Journal of Clinical Immunology (2020) 40:602–609
https://doi.org/10.1007/s10875-020-00775-w

ORIGINAL ARTICLE

Health-Related Quality of Life and Multidimensional Fatigue Scale in Children with Primary Immunodeficiencies

Saida Ridao-Manonellas[1] · Anna Fábregas-Bofill[1] · Gloria Núñez-Rueda[1] · Míriam González-Amores[1] · Marina García-Prat[1] · Laura López-Seguer[1] · Jacques G. Rivière[1] · Andrea Martín-Nalda[1] · Natalia Mendoza-Palomar[1] · Susana Melendo-Pérez[1] · Pere Soler-Palacín[1,2]

Received: 21 November 2019 / Accepted: 23 March 2020 / Published online: 15 April 2020

Abstract

Purpose Patients with primary immunodeficiency disease (PID) have an increased risk of experiencing physical activity limitations, social difficulties, and psychological problems due to their chronic condition. Evaluation of their health-related quality of life (HRQOL) and fatigue is crucial in these patients to help understand their complex disease and provide adequate medical care.

Methods In this study, we evaluated HRQOL and fatigue in pediatric and young adult patients with PID attending our center. Participants completed the Pediatric Quality of Life Inventory (PedsQL), version 4.0, and the PedsQL multidimensional fatigue module, standard version.

Results Fifty-three PID patients were recruited (age range: 2–23 years). The mean HRQOL score obtained was 66.61 (SD: 18.73) out of 100, and the emotional and work/school dimensions were the ones most highly affected. There were no significant differences in reported quality of life between patients and their caregivers. The mean patient-reported fatigue value was 68.81 (SD: 17.80) out of 100, and the rest-related dimension was the one most highly affected. In the caregivers' assessment, general fatigue was the most highly affected dimension.

Conclusions The results of this study show that quality of life is poor and fatigue measures are considerably increased in our young adult and pediatric patients with PIDs. These findings can indicate areas requiring more intensive interventions, and they will serve as a basis for comparison of future results.

Keywords Primary immunodeficiencies · health-related quality of life · fatigue · children · adolescence

Introduction

Primary immunodeficiency diseases (PIDs) are a group of genetic disorders caused by quantitative and/or qualitative impairment of the immune response. PID patients have an increased susceptibility to recurrent and to severe infections and a predisposition to develop allergies, autoimmune conditions, inflammation, and cancer, among other manifestations [1]. The onset of PID can take place at any age, but it often occurs in childhood. Although the associated prognosis and survival rates have improved in recent years, PID patients still have an increased risk of developing complications that affect their physical and emotional status [2–4]. The PID burden can limit social activities and increase the risk of school or work absenteeism due to limitations in physical contact, hospital visits, hospitalizations, and multi-treatment regimens [3, 5, 6]. These constraints affect the patient's quality of life and psychological status and may lead to symptoms of anxiety or depression [6, 7].

Evaluation of quality of life in patients with a chronic condition is essential to assess progression of the disease and provide appropriate medical care. It is also important to estimate the disease burden and common complications and how they impact daily life [8, 9]. Health-related quality of life

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10875-020-00775-w) contains supplementary material, which is available to authorized users.

✉ Pere Soler-Palacín
psoler@vhebron.net

[1] Paediatric Infectious Diseases and Immunodeficiencies Unit (UPIIP), Hospital Infantil Vall d'Hebron (HIVH), Jeffrey Modell Foundation Excellence Centre, ERN RITA Centre, Vall d'Hebron Research Institute (VHIR), Passeig Vall d'Hebron 119-129, 08035 Barcelona, Catalonia, Spain

[2] Universitat Autònoma de Barcelona, Barcelona, Catalonia, Spain

(HRQOL) is a multidimensional concept that includes physical, mental, emotional, and social functioning, as well as subjective well-being [10, 11]. HRQOL measures quality of life as perceived by the patients rather than from the healthcare professionals' viewpoint [10].

