

Quality of life and behavioral functioning in Dutch pediatric patients with hereditary spherocytosis

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Abstract The objective of this study was to evaluate health-related quality of life (HRQoL) and behavioral functioning in pediatric patients with hereditary spherocytosis (HS). A cross-sectional study was conducted in 132 Dutch children and adolescents with HS and aged 8–18 years of whom 48 underwent splenectomy prior to the study. HRQoL was assessed using the KIDSCREEN-27, and behavioral functioning was evaluated using the strength and difficulties questionnaire (SDQ). Scores of pediatric patients with HS were compared to a Dutch norm population. Additionally, the effects of three factors were assessed: fatigue, self-image, and parents' perceived vulnerability (measured with the checklist individual strength, the self-perception profile for children and adolescents, and the child vulnerability scale). Both unsplenectomised and splenectomised pediatric patients reported lower HRQoL on the domain physical well-being (KIDSCREEN-27) compared to Dutch peers. For behavioral functioning, parents of both groups reported more emotional problems (SDQ) compared to the norm population. Pediatric patients with lower scores on physical well-being experienced more fatigue. The patients' perceived social acceptance and parents' perceived vulnerability appeared as determinants of

emotional problems. **Conclusion:** Pediatric patients in the current study generally report few complaints, and the results suggest that these patients overall have a strong ability to cope with HS. Despite these few complaints, fatigue and parents' perceived vulnerability seem to be important determinants for lower HRQoL and more emotional problems. Therefore, screening on these factors could serve as an addition to the treatment of HS, to help pediatric patients who are at risk for lower HRQoL or more emotional problems.

Keywords Hereditary spherocytosis · HRQoL · Behavioral functioning · KIDSCREEN · SDQ

Abbreviations

HS	Hereditary spherocytosis
HRQOL	Health-related quality of life
SDQ	Strengths and difficulties questionnaire
CIS	Checklist individual strength
SPPC/SPPA	Self-perception profile for children/adolescents
CVS	Child vulnerability scale

Introduction

Hereditary spherocytosis (HS) is an inherited hemolytic anemia characterized by the production of sphere-shaped rather than regular donut-shaped red blood cells. The odd shape of these blood cells (named "spherocytes") is caused by a reduction or dysfunction of one or more proteins of the red blood cell cytoskeleton: ankyrin, band 3, protein 4.2, and α and β spectrin [14]. Spherocytes have a shorter life span than regular red blood cells which will lead to hemolysis. Splenectomy is effective in reducing hemolysis, but benefits have to be balanced against risks, especially in pediatric patients with a mild or moderate phenotype of HS [4, 18, 19]. Clinical features of HS

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consist of fatigue, pale skin, yellowish sclera, jaundice, and splenomegaly.

In the last couple of years, knowledge about the etiology and impact of treatment courses on HS has grown. However, little is known about the psychosocial adaptation to HS. Psychosocial adaptation can be measured in terms of health-related quality of life (HRQoL) [9] and in terms of behavioral functioning [25]. As pediatric patients with HS experience fatigue, they might have a decreased quality of life, as was suggested in other studies in children with a chronic disease [8]. Furthermore, HS can influence appearance, which can influence self-image and self-esteem [25]. Also, parents of chronically ill children generally have increased perceptions of the child's vulnerability, which can affect the child's development [1, 10].

To date, no studies have examined HRQoL and behavioral functioning in a large population of pediatric patients with HS. Two studies have examined HRQoL of patients with HS; however, both of these studies focused on treatment options [22, 2]. The aim of the present study was twofold:

The primary aim was to evaluate psychosocial adaptation of pediatric patients with HS in the Netherlands in terms of HRQoL and behavioral functioning. In this cross-sectional design, pediatric patients with HS ranging from 8 to 18 years were included, and the cohort consisted of both unsplenectomised and splenectomised pediatric patients. HRQoL and behavioral functioning of both groups were compared to a norm population of healthy Dutch children and adolescents.

