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The relationship between anxiety and quality of life in children with hereditary angioedema

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Abstract

Background: The severe life-threatening characteristics of hereditary angioedema (HAE) with C1-inhibitor deficiency (C1-INH-HAE) can affect anxiety levels among pediatric patients. This emotional burden together with the physical restrictions of C1-INH-HAE may decrease children's health-related quality of life (HRQoL).

Objective: (1) To compare anxiety state and trait between children with C1-INH-HAE and healthy controls (2) To examine the relationship between the level of anxiety of children with C1-INH-HAE, their disease activity/affected sites and their HRQoL (3) To predict the HRQoL of children with C1-INH-HAE based on their anxiety level and disease activity/affected sites.

Methods: Thirty-three children with C1-INH-HAE (aged 5-18 years) and 52 healthy controls were recruited from Israel and Hungary. All children completed the State Trait Anxiety Inventory for Children (STAIC), the Pediatric Quality of Life Inventory (Peds-QL) demographic questionnaire and a disease activity and site questionnaire. Disease activity was defined as the number of attacks in last year.

Results: Both anxiety state and trait were significantly higher among children with C1-INH-HAE as compared to the controls (44.74 ± 10.56 vs. 38.76 ± 10.67 , $p < 0.01$, 29.21 ± 5.16 vs. 25.23 ± 4.09 , $p < 0.001$ in comparison). Significant differences were found between C1-INH-HAE patients with HAE attacks, asymptomatic C1-INH-HAE patients and healthy controls in both anxiety state ($F_{56,2} = 4.69$, $p = .001$) and trait ($F_{56,2} = 9.06$, $p < .0001$). A higher anxiety trait was correlated with the number of angioedema affected sites ($r = .52$, $p = .003$). The presence of HAE attacks and higher anxiety trait predicted a lower HRQoL in children with C1-INH-HAE.

Conclusions: C1-INH-HAE children have higher anxiety trait and state which correlate with reduced HRQoL domains.

Key words: anxiety; children; hereditary angioedema with C1-inhibitor deficiency; pediatrics; PedsQL™ 4.0; quality of life.

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Introduction

Hereditary angioedema (HAE) caused by C1-inhibitor (C1-INH) deficiency is a rare and life-threatening disorder characterized by spontaneous, recurrent attacks of swelling in various regions of the body (1), causing pain and functional disabilities (2). HAE with C1-inhibitor deficiency (C1-INH-HAE) attacks may be triggered by mechanical trauma, infection, and medical interventions as well as by emotional stress and anxiety (3,4) and significantly reduce patients' quality of life (QoL) (5).

In recent years, there has been a growing interest in the mental health implications of C1-INH-HAE (6). The existing literature suggests that the interaction between the immune system and the central nervous system may lead to changes in mood and anxiety (7, 8). In their study, Fouche et al. (6) noted that increased activation of inflammatory mechanisms, particularly IL-1 β , may be linked to both exacerbating symptoms associated with HAE swelling attacks and behavioral changes in adults.

On one hand, the disease characteristics, the activity limitations during attacks (9), and the limited outcomes of the treatment may raise anxiety, and on the other hand anxiety may trigger HAE attacks, emphasizing that this vicious cycle may contribute to reduced quality of life among patients. Thus, anxiety symptoms should be screened and treated in the diagnosis and intervention of HAE.

The relation between anxiety, pain, recovery from disease and QoL (10) was also reported among children with allergic conditions, such as asthma (11). Rosa et al (4) identified high levels of anxiety among patients with HAE before dental procedures. Nevertheless, most existing knowledge about anxiety in HAE is based on adult patients and refers to anxiety as a general domain.

According to previous studies, children are able to report about their anxiety level (12).

Hence, evaluating anxiety based on children's report may provide important data for intervention of HAE.

The present study focuses on the anxiety of children with HAE and studies two anxiety domains: *state anxiety*, which refers to anxiety as a fleeting emotional state that involves unpleasant feelings of tension and apprehensive thoughts. This condition is subject to continual fluctuation as a result of temporal changes in the environment. The second is *trait anxiety* which is a general proneness to anxious behavior rooted in the personality (13).