Several studies have evaluated the relationship between the characteristics of patient populations and their quality of life and have compared HRQOL between patients with a chronic condition and healthy individuals [2, 4, 5, 7, 12–18].

Other HRQOL studies in both pediatric and adult PID patients have shown that the therapies used can also affect quality of life, a finding similarly reported by their caregivers [2, 12, 14, 15, 19–21]. Patients generally prefer home-based administration and short-term treatment. In this line, patients administered home-based, short-term subcutaneous immunoglobulin replacement therapy (IGRT) have shown fewer depression symptoms than those receiving intravenous IGRT at the hospital [20–24]. In addition, patients undergoing curative hematological stem cell transplantation (HSCT) have reported better quality of life than patients with similar disease requirements who did not receive this procedure [25, 26].

Since 2016, our group has implemented a program named *I Have A PID, But I Am Not Alone*, whose main purpose is to offer psychological and social support to PID patients and their families. Seventy PID patients and 140 relatives have benefited from it to date. The program is led by a psychologist who works with a multidisciplinary team (physicians, nurses, and social workers) to offer the patients and their families on the following topics: comprehension of the disease, acceptance of the diagnosis, adherence to treatment, and management of anxiety and depression, if required. Within the program, group activities are organized as well as informative talks in the patient's schools to facilitate the understanding of the disease to the entire patient environment. Psychological intervention takes places both in an outpatient and inpatient setting. Throughout the program, healthcare providers aim to ensure that the patients' emotional and mental functioning is preserved and their quality of life is at the highest level possible.

Within our continuing efforts to provide optimal care for this patient population, we encountered the need to determine their current status regarding quality of life and fatigue. The results would bring to light areas requiring a more intensive intervention and would serve as a basis for comparison of future results. Hence, the aim of this study was to evaluate HRQOL and fatigue in children and young adults with PID attended in our unit.

Methods

Study Design and Participants

A prospective, cross-sectional, observational study covering 1 year was initiated in 2018 to assess HRQOL and fatigue in pediatric and young adult PID patients and their caregivers. The study included patients with a confirmed diagnosis of PID as defined by the International Union of Immunological Societies (IUIS) classification [27] and followed up in our unit within the program *I Have A PID, But I Am Not Alone*, together with their caregivers. Only children taking part in this special support program were eligible for inclusion and this action was already running for 2 years before this study started. Caregivers and participants ≥ 18 years of age signed the study informed consent (IC), participants aged ≥ 12 and < 18 years signed the IC along with their legal tutor, and participants < 12 years had their caregivers sign the IC on their behalf.

Data were collected at one time point within the period of January to December 2018. Participants were recruited during the routine follow-up hospital visits. Patient and caregiver sociodemographic data were collected from the medical records and medical interviews. The information was coded to protect the participants' privacy.

Definitions and Measures

Patients were evaluated with the Pediatric Quality of Life Inventory (PedsQL) Measurement Model (Spanish, version 4.0) and the PedsQL multidimensional fatigue scale (Spanish, standard version), both of which have been validated for use with these objectives [28–31]. The questionnaires were completed by patients ≥ 5 years of age and by the caregivers of patients 2 to 18 years of age. The two questionnaires were provided independently to patients and caregivers to avoid bias when answering them. The questionnaires for children and adolescents had age-appropriate, self-report formats, whereas those for caregivers had a parent proxy format. Quality of life was scored as the mean of the sum of four dimensions (physical, emotional, social, and school/work activities). Each dimension scored from 0 to 100, and the higher the value indicated, the better was the reported quality of life.

The PedsQL multidimensional fatigue module is composed of three dimensions: general, sleep/rest, and cognitive. Each dimension scores from 0 to 100, with higher values indicating lower levels of fatigue.

We also used the Eastern Cooperative Oncology Group (ECOG) performance status [32] and level of dependence criteria to assess how PID affected the quality of life of participating patients from the healthcare workers' perspective. Dependency was evaluated according to the assessment scale of the Catalonian Regional Government, in which 4 levels of dependence are established: independence, low or moderate dependence, high dependence, and very high or total dependence [33].

