

Quality of life, anxiety, depression and satisfaction with life in patients treated with insect venom immunotherapy

Marek Niedożytko¹, Mikołaj Majkowicz², Marta Chelmińska¹, Tomasz Buss³, Marta Gruchała-Niedożytko⁴, Ewa Jassem¹

¹Department of Allergology, Medical University of Gdansk, Poland

Head: Prof. Ewa Jassem MD, PhD

²Department of Quality of Life Research, Medical University of Gdansk, Poland

Head: Prof. Mikołaj Majkowicz MD, PhD

³Department of Palliative Care, Medical University of Gdansk, Poland

Head: Prof. Monika Lichodziejewska-Niemierko MD, PhD

⁴Department of Clinical Nutrition, Medical University of Gdansk, Poland

Head: Sylwia Malgorzewicz MD, PhD

Post Dermatol Alergol 2012; XXIX, 2: 74–79

Abstract

Introduction: Insect venom allergy (IVA) is related to a higher risk of life-threatening anaphylactic reactions, resulting in decreased quality of life (QoL).

Aim: The aim of the study is to: (1) assess the QoL, anxiety and depression among patients treated with venom immunotherapy (VIT) and influence of VIT on the QoL, (2) compare patients with improvement and deterioration in VQLQ during VIT and (3) to assess QoL among bee venom allergic patients.

Material and methods: A total of 71 patients with VIT were studied. The following questionnaires were used (before and after 1 year of VIT): HADS (Hospital Anxiety and Depression), STAI (Spielberg State-Trait Anxiety Inventory for Adults), Cantril's Self-Anchoring Ladder, VQLQ (Vespid Allergy Quality of Life Questionnaire).

Results: The VQLQ before VIT for wasp allergic patients was 3.7 (SD = 1.9) and improved after 1 year of VIT to 4.3 (SD = 1.9), $p = 0.007$. Improvement of VQLQ was found in 23 subjects (44%), and deterioration in 8 (15%) wasp allergic patients. The VQLQ of patients who experienced deterioration in VQLQ was significantly higher before VIT than the remaining patients, $p = 0.001$. Pathological anxiety was diagnosed in 23 subjects (33%). Validation of the questionnaire was not possible for bee allergic patients.

Conclusions: Quality of life of Polish IVA patients is comparable to other populations. Anxiety, not depression, was more prevalent in IVA patients than in the general population. The therapy improves QoL, especially in women and patients with impaired QoL before treatment. The VQLQ questionnaire has been validated among Polish patients allergic to wasp and not bee venom.

Key words: insect venom allergy, immunotherapy, quality of life, anxiety, depression, Vespid Allergy Quality of Life Questionnaire.

Introduction

The prevalence of insect venom allergy in the population is estimated at 1-3% [1]. For the majority of patients, systemic reaction to sting is the first life-threatening health condition in life, related with high anxiety and feeling of dying during the reaction. The risk of re-occurrence of anaphylaxis among patients with the most severe reactions is quite high and is estimated at 70% in the following years [2, 3].

Insect venom allergy (IVA) is one of the most egalitarian in medicine. In contrast to the majority of diseases

(coronary artery disease, diabetes, hypertension, lung cancer, COPD and others), the style of life, wealth or nutrition makes only a minor contribution to the pathology [2, 3]. Usually, the general health condition of insect venom allergic patients is normal, in contrast to subjects suffering from cancer, heart failure or other life-threatening or other chronic disorders with daily symptoms. Anaphylaxis influences not only the physical but in most cases also the social and psychological domain of life, due to limitations on daily activities related to avoidance strategies in order to prevent a re-sting and the presence of anxiety

Address for correspondence: Marek Niedożytko MD, PhD, Department of Allergology, Medical University of Gdansk, 7 Debinki, 80-210 Gdansk, Poland, phone: +48 58 349 16 26, fax: +48 58 349 16 25, e-mail: mnied@gumed.edu.pl

in contact with insects [4, 5]. Since the patients have no symptoms of the disease if not stung, the influence on social life is becoming more important [2-5]. The need to measure quality of life, specifically addressing patients with insect venom allergy, led to the development of the VQLQ (Vespid Allergy Quality of Life Questionnaire). So far, only Dutch and English language versions of the health-related VQLQ questionnaire are available [4, 5]. Therefore, considering the differences in risk perception, cultural and sociological impacts between countries, it was interesting to examine whether factors influencing the insect venom specific quality of life are also relevant in the Polish population. The VQLQ questionnaire was developed to measure the quality of life of wasp-allergic patients, however the bee venom allergy is an important problem in Poland, where about 25% of patients suffer from bee allergy [6].

