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Health-Related Quality of Life among Children with Hereditary Angioedema

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Abstract

Background: The clinical expressions of hereditary angioedema with C1-inhibitor deficiency (C1-INH-HAE) and its related burden may negatively affect patient quality of life. This study aims to assess health-related quality of life (HRQoL) in children with C1-INH-HAE.

Methods: Children (N=98: 34 C1-INH-HAE patients, 64 healthy controls) aged 3–18 years were recruited in Israel and Hungary. All individuals completed a demographic questionnaire, a disease activity and site questionnaire, and the Pediatric Quality of Life Inventory (PedsQL™) 4.0 Generic Core Scales (child self-report and maternal proxy report) to assess HRQoL.

Results: Among C1-INH-HAE patients, 9 (26.5%) had 1–5 attacks/year; 6 (17.6%) had 6–18 attacks/year, 8 (23.5%) had 25–60 attacks/year, and 11 (32.4%) were asymptomatic over the previous year. Children with C1-INH-HAE attacks demonstrated lower HRQoL than healthy

control children across the total score, school, and psychosocial dimensions of the PedsQL™.

The number of C1-INH-HAE attacks negatively correlated with the total HRQoL score ($r=-.48$, $p=.008$), school related HRQoL ($r=-.39$, $p=.02$), and psychosocial HRQoL ($r=-.43$, $p=.01$). Patients with multi-site laryngeal, abdominal, and peripheral C1-INH-HAE attacks had a lower HRQoL compared with those who experienced solely peripheral attacks across the total score ($p=.04$), physical ($p=.04$), and school ($p=.02$) domains. There was no significant difference between asymptomatic C1-INH-HAE patients and healthy controls.

Conclusions: Children with symptomatic C1-INH-HAE demonstrate impaired HRQoL compared with healthy controls. HRQoL was affected by the frequency and site of C1-INH-HAE attacks and mostly in the school and physical domains.

Abstract

key words: C1-inhibitor; Children; Complement-1 esterase inhibitor defects; Hereditary angioedema; PedsQL™ 4.0; Quality of life; Symptom assessment.

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Introduction

Hereditary angioedema with C1-inhibitor deficiency (C1-INH-HAE) is a rare autosomal dominant disease estimated to affect 1 individual per 50,000, with a reported prevalence of 1:10,000 to 1:150,000 (1,2). C1-INH-HAE is associated with either a quantitative (Type 1) or qualitative (Type 2) deficiency of C1-esterase inhibitor. Patients with C1-INH-HAE experience recurrent, unpredictable attacks of edema primarily affecting the skin, intestinal tract, and upper airways. These sudden attacks and the cutaneous and/or mucosal swellings may be painful, disfiguring, or even life-threatening in the case of laryngeal involvement. The angioedema results from excessive production of bradykinin, a potent vasodilator mediator. Attacks typically develop and resolve slowly, lasting 2–5 days. Clinical expression is variable with rare individuals carrying causative mutations but remaining asymptomatic, and other patients experiencing frequent attacks with a wide range of disabling symptoms, severe pain, or disfigurement (3,4).

The onset of C1-INH-HAE symptoms is variable. Reports note that C1-INH-HAE manifests in the first or second decade of life, mainly during the age range of 4–11 years (5,6). Although fatal attacks are rare in childhood, life-threatening attacks have been reported even in young children (7,8). Moreover, early onset of symptoms and frequent attacks in childhood predict more severe disease in adulthood (5).

The clinical expressions of C1-INH-HAE and its related burden may negatively affect the patients' quality of life (QoL). Evidence of the effect of C1-INH-HAE or its treatment on health-related QoL (HRQoL) in adults has been investigated using generic instruments (9–12). These studies indicate that adult patients with C1-INH-HAE have diminished QoL in the physical and psychological domains (13). Recently, Prior et al., (3,14) who developed a disease-specific QoL questionnaire for adult patients with C1-INH-HAE, reported the negative impacts of the disease on the person's physical, social, and emotional HRQoL. Until

now, only one study (15) has partially addressed the question of QoL in children with the condition. That study, which involved all 36 Swedish children aged 1–17 years with C1-INH-HAE, undertook a parental assessment of the child's QoL in the preceding week using a single-item seven-step visual analogue scale (VAS) for facial expressions.

