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REGULAR ARTICLE

Primary antibody deficiency: The impact on the quality of life and mental health of affected children and their parents

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Abstract

Aim: To evaluate health-related quality of life, mental health and treatment-related stress responses in children with primary antibody deficiency and both their parents.

Methods: Children and their parents completed the standardised questionnaires Pediatric Quality of life Inventory, Strength and Difficulties Questionnaire and Impact of Event Scale. Parents also completed standardised questionnaires regarding their own mental health and quality of life. The results were compared to those of healthy children, kidney transplanted children and children in remission from acute lymphoblastic leukaemia.

Results: Children with primary antibody deficiency reported a poorer health-related quality of life compared to healthy children and children in remission from acute lymphoblastic leukaemia. They reported poorer mental health compared with healthy children. Mothers of children with primary antibody deficiency reported poorer mental health compared to mothers of healthy children but comparable to mothers of chronically ill children. Parents reported a similar quality of life as the general Norwegian population. Treatment with subcutaneous immunoglobulin infusions at home is generally well tolerated, but some report severe treatment-related stress.

Conclusion: Primary antibody deficiency has a significant impact on quality of life and mental health of affected children. Patients and parents with severe treatment-related stress should be identified and helped.

KEYWORDS
Health-related quality of life, home-treatment with subcutaneous immunoglobulin, mental health, primary antibody deficiency

Abbreviations: HRQOL, Health-related quality of life; ALL, Acute lymphoblastic leukaemia; IVIG, Intravenously administered immunoglobulins; SCIG, Subcutaneously administered immunoglobulins; SDQ, Strength and difficulties questionnaire; PedsQL, Pediatric Quality of Life Inventory Version 4.0; QOLS, Quality of Life Scale; GHQ-30, The General Health Questionnaire 30; IES-15, Impact of Event Scale-15; SD, Standard deviation.

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1 | INTRODUCTION

Primary immunodeficiency comprises a heterogeneous group of rare inherited disorders. The largest subgroup of primary immunodeficiency is primary antibody deficiencies.[1] There are several forms of antibody deficiency in which either the quantity and/or function of antibodies are reduced. Antibody deficiency makes these patients vulnerable to recurrent infections and in some cases, chronic organ damage. Primary antibody deficiency may also be associated with failure to thrive, chronic fatigue, autoimmune disorders and malignant disease.[2]

Over the last decades, immunoglobulin replacement therapy has led to a substantial improvement in the outcome of antibody deficiency. Intravenously administration of immunoglobulin (IVIG) has been most common, but the trend has shifted to subcutaneous infusions (SCIG), which has shown advantages both on physical health and quality of life.[3,4] Subcutaneous administration of immunoglobulin was established early in Scandinavia,[5,6] and all children in the present study were treated with weekly SCIG at home.

Treatment with immunoglobulin infusion may be associated with anxiety or stress. Some patients experience pain and needle phobia. Younger children may need to be held tightly throughout the infusion, which is potentially traumatic for both the child and the caregiver. The treatment requires systematic planning and follow-up and may represent a reminder of the disease. The role of SCIG as a stressor is uncertain.

A recent systematic review and meta-analysis found that children with primary immunodeficiency reported significantly lower health-related quality of life (HRQOL) compared to healthy individuals and in general also lower HRQOL compared to children with other chronic diseases.[7]

To our knowledge, there are no previously published studies on the mental health or quality of life of the parents of children with antibody deficiency. We hypothesise that the challenge of caring for a child with immunodeficiency, including weekly administration of SCIG at home, will influence parents' quality of life and mental health. Parental wellbeing is also known to be an important factor that influences children´s mental health and quality of life.[8,9]

The aim of this questionnaire-based cross-sectional study was to assess mental health and HRQOL of children with antibody deficiency and their parents in Norway. Mental health and quality of life of these children were compared to healthy children, to children in remission from acute lymphoblastic leukaemia (ALL) and to children who previously received a kidney transplant. Additionally, we wanted to identify stress responses to SCIG treatment.

