ORIGINAL ARTICLE

A CLINICAL STUDY OF URTICARIA AND ANGIOEDEMA WITH PARTICULAR REFERENCE TO THE ETIOLOGY

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ABSTRACT

Introduction: Urticaria is one of the most distressing, frustrating and challenging dermatological condition for both patients and doctors as well. The aim of present study is to find out causes of urticaria, age and sex distribution and association with atopy and other systemic diseases.

Methods: The prospective study of 500 cases of urticaria was carried out in Skin V D department from June 1995 to May 2010. All the cases having wheals and or angioedema were included in the study. Detailed clinical history was taken to find out etiology and aggravating factors.

Results: In our study maximum numbers of cases Maximum numbers of cases (127) belonged to the age groups 21 to 30 and 31 to 40 years. The youngest was eight months old and the oldest was 85 years of age. Females (307) outnumbered males (193) in the present study. Food induced urticaria was found in 136(27.2%), due to drugs in 128(25.6%), physical urticaria in 83(16.6%), infestation as a cause of urticaria in 14(2.8%), infection in 16(3.2%), dust in 07(1.2%), atopy in 03(0.86) endocrine disease in 03(0.6%) including thyroid disorder in 1(0.2%),contact with wool in 01(0.29%) and carcinoma in 01(0.2%). In 133(26.6%) patients we were not able to find the cause and those where labeled as idiopathic urticaria.

Conclusion: That there is little relation between cause identified by history and confirmation by investigation. Routine laboratory tests are of limited value in finding the etiology. History taking is most important tool.

Key words: Urticaria, Angioedema, Clinical study, History, Etiology

INTRODUCTION

Urticaria is a Latin word derived from 'urtica' means nettle. Nettle is common variety of wild weed prevalent in Europe. Urticaria is a widespread debilitating condition characterized by intensely itchy, evanescent lesions known as wheals. Various etiological factors have been considered as a cause of urticaria. However in 50 % of cases of chronic urticaria, no cause is found even after extensive investigations.[1] A definite etiology is more commonly found in acute than chronic urticaria.

The perception of food hypersensitivity is much commoner than true. The wheal should recur regularly following meal with particular food item and there should not be any wheal on avoiding that food item or fasting. The prick test, intradermal test and RAST have limited role in diagnosis of food induced urticaria.

There must be causal relation to implicate infection as a cause of urticaria i.e. the infection should be documented during the episode of urticaria and on treating the infection, urticaria should resolve.

Even though thyroid auto antibodies have been repeatedly found in chronic urticaria, its significance in pathogenesis is not clear. Routine test for thyroid auto antibodies is not advised in all cases.

It was observed that there is little relation between identified cause by history and confirmation by investigation in many studies.

MATIRIALS AND METHODS

The prospective study of 500 cases of urticaria was carried out in Skin V D department from June 1995 to May 2010. All the cases having urticaria and or angioedema were included in the study.

An informed consent about study was taken from each patient before enrolling him or her in to the study. All patients were provided information about their disease and its management.

Detailed clinical history was taken to find out etiology and aggravating factors such as: food, history suggestive of septic foci, any illness, ingestion of drugs, self medication, personal and family history of atopy.

Diagnosis was confirmed by elimination of suspected food or drug and rechallenge with same in less severe cases. Only those cases were considered as having infection induced urticaria, in which infection was present during the episode of urticaria and on treating the infec-

tion urticaria resolved.

Thorough general examination, systemic examination, gynecological check up for women, Ear, Nose & Throat (ENT) and dental check up to find out foci of infection were carried out.

Basic investigations like Complete Blood Count (CBC), Erythrocyte Sedimentation Rate ESR), Absolute Eosinophil Count (AEC), urine routine and microscopic examination and stool examination for ova and cysts were carried out. Other relevant investigations according to history were carried out.

RESULT

A study of 500 cases was carried out and their age and sex distribution and associated findings was noted and compared with previous studies.[2,3,4,5] (Table 1A & B) Maximum number of cases 127(25.4%) belonged to the age group 21 to 30 and 31 to 40 years. The youngest case was eight months old and the oldest was 85 years of age. The duration of the disease at the time of presentation varied from less than 24 hours to more than 10 years. (Table 1A&B) Female (307) outnumbered male (193) in present study.

Table 1(A): Age and sex wise distribution of cases of urticaria and /or angioedema.

