

Health-related quality of life in Polish adolescents with *Hymenoptera* venom allergy treated with venom immunotherapy

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Abstract

Introduction: Venom allergy, though rare, may seriously influence health-related quality of life (HRQoL). There is a paucity of research on HRQoL of adolescents and young adults with *Hymenoptera* venom allergy. The aim was to assess the level of HRQoL and to evaluate its independent predictors in Polish adolescents and young adults treated with venom immunotherapy.

Material and methods: A multicenter cross-sectional study based on the Vespidae Allergy Quality of Life Questionnaire (VQLQ) adapted for Polish adolescents was used. The study sample included 87 patients (14-21 years) studied at different stages of venom immunotherapy (VIT). Statistical analysis was done with multivariate linear regression.

Results: Anxiety level was higher in patients with 4th grade of Mueller's classification (anaphylactic shock) than in those with 3rd grade ($B = 0.84$, 95% CI = 0.07-1.61, $p = 0.03$). Caution increased along with an increase of anxiety of adolescents treated with VIT ($B = 0.54$, 95% CI = 0.39-0.68, $p < 0.01$). Level of limitations increased with increasing caution of adolescents ($B = 0.63$, 95% CI = 0.35-0.91, $p < 0.01$). Discomfort increased along with a rise of caution of patients ($B = 0.38$, 95% CI = 0.22-0.55, $p < 0.01$). Similarly, it increased with an increase of their feeling of limitations ($B = 0.37$, 95% CI = 0.23-0.51, $p < 0.01$). The level of discomfort in adolescents treated with VIT was lower in those who were treated with conventional protocol in comparison to those treated with rush or ultra-rush ones ($B = -0.47$, 95% CI = $-0.90 - -0.03$, $p = 0.04$).

Conclusions: Severity of anaphylactic reaction is an independent determinant of anxiety level in adolescents treated with VIT. The VIT protocol affects HRQoL of treated patients.

Key words: Vespidae Allergy Quality of Life Questionnaire, insect allergy, disease burden.

Introduction

Hymenoptera venom allergy (HVA), though rare, is a potentially life-threatening disorder, which requires a high level approach, appropriate to allergy intensity. Mueller’s four-grade classification of systemic reactions to insect stings includes general urticaria (grade I), angioedema (grade II), stridor or wheezing (grade III) and anaphylactic shock (grade IV). Subcutaneous injections of venom immunotherapy (VIT) are a treatment of choice for patients with grades III and IV. In patients with grades I and II, additional factors, such as high exposure to venoms or impaired health-related quality of life (HRQoL) due to venom allergy, are taken into consideration before making a decision of VIT introduction. The VIT procedure consists of two phases: the incremental dose phase and the maintenance dose phase. The incremental dose phase employs different protocols, which allow for achieving the maintenance dose phase from within 12 weeks (conventional) to a few days (rush) or a few hours (ultra-rush). The maintenance dose is given every 4-6 weeks usually for 3-5 years [1, 2].

The impact of insect venom allergy on HRQoL may be associated with several social restrictions and limitations in everyday activities of adolescents. These social limitations influenced by health conditions also trigger changes in psychological well-being: fear, anxiety, uncertainty and loss of safety can be expected as a risk of insect venom allergy consequences. The extent to which psychosocial consequences of allergy are a burden to adolescent patients may be influenced by sociodemographic (e.g. gender, age or place of residence) or medical (e.g. grade of anaphylactic reaction or VIT duration) factors (Figure 1).

Several instruments have been developed to measure HRQoL in children and adolescents suffering from different health conditions including

allergic diseases [3-9]. However, the spectrum of HRQoL scales addressed to adolescents is still outnumbered by scales addressed to adult patients [10-13].

To assess HRQoL in adult patients with yellow jacket (*Vespula*) allergy, the Vespid Allergy Quality of Life Questionnaire (VQLQ) was developed [14]. The presented results come from the first multi-center study conducted with adaptation of VQLQ for Polish adolescents treated with VIT [15].

The aim of the study was to assess HRQoL in adolescents and young adults with yellow jacket or honey bee allergy, treated with VIT in Poland, and to evaluate the impact of demographic, social and medical factors on patients’ HRQoL.

