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ORIGINAL ARTICLE

Chronic spontaneous urticaria in clinical practice: A pilot survey about attitudes and perceptions on assessment, diagnostic work-up and dietary management

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Running title: A survey on CSU management; Word count: 2081 References: 15; Tables: 3

All authors have made substantial contributions to ALL of the following: substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work AND drafting the work or revising it critically for important intellectual content AND final approval of the version to be published AND agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Abstract

DCEMI TQWPF < Chronic spontaneous urticaria (CSU) is a heterogeneous condition whose mana/ i go gpv'can be complex and challenging.

Vj g''qdlgevkxg''ku''vo evaluate physicians' attitudes regarding practical aspects of CSU manage/ o gpv.''Including adherence to international guidelines, criteria and instruments for CSU cuuguuo gpv.''prescription of laboratory investigations and role of dietary measures.

OGVJ QFU: A cross-sectional survey was conducted using a study-specific questionnaire. It was administered to a group of physicians with a specialist interest in CSU from different areas of Italy definable as "CSU experts" (Group A; n=21) and subsequently to other physicians who managed CSU only occasionally in their clinical activity (Group B; n=25).

EQPENWUKQP U<Vj g'tguwmu'qh'vj g'r tgugpv'r krqv'uwtxg{"uggo "vq'uwi i guv'vj g'j gvgtqi gpgkv{"qh'vj g" crrtqcej gu'wugf 'hqt'EUW'o cpci go gpv'kp'erkpkecn'r tcevkeg0

Key words: Chronic spontaneous urticaria. Clinical practice. Guidelines. Assessment. Disease severity. Diet. Laboratory examinations.

Introduction

Chronic spontaneous urticaria (CSU) is a common disease characterized by the spontaneous occurrence of wheals, angioedema or both for more than 6 weeks [1].

CSU is a heterogeneous disorder whose management can be complex and challenging, causing frustration of many patients and their treating physicians [2,3]. The disease is associated with a marked impairment of quality of life, interpersonal relationships, daily activities, and emotional and mental well-being of patients [4].

The international evidence- and consensus-based urticaria guidelines provided a definition and classification of urticaria and recommendations regarding diagnosis, management and treatment of common urticaria subtypes, including CSU [1].

The impact of guidelines on CSU management in clinical practice is not known [5].

The aim of the present study was to evaluate physicians' attitudes regarding practical aspects of CSU management, such as adherence to international guidelines, as well as criteria and instruments used for CSU assessment, prescription of laboratory investigations and role of dietary measures.

Methods

A cross-sectional survey was conducted between January 2019 and March 2019 on a group of physicians with a special interest in treating CSU patients from different areas of Italy. They were asked to answer a study-specific questionnaire. The same questionnaire was administered to other physicians selected from their teams who managed CSU only occasionally in their clinical activity. Questions covered the use and perceived utility of international guidelines, the criteria used for the assessment of CSU severity and refractoriness to treatment, as well as the role of dietary measures in CSU management and the diagnostic tests most frequently prescribed in patients with longstanding and/or severe CSU.

The majority of the data analysis was performed in a descriptive way. In order to analyse differences between health care professionals on the basis of their level of expertise and knowledge, participants

were divided into two groups: CSU experts (group A) and specialists without regular activities of CSU management in their practice (Group B).

Comparisons between the two groups in questionnaire responses were examined using the Fisher's exact test; $P \le 0.05$ was considered statistically significant.

The statistical analysis was performed using the software with the statistical software SAS (release 9.4; SAS Institute, Inc., Cary, North Carolina).

Results

A total of 46 participants (40 dermatologists, 2 allergists, and 4 allergists and dermatologists) completed the survey.

The management of CSU patients occurred either in dedicated urticaria clinics within hospitals or university clinics (18 participants), but also private practice (n=11), public outpatient clinics (n=8) or non-dedicated services within hospital or university clinics (n=6), whereas very few participants reported mixed types of medical settings. In the subgroup of 21 CSU experts (group A), three did not specify any specific setting whereas 70% of them mostly managed CSU patients in dedicated urticaria units. Group B was composed by 25 dermatologists who, apart from a few exceptions, occasionally managed CSU patients within three main settings: public outpatient clinics (n=8), private practice (n=8) or non-dedicated hospital services (n=6).

Table I shows detailed results of the survey about guidelines, disease assessment and diets.

