

Health-related quality of life in Danish children with hereditary angioedema

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ABSTRACT

Background: The potentially life-threatening disease hereditary angioedema with C1-inhibitor deficiency (C1-INH-HAE) can have considerable impact on the health-related quality of life (HRQoL) in adult patients. Half the patients with C1-INH-HAE develop symptoms before the age of 10 years. However, the HRQoL in children with C1-INH-HAE is almost unexplored.

Objective: To investigate HRQoL in Danish children with C1-INH-HAE, including possible correlations to disease severity and attack frequency.

Methods: All Danish children ages 2–18 years with C1-INH-HAE were invited to complete questionnaires regarding HRQoL; 14 (93%) agreed. Child self-report forms were used for children ages ≥ 5 years. The instruments used were the PedsQL (Child Self-Report and Parent Proxy-Report forms); the Children's Dermatology Life Quality Index; a nonvalidated, disease-specific quality-of-life questionnaire; and two visual analog scales that rated general health.

Results: The HRQoL scores in our study were comparable with the normal scores for healthy children and better than the scores in the only other study dedicated to HRQoL in children. Children with recent attacks had lower scores, whereas HRQoL scores were not correlated to overall disease severity or age. Surprisingly, home therapy was associated with lower HRQoL; however, home therapy was also correlated to a higher overall severity score and more frequent attacks. There was a strong child-parent agreement in the PedsQL forms, but scores were independent of whether the child had a family history of C1-INH-HAE or sporadic C1-INH-HAE and whether the parent completing the Parent Proxy-Report form carried the disease.

Conclusion: Overall, the children assessed on average had a normal HRQoL and better than those with other common skin disorders. However, according to our findings, health care providers should be especially attentive to HRQoL when children with C1-INH-HAE become symptomatic.

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Hereditary angioedema (HAE) with C1-inhibitor deficiency (C1-INH-HAE) is a genetic disease characterized by recurrent attacks of subcutaneous swellings. Life-threatening episodes can occur in the upper airways, and painful abdominal attacks and disfiguring cutaneous swellings can interfere with work, school, and other daily activities. Consequently, C1-INH-HAE can have considerable impact on health-related quality of life (HRQoL).^{1,2} HRQoL in adult patients with C1-INH-HAE has often been investigated with generic instruments or questionnaires for dermatologic con-

ditions.^{1–8} Recently, an HAE-specific HRQoL questionnaire was developed, but it has not yet been evaluated in children.⁹ HRQoL in children with C1-INH-HAE has only been sparsely explored.^{10–12} Our aim was to investigate HRQoL in Danish children with C1-INH-HAE, including its correlation to disease severity and attack frequency.

METHODS

An observational, cross-sectional study was undertaken at the Danish HAE Centre, Odense University Hospital, from May 2013 to August 2014. At that time, the Danish C1-INH-HAE cohort comprised 15 children ages 2–18 years, and 14 children (93%) agreed to participate in the study. Parental written consent was granted to retrieve clinical information from the medical records. According to the Regional Scientific Ethical Committees for Southern Denmark, their approval was not required for this study. The study was approved by the Danish Data Protection Agency (15/31091). We asked participants to complete four different HRQoL instruments twice with a 6-month interval. All questionnaires were sent to the families. The parents were permitted to assist younger children but were instructed not to influence their response.

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Questionnaires

The Pediatric Health-Related Quality of Life 4.0 Generic Core Scales (PedsQL, Mapi Research Trust, Lyon, France) is designed to measure general HRQoL and yields a 0–100 total score, a physical health score, and a psychosocial health score; higher scores reflect better HRQoL.¹³ We used the Child Self-Report forms for ages 5–7, 8–12, and 13–18 years, and the Parent Proxy-Report forms for ages 2–4, 5–7, 8–12, and 13–18 years. A Danish version of the questionnaire is provided by the producers, and published norms are available.¹³ The Children's Dermatology Life Quality Index (CDLQI) is designed to measure concepts such as physical discomfort, social discomfort, and activity limitation in children with skin conditions.¹⁴ The instrument yields a total score (maximum score, 30); higher scores reflect more impaired HRQoL. A Danish version of the questionnaire is provided. No published norms are available.