Material and methods

Patient recruitment

The study sample consisted of 87 adolescents and young adults, aged from 14 to 21 years (mean age: 17.0 years, SD 2.1 years), who were treated with VIT in September of 2008 in five clinical centers in Poland, covering almost the whole population at this age treated with VIT in Poland at that time. Patients were included in the study after completion of the written consent form by themselves and by one of their parents. The study was approved by the Ethics Committee of Jagiellonian University (number of decision: KBET no. 67/L/2007). The characteristics of the group are listed in Table I.

Measures

Face-to-face interviews were conducted using a structured questionnaire containing demographic data, and the adaptation of VQLQ for Polish adolescents. Vespid Allergy Quality of Life Questionnaire is a tool consisting of 14 items concerning

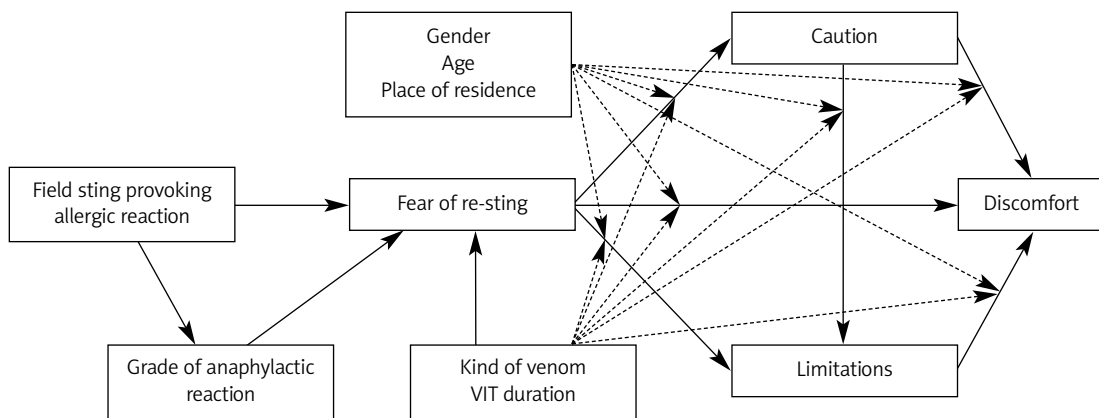


Figure 1. Model of the study
 Solid lines represent both 1. hypothetical medical factors which may influence the level of HRQoL and 2. the hypothesized relationship between particular dimensions of HRQoL. Dashed lines represent the hypothetical impact of confounding variables on the level of particular dimensions of HRQoL.

the following: anxiety of being stung by insects, behaviors to avoid further stinging (caution), limitations in outdoor activities during summer and feeling of being troubled by looking for insects in different settings (discomfort) [15]. Every item has a 7-point Likert response scale. Scores of particular subscales were computed as the algebraic mean of its items, resulting in scores ranging from 1 (reflecting the lowest level of measured latent variables) to 7 (reflecting the highest one: highest anxiety, highest caution, etc).

Gender of patients, age and place of residence were treated as potential socio-demographic predictors of HRQoL. Due to a relatively small number of girls in the study sample, and different patterns of relationship between dimensions of quality of life and age observed in boys, these two sociodemographic variables were combined into one cross-product variable indicating differences between younger boys (aged 17 years and less) and older boys (aged 18 years and more) in relation to girls (irrespectively of their age), treated as the reference category for this variable. Place of residence was used as a binary variable differentiating those living in villages from those living in towns as the reference category.

Medical factors, such as kind of culprit insect, incremental dose protocol and grade of clinical reaction after being stung, were used as dummy variables. Namely the treatment against wasp venom,

rush protocol and 3rd grade of Mueller's classification were taken as respective reference categories. Four patients treated with VIT against both venoms were included in the wasp venom treated group.

Such variables as age of patients, age at first sting, number of stings before VIT, age at VIT introduction, and duration of VIT were also tested as potential predictors of HRQoL and used in the analysis as continuous variables.