Key Notes

- Using standardised and validated questionnaires, we found that children with primary antibody deficiency and their mothers had poorer mental health compared to healthy individuals.
- Children with primary antibody deficiency had poorer health-related quality of life compared to healthy children and children in remission from acute lymphoblastic leukaemia.
- Home-treatment with subcutaneous immunoglobulin infusion was occasionally associated with severe stress in both patients and parents.

2 | PATIENTS AND METHODS

2.1 | Participants

Thirty children with primary antibody deficiency, three to 18 years of age, who received regular SCIG treatment at home, were eligible for the study. An overview of the patients and questionnaires is presented in Figure 1. All patients were under follow-up care with the Paediatric Outpatient Clinic at Oslo University Hospital, Rikshospitalet. Families were informed about the study and invited to participate by telephone or when they attended the hospital. The questionnaires were distributed by a nurse or a medical student at the hospital or sent by mail. Each family received 12 to 15 questionnaires, depending on the age of the child. We estimated the time needed to fill out the questionnaires to be about one hour. The costs related to printing and distribution of the questionnaires were minor. Most responders completed the questionnaires at home and returned them by mail in a prepaid envelope. Each family was contacted at least twice by phone to answer any questions regarding the study protocol and as a reminder. Seventeen families returned surveys. Not all family members (patient and parents) participated, and in some families, one or more of the questions or questionnaires were left out. As a result, depending on the specific outcome variable, the number of responders in analyses and results varied between 12 and 16. Socio-demographic characteristic was obtained by the parent report and are presented in Table 1. Self-reported medical data from the last year were obtained on infections, fever, days lost from school, unplanned visits to health care, limitations in leisure activities, medication, administration of SCIG, treatment satisfaction and compliance. Data are presented in Table 2. Diagnoses were based on clinician reports and are presented in Table 3.

Data on HRQOL and mental health of children with antibody deficiency were compared to 42 healthy children, 38 paediatric patients who underwent renal transplantation and 40 children in remission from ALL. The mental health of the mothers was also compared among these four groups. The control and comparison groups were published in previous studies and are extensively elaborated in the papers by Diseth and Reinfjell.[10,11] No significant differences were found among the groups in terms of gender, age or socio-demographic characteristics. As these previous studies did not include fathers, we do not have relevant comparison groups for data collected from fathers in our study. Regarding the parents' quality of life, we lack data from the ALL group and the group of healthy children. Our collected data are therefore compared with reference values of the general Norwegian population and to mothers in the transplant group.