Since disease symptoms in childhood may continue into adulthood and impact the growing child (16), it is important to refer to various aspects of the HRQoL of children with C1-INH-HAE. This information may optimize intervention outcomes, and the development and wellbeing of children with C1-INH-HAE. Hence, profiling HRQoL should adopt a broad perspective that includes physical health, psychological state, independence, social relationships, and the child's perception of environmental influences on his/her HRQoL (17). Based on the above, the aims of this study were to: (1) Compare the HRQoL of children with C1-INH-HAE and healthy controls using the PedsQLTM 4.0 questionnaire based on child self-reports regarding the previous month; (2) Examine the relationship between HRQoL, as reported by the children, and disease activity as expressed by the number of attacks and the type of attacks in the previous 12 months; and (3) To compare HRQoL reports between C1-INH-HAE patients and their mothers as reported in the PedsQLTM 4.0 questionnaire parent proxy-report forms.

Methods

Subjects

This cross-sectional study included 98 children aged 3–18 years who were recruited in Hungary (n=44) and Israel (n=54). In each country, the participants were divided into two groups: healthy controls and children with C1-INH-HAE (the study group). Among the children from Hungary, the study group included 19 children aged 3–17 years and the control group included 25 children aged 5–17 years. Among the children from Israel, the study group

included 15 children aged 5.5–18 years and the control group included 39 children aged 5–17.5 years.

In Hungary and Israel, danazol and tranexamic acid are available for prophylaxis in children. For acute attacks, plasma-derived C1-inhibitor (Berinert®) is licensed for children in both countries.

Exclusion criteria included the presence of a mental health disorder, intellectual disability, or any chronic medical condition requiring specialist treatment.

Evaluation of Quality of Life and Disease Activity

The Pediatric Quality of Life Inventory (PedsQL) was developed by Varni JW, et al (18). This questionnaire assesses the HRQoL of children and adolescents irrespective of their health status (19). The PedsQL is developmentally appropriate and has versions for different respondents (child and parent proxy) for children in different age groups (ages 2–18 years; child self-report ages 5–7 years, 8–12 years, 13–18 years; parent proxy report ages 2–4 years, 5–7 years, 8–12 years, 13–18 years). Both the child and parent proxy reports were found to have high internal consistency and construct validity in a study conducted among 2,500 pediatric patients and over 9,500 healthy children aged 5–16 years in California (20). Several previous studies have used and validated the PedsQL questionnaire in Hungary and Israel (21-23).

The PedsQL encompasses four dimensions: (1) physical functioning (eight items), (2) emotional functioning (five items), (3) social functioning (five items), and (4) school functioning (five items). A higher order dimension, the psychosocial health dimension, encompasses emotional and social functioning (20,24). The respondent marks the frequency of problems that occurred with the child/adolescent in the past one month on a five-point response Likert scale (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem), which was used for all items.

All the items were then reverse scored and transformed into a 0–100-point scale (0 = 100; 1 = 75; 2 = 50; 3 = 25; 4 = 0). A higher total score indicates a better HRQoL.

C1-INH-HAE disease activity was expressed by the number of attacks in the last year prior to recruitment to the study and completing the PedsQL questionnaire and by the sites of angioedema attacks. Group A consisted of patients who had laryngeal, abdominal and peripheral attacks; Group B included patients who had abdominal and peripheral attacks; Group C comprised patients who had only peripheral angioedema attacks, and Group D consisted of individuals who were asymptomatic.

