

Anisakis simplex Hypersensitivity Is Associated with Chronic Urticaria in Endemic Areas

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Key Words

Chronic urticaria • *Anisakis simplex* • Food allergy

Abstract

Background: Chronic urticaria (CU) may affect up to 1% of the general population. *Anisakis simplex* hypersensitivity is frequent in areas where raw fish is consumed and *A. simplex* allergy represents a relevant cause of acute urticaria. We assessed the possible association between CU and *A. simplex* sensitization in an area where marinated fish is very frequently eaten. **Methods:** A thorough history of CU was sought in 919 adults seen at the Allergy Center, Bari. CU patients and 187 controls underwent skin-prick testing with a commercial extract of *A. simplex*, and reactors were recommended a 6-month raw-fish-free diet regimen. Responders were followed after a further 3 months. **Results:** Of 919 subjects, 213 (23%) met the criteria for CU and 106/213 (49.7%) were sensitized to *A. simplex* with a significant difference between patients aged >65 or <65 years (56 vs. 41%, respectively; $p < 0.05$). All patients hypersensitive to *A. simplex* were regular consumers of marinated fish. In a control population without CU, the prevalence of *A. simplex* sensitization was 16% ($p < 0.001$). The 6-month diet regimen led to the disappearance of urticaria in 82/106 cases (77%) versus 1/42 (2%)

subjects who did not change their dietary habits ($p < 0.001$). All nonresponders were sensitized to house-dust mites. Of 75 responders who were followed-up after 3 months, CU relapsed in 88% of those who had reintroduced raw fish versus 14% of those who were still on the diet ($p < 0.001$). **Conclusion:** In areas where raw or marinated fish is frequently eaten, *A. simplex* hypersensitivity is a frequent cause of CU.

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Introduction

Chronic urticaria (CU) is a common clinical condition characterized by the occurrence of wheals and/or angioedema for more than 6 weeks. The prevalence of CU has been estimated at 1% of the general population [1], but the real prevalence probably exceeds this figure. Based on studies carried out during the last 2 decades, it is currently believed that the origin of the disease is frequently autoreactive or autoimmune [2–4] although the pathogenesis remains ‘idiopathic’ in a number of cases.

The nematode *Anisakis simplex*, a parasite in fish, cephalopods, crustaceans and marine mammals, may sensitize humans following the ingestion of fish and cause abdominal pain, urticaria, angioedema or even

Table 1. Clinical features of the study population and comparison between patients aged younger or older than 65 years (%)

	Total	>65 years	<65 years	p
Patients	919	461	458	
History of CU	213 (23)	127/461 (28)	86/458 (19)	<0.001
CU patients positive on <i>A. simplex</i> SPT	106 (50)	71/127 (55)	35/86 (40)	<0.02
CU patients reactive to both <i>A. simplex</i> and HDM	48 (45)	25/71 (35)	23/35 (65)	<0.002
Response to restriction diet	82 (77)	54/71 (76)	28/35 (80)	NS

HDM = House-dust mite.

anaphylaxis in sensitized individuals [5–7]. The recent EAACI/GA2LEN/WAO guidelines on urticaria have included *A. simplex* hypersensitivity among the possible causes of CU [8], but so far, few studies have specifically addressed this issue [9–12]. Recently, an Italian multi-center study [13] showed large differences in the prevalence of *A. simplex* sensitization and clinical allergy to *A. simplex* between different areas of the country, with the maximum prevalence along both the Adriatic and Tyrrhenian coasts. In this study, we investigated the prevalence of CU and its possible causes in adult patients living in the area of Bari, where eating marinated anchovies is an age-old tradition and the prevalence of *A. simplex* hypersensitivity is high.