The EAACI/GA²LEN/EDF/WAO guidelines were regarded as very or moderately useful by the majority of participants, without significant differences between groups, and were regularly or frequently used in clinical practice by all participants in group A and 76% of group B dermatologists (Table I). Significantly more members of group A (the experts) reported to follow always the guidelines (71.4%) as compared to only 20% of group B participants (the non-experts) (*P*=0.0008). With regard to the instruments for the assessment of CSU severity/activity and disease-related quality of life, they were believed to be moderately or very useful by 57.1% and 38.1% of group A

participants, and 40% and 12% of group B participants, respectively. These instruments were considered of little utility by a significantly larger proportion of subjects in group B as compared to group A (48% versus 4.8%, respectively; P=0.0022) (Table I). Consequently, such instruments were used in clinical practice significantly more often by CSU experts as compared to group B members (Table I). In group B, 44% of participants reported that they never used such measures in everyday practice (versus 0% in group A, P=0.0004).

In the total population, Urticaria Activity Score (UAS) over 7 days (UAS7) was the most used instrument (reported by 100% of the 35 users of instruments assessing disease severity and quality of life), followed by Dermatology Life Quality Index questionnaire (17.1%), Chronic Urticaria Quality of Life Questionnaire (17.1%), the Urticaria Control Test (11.4%) and the Angioedema Activity Score (2.8%).

Among the principal aspects that were taken into account for the assessment of CSU severity in routine practice (Table II), itch severity (71.7%) and interference with sleep (71.7%) were those most frequently reported, followed by angioedema (65.2%), interference with daily activities (56.5%), frequency of episodes (54.3%), psycho-relational consequences (50%) and UAS7 (43.5%). Variation in the frequency of CSU episodes (69.6%) and patient dissatisfaction (65.2%) were indicated as the foremost parameters for defining refractoriness of CSU to treatment, followed by UAS7 (50%) and change in itch severity (47.8%) (Table II).

As concerns the role of diet in CSU management (Table I), dietary measures were negatively rated and less frequently adopted in clinical practice in a higher proportion of CSU experts as compared to participants in group B (Table I). Diets were frequently suggested for CSU patients by nearly three quarters of group B members and by only 4.8% of CSU experts (*P*<0.00001).

Survey participants were finally asked to indicate the type of examinations that were commonly prescribed in patients with longstanding and/or uncontrolled CSU regardless of their history (Table III). All physicians recommended full blood count and 95.6% of them thyroid autoantibodies. The

other laboratory investigations most often prescribed reported were erythrosedimentation rate (ESR) and/or C-reactive protein (CRP) and thyroid function tests.

Discussion

Our results revealed an overall high rate of knowledge of the EAACI/GA²LEN/EDF/WAO guidelines and adherence to these guidelines for the management of CSU in clinical practice among the survey participants irrespective of their level of expertise. The majority of respondents positively rated the guidelines utility and stated to follow such guidelines frequently or very frequently. Significantly more specialists with considerable experience in CSU patient care reported that the international guidelines were always followed in clinical practice.

Guidelines are developed to improve medical decision making and to give guidance and recommendations for patient management in clinical practice. Nevertheless, guideline recommendations cannot always be implemented in everyday practice and may not always reflect the complexity of particular circumstances [5].

A cross-sectional survey study performed in 2009 in a sample of 776 German physicians working in private practice and consisting of dermatologists, general practitioners and paediatricians showed that the real-life management of CSU does not sufficiently comply with the guidelines [6].

A recent worldwide survey on CSU management collecting 1140 questionnaires filled in mostly by allergists/clinical immunologists from 99 countries [5] showed that almost one-third of physicians deviated from a guideline or did not follow it. Reliance on own clinical experience was the most frequent reason for deviating from the guidelines or not following them. Young and less experienced physicians more often used a guideline and less often deviated than older and experienced physicians [5].

In our survey, group B members, who sporadically managed CSU patients, were less likely to give a positive opinion about instruments created to evaluate CSU activity/severity and influence on quality of life and were also less inclined to use these tools. Significantly more physicians in Group A

reported a regular use of such instruments in their practice or for research purposes. Interestingly, UAS7 was recognized as the most important instrument. UAS7 is a simple scoring system that has been validated and corresponds to the sum of the daily intensity of itch and number of wheals scores registered by the patient over 7 consecutive days [7]. The UAS7 has been proposed as a helpful instrument to determine disease activity and response to treatment of patients with CSU in routine clinical practice [1]. Nevertheless, it should be pointed out that the instruments developed for the assessment of CSU severity and quality of life were always or frequently used by only 47.6% of CSU experts and exclusively for research purposes by 19.1% of them, thus supporting the fact that such tools are not yet completely incorporated into routine clinical practice among CSU experts.