Statistical analysis

Mean and SD for normal distributions of continuous variables, or otherwise the median and quartiles, were used. Comparison of distributions of variables measured at ordinal or interval level was done with the Mann-Whitney test when two groups were compared, and with the Jonckheere-Terpstra test otherwise. Strength of association between variables measured at ordinal or interval level was measured with the Kendall tau-b correlation coefficient.

Assessment of determinants of HRQoL in every dimension was done with multivariate linear regression modeling. The results are presented as raw (B) regression coefficients and 95% CIs. Values of *p* lower than 0.05 were treated as statistically significant. Statistical analysis was conducted with SPSS 15 for Windows.

Results

Socio-demographic and medical characteristics

The study sample consisted mainly of boys (83%), and mostly residents of rural areas (63%). Mean age of adolescents was 17.0 years (SD 2.1 years). The number of patients allergic to either bee venom or yellow jacket venom was almost equal. The majority of patients were treated with the rush protocol and most of them reported 3rd grade of Mueller's classification before VIT (Table I).

The patients were studied at different periods of VIT course, with a median of 3 years of treatment (Q1 = 1, Q3 = 5). The median age of the first sting was 10 years (Q1 = 7, Q3 = 12) while the median age at beginning VIT was 13 (Q1 = 12, Q3 = 15). The median number of stings before VIT was 3 (Q1 = 1, Q3 = 7).

Univariate analysis

Among the analyzed dimensions of HRQoL, the highest median was observed for the anxiety and caution subscales, the lowest for discomfort (Table II).

Older boys had significantly lower medians of anxiety and feeling of limitations than younger ones and girls (irrespectively of their age). A similar pattern was noted in caution. Significant differences in anxiety were observed in relation to severity of anaphylactic reaction: the median values

Table I. Medical characteristics of the group

Parameter	N	%
Gender and age		
Girls	15	17.2
Younger boys	40	46.0
Older boys	32	36.8
Place of residence		
Town	32	36.8
Village	55	63.2
Immunotherapy against		
Wasp	40	46.0
Bee	43	49.4
Both	4	4.6
Mueller's grade before VIT		
2	9	10.3
3	54	62.1
4	24	27.6
Protocol		
Ultra-rush	16	18.4
Rush	46	52.9
Conventional	25	28.7

Table II. Average levels of particular dimensions of quality of life

Variable	Median	1 st Quartile	3 rd Quartile
Anxiety	3.5	2.5	5.0
Caution	3.5	2.8	4.5
Limitations	3.0	1.0	4.0
Discomfort	2.2	1.3	3.0

Table III. Differences in quality of life level due to analyzed factors

Variable	Median	1 st Quartile	3 rd Quartile	Value of <i>p</i>
Anxiety				
Gender and age:				
Girls	4.0	3.5	5.0	0.02
Younger boys	4.0	2.5	5.9	
Older boys	3.0	2.0	4.0	
Mueller's grade before VIT:				
2	3.0	1.5	4.3	0.03
3	3.5	2.5	4.6	
4	4.0	3.1	5.9	
Caution				
Gender and age:				
Girls	3.5	3.0	4.5	0.05
Younger boys	4.0	3.0	5.4	
Older boys	3.0	2.3	3.7	
Place of residence:				
Town	3.8	3.1	5.3	0.05
Village	3.3	2.5	4.5	
Limitations				
Gender and age:				
Girls	3.0	2.0	5.0	0.01
Younger boys	3.0	1.0	5.0	
Older boys	2.0	1.0	3.0	

of anxiety increased along with Mueller's grade. Higher caution was reported by residents of urban areas (Table III).

Multivariate analysis

The multivariate linear regression model showed that anxiety increased along with a rise of Mueller's grade: in patients with 4th grade (life-threatening reaction), it was significantly higher than in other patients. The level of anxiety of adolescents treated with VIT was lower in older boys than in girls (irrespectively of their age); however, this difference was of borderline significance (Table IV).