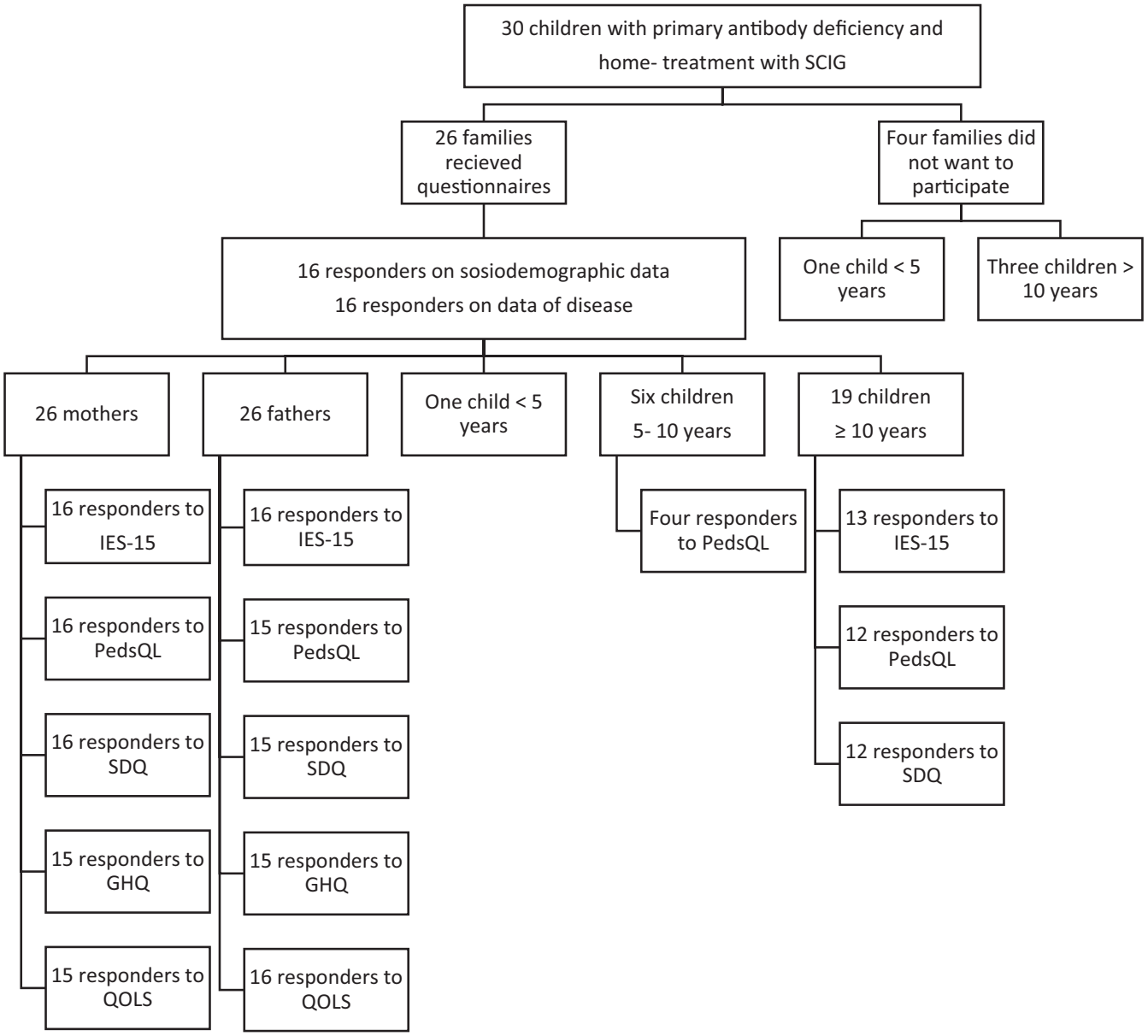

FIGURE 1 Overview of the patients eligible for the study and the responders for each questionnaire

2.2 | Questionnaires

The Strength and Difficulties Questionnaire (SDQ)[12] was used for assessing patients' mental health and psychosocial functioning. SDQ is scored into five subscales and the Total Difficulties Score, which is a summary score. The SDQ self-report was developed for children above the age of 10. *The Pediatric Quality of Life Inventory™* Version 4.0 *(PedsQL)*[13] was used as an instrument for measuring patients HRQOL. PedsQL contains 23 items, distributed in four different scales and can be summarised in the Total Scale Score. The PedsQL self-report is developed for children above the age of five. For both SDQ and PedsQL, we obtained both parents' proxy report and when appropriate, the child's self-report. *The Quality of Life Scale (QOLS)*[14] was used to assess quality of life of the parents and the *General Health Questionnaire (GHQ-30)*[15] is a mental health questionnaire for detecting minor psychiatric disorders. In our study, it was used as a screening instrument for parents' overall psychological distress. Clinically important psychological distress was defined as a GHQ-30 case score of ≥5. These four questionnaires are thoroughly described in previous work.[10] *The Impact of Event Scale (IES-15)*[16] is a measure for stress reactions after potentially traumatic events. In our study, IES-15 was used to measure stress related to weekly subcutaneous infusion of immunoglobulin at home. Children older than 10 years completed a self-report. Additionally, parents of children of all ages were asked about their own stress response. Total scores ≥20 denote severe and clinically important responses. IES-15 has shown satisfactory psychometric properties.[16,17]

TABLE 1 Socio-demographic characteristics

Gender, *n* (%)	
Girls	8 (50)
Boys	8 (50)
Age at inclusion (years)	
Median (range)	13 (7–17)
Parental characteristics	
Household, *n* (%)	
Two parents	14 (87.5)
Single parent	2 (12.5)
Age in years median (range)	
Mothers	38.5 (31–51)
Fathers	40 (33–55)
Level of education, *n* (%)	
Mothers	
Under education	3 (18.8)
High school graduate	5 (31.3)
Post high school	8 (50.0)
Fathers	
Elementary school	1 (6.7)
High school graduate	6 (40.0)
Post high school	8 (53.3)
Community, *n* (%)	
Urban	5 (31.3)
Rural	11 (68.8)
Home, *n* (%)	
Own house	16 (100)
Economy, *n* (%)	
Very satisfying	1 (6.7)
Good	5 (33.3)
Average	9 (60.0)
Poor	0 (0)

Socio-demographic characteristics of 16 children with antibody deficiency and their parents. Response rate was incomplete, with only 15 families filling out some questions.