When survey participants were asked to select the most important features they usually took into consideration for the assessment of CSU severity and refractoriness to therapy, UAS7 was reported by 43.5% and 50% of respondents, respectively. Itch severity, interference with sleep and presence of angioedema were the leading items considered for assessing CSU severity. The refractoriness to treatment was most frequently judged based on the frequency of CSU episodes, as reported by 69.6% of survey participants, while 65.2% of respondents emphasised the importance of patient dissatisfaction, a generic non-standardized definition pointing out the relevance of patient-perceived outcomes.

The role of diet in CSU management is still perceived as very important by both patients and physicians, but also extremely controversial. The international guidelines included avoidance diet protocols among the extended diagnostic procedures that can be proposed to CSU patients depending on history and pseudoallergen-free or low-histamine diets among the alternative treatment options [1], but these dietary regimens have an overall modest scientific support.

Some studies have shown that low-histamine and pseudoallergen-low diets are an inexpensive tool that can improve symptoms in CSU patients [8-10]. Nevertheless, the use of dietary measures is not universally well accepted and can sometimes be time-consuming and difficult to explain and handle in everyday practice. A systematic review has recently outlined that diets may be beneficial in

individual patients [11], although the overall level of available evidence seems to be low because of the lack of systematic randomized double-blind controlled studies [1].

A cross-sectional survey conducted in health care professionals with experience in chronic urticaria in the United Kingdom (55 allergists/immunologists, 64 dermatologists and 43 dietitians) revealed that dietary measures were used by only a quarter of the participating physicians [12].

In our survey, the role of diet in CSU management appeared to be downsized more often by CSU experts. Group B physicians (the non-experts) tended to use dietary measures more frequently in comparison with group A physicians.

Concerning routine diagnostic measures in CSU patients, the EAACI/GA²LEN/EDF/WAO guidelines have recommended limited investigations, with basic tests including differential blood count and CRP and/or ESR. Additional tests are indicated as an extended diagnostic program based on the patient history and examination, especially in patients with longstanding and/or uncontrolled disease, whereas intensive and costly general screening programs are strongly advised against [1]. It is well known that, despite efforts to identify underlying causes, the majority of CSU cases remain idiopathic [13], and routine laboratory testing in CSU patients with normal history and examinations has been shown to be not cost-effective [14]. It should be underlined that, in our survey, physicians were simply asked to indicate diagnostic testing most commonly taken into account for patients with longstanding and/or uncontrolled CSU, regardless of history. Therefore, the question was simply intended to appraise the physicians' perceptions and experience regarding the possible causes and/or associations of CSU in severe and longstanding cases and it was not formulated to obtain precise information on the type and number of tests actually prescribed in practice for such cases. Moreover, survey participants were invited not to consider in their answer the patients' thorough history, that is regarded as the most important diagnostic procedure for CSU [1,4].

In our study, for patients with longstanding uncontrolled CSU, regardless of history, all physicians recommended full blood count. The other investigations most frequently prescribed were thyroid autoantibodies (95.6%), ESR and/or CRP (89.1%) and thyroid function tests (80.4%), suggesting a

robust awareness of the association between CSU and thyroid autoimmune diseases among survey participants [15]. In the UK cross-sectional survey performed by Wu et al [12], the most common investigations reported were full blood count, thyroid function and thyroid stimulating hormone. Antinuclear antibodies were recommended by nearly half of the physicians in our study. Although parasitic infections are believed to be a rare cause of CSU in Western countries and also allergy is thought to be rarely implicated in CSU [1], in our survey stool examinations for parasites and skin prick tests were suggested by about half of physicians.

Our study has several limitations. Selection bias and the limited size of the sample, as well as the preponderance of dermatologists, unquestionably hamper definite conclusions. Nonetheless, the results suggest the heterogeneity of the approaches used for CSU management in clinical practice.

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TABLE I. - Results of the survey regarding guidelines, CSU assessment and diets.