Statistical Analysis

A descriptive analysis was carried out. Percentages and frequencies were calculated for qualitative variables, and the chi-square or Fisher test were used for comparisons. For quantitative variables, the mean (standard deviation) and median (25th and 75th percentiles) were calculated and the Mann Whitney *U* or Kruskal Wallis test was used for the comparisons, as appropriate, depending on the number of groups. Spearman's correlation coefficient was calculated for quantitative variables. To compare quality of life and fatigue scores between patients and their caregivers, the Wilcoxon signed rank test was performed. Finally, a multivariate linear regression model was fitted with the scale scores as the outcome measure. A likelihood test and the Akaike information criterion were used to select the variables. All analyses were carried out using STATA, 15.1 (StataCorp LLC, Texas, USA).

Results

Clinical and Sociodemographic Data

In total, 107 participants were recruited from the *I Have A PID, But I Am Not Alone* program: 53 patients (pediatric and young adult cohort) and 54 caregivers (relatives' cohort). Of the 70 patients initially screened, 17 were excluded due to their young age (< 2 years) or inability to attend a follow-up visit at our center during the data collection period. The participants' sociodemographic data are shown in Table 1, and the type of PID, disease severity, and treatment data in Table 2. Mean inclusion in the program was 1.51 years (SD: 0.72).

The patients' mean age at diagnosis was 6.64 years (SD: 5.31), and almost all of them (92.45%) had some organ damage at the time the study was carried out. The lungs were the most commonly affected organ (64.15%), followed by the skin (37.74%). Fourteen patients had undergone HSCT, and 4 of them (7.55%) had some degree of chronic graft-versus-host disease (cGVHD) when they were included.

In those patients receiving intravenous IGRT, mean elapsed time between last infusion and the day of assessment was 20.14 (SD: 4.59) meaning that most patients were evaluated the same day of infusion.

According to the healthcare professionals' assessment of the level of dependence and the ECOG disability scores, around two thirds of patients showed some impact on their quality of life on both scales.

Quality of Life and Fatigue

Forty-six patients and 54 caregivers answered the PedsQL HRQOL and multidimensional fatigue questionnaires. The mean score on the patients' HRQOL questionnaires was 66.61 (SD: 18.73). The social and physical dimensions were

Table 1 Sociodemographic data of patients and their caregivers

		Patients $N = 53$	Caregivers $N = 54$
Age, years, mean (SD)		11.12 (5.49)	43.00 (5.57)
Age range, years		Age range: 2–23 years	Age range: 29–57 years
Sex, *n* (%)	Female	22 (41.51)	36 (66.67)
	Male	31 (58.49)	18 (33.33)
Origin, *n* (%)	Spain	48 (90.57)	42 (77.78)
	Rest of Europe	2 (3.77)	3 (5.56)
	South America	1 (1.89)	1 (1.85)
	Africa	1 (1.89)	7 (12.96)
	Asia	1 (1.89)	1 (1.85)
Family unit, *n* (%)	Nuclear	46 (86.79)	46 (86.79)
	Single-parent	2 (3.77)	2 (3.77)
	Large	1 (1.89)	1 (1.89)
	Other	4 (7.55)	4 (7.55)
Educational level, *n* (%)	No schooling	7 (13.21)	4 (7.41)
	Primary school	28 (52.83)	9 (16.67)
	Secondary school	16 (30.19)	16 (29.63)
	Post-obligatory studies	1 (1.89)	19 (35.19)
	University	1 (1.89)	6 (11.11)
Employment situation, *n* (%)	Active	NA	39 (72.22)
	Unemployed	NA	12 (22.22)
	Other	NA	3 (5.56)

Table 2 Type of PID, number of affected organs, therapy, level of dependency, and ECOG ($N = 53$)