Study Design and Ethical Considerations

This study was performed in three clinical centers: 1. Semmelweis University, Budapest, Hungary 2. Sourasky Medical Center (Ichilov), Tel Aviv, Israel 3. Bnai Zion Medical Center, Haifa, Israel. After receiving approvals from each participating institution's Helsinki Ethic Committee, an advertisement was published in each clinic calling children and mothers to participate in a study about HRQoL among children with C1-INH-HAE. Mothers who wished to participate in the study with their children signed a consent form. Then, they completed the demographic and disease activity questionnaires and the PedsQL parental version while their children completed the child's version of the PedsQL.

Data Analysis

After performing descriptive analyses, Chi square analysis examined whether differences exist between the groups' socio-demographic parameters. MANCOVA examined the significance of the differences between the study and control groups with respect to their HRQoL scores based on child report and maternal reports with mother's years of education held as a covariate. Student's paired t-testing compared the total scores of the dependent measures between the groups. MANOVA with Scheffe post hoc examined the significance of the differences between the study subgroups.

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Due to an abnormal distribution of disease activity, Spearman correlation was used to examine the correlation between disease activity and HRQoL based on child/maternal reports in the study group. The level of significance was set at .05 for all statistical tests.

Results

Population and demographics

The C1-INH-HAE study group included 34 children aged 12.3 ± 4.0 years (age range 3–18 years), 19 females (55.8%), all had C1-INH-HAE type I. No significant differences were found in the socio-demographic information between groups in the Hungarian samples, except for mother's education level, which was significantly higher in the control group than in the study group ($\chi^2=24.07$, $p<.001$). Similar results were found in the Israeli sample ($\chi^2=10.42$, $p=.006$). When comparing Israel and Hungary, a higher percentage of mothers among the Hungarian controls had academic education as compared with the mothers in the Israeli control group, ($\chi^2=23.23$, $p<.0001$). Table 1 summarizes the participants' socio-demographic information. Since no significant differences were found between the study/control groups in most socio-demographic measures (Table 1), all children with C1-INH-HAE and normal controls were combined into one study group and one control group, respectively.

Health-related quality of life: PedsQL 4.0

Comparing HRQoL between children with C1-INH-HAE and healthy controls:

Based on children's reports, no significant differences were found between the patients and the healthy controls in any of the HRQoL measures in the Hungarian samples. In contrast, in the Israeli sample, the control group reported significantly higher physical ($F_{52,1}=4.78$; $p<.001$), school-related ($F_{52,1}=11.02$; $p<.001$), and total HRQoL ($t_{52}=2.69$; $p<.01$) than the C1-INH-HAE group. When comparing the countries, the Israeli control group reported significantly higher HRQoL than the Hungarian control group in physical, social, emotional,

and total HRQoL. Table 2 depicts the PedsQL scores based on child self-reports in both groups. Since no significant differences in HRQoL were found between children's reports in both study groups, the following analysis referred to all study children with C1-INH-HAE as one group.

The relationship between children self-reported HRQoL and disease activity:

C1-INH-HAE is mainly characterized by unpredictable episodic attacks. Thus, we sought to examine the relationship between HRQoL, as reported by the children, and disease activity as expressed by the number of attacks in the last year.

Descriptive statistics revealed that 11 out of 34 patients (32.4%) with C1-INH-HAE did not have any attacks in the last year. Nine C1-INH-HAE patients (9/34, 26.5%) had 1–5 attacks/year; 6 patients (6/34, 17.6%) had 6–18 attacks/year, and 8 patients (8/34, 23.5%) had 25–60 attacks in the last year. Girls had a greater number of C1-INH-HAE attacks than boys (17.7 ± 19.8 vs. 7.0 ± 14.7 , $p=.05$). Of the 23 children who suffered attacks in the last year, 5 patients had laryngeal, abdominal, and peripheral attacks (Group A), 12 patients had abdominal and peripheral attacks (Group B), and 6 patients had only peripheral angioedema attacks (Group C). The 11 remaining individuals were asymptomatic (Group D). Four patients received prophylactic treatment: 2 in group A (1-Plasma-derived C1-INH, 1-Hexacapon) and 2 in group B (1-Plasma-derived C1-INH, 1-Danazol). Greater disease activity was significantly correlated with lower total HRQoL score ($r=-.488$, $p=.008$), with lower school related HRQoL ($r=-.39$, $p=.02$), and with lower psychosocial HRQoL ($r=-.43$, $p=.01$) on the basis of the child HRQoL reports.