With PedsQL as a structural model, we prepared a nonvalidated, disease-specific questionnaire. We reviewed items from the HAE-specific HRQoL questionnaire for adults, an angioedema-specific questionnaire, and some disease-specific questionnaires for other chronic, pediatric diseases, *e.g.*, food allergy.^{9,15,16} We selected 13 items that address concepts such as worry or anxiety, feeling of being in control, emotions regarding medical treatment, and avoidance behavior. This instrument yields a total sum score, with higher scores that reflect more impaired HRQoL (maximum score, 52). Two visual analog scales (VAS) ("VAS line" and "VAS smiley") were used to rate general health. One was a 10-cm line for which 0 and 100 represent the worst and best imaginable health status, respectively (modified from Ravens-Sieberer *et al.*¹⁷ and Wehby *et al.*¹⁸). The other scale comprised five smileys, which ranged from very unsatisfied to very satisfied (modified from Jäger¹⁹), which was linearly transformed to a 0–100 scale, with a higher score reflecting better health. Children ages 5–18 years were asked to complete the CDLQI, the disease-specific questionnaire, and the VAS instruments.

Disease Severity and Attack Frequency

For patients with C1-INH-HAE, we used a clinical severity score developed by Bygum *et al.*²⁰ Based on age at disease onset, body sites ever affected, and the need for long-term prophylaxis, the severity score ranges from 0 to 10; a higher score reflects more severe disease. Information about disease severity and attack frequency was retrieved from the medical records. Each parameter was measured twice, coherent with the first and second HRQoL assessment.

Table 1 Patient characteristics

No. patients	14 (6 girls)
Age, median (range), y	
At first assessment	12 (4–18)
At second assessment	12.5 (5–18)
No. patients with C1-INH-HAE, type I/II	13/1
No. patients with a family history/sporadic	11/3
Symptomatic (at least 1 C1-INH-HAE attack)/asymptomatic	12/2
Age at onset, median (range), y	4 (3–11)
No. attacks, median (range)*	
Within the last month	0 (0–6)/0 (0–6)
Within the last year	4.5 (0–53)/1.5 (0–55)
Therapies used within the last year (8/10 children treated)*	
C1-INH concentrate	
ODT	7/8
STP	0/1
Tranexamic acid	
ODT	2/2
LTP	1/1
Bradykinin receptor antagonist	0/1#

C1-INH-HAE = Hereditary angioedema with C1-inhibitor deficiency; C1-INH = C1-inhibitor; ODT = on-demand treatment; STP = short-term prophylaxis; LTP = long-term prophylaxis.

*At or from the first assessment/second assessment.

#The patient was 18 years old.

Analyses

Median and mean scores and standard deviations in each instrument were calculated for the first and second assessment, and for the pooled samples. Internal consistency was determined by using the Cronbach α coefficient; estimates of ≥ 0.70 were considered acceptable. The intraclass correlation between the first and second assessment was calculated. We applied the non-parametric Wilcoxon rank sum test to test for group differences in HRQoL scores and calculated Spearman correlation coefficients ($p < 0.1$ was considered significant). The StataIC 14 software (StataCorp. LP, College Station, TX) was used for statistical analyses.

RESULTS

We included 14 children with C1-INH-HAE. Their demographic and clinical characteristics are outlined in Table 1. Home therapy with C1-INH concentrate were established for eight children. Of these, five children

Table 2 HRQoL and general health in children with C1-INH-HAE (pooled results)

