CLINICOETIOLOGICAL PROFILE AND OUTCOME OF URTICARIA IN CHILDREN AGED 1 MONTH TO 15 YEARS IN A TERTIARY CARE CENTER - A DESCRIPTIVE STUDY

Ebin Roshan Paul, Prameela Joji, Asha Zacharia, Anjali Ann Chacko, Varsha V P, Aiswarya Das

1. Dr Ebin Roshan Paul, Assistant Professor, Department of Paediatrics, PK DAS Institute of Medical Sciences, Ottapalam, Kerala, India.
2. Dr Prameela Joji, Medical Superintendent and PICU Consultant,KIMSHealth Hospital, Trivandrum, Kerala, India.
3. Dr Asha Zacharia, Consultant Dermatologist, KIMSHealthHospital, Trivandrum, Kerala, India.
4. Dr Anjali Ann Chacko, Assistant Professor, Department ofPaediatrics, PK Das Institute of MedicalSciences, Ottapalam, Kerala, India.
5. Dr Varsha V P, Assistant Professor, Department ofPaediatrics, PK Das Institute of MedicalSciences, Ottapalam, Kerala, India.
6. Dr Aiswarya Das,Assistant Professor, Department ofPaediatrics, PK Das Institute of MedicalSciences, Ottapalam, Kerala, India.

Correspondence: Dr Ebin Roshan Paul, ebinroshan@gmail.com, 7558857571

Address: Flat 132, Doctors' Apartment,PK Das Institute of MedicalSciences, Ottapalam, Kerala,India, Pin 679522

ABSTRACT

INTRODUCTION: Urticaria is a common condition in paediatric age group with highest impact on quality of life. Despite the ease of diagnosis etiology of urticaria is often difficult to establish even after extensive investigations and follow up. Urticaria Activity Score (UAS) which is a well-established Likert-type symptom intensity scale (0 to 3) measures the disease severity and monitor treatment results. We used UAS score at time of presentation for assessing the severity and monitoring response.

OBJECTIVE: To determine the Clinicoetiological profile of urticaria in children and its outcome based on duration of illness and UAS scoring.

METHODOLOGY: We conducted a descriptive study of urticaria in 144 children aged 1 month to 15 years at KIMS Hospital, Trivandrum from April 2015 to March 2017.

Children who presented with clinical features of urticaria were enrolled in to our study. Clinicoetiological profile was determined based on history and relevant investigations. We scored the severity of urticaria based on UAS (Urticaria Activity Score) system at time of presentation and final outcome was noted in terms of duration of illness in hours.

STATISTICAL METHODS: The statistical data was analyzed using the software SPSS version 16. All the numerical data were expressed as mean standard deviation. Correlation between duration of illness and UAS score were analyzed with spearman correlation. A p-value <0.05 was considered as significance.

RESULTS AND DISCUSSION: Mean age of our study population was 5.6 +/- 3.3 years. Of that more than ¾ of the population had acute urticaria 75%(n=108) others had chronic urticaria 5.6%(n=8), acute on chronic urticaria 9.7%(n=14), acute on recurrent urticaria 9.7%(n=14). Etiological profile showed idiopathic (27.8%) followed by equal numbers were triggered by infection (22.9%) and food (22.9%). Mean duration of illness was 66.0 hours (2.75 days). There was a statistically significant positive correlation between UAS score and duration of illness (p value <0.05) and correlation coefficient (r^2) was (0.569).

CONCLUSION: Acute urticaria was the commonest presentation in our study population. Even though the etiology remained idiopathic in majority of cases infection and food were identified as the significant triggers. There was statistically significant positive correlation between duration of illness and UAS scoring. Initial UAS score at presentation can be used to predict the duration of illness and severity.

Key words: Urticaria, clinical profile, etiology, UAS, prognosis, children.

INTRODUCTION AND BACKGROUND

Urticaria (hives) probably is one of the oldest diseases, as old as antiquity known to human kind and remained as subject of challenge to medical science, despite extensive research studies. Urticaria is a common skin condition in children presenting as itching, redness, wheals and edema. The diagnosis is often based on the clinical findings, but in contrast to its easiness of diagnosis, etiological factors are often very difficult to determine. In most of cases the disease is relatively mild but it is recurrent and frustrating for both the parents and the treating physicians. Rarely it manifests as systemic anaphylaxis, which may be life threatening also.

Urticaria is a common disease in pediatric age group with highest impact on quality of life and requires frequent visits to pediatric emergency room, outpatient department and inpatient department. It is estimated to affect 15% to 25% of population at some point in their life.[1]Urticaria, commonly called ‘hives,’ has a long rich history in documented medicine dating back at least to the 10th century B.C when it was called ‘Feng Yin Zheng’ in China. Many cultures have described urticaria in ways and different names. In the 4th century B.C, Hippocrates noted the similarity

between urticaria and contact with stinging nettles, and insect bites and called the condition as 'cnidosis'.[2]

Urticaria is usually presented as a recurrent, transient, pruritic, erythematous, raised wheals, with flat tops and edema that may become tense and painful. The wheals are transient, and in most types last for less than 24 hours.[3] They can, however become confluent and form plaques. The area surrounding the wheal is commonly erythematous but well circumscribed and blanches with pressure. Urticaria may coalesce and thus creates appearance of irregular margins, but remains well defined. Typical urticarial lesions are markedly pruritic and not associated with pain or burning sensation mostly transient in nature, last for few hours to days and leaves without any scar or dyspigmentation. Atypical urticaria lesions can be