The secondary aim was to explore the effect of fatigue, self-image, and parents' perceived vulnerability on HRQoL and behavioral functioning.

Materials and methods

Participants

The cross-sectional study was conducted between November 2009 and January 2010. Pediatricians of all hospitals in the Netherlands ($n=91$) were asked to invite pediatric patients with HS and their parents. As a result, pediatric patients with HS in 42 hospitals received a letter of invitation to the study. Inclusion criteria were the following: [1] aged between 8 and 18 years [2], availability of communication through e-mail for both parents and patients [3], and good understanding of written Dutch language. Socio-demographic information was obtained from both pediatric patients and parents. The following information was collected about the pediatric patient: gender, age, country of birth, age of diagnosis, total number of blood transfusions, and splenectomy (y/n). From

the parents, the following information was obtained: level of income and marital status. Level of income was divided in three levels: below average, average, and between 1 and 2× average, based on the modal income (€30,500) in the Netherlands according to the Central Bureau of Statistics.

Procedure

Both patient and parent received a reply card and response envelope, which served as an application form and as informed consent for the study. After returning the reply card, both patient and parent received an e-mail with a link directing them to the website where they could complete the questionnaires. If a participant did not complete the questionnaires, a reminder was sent to his or her e-mail address after 2 weeks. The study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants gave their informed consent prior to their inclusion in the study.

Questionnaires

An online survey was developed in cooperation with a survey website (NETQ), which consisted of existing self-report questionnaires for the pediatric patients and proxy-report questionnaires for the parents. It took approximately 30 min (parents) and 45 min (patients) to complete the questionnaires.

Self-report questionnaires

HRQoL was evaluated using the KIDSCREEN-27, a self-report questionnaire consisting of 27 items [15]. The KIDSCREEN-27 is applicable for both healthy and chronically ill children and adolescents aged between 8 and 18 years and consists of five domains of HRQoL. Items are scored on a five-point scale; higher scores indicate better HRQoL. The KIDSCREEN-27 has been shown to have robust psychometric properties. The internal consistency of the domains was between 0.81 and 0.84, and the test-retest reliability of the domains ranged from 0.61 to 0.74 [15].

Fatigue was assessed using the self-report checklist individual strength (CIS) [23]. This 20-item questionnaire measures four aspects of fatigue, which are translated to four domains and together comprise a multidimensional total fatigue score. The items are scored on a Likert scale with higher scores representing more fatigue (scale range=1 to 7). As this scale is originally developed for adults, only Dutch adult norms were available. Therefore, in this study, only standard scores were used in the statistical analysis. In the current study, the CIS had an internal consistency (Cronbach's α) of 0.95 (total score).

To assess self-image, pediatric patients with HS completed the Dutch version of the self-perception profile for children and adolescents, respectively, the SPPC (8–12 years) [23] and the SPPA (13–18 years [21]). Both questionnaires consist of 6 perceived competence domains and in total 36 items (SPPC) or 35 items (SPPA). Each item is scored 1 to 4; a higher score reflects a higher degree of perceived competence. The psychometric properties of both the SPPC and SPPA have been examined in a representative sample of Dutch children and adolescents and have acceptable internal consistency and test-retest stability [21, 19].

Parent proxy-report questionnaires

Behavioral functioning was measured with the Dutch proxy-report (4–16 years) version of the strength and difficulties questionnaire (SDQ) [20]. The SDQ contains 20-problem items across four domains (emotional problems, conduct problems, hyperactivity, and peer relationship problems) and 5 pro-social behavior items. The problem items add up to a total problem score ranging from 0 to 40 with a higher score indicating more behavioral difficulties. The pro-social behavior scale gives a total score of 10 for positive pro-social behavior with a higher score indicating more strength. The psychometric properties of the SDQ have been examined in a sample of Dutch children and adolescents and have acceptable internal consistency and test-retest stability [13].