Scale	No. Children	Median	Mean (range)*	Mean $\pm$ SD	Interpretation
PedsQL Child Self-Report					
Total score	24	89.1	84.0 (26.1–100) [82.9]	± 18.6	Score range, 0–100
Physical health	24	95.3	89.9 (34.4–100) [86.9]	± 16.0	Higher scores reflect better HRQoL
Psychosocial health	24	89.1	81.9 (21.7–100) [80.7]	± 20.0	
PedsQL Parent Proxy-Report					
Total score	28	90.2	83.4 (29.4–100) [81.3]	± 18.8	Score range, 0–100
Physical health	28	95.3	88.8 (15.6–100) [83.2]*	± 21.2	Higher scores reflect better HRQoL
Psychosocial Health	28	87.5	80.4 (30–100) [80.2]*	± 19.4	
CDLQI	24	0	2.0 (0–21)	± 5.9	Score range, 0–30
					Higher scores reflect more impaired HRQoL
Disease-specific questionnaire	23	2	5.6 (0–43)	± 10.0	Score range, 0–52
					Higher scores reflect more impaired HRQoL
VAS line	22	93.5	86.0 (16–100)	± 23.3	Score range, 0–100
VAS smiley	22	87.5	84.1 (25–100)	± 19.8	Higher scores reflect better general health

HRQoL = Health-related quality of life; C1-INH-HAE = hereditary angioedema with C1-inhibitor deficiency; SD = standard deviation; PedsQL = Pediatric Health-Related Quality of Life 4.0 Generic Core Scales; CDLQI = Children's Dermatology Life Quality Index; VAS = visual analog scale.

*Data in brackets are published norms for healthy children (from Ref. 13).

was trained in self-administration (at age range, 10.4–16.4 years), and, in three children, treatment was administered by the parents (established when the children were 5.8–12.1 years old). In seven children, both sets of questionnaires were returned as desired with a 6-month interval. In four cases, the second set of questionnaires was not returned immediately, so the families were reminded by e-mail and telephone calls, and eventually the questionnaires were returned 12 months after the first assessment. In three other cases, both sets of questionnaires were lost, so new copies were sent in at the end of the study period with a 1-month interval. Ultimately, all the families completed both sets of questionnaires, *i.e.*, there were no dropouts. The median interval between the two assessments was 6 months (range, 1–12 months).

In the first assessment, the parents of all 14 children completed the PedsQL Parent Proxy-Report forms, and all 11 children ages ≥ 5 years completed the other instruments. In the second assessment, 13 children were old enough to complete all the instruments; however, there were three missing questionnaires (two VAS and one disease-specific). The intraclass correlations showed good levels of agreement between the first and second assessments in all the instruments (correlation coefficients 0.71–0.99; $p < 0.01$). Because

the aim was not to measure change over time, the results from the two assessments were pooled for the statistical analyses. This gave a total of 22 to 28 cases, depending on missing responses and questionnaires that did not include the youngest children. The results are outlined in Table 2. The Cronbach α for each instrument ranged from 0.81–0.95, which demonstrates a good internal consistency.^{13,21} Histograms with the distribution of scores are presented in Fig. 1 (VAS line and VAS smiley were merged into one mean score). The histograms display that the data were not normally distributed and, therefore, nonparametric tests were chosen for the statistical analyses.

There was significant correlation between age and monthly attack frequency (Spearman correlation coefficient $\rho = 0.37$; $p = .05$) but not between age and HRQoL (Table 3). However, the median number of attacks within the last month was zero, so the number of attacks was transformed to a binary variable of having had or not having had any attacks within the last month. Of the 28 pooled cases, 8 patients had one or more attacks within the last month, 20 patients had no attacks. Likewise, we did a median split on the severity score. The median severity score was 5.5 points (range, 0–10 points) in both assessments. We tested whether having one or more attacks within the

