Original Article

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Aetiological Approach of Urticaria and Angioedema in Patients Attending Skin Department at Tertiary Care Hospital

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Abstract

Background:Urticaria is a vascular reaction characterized by appearance of wheal which is immunological or non-immunological.Urticaria is one of the most distressing, frustrating and challenging dermatologicalconditions for both patients and doctors.Although usually not life threatening, it often impairs quality of life to a degree comparable with triple coronary heart disease.Only curative treatment is to find out cause and eliminate. ***Aims:*** To study the various aetiology of urticaria and to perform Autologous Serum Skin Test (ASST) as a screening test in chronic spontaneous urticaria (CSU).***Materials and Methods:***A prospective study of aetiology of urticaria in 312 patients was carried out over a period of 3 years in skin outpatient department at tertiary care hospital.The diagnosis was based on history and confirmed by elimination and rechallenge in less severe cases of food and drug.CSUwas diagnosed after excluding other aetiology and ASST was performed in all cases of urticaria labelled as CSU. Specific investigations like TSH were done as and when necessary.***Statistical analysis:*** mean, standard deviation, chi square test, z test. ***Results:***Most common type wasCSU(28.21%) followed by food (25.64%), drugs(21.47%) and physical urticarial (10.89%).Urticaria associated with infection in 4.8%, multiple causes(2.88%) and by aerosol (dust/mite/pollen in 2.24%). Atopy in 1.28%, mosquito bite, associated with thyroid disease, contrast induced,premenstrual precipitation etc. were found in <1%. Among CSU 19.31%were ASST positive.***Conclusion:*** Most common type of urticaria was CSU followed by food and drugs. Among food most common cause was citrous food. Most common drug causing urticaria were NSAIDS followed by Sulphonamides and cephalosporin.

Keywords: Urticaria; Angioedema; Aetiology; CSU; ASST.

Introduction

Approach to the patient with urticaria first demands a search for the aetiology, whether endogenous which is triggered by emotions or occult systemic disease.Exogenous which is precipitated by inhalation, ingestion, injection, infection or physical.Urticaria may be acute (the disease resolving in less than 6 weeks) or chronic (continuous disease lasting for 6 weeks or more).It is very difficult to find out cause, majority of cases we were not able to find out cause were labelled as idiopathic or chronic spontaneous urticaria (CSU) in chronic cases.The autologous serum skin test (ASST) is currently the best in vivo clinical test for detection of autoantibodies in CSU.

Materials and Methods

In a present study, total 312 patients of all age group having clinical features of urticaria (wheal) who fulfilled the inclusion criteria were included. They were selected from the patients attending Dermatology Outpatient Department (OPD) of GMERS Medical College and Hospital, Gotri, Vadodara and studied during period of January 2015 to December 2018.

A prospective study of etiology of urticaria in 312 patients was carried out over a period of 3 years in skin outpatient department at tertiary care hospital.An informed consent about study was taken from each patient before enrolling him or her into the study. All

patients were provided information about their disease and its management. Detailed clinical history was taken to find out aetiology and aggravating factors such as: food, history suggestive of septic foci, any illness, ingestion of drugs, self-medication, personal and family history of atopy etc.[3]Thediagnosis was based on history and confirmed by elimination and rechallenge in less severe casesof urticaria suspected due to drugs and food. Routine laboratory investigations in terms of complete blood count, liver and renal function test,blood sugar and urine analysis were done on all cases. ASST was performed after excluding other aetiology and specific investigations like TSH were done as and when necessary. Mask test was done in suspected cases of urticaria due to dust, aerosol and pollen.Antihistamines were discontinued(At least 2 days for short acting antihistaminics,6 days for Desloratadine and 2 weeks for Doxepin). Systemic steroids were discontinued for at least 2 weeks.

The ASSTwas performed by injecting 0.05 ml of the patient's own serum intradermally into the left flexor forearm 2 inches below the antecubital crease and a saline control 0.05 ml2 inches away from it on same forearm.A reading of the wheal and flare was taken after 30 minutes. A wheal and flare of more than 1.5 mm diameter than that of the control was considered positive.It is calculated by using D = (d1 + d2) / 2, where d1=maximum vertical and d2= maximum horizontal diameters of the wheals, D is average diameter.