Importantly, when comparing HRQoL between three groups: healthy controls, children who had no C1-INH-HAE attacks during the last year, and children who had attacks, Scheffe post hoc analysis revealed that patients with attacks had significantly lower emotional HRQoL ($p=.03$) and lower school HRQoL ($p=.001$) than those with no attacks and the

healthy controls ($p < .0001$) and lower psychosocial HRQoL than those with no attacks ($p = .02$) and healthy controls ($p = .01$). Total HRQoL was significantly lower among children with attacks as compared with those with no attacks ($p = .006$) and healthy controls ($p = .03$) (Table 3).

No gender effect was found. Age significantly correlated with better social HRQoL only in the control group ($r = .41$; $p = .01$).

The relationship between child-reported HRQoL and disease activity level:

Table 4 shows the HRQoL scores of healthy controls, patients who experienced < 5 C1-INH-HAE attacks per year, and patients who had ≥ 5 attacks per year. Patients who had ≥ 5 attacks/year had a significantly lower total HRQoL score than patients who had < 5 attacks/year ($p = .05$) and healthy controls ($p = .04$), while the healthy controls and patients who had < 5 attacks/year had similar total HRQoL scores. A similar trend was found when comparing physical HRQoL between patients who had ≥ 5 attacks per year and those who had < 5 C1-INH-HAE attacks/year ($p = .04$).

Psychosocial and school-related HRQoL scores were also significantly lower among patients who had ≥ 5 attacks per year compared with controls ($p = .05$; $p = .002$ respectively). A trend toward significance was found when comparing patients who had ≥ 5 attacks per year with those who had < 5 C1-INH-HAE attacks/year ($p = .08$; $p = .07$, respectively).

Comparing HRQoL between four groups of patients according to the site(s) of the angioedema attacks

HRQoL was then compared between four groups of patients according to the site(s) of the angioedema attacks. Scheffe post hoc analysis revealed that group A had a significantly lower physical HRQoL than Group D ($p = .01$) and Group C ($p = .04$). No significant difference was found between the four groups for emotional and social HRQoL. However, group A had a significantly lower school-related HRQoL than group D ($p = .001$) and group C ($p = .02$).

Group B had a significantly lower HRQoL than group D ($p=.02$). Scheffe post hoc analysis revealed that group D had a significantly higher psychosocial HRQoL than group A ($p=.006$) and group B ($p=.02$). Group D had a significantly higher total HRQoL than group A ($p=.002$) and group B ($p=.04$). Group C had a significantly higher total HRQoL than group A ($p=.04$) (see Table 5).

Results from maternal proxy reports

Concurrent validity was found between the child and maternal versions of the Peds-QL in the following HRQoL scales: emotional domain ($r=.63$; $p<.0001$), school domain ($r=.57$; $p\leq.01$), psychosocial domain ($r=.63$; $p<.0001$), and in the total HRQoL score ($r=.61$; $p<.0001$). We referred only to mothers, based on previous studies showing that mothers' characteristics correlated with their children's quality of life (25,26). As presented in Table 6, several significant correlations were found between children's and maternal reports among the combined Hungarian and Israeli study groups. No significant difference was found for maternal reports regarding their children's HRQoL between the Israeli and the Hungarian study groups, nor between children with no attacks and those with attacks. No significant correlations were found between mothers' reports and their child's disease activity.

Discussion

The purposes of this study were to assess HRQoL in children with C1-INH-HAE, compare it with the HRQoL of healthy controls, and examine its relation to the number and site of angioedema attacks. To the best of our knowledge, this is the first study to evaluate the HRQoL of children with C1-INH-HAE using a validated generic questionnaire (the PedsQLTM 4.0), which is based on child self-report and on parent proxy reports. HRQoL measurement has emerged as an important health outcome in clinical trials, clinical practice improvement strategies, healthcare service research, and evaluation. The ability of pediatric HRQoL measurements to identify children with special needs and to demonstrate the cost

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advantages of providing timely, targeted interventions to address those needs may ultimately provide the momentum required to incorporate HRQoL measurement routinely into pediatric clinical settings (19). The PedsQL is a multidimensional questionnaire that refers to the physical, emotional, social, and school dimensions of a child's life.