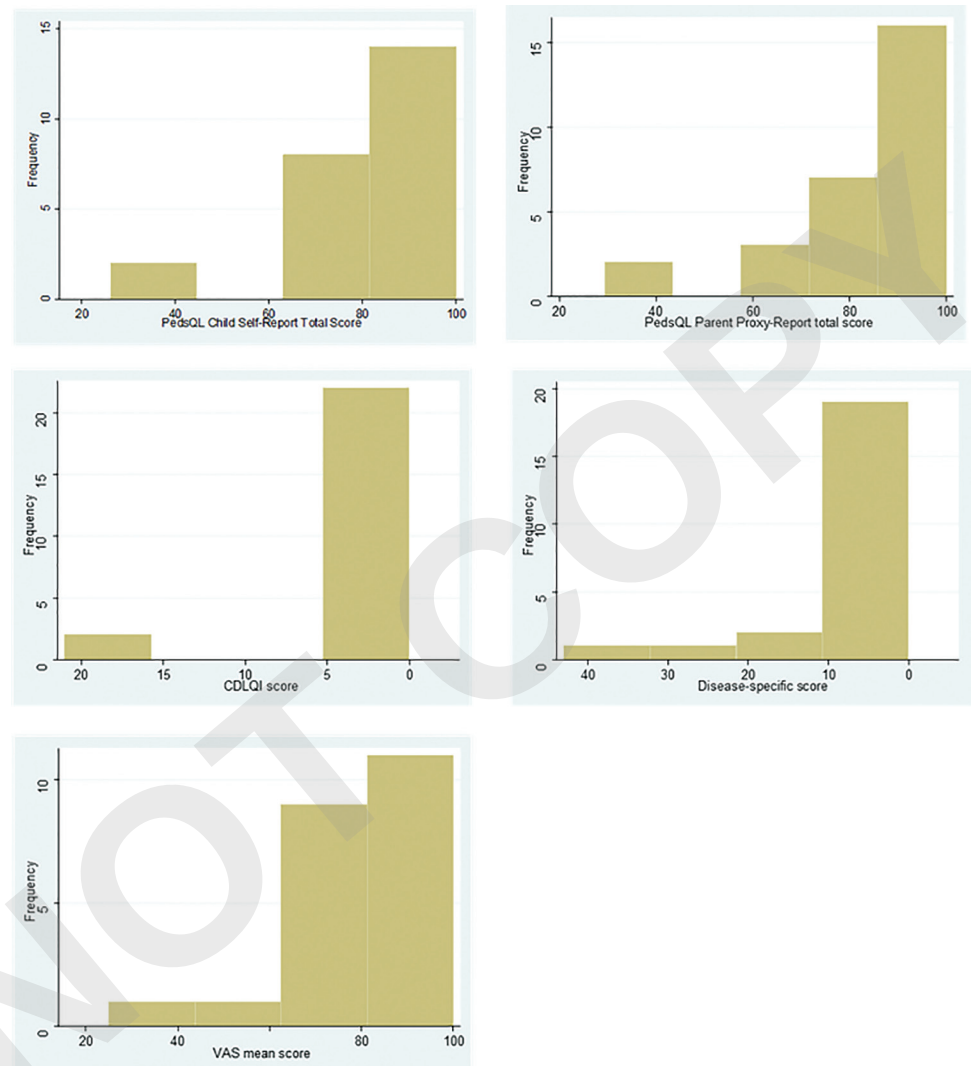


Figure 1. Distribution of HRQoL and general health scores in children with C1-INH-HAE. The CDLQI and disease-specific scores are decreasing from left to right, as lower scores reflect a better HRQoL in these instruments. PedsQL = Pediatric Health-Related Quality of Life 4.0 Generic Core Scales; CDLQI = Children's Dermatology Life Quality Index; VAS = visual analog scale.

last month was related to lower HRQoL (Wilcoxon rank sum test). For subjects without attacks, the median PedsQL Child Self-Report and Parent Proxy-Report scores were significantly higher than for subjects with recent attacks, and the scores were lower for the CDLQI and the disease-specific questionnaire (Table 3). We also investigated whether a higher severity score was related to a lower HRQoL but found no evidence of this.

Children's and parents' scores in PedsQL correlated highly (Spearman correlation coefficients for total score, physical health score, and psychosocial health score were 0.88, 0.87, and 0.88, respectively [$p < 0.01$]) but seemed to be independent of whether the parent completing the Parent Proxy-Report form was also a patient with C1-INH-HAE. Likewise, we did not find any difference in HRQoL across children with sporadic C1-INH-HAE compared with those with a family history of C1-INH-HAE (Table 3). We also investigated the effect of home therapy. We found no significant difference in PedsQL Child Self-Report or the disease-

specific questionnaire, but the Parent Proxy-Report scores were significantly lower among children treated at home compared with those who were not treated. The same trend was seen in CDLQI and VAS scores.

