

Health-related quality of life in children with hereditary angioedema compared with patients with histaminergic angioedema

Melike Ocak, M.D.,¹ Ercan Nain, M.D.,² Aysegul Akarsu, M.D.,¹ Umit Murat Sahiner, M.D.,¹ Bulent Enis Sekerel, M.D.,¹ and Ozge Soyer, M.D.¹

ABSTRACT

Background: Hereditary angioedema (HAE) is a potentially life-threatening disease that remarkably impacts patients' health-related quality of life (HRQoL). This study evaluated the HRQoL in children with HAE and compared it with healthy controls and patients with histaminergic angioedema (HA).

Methods: Fifty-nine children with HAE (median [interquartile range {IQR}], ages, 8.9 years [5.4–12.6 years]), 60 children with HA (median [IQR] ages, 10.3 years [8–15.4 years]), and 72 healthy controls (median [IQR] ages, 10.3 years [6.6–13.9 years]) were recruited. All the children and their families completed the age-adapted KINDL generic instrument for assessing health-related quality of life in children and adolescents.

Results: The total HRQoL score and other subscales scores of both the patients with HAE and patients with HA, and the parent-proxy reports were significantly lower than those of the healthy children ($p < 0.05$). In the patients with HAE, the age at symptom onset was positively correlated with physical well-being ($r = 0.335$; $p = 0.043$) and negatively correlated with self-esteem ($r = -0.324$; $p = 0.049$). In addition, the physical well-being scores were affected by the site of attacks, which was significantly lower in the patients with abdominal pain attacks ($p = 0.045$). The family scores and total scores were statistically significantly higher in the HA group than the HAE group ($p < 0.001$ and $p = 0.009$, respectively). A significant correlation was found between self-report and parent-proxy HRQoLs in total and all subscales scores in the patients with HAE. For HA, there were no significant correlations for family scores.

Conclusion: HAE caused significant impairment of the HRQoL of children and their families, and affected their lifestyle and quality of life. In pediatric patients with HAE, the HRQoL is mainly related to age at symptom onset and the site of attacks. Although patients with HAE are affected more negatively than the patients with HA, HA affected the quality of life as well.

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Recurrent angioedema (RA) is characterized by intermittent, sudden, and unexpected swellings of the submucosal or subcutaneous tissues.¹ With or without wheals, RA is commonly recognized as histaminergic angioedema (HA) in clinical practice.² However, hereditary angioedema (HAE) should also be considered in patients with RA, although its prevalence is estimated as 1:50,000.³ It is often difficult to distinguish angioedema of HAE and HA based on the clinical manifestations.⁴ Angioedema is usually self-limited but can be painful, depending on the size, duration, and location, and can even be life-threatening in the case of upper airway swelling. In addition, the occurrence of angioedema significantly affects daily activities, free time, and social relationships, and causes

high levels of absenteeism, missing school, and/or workdays.^{1,5}

Health-related quality of life (HRQoL) is a conceptually evolving term, which is the individual perception of the impact of a disease, disability, or symptom across physical, psychological, social, and well-being issues. The HRQoL assessment is considered a comprehensive evaluation of patient health status, disease burden, and response to treatment. It also enables identifying physical, mental, and social health issues that are not noticed in a conventional clinical assessment.^{6,7} The most commonly used tools to measure HRQoL are questionnaires that contain various parameters (physical, social, emotional, cognitive, working, symptoms, treatment of secondary effects).⁸

RA has a negative impact on patients' HRQoL, because patients have unpredictable attacks and cannot make plans for traveling, have certain hobbies, or engage in social opportunities.⁹ Higher levels of depression and anxiety were reported in patients with HA and patients with HAE compared with the general population.^{10,11} Although some studies have shown that RA with HA or HAE negatively affects HRQoL, it is unknown whether

From the ¹Department of Pediatric Allergy, Hacettepe University Faculty of Medicine, Ankara, Turkey; and ²Department of Pediatric Allergy, Sanliurfa Training and Research Hospital, Sanliurfa, Turkey

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Address correspondence to Ozge Soyer, M.D., Department of Pediatric Allergy, Hacettepe University Faculty of Medicine, 06100 Ankara, Turkey

E-mail address: ozgeusoyer@gmail.com

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HA or HAE has more impact on HRQoL scores.^{12–15} Thus, this study aimed to clarify the differences of HRQoL between HAE and HA in children and to compare with age-matched healthy controls.