The aims of this study were: (1) to compare the anxiety state and trait between children with C1-INH-HAE and healthy controls in each country and in the general sample (2) to examine whether the anxiety levels of children with C1-INH-HAE were related to their disease characteristics and to their health-related quality of life (HRQoL) (3) to examine the relative contribution of anxiety and disease severity (number of attacks per year) to the prediction of HRQoL of children with C1-INH-HAE.

Methods:

Participants

This cross-sectional study included 85 children, aged 5-18 years. The children were recruited from Hungary (n=28) and from Israel (n=57). The HAE group included 33 children, 18 from Hungary (10 females, 8 males, child's mean age 12.82 ± 3.83 (year $\pm$ SD), age range 4.5-17.76 years) and 15 from Israel (9 females, 6 males, children's mean age 12.42 ± 4.03 (year $\pm$ SD), age range 5.5-18 years). The healthy controls included 52 subjects, ten from Hungary (4 females, 6 males, child's mean age 11.31 ± 2.71 (years $\pm$ SD) , age range 7-17 years) and 42 from Israel (29 females, 23 males, children's mean age 9.28 ± 3.04 (years $\pm$ SD), age range 5-

8 years). No significant group-age interaction was found. Exclusion criteria included patients with mental health disorders, intellectual disability, or any chronic medical condition requiring a specialist's treatment. No significant differences were found in the gender distribution of either country.

Instruments

Demographic questionnaire – This questionnaire was designed by the authors and included data on family socio-demographic status, child's health status, medications, treatments and para-medical therapies. The questionnaire was completed by the children's parents.

State-Trait Anxiety Inventory for Children (STAIC) (13) – This questionnaire was used to measure anxiety in children. The instrument is designed to be used with upper elementary or junior high school aged children and consists of two twenty-item scales: Trait Anxiety and State Anxiety. The measure is easy to read and can be administered verbally to younger children. The STAIC offers high reliability and satisfactory validity (13). The STAIC is widely used to assess children's anxiety and is validated in Hebrew (13a).

The Pediatric Quality of Life Inventory (PedsQL) – This was presented by Varni JW, et al (14) and assesses the HRQoL of patients or healthy population among children and adolescents (15). The PedsQL has a version for child/adolescent self-report and for parents' proxy report. Both reports were found to have high internal consistency and construct validity in a study conducted among 2500 pediatric patients and over 9500 healthy children aged between 5 to 16 years in California (16). 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 of the Psychosocial Health dimension encompasses the emotional and social functioning (16,17). The respondent marks the frequency of problems which 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) 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.

The PedsQL is validated in Hebrew (<http://www.pedsq.org/PedsQL-Translation-Tables.pdf>).

C1-INH-HAE disease activity was expressed by the number of attacks in the last year prior to recruitment to the study, completion of the PedsQL questionnaire and by the sites of HAE 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 HAE attacks, and Group D consisted of asymptomatic individuals.

Procedure

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 Helsinki approvals from each institute, an advertisement was published in each clinic calling children and mothers to participate in a study about HRQoL among children with HAE. Mothers who participated in the study with their children signed a consent form.

They then completed the demographic and health status questionnaire while their children completed the child's version of the STAIC and the PedsQL.

Data Analysis

After performing descriptive analyses, MANOVA was used to examine the significance of the differences between the study and the control group in the dependent variables sub-scores. When comparing the total scores of the dependent measures between both groups, T-tests were used.

MANOVA with Bonferroni post hoc was used to examine the significance of the differences between the study sub-groups. ANOVA was used to examine the differences in anxiety between three groups – children with attacks; children with no attacks and healthy controls. The Spearman test was used to examine the correlation between the disease affected sites and children's anxiety level. Pearson test was used to examine the correlation between the disease severity according to the total number of attacks and children's anxiety. Stepwise linear regression was performed to investigate the relative contribution of anxiety, disease severity (number of attacks per year) and the presence of attacks in predicting HRQoL children with C1-INH-HAE. The level of significance was set at $p \leq .05$.