DISCUSSION

This was one of the first studies dedicated to HRQoL in children with C1-INH-HAE and the first, to our knowledge, to include all children from a national C1-INH-HAE cohort. Because no disease-specific questionnaire for children with C1-INH-HAE exists, we chose multiple instruments as well as child and parent reports. We did not include reference groups, but some information can be obtained by comparing our results with published norms and other studies when applying the same instruments. Overall, the mean scores in our study were in the upper end of the score ranges. A few children with frequent attacks drove most of the moderate reduction in HRQoL, whereas children with few symptoms had better scores.

Table 3 Relations between HRQoL and clinical variables

	PedsQL Child Self-Report Score	PedsQL Parent Proxy-Report Score	CDLQI Score	Disease-specific Score	VAS Score
Age					
ρ	0.07	-0.06	-0.02	0.14	-0.11
p	0.758	0.791	0.929	0.545	0.612
Attack(s) within the last month (yes/no)					
z	2.77*	2.96*	-2.51*	-2.28*	3.4*
p	0.006	0.003	0.012	0.023	<0.01
Severity (>/<5.5)					
z	0.94	1.27	-1.43	-1.09	1.51
p	0.348	0.205	0.154	0.276	0.132
PedsQL Parent Proxy-Report					
r	0.88*				
p	<0.01				
Parent status (patient/not patient)					
z	-1.20	-0.76	0.54	0.98	-0.96
p	0.229	0.447	0.589	0.329	0.338
Disease origin (sporadic/family history)					
z	-0.64	-0.64	1.58	0.04	-0.07
p	0.525	0.518	0.114	0.971	0.941
Home therapy (yes/no)					
z	1.56	1.78*	-1.76*	-0.63	1.90*
p	0.119	0.074	0.078	0.526	0.057

HRQoL = Health-related quality of life; PedsQL = Pediatric Health-Related Quality of Life 4.0 Generic Core Scales; CDLQI = Children's Dermatology Life Quality Index; VAS = visual analog scale; ρ = Spearman correlation coefficient; z = Wilcoxon rank sum test.

* $p < 0.1$.

Surprisingly, the PedsQL mean scores were similar to or even better than the published norms for healthy children.¹³ Our study population also scored higher than children with C1-INH-HAE in the only other study dedicated to HRQoL in childhood C1-INH-HAE.¹⁰ In that study, the PedsQL mean total scores were 81.81 and 79.93 among 19 Hungarian and 15 Israeli children, respectively. Also, children in our cohort scored considerably higher than children with other chronic health conditions, such as allergy, asthma, and diabetes.^{13,22} One reason may be that Danish patients diagnosed with C1-INH-HAE have free access to effective therapy, and home therapy with C1-INH concentrate is particularly focused.²³ Thus, treatment with danazol (which has several possible adverse effects) has been avoided in the Danish pediatric cohort. This could partly explain why children in our study had higher PedsQL scores than the Hungarian and Israeli children.

The child-parent agreement in PedsQL was high in our study and also in the Hungarian-Israeli study.¹⁰ The strong agreement could reflect that the children's reports may have inadvertently been skewed by paren-

tal influence. Conversely, it could simply be that parents and children agree on this disease and its influence on the child, which is supported by the findings by Engel-Yeger *et al.*¹⁰ However, in a study that comprised 144 boys with hemophilia in which the mean scores in PedsQL were comparable with our study, the child-parent agreement was only 0.36.²⁴ We investigated whether the parents' disease status influenced their scores in PedsQL but found no evidence of this. Likewise, there was no correlation between scores and whether the child had a family history or sporadic C1-INH-HAE (however, only three patients had sporadic C1-INH-HAE). Thus, it was not evident if the inheritance aspect could influence the perception of HRQoL, and, to our knowledge, this area has not been discussed further in the literature.