METHODS

Study Population

This prospective study was conducted at the Pediatric Allergy Department, Hacettepe University Ihsan Doğramacı Children's Hospital, and Sanliurfa Training and Research Hospital, between January 2017 and February 2020. Fifty-nine children with HAE, 60 children with recurrent HA, and 72 age- and gender-matched healthy controls were enrolled in the study. The patients with HAE were diagnosed with clinical and laboratory findings according to the international WAO/EAACI guideline³ for HAE. HAE types I and II are caused by autosomal dominant mutations in the C1 inhibitor (C1-INH) encoding gene, which leads to deficiency (HAE type I) or functional inactivity (HAE type II) of C1-INH protein. HAE type III is associated with the normal C1-INH level and activity caused by factor XII, plasminogen, angiopoietin, kininogen 1 gene mutations, and cases with unknown causes.³ The patients who responded to treatment with antihistamines and/or corticosteroids within 12 hours were considered as patients with HA.¹⁶

Only patients with idiopathic HA who had two or more attacks were included in the study, whereas allergen exposures (*e.g.*, food, medications) were excluded. Patients without any atopic symptoms (queried by using the International Study of Asthma and Allergies in Childhood questionnaire¹⁷), angioedema attacks, and chronic diseases were defined as healthy controls. The files of the patients with HAE and those with HA were reviewed by using a template that included the gender, age at diagnosis, age at symptom onset, the average number of attacks within the past year, lifetime angioedema frequency, duration of symptoms, physical locations of all angioedema attacks, and family history. For healthy controls, only age and gender were recorded. The study was approved by the local ethics committee of the Hacettepe University Faculty of Medicine.

Questionnaire

Patients and their families were given instructions by the researchers on how to complete the age-adapted KINDL questionnaire and then they marked the items themselves. During the study period, the questionnaire was carried out only one time in patients' clinic visits. KINDL is the generic scale that has been developed globally and validated for use with Turkish children and adolescents.¹⁸ Three versions of the questionnaire are available as self-report measures for different age groups: Kiddy (ages 4–6 years), Kid (ages 7–13 years),

and Kiddo (ages 14–17 years). Also, there are two different forms of the questionnaire in the parents' proxy-reports: the Parents' Questionnaire Kiddy (ages 3–6 years) and the Parents' Questionnaire Kid and Kiddo (ages 7–17 years).

The Kiddy-KINDL report contains 12 items in six subscales, whereas the Kid-KINDL and the Kiddo-KINDL have 24 items in six subscales. These six subscales include physical well-being, emotional well-being, self-esteem, family, friends, and school. Similarly, the parents' questionnaire includes the same subclasses as the children, but the Kiddy group parent's questionnaire has an additional subclass that contains additional questions. Each item of each subscale has a score that ranges from 1 to 5 on a Likert scale (1, never; 2, seldom; 3, sometimes; 4, often; and 5, all the time). With regard to the negative questions, scores were reversed (0, all the time; 5, never). Six subscale scores and one total score (24 items) are computed and transformed into a 0–100 scale, which means that higher scores indicate better HRQoL. However, the Kiddy-KINDL version, which consists of 12 questions, is evaluated only with a total score.¹⁸

Statistical Analysis

Statistical analysis was performed by using version 22.0 of the SPSS program (SPSS, Chicago, IL). A descriptive analysis was used for the characterization of patients. The Pearson χ^2 test or the Fisher exact test was used for comparison between the rates in different groups. Values for continuous variables were given as either mean $\pm$ standard deviation (SD) or as median (interquartile range [IQR]), based on the normality of distribution. Any differences in the parameters between the groups were tested for significance by one-way analysis of variance (ANOVA) test. In addition, after one-way analysis of variance, *post hoc* analyses for multiple comparisons were carried out by using the Tukey honest significant differences test. The correlation of two data was performed with the Spearman ρ coefficient. A value of $p < 0.05$ was considered significant.