The Dutch version of the child vulnerability scale (CVS) was used to assess parents' perceptions of their child's general vulnerability [10]. Each of the eight items is scored on a four-point Likert scale ranging from 1 to 4. A higher score reflects a higher amount of perceived vulnerability. The scale is scored by summing up the responses. Acceptable reliability and validity have been previously reported [10, 18].

Statistical analysis

The Statistical Package for Social Sciences (SPSS) version 21.0 was used for statistical analyses. The online survey was constructed in such a way that it was not possible to leave a question unanswered; therefore, no missing values existed. Pediatric patients in the total sample followed a different treatment path; splenectomised pediatric patients are likely to have experienced many complaints in the pre-splenectomy, whereas most unsplenectomised pediatric patients have low complaints and are therefore not in need of splenectomy. This resulted in a non-homogenous sample. As splenectomised and unsplenectomised pediatric patients are not comparable, results for both groups were analyzed separately.

Regarding our primary aim, one-way sample *t* tests were used to compare the results of the KIDSCREEN-27 and the SDQ for both the unsplenectomised and splenectomised

group to the Dutch norm population. Effect sizes (*d*) were calculated by dividing the difference in mean score between patients and the Dutch norm population by the SD of the Dutch norm population. According to Cohen [19], effect sizes between 0.2 and 0.5 are considered small, effect sizes between 0.5 and 0.8 moderate, and effect sizes >0.8 large.

Regarding our secondary aim, a forced entry hierarchical regression analysis was conducted to explore the effect of fatigue, self-image, and parents' perceived vulnerability on HRQoL and behavioral functioning. For both HRQoL and behavioral functioning, only the domains where significant differences were found between pediatric patients with HS and the norm population were used as outcome variable in the regression analysis. This resulted in two regression analyses on physical well-being (KIDSCREEN-27) and emotional problems (SDQ) for both splenectomised and unsplenectomised pediatric patients. Age and gender were included as a first step in the regression model. As a second step, fatigue, self-image, and perceived vulnerability were entered. Considering the power of the regression model, not all domains could be entered in the model. For the CIS and the CVS, a total score can be calculated; however, the SPPC and SPPA consist of five separate domains. Therefore, only the domains with the highest correlations to the outcome variables were entered in the model. For each regression model, the explained variance (R^2) was determined, as well as the change in explained variance (ΔR^2). Variables predicting one of the outcome measures with $p < 0.05$ were considered significant determinants.

Results

Socio-demographic and medical information

Of the 226 families who received an invitation letter, 132 pediatric patients and their parents completed the questionnaires (response rate 58 %). The sample consisted of 84 unsplenectomised pediatric patients and 48 splenectomised pediatric patients. Table 1 displays the clinical and socio-demographic characteristics of both groups. For both groups, 121 pediatric patients with HS came from households with two caregivers and 78 unsplenectomised pediatric patients and 46 splenectomised pediatric patients came from families with an average or higher income. Of the unsplenectomised pediatric patients, five received more than five blood transfusions during their life.

HRQoL and behavioral functioning

Pediatric patients in both the unsplenectomised and splenectomised group reported a significantly lower HRQoL on the domain physical well-being compared to their Dutch

Table 1 Characteristics of pediatric patients with HS and their parents

	Unsplenectomised (<i>n</i> =84)	Splenectomised (<i>n</i> =48)
Children		
Gender		
Male	38	24
Female	46	24
Age in years, median (range)	12 (8–18)	14 (8–18)
Country of birth		
The Netherlands	80	47
Other	4	1
Age of diagnosis in years, median (range)	2 (1–17)	1 (1–14)
Number of blood transfusions		
No transfusions	36	10
1–5 transfusions	43	25
More than 5 transfusions	5	13
Parents		
Level of income ^a		
Below average	6	2
Average	18	9
Between 1 and 2× average	41	23
More than 2× average	19	14
Marital status		
Married/living with a partner	77	44
Separated/widowed/other	7	4

^a Information on income levels obtained from the Central Dutch Bureau of Statistics CBS. Average income €30.500

peers (Table 2). For the other domains, no significant differences were found when pediatric patients with HS were compared to their Dutch peers.