Aim

The aim of the study was to assess the quality of life (QoL), anxiety and depression among patients treated with venom immunotherapy (VIT) and the influence of VIT on the QoL in Polish patients with IVA. The second endpoint was to compare patients with improvement and deterioration in VQLQ during VIT in order to predict the effect of the treatment on the quality of life, which may enable improvement of treatment protocols in the future. The third point was to assess VQLQ among bee venom allergic patients.

Material and methods

Patients with a history of grade III and IV systemic reaction according to the Mueller scale [7] were eligible for the study. IVA was diagnosed according to EAACI guidelines based on history and additional examinations (skin prick tests, intracutaneous tests, specific IgE for bee, wasp and hornet venom) [2, 3]. The allergen used in VIT was chosen on the basis of the recognition of the sting after reaction, concomitant circumstances to the sting and specific IgE.

The initial phase was performed with a 5-day rush procedure in accordance with the manufacturer's instructions. Maintenance doses (100 µg) of venom immunotherapy were administered every 4-6 weeks. All patients were informed that they should be equipped with a rescue kit containing adrenaline, oral steroids and antihistamine drugs during all steps of diagnosis and treatment.

Patients were offered the following Polish validated questionnaires: VQLQ (Vespid Allergy Quality of Life Questionnaire) [4, 5], HADS (Hospital Anxiety and Depression) [8], STAI (Spielberg State-Trait Anxiety Inventory for Adults) [9], and Cantril's ladder [10]. The first measurement was taken during the initial phase of VIT in 2003/2004 and 2004/2005. The second measurement was performed

after one year of treatment, when they all were still on treatment.

The English version of the VQLQ questionnaire [4, 5] was translated into Polish by two independent Polish native speakers. In the second step, the translation was translated back into English by two independent English native speakers. The final version was compared with the original English version. Since no major differences in the translations and the original version were found, the final Polish version was used in the study. The VQLQ questionnaire consists of 14 questions with 7 possible answers ranging from 1 (severe impairment of QoL) to 7 (no impairment in QoL) [4, 5].

The VQLQ questionnaire was developed for wasp allergic patients. In the present study it has also been tested for QoL in bee venom allergic patients.

The HADS is a questionnaire measuring anxiety and depression in hospitalized patients. The questionnaire has two scales measuring anxiety and depression. The scores of the questionnaire range from 0 to 21. Results from 0 to 7 are regarded as normal, 8 to 10 as borderline, and above 11 indicate high anxiety or depression [8].

The STAI is a questionnaire measuring two independent aspects of anxiety: state and trait. The questionnaire has two scales, each containing 20 questions. The trait scale was used in this study. The score of the questionnaire ranges from 0 to 100. A score below 39 indicates a low level of anxiety, between 40 and 60 – normal anxiety, and 61 and above – pathological anxiety [9].

Cantril's Self-Anchoring Ladder measures present and anticipated future satisfaction with life. Steps of the ladder are numbered 0 (lowest) through 10 (highest) [10].

Statistical analysis

Data on continuous variables (age, VQLQ) were presented as medians and standard derivations (SD). The way the VQLQ score was calculated was published before [3, 4]. The differences in VQLQ scores and HADS between groups were analyzed using the U Mann Whitney Test. Values of $p < 0.05$ were considered statistically significant. Investigation of the internal consistency of the questionnaire was calculated with Cronbach α . Correlation coefficients of VQLQ with the HADS, STAI and Cantril's ladder were calculated with Pearson's correlation. The χ^2 was used to compare the number of patients with anxiety and depression in the studied subgroups. Statistica 8.0 PL (StatSoft, Tulsa, USA) software was used for statistical analysis.