RESULTS

Population and Demographics

The study group consisted of 59 children with HAE (median [IQR] age, 8.9 years [5.4–12.6 years]; 37.3% boys), 60 children with HA (median [IQR] age, 10.3 years [8–15.4 years]; 46.7% boys), and 72 healthy controls (median [IQR] age, 10.3 years [6.6–13.9 years]; 37.5% boys). A total of 50 patients (84.7%) had HAE type I, 4 patients (6.8%) had HAE type II, and 5 patients (8.5%) had HAE type III. There was no difference among the groups in terms of gender and distribution of age ($p > 0.05$). The median (IQR) age of symptom onset was 6.1 years (3.1–10 years) in the HAE group and 7.8 years (4.6–11.9 years) in the HA group ($p > 0.05$). However, the median (IQR)

age of diagnosis for the patients with HAE was 5.5 years (2.3–8.7 years) and significantly lower in the HAE group ($p < 0.001$) due to screening of children of families with HAE (Table 1).

Questionnaire Results

The mean $\pm$ SD total HRQoL scores for the children in the HAE and HA groups were 76.1 ± 13.2 and 81.4 ± 10.5 , respectively, and for the children in the control group were 93.1 ± 4.5 ($p < 0.001$). The total HRQoL score and other subscales scores of the healthy children were significantly higher than both the HAE and HA groups ($p < 0.05$). The total HRQoL score for the patients with HAE was not affected by age, age at symptom onset, age at diagnosis, and HAE attack frequencies and site ($p > 0.05$). However, when evaluated according to its subscales scores, age at symptom onset was positively correlated with physical well-being ($r = 0.335$; $p = 0.043$) and

was negatively correlated with self-esteem ($r = -0.324$; $p = 0.049$). Physical well-being scores were affected by the site of HAE attacks.

The patients who had attacks accompanied by abdominal pain had significantly lower physical well-being scores ($p = 0.045$). With the HAE group compared with the HA group, there was no significant difference in physical well-being, emotional well-being, self-esteem, friends, and school subscales ($p > 0.05$). The mean $\pm$ SD family scores and mean $\pm$ SD total scores were 78.2 ± 11.2 and 76.1 ± 13.2 , respectively, in the HAE group, and were 88.6 ± 11.2 and 81.4 ± 10.5 , respectively, in the HA group, family scores and total scores were statistically significantly higher in the HA group ($p < 0.001$ and $p = 0.009$, respectively) (Table 2).

In the parent-proxy reports, the mean $\pm$ SD total HRQoL scores in the HAE and HA groups were 78.4 ± 10.9 and 82.5 ± 10.3 , respectively, and in the control

Table 1 Characteristics of the patients

Characteristic	HAE Group (n = 59)	HA Group (n = 60)	Control Group (n = 72)	p
Gender, male n, (%)	22 (37.3)	28 (46.7)	27 (37.5)	0.260
4–6 years	n = 17	n = 6	n = 15	
7–13 years	2 (11.8)	3 (50)	5 (33.3)	
	n = 28	n = 36	n = 37	
14–17 years	15 (53.6)	18 (50)	14 (37.8)	
	n = 14	n = 18	n = 20	
	5 (35.7)	7 (38.9)	8 (40)	
Age, median (IQR), y: median age of all patients	8.9 (5.4–12.6)	10.3 (8–15.4)	10.3 (6.6–13.9)	0.151
4–6 y	4.2 (2.7–5.4)	4.8 (4.5–5.6)	4.5 (4–5.4)	
7–13 y	9.6 (8.2–11.5)	8.8 (8–11.2)	10.2 (7.6–11.5)	
14–17 y	15.8 (13.9–17.7)	16.9 (15.5–17.8)	14.9 (14.1–16.5)	
Age at symptom onset, median (IQR), y	6.1 (3.1–10)	7.8 (4.6–11.9)	—	0.065
Age at diagnosis, median (IQR), y	5.5 (2.3–8.7)	8 (6.3–12)	—	<0.001
Frequency of angioedema episodes within last year, median (IQR)	3 (2–5.5)	5 (2–10)	—	0.148
Lifetime number of angioedema episodes, median (IQR)	10 (3–20)	8.5 (4–20)	—	0.999
Locations of angioedema, n (%)				
Upper extremity	29 (49.2)	29 (48.3)	—	0.054
Lip	20 (33.9)	42 (70)	—	0.016
Face	20 (33.9)	26 (43.3)	—	0.749
Lower extremity	19 (33.2)	24 (40)	—	0.671
Eye lids	17 (28.8)	40 (66.7)	—	0.006
Abdomen	16 (27.1)	—	—	<0.001
Oral cavity	4 (6.8)	10 (16.7)	—	0.282
Larynx	3 (5.1)	—	—	0.138
Genital	2 (3.4)	13 (21.7)	—	0.016
Family history of AE, n (%)	52 (88.1)	5 (8.3)	—	<0.001