Type of PID, *n* (%)	Combined immunodeficiencies	6 (11.32)
	Well-defined PID syndromes	11 (20.75)
	PID without genetic confirmation	11 (20.75)
	Predominantly antibody deficiencies[a]	9 (16.98)
	Defects of phagocyte number or function	13 (24.53)
	Immune dysregulation	1 (1.89)
	Defects in intrinsic and innate immunity	1 (1.89)
	Complement deficiencies	1 (1.89)
Number of affected organs, *n* (%)	0	4 (7.55)
	1	18 (33.96)
	2	17 (32.08)
	3	10 (18.87)
	4	2 (3.77)
	5	1 (1.89)
	6	1 (1.89)
Therapy, *n* (%)	Antibiotic prophylaxis	32 (60.38)
	IGRT	19 (35.85)
	- Subcutaneous	12 (63.15)
	- Intravenous	7 (36.85)
	Immunosuppressant therapy	9 (16.98)
	No pharmacological therapy	6 (11.32)
HSCT, *n* (%)		14 (26.42)
Gene therapy, *n* (%)		1 (1.86)
Years after diagnosis, mean (SD)		6.64 (5.31)
Years after HSCT, mean (SD)		2.53 (1.63)
Levels of dependency, n (%)	Independence	20 (37.74)
	Low or moderate dependence	25 (47.17)
	High dependence	5 (9.43)
	Very high or total dependence	3 (5.66)
ECOG grade, n (%)	0	20 (37.74)
	1	23 (43.40)
	2	5 (9.43)
	3	2 (3.77)
	4	3 (5.66)

HSCT hematological stem cell transplantation, *IGRT* immunoglobulin replacement therapy, *PID* primary immunodeficiency disease, *ECOG* Eastern Cooperative Oncology Group

[a] Patients with selective IgA deficiency were not included

the least affected ones, whereas the dimension focused on school/work activities received the poorest score by patients. There were no significant differences between quality of life values reported by patients and their caregivers (Table 3).

A mean value of 68.81 (SD: 17.80) was obtained on the patients' fatigue scale. The cognitive dimension and general fatigue dimension were the least affected scores, and both of these were rated slightly better by caregivers than patients. Patients gave the rest-related dimension the poorest rating on this scale, whereas caregivers gave general fatigue the poorest rating. There were only significant differences between patients and caregivers in the sleep-rest dimension (Table 3).

Univariate and Multivariate Analyses

Sex, age, affected organ, type of PID, disease progression, and sociodemographic characteristics were included in the analyses, together with overall quality of life and overall fatigue reported by the participants. The univariate analysis showed that male patients had better quality of life ($p = 0.0012$) and less fatigue ($p = 0.0115$) than females. There was a negative correlation between the degree of dependence and quality of life, and between the ECOG disability grade and quality of life (Table 4).

Table 3 Mean (SD) and signed-rank test (p value) PedsQL scores for quality of life and fatigue reported by patients and caregivers

	Dimension	Patients $N = 46$	Caregivers $N = 54$	Signed-rank test p value
Quality of life	Physical	66.71 (26.47)	67.13 (24.88)	0.464
	Emotional	64.89 (21.20)	62.22 (22.14)	0.155
	Social	74.02 (21.02)	72.78 (24.66)	0.193
	Work/School	60.76 (19.23)	62.00 (21.98)	0.966
	Total	66.61 (18.73)	66.55 (20.39)	0.322
Fatigue	General	70.20 (25.76)	73.92 (25.17)	0.269
	Rest	65.94 (17.84)	74.54 (20.16)	0.045*
	Mental	70.29 (26.41)	79.63 (23.77)	0.195
	Total	68.81 (17.80)	76.02 (19.07)	0.227

*Statistically significant variables

Multivariate analysis showed that quality of life decreased as the ECOG grade increased, adjusted by sex and age. It also confirmed the relationship between quality of life and sex, showing that male patients reported better quality of life than females. Aging had a negative residual effect on quality of life (Tables 4 and 5).

While no significant differences were observed between our data and those provided by other studies including PID patients, those were found in all dimensions of quality of life when comparing with studies including healthy individuals with similar characteristics [7, 12, 14, 16]. These differences remain similar in general, rest, and total fatigue scores but not in the cognitive dimension [34] (Suppl. Tables 1, 2, and 4).

