Heterogeneous predisposing factors and etiology in uvula edema patients

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Abstract

Background: Edema of the uvula (EU) may appear in isolation or in association with other associated clinical manifestations such as urticaria, angioedema or anaphylaxis. EU may lead to upper airway obstruction, provoking obstructive respiratory distress and asphyxia.

Objective: We sought to investigate the etiology of, and predisposing factors for, EU in a large population of patients referred to an outpatient clinic.

Methods: In this 3-year-follow-up cohort study, 171 patients presenting with EU were identified and classified as having isolated EU or non-isolated EU. The etiology of each patient's condition was studied and possible predisposing factors recorded. An allergy work-up and a statistical study (bivariate/multivariate analyses) were performed.

Results: The predisposing factors for both groups of EU patients were found to be different. The etiology of the problem was identified for the majority of the patients; allergy to *Anisakis simplex* was the most common cause for both groups. Non-steroidal anti-inflammatory drugs and antibiotics were also found as etiologies for both groups.

Conclusions: Isolated EU was found to be associated with snoring, an elongated uvula and having suffered from previous episodes of EU. Associations among groups of EU patients and gender, obesity, smoking, alcohol consumption, personal and family atopy or obstructive sleep apnea, were not demonstrated. Allergy to *A. simplex* was the most commonly recorded cause.

Resumen

Antecedentes: El edema de úvula (EU) puede aparecer aislado o en asociación con otras manifestaciones clínicas, tales como urticaria, angioedema o anafilaxia. En cualquier caso, puede provocar una obstrucción de la vía aérea superior que a veces puede ser grave.

Objetivo: Intentamos investigar la etiología y los factores predisponentes del EU de una gran población de pacientes derivados a nuestras consultas.

Métodos: En este estudio de cohortes de 3 años de seguimiento, se valoraron 171 pacientes que presentaban EU, clasificándose como EU aislado o EU no aislado. Se estudió la etiología de la condición clínica de cada paciente y se registraron los posibles factores predisponentes en cada caso, a través de un estudio alergológico y estadístico, con el fín de comprobar una asociación significativa entre ellos.

Resultados: Se encontró que los factores predisponentes para ambos grupos de pacientes eran diferentes. Una etiología fue identificada para la mayoría de los pacientes, siendo la alergia a *Anisakis simplex* la causa más común para ambos grupos. Los fármacos antiinflamatorios no esteroideos y los antibióticos también fueron identificados como etiologías para ambos grupos.

Conclusiones: Encontramos que el EU aislado se asoció con roncopatía, úvula elongada y haber sufrido episodios previos de EU. No se demostró asociación entre ambos grupos de pacientes con el sexo, obesidad, tabaquismo, hábito enólico, atopia personal y familiar o apnea obstructiva del sueño. La alergia a *A. simplex* fue la causa más frecuentemente demostrada.

Palabras clave: Alergia. *Anisakis simplex*. Úvula elongada. Obesidad. Tabaquismo. Roncopatía. Edema de úvula.

Introduction

The uvula is a muscular organ whose function includes the secretion of thin saliva and the sealing of the pharynx during speech and swallowing [1,2]. Edema of the uvula (EU) is an entity without defined, established and/or standardized diagnostic criteria. Its diagnosis is based on clinical features. EU can provoke obstructive respiratory distress and asphyxia [1-3]. It may appear in isolation (EU without associated clinical manifestations, isolated EU) [3,4] or in association with other manifestations such as urticaria, angioedema in other locations, asthma, or anaphylaxis (EU with associated clinical manifestations) [5,6].

EU can be a motive for consultation in the emergency room (ER) and in the allergy department, and could be of interest for different physicians managing this disease. Therefore, the aim of the present observational study was to characterize and compare the predisposing factors and etiology of two types of EU, isolated EU and EU with associated clinical manifestations, in a large cohort of patients referred to an outpatient clinic.