HAE = Hereditary angioedema; HA = histaminergic angioedema; IQR = interquartile range; AE = angioedema.

Table 2 KINDL Questionnaire scores of the children according to group

	Questionnaire Score			<i>p</i> [*]	<i>p</i> [#]	<i>p</i> [§]	<i>p</i> [¶]
	HAE Group, mean ± SD (<i>n</i> = 59)	HA Group, mean ± SD (<i>n</i> = 60)	Control Group, mean ± SD (<i>n</i> = 72)				
Physical well-being	74.5 ± 16.7	74.6 ± 19.1	94.1 ± 5.3	<0.001	0.999	<0.001	<0.001
Emotional well-being	80.5 ± 14	84.3 ± 12.6	94.6 ± 6	<0.001	0.224	<0.001	<0.001
Self-esteem	68.1 ± 17.2	74.1 ± 20.4	93.4 ± 5.4	<0.001	0.148	<0.001	<0.001
Family	78.2 ± 11.2	88.6 ± 11.2	94.6 ± 4.9	<0.001	<0.001	<0.001	0.002
Friends	83.3 ± 11.6	85.9 ± 14.6	93.8 ± 5.4	<0.001	0.494	<0.001	0.001
School	75.1 ± 16.3	80.1 ± 16	94.3 ± 5.5	<0.001	0.163	<0.001	<0.001
Total scores	76.1 ± 13.2	81.4 ± 10.5	93.1 ± 4.5	<0.001	0.009	<0.001	<0.001

KINDL = name of the questionnaire; HAE = hereditary angioedema; SD = standard deviation; HA = histaminergic angioedema.
 $p < 0.05$.

*Comparison of HAE, HA, and control groups.

#Comparison of HAE and HA groups.

§Comparison of HAE and control groups.

¶Comparison of HA and control groups.

group was 93.3 ± 2.4 ($p < .001$). The total HRQoL score and other subscales scores of healthy children's parent proxy were significantly higher than both the HAE and HA groups for all age groups ($p < 0.05$). The family, school, and total scores were significantly lower in HAE group as compared to HA group ($p = 0.008$, $p = 0.037$, $p = 0.026$, respectively) (Table 3).

Agreement between Children's Self-Reports and Their Parents' Reports in HRQoL

The correlation between the self-report and the parent-proxy report was assessed for HAE and HA. A

significant correlation was found between the self-report and the parent-proxy HRQoL in the total and all subscales scores in the patients with HAE. Strong correlations were observed in physical well-being ($r = 0.824$; $p < 0.001$) and emotional well-being ($r = 0.735$; $p < 0.001$); moderate correlations in friends ($r = 0.498$; $p = 0.001$), school ($r = 0.426$; $p = 0.005$), and total score ($r = 0.560$; $p < 0.001$); and weak correlations in family ($r = 0.394$; $p = 0.010$) and self-esteem ($r = 0.304$; $p = 0.050$).

When the correlation between the self-report and parent-proxy report was evaluated for the HA group, there were no significant correlations for family scores.