Comparing anxiety and HRQoL among children with C1-INH-HAE in Israel and Hungary

No significant difference was found between children with C1-INH-HAE in Israel and Hungary in anxiety state level (45.31 ± 17.56 ; 50.33 ± 2.67 , respectively, $t_{29} = 1.02$; $p = .24$), nor in anxiety trait (28.83 ± 5.45 ; 29.75 ± 4.86 , respectively, $t_{29} = -.47$; $p = .64$). No significant difference was found between the groups in their HRQoL. Table 1 summarizes HRQoL scores in all groups. Thus, we referred to them as one group in further data analysis.

Comparison of the anxiety state and trait between children with C1-INH-HAE and healthy controls, in each country and in the general sample

The Hungarian subjects with C1-INH-HAE had significantly higher anxiety state and trait than the controls. In the Israeli group, even though anxiety state and trait were higher among children with HAE than among the controls, the difference was significant only for anxiety trait. When comparing children (Israel + Hungary) with C1-INH-HAE to typical controls, children with C1-INH-HAE showed significantly higher anxiety state and trait than the controls ($t_{81}=-2.47$, $p=.01$; $t_{81}=-3.86$, $p<.0001$, respectively). Table 2 summarizes anxiety state and trait scores in all groups.

Anxiety in C1-INH-HAE children in relation to disease activity and affected sites

Descriptive statistics revealed that 23 out of 33 (69.7%) HAE patients had HAE attacks during the last year prior to study recruitment. Nine of them (9/33, 27.3%) had 1–5 attacks/year; 8 patients (8/33, 24.2%) had 6–18 attacks/year, and 15 patients (5/33, 15.2%) had 24–60 attacks in the last year. Ten out of 33 patients (30.3%) with C1-INH-HAE did not have any attacks in the last year. Significant differences were found when comparing children with attacks, children with no attacks and healthy controls in both anxiety state ($F_{56,2}=4.69$, $p=.001$) and trait ($F_{56,2}=9.06$, $p<.0001$). Anxiety state was significantly higher among children with no attacks than among the controls (mean difference =10.81; $p=.03$). Children with no attacks had significantly higher HRQoL than children with attacks in the Emotional domain (mean difference=16.31, $p=.04$; $F_{43,2}=4.01$, $p=.02$) and in the School domain (mean difference=21.63, $p=.002$; $F_{43,2}=13.55$, $p<.0001$). Children with attacks had significantly lower HRQoL than the controls in the Social domain (mean difference=12.35, $p=.02$; $F_{43,2}=4.44$, $p=.02$) and in the School domain (mean difference=27.13, $p<.0001$; $F_{43,2}=13.55$,

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$p < .0001$). Anxiety trait was significantly higher among children with attacks than among the children with no attacks (mean difference = 4.05; $p = .04$) and among the controls (mean difference = 4.97; $p < .0001$). However, no significant correlation was found between children's anxiety and disease severity as measured by the number of attacks per year.

Among the 23 children who suffered from HAE attacks, 4 patients who belonged to Group A (laryngeal, abdominal and peripheral attacks) had a higher anxiety trait level (34.66 ± 4.0) compared to Group B (abdominal and peripheral attacks) (12 patients, 31.51 ± 5.1), Group C (peripheral HAE attacks) (7 patients, 27.42 ± 3.5) and the 10 remaining individuals who were asymptomatic (Group D) (26.51 ± 4.5). Statistically, the greater the number of the affected sites, the higher the children's anxiety trait was ($r = .52$, $p = .003$). Regarding the anxiety state, no statistical differences between these groups were identified.

The correlation between children's anxiety and HRQoL among HAE children In the study group, children's anxiety trait correlated with lower emotional HRQoL ($r = -.67$, $p < .0001$); school-related HRQoL ($r = -.65$, $p < .0001$); and with total HRQoL ($r = -.65$, $p < .0001$). Among HAE children with **no** attacks, anxiety trait was significantly correlated only with lower emotional HRQoL ($r = -.65$, $p = .04$). More correlations between the anxiety trait and HRQoL was found among children **with** HAE attacks: their anxiety trait significantly correlated with lower emotional HRQoL ($r = -.59$, $p = .006$); lower social HRQoL ($r = -.47$, $p = .04$); lower school-related HRQoL ($r = -.61$, $p = .004$) and the total HRQoL ($r = -.624$, $p = .004$) (see Figure 1).