Materials and Methods

Study population and data collection protocol

This prospective longitudinal cohort study was approved by the Ethics Review Board of the University Hospital of Alcalá de Henares (Madrid, Spain). The study subjects were 171 consecutive patients with a diagnosis of EU (without and with other associated clinical manifestations) who attended our Clinical Immunology and Allergy Outpatient Dept. between April 2009 and September 2013. The majority (around 90%) was referred by the staff of the ER at our hospital; the remainder was referred by their

general practitioners. At the first visit, a direct visual observation of the uvula was made, a questionnaire with emphasis on personal and family angioedema and atopy events completed, and a detailed clinical interview recorded on the use of concomitant medications and possible predisposing factors and etiologies [5]. Moreover, an allergy work-up was performed.

Skin-prick-tests (SPT) to common food- and air borne allergen broad panel with negative (50% glycerinated saline) and positive (histamine, 10 mg/mL) controls were performed (Roxall Laboratories, Bilbao, Spain) [7]. Whether a positive outcome was clinically relevant, a patient-based, tailored strategy was carried out on basis of planning an ahead step by step. In fact, skin-prick-pricks (SPP) were carried out with selected foods (fresh or cooked foods) according to a single patient's anamnesis [8]. SPT and SPP tests were considered positive whether papule ≥3 mm than negative control in each patient [7]. In spite of air born allergens are never involved in angioedema cases, we performed the tests in all patients in order to confirm/discard an atopic background. Blood was also taken for blood count preparation, for general biochemical analysis, to determine the erythrocyte sedimentation rate, and to examine the thyroid hormone profile (including anti-thyroid antibodies), anti-nuclear antibodies, C-reactive protein, complement levels (C3, C4 and C1 inhibitor), hydatidosis serology, serum baseline tryptase levels, serum total IgE and serum specific IgE levels depending on cutaneous results to common food- and air borne allergens. Serum total IgE, specific IgE and baseline tryptase levels were measured by ImmunoCAP™ (ThermoFisher, Massachusetts, USA). Allergy to *Anisakis* was stablished in all cases by mean of SPT, serum specific IgE levels, and after following the anti-*Anisakis* conditions (fish and cephalopods frozen at −20º C for at least 48 hours) [9]. Food and drug allergies were determined based on a convincing medical history, cutaneous tests (SPT and SPP to

foods; SPT and intradermal tests to drugs), specific IgE testing, and/or challenge tests as previously described [7,8,10]. The diagnosis for antibiotics and non-steroidal anti-inflammatory drugs (NSAIDS) allergy was fulfilled following established procedures [7,8,10]. It is noteworthy there is not a test specifically determined to acquired angioedema related to angiotensin-converting enzyme inhibitors (ACEI)/angiotensin II receptor antagonists (ARA-II) (bradykinin-mediated angioedema). This entity was diagnosed following established criteria [11]. Once the results were obtained, the patients returned for a diagnostic visit. Furthermore, each patient was followed-up during a 3-year-period in order to establish some change on its diagnosis.

The patients were classified as either having EU without associated clinical manifestations (isolated EU) or EU with associated clinical manifestations, as previously described [4,5]; so, whether there was or not was other associated clinical manifestations such as urticaria, angioedema in other locations, asthma, or anaphylaxis with/without hypotension [4-6]. We named '*non-isolated EU patients*' to this latter group of patients (EU with associated clinical manifestations). Following this study protocol, the etiology (or causative factor) of each patient's condition was then studied, and possible predisposing factors recorded. *Predisposing factors* were defined as personal behaviors, environmental exposures, or inborn or inherited characteristics associated with an increased occurrence of EU, and *etiology or causative factors* as events or behaviors that directly influence the appearance of EU [12]. Subjects were considered to be *smokers* if they smoked at least one cigarette, pipe or cigar per day, *ex-smokers* if they had completely halted the consumption of all types of tobacco at least 6 months before the first visit, and *non-smokers* if they had never smoked [13]. We classified our patients according to the Mediterranean alcohol-drinking patterns as follows: *low intake* (women <5g alcohol/d, men <10g alcohol/d), *moderate intake*