Age group	Male	Female	Total	% in present study	Sarojini[2] et al
0-10	24	22	46	9.2	2
11-20	29	28	57	11.4	33
21-30	43	84	127	25.4	34
31-40	41	86	127	25.4	15
41-50	30	61	91	18.2	08
51-60	13	17	30	6.0	08
61-70	4	7	11	2.2	01
71-80	8	2	10	2.0	_
81-90	1	_	1	0.2	_
Total	**193**	**307**	**500**	100	**100**

Table 1B: Sex wise comparison of different studies of urticaria and /or angioedema

	Male	Male (%)	Female	Female (%)
Present study	193	38.6	307	61.4
Pasricha[3]	286	83.13	58	16.86
Sarojini[2]	56	56	44	44
Gurinderjit4Singh	46	46	54	54
Kaur S[5]	60	60	40	40

Table 2 A: probable etiology of cases of urticaria and /or angioedema.

Etiology	Male (N=193)	Female (N=307)	Total* (N=500)	Present Study#	Sarojini et al[2] (N=100) #	P Gaiget al[6] (N=147) #	Martina et al[7] (N=220) #	Juhlin et al[8] (N=330) #
Food	51	85	136	27.2	5	9.5	6.8	48
Idiopathic	38	95	133	26.6		53.1		
Drug	59	69	128	25.6	27	2	9	32
Infestation	4	10	14	2.8			1.8	
Insect bite	3	7	10	2.0				
Physical	39	44	83	16.6	32	2	33.2	20
Dust	1	6	7	1.4	2			
Pollen						4.1		
Infection	4	12	16	3.2	35			
Carcinoma	0	1	1	0.2				
Endocrine	1	2	3	0.6	1			
Systemic illness						11.6	1.4	6.5
Atopy	1	3	4	0.8				33.3
Psychological					3			16
Contact	0	1	1	0.2			9	
Allergy						7.5		
Abdominal problems								44
Contact with animals						3.4		
Others						6.8		

*****36 patients multiple etiological factors; #Figures in percentage

Table 2 B: comparison of Probable etiology of urticaria and /or angioedema in different studies

	Male (n=39)	Female (n=44)	Total (n=83)	%In present study	% inSarojini[2] et al
Pressure	24	22	46	9.2	16
Cholinergic	5	6	11	2.2	3
Aquagenic	4	2	6	1.2	2
Solar	2	3	5	1.0	_
Cold	3	3	6	1.2	21

Table 3: Urticaria and Angioedema

	Male	Female	Total
Angioedema	6	9	15
Both	16	36	52
Urticaria	171	262	433
Total	193	307	500

Probable etiologic factors were identified on the basis of history and compared with findings of other studies. (Table 2A)[2,6,7,8] Food induced urticaria (Table 4) was found in 136(27.2%), history of side effects of drugs (Table 5) in 128(25.6%), physical urticaria(Table 2B) in 83(16.6%), infestation as a cause of urticaria in 14(2.8%), infection in 16(3.2%), dust in 07(1.2%),atopic in 03(0.86) endocrine disease in 03(0.6%) including thyroid disorder in 1(0.2%),contact with wool in 01(0.2%) and carcinoma in 01(0.2%). In 133(26.6%) patients we were not able to find cause where we labeled it as an idiopathic urticaria.

Table: 4 Various Foods and Urticaria: Causal relation?

Food	Male (n=51)	Female (n=85)	Total (n=136)	% In present study	% In Pasricha et al[3] (n=40)
Citrus Food	12	25	37	27.21	-
Yoghurt	09	11	20	14.71	-
Milk product	-	-	-	-	05
Multiple	03	15	18	13.24	-
Bajra	01	01	02	1.47	-
Rice	01	01	02	1.47	08
Wheat	-	-	-	-	03
Mathi	01	-	01	0.74	-
Cow Pea	-	01	01	0.74	0 1
Pulse	-	-	-	-	10
Cabbage	01	-	01	0.74	-
Brinjal	07	14	21	15.44	-
Green chili	03	02	05	3.68	-
Lady Finger	01	01	02	1.47	-
Papaya	-	02	02	1.47	-
Orange	-	-	-	-	01
Spinach	-	01	01	0.74	
Potato	-	-	-	-	04
Ice cream	-	02	02	1.47	-
Sweet	01	-	01	0.74	-
Piper mint	01	-	01	0.74	-
Tea	-	-	--	-	02
Unknown	01	-	01	0.74	-
Fish	03	05	08	5.88	-
Chicken	02	01	03	2.21	-
Other Sea Food	-	01	01	0.74	-
Other Non vegetarian Food	04	02	06	4.41	01
Egg	-	01	01	0.74	0 5