TABLE 2 Medical data

Infections, median (range)	4.5 (0–14)
Fever, *n* (%)	
Under 10 days	13 (86.7)
10–25 days	2 (11.8)
Over 25 days	0 (0)
Unplanned doctor visits, *n* (%)	
More than once a month	0 (0)
Once every half year to once a month	3 (20)
Less than once every half year	12 (80)
Additional health problems, median (range)	2 (0–6)
Days lost at school, n (%)	
Under 10 days	9 (60)
10–25 days	3 (20)
Over 25 days	3 (20)
Participation of leisure activities, *n* (%)	
Prevented	7 (46.7)
Normal	8 (53.3)
Treatment in addition to SCIG, median (range)	1 (0–2)
Treatment satisfaction, *n* (%)	
Good	8 (50)
Reduced	8 (50)
Treatment administration, *n* (%)	
Self	7 (43.8)
Parent	6 (37.5)
Self or parent	3 (18.8)
Local site reaction, *n* (%)	
Yes	7 (43.8)
No	9 (56.3)
Compliance, *n* (%)	
Good	14 (87.5)
Reduced	2 (12.5)

Disease- and treatment characteristics of 16 children with antibody deficiency based on self-report from the last year. Response rate was incomplete, with only 15 families filling out some questions.

TABLE 3 Diagnosis *n* (%)

Common variable immunodeficiency	7 (41.2)
X-linked agammaglobulinemia	5 (29.4)
Ataxia-Telangiectasia	2 (11.8)
Unspecified hypogammaglobulinemia	1 (5.9)
SCID after bone marrow transplantation	1 (5.9)
22q11 deletion syndrome	1 (5.9)

Diagnosis of children with primary antibody deficiency.

2.3 | Statistics and ethics

Continuous variables are presented as the mean value ± standard deviation (SD) or as the median and range if skewed. Categorical variables are presented as proportions and percentages. Correlation between normally distributed variables was calculated using Pearson's correlation coefficient. For between-group comparisons, we used independent sample t test and paired t test. All analyses were performed in SPSS version 22 (SPSS, Chicago, IL) with a 5% statistical significance level.

Written informed consent was obtained from patients and parents prior to study start. This protocol was approved by the Regional Committee for Research Ethics (2013/1224) and was performed in accordance with the Declaration of Helsinki.

3 | RESULTS

The results from PedsQL and SDQ are presented in Table 4. Children with antibody deficiency exhibited poorer HRQOL on all subscales compared to healthy children. Children with

TABLE 4 Quality of life and mental health of children with PAD and comparison groups