(women 5–25g alcohol/d, men 10–50g alcohol/d) and *high intake* (women >25g alcohol/d, men >50g alcohol/d) [14]. *Lifetime abstainers* were defined as people who have never consumed alcohol [15]. *Heavy episodic drinking (alcohol transgression)* was defined as 60 or more grams of pure alcohol on at least one single occasion at least monthly [15]. Patients with a body mass index (BMI) class of >30 kg/m^2 and between 26–30 kg/m^2 were described as *obese* and *overweight* respectively [16]. Those with a BMI class of 20–25 kg/m^2 were considered to have a *healthy weight* [16]. *Obstructive sleep apnea (OSA)* was clinically defined by the occurrence of daytime sleepiness, loud snoring, witnessed breathing interruptions, or awakenings due to gasping or choking in the presence of at least 5 obstructive respiratory events (apneas, hypopneas or respiratory effort related arousals) per hour of sleep in the polysomnogram [17]. *Snoring* was defined as a rough rattling noise made on inspiration during sleep by vibration of the soft palate and the uvula [18]. *Atopy* was defined as a clinical hypersensitivity state or allergy with a hereditary predisposition or the inherited tendency to develop an allergy [19]. The number of previous EU events was also recorded for each patient. On the other hand, we included some medical conditions hitherto described in previous works as etiologies of EU, such as upper respiratory tract infection, pharyngeoesophageal reflux, hereditary angioedema with FXII mutation (FXII-HAE), and tonsillectomy [5,20,21], as well as others do not described so far (antibiotics, pollen immunotherapy, hymenoptera venom, and cancer).

Statistical analysis

Quantitative variables were described as means ± standard deviation for normally distributed data, or, as medians plus interquartile range for nonnormally distributed

data. Categorical variables were described using absolute and relative frequencies. Comparisons between continuous variables in different groups were made using the Student t test or the Mann-Whitney U test, as appropiate. Categorical qualitative variables were compared using the Pearson χ^2 test or the Fisher exact test. Multiple, stepwise, forward logistic regression (*in P* value cut-off point less than .05, *out P* value cut-off point less than .1) was performed, employing factors significant in bivariate and multivariate analyses, to examine the association between predisposing factors/etiologies and isolated/non-isolated EU. The results were presented as Odds Ratio (OR) and 95% confidence intervals (95%CI). All calculations were performed using SPSS 20.0 software (SPSS Inc., Chicago, Illinois, USA). A *P* value less than .05 was considered statistically significant.

Results

Patient characteristics

The mean age of the patients was 47 ± 17 years (range 13–91 years); 65.5% were men. One hundred and thirteen patients had isolated EU (66.1%) and 58 had non-isolated EU (33.9%). Table 1 shows the main descriptive data for the patient sample.

Patients diagnosed with isolated EU and patients diagnosed with non-isolated EU show different predisposing factors

The most commonly recorded predisposing factors for EU as a whole were snoring (recorded in 107 patients, 62.6%), personal atopy (75 patients, 43.9%) and being a smoker (72 patients, 42.1%) (Table 1).

Differences were seen, however, in the predisposing factors for isolated EU and non-isolated EU. The percentage of smokers, alcohol consumers (without risk to health), and snorers, was significantly higher (more than double) in the isolated EU group than in the non-isolated EU group, and the former had four times as many subjects with an elongated uvula and nearly four times as many with a history of previous (or recurrent) EU episodes. Ten patients in the isolated EU group, and none in the non-isolated EU group, had OSA syndrome (Table 1). We highlight that both the patients with suspected OSA syndrome and the snorers were referred to the Pulmonology and ENT Departments for definitive diagnosis, before being included in our series. In both Services, an overlapping or confounding pathology was also ruled out in both groups of patients.

Multiple logistic regression analysis confirmed that patients with isolated EU reported snoring significantly more often (OR, 3.45; 95%CI, 1.80-6.78), and significantly more had suffered previous (or recurrent) episodes of EU (OR, 4.06; 95%CI, 2.08-7.95) than patients with non-isolated EU. Further, significantly more had an elongated uvula (OR, 4.82; 95%CI, 2.00-11.57). Medical conditions did not reach a statistical significance (P=.05) (Table 2).