The main outcome of the present study was the significant association found between the frequency of C1-INH-HAE attacks and HRQoL. The lack of a significant difference in HRQoL between C1-INH-HAE patients as compared with the healthy controls in the Hungarian sample could be explained by the high percentage of individuals with a low number of attacks in Hungary. Eight out of 19 (42.1%) patients in this group did not suffer from C1-INH-HAE attacks during the last year. The Israeli patients recruited to this study had a higher average number of C1-INH-HAE attacks/year as compared with their Hungarian counterparts. The combined patient group had a lower HRQoL score in comparison with the healthy control group. Additionally, a negative correlation was found between the number of C1-INH-HAE attacks and HRQoL.

The second finding was the relationship between the type of the attack and HRQoL scores. Patients who experienced combined laryngeal, abdominal, and peripheral attacks had the lowest HRQoL scores. Laryngeal angioedema attacks have the potential for airway obstruction, with potentially lethal consequences. Therefore, these attacks constitute a medical emergency, requiring immediate treatment and hospitalization. Recurrent abdominal attacks involve symptoms of tenderness, crampy pain, and nausea or vomiting, whereas peripheral attacks target the limbs. Attacks can be severe and acute in onset, or may be recurrent, chronic, and of moderate severity. These attacks often cause patients to seek medical attention (27,28). The most-affected HRQoL domains for patients experiencing multi-site attacks were the school, physical, and psychosocial domains, probably because such attacks led to missing days in school and abstention from physical activity, which can

trigger an attack. Additionally, C1-INH-HAE patients in Group A reported a significantly greater number of attacks compared with patients in Group C (34.8 ± 16.7 vs. 3.6 ± 3.9 , $p = .003$).

C1-INH-HAE attacks are highly variable and unpredictable. Patients can be asymptomatic for long periods or experience frequent attacks that can influence HRQoL. Frequency can range from 1 attack/year to more than 26 attacks/year on average, with rare patients reporting more than 100 C1-INH-HAE attacks per year (4, 29). In our study, the average number of attacks experienced by C1-INH-HAE symptomatic patients was 19.2/year, ranging from 1–60 attacks/year. Recurrent C1-INH-HAE attacks, which can last a few days, can lead to high absenteeism, poor school performance, and impaired social life. In a Swedish study including adults and children, 33 of 74 participants (44.6%) had been absent from work or school during the latest attack and, of those with a severe attack, 81% had been absent. The authors of that study concluded that increased C1-INH-HAE attack frequency had a negative effect on QoL (30). The fear of an upcoming attack can cause emotional distress and anxiety, which also negatively impact educational and vocational achievement, and social life. A patient who fears a sudden C1-INH-HAE attack may avoid physical exertion, express psychological stress, and withdraw from social activities. Such avoidance is often associated with depressive loss of self-esteem. Although full physical recovery may occur between C1-INH-HAE attacks, the emotional and HRQoL impairment may continue even between attacks (9,30,31) as has been described for other episodic disorders, such as migraine (32). Recently, a comprehensive review article (31,33) described the wide-ranging burden of hereditary angioedema on the HRQoL of adults. The authors emphasized the psychosocial factors that appear between attacks and included stress driven by uncertainty, anxiety about passing the disease on to their children, an inability to plan things or travel, and their limited participation in exercise and sport. Some of these factors are also relevant for children (33).