Parents of both unsplenectomised and splenectomised pediatric patients with HS reported more emotional problems

compared to the Dutch norm population (Table 3). Parents of splenectomised pediatric patients with HS reported less conduct problems and hyperactivity/inattention compared to the norm population. For the other domains, no differences were found.

Determinants of HRQoL and behavioral functioning

Results of the exploratory forced entry hierarchical regression analyses are summarized in Table 4. In all regression models, age and gender were entered as determinants in the first step. Fatigue, parents' perceived vulnerability, and various subscales of self-image were added in the second step.

For the unsplenectomised group, the three subscales of self-image that had correlated highest to the outcome variables were included in the models (athletic competence, social acceptance, and physical appearance for HRQoL; scholastic competence, social acceptance, and global self-worth for behavioral functioning). Correlations ranged from 0.22 to 0.52 for HRQoL and from 0.39 to 0.49 for behavioral functioning. This resulted in a total of five predictors in the second step. Both regression models reached significance with an explained variance of 53 % for physical well-being and 40 % for emotional symptoms. In the model of HRQoL, fatigue and parents' perceived vulnerability appeared as significant determinants for physical well-being. In the model of behavioral functioning, parents' perceived vulnerability, scholastic competence, and social acceptance appeared as significant determinants for emotional symptoms.

For the splenectomised group, two similar regression analyses were conducted (Table 4). Since this group was smaller (*n*=48 for HRQoL and *n*=42 for behavioral functioning), only four predictors could be entered to maintain adequate power. The two subscales of self-image that had correlated highest to the outcome variables were included in the models (social acceptance and athletic competence for HRQoL; social

Table 2 Mean HRQoL scores (KIDSCREEN-27) of children with HS (unsplenectomised and splenectomised) compared with the Dutch norm population

Subscale	Unsplenectomised children				Splenectomised children							
	Children with HS		Norm population		<i>P</i> ^a	<i>d</i>	Children with HS		Norm population		<i>P</i> ^a	<i>d</i>
	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)			<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)		
Physical well-being	84	49.4 (9.6)	1,960	52.7 (10.0)	0.002 ^a	0.3	48	50.0 (8.1)	1,960	52.7 (10.0)	0.026 ^a	0.3
Psychological well-being	84	51.3 (8.5)	1,960	52.4 (9.1)	0.219	0.1	48	52.6 (10.1)	1,960	52.4 (9.1)	0.907	0.0
Parents and autonomy	84	54.8 (9.7)	1,960	53.9 (9.5)	0.390	0.1	48	55.3 (9.4)	1,960	53.9 (9.5)	0.316	0.1
Peers and social support	84	53.3 (10.4)	1,960	52.3 (9.1)	0.342	0.1	48	52.3 (11.0)	1,960	52.3 (9.1)	0.977	0.0
School	84	54.9 (8.7)	1,960	53.1 (9.8)	0.059	0.2	48	53.3 (9.7)	1,960	53.1 (9.8)	0.881	0.0

KIDSCREEN-27 scores range from 0 to 108, higher scores represent better HRQoL

d effect size

^a Children with HS vs Dutch norm data

Table 3 Behavioral and emotional problems assessed by the strengths and difficulties questionnaire of children with HS (unsplenectomised and splenectomised) compared with the Dutch norm population