Table: 5 Drugs and Urticaria in present study

Drug	Male	Female	Total (%)
Ibuprofen	5	5	10 (7.8)
Other NSAIDS	13	20	33 (25.8)
Aceta-Aminophen	1	7	8 (6.3)
Chloroquine	-	2	2 (1.6)
Cotrimoxazole	1	1	2 (1.6)
Doxycycline	4	-	4 (3.1)
Amoxicillin	5	-	5 (3.9)
Cephelexin	1	2	3 (2.3)
Augmentin	1	-	1 (0.8)
Ketaconazole	1	-	1 (.8)
Vitamin A D	-	4	4 (3.1)
Folic acid (yellow)	-	1	1 (0.8)
Multivitamins (red)	-	1	1 (0.8)
Pseudo Ephedrine	-	1	1 (0.8)
Omeprazole	1	-	1 (0.8)
Depandal m		1	1 (0.8)
Unknown	26	24	50 (39.1)
Total	**59**	**69**	**128 (100)**

DISCUSSION

In present study out of 136 patients of suspected food induced urticaria, 86 improved after complete dietary elimination of suspected food item, 18 showed no response to elimination, 32 lost to follow up.

In Pasricha et al[9] study of 155 patients of suspected food induced urticaria, 30 patients improved after complete dietary elimination of suspected food item, 38 showed no improvement and were considered idiopathic, while 87 were lost to follow up.

Uppal and Shrinivas[10] described a patient who had wheat induced urticaria. Skin prick tests were negative with whole wheat and wheat antigen in commercial food series but were positive with raw wheat components including Samba Rava. Oral challenge with Samba Rava led to urticaria in half an hour. The authors concluded that patient had wheat induced urticaria.

Ronald A. Simon[11] studied 65 subjects (44 women, 21 men; ages 14-67). All had urticaria for > 6 weeks with-

out discernible etiology. Screening challenges to the 11 additives most commonly associated with chronic idiopathic urticaria (CIU) were performed in a single-blind fashion. Subjects continued to take antihistamines at minimum effective dosage. Twenty of the subjects gave a history of adverse reaction to additives, out of which 4 had history of reaction to MSG. The dose of Monosodium glutamate (MSG) given was 2500 mg. He was unable to demonstrate MSG- induced urticaria in any of their CIU patients. He concluded that MSG is an unusual (<3% at most) exacerbant of CIU.

Doeglas et al[12] studied 141 patients with chronic urticaria, collected data over a three-year period in a department of Dermatology. Physical urticaria was found in 55% of patients. Atopy was not more frequent than control group, except in patient with idiopathic urticaria and urticaria facticia. Drugs were not a frequent cause of chronic urticaria in his study, one case of penicillin allergy was reported. Provocation test with Aspirin were positive in 26% of 131 patients in a second section.

Drugs were a common cause of urticaria and angioedema in present study. Commonest drugs were NSAIDS (51), followed by antibacterial drugs in 14 cases. We were not able to find a cause in 50 cases of drug induced urticaria and angioedema.

Juhlin L[8] investigated 330 consecutive patients with recurrent urticaria of 3 months to 40 years duration from 1972-1978, a questionnaire was used. Fifty men and fifty women had only urticaria. The rest had both urticaria and angioedema and most of them were women between 24 and 30 years of age. A personal history of atopy was found in more than one third patients. Nasal polyp, migraine and arthralgia were found in 6-7 % of the patients. Severe psychiatric problems were mentioned by 16%. Abdominal problems mainly gastritis were described by 44%. History of side effects from drugs was found in 32% of the patients. Food was mentioned as a worsening factor by 30% and drinks by 18%. Fruits vegetables and nuts were the most common. Despite all cases with physical urticaria were excluded, physical factors such as exercise was considered to make urticaria worse by 20%. Martina M.A. et al[7] studied 220 patients with urticaria and angioedema. The patients were followed up for 1-3 years. Physical urticaria was found in 73 (33.2%) patients, combination of physical urticaria and chronic idiopathic urticaria was found in 24 (10.9%). Drugs as a provocating factor was found in 20 (9%) patients, confirmed by rechallenge after discontinuation of suspected drugs. Food as an etiological factor was found in 15(6.8%) patients. Eggs, alcohol, beef and apple/ pears were found to be the most likely cause of urticaria and angioedema. In 4(1.8%) out of 10 patients with parasitic infection the complaint disappeared after treatment. The internal diseases probably related to urticaria: Sjogrens syndrome, systemic lupus erythematosus and paraproteinemia were found in 3 (1.4%) and contact urticaria to latex and preservatives in 2 (9%) patients.

In present study 1 case of contact urticaria due to wool was reported.

P. Gaig et al[6] conducted population based study among adults in Spain, in which they questioned 5003 individuals. The results have the limitations of a phone survey. Urticaria was found to be significantly higher in women than in men in the proportion of 4:1 (Table 1). Based on the questionnaire, 17 (11.6%) patients believed that their urticaria was because of some hidden illness, 11 (7.5%) patients thought that it was due to allergy, due to pollen in 6 (4.1%) patients, contact with animals in 5 (3.4%) patients, sun rays in 3(2%) patients, drug allergy in 3 (2%), food in 14 (9.5%), other causes in 10 (6.8%) , unknown etiology in74 (50.3%) and 4(1.8%) persons did not answer or did not know. {So we labeled 78(53.1%) cases as idiopathic in table 2A}

There were 36 cases suspected to have urticaria due to infestation in present study; ova/cyst was detected in 17 out of them. Twelve cases improved with anti-helminthic therapy, 5 showed no improvement. Two cases of scabies with urticaria responded to anti-scabetic treatment.