The study was approved by the Ethical Committee of the Medical University of Gdansk.

Results

A total of 71 successive patients treated because of their IVA in the Department of Allergology, Medical Uni-

Table 1. Patient characteristics

Gender	Men 27 (38%)		Women 44 (62%)	
Venom	Bee 19 (26%)		Wasp 52 (74%)	
Severity of reaction according to Mueller	III 26 (36%)		IV 45 (64%)	
Severity of reaction in bee and wasp allergic patients	Bee III grade 7 (36%)	Bee IV grade 12 (64%)	Wasp III grade 19 (36%)	Wasp IV grade 33 (64%)
Gender differences in wasp and bee allergic patients	Men allergic to bee venom 11 (56%)	Women allergic to bee venom 8 (44%)	Men allergic to wasp venom 16 (30%)	Women allergic to wasp venom 36 (70%)

versity of Gdansk (Poland), during the years 2003-2005 were included in this study.

A clinically relevant allergy to wasp venom was diagnosed in 52 patients (73%) and to bee venom in 19 (27%) of patients. The differences in gender distribution and severity of the reaction were insignificant and are presented in Table 1.

VQLQ validation for wasp allergic patients

The internal consistency assessment by Cronbach α was 0.92. Cross sectional validity of the Polish version of VQLQ questionnaire was used by comparing the result of VQLQ and HADS, STAI and Cantril's ladder. The hypothesis was to compare the results of the new instrument (VQLQ) with validated and widely used tests.

The correlation of results obtained by HADS and VQLQ was median (before VIT: HADS A $r = 0.3$ HADS D $r = 0.45$; after treatment HADS A $r = 0.41$ HADS D $r = 0.23$; $p < 0.05$). The correlation between the result of STAI trait and VQLQ was before treatment $r = 0.4$; after treatment

$r = 0.38$ ($p < 0.05$). No correlation was found between the results of VQLQ and Cantril's ladder.

Longitudinal instrument validation was made by correlating the change in the results of VQLQ and HADS, STAI and Cantril's ladder results. The results were: HADS A $r = 0.27$, HADS D $r = 0.14$, STAI $r = 0.09$, Cantril's ladder $r = 0.41$ present and $r = 0.38$ anticipated future satisfaction with life; $p < 0.05$.

VQLQ results in wasp allergic patients

The overall mean VQLQ score before start of VIT for wasp allergic patients was 3.7 (SD = 1.9) and improved after 1 year of treatment to 4.3 (SD = 1.9), $p = 0.007$. The overall mean change in VQLQ is 0.58 (SD = 1.6).

The VQLQ before treatment in women was significantly lower compared to men ($p = 0.001$). Mean VQLQ in women improved after treatment $p = 0.002$, resulting in a mean change of 0.89. Mean VQLQ among men did not change after treatment, resulting in a mean change of 0.1. The VQLQ before treatment of patients with grade III reaction did not differ from patients with grade IV reaction (Table 2).

A clinically significant improvement in VQLQ score (> 0.5) was found in 23 subjects (44%), no change in VQLQ score (between -0.5 and 0.5) in 21 (41%), and a deterioration of VQLQ score (< -0.5) in 8 patients (15%). More men (5 [62%]) experienced deterioration, more women (18 [79%]) – improvement in VQLQ ($p = 0.03$).

The mean age of 23 patients with improvement of VQLQ was 45.8 years (SD 13.4), among them 18 women (78%) and 5 men (22%). The VQLQ before VIT was insignificantly lower, compared to the other patients ($p = 0.056$) (Table 3).

The mean age of 8 patients with worsening of VQLQ was 40 years (SD 13.8); among them 3 women (37%) and 5 men (63%). The VQLQ before VIT was significantly higher than the remaining patients ($p = 0.001$) (Table 3).