Table IV. Independent determinants of anxiety according to multivariate linear regression model

Variable	<i>B</i>	Value of <i>p</i>	95% CI for <i>B</i>	
Younger boys vs. girls	-0.44	0.37	-1.40	0.53
Older boys vs. girls	-0.97	0.08	-2.05	0.10
Mueller's grade: 2 vs. 3 (ref.)	-0.31	0.62	-1.51	0.90
Mueller's grade: 4 vs. 3 (ref.)	0.84	0.03	0.07	1.61
VIT duration (cont.)	-0.01	0.09	-0.03	0.00

Table V. Independent determinants of limitations level according to multivariate linear regression model

Variable	<i>B</i>	Value of <i>p</i>	95% CI for <i>B</i>	
Younger boys vs. girls	-0.31	0.60	-1.47	0.86
Older boys vs. girls	-1.57	0.03	-2.98	-0.16
Place of residence: rural vs. urban areas (ref.)	0.33	0.64	-1.06	1.72
Anxiety	0.17	0.15	-0.06	0.40
Caution	0.63	0.00	0.35	0.91
Younger boys place of residence	0.50	0.54	-1.12	2.11
Older boys place of residence	1.41	0.12	-0.37	3.19

Caution of adolescents treated with VIT increased along with an increase of their anxiety ($B = 0.54$, 95% CI = 0.39-0.68, $p < 0.01$). The difference in caution between residents of villages and residents of towns was of borderline significance ($B = -0.44$, 95% CI = 0.93-0.04, $p = 0.07$).

Level of limitations increased along with caution of adolescents, and it was significantly lower in older boys in comparison to girls, both living in towns; however, differences between boys regarding place of residence were not significant (Table V).

Discomfort increased along with a rise of caution and the feeling of limitations ($B = 0.38$, 95% CI = 0.22-0.55, $p < 0.01$ and $B = 0.37$, 95% CI = 0.23-0.51, $p < 0.01$, respectively). The level of discomfort was lower in those who were treated with the conventional protocol in comparison to those treated with rush or ultra-rush ones ($B = -0.47$, 95% CI = -0.90 - -0.03, $p = 0.04$).

Discussion

Health-related quality of life in HVA patients is poorly evaluated. Until the development of VQLQ by Oude-Elberink, which was the first measurement tool specific for vespidual venom allergic adults, other attempts had a rather exploratory character [1, 14, 16, 17]. The present study is the first part of multicenter research examining at the same time

point HRQoL in almost the entire population of VIT-treated Polish adolescents. The studies based on VQLQ were performed in the Netherlands and English-speaking countries; however, up till now VQLQ has been applied as a unidimensional index and verification of its multidimensionality is not known to the authors [14, 18].

The median level of QoL reported by Polish adolescents ranges from 2.2 to 3.5. This suggests that HRQoL of Polish adolescents, regardless of the kind of insect causing sensitization, is less impaired than that of Dutch adults with wasp venom allergy. Oude-Elberink reports mean scores of the VQLQ scale of 4.3 in pre-treatment measurements and 4.6 after 1 year of treatment [18]. In another paper, the same author reported scores of 3.3 in pre-treatment measurements vs. 4.4 after 1 year of treatment in patients who were randomly selected for treatment with VIT or Epipen adrenaline in auto-syringe, reporting improvement in HRQoL in both groups. A somewhat different situation was reported by patients who decided about VIT treatment themselves: they reported improvement from 2.8 to 4.3 after 1 year of treatment [19].

The results of factor analysis suggesting multidimensionality of the scale [15, 20] are supported by the results of linear regression multivariate models presented in this study, which resembles the results obtained in a study using adaptation of VQLQ for Polish children [21]. The multivariate models revealed social and medical factors influencing the scores of analyzed dimensions of HRQoL in adolescents treated with VIT: significant associations were revealed between Mueller's grade of anaphylactic reaction and anxiety, place of residence and limitations, as well as between the protocol of VIT and level of discomfort.

We observed a deteriorated level of HRQoL, reflected in an increase of anxiety along with a rise of Mueller's grade, reported in the sting history before treatment. This is not consistent with the Dutch results, which revealed no correlation of the VQLQ score with the degree of systemic reaction [18]. It is possible that this effect exists, but might have been suppressed by "including" anxiety level in the total score of VQLQ.

An observed significant positive relationship between anxiety and caution means that higher anxiety of being stung results in higher care to avoid it. This result is consistent with the observation made in samples of Polish children with HVA and their parents [21]. We also noted a lower level of caution in adolescents from rural areas. Perhaps they were more accustomed to the presence of *Hymenoptera*, as one third of patients living in rural areas are bee-keepers family members.