Results

Total 312 patients attended outpatient department of dermatology at a tertiary care hospital were enrolled. Causality relationship was established on basis of precipitating/exacerbating factors, investigations and by exclusion.

Age in years	Male	Female	Total	Percentage (%)	Patel RM et al [3](%)
0 - 10	6	9	15	4.81	9.2
11 - 20	19	23	42	13.46	11.4
21 - 30	38	44	82	26.28	25.4
31 - 40	27	48	78	24.03	25.4
41 - 50	18	31	49	15.70	18.2
51 - 60	12	18	30	9.61	6.0
61 - 70	10	6	16	5.13	2.2
71 - 80	0	1	1	0.32	2.0
81 - 90	1	1	2	0.64	0.2

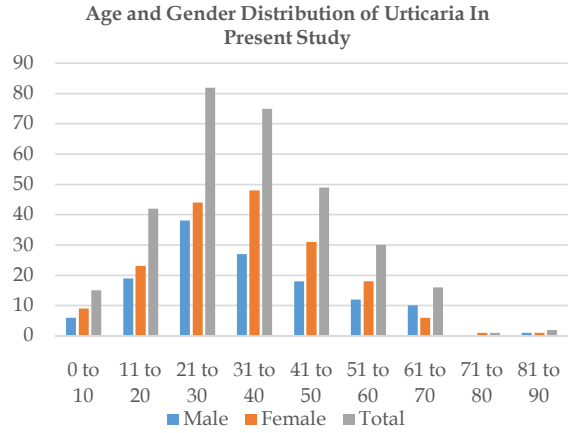

Fig. 1: Age and gender distribution in present study.

Table 2: Urticaria and Angioedema

	In present study			Patel RM et al[3]		
	Male	Female	Total	Male	Female	Total
Angioedema	5	8	13	6	9	15
Both	15	18	33	16	36	12
Urticaria	111	155	266	171	262	433

Table 1: Age and sex wise distribution of cases of urticarial.
Table 3: Probable etiology of urticaria and /or angioedema.

Aetiology	Present study Total	Present study Percentage (%)	Sarojini et al[1] (N=100) (%)	Juhlin et al[2] (N=330) (%)	Patel RM et al[3] (N=500) (%)	Patel SJ et al[4] (N=300) (%)
Idiopathic	88	28.21	-	53.1	26.6	-
Food	80	25.64	5	9.5	27.2	20
Drug	67	21.47	27	2	25.6	18.33
Physical	34	10.89	32	2	16.6	15.66
Infection	15	4.80	35	-	3.2	41
Aerosol	7	2.24	-	-	1.4	4
Multiple Cause	9	2.88	-	6.8	-	-
Associated with Thyroid Disease	3	0.96	1	-	0.6	-
Autopsy	4	1.28	-	7.5	0.8	15
Premenstrual	1	0.32	-	-	-	-
Colour Work	1	0.32	-	-	-	-
Insect Bite	2	0.64	-	-	2	-
ContrastInduced	1	0.32	-	-	-	-

The mean age of patients was 34.67 yearsand standard deviation 14.74. There were 131(41.98%)Male and 181(58.01%)Female (Fig.1). In present study we found that majority of the patients 82 (26.28%) belonged to 21-30 years of age group, followed by 75 (24.03%) belonged to 31-40 years of age. Minimum number of patients were 1 (0.32%) who belonged to 71-80 years of age group.

The most common type was CSU (28.21%) followed by food (25.64%), drugs (21.47%) and physical urticaria (10.89%). Followed by Urticaria associated with infection in 4.8%, multiple causes (2.88%) and by aerosol (dust/mite/pollen in 2.24%). Atopy in 1.28%, mosquito bite, associated with thyroid disease, contrast induced, premenstrual precipitation etc. were found in <1%.