VQLQ results in bee allergic patients

In the group of patients allergic to bee venom, the VQLQ score before start of venom immunotherapy was 4.5 (SD = 1.6) and did not improve after 1 year of treat-

Table 2. Differences in VQLQ results in wasp allergic patients

Gender differences in VQLQ results		
VQLQ before VIT*	Men 4.8 (SD = 1.7)	Women 3.1 (SD = 1.80)
VQLQ after VIT	Men 5.0 (SD = 1.7)	Women 4.0 (SD = 2.0)
Change in VQLQ	Men 0.004	Women 0.89**
Differences according to the severity of reaction in Mueller scale		
VQLQ	III 3.8 (SD = 1.9)	IV 3.6 (SD = 1.9)
Difference in VQLQ according to the culprit insect before VIT		
VQLQ	Bee 4.5 (SD = 0.37)	Wasp 3.7 (SD = 0.26)
Difference in VQLQ according to the culprit insect after VIT		
VQLQ	Bee 4.84 (SD = 1.87)	Wasp 4.35 (SD = 1.96)
Difference in change of VQLQ during VIT according to the culprit insect		
Change in VQLQ	Bee 0.5 (SD = 1.21)	Wasp 0.58 (SD = 1.68)

* $p = 0.001$, ** $p = 0.002$

ment with VIT (4.8; SD = 1.8). This means that the VQLQ questionnaire could not be validated for bee venom allergic patients.

HADS results

A HADS – D score above 11 (indicating depression) was found in 7 patients (10%). The HADS score characteristic of high anxiety (HADS A above 11) was found in 23 subjects (32%). High anxiety was found to be more frequent in women: 18 (40%) than in men 5 (19%); however, this difference was not statistically significant, similarly to differences between patients allergic to bee and wasp and the prevalence of depression between men and women.

STAI results

Anxiety as a trait (STAI > 60) was present in 3 subjects (4%) before VIT and in 1 patient (1%) after 1 year of treatment. The correlation between anxiety measured by HADS and STAI state was 0.47; $p < 0.05$. HADS A measures high anxiety not pathological thus some patients are classified as having high anxiety by HADS but their STAI result is still normal.

Cantril's ladder results

The highest score with anticipated *present* satisfaction with life (scores 9-10) was found in 13 subjects (18%) before VIT and 12 (17%) after 1 year of treatment. On the other hand, the lowest scores (5 and below) were observed in 16 patients (23%) before and 14 subjects (20%) after VIT. No differences were found between men and women and patients allergic to bee or wasp venom. This measure increased in 27 cases (38%), remained stable in 19 (26%) and decreased in 25 subjects (37%).

The highest satisfaction with anticipated *future* satisfaction with life (scores 9-10) was found in 20 subjects (28%) before VIT and 12 (17%) after 1 year of treatment. On the other hand, the lowest scores (5 and below) were observed in 17 patients (25%) before and 13 subjects (18%) after VIT. This measure increased in 27 (38%) cases, remained stable in 18 (25%) and decreased in 26 subjects (38%).

Discussion

In this study, we demonstrate firstly that VIT improves the quality of life of venom allergic patients, especially in women and patients with marked deterioration of quality of life. Secondly, insect venom allergic patients are more anxious but not more depressive than the general population. And finally, it has been possible to validate the Polish version of VQLQ for wasp allergic patients, but not for bee venom allergic patients.

The high internal consistency of the questionnaire is proved by means of Cronbach α method. Validation of the questionnaire shows similar results in Polish versions

Table 3. Comparison of wasp allergic patients with improvement ($n = 23$) and deterioration ($n = 8$) in VQLQ

Item	Patients with improvement of VQLQ (change in VQLQ > 0.5)	Patients with deterioration of VQLQ (change in VQLQ < -0.5)
Age [years]	45.8 (SD = 13.4)	40 (SD = 13.8)
Gender [%] (M/F)**	22/78	62/38
VQLQ before VIT*	3.12 (SD = 1.7)	5.7 (SD = 1.55)*
Severity of reaction [%] (III/IV)	35/65	62/38
Anxiety measured by HADS A, n (%)	9 (39%)	1 (10%)

* $p = 0.001$, ** $p = 0.03$

of instruments validated and used before. The correlation of disease specific instrument (VQLQ) with results of treatment is better than the other instruments used, because it covers aspects of life related specifically to IVA. The VQLQ of Polish patients with IVA (VQLQ 3.7 SD = 1.9) is similar to that described previously in the Dutch population (VQLQ 3.28, SD = 1.37) [4, 5]. The VQLQ after 1 year of treatment in nonrandomized Dutch patients increased significantly to 4.29, in the described population of Polish patients the increase is also significant: after treatment the VQLQ was 4.3 [4, 5]. In this study, patients were not randomized and all were treated with VIT.