Table 3 The parents' KINDL questionnaire scores according to group

	Questionnaire Score			<i>p</i> [*]	<i>p</i> [#]	<i>p</i> [§]	<i>p</i> [¶]
	HAE Group, mean ± SD (<i>n</i> = 59)	HA Group, mean ± SD (<i>n</i> = 60)	Control Group, mean ± SD (<i>n</i> = 72)				
Physical well-being	75.8 ± 15.5	78.4 ± 17.2	92.6 ± 6.6	<0.001	0.556	<0.001	<0.001
Emotional well-being	81.7 ± 13.2	84.2 ± 13.9	93.5 ± 6	<0.001	0.438	<0.001	<0.001
Self-esteem	74.7 ± 16.5	78.8 ± 17.6	93.4 ± 5.7	<0.001	0.247	<0.001	<0.001
Family	81.3 ± 13.3	87.3 ± 12.7	94.0 ± 5.7	<0.001	0.008	<0.001	0.001
Friends	79.9 ± 12.4	83.6 ± 12.9	93.1 ± 6.5	<0.001	0.153	<0.001	<0.001
School	77.4 ± 14.3	83.1 ± 16	93.6 ± 6	<0.001	0.037	<0.001	<0.001
Total scores	78.4 ± 10.9	82.5 ± 10.3	93.3 ± 2.4	<0.001	0.026	<0.001	<0.001

KINDL = name of the questionnaire; HAE = hereditary angioedema; SD = standard deviation; HA = histaminergic angioedema.
 $p < 0.05$.

*Comparison of HAE, HA, and control groups.

#Comparison of HAE and HA groups.

§Comparison of HAE and control groups.

¶Comparison of HA and control groups.

However, strong correlations were found only with physical well-being ($r = 0.700$; $p < 0.001$), whereas moderate correlations were in self-esteem ($r = 0.465$; $p < 0.001$), school ($r = 0.616$; $p = 0.001$), and total score ($r = 0.575$; $p < 0.001$), also weak correlations were in emotional well-being ($r = 0.348$; $p = 0.010$), and friends ($r = 0.367$; $p = 0.006$). The correlation between the self-report and the proxy reports for all subscales and total scores on the KINDL questionnaire is shown in Fig. 1.

DISCUSSION

The purposes of this study were to evaluate HRQoL in children with HAE, compare it with the HRQoL of healthy controls and the patients with HA. We used the KINDL questionnaire, which is a multidimensional questionnaire that requires little time to complete and provides more comprehensive information on general HRQoL.¹⁸ The physical well-being, emotional well-being, self-esteem, friends, and school scores were comparable in patients with HAE and patients with HA but were significantly lower than in healthy children. A significant correlation was found between the self-report and parent-proxy HRQoL in the total and all subscales scores in the patients with HAE. However, in the patients with HA, no significant correlations for family scores were found, whereas the other scores had significant correlations. For the patients with HAE, age at symptom onset was correlated with physical well-being and self-esteem; also physical well-being scores were affected by the site of HAE attacks.

Analysis of the data consistently demonstrated that HAE causes significant impairments in patients' HRQoL scores and impacts their family life and lifestyle.^{12,13} However, few data are available on the impact of the disease on HRQoL that evaluated the physical, emotional, social, and school dimensions of children with HAE.^{19–21} A study that included 34 patients ages 3–18 years with symptomatic C1-INH HAE demonstrated lower HRQoL than healthy control children across the total score, school, and psychosocial dimensions of the Pediatric Quality of Life Inventory (PedsQLTM).¹⁹ Kessel *et al.*²² reported that anxiety state and trait were significantly higher among children with C1-INH HAE, which correlated with reduced HRQoL compared with the controls. Another study, of Danish children with HAE, showed that the HRQoL scores, which were better than in other studies, were comparable with the normal scores for healthy children.²³ In our study, the patients' HRQoL scores were significantly lower than those in the healthy group in terms of similar total and subscale scores.