Patients and Methods

Patients and Skin Tests

A total of 919 adult subjects (297 males/622 females of 17–83 years of age), referred to the outpatient Allergology Unit of Bari University Hospital in the course of 1 month, made up the starting population. Subjects were visited and interviewed in order to estimate the prevalence of CU. A history of recurrent or persistent wheals and/or angioedema for >6 weeks was considered diagnostic for CU. Subjects with a history of CU underwent a series of skin prick tests (SPTs) with commercial food extracts including hazelnut, peanut, celery, soy, banana, peach, wheat flour, rice, maize, tomato, codfish, tuna, salmon, sardine, shrimp, cow's milk, egg-white, house-dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) (Bayer, Milan, Italy) and with *A. simplex* (2 mg protein/ml; ALK Abellò, Bollate, Italy). In order to assess the prevalence of *A. simplex* sensitization in the general population, the SPT with *A. simplex* extract was also carried out in 187 subjects [75 males/112 females with a mean age of 47.3 years (range 22–81 years)] without a history of CU. SPTs were performed and analyzed according to the EAACI guidelines [14]. Histamine of 10 mg/ml and saline were used as controls.

Elimination Diet

All patients with both a history of CU and evidence of *A. simplex* sensitization were recommended an *A. simplex*-free diet reg-

imen for 6 months, with the aim of assessing the relevance of sensitization to the parasite according to the prevalence of CU in this area. The diet regimen completely excluded any food based on raw or marinated fish. Only a complete and persistent disappearance of the skin disease – a few days after the start of the diet regimen and lasting until the control visit – was considered a positive response. Patients who responded to the *A. simplex*-free diet were recalled for 1 further clinical control 3 months after the last control visit. On that occasion, dietary habits as well as the recurrence of skin symptoms were investigated with special care.

Statistics

Proportions were compared by a χ^2 test with a Yates correction. Probability values of <5% were considered statistically significant.

Results

General Findings

Results are summarized in table 1. In view of the possible differences in diet and duration of exposure to the parasite, the study group was also analyzed by age; 461 (158 males/303 females) were aged >65 years and 458 were aged <65 years (139 males/319 females; mean age 36.2 years and range 17–64 years). A total of 213/919 (23%) subjects met the criteria for CU with a statistically significant difference between older and younger subjects [127/461 (28%) subjects aged >65 years vs. 86/456 (19%) subjects aged <65 years; $p < 0.01$].

A total of 106/213 (49.7%) patients with CU were sensitized to *A. simplex*, again with a statistically significant difference between patients older or younger than 65 years [71/127 (56%) vs. 35/86 (41%), respectively; $p < 0.05$]. All patients hypersensitive to *A. simplex* were regular consumers of marinated anchovies or marinated bluefish (regular consumption was defined as the ingestion of marinated fish 4–6 times per week). Younger *A. simplex*-hypersensitive patients showed a higher prevalence of mite and/or shrimp hypersensitivity than older ones

Table 2. Prevalence of CU at the 3-months follow-up visit (%)

	Total	>65 years	<65 years
Patients	75	50 (67)	25 (33)
Returned to nonrestricted diet	24 (32)	14 (28)	10 (40)
CU-positive	21 (88)	12 (86)	9 (90)
Still on restriction diet	51 (68)	36 (72)	15 (60)
CU-positive	7* (14)	5 (14)	2 (13)

* $p < 0.0001$ compared to patients who stopped the restriction diet.

[23/35 (65%) vs. 25/71 (35%), respectively; $p < 0.002$] and a higher prevalence of clinical allergy to house-dust mites [16/35 (46%) vs. 12/71 (17%), respectively; $p < 0.002$]. In contrast, the prevalence of shrimp allergy did not differ between the 2 groups [7/35 (20%) vs. 13/71 (18%), respectively; $p =$ not significant]. The prevalence of *A. simplex* hypersensitivity in the control group without CU was 16% (30/187; $p < 0.001$ when compared with the study group).

Elimination Diet

All 106 CU patients followed the prescribed 6-month diet regimen which led to the complete and persistent disappearance of skin symptoms in 82 cases (77%), and without differences between the older and younger subgroups [54/71 (76%) vs. 28/35 (76%), respectively; $p =$ not significant]. Interestingly, 24/24 (100%) subjects who did not respond to the elimination diet versus 24/82 (29%) patients who did respond to the diet were hypersensitive to house-dust mites ($p < 0.001$). Notably, in the general population living in the study area seen at the Allergy Center, the prevalence of house-dust mite hypersensitivity is about 30% [15]. Forty-two CU patients not sensitized to *A. simplex* did not change their dietary habits and were followed up at 6 months. Among these, the rate of CU disappearance was 2% (1/42; $p < 0.001$ compared to CU-positive/*A. simplex*-positive subjects).