	Group A (n=21)	Group B (n=25)	P Value
EAACI/GA ² LEN/EDF/WAO guidelines	, ,		
Utility in clinical practice			
Scarce	0	1 (4%)	1
Moderate	3 (14.3%)	9 (36%)	0.1765
Considerable	18 (85.7%)	15 (60%)	0.0987
Use in clinical practice			
Never	0	0	1
Rarely	0	1 (4%)	1
Sometimes	0	5 (20%)	0.0536
Frequently	6 (28.6%)	14 (56%)	0.0791
Always	15 (71.4%)	5 (20%)	0.0008
Instruments assessing disease severity and quality of life			
Utility in clinical practice			
Scarce	1 (4.8%)	12 (48%)	0.0022
Moderate	12 (57.1%)	10 (40%)	0.3746
Considerable	8 (38.1%)	3 (12%)	0.08
Use in clinical practice			
Never	0	11 (44%)	0.0004
Rarely	2 (9.5%)	5 (20%)	0.4285
Sometimes	5 (23.8%)	4 (16%)	0.7114
Frequently	3 (14.3%)	4 (16%)	1
Always	7 (33.3%)	1 (4%)	0.0161
Only for research purposes	4 (19.1%)	0	0.0367
Dietary measures			
Utility in clinical practice			
Scarce	11 (52.4%)	2 (8%)	0.0012
Moderate	10 (47.6%)	19 (76%)	0.0679
Considerable	0	4 (16%)	0.1142
Use in clinical practice			
Never	2 (9.5%)	0	0.2029
Rarely	8 (38.1%)	1 (4%)	0.0067
Sometimes	9 (42.8%)	4 (16%)	0.0559
Frequently	1 (4.8%)	18 (72%)	< 0.00001
Always	1 (4.8%)	2 (8%)	1

CSU= chronic spontaneous urticaria; EAACI/GA²LEN/EDF/WAO= European Academy of Allergology and Clinical Immunology (Dermatology Section)/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization

TABLE II. - Survey results regarding the assessment of CSU severity and refractoriness in clinical practice.

	Physicians
	n (%)
Principal items considered for the assessment of severit	ty
Itch severity	33 (71.7%)
Interference with sleep	33 (71.7%)
Angioedema	30 (65.2%)
Interference with daily activities	26 (56.5%)
Frequency of episodes	25 (54.3%)
Impact on psycho-relational aspects	23 (50%)
UAS7	20 (43.5%)
Average daily number of wheals	15 (32.6%)
Results of quality of life questionnaires	5 (10.9%)
Urticaria Control Test	1 (2.2%)
Principal items considered for the assessment of refract	toriness to therapy
Frequency of episodes (change vs baseline)	32 (69.6%)
Patient dissatisfaction	30 (65.2%)
UAS7	23 (50%)
Itch severity (change vs baseline)	22 (47.8%)
Number of wheals (change vs baseline)	16 (34.8%)
Results of quality of life questionnaires	5 (10.9%)
Urticaria Control Test	4 (8.7%)

Results are reported as number (%) of respondents in the total population (n= 46); ≥ 1 item was reported by each participant CSU= chronic spontaneous urticaria; UAS= urticaria activity score

TABLE III. - Survey results regarding investigations prescribed in clinical practice for longstanding uncontrolled CSU.

Investigations	Physicians		
	n (%)		
Full blood count	46 (100%)		
Thyroid autoantibodies	44 (95.6%)		
ESR and/or CRP	41 (89.1%)		
Thyroid function tests	37 (80.4%)		
Antinuclear antibodies	24 (52.2%)		
Prick tests	21 (45.6%)		
Stool examinations for parasites	21 (45.6%)		
Tests for Helicobacter pylori	16 (34.8%)		
Autologous serum skin test	11 (23.9%)		
Tests for inducible/physical urticarias	7 (15.2%)		
Skin biopsy	3 (6.5%)		
Other tests, further specified by each participant			
D-dimer	8 (17.4%)		
Total IgE	6 (13%)		
Viral hepatitis markers	2 (4.3%)		
Chest radiography and abdomen ultrasound examination	2 (4.3%)		
Viral serology (not specified)	1 (2.2%)		
Tryptase	1 (2.2%)		

Results are reported as number (%) of respondents in the total population (n=46); ≥ 1 item was reported by each participant CSU= chronic spontaneous urticaria; ESR= erythrosedimentation rate; CRP= C-reactive protein