Especially in developing countries, patients diagnosed with HAE might have difficulty accessing the

C1-INH concentrate, so this condition might make them anxious about the treatment. In addition, these children may not be getting enough psychological support when dealing with such a difficult disease. For this reason, these patients should be evaluated psychologically in all physician visits, and, if the impairment in the quality of life is detected, then psychologist support should be provided. Similar to the literature, a correlation was found between patients and parent-proxy scores, which were lower than in the healthy controls in our study.¹⁹ The significant correlations between the child and parent-proxy reports with respect to the child's HRQoL suggested that parents and children perceived many of the effects of HAE on the child similarly. This supports the ability of health care providers to rely on parents' reports during the intervention process.

Children with HAE usually have fewer and milder attacks than adults, and worsening is typically seen during adolescence.^{24,25} Some of the children in our cohort were either asymptomatic or only had a few episodes, and no children received long-term prophylactic treatment with C1-INH concentrate during the year studied. With regard to this, the total HRQoL score was not affected by the frequency of the HAE attacks. In contrast to our study, previous studies reported a significant correlation between the frequency of attacks and a lower HRQoL.^{19,23} The second important finding was physical well-being scores were affected by the site of HAE attacks. A study that included 33 children ages 5–18 years with C1-INH HAE reported that the children with a higher number of affected sites have greater anxiety traits, especially those who experienced laryngeal, abdominal, and peripheral attacks.²² This study showed that the patients who had attacks accompanied by abdominal pain had the lowest physical well-being scores.

In recent years, some studies showed that HA has a significant impact on HRQoL.^{26,27} Actually, in one study, the effect of HA on HRQoL was comparable with that experienced by patients with ischemic heart disease, with considerable significant energy loss, sleep disturbance, and emotional disturbance.²⁸ One study that included 62 adult patients with chronic urticaria reported that the presence of angioedema impaired patients' quality of life even further.²⁹ In the present study, HRQoL was detected as low compared with healthy controls such as in other studies. This was the first study to compare the HRQoL in children with HA and HAE.

Our study showed that patients with HAE had lower total HRQoL and family scores than patients with HA. This may be related to the chronic course of the disease, difficulties in accessing treatment, and the presence of life-threatening attacks. The management of HAE treatment is more complicated, difficult, and