Among drugs, NSAIDS28(42%) were most common in present study followed by Sulphonamides in 11(16%) andCephalosporin in7(10%). History ofAnti Koch's Treatmentwas present in 5(7%) followed byUnknown drugin 7(10%) and Losartan in3(4%). Antibacterial like Augmentin was found in 2(3%), Ciprofloxacin in 1(2%), Metronidazole1(2%) andNorfloxacin1(2%) in present study.

Table 4: Drug and Urticaria.

Drug	Total	Percentage (%)	Patel RM et al[3] (%)
NSAIDS	28	42	33.6
Sulphonamides	11	16	-
Cephalosporin	7	10	2.3
AKT	5	7	-
Unknown drug	7	10	39.1
Losartan	3	4	-
Augmentin	2	3	3.9
Ciprofloxacin	1	2	-
Metronidazole	1	2	-
Norfloxacin	1	2	-

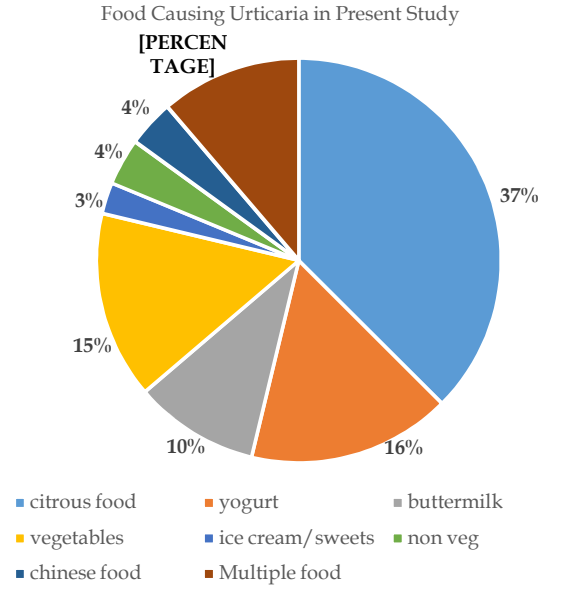

Fig. 2: Food Causing Urticarial.

Fig. 3: Centrifuge Machine(Model: CF-866;Lab line).

Fig. 4: Centrifugation at the rate of 2500 rpm for 15 minutes.

Fig. 5: Autologous serum skin test kit used in present study.

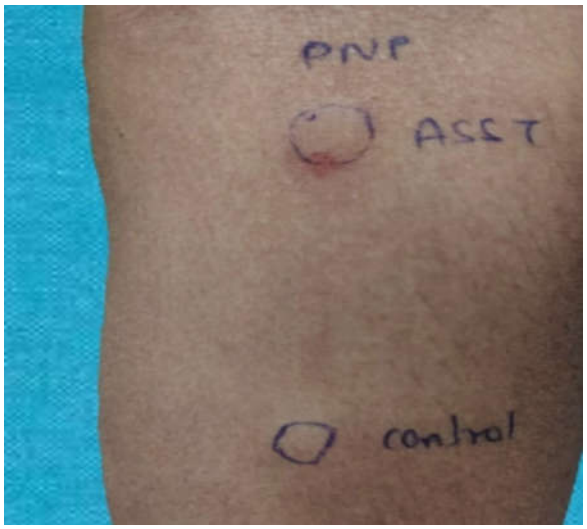

Fig. 6: Positive ASST showing induration at test site with diameter >1.5 mm than control.

Fig. 7: Wheals.

Table 4: Various Foods and Urticaria: Causal relation?

Food	Total in present study	Percentage in present study (%)	Pasricha Et al[4] (n=40) (%)	Patel RM et al[3] (%)
Citrous food	30	37	-	27.21
yogurt	13	16	-	14.71
buttermilk	8	10	-	-
vegetables	12	15	-	22.07
Ice cream/sauce	2	3	-	1.47
Non vegetarian	3	4	6	8.84
Chinese food	3	4	-	-
Multiple food	9	11	-	13.24
Milk products	-	-	5	-
Rice	-	-	8	1.47
Wheat	-	-	3	-
Pulse	-	-	10	-
Orange	-	-	1	-
Cow pea	-	-	1	0.74
Potato	-	-	4	-
Tea	-	-	2	-

Among food, citrous food was most common in 30(37%) followed by yogurt in 13(16%), buttermilk in8(10%) and vegetables 12(15%). History of precipitation by Ice cream/sauce in 2(3%), non-vegetarian food in 3(4%), Chinese food in 3(4%) and multiple foods in9(11%) in present study.