There was no difference in the presence of ova or cyst in stool of patients, (19.66% in 300) as compared to control (18%) in a study by Ghosh S et al.[13] Following anti-helminthic therapy, in 81% there was no improvement or worsening.

In a study by Godse et al [14]eosinophilia did not correspond to worm infestation. They treated 4 out of 5 patients with worm in stool without any improvement in urticarial episode after treatment.

In present study eosinophilia was detected in 18 cases, not responding to anti-helminthic treatment, history of drugs was there in 4 out of 18.

In another study by Federman DG et al [15] remission of urticaria with eradication of H. Pylori was seen in 30.9%, as compared to 21.7% in which H. Pylori was not eradicated and in 13.5% who were H. pylori negative.

In present study H. Pylori was not detected in any case out of 36 examined.

Five patients responded to antifungal treatment for dermatophytosis out of 16 suspected in present study. The intradermal test for candida was not done.

In a series of 100 patients by James J et al[16], 36% showed intradermal test positivity with candida antigen. After anti-candida treatment, urticaria cleared in almost equal number of patients in prick test positive (8%) and negative group (06%). There was no significant difference between prick test positive and negative individual except atopy (47 % vs. 17 %). So any positive intradermal or prick test should be interpreted with positive clinical evidence.

In present study, 2 patients of urticaria resolved after cure of Mumps and one patient of urticaria with pulmonary tuberculosis responded to AKT.

Seven patients (one male and six females) had urticaria considered to be due to house dust mite (inhalation), based on history. Intradermal test was not done because of non availability. They all improved after avoiding exposure to dust while performing household duties and with use of mask.

Sixty four percent patients of chronic urticaria were shown to have house dust mite based on patients' history, intradermal test and in vitro analysis in Mahesh et al study.[17]A suspected case of inhalant induced urticaria is confirmed by mask test.

In a study by Pasricha et al[9] mask test lead to improvement in 2 cases out of 70, no improvement in 38 cases, while 30 were lost to follow up.

History of atopy was found in 3 cases of urticaria in present study but causal relation with urticaria was not proved.

Sarojini et al [2] showed no difference in the incidence of personal or family history of atopy in patients of urticaria as compared to control.

One patient with chronic urticaria responded to antithyroid treatment in present study. Routine test for thyroid auto antibodies was not done in all cases.

The frequency of thyroid autoantibody was significantly higher in patient with chronic urticaria than in healthy control (29.28% vs. 5.52%, $p< 0.001$), on comparing 140 patients of chronic idiopathic urticaria with 181 age and sex matched healthy volunteers observed by Cebeci et al.[18]

Ninety patients (14.42%) out of 624 of CIU had thyroid auto antibodies (TA) as compared to less than 6% of normal subjects which had TA in study by Leznoff et al.[19]

One patient had urticaria in pregnancy, resolved after delivery. Another patient had urticaria regularly during menstrual period in present study.

Emotional stress may be the precipitating factor in some cases. Shobana et al reported 3 patients of resistant chronic urticaria responded to oral Imipramine (50 to 75 mg per day for 8 weeks).[20]

We had 15 cases of angioedema without urticaria, 52 patients had both urticaria and angioedema, while 433 patients had urticaria without angioedema.

Lorenza C. al[21] examined 929 consecutive patients for recurrent angioedema without urticaria, 153 patients were lost to follow up. Among the 776 patients with adequate data, these types of angioedema were identified, 124(16%) related to external agents such as drug, insect bite or foodstuff; 85(11%) related to angiotensin converting enzyme inhibitor; 55(7%) associated with autoimmune diseases or infection; and 197 (25%) caused by C1 inhibitor deficiency.

Urticaria has been reported with insertion of metal pin in bone, dental amalgam and dental prosthesis by Espana A. et. al.[22]

CONCLUSION:

Food was a common cause of urticaria and angioedema in present study 27.2% of cases, followed by drugs in 25.6%. In 26.6% patients we were not able to find cause.

No proved case of dental infection as a cause of urticaria was found in present study. There are very few reports to suggest dental infections as a cause of urticaria, hence routine screening for dental infection does not help much.

Routine laboratory tests are of limited value in finding the etiology. Diagnosis is mainly done on basis of history. History taking is most important tool to find out cause of urticaria.

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