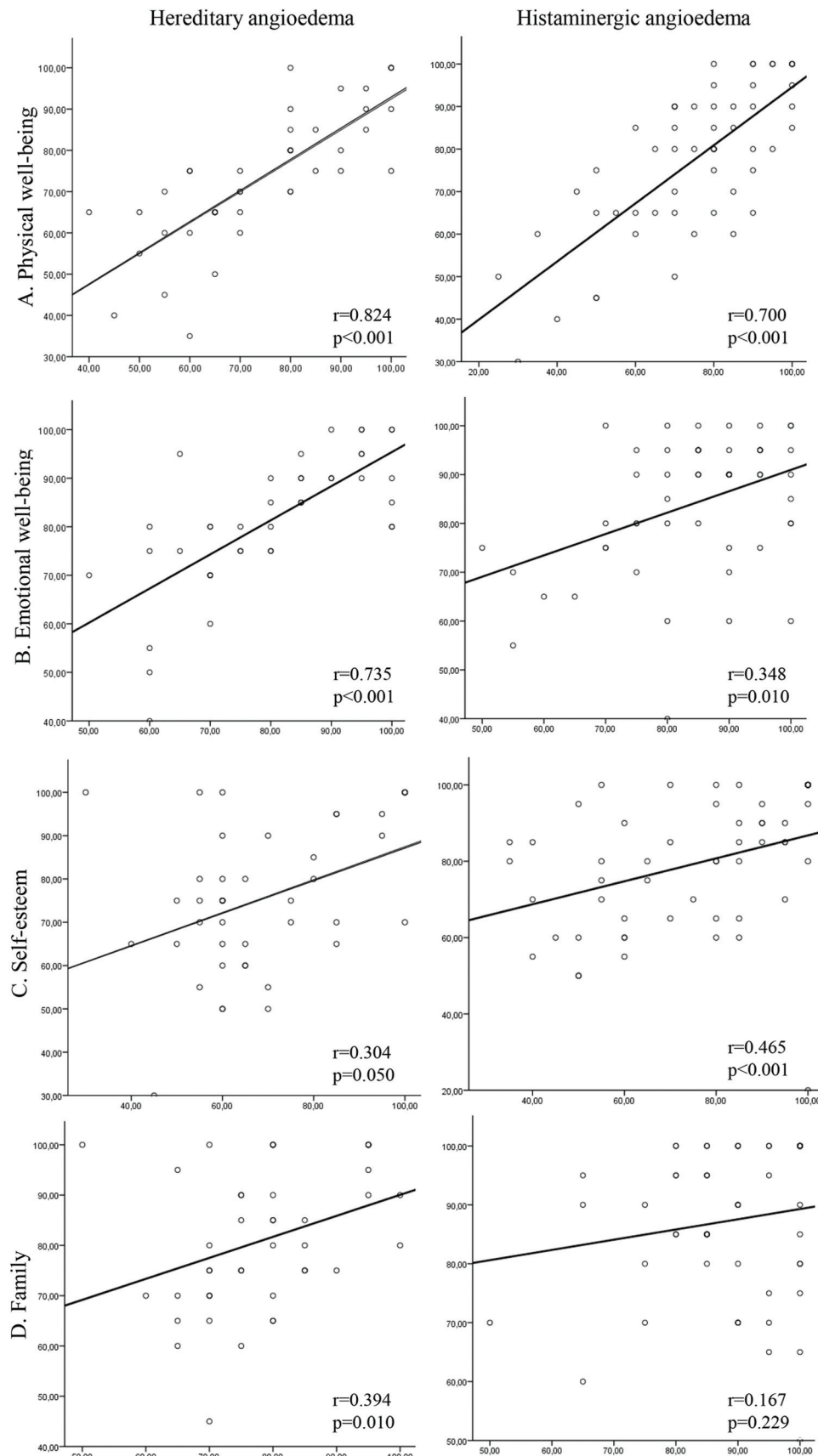


Figure 1. Scatter plot graphics and the correlation between self-report (x-axis) and proxy-reports (y-axis) for the KINDL questionnaire.