	PAD	M-PAD	F-PAD	KTX	M-KTX	ALL	M-ALL	Healthy	M-Healthy
PedsQL	*n = 16*	*n = 16*	*n = 15*	*n = 30*	*n = 32*	*n = 40*	*n = 36*	*n = 42*	*n = 38*
Total score	73.2 (12.1)	62.3 (11.7)	63.2 (17.5)	69.1 (18.0)	68.4 (19.2)	81.7 (12.6)*	79.4 (12.5)**	89.0 (7.6)**	89.6 (10.3)**
Psychosocial health	74.5 (13.4)	63.5 (10.4)	65.3 (14.6)	67.0 (18.1)	67.7 (18.9)	79.3 (14.0)	75.9 (14.2)**	87.2 (9.2)**	88.1 (11.3)**
Physical Functioning	70.6 (13.7)	60.2 (19.6)	59.2 (26.7)	74.9 (17.0)	69.4 (23.1)	86.3 (12.1)**	86.1 (13.7)**	92.3 (6.5)**	92.5 (10.5)**
Emotional Functioning	73.0 (19.0)	67.3 (12.0)	67.8 (16.2)	69.5 (15.8)	70.0 (21.4)	75.1 (18.7)	70.3 (15.6)	83.2 (12.7)*	85.0 (13.5)*
Social Functioning	85.9 (15.1)	66.3 (19.8)	68.1 (23.9)	73.7 (21.5)*	67.8 (27.1)	86.0 (14.1)	82.8 (15.5)*	92.5 (7.7)*	93.2 (9.9)**
School Functioning	64.7 (18.1)	56.9 (15.6)	60.1 (18.0)	63.1 (17.8)	62.9 (23.2)	76.6 (16.4)*	74.4 (19.9)**	86.0 (13.0)**	86.1 (14.6)**
SDQ	*n = 12*	*n = 16*	*n = 15*	*n = 26*	*n = 31*	*n = 39*	*n = 36*	*n = 41*	*n = 38*
Total difficulties	8.8 (4.5)	9.3 (5.4)	9.7 (4.5)	11.6 (5.7)	10.7 (6.3)	7.4 (4.8)	7.6 (5.2)	5.7 (4.3)*	4.2 (3.6)*
No.(%) cases	0 (0)	0 (0)	1 (6.3)	2 (7)	4 (13)	1 (3)	2 (6)	0 (0)	0 (0)
No.(%) borderline	1 (8.3)	3 (19)	1 (6.3)	6 (23)	3 (10)	0 (0)	3 (8)	1 (2)	0 (0)
Emotional problems	2.7 (2.2)	2.6 (1.7)	3.0 (1.9)	3.6 (2.1)	2.7 (2.0)	2.5 (2.1)	1.6 (1.8)	1.8 (2.2)	0.8 (0.9)*
Conduct problems	1.3 (1.1)	1.4 (1.6)	1.7 (1.3)	1.9 (1.6)	1.8 (1.5)	2.1 (1.5)*	1.5 (1.3)	1.8 (1.4)	1.0 (1.2)
Hyperactivity problems	3.6 (2.2)	3.1 (2.4)	2.7 (1.8)	3.6 (2.2)	3.7 (2.5)	3.1 (1.9)	2.8 (2.7)	3.3 (2.3)	1.7 (2.0)
Peer problems	1.7 (1.3)	2.2 (2.4)	2.3 (2.3)	2.5 (2.2)	2.6 (2.5)	2.3 (1.9)	1.6 (1.9)	1.6 (1.7)	0.8 (1.0)*
Prosocial behaviour	8.8 (1.4)	7.7 (1.8)	8.6 (1.3)	7.9 (2.1)	7.8 (2.2)	7.6 (1.8)*	8.0 (1.9)	7.9 (1.8)	8.9 (1.4)*

Health-related quality of life and Strength and Difficulties Questionnaire in children with primary antibody deficiency (PAD), kidney transplanted children (KTX), children in remission from acute lymphoblastic leukaemia (ALL) and healthy children (Healthy). All groups contain both child self-reports and mother proxy reports (M-PAD, M-KTX, M-ALL and M-Healthy). In addition, while data on father proxy reports from the antibody deficiency group is presented (F-PAD), statistical analyses are not performed on this data. Data are presented as the mean with standard deviation in parenthesis unless stated otherwise.

*Significant at the 0.05 level (two-tailed).

**Significant at the 0.001 level (two-tailed) with respect to difference between M-PAD and M-KTX/ALL/healthy children.

antibody deficiency had overall comparable HRQOL to transplanted children but lower scores on several subscales, including the PedsQL total score, compared to children in remission from ALL. This is consistent both for the child self-report and mother proxy report. Children with antibody deficiency had better social function than transplanted children based on self-report. Mothers of children with antibody deficiency reported their children to have significantly lower HRQOL total score (t = 2.30, P = 0.037) and emotional function (t = 2.91, P = 0.011) compared to children's self-report. No significant differences were observed between the fathers' reports and children's self-reports in the antibody deficiency group. The response rate on PedsQL was 50%–57%.