The significant correlations between the child and maternal proxy reports regarding the child's HRQoL suggests that mothers and children similarly perceive most of the effects of C1-INH-HAE attacks on the child's HRQoL. This supports the concurrent validity of the PEDS-QL and the ability of health providers to trust mothers' report in the intervention process. Mothers' sensitivity in regard to their children's HRQoL and the children's ability to report the way they perceive their HRQoL highlight the importance of referring to both voices in the intervention process. This may also elevate child and parental involvement and commitment to the process and in this way enhance child HRQoL and well-being.

The relatively small sample size, gathered from two different countries; the wide age range of the participants, and the use of the generic version of the PedsQL, which has not been validated for use in C1-INH-HAE, may all limit the generalizability of the main findings. The generic questionnaire may also be less sensitive than a C1-INH-HAE-specific questionnaire to changes experienced by patients in the course of disease.

We conclude that HRQoL in C1-INH-HAE pediatric patients is mainly related to the number and type of C1-INH-HAE attacks. C1-INH-HAE patients who experience multi-site laryngeal, abdominal, and peripheral attacks tend to have lower HRQoL than those whose attacks occur less frequently and in fewer locations. The management of C1-INH-HAE encompasses a number of actions that go beyond acute treatment of edematous attacks of C1-INH-HAE. These include psychological and social interventions to help affected individuals to live a normal life and minimize the effects of the disease and its treatment on the various aspects of daily living and well-being. Reducing the number and rate of C1-INH-HAE attacks may improve HRQoL. Additionally, a HRQoL measures scoring system may be useful to evaluate the efficacy of therapy in pediatric C1-INH-HAE.

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Table 1 Comparing HRQoL between Hungarian and Israeli groups based on reports of patients with C1-INH-HAE

	Hungary		Israel		
	Study group	Controls	Study group	Controls	
	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)	Comparing Israeli and Hungaian Controls p
Physical HRQoL	86.18 (16.57)	81.51 (16.48)	82.08 (15.74)	89.34* (8.51)	.015
Emotional HRQoL	76.57 (20.34)	70.61 (21.17)	82.01 (14.97)	81.28 (12.65)	.014
Social HRQoL	87.89 (14.27)	85.81 (15.79)	88.01 (11.46)	92.91 (8.13)	.021
School related HRQoL	76.57 (19.29)	83.01 (14.64)	67.67 (19.26)	82.05** (11.91)	NS
Psychosocial HRQoL	80.35 (15.08)	79.81 (14.87)	79.22 (12.06)	85.41 (6.35)	NS
Total HRQoL	81.81 (13.83)	80.22 (14.82)	79.93 (11.98)	86.39** (5.71)	.022

NS = not significant

Table 2 Comparing HRQoL between the healthy controls, patients with C1-INH-HAE from the combined study group with no attacks and those with attacks

C1-INH-HAE patients							
	No attacks		Attacks		Healthy controls		
	Mean	sd	Mean	sd	Mean	sd	p
Physical HRQOL	90.34	11.13	82.11	17.68	86.27	12.72	NS
Emotional HRQOL	90.01	15.01	72.95	17.36	77.11	17.17	.03
Social HRQOL	92.72	10.09	85.01	13.62	90.13	12.12	NS
School related HRQOL	86.81	10.55	66.36	19.58	82.42	12.94	.0001
Psychosocial HRQOL	89.84	7.91	74.77	13.54	83.22	10.78	.001
Total HRQOL	89.97	7.49	76.61	13.11	83.98	10.61	.003

NS = not significant

sd = standard deviation

#p values of between-subjects effects

Table 3 Comparing HRQoL between the healthy controls, patients with C1-INH-HAE who had less than 5 HAE attacks and who had ≥ 5 attacks per year

C1-INH-HAE patients							
	0-4 attacks		≥ 5 attacks		Healthy controls		
	Mean	sd	Mean	sd	Mean	sd	p
Physical HRQoL	90.62	12.01	78.71	17.94	86.27	12.72	.04
Emotional HRQoL	83.82	18.41	73.12	17.01	77.11	17.17	NS
Social HRQoL	89.71	14.41	85.31	11.17	90.13	12.12	NS
School related HRQoL	79.11	16.97	66.87	20.64	82.42	12.94	.002
Psychosocial HRQoL	84.21	13.16	75.11	13.38	83.22	10.78	.04
Total HRQoL	85.81	10.82	76.01	13.69	83.98	10.61	.02