The causative factors of isolated EU and non-isolated EU were similar

The cause of EU was determined in 133 patients (77.8% of the patients). Overall the most common cause was food-associated allergy (total 63 patients; 37 patients diagnosed with isolated EU [58.7%], 26 patients diagnosed with EU with other manifestations [41.3%]; no significant difference [NSD]), followed by a reaction to drugs (total 38 patients; 20 patients diagnosed with isolated EU [52.6%], 18 patients

diagnosed with non-isolated EU [47.4%]; NSD) and finally idiopathic causes (total 38 patients; 28 patients diagnosed with isolated EU [73.7%], 10 patients diagnosed with non-isolated EU [26.3%]; NSD). However, a significant difference was seen between the isolated EU group and the non-isolated EU group with respect to associated medical conditions (total 32 patients; 28 patients diagnosed with isolated EU [87.5%], 4 patients diagnosed with non-isolated EU [12.5%]; *P*=.02) (Table 3).

The most commonly detected food-associated EU-causing agents were *Anisakis simplex* (total 35 patients; 23 patients diagnosed with isolated EU [65.4%], 12 patients diagnosed with non-isolated EU [34.3%]; NSD), lipid transfer protein (total 19 patients; 9 patients diagnosed with isolated EU [47.4%], 10 patients diagnosed with non-isolated EU [52.6%]; NSD), and shellfish (total 9 patients; 5 patients diagnosed with isolated EU [55.6%], 4 patients diagnosed with non-isolated EU [44.4%]; NSD) (Table 3). Those patients with *Anisakis* allergy had a mean specific IgE titer of 7.42 ± 12.82 kU/L (range 0.38−58.70). Another four patients were *Anisakis*-sensitive (IgE levels of 0.40, 0.68, 0.70, and 1.02 kU/L). During the three years following the present study, these 4 patients had further EU episodes despite following the anti-*Anisakis* conditions as above mentioned [9], suggesting that *Anisakis* was not the cause of their EU episode(s).

Drug-induced EU was the second most common etiology (in 38 patients, 22.2%) (Table 3). The most frequently involved drugs were ibuprofen (total 10 patients; 5 patients diagnosed with isolated EU [50.0%], 5 patients diagnosed with non-isolated EU [50.0%]; NSD), amoxicillin (total 8 patients; 2 patients diagnosed with isolated EU [25.0%], 6 patients diagnosed with non-isolated EU [75.0%]; NSD), and ACE inhibitors/ARA-II (total 7 patients; 6 patients diagnosed with isolated EU [85.7%], 1 patient diagnosed with non-isolated EU [14.3%]; NSD). One patient diagnosed with non-isolated EU caused by enalapril also presented with edema of the lips.

The medical conditions most commonly associated with EU - in particular isolated EU - appeared to be alcohol transgression (total 16 patients; 16 patients diagnosed with isolated EU [100%], 0 patients diagnosed with non-isolated EU [0.0%]; *P*<.001) and upper respiratory tract infection (total 7 patients; 7 patients diagnosed with isolated EU [100%], 0 patients diagnosed with non-isolated EU [0.0%]; NSD) (Table 3). However, logistic regression analysis ruled out any significant association with either (*P*=.05) (Table 2).

None of the other analyzed variables, highlighting serum total IgE and baseline tryptase levels, and complement study, reached statistical significance and did not appeared to be causative agents or associated conditions of isolated EU or non-isolated EU (Table 4).

Discussion

This manuscript describes a large, Spanish cohort of patients with EU. The present results show that the predisposing factors for isolated EU are different to those that predispose for non-isolated EU; the patients with isolated EU were more often snorers, had an elongated uvula, and had more commonly experienced previous episodes of EU. Association among groups of EU patients and gender, obesity, smoking, alcohol consumption, personal and family atopy or OSA, were not demonstrated. The etiology of the condition was identified in the majority of patients; allergy to *A. simplex* was the most common in both isolated EU and non-isolated EU patients.