According to children's self-report and mothers' proxy report, children with antibody deficiency reported more mental health problems compared to healthy children, as they had a significantly higher SDQ Total Difficulties Score. Children with antibody deficiency reported fewer conduct problems and more prosocial behaviour compared to children in remission from ALL. Otherwise, no differences were observed among the three groups of chronically ill children. According to the fathers' report, one child with antibody deficiency was scored as a 'case', indicating that the child was defined to be in a group with a high risk of mental health disorders. There was no significant difference between the SDQ self-report and SDQ parent proxy report within the antibody deficiency group. The only correlation found between SDQ Total Difficulties Score or PedsQL total score and patients' medical data was a correlation between Total Difficulties Score by father report and number of additional medical problems (r = 0.67, P < 0.05). The response rate to SDQ was 50% to 57%.

The results from the GHQ-30 questionnaire are presented in Table 5, and the response rate was 50%. Mothers of children with antibody deficiency reported more psychological distress than mothers of healthy children but were similar to mothers in the two other groups of chronically ill children. Regarding quality of life of parents in the antibody deficiency group, we found a mean QOLS total score of 82.4 (SD 12.0) for 15 mothers and 83.8 (SD 12.2) for 16 fathers. This was not significantly different from the QOLS reference values from the general Norwegian population.[18] Mothers of kidney transplanted children reported significantly better quality of life (mean 90.44, SD 10.04) compared to mothers of children with antibody deficiency.

Children with antibody deficiency reported an IES-15 mean score of 6.9 (SD 11.9, median 3) with a response rate of 62%. Sixteen parents completed IES-15 with a response rate of 53%. Mothers reported a mean score of 4.8 (SD 7.1, median 2). Fathers reported a mean score 3.8 (SD 5.5, median 3). One child, one mother and one father had a score ≥20 indicating a clinically important stress-related cognition and behaviour related to the weekly subcutaneous infusion of immunoglobulins. These individuals represented three different families. We identified a strong correlation between number of days with fever and both child-reported stress response (r = 0.81, P < 0.01) and mother-reported stress response (r = 0.85, P < 0.01). A correlation was also observed between self-reported stress and treatment satisfaction (r = 0.67, P < 0.05). Father-reported stress response was not significantly correlated with any of the medical data.

4 | DISCUSSION

Oslo University Hospital has treated children with primary antibody deficiency with subcutaneous immunoglobulins for three decades. Several studies have shown advantages for SCIG compared to IVIG, also with regards to quality of life.[3] Despite general treatment satisfaction, even the first published paper on home-based SCIG in children highlighted some negative experiences for both patient and parents.[5] This study supports these earlier findings. Most patients and parents tolerate the SCIG treatment well. However, one mother, one father and one child from three different families reported serious stress related to the weekly SCIG treatments. In this study, parents administered the treatment in 64% of cases, which can be traumatic for both parents and child. Fifty per cent of the patients reported no treatment-related problems at all, while the other half reported their treatment satisfaction to be lower. Reasons given for this were as follows: the needle stick; the required planning of the treatment; the treatment as a reminder of disease. In clinical practice, both patients and parents' experiences with SCIG treatment should be taken into consideration. For a minority of people, negative experiences or stress responses are prominent, and alternative treatment options or arrangements should be considered. One could consider hospital-based intravenous treatment or administration of either subcutaneous or intravenous infusions performed by home-care nurses.

TABLE 5 Parental mental health

Mental health	Mother antibody deficiency	Father antibody deficiency	Mother transplanted	Mother ALL	Mother healthy
GHQ-30	*n = 15*	*n = 15*	*n = 31*	*n = 34*	*n = 37*
Case score; mean (SD)	5.5 (8.9)	4.5 (6.5)	2.1 (4.8)	3.3 (6.7)	1.2 (3.3)*
- no. (%) case; cut-off 5–30	5 (33.5)	4 (26.8)	5 (16.1)	6 (17.6)	2 (5.4)

Parental mental health by The General Health Questionnaire.

*Significantly different at the 0.05 level (two-tailed) from mother antibody deficiency.