Predicting HRQoL of children with C1-INH-HAE by their anxiety and disease activity/affected sites

Stepwise linear regression analysis revealed that the independent variables predicted only emotional and school-related HRQoL. For emotional HRQoL, two models were yielded: the first included anxiety trait as a significant predictor, accounting for 45% of the variance ($F_{1,28}=22.61$, $p<0.001$); the second added the anxiety state as a significant predictor accounting for additional 8% of the variance ($F_{1,28}=4.83$, $p=0.03$). For school-related HRQoL, two models were yielded: the first included anxiety trait as a significant predictor, accounting for 42% of the variance ($F_{1,28}=19.95$, $p<0.001$); the second added the presence of attacks as a significant predictor accounting for additional 10% of the variance ($F_{1,28}=6.1$, $p=0.02$) (see Table 3).

Discussion

This is

one of the first studies that examined anxiety state and trait in children with HAE. The self-report inventory used indicates the intensity of feelings of anxiety; it distinguishes between state anxiety, a temporary condition experienced in specific situations, and trait anxiety. We found that children with HAE show greater trait and state anxiety than healthy controls.

Trait anxiety reflects an individual's predisposition to experience or display anxiety-relevant thoughts, feelings, and behaviors in everyday life. Individual differences in anxiety sensitivity are hypothesized to emerge from the combined influence of genetic variation along with experiences that lead to the acquisition of beliefs about the potentially aversive consequences of anxiety-related states (18, 19). Importantly, high levels of trait anxiety are often found in individuals with anxiety disorders, panic disorder and depression (20, 21, 22).

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It might be suggested that the children with HAE experience the burden of the disease in the same way adults do. Considering that physical and psychological stress may trigger HAE attacks (4), it is of the utmost importance to evaluate anxiety in children, as well. Since school-aged children manage anxiety self-reports better than younger children (12), clinicians should identify the appropriate age to use a child's self-report.

The results also revealed that the anxiety of children with HAE is related to the clinical features of the disease. Hence, children with a higher number of affected sites have greater anxiety trait. HAE patients who suffer from laryngeal, abdominal and peripheral attacks suffer from higher levels of anxiety trait, similar to previous findings that they have the lowest HRQoL among HAE patients (5). The relationship between anxiety and affected body sites was mentioned by Nygren et al. (23). The authors noted that psychological stress was the most common trigger for abdominal attacks. Fouche et al. (6) who examined adult patients with HAE highlighted that worsening depression and anxiety may modify the severity of the HAE. Additionally, in previous studies, one of the most common trigger associated with HAE attacks was emotional distress (24,25).

The present study also revealed for the first time that the presence of attacks was a significant factor in differentiating between anxiety trait level of children with HAE, and differentiated between children with no attacks and healthy controls, but it also differentiated between children with no attacks and those with attacks and was significantly higher in the latest group. Yet, in this stage it is difficult to state whether the HAE disease activity increases the anxiety trait or vice versa. Moreover, elevated anxiety, and mainly anxiety trait, was related to the children's HRQoL. While it was reasonable to understand the relationship between anxiety and emotional HRQoL, anxiety was also found to be a significant factor in predicting school-related HRQoL. The presence of attacks added to this prediction. The negative impacts of HAE on school-related QoL were already reported (5). Studies on adult patients

with HAE found that they experience greater distress related to their education and careers due to work and school absenteeism and productivity impairment during and between attacks (26), emphasizing the necessity to refer to anxiety impacts on various HRQoL domains, and elevating the awareness of teachers to HAE characteristics and emotional outcomes. Finally, it would be important to look for a connection between the genetic origin of HAE and anxiety trait.

This study has some limitations, it is based on a relatively small sample and on a large age range. Further studies should support the reports of children with HAE about their emotional status with their parents' report. Studies should also explore whether the relationship among HAE characteristics, children's anxiety level and HRQoL, have unique expressions in specific age groups. In addition, studies should examine the efficacy of intervention programs that focus on the physical and emotional aspects on the quality of life of children with HAE.