An elongated uvula, snoring, obesity, smoking and OSA have all been reported as predisposing factors for EU [1,5,6]. Certainly, an elongated uvula - a rare malformation - was seen in 52 of the present patients (45 isolated EU, 7 non-isolated

EU); in all of them, it rested clearly on the dorsum of the tongue. Each patient distinguished truly his/her EU episode from his/her elongated uvula, supported by the physician documentation of EU in the corresponding acute setting (ER at our hospital or their general practitioners). However, in the present work, smoking and obesity were not linked to EU, due to there was not significant differences between isolated EU and non-isolated EU patients. Moreover, interestingly, the present patients diagnosed with OSA syndrome (8.8%) suffered exclusively from isolated EU, though this is difficult to explain.

To date, EU has been associated with four major causative groups: food-induced, drug-induced, medical condition-associated, and idiopathic EU [5,20,22]. In the present work, a cause was established for 133 patients; the most common (both for isolated EU and non-isolated EU) was allergy to *A. simplex* (35 out of the total 171 patients [20.5%]). In the largest series of EU patients described so far, however, such sensitivity was the causal factor in only 1 patient (1.7%) [5]. The involvement of *Anisakis* in the present patients may be explained in two ways. First, the consumption of uncooked fish is more common in central Spain (13.8% of all fish consumption) than in the area where the abovementioned study was performed, i.e., the Mediterranean area of Spain (4.8%). In agreement, the prevalence of IgE-mediated sensitivity (45.6% and 27.2% respectively) and allergy (23.8% and 9.8% respectively) to *Anisakis* are different in these areas [23]. Furthermore, the majority of fish consumed in central Spain comes from the North Atlantic, where *Anisakis*-infested fish are more common than in the Mediterranean Sea [24]. Epidemiological findings such as these are important in guiding prevention and treatment. Moreover, these 35 patients had no further episodes of EU when they followed a strict *Anisakis* avoidance diet over the following years, including 12 *Anisakis*-allergy patients with non-isolated EU. Daschner *et al* also

reported *Anisakis* to be the most common cause of EU in the 17 patients they studied [22]. However, these authors could only establish a cause for under one third of their subjects. They also identified snoring as a predisposing factor, but no observations were made regarding the influence of an elongated uvula.

The etiology of the EU of a proportion of the present patients was drug-induced. NSAIDS and ACE inhibitors/ARA-II were the cause of 8.8% and 4.1% of cases (isolated EU plus non-isolated EU) respectively. These figures are similar to those reported in a series of 58 patients by Alcoceba *et al* (5.2% and 3.4% respectively) [5]. In the present work, allergies to antibiotics (demonstrated by a convincing medical history, cutaneous tests and, in selected cases, by a challenge test) accounted for 7.0% of all cases of EU (isolated EU plus non-isolated EU) (Table 3). Interestingly, antibiotics have never before been described as a cause of EU.

In the present work, alcohol transgression and upper respiratory tract infection were the medical conditions most commonly associated with EU - exclusively with respect to isolated EU. The reason for this, however, remains unclear. On the other hand, we identified a mutation (Thr318Lys) in FXII gen along with a normal C1 inhibitor protein level and normal C1 inhibitor activity function in our patient diagnosed with FXII-HAE [11]. She was instructed to self-administration of icatibant by subcutaneous injection in the abdomen if necessary. We highlight 3 cancer patients had no more EU episodes after receiving their adequate anti-tumour treatment. However, in spite of all presented data, we had the impression that several factors were needed to produce EU.

We know that a great limitation of this study is the absence of a healthy control group to identify risk factors for development of EU (independently of being isolated or

not). Other limitation consists in the regional differences on diets and the prevalence of infections in the world. Regarding *Anisakis*, we are aware of the limitations/shortcomings of this aspect because our data cannot be extrapolated to many other populations. Nevertheless, we highlight as strengths of the study, the size of the sample and the length of follow-up for 3 years after diagnosis. Taking into account all these data in our area, we suggest as a helpful strategy to improve diagnostic and therapeutic approach, to discard *Anisakis* and involved foods/drugs as causes, as well as, to perform an inspection of the uvula and know whether the patient suffers from snoring as possible predisposing factors. These 4 factors (*Anisakis*, foods/drugs, elongated uvula, and snoring) accounted for the vast majority of cases of uvula edema in our study.