An observed increase of feeling of limitations during summer along with a rise of caution indicates that behaviors aimed at avoiding being stung

result in abandonment of different activities. Studies conducted in Polish children with HVA did not confirm a similar relationship, whereas the same analysis conducted in their parents showed a decrease in limitations imposed on their children along with an increase of parental anxiety, which may suggest that placing limitations on one's children is a consequence of felt anxiety and the most obvious way to decrease that feeling [21].

We observed a significant difference in the level of limitations between older boys (aged 18 years and over) and girls, both living in towns, but such differences did not exist between adolescents living in rural areas. It seems to be a combined effect of differences regarding the level of risk of being stung and differences regarding the social context of changes related to achieving the age of maturity.

The noted significant positive influence of both caution and limitations on discomfort means that a higher feeling of discomfort is related to avoidance behaviors, and results in a higher feeling of limitations. A similar impact of caution on the level of discomfort was observed in parents of children treated with VIT in Poland [21].

We also observed a lower level of discomfort in patients treated with a longer lasting conventional protocol. From the medical point of view, shorter protocols, though requiring a higher number of subcutaneous injections in a short time, are safe, and they allow immunoprotection to be achieved in a shorter time, and at lower costs, so there is a rising tendency in health care to use shorter protocols worldwide, including in Poland [22]. It is also difficult to explain why a shorter duration of the initial phase of treatment may increase the feeling of discomfort expressed as being troubled by looking for insects in different situations. It may suggest that this subscale covers a broader sense of burden of treatment and disease itself, but also the necessity of improving the medical information on advantages of shorter protocols. A similar relationship between HRQoL, symptoms of disease and specificity of treatment was also observed in asthmatic patients [23].

In conclusion, we observed the following significant relationships: impact of anxiety upon caution, impact of caution upon limitations level, and impact of both caution and limitations upon discomfort. These results partly resemble the results of the study on the HRQoL of children with HVA treated with VIT and their parents, which showed a significant impact of anxiety on caution in children and their parents, whereas in their parents an additional significant relationship was observed between anxiety and limitations imposed by them on their children, and between parental caution and discomfort [21].

An observed decrease in the level of anxiety along with VIT duration needs to be confirmed in follow-up studies, to verify whether the observed relationship reflects real improvement in HRQoL or only a response shift effect. This result also suggests that anxiety seems to be the most important dimension of HRQoL in adolescents treated with VIT.

We did not observe any differences in HRQoL between patients treated against bee and wasp stings, indicating that the tool designed for vespid allergic patients turned out to be useful regardless of the kind of sensitization. This supports the conclusion that problems experienced by all HVA patients, irrespective of the kind of culprit insect, have a lot in common.

The study showed an inverse relationship of borderline significance between VIT duration and level of anxiety, suggesting that VIT may improve HRQoL in some dimensions. However, the cross-sectional design of the study does not let us make such an interpretation. Differences between adolescents and children, concerning factors influencing particular dimensions of HRQoL, may reflect real differences concerning the behavioral or social context of their situation (healthy parents of affected children vs. affected children or adolescents), but also may be biased by different characteristics of the adapted scales used in both studies (factor structure, reliability, scale ranges and distribution, sensitivity for different confounding factors).

Previous studies of HRQoL in patients with HVA are limited to adults. The results of studies conducted in adolescents with food allergy suggest that this age group may differ from others with regard to risk-taking and coping strategies [24]. The estimation of a serious decrease in HRQoL due to venom allergy may justify the introduction of specific venom immunotherapy in certain patients with less severe systemic reactions (urticaria, angioedema). Up till now, the decision about the VIT protocol has depended only on medical factors [25]. The present results confirm the need to conduct such studies and use of such sophisticated tools for measuring HRQoL in this group of patients.

In conclusion, place of residence influences HRQoL in *Hymenoptera* allergic adolescents. Severity of anaphylactic reaction is an independent determinant of anxiety level in adolescents treated with VIT. The VIT protocol influences HRQoL of treated patients.

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