When comparing our data with those obtained in other studies including patients with other chronic diseases, no consistent differences were observed, although a trend towards worse scores were observed when compared with juvenile idiopathic arthritis (JIA) and diabetes mellitus (DM) patients but not with cystic fibrosis (CF)–affected individuals [7, 14, 16, 34] (Suppl. Tables 3 and 4).

Discussion

The data obtained in this study show that children and young adults with PID have a poorer quality of life than the healthy pediatric population in all dimensions included in the standardized assessment instruments used. Work/school activity and the emotional dimension received the lowest scores by both patients and their caregivers. The social dimension was better rated by both these groups, and most patients considered that they had no difficulties in their relationships or interactions with friends. These results, the first obtained in pediatric patients with PID and their caregivers in Southern Europe, are consistent with those reported in quality of life studies in PID conducted in other countries and using the same questionnaires [7, 12, 14, 16, 18]. The social and physical

Table 4 Correlations between sociodemographic data and PedsQL quality of life and fatigue scores (univariate model)

	Quality of life correlation	**Fatigue correlation**
Age	− 0.180	− 0.119
Years after diagnosis	− 0.211	− 0.062
Years after HSCT	+ 0.266	+ 0.299
	Quality of life p value	**Fatigue p value**
Sex	0.0012*	0.0115*
Type of PID	0.2593	0.5366
Organ involvement (0/1/2/3/4/5/6)	0.0796	0.4517
Pharmacological treatment (yes/no)	0.8454	0.2496
IGRT	0.8199	0.7671
Subcutaneous IGRT	0.4628	0.7866
Intravenous IGRT	0.2090	0.4429
Level of dependency	0.0014*	0.2059
ECOG	0.0018*	0.1784

ECOG Eastern Cooperative Oncology Group grade, *IGRT* immunoglobulin replacement therapy

*Statistically significant variables

Table 5 Coefficient, confidence interval, and *p* value for PedsQL quality of life and fatigue scores analyzed with sex, age, and ECOG grade (multivariate model)

	Quality of life			Fatigue		
	Coef.	(95%CI)	*p* value	Coef.	(95%CI)	*p* value
Sex						
Female	0			0		
Male	10.784	(1.945;19.624)	0.027	13.437	(3.777; 23.096)	0.0092
Age	− 0.870	(− 1.769; 0.028)	0.0649			
ECOG						
0	0		0.0015			
1	− 5.921	(− 14.794;2.951)				
2	− 28.095	(− 43.977; − 12.213)				
3	− 10.141	(− 31.311;11.029)				
4	− 32.079	(− 49.066; − 15.091)				

ECOG Eastern Cooperative Oncology Group

dimensions received the highest scores and emotional and school/work items the lowest also in these studies (Suppl. Table 1). Our findings also concur with those obtained in studies showing that other chronic diseases have a major impact on the quality of life [18]. Therefore, PID can be considered a chronic condition having a considerable negative effect on quality of life.

Our data regarding fatigue in PID patients also show an increase in this factor in their daily lives. Sleep habits received the poorest rating by patients, but general fatigue (feeling tired and weak) scored the worst by caregivers. Patients reported a greater level of fatigue than their caregivers in all dimensions. These high fatigue scores are consistent with the results of a study reporting that adults with PID show greater fatigue than the general population beyond the age of 8 years [35]. Therefore, PIDs should also be considered a group of chronic diseases with significant impact on fatigue.

Of note, no significant differences were found in HRQOL according to age but we found that quality of life and fatigue differed according to sex. Female patients reported poorer HRQOL and fatigue scores than males. Whereas most studies have found no differences by sex [7, 12, 14, 16], others have shown poorer scores in these dimensions in females. The reason for this is not entirely clear and may reflect differing social dynamics experienced by females compared with males or a gender difference in the effects of their underlying disease [3].