In conclusion, the present results suggest snoring, an elongated uvula and having suffered previous EU episodes to be predisposing factors for isolated EU in our clinic population. *Anisakis* allergy was the most common association with EU in our series. Such knowledge may help in the prevention and management of EU, which can sometimes be a severe condition. However, no medical condition was firmly associated with either isolated EU or non-isolated EU, and it seems difficult to act on these aspects. Further investigation must be carried out in order to clarify other causes and predisposing factors of EU and the interaction among them.

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Prior Presentations

Preliminary findings from this study were presented in poster form at the November 2010 Meeting of the Spanish Society of Allergy and Clinical Immunology (Madrid, Spain), and in oral form at the October 2014 Meeting of the Spanish Society of Allergy and Clinical Immunology (Salamanca, Spain).

Conflicts of interest

The authors declare they have no conflicts of interest.

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Table 1. Demographic characteristics, predisposing factors, and etiology regarding two clinical groups of patients diagnosed with EU.

Parameters	Isolated EU	Non-isolated EU
Total patients (n=171), No. (%)	113 (66.1)	58 (33.9)
Male sex, No. (%)	77 (68.1)	35 (60.3)
Mean (SD) age, y	46 (16)	48 (18)
Tobacco consumption, No. (%)		
Non-smokers	46 (40.7)	27 (46.6)
Smokers	54 (47.8)	18 (31)
Ex-smokers	13 (11.5)	13 (22.4)
Alcohol intake, No. (%)		
Lifetime abstainer	76 (67.3)	48 (82.8)
Low	24 (21.2)	7 (12.1)
Moderate	10 (8.8)	2 (3.4)
High	3 (2.7)	1 (1.7)
BMI class, No. (%)		
Obese	36 (31.9)	16 (27.6)
Overweight	38 (33.6)	21 (36.2)
Healthy	39 (34.5)	20 (34.5)
Snorers, No. (%)	82 (72.6)	25 (43.1)
OSA syndrome, No. (%)	10 (8.8)	0
Elongated uvula, No. (%)	45 (39.8)	7 (12.1)
Personal atopy, No. (%)	49 (43.4)	26 (44.8)
Family atopy, No. (%)	27 (23.9)	11 (19)
Patients with previous/recurrent episodes, No. (%)	77 (68.1)	20 (34.5)
Etiology, No. (%)		
Foods	37 (32.7)	26 (44.8)
Drugs	20 (17.7)	18 (31)
Medical conditions	28 (24.8)	4 (6.9)
Idiopathic	28 (24.8)	10 (17.2)

EU, edema of the uvula; SD, standard deviation; OSA, obstructive sleep apnea; Obese, body mass index (BMI) >30 kg/m^2; Overweight, BMI = 26–30 kg/m^2; Healthy weight, BMI = 20–25 kg/m^2. 'Patients with previous/recurrent episodes'

refers to patients who had suffered previous episodes of EU before a definitive diagnosis was established during the diagnostic visit.

| | | Bivariate | | | Multivariate | |
	OR	95%CI	*P* Value	OR	95%CI	*P* Value
Male sex	1.41	0.73-2.71	.31			
Smokers	2.03	1.04-3.96	.04			
Alcohol consumers	2.34	1.06-5.13	.03			
BMI class (Kg/m^2)						
Obese (>30)	1.15	0.52-2.56	.72			
Overweight (26-30)	0.93	0.45-1.98	.85			
Healthy (20-25)	1	–	–			
Snorers	3.45	1.80-6.78	<.001	2.46	1.18-5.16	.02
Elongated uvula	4.82	2.00-11.57	<.001	2.71	1.04-7.04	.04
Personal atopy	0.94	0.50-1.78	.85			
Family atopy	1.34	0.61-2.94	.46			
Patients with previous episodes	4.06	2.08-7.95	<.001	2.95	1.44-6.04	.003
Etiology						
Foods	1.67	0.87-3.19	.12			
Drugs	2.09	1.00-4.37	.05			

Table 2. Logistic regression analysis of the predisposing factors and etiology between both groups of EU patients.