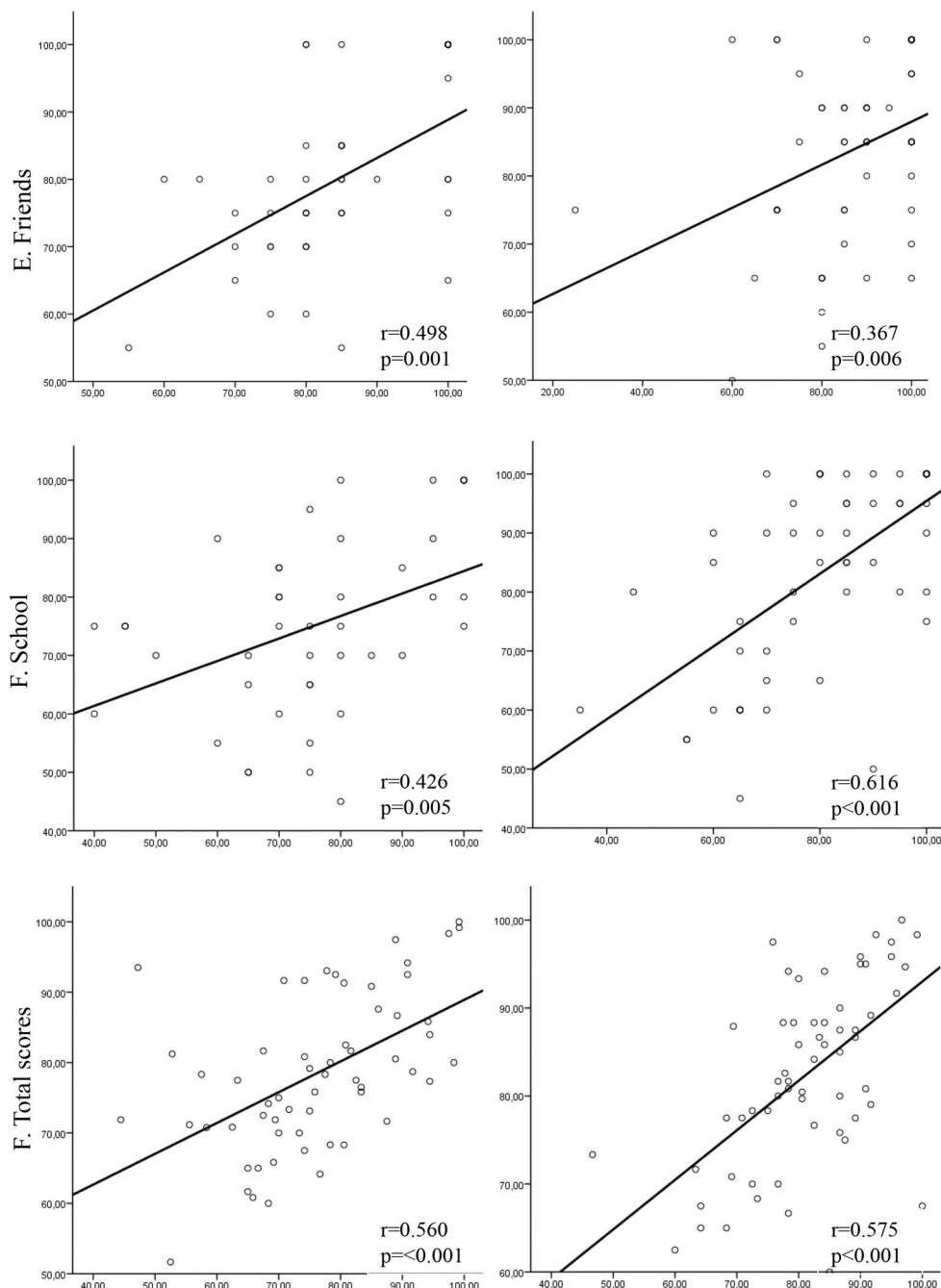


Figure 1. Continued

expensive than HA. Whereas more easily accessible medicines such as antihistaminics and corticosteroids are the main therapy for HA,³⁰ C1-INH concentrate and icatibant are used in HAE treatment.³ In developing countries, access to C1-INH concentrate or icatibant may often be difficult due to transportation and cost problems. HA is a condition that most clinicians frequently encounter daily and have sufficient management knowledge.

However, because HAE is a rare disease, clinicians may not be familiar with the disease or its treatment

in the emergency department. Because HAE is little known by clinicians, the symptoms are difficult to recognize, the diagnosis is not considered at first encounter, and laryngeal edema leads to mortality, which increases the family's anxiety. The low family score might also be related to the family's anxiety about their child's future health and social life. Although some scores are lower in the patients with HAE, HA negatively affects the quality of life as much as HAE does. In fact, HA is a condition that can be controlled with antihistamines, is self-limiting

for up to 72 hours, and not life-threatening in childhood.³⁰

However, insufficient knowledge of patients and families about the disease negatively affects their HRQoL. Therefore, to reduce the negative impact of a controllable disease on the quality of life, clinicians should provide information about the disease and decrease their anxiety by answering their questions. The strength of our study was that the sample size was wide for pediatric patients with HAE and the presence of both HA and healthy groups to compare HRQoL scores. However, there were some limitations to the present study. The use of the generic KINDL questionnaire, which has not been validated for use in HAE, may limit the generalizability of the main findings. The generic questionnaire may also be less sensitive to changes experienced by patients during the disease than an HAE-specific questionnaire.

CONCLUSION

HAE causes significant impairment in the HRQoL of patients and impacts the patients' family life and lifestyle. We concluded that, in pediatric patients with HAE, the HRQoL is mainly related to age at symptom onset and the type of attacks. The patients with HAE who experienced abdominal attacks tended to have lower HRQoL than the other sites of attacks. Finding a correlation between patients and parental surrogates proves the importance of caregivers' role in HAE treatment.

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