Among 88 CSU cases 17(19.31%) were ASST Positive and 71(80.68%) were negative. Among 51 females with CSU, 10(19.60%) were positive to ASST and 41(80.39%) were negative; Out of 37 males, 7(18.91%) were ASST positive and 30(81.08%) were negative.There was no statistical significance of association between gender and ASST positivity (**P=0.93**).

Among 17 ASST positive patients the mean age ranged between 35.88±10.22 years. There was no statistical significance between ASST positivity and age. (**P=0.47**)
Among 88 CSU patients, 15 had history of urticaria and angioedema, out of which 4(26.66%) were ASST positive and 11(73.33%) were negative for ASST. There was nostatisticallysignificant association between ASST positivity and angioedema. (**P=0.42**)

Discussion

In present study we found that majority of the patients 82 (26.28%) belonged to 21-30 years of age group, followed by 75 (24.03%) belonged to 31-40 years of age. Minimum number of patients were 1 (0.32%) who belonged to 71-80 years of age group. The mean age of patients was 34.67±14.74 years. Study done by Dharani et al[5], in which age distribution ranged between 18-70 years, with maximum number of chronic urticaria patients belonging to 21- 30 years (37%) followed by 31-40 years (21%). The mean age distribution in Chronic Urticaria patients was 36.32±12.85 years.

In present study out of 88 patients of CSU, in which ASST was performed, 17(19.31%) were ASST positive. In Dharani et al[5] out of 100 patients of CSU, 37% were ASST positive. In Patel et al[6]out of 250 patients of CSU, 60% were ASST positive. In present study out of angioedemapatients, 26.66% were ASST positive.In Dharani et al[5]
48.6% were ASST positive.

In present study out of 97 patients of suspected food induced urticaria, 52 improved after complete dietary elimination of suspected food item, 17 showed no response to elimination were considered as CSU, 28 lost to follow up. In Pasrichaet al7study 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.

Doeglaset al[9]studied 141 patients with chronic urticaria in which Physical urticaria was found in 55% of patients. In present study,10.89% had physical urticaria. Sarojiniet al[1] studied 100 chronic urticaria patients, urticaria due to drug and infections were found 27% and 35% respectively. In present study, urticaria due to drug and infections were found 21.47% and 4.80% respectively.P Gaiget al[10] studied 147 chronic urticaria patients, in which 51.1% were labelled idiopathic. Urticaria due to drugs were 2% and food were 9.5%.

In a study by Pasrichaet al[7] mask test led to Improve ment in 2 cases out of 70, no improvement in 38 cases, while 30 were lost to follow up.

Most cases of chronic spontaneous urticaria wereconsidered as an idiopathic. It has recently been accepted that autoimmunity plays a critical role in its pathogenesis in some of the patients.Urticaria may be caused or exacerbated by several drugs. More common culprits include aspirin, other nonsteroidal anti-inflammatory drugs, opioids, ACE inhibitors, and alcohol.A single patient may have more than one type.In 1983, Leznoff et al[11],suggested an autoimmune basis for the urticaria. This was after the observation that there was an association between thyroid disease and Chronic Spontaneous Urticaria. After that in 1988 Gruber *et al*,detected functional anti-IgE antibodies and proposed that these could be the cause of urticarial wheals. It is now well-established that about 30-50% patients with Chronic spontaneous Urticaria have circulating functional auto antibodies against the high-affinity IgE receptor (FCeRIa) or against IgE. Also, urticaria has been associated with a number of autoimmune diseases.A few of them are systemic lupus erythematosus, cryoglobulinemia, neoplasms, juvenile rheumatoid arthritis and autoimmune thyroid disease, including Grave's disease.Urticaria is a feature of Muckle-Wells syndrome (amyloidosis, nerve deafness and urticaria) and Schnitzler syndrome (fever, joint/bone pain, monoclonal gammopathy and urticaria).About 30%-50% of patients with chronic idiopathic urticaria have circulating histamine releasing autoantibodies to the high-affinity IgE receptor FceRI on basophils and mast cells or, less commonly, antibodies to IgE. The term autoimmune urticaria is increasingly being accepted for this subgroup of patients.The autologous serum skin test (ASST) is currently the best in vivo clinical test for detection of in vitro basophil histamine-releasing activity.