Our data show no relationships between the PID diagnosis and HRQOL or fatigue scores. However, other studies have reported that certain PID types are associated with poorer HRQOL [2, 12, 16]. We mention that our study population was selected from the *I Have A PID, But I Am Not Alone* program and the distribution of their diagnoses differs from that of the complete cohort of patients attended in our unit (data not shown). In future studies, it could be of interest to include all PID patients followed up at our center, regardless of whether or not they received psychological support.

Regarding the therapy provided, we did not find statistical significance. However, our results should be interpreted with caution as only 19 of the 53 patients included were receiving IGRT and 12 of them were treated by subcutaneous administration. In addition, some patients allocated to subcutaneous treatment had physical limitations, and home-based treatment was considered the better option by physicians, patients, and their caregivers.

Also, it is necessary to take in consideration that assessment was performed on the same day of infusion in 5 of the 7 patients and this could be a limitation of the study because of a potential wear-off effect [36].

Other studies investigating this potential relationship found that patients receiving intravenous IGRT reported lower quality of life scores than those receiving subcutaneous replacement therapy [22].

Health professional–defined variables, such as the ECOG performance grade and the patient's level of dependence, showed a negative correlation with HRQOL and fatigue. These findings support the idea that professional assessment is consistent with that of patients and caregivers and they promote an active role for healthcare professionals in detecting patients with a potential for complications that could affect quality of life and psychological status.

Although sample size is usually a limitation in the study of rare diseases, we managed to recruit a larger sample than the average included in other studies [7, 12, 14, 16]. Nonetheless, a multicenter study with a larger number of patients would be needed to identify variables with the greatest impact on quality of life and fatigue in each specific PID diagnosis and would allow a more strict severity assessment thanks to greater clinical homogeneity between patients as well as multivariate analysis to establish the exact role of each variable in

HRQOL and fatigue scores. Furthermore, it would be of interest to include healthy controls or patients with other chronic conditions in future studies to better define the impact of PID on HRQOL and fatigue. Another limitation of the study is that the participants were part of a psychological support program in addition to their standard medical care at our center. Therefore, the study population may be biased as patients with a more complex condition are more likely to be included in these specialized programs. However, our HRQOL results were very similar to those obtained in other studies, which could indicate that the weight of this selection bias was limited.

As already mentioned in the recently published meta-analysis by Peshko et al., there is an urgent need to develop PID-specific instruments and rigorously evaluating existing measures because no disease-specific instruments are available for children (proxy- or self-report) [18].

To conclude, the results of this study support the value of assessing HRQOL and fatigue parameters in PID patients to identify areas in which the standard of care should be improved. The data obtained here, which provide information on the patients' physical, emotional, and social functioning, can be analyzed in relation to the interventional model, methods, and allocation of resources currently provided by our unit. Furthermore, these findings can be used as a basis to assess the efficacy of future interventions aimed at improving our PID patients' quality of life.

Acknowledgments We are deeply grateful to the affected individuals and their families who participated in this study. The authors thank Celine Cavallo for English language support and acknowledge Santiago Pérez-Hoyos for carrying out the statistical analysis. The program *I Have A PID, But I Am Not Alone* is conducted with the support of the Barcelona PID Foundation, the Catalan Association of Primary Immune Deficiencies (ACADIP), and the social work of La Caixa Foundation.

Compliance with Ethical Standards

Conflict of Interest The authors declared that they have no conflict of interest.