Seventy-five diet responders consented to undergo a follow-up visit 3 months after the last control. Of 24 patients who had stopped the restriction diet and had resumed eating marinated fish, 21 (88%) reported a relapse of CU versus 7/51 (14%) who were still following the fish restriction diet regimen ($p < 0.001$; table 2). In those who stopped the restriction diet, urticaria relapsed about 1–2 h after the ingestion of marinated fish and lasted up to 8 h in all cases; it responded to antihistamine treatment in all the cases and no patient had to seek care at the emergency room.

Discussion

Our observations show an association, and strongly suggest a causal relationship between *A. simplex* allergy and CU in adult patients living in areas where raw or marinated fish is frequently eaten, like the Adriatic coast. We found that more than 10% of adult subjects of any age admitted to our center for any reason were sensitized to the parasite. This proportion is in line with that found in the same area in a recent Italian multicenter study [13]. The age-old habit of eating raw or marinated fish may well explain this high prevalence confirming data from our center [16]. More than 20% of the subjects studied met the criteria for CU, a proportion that is much higher than that reported in patients attending general allergy departments in other areas of Italy. In addition, CU patients from Bari showed a significantly higher prevalence of *A. simplex* sensitization than controls without CU. Among CU patients, those aged >65 years were more frequently sensitized to *A. simplex* than the younger patients, confirming that in areas characterized by the habit of consuming raw or marinated fish, *A. simplex* sensitization increases with age.

These observations prompted us to try a 6-month raw-fish-free diet regimen that eventually demonstrated the relevance of *A. simplex* intake in the pathogenesis of CU in >75% of these subjects. The further follow-up of patients responding to the *A. simplex*-free diet regimen clearly demonstrated that stopping the diet was associated with a relapse of CU in a large proportion of cases. Clearly, the habit of eating raw or marinated fish frequently may well explain why these subjects met the diagnostic criteria for recurrent or chronic, rather than acute urticaria, as is generally the case for *A. simplex* allergy. Although the relationship between *A. simplex* sensitization and recurrent episodes of acute urticaria has been known for many years, the association with CU is still controversial [9–11]. Lopez-Saez et al. [12] found an elevated rate of *A. simplex* sensitization in patients with CU but the clinical relevance of such observation remained undetermined. This is the first clinical study that in a sound scientific way supports the statement in the EAACI/GA2LEN/EDF/WAO guidelines that *A. simplex* hypersensitivity can be a cause of CU [8], although our findings cannot be extrapolated to other geographic areas or to populations with other dietary habits [17]. All CU patients who were nonresponders to the elimination diet were house-dust mite reactors. Although we did not perform a component-resolved diagnosis with recombinant allergens to confirm our hypothesis, this observa-

tion suggests sensitization to cross-reacting allergens in mites and *A. simplex*. Thus, it is possible to hypothesize that these subjects had chronic spontaneous urticaria and that their (symptomless) *A. simplex* sensitization was the consequence of primary sensitization to house-dust mite allergens, such as tropomyosin. Although the clinical relevance of *A. simplex* tropomyosin (a heat-stable allergen) is most probably negligible, as shown by the fact that shrimp-allergic patients tolerate fish (either raw or cooked), and that the clinical association between shrimp and fish allergy is an exceptional event, in order to ex-

clude that *A. simplex* tropomyosin played a role, a complete fish-elimination diet (including both raw and cooked fish) regimen should have been performed.

In conclusion, we demonstrate that in certain areas, such as the southern Adriatic coastal zone, CU may be associated with *A. simplex* sensitization; our findings propose that proper investigations should be conducted (e.g. an easy and cheap SPT with commercial *A. simplex* extract) for adults with CU, and to try a raw-fish-elimination diet if SPT scores are positive.

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