Subscale	Unsplenectomised children				Splenectomised children							
	Children with HS		Norm population		<i>P</i> ^a	<i>d</i>	Children with HS		Norm population		<i>P</i> ^a	<i>d</i>
	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)			<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)		
Total difficulties	78	8.1 (6.0)	300	6.7 (5.3)	0.050	0.3	42	8.4 (6.9)	300	6.7 (5.3)	0.127	0.3
Emotional symptoms	78	2.8 (2.4)	300	1.8 (1.9)	0.000 ^a	0.5	42	2.7 (2.8)	300	1.8 (1.9)	0.046 ^a	0.5
Conduct problems	78	1.1 (1.5)	300	1.0 (1.4)	0.706	0.1	42	0.5 (0.9)	300	1.0 (1.4)	0.000 ^a	0.4
Hyperactivity/inattention	78	2.9 (2.4)	300	2.7 (2.7)	0.414	0.1	42	3.7 (2.9)	300	2.7 (2.7)	0.025 ^a	0.4
Peer problems	78	1.3 (1.8)	300	1.1 (1.6)	0.409	0.1	42	1.5 (2.3)	300	1.1 (1.6)	0.335	0.3
Pro-social	78	8.5 (1.9)	300	8.5 (1.5)	0.903	0	42	8.7 (1.5)	300	8.5 (1.5)	0.463	0.1

SDQ scores range from 0 to 40; higher scores indicate more behavioral difficulties

SDQ pro-social subscale scores range from 0 to 10; higher scores indicate better functioning

d effect size

^a Children with HS versus Dutch norm data

acceptance and scholastic competence for behavioral functioning), with correlations ranging from 0.53 to 0.59 for HRQoL and from 0.48 to 0.50 for behavioral functioning. Both regression models reached significance with an explained variance of 70 % for physical well-being and 49 % for emotional problems. In the model of HRQoL, fatigue and social acceptance appeared as significant determinants for physical well-being. In the model of behavioral functioning,

parents’ perceived vulnerability and social acceptance appeared as significant determinants for emotional symptoms.

Overall, the results of the regression models indicate that pediatric patients with HS who experience more fatigue and less social acceptance report lower physical well-being. Moreover, pediatric patients who are perceived by their parents as more vulnerable and who experience less social acceptance report more emotional symptoms.

Table 4 Standardized regression coefficients *b* from the hierarchical regression analysis predicting HRQoL and behavioral functioning in non-splenectomised children and splenectomised children with HS

Unsplenectomised children				Splenectomised children			
HRQoL (<i>n</i> =84)		Behavioral functioning (<i>n</i> =78)		HRQoL (<i>n</i> =48)		Behavioral functioning (<i>n</i> =42)	
Physical well-being		Emotional symptoms		Physical well-being		Emotional symptoms	
<i>Step 1</i>		<i>Step 1</i>		<i>Step 1</i>		<i>Step 1</i>	
Age	−0.035	Age	−0.144*	Age	−0.187	Age	−0.026
Gender	−0.171	Gender	0.013	Gender	−0.235	Gender	0.074
<i>R</i> ²	0.03	<i>R</i> ²	0.02	<i>R</i> ²	0.102	<i>R</i> ²	0.01
<i>F</i>	1.24	<i>F</i>	0.80	<i>F</i>	2.57	<i>F</i>	0.12
<i>Step 2</i>		<i>Step 2</i>		<i>Step 2</i>		<i>Step 2</i>	
Fatigue	−0.473*	Fatigue	0.076	Fatigue	−0.527*	Fatigue	0.076
Vulnerability	−0.185*	Vulnerability	0.224*	Vulnerability	0.165	Vulnerability	0.400*
Athletic competence	0.218	Scholastic competence	−0.255*	Social acceptance	0.252*	Social acceptance	−0.348*
Social acceptance	0.013	Social acceptance	−0.232*	Athletic competence	0.270	Scholastic competence	−0.141
Physical appearance	−0.072	Global self-worth	−0.095	ΔR^2	0.59*	ΔR^2	0.48*
ΔR^2	0.50*	ΔR^2	0.38*	<i>R</i> ²	0.70	<i>R</i> ²	0.49
<i>R</i> ²	0.53	<i>R</i> ²	0.40	<i>F</i>	15.59* ^a	<i>F</i>	5.57* ^a
<i>F</i>	12.07* ^a	<i>F</i>	6.56*				