Urticaria has been reported to be associated with a number of infections; however, these associations are not strong and may be spurious. Infectious agents reported tocause urticaria include hepatitis B virus, Streptococcu
s and Mycoplasma species,Helicobacterpylori, Mycobac
-terium tuberculosis, and herpes simplex virus[8]. Fungal infections such as onychomycosis, tinea pedis and candida have beenconsidered aspossibleassociations.

Some authors suggest that the aetiology of disease for a portion of Chronic Spontaneous Urticaria patients is a pseudo allergy to food ingredients. The concept of pseudo allergic reactions was introduced in 1983 to describe responses to a food or chemical that mimicked the signs and symptoms of an allergic reaction but without isolation of specific IgE antibodies against the offending agent. Implicated agents include preservatives,sweeteners, artificial food dyes, aromatic volatile compounds inherbs, wine, salicylic acid, orange oil, alcohol and high dietary fats.Chronic Spontaneous Urticaria exacerbated by specific foods is fairly common, particularly among infants and children. Frequently implicated food additives are tartrazine, other azo dyes including amaranth and sunset yellow, benzoic acid compounds, etc.

The basophil histamine release assay is currently the "gold standard" for detecting functional autoantibodies in patients with chronic idiopathic urticaria. However, this bioassay is difficult to standardize because it requires fresh basophils from healthy donors and is time consuming. Western blotting and other non-functional assays, including enzyme-linked immunosorbent assay and flow cytometry using chimeric cell lines expressing the human FceRI, may be useful for screening sera in the future but need to be validated. Hence, ASST is the only practicable test available to clinicians to detect autoimmune urticaria.

In the Western literature, a positive ASST has been reported in 25% to 45% of patients of chronic idiopathic urticaria.The ASST has a sensitivity of 70% and a specificity of 80% when read as a pink serum-induced wheal 1.5 mm or greater than an adjacent normal saline control injection at 30 minutes, although experience is required to obtain reproducible results.A positive test is suggestive but not diagnostic of an autoimmune basis for patient's urticaria. Confirmation is needed by in vitro testing of the patient's serum for anti-Fc RI or anti-IgE autoantibodies.[13]

Patients with autoimmune autoantibodies have no distinctive diagnostic clinical features. Autoimmune and non-autoimmune cases are indistinguishable clinically and histologically.[13]However, they do tend to have more severe urticaria. Nettis, et al found ASST cannot be used alone either to predict severity of urticaria or to define it as 'autoimmune'.We found the incidence of autoimmune urticaria to be 19.31% which is much lower than reports from Western countries. This test can be done by a dermatologist to determine whether chronic idiopathic urticaria is autoimmune in origin. This is especially important from a management viewpoint since immunosuppressive therapies may be tried if conventional approaches of management are unsuccessful.[12]

Conclusion

Most common cause of urticaria in present study was chronic spontaneous urticaria,followed by food and drugs. Among food most common cause was citrous food. Most common drugs causing urticaria were NSAIDS followed by Sulfonamides and cephalosporin. Laboratory tests were not of much help in making an etiological diagnosis.Hence for establishing a causativeagent, through history and physical examination followed by judicious use of laboratory test are indicated. Routine laboratory tests are of limited value in finding the aetiology. Diagnosis is mainly done on basis of history. History taking is most important tool to find out cause of urticaria[5]. A positive ASSTtest is suggestive but not diagnostic of an autoimmune basis for the patient's chronic spontaneous urticaria.

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