References

1. McCusker C, Upton J, Warrington R. Primary immunodeficiency. Allergy Asthma Clin Immunol. 2018;14(2):61.
2. Aghamohammadi A, Montazeri A, Abolhassani H, Saroukhani S, Pourjabbar S, Tavassoli M, et al. Health-related quality of life in primary antibody deficiency. Iran J Allergy Asthma Immunol. 2011;10(1):47–51.
3. Tcheurekdjian H, Palermo T, Hosstoffer R. Quality of life in common variable immunodeficiency requiring intravenous. Ann Allergy Asthma Immunol. 2004;93(2):160–5.
4. Zebracki K, Palermo TM, Hostoffer R, Duff K, Drotar D. Health-related quality of life of children with primary immunodeficiency disease: a comparison study. Ann Allergy Asthma Immunol. 2004;93:557–61.
5. Mozaffari H, Pourpak Z, Pourseyed S, Moin M, Farhoodi A, Aghamohammadi A, et al. Health-related quality of life in primary immune deficient patients. Iran J Allergy Asthma Immunol. 2006;5(1):23–7.
6. Lavigne J, Fair-Rotman J. Psychological adjustment to pediatric physical disorders: a meta-analytic review. J Pediatr Psychol. 1992;17(2):133–57.
7. Kuburovic NB, Pasic S, Susic G, Stevanovic D, Kuburovic V, Zdravkovic S, et al. Health-related quality of life, anxiety, and depressive symptoms in children with primary immunodeficiencies. Patient Prefer Adherence. 2014;8:323–30.
8. Abolhassani H, Aghamohammadi A, Abolhassani F, et al. Health policy for common variable immunodeficiency: burden of the disease. J Invest Allergol Clin Immunol. 2011;21(6):454–8.
9. Sadeghi B, Abolhassani H, Naseri A, et al. Economic burden of common variable immunodeficiency: annual cost of disease. Exp Rev Clin Immunol. 2015;11(5):681–8.
10. Mathew F, Steven D, Janine D, Stephen B. What are quality of life measurements measuring? BMJ. 1993;316(7130):542–54.
11. Eiserc C, Morse R. The measurement of quality of life in children: past and future perspectives. J Dev Behav Pediatr. 2001;22(4):248–56.
12. Ataeinia B, Montazeri A, Tavakol M, Azizi G, Kiaee F, Tavakolinia N, et al. Measurement of health-related quality of life in primary antibody-deficient patients. Immunol Invest. 2017. https://doi.org/10.1080/08820139.2016.1258710.
13. Barlogis V, Mahlaoui N, Auquier P, Pellier I, Fouyssac F, Vercasson C, et al. Physical health conditions and quality of life in adults with primary immune deficiency diagnosed during childhood: a CEREDIH study. J Allergy Clin Immunol. 2016;139(4):1275–81.
14. Routes J, Tavares-Costa-Carvalho B, Grimbacher B, Paris K, Ochs HD, Filipovich A, et al. Health-related quality of life and health resource utilization in patients with primary immunodeficiency disease prior to and following 12 months of immunoglobulin G treatment. J Clin Immunol. 2016;36:450–61.
15. Jiang F, Torgerson TR, Ayars AG. Health-related quality of life in patients with primary immunodeficiency disease. Allergy Asthma Clinical Immunol. 2015. https://doi.org/10.1186/s13223-015-0092-y.
16. Titman P, Allwood Z, Gilmour C, Malcolmson C, Duran-Persson C, Cale C, et al. Quality of life in children with primary antibody deficiency. J Clin Immunol. 2014;34:844–85.
17. Piazza-Waggoner C, Adams CD, Cottrell L, Taylor BK, Wilson NW, Hogan MB. Child and caregiver psychosocial functioning in pediatric immunodeficiency diseases. Ann Allergy Asthma Immunol. 2006;96:298–303.
18. Peshko D, Kulbachinskaya E, Korsunsky I, Kondrikova E, Pulvirenti F, Quinti I, et al. Health-related quality of life in children and adults with primary immunodeficiencies: a systematic review and meta-analysis. J Allergy Clin Imm Pract. 2019;7(6):1929–1957.e5.
19. Español T, Prevot J, Drabwell J, Sondhi S, Olding L. Improving current immunoglobulin therapy for patients with primary immunodeficiency: quality of life and views on treatment. Patient Prefer Adherence. 2014;8:621–9.
20. Berger M, Murphy E, Riley P, Bergman GE. Improved quality of life, immunoglobulin G levels, and infection rates in patients with primary immunodeficiency diseases during self-treatment with subcutaneous immunoglobulin G. South Med J. 2010;103(9):856–63.
21. Fasth A, Nyström J. Quality of life and health-care resource utilization among children with primary immunodeficiency receiving home treatment with subcutaneous human immunoglobulin. J Clin Immunol. 2008;28:370–8.
22. Gardulf A, Nicolay U, Math D, Asensio O, Bernatowska E, Böck A, et al. Children and adults with primary antibody deficiencies