Anxiety should be evaluated based on parents and children's reports. This combined data may be important for interventions of HAE. This approach may reduce the chances to trigger disease attack, elevate patients' sense of control and independence and improving chances for long-term success in their careers and personal lives and even might reducing the transition from high anxiety trait to anxiety disorder (9, 4). Prospective studies are needed to capture the temporal relationship between anxiety trait and other emotional symptoms such as depression, and diagnosis and treatment of HAE. This may raise the awareness of health providers to this relationship and in tailoring the optimal intervention program for their patients (6).

To summarize, the elevated anxiety trait and state among children with HAE highlights the emotional burden they may experience. Their anxiety is related to the disease characteristics, and to the existence of the attacks, but also to the children's HRQoL, mainly in the emotional

and school-related domains. Hence, careful attention should be given to anxiety and its relation to QoL in the clinical evaluation of HAE.

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Legend

Figure 1. **Relationship between the anxiety trait and HRQOL domains among children with HAE attacks.** Higher anxiety is related to worse total quality of life ($r = -0.62$, $p \leq 0.01$), lower school related quality of life domain ($r = -0.61$, $p \leq 0.01$), lower emotional quality of life domain ($r = -0.59$, $p \leq 0.01$) and social quality of life domain ($r = -0.48$, $p \leq 0.05$).

Table 1: Comparing HRQOL between groups based on children's reports

	Hungary			Israel				
	C1-INH-HAE patients (n=18)	Healthy controls (n=10)		C1-INH-HAE patients (n=15)	Healthy controls (n=42)			
	Mean (SD)	Mean (SD)	Difference within the Hungarians	Mean (SD)	Mean (SD)	Difference within the Israeli sample	Difference between study and control group	Difference between Israeli and Hungarian study groups
Physical HRQOL	86.11 (17.05)	93.43 (6.66)	NS	82.08 (15.73)	90.76 (11.16)	*	*	NS
Emotional HRQOL	75.83 (20.68)	85.51 (15.53)	NS	82.01 (14.97)	81.52 (11.22)	NS	NS	NS
Social HRQOL	87.78 (14.67)	98.01 (3.49)	*	88.01 (11.46)	95.43 (7.82)	NS	**	NS
School HRQOL	76.38 (19.83)	93.01 (6.32)	*	67.67 (19.26)	81.95 (12.76)	**	**	NS
Psychosocial HRQOL	80.01 (15.45)	92.16 (5.83)	*	79.22 (12.06)	86.31 (8.71)	NS	**	NS
Total HRQOL	81.52 (14.18)	92.48 (5.54)	*	79.93 (11.98)	87.42 (8.15)	**	**	NS

* p≤.05; **p≤.01; NS-not significant

SD = not significant

Table 2 Comparing anxiety level between groups based on children's reports

	Hungary			Israel			Total sample		
	C1-INH-HAE patients	Healthy controls	t ₂₆	C1-INH-HAE patients	Healthy controls	t ₅₃	C1-INH-HAE patients	Healthy controls	t ₈₁
Anxiety state	48.66 (1.28)	46.61 (2.31)	3.06**	39.3077 (14.87)	36.91 (11.04)	.63	44.74 (10.56)	38.76 (10.67)	2.47**
Anxiety trait	28.83 (5.45)	24.11 (2.37)	2.59**	29.7500 (4.86406)	25.51 (4.39)	2.88**	29.21 (5.16)	25.23 (4.09)	3.83***

** p≤.01; *** p≤.001

Table 3 Predicting HRQOL of children with C1-INH-HAE by their anxiety and disease activity/affected sites.

	Model 1			Model 2		
Variable	B	SE B	β	B	SE B	β
Emotional HRQOL						
Anxiety trait	2.47	.52	-.69***	-2.69	.49	-.73***
Anxiety state				-.53	.24	-.29*
R ²		45			53	
F _{1,28} for change in R ²		22.61***			4.83*	
School HRQOL						
Anxiety trait	-2.46	.55	-.65***	-1.95	.55	-.51**
Presence of attacks				-14.58	5.89	-.35*
R ²		42			52	
F _{1,28} for change in R ²		19.95***			6.11*	

* p≤.05; ** p≤.01; *** p≤.001

Figure 1: The significant correlations between the anxiety trait and HRQOL domains among children with HAE attacks