Medical conditions	0.23	0.07-0.68	<.01	0.31	0.09-1.02	.05
Idiopathic	0.63	0.28-1.41	.26			

EU, edema of the uvula; OR, Odds ratio; 95%CI, 95% confidence interval; BMI, body

mass index.

Table 3. Etiology of isolated EU and non-isolated EU in our series.

Causative factor, No. (%)	Total patients (n = 171)	Isolated EU (n = 113)	Non-isolated EU (n = 58)
Foods	63 (36.8)	37 (58.7)	26 (41.3)
Anisakis	35 (20.5)	23 (65.4)	12 (34.3)
LTP	19 (11.1)	9 (47.4)	10 (52.6)
Shellfish	9 (5.3)	5 (55.6)	4 (44.4)
Drugs	38 (22.2)	20 (52.6)	18 (47.4)
NSAIDs	15 (8.8)	7 (46.7)	8 (53.3)
Ibuprofen	10 (5.8)	5 (50)	5 (50)
Dexketoprofen	2 (1.2)	1 (50)	1 (50)
Aspirin	2 (1.2)	1 (50)	1 (50)
Metamizole	1 (0.6)	-	1 (100)
Antibiotics	12 (7)	4 (33.3)	8 (66.7)
Amoxicillin	8 (4.7)	2 (25)	6 (75)
Cefuroxime	2 (1.2)	2 (100)	-
Moxifloxacin	1 (0.6)	-	1 (100)
Clarithromycin	1 (0.6)	-	1 (100)
ACE inhibitor/ARA-II	7 (4.1)	6 (85.7)	1 (14.3)
Enalapril	3 (1.8)	2 (66.6)	1 (33.3)
Lisinopril	2 (1.2)	2 (100)	-
Valsartan	1 (0.6)	1 (100)	-
Olmesartan	1 (0.6)	1 (100)	-
Medical conditions	32 (18.7)	28 (87.5)	4 (12.5)
Alcohol transgression	16 (9.4)	16 (100)	-
Upper respiratory tract infection	7 (4.1)	7 (100)	-
Cancer	3 (1.8)	2 (66.6)	1 (33.3)
Breast	2 (1.2)	1 (50)	1 (50)
Lung	1 (0.6)	1 (100)	-
Pharyngeoesophageal reflux	2 (1.2)	2 (100)	-
Pollen immunotherapy	1 (0.6)	-	1 (100)
Hymenoptera venom	1 (0.6)	-	1 (100)
FXII-HAE	1 (0.6)	-	1 (100)
Tonsillectomy	1 (0.6)	1 (100)	-
Idiopathic	38 (22.2)	28 (73.7)	10 (26.3)

EU, edema of the uvula; LTP, lipid transfer protein; NSAID, non-steroidal anti-inflammatory drug; ACE, angiotensin-converting enzyme; ARA-II, angiotensin II receptor antagonist; FXII-HAE, hereditary angioedema with FXII mutation; - means no patient.

Table 4. Statistics regarding two clinical groups of patients diagnosed with EU.

Serum parameters	Isolated EU (113 patients)	Non-isolated EU (58 patients)
Total IgE	63 [38-123.5]	71 [42.5-179]
Baseline tryptase	3.6 [2.65-5.15]	3.4 [2.7-4.93]
C3	108 [84-127.5]	112 [85-125]
C4	26 [17-32]	28.5 [18-34]
C1-INH	28 [25.5-30.5]	28 [26-30.3]

EU, edema of the uvula; IgE, immunoglogulin E; C1-INH, C1-esterase inhibitor.

Total IgE, normal to 100 IU/ml; Baseline tryptase, normal to 11.4 µg/L; C3, ranged

from 75 to 150 mg/dl; C4, ranged from 12 to 40 mg/dl; C1-INH, ranged from 22 to

34 mg/dl. Data are expressed as median and interquartile range (in brackets).