NS = not significant

sd = standard deviation

#p values of between-subjects effects

Table 4 Comparing HRQoL between the combined study groups with the different types of HAE attacks

	Group A (n=4)		Group B (n=12)		Group C (n=7)		Group D (n=11)		Healthy controls (n=64)		
	Mean	sd	Mean	sd	Mean	sd	Mean	sd	Mean	sd	F _{3,30}
Physical HRQoL	61.71	12.59	83.85	16.41	88.83	14.64	90.34	11.13	86.27	12.72	4.336*
Emotional HRQoL	70.01	13.54	72.51	19.48	77.85	16.79	90.01	15.01	77.11	17.17	2.505
Social HRQoL	77.51	15.54	85.41	14.53	90.71	10.17	92.72	10.09	90.13	12.12	1.746
School HRQoL	46.25	11.08	65.41	18.76	77.85	15.23	86.81	10.55	82.42	12.94	8.615***
Psychosocial HRQoL	64.58	11.57	74.44	13.31	82.14	11.21	89.84	7.91	83.22	10.78	6.491**
Total HRQoL	63.86	10.19	76.79	12.24	83.81	10.31	89.97	7.49	83.98	10.61	7.361***

Group A: laryngeal, abdominal and peripheral attacks. Group B: abdominal and peripheral attacks. Group C: peripheral attacks.

Group D: asymptomatic

* p≤.05; ** p≤.01; *** p≤.001

Table 5 Comparing HRQoL between the combined study groups with the different types of HAE attacks

	Group A (n=4)		Group B (n=12)		Group C (n=7)		Group D (n=11)		Healthy controls (n=64)		
	Mean	sd	Mean	sd	Mean	sd	Mean	sd	Mean	sd	F _{3,30}
Physical HRQoL	61.71	12.59	83.85	16.41	88.83	14.64	90.34	11.13	86.27	12.72	4.336*
Emotional HRQoL	70.01	13.54	72.51	19.48	77.85	16.79	90.01	15.01	77.11	17.17	2.505
Social HRQoL	77.51	15.54	85.41	14.53	90.71	10.17	92.72	10.09	90.13	12.12	1.746
School HRQoL	46.25	11.08	65.41	18.76	77.85	15.23	86.81	10.55	82.42	12.94	8.615***
Psychosocial HRQoL	64.58	11.57	74.44	13.31	82.14	11.21	89.84	7.91	83.22	10.78	6.491**
Total HRQoL	63.86	10.19	76.79	12.24	83.81	10.31	89.97	7.49	83.98	10.61	7.361***

Group A: laryngeal, abdominal and peripheral attacks. Group B: abdominal and peripheral attacks. Group C: peripheral attacks.

Group D: asymptomatic

* p≤.05; ** p≤.01; *** p≤.001

Table 6 The correlations between patients with C1-INH-HAE and mother's reports regarding child's HRQoL

	Physical HRQoL- child	Emotional HRQoL- child	Social HRQoL- child	School related HRQoL- child	Psychosocial HRQoL- child	Total HRQoL- child
Physical HRQoL- mother	NS	NS	.41 [*]	.58 ^{***}	.52 ^{**}	.53 ^{***}
Emotional HRQoL-mother	NS	.63 ^{***}	NS	.62 ^{***}	.62 ^{***}	.58 ^{***}
Social HRQoL-mother	NS	NS	NS	NS	NS	NS
School related HRQoL-mother	NS	.69 ^{***}	NS	.57 ^{***}	.NS	.56 ^{***}
Psychosocial HRQoL-mother	NS	.66 ^{***}	NS	.62 ^{***}	.63 ^{***}	.58 ^{***}
Total HRQoL- mother	NS	.61 ^{***}	NS	.63 ^{***}	.64 ^{***}	.61 ^{***}

* p≤.05; ** p≤.01; *** p≤.001