We found a strong association between number of days with fever and mothers' and children's treatment-related stress. This might suggest that patients who experience a good effect of treatment with few episodes of fever also tolerate the treatment better. Fever in children with antibody deficiency may be a serious sign and can trigger stress. Based on clinical experience, we find it important that the family and the paediatrician together determine a plan for how to proceed in case the child gets a fever.

This is the first Norwegian study to utilise a selection of several standardised methods to examine the quality of life and psychological aspects of paediatric antibody deficiency. The finding that HRQOL of children with antibody deficiency is lower compared to healthy children is consistent with the recent meta-analysis by Peshko et al.[7] The findings presented here add to the growing evidence indicating that living with an immunodeficiency has an impact on HRQOL that is at least comparable to the impact of several other chronic diseases.

Children with antibody deficiency and to some extent their parents report particularly low scores on HRQOL related to school function. Similar findings have also been shown in previous studies.[19–22] Even though SCIG treatment reduces the number of days lost at school,[23] problems of keeping up with schoolwork and days lost from school still compromise HRQOL in children with antibody deficiency. In this study, 40% of children with antibody deficiency lost more than 10 days a year of school attendance, while 20% lost over 25 days. Such negative school experiences can lead to negative consequences later in life. Among Norwegian adults with antibody deficiency, unemployment is associated with lower quality of life.[24] These adults report school experiences related to their immunodeficiency as a major burden.

We also found that children with antibody deficiency exhibit higher overall rates of psychological difficulties compared to healthy children but similar to children with other chronic diseases. This is consistent with earlier findings.[20] In our experience, using a multidisciplinary approach to educate the family about the illness can help them cope with all aspects of the illness, including the psychological aspects. Sharing experiences with other patients and families through the patient organisation also provides valuable support for many families.

In light of the limited number of patients with primary antibody diseases in Norway and the suboptimal response rates in this study, our findings must be interpreted with caution. However, we see the high degree of consistency between our findings and previous studies on quality of life or mental health of children with antibody deficiency as a strength of our results.

Mothers of children with antibody deficiency underestimate the HRQOL of their children. This is in contrast to previous data on children with antibody deficiency[7] but is a known phenomenon in paediatrics.[25,26] This underestimation may be a sign of overprotection or worried mothers who tend to notice negative feelings in their children, and it proves the importance of adding the child's and father's perspective in quality of life studies. On the other hand, in our study, the mother's and children's reports on mental health were in accordance with each other. No significant difference was found between the father proxy report and the child self-report in either HRQOL or mental health.

Mothers of children with antibody deficiency report more psychological distress compared to mothers of healthy children but similar to mothers of other chronically ill children. This finding highlights the burden of caring for a child with chronic disease and indicates that paediatric antibody deficiency has a large impact on family life.

4.1 | Strength and limitations

This is the first study on quality of life and mental health in Norwegian children with primary antibody deficiency. It is a single-centre study, and we obtained both self-reports, mother proxy reports and father proxy reports. We had relevant controls and comparison groups for data obtained by child self-reports and mother proxy reports. To our knowledge, this is the first study to address quality of life in children with antibody deficiency together with quality of life and mental health of the parents. We also examined both patients' and parents' treatment-related stress.

However, this study has several limitations. The number of patients is small, and they represent a heterogeneous group of antibody deficiency disorders. Thus, no comparisons were done within the study group. We performed several analyses without correcting for type I error. The cross-sectional design of this study does not allow us to control for pre-morbid function or to draw conclusions on causes. Our study is based on questionnaires. Used alone, such data may underestimate psychosocial dysfunction and psychopathology. Complementing with semi-structured or qualitative interviews could provide more precise evaluation.[27] Furthermore, the response rate to our questionnaires was low. Due to the high rate of attrition, these results should be interpreted with caution. Reasons for not completing the surveys were primarily not finding the time to respond to the questionnaires. This could lead to a bias in terms of an overestimation of HRQOL if it is easier to find time and motivation for responding to questionnaires when you feel well, or in terms of an underestimation of HRQOL if motivation for responding is associated with a need to inform health care that your situation is unsatisfactory. To avoid high attrition in our forthcoming studies, families will be invited to complete study questionnaires not at home after receiving them by mail, but on site whilst attending the hospital.

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