gain quality of life by subcutaneous IgG self-infusions at home. J Allergy Clin Immunol. 2004;114:936–42.
23. Heath J, Lehman E, Saunders EF, Craig T. Anxiety and depression in adults with primary immunodeficiency: how much do these patients experience and how much do they attribute to their primary immunodeficiency? Allergy Asthma Proc. 2016;37(5):409–15.
24. Sultan S, Rondeau E, Levasseur MC, Dicaire R, Decaluwe H, Haddad E. Quality of life, treatment beliefs, and treatment satisfaction in children treated for primary immunodeficiency with SCIg. J Clin Immunol. 2017;37(5):496–504.
25. Cole T, McKendrick F, Titman P, Cant AJ, Pearce MS, Cale CM, et al. Health related quality of life and emotional health in children with chronic granulomatous disease: a comparison of those managed conservatively with those that have undergone haematopoietic stem cell transplant. J Clin Immunol. 2013;33(1):8–13.
26. Heimall J, Puck J, Buckley R, Fleisher TA, Gennery AR, Neven B, et al. Current knowledge and priorities for future research in late effects after hematopoietic stem cell transplantation (HCT) for severe combined immunodeficiency patients: a consensus statement from the second pediatric blood and marrow transplant consortium international conference on late effects after pediatric HCT. Biol Blood Marrow Transplant. 2017;23:379–87.
27. Picard C, Gaspar HB, Al-Herz W, Bousfiha A, Casanova JL, Chatila T, et al. International Union of Immunological Societies: 2017 primary immunodeficency diseases committee report on inborn errors of immunity. J Clin Immunol. 2018;38(1):96–128.
28. Varni JW, Limbers CA, Burwinkle TM. Impaired health-related quality of life in children and adolescents with chronic conditions: a comparative analysis of 10 disease clusters and 33 disease categories/severities utilizing the PedsQL 4.0 Generic Core Scales. Health Qual Life Outcomes. 2007;5:43.
29. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL™ 4.0 as a pediatric population health measure: feasibility, reliability, and validity. Ambul Pediatr. 2003;3(6):329–41.
30. Gordijn MS, Cremers E, Kaspers G, Gemke R. Fatigue in children: reliability and validity of the Dutch PedsQL™ Multidimensional Fatigue Scale. Qual Life Res. 2011;20:1103–8.
31. Crichton A, Knight S, Oakley E, Babl FE, Anderson V. Fatigue in child chronic health conditions: a systematic review of assessment instruments. Pediatrics. 2015;135(4):e1015–31.
32. Oken M, Creech R, Tormey D, Horton J, Davis TE, McFadden E, et al. Toxicity and response criteria of the eastern cooperative oncology group. Am J Clin Oncol. 1982;5:649–55.
33. Departament de Treball, Afers socials i Famílies. What is dependency and how is it recognized?. In: Generalitat de Catalunya. 2014. Available at: http://treballiaferssocials.gencat.cat/ca/ambits_tematics/persones_amb_dependencia/que_es_i_com_es_reconeix_la_situacio_de_dependencia/. Last accessed 10 Jul 2019.
34. Nap-van der Vlist MM, Dalmeijer GW, Grootenhuis MA, Van der Ent CK, Van den Heuvel-Eibrink MM, Wulffraat NM, et al. Fatigue in childhood chronic disease. Arch Dis Child. 2019;104:1090–5.
35. Hajjar J, Guffey D, Minard CG, Orange JS. Increased incidence of fatigue in patients with primary immunodeficiency disorders: prevalence and associations within the US immunodeficiency network registry. J Clin Immunol. 2017;37(2):153–65.
36. Rojavin MA, Hubsch A, Lawo JP. Quantitative evidence of wear-off effect at the end of the intravenous IgG (IVIG) dosing cycle in primary immunodeficiency. J Clin Immunol. 2016;36(3):210–9.