It was stated before that QoL impairment may be regarded as an indication for therapy in subjects with milder systemic reactions [3]. In this study, after 1 year of treatment we found 3 groups of patients with respect to QoL change: (1) those, who experience improvement in VQLQ, (2) patients without change and also (3) patients who experienced deterioration in VQLQ. The most interesting groups are patients with improvement and deterioration in the QoL. The finding that treatment may worsen quality of life indicates that in some cases, therapy should be tailored to prevent the deterioration of VQLQ. It is likely that the male gender and high QoL before VIT may indicate worsening of QoL despite the relevant clinical benefit which patients experience owing to the therapy. Thus, the question arises whether the treatment might be limited to 3 years in patients with grade III reaction and deterioration of VQLQ. Especially, if the deterioration is still present at this time point and modification of VIT scheme does not lead to the improvement of quality of life. In contrast, female gender, low QoL, anxiety and depression are symptoms which describe patients experiencing improvement in VQLQ. This observation supports previous findings that patients with lower grades of reaction than III might benefit from VIT by improvement in the quality of life [3].

In both Dutch and Polish patients, gender differences were observed. The QoL of women was more impaired in

comparison with men. The gender effect in the Polish population is even more significant than in the Dutch population. In contrast to the Dutch, VQLQ of men in Poland did not improve after VIT. This might be caused by high VQLQ of Polish males before VIT, higher even than in females after treatment. This discrepancy might be caused by cultural and psychological differences between countries. The female predominance among patients with IVA seems to be important. Women tend to incorporate disease in their social life and share the information about their own disease; on the other hand, they experience lowered self-efficacy and personal control, thus their quality of life is lower than in males [11-16]. The male way of facing disease is to minimize the illness, which may lead to underestimation of the symptoms and possibly difficulties in coping in life-threatening situations [11-16]. This phenomenon may explain the difference in VQLQ between men and women. Furthermore, it is likely that there are male patients who experienced the anaphylactic reaction but did not look for the proper treatment including VIT. This may happen partially owing to the fact that the information about the need of VIT is not always provided at the emergency unit when the patient is discharged from hospital.

In the present study, in contrast to the Dutch study [4, 5], patients with allergy to bee and wasp were included. The majority of studied patients were not sure if the culprit insect was bee or wasp. Poland is one of the biggest producers of honey; beehives are often built in the gardens localized in the close neighborhood of buildings. Furthermore, knowledge of the differences between *Hymenoptera* species is not prevalent among the general population, and many patients did not see the culprit insect. Therefore, our hypothesis was that the quality of life of patients allergic to bee venom does not differ from wasp allergic patients. The VQLQ questionnaire was designed for patients with wasp allergy. In our study, no change in VQLQ score in patients allergic to the bee venom was found, therefore the VQLQ questionnaire could not be validated for patients with a bee venom allergy. There are a few reasons for these differences. Most of the bee venom allergic patients, in contrast to the wasp allergic group, were male. Bee venom allergic patients had higher VQLQ before treatment. Finally, the VQLQ questionnaire was designed for wasp allergic patients and may not cover the items important for subgroups of bee allergic patients, such as farmers, gardeners or bee keepers. Thus, the usage of VQLQ should be restricted to wasp venom allergic patients only.

Anxiety was diagnosed in 23 subjects (33%) using HADS questionnaire and in 7 (10%) using STAI. The prevalence of depression was lower and using HADS was diagnosed in 7 cases (10%). The WHO "Psychological Problems in General Health Care" study estimated the prevalence of described disorders in primary care patients as 10.2% for anxiety and 11.7% for depression [13]. Thus,

the prevalence of anxiety in insect venom allergic patients is higher in comparison to the general population, which may be caused by the severity and unpredictable nature of IVA. The prevalence of depression in IVA patients is similar to the general population. The difference in VQLQ in patients with depression did not reach statistical significance, probably owing to the low number of patients. Both data indicate that depression does not decrease the quality of life of the IVA patients. The difference in VQLQ between patients with anxiety diagnosed by previously validated instruments confirms the discriminative validity of the Polish version of VQLQ. Furthermore, the instrument measures aspects of health which were not covered by previous instruments, which may explain why the correlation of results was medium. Thus, the need of a health-related questionnaire in this group of patients was confirmed.