Children with C1-INH-HAE generally have fewer and less severe attacks than adults, and worsening around puberty is typically seen.^{25,26} Accordingly, most children in our cohort were either asymptomatic or had only a few attacks, and no children were on long-term prophylactic therapy with C1-INH concen-

trate in the studied year. We found a significant correlation between higher age and more frequent attacks. Likewise, we found a significant correlation between attacks within the last month and a lower HRQoL in accordance with the Hungarian-Israeli study.¹⁰ In addition, that study showed that patients with combined laryngeal, abdominal, and peripheral attacks had the lowest HRQoL scores.¹⁰ In our cohort, however, we found no correlation between severity score and HRQoL.

With regard to home therapy, we made the somewhat paradoxical observation that being treated at home was associated with lower HRQoL. However, home therapy is usually offered to patients with more frequent and/or debilitating attacks, which could explain the effect on HRQoL. Thus, home therapy was correlated to a higher severity score ($z = -3.86, p < 0.01$) and more frequent attacks ($z = -2.34, p = 0.019$), and the lower HRQoL was not a consequence of home therapy. Instead, results of several studies indicate that home therapy is associated with HRQoL benefits over time.^{5,7,27–29}

Generally, all our instruments agreed on the rating of HRQoL. We chose to include the CDLQI because the original version of this instrument was previously used to measure HRQoL in adult patients with C1-INH-HAE.⁵ The mean score in the CDLQI was 2.04, which was comparable with children with warts or alopecia, and corresponded to a “small effect” on the child’s life.^{14,30} In comparison, children with eczema or psoriasis often score considerably lower.^{14,31–33} Because the CDLQI questions specifically focused on “your skin problem,” the dermatologic aspects of C1-INH-HAE may have been overemphasized. We used the nonvalidated, disease-specific questionnaire to investigate if other aspects than the generic and dermatologic ones could be illuminated. The results supported the findings in the other instruments, but no essential knowledge was added, and, for more comprehensive studies, we await a children’s version of the HAE-specific HRQoL questionnaire.

In addition to the detailed questionnaires, we applied two VAS instruments to rate general health. VAS has a quick adaptability and may be particularly useful when the goal is to screen for low general health or HRQoL. In a recent Swedish study, a seven-step VAS smiley was used to investigate quality of life in children with C1-INH-HAE.¹¹ They reported a good overall quality of life with children with symptoms that scored a bit lower than children who were asymptomatic, which is in accordance with our findings. Thus, a simple VAS instrument could be a useful screening measure for general health or HRQoL in routine control of children with C1-INH-HAE.

Our cohort only comprised 14 children, and the same group of patients was measured twice. Thus,

data were not independent, and the small sample size might have influenced the statistical power. Notwithstanding, we confirmed a general pattern across several outcome measures. In addition, the number was sizeable for this ultra-rare condition, and the study comprised all eligible Danish children with C1-INH-HAE. To manage the considerable age range, we used age-specific forms when available. Likewise, we tried to handle the differing intervals between the two assessments by calculating severity scores and the number of attacks according to the date when the HRQoL questionnaires were completed.

CONCLUSION

The children with C1-INH-HAE who were assessed had, on average, a normal HRQoL and better than those with other common skin disorders. We found evidence, however, that HRQoL related strongly to recent attacks across various ways of eliciting HRQoL. Analysis of our data indicated a close link between children’s and parents’ answers, but there seemed to be no relationship between HRQoL and severity score, disease origin, or whether the parents completing the Parent Proxy-Report forms carried the disease themselves. A simple VAS instrument screening for general health or HRQoL may be useful in routine practice. Likewise, the PedsQL has now proved to be useful in two pediatric C1-INH-HAE HRQoL studies,¹⁰ and our studies agreed that most HRQoL impairment was found among children with more frequent attacks. This knowledge indicated that health care providers should be especially attentive to HRQoL when children with C1-INH-HAE become symptomatic.

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