patient's perception of his condition and its impact on his life. This will positively impact in creating suitable interventions and offering the necessary support to improve IEI patients' QOL. This study, up to our knowledge, is the first one to explore the QOL of IEI patients and assess their perceived physical, emotional, social, and school functioning in KSA and in the Arab world. This in addition to finding any pertinent associations that affected the reported QOL.

In this study, the sample's age distribution was almost equally divided between the age categories except for those older than 18 years of age which can be explained by the fact that IEI disorders are diagnosed at an early age and although patient outcomes and survival have considerably improved in the last few decades [30], delayed diagnosis and absence of proper management with prophylactic antimicrobial medications, intravenous or subcutaneous immunoglobulins, which is the mainstay of treatment in patients with antibody deficiencies and with bone marrow transplantations for patients with

combined immunodeficiencies, can lead to poor prognosis and a lower life expectancy. Another remarkable characteristic was absence of schooling for almost a third of the sample, which is associated with the large portion of patients in the age group 2-6 years old. In this age category, many IEI patients are not attending any school or nursery because they are seen as either too young or too sick. In this case and in this Saudi context, parents might decide to delay schooling for these patients or even in some extreme cases and depending on the severity of the condition itself to drop schooling altogether. These findings contradict what is already known in the literature about how improved clinical care for IEI patients was associated with improved QOL [20,21] and even decreasing absenteeism from school or work [27]. The mean scores for the different domains revealed that school functioning had the lowest score among the rest of the physical, emotional, and social domains and that is consistent with another study that has the lowest score for school functioning when parent reported [26,31].

In terms of variation of mean scores of the different domains across several predictors, emotional score was significantly lowest in the older than 18-year-olds followed by the 6-12 years age category. This is concordant with the literature that reports a lower QOL with older age among IEI patients [32]. As the disease progresses with age, comorbidities are also responsible for increasing the disease burden and negatively affecting the QOL [23,24,33]. In addition, as patients get older, their awareness of their disease and its impact on their lives increases and is reflected as poor QOL perception. The age group of 6 –12 -year-olds also reported a lower score, which is probably associated with this age category being a transitional period between childhood and adolescence, which can be a challenging period that is characterized by emotional instability.

The area of residence, specifically patients living in the Saudi capital, Riyadh, reported significantly higher mean scores for the physical domain and the total score, compared to those who lived outside Riyadh. This could be related to the patients' easier access to healthcare facility, which in turn yields a higher compliance to treatment and better patient outcomes. It is also important to note that the pediatric daycare unit at our hospital is one of the largest in the country and most of our IEI patients require this access once or even twice per month. One Turkish study also reported that difficulty to travel to the hospital might be associated with poor health outcomes and QOL [20].

The type of reporting and whether QOL was reported by parents versus self-report, had no significant association with mean QOL scores, although the scores were in general lower when self-reported. This mismatches with data from other studies that showed lower QOL scores when reported by parents [26]. Finally, social score was significantly higher among those with an unemployed parent which is discordant with Jiang et al study [33] that reported unemployment as a factor that negatively impacts

QOL. On the other hand, another study failed to find any significant association between employment status of parents and the child's QOL [31]. Our result can be related to the increase in parental contact time with the child, which is reflected as an improvement in the child's social skills especially with the parent being more available to observe his social life and even encourage it.

4.1 Strengths and Limitations

Our study has several strengths. To the best of our knowledge, it is the first study of its kind that has been conducted in Saudi Arabia and the MENA region regarding QOL of IEI patients. In addition, the use of the validated PedsQL questionnaire adds to the internal validity of the study. Another important aspect is that the study sample originated from one of the largest pediatric daycare unit in the country, which also gives a clearer picture of IEI patients in Saudi Arabia. The non-random consecutive sampling approach that was used to include the total number due to rarity of the disease and the study being a single-centered study, might limit the generalizability of the study findings.

5. Conclusion and Future directions

To our knowledge, this is the first study that explores QOL of IEI patients in Saudi Arabia and in the MENA region. It also examines the associations of some socio-demographic variables with the reported QOL. This study showed IEI patients suffer from a low QOL score, that influences both school and emotional functioning. QOL scores were significantly associated with parents' employment status and patients' age. Living in proximity to healthcare centers, was associated with higher physical functioning and total scores. Following this exploratory QOL study, future multi-center studies in Saudi Arabia are warranted to confirm these results and to improve the external validity of our overall conclusion.

6. Declarations

6.1 Conflict of Interest Statement

The authors have no conflict of interests to declare.

6.2 Funding Disclosure

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

6.3 Ethical Considerations

Ethical approval was sought from King Abdullah International Medical Research Centre (KAIMRC) and informed consent was taken from the study subjects or their legal guardians. Patients' confidentiality and privacy were maintained throughout the research.

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