Satisfaction with life measured by Cantril's ladder was described previously in a group of 2893 students in Poland. The lowest scores indicating poor satisfaction with life were found in 31% of cases [14, 15]. In this study, the proportion of satisfied individuals was lower (23% before VIT). Furthermore, a statistically insignificant trend to decrease the numbers of patients with low satisfaction with life after treatment was found.

In conclusion, national language versions of such validated health related questionnaires as VQLQ are important in the treatment of patients with IVA. The VQLQ questionnaire has been validated among Polish patients allergic to wasp not bee venom. The quality of life of insect venom allergic patients is as impaired as in patients in other populations. Anxiety, not depression, was more prevalent in IVA patients than in the general population. The therapy improves QoL especially in women and patients with impaired QoL before treatment.

References

1. Golden D. Stinging insect allergy. *Am Fam Phys* 2003; 67: 2541-6.
2. Biló B, Rueff F, Mosbech H, et al. Diagnosis of Hymenoptera venom allergy. *Allergy* 2005; 60: 1339-49.
3. Bonifazi F, Jutel M, Bilo B, et al. Prevention and treatment of hymenoptera venom allergy: guidelines for clinical practice. *Allergy* 2005; 60: 1459-70.
4. Oude Elberink J, de Monchy J, Golden D, et al. Development and validation of a health-related quality-of-life questionnaire in patients with yellow jacket allergy. *J Allergy Clin Immunol* 2002; 109: 162-70.
5. Oude Elberink J, De Monchy J, Van Der Heide S, et al. Venom immunotherapy improves health-related quality of life in patients allergic to yellow jacket venom. *J Allergy Clin Immunol* 2002; 110: 174-82.
6. Gorska L, Chelminska M, Kuziemski K, et al. Analysis of safety, risk factors and pretreatment methods during rush hymenoptera venom immunotherapy. *Int Arch Allergy Immunol* 2008; 147: 241-5.
7. Mueller HL. Diagnosis and treatment of insect sensitivity. *J Asthma Res* 1966; 3: 331-3.

8. Zigmond AS, Snaith RP. The Hospital Anxiety And Depression Scale. *Acta Psychiatr Scand* 1983; 67: 361-70.
9. Spielberg C, Gorsuch R L, Lushene R. The state-trait anxiety inventory. Consulting Psychologists Press, Palo Alto 1970.
10. Cantril H. The pattern of human concerns. Rutgers University Press, New Brunswick 1965.
11. DunnGalvin A, Hourihane J, Frewer L, et al. Incorporating a gender dimension in food allergy research: a review. *Allergy* 2006; 61: 1336-43.
12. Bandura A. Social learning theory. Prentice-Hall, Englewood Cliffs 1977.
13. Flokstra-de Blok B, DunnGalvin A, Vlieg-Boerstra B, et al. Development and validation of the self-administered food allergy quality of life questionnaire for adolescents. *J Allergy Clin Immunol* 2008; 122: 139-44.
14. Sartorius N, Ustün T, Lecrubier Y, Wittchen H. Depression comorbid with anxiety: results from the WHO study on psychological disorders in primary health care. *Br J Psychiatry* 1996; 30: 38-43.
15. Oblacińska A, Woynarowska B. Zdrowie subiektywne, zadowolenie z życia i zachowania zdrowotne uczniów szkół ponadgimnazjalnych w Polsce w kontekście czynników psychologicznych i społecznych [Polish]. Instytut Matki i Dziecka, Warsaw 2006.
16. Chen W, Mempel M, Schober W, et al. Gender difference, sex hormones, and immediate type hypersensitivity reactions. *Allergy* 2008; 63: 1418-27.