Athletic competence, social acceptance, and global self-worth are subscales of the SPPC and SPPA

* *p*<0.05, ^a Significant model *p*< 0.05

Discussion

This is the first study to assess HRQoL and behavioral functioning in a large population of pediatric patients with HS. In general, the HRQoL and behavioral functioning of pediatric patients with HS appeared similar to their healthy peers, except for lower physical HRQoL and more emotional problems. Fatigue seems to have an influence on physical HRQoL scores, both for pediatric patients with and without splenectomy. As fatigue is one of the core complaints in HS, pediatric patients who report more fatigue are likely to experience more problems in physical activity, energy, and fitness. However, as fatigue is hard to quantify, we should be careful when interpreting these findings. Nevertheless, studies in patients with HIV, MS, and cancer also found an association between fatigue and HRQoL [12, 14, 24].

Parents' perceived vulnerability of the pediatric patient and the patient's perceived social acceptance seem to influence emotional symptoms. Similar results on perceived vulnerability were found in a study in children with cancer [7], suggesting that parents who perceive their child as vulnerable may transmit this feeling to their child which can result in increased anxiety or emotional problems. Pediatric patients who feel less socially accepted also report lower physical well-being and display more emotional problems. The relationship between social acceptance and emotional symptoms was also shown in a study on bullying: young teenagers who are bullied or victimized experience more emotional problems [5].

Besides the lower HRQoL on the physical domain and higher scores on emotional problems, pediatric patients with HS did not differ from their healthy peers in HRQoL and behavioral functioning, suggesting that pediatric patients with HS generally seem to have a strong ability to cope with their disease. Regarding the fact that almost all the pediatric patients in the current sample come from a two-parent household with an average to high education and average to good socioeconomic status, these results could be explained by the strong family cohesion pediatric patients with HS experience. Burlew et al. found that family relations serve as a predictor for good adjustment to sickle-cell disease [6]. Also, good adjustment to chronic diseases is typically reported in stable families [25].

While interpreting the results of this study, strengths and limitations should be addressed. Findings of this study are strengthened by the use of questionnaires for HRQoL and behavioral functioning that are widely used and validated in many countries. Secondly, this study focused on both self- and proxy-report, which gives a broad view of psychosocial functioning. Also, because all questionnaires were filled in online, no questions could be missed, misinterpreted, or incorrectly entered in data analyses. However, the cross-sectional study design did not enable us to assess HRQoL and behavioral functioning in the same pediatric patients pre- and post

splenectomy. It would be of additive value to use a longitudinal study design in future research. Moreover, it was not possible to compare the amount of fatigue of pediatric patients with HS to a Dutch norm population of healthy children and adolescents, as an age appropriate questionnaire was not available at the time the study was conducted. It would be interesting to compare both pediatric patients with and without splenectomy to healthy peers in future research, to further evaluate the benefit of the splenectomy on HRQoL. Finally, the results on behavioral and emotional problems should be interpreted with caution because parametric tests were conducted on non-normally distributed data. Using nonparametric tests to compare the pediatric patients with the normative sample would have been preferable but this was impossible since the raw data of the normative sample were not available.

Despite these limitations, this is the first study assessing HRQoL and behavioral functioning in pediatric patients with HS. Results of this study suggest that these patients generally have a strong ability to cope with HS. However, pediatric patients with HS do report lower physical HRQoL, and parents report more emotional problems. Both fatigue and parents' perceived vulnerability seem to be important indicators for lower HRQoL and more emotional problems. Based on the results of this study, we believe it is important to systematically monitor HRQoL and behavioral functioning in pediatric patients with HS, to improve patient care.

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Conflict of interest The authors declare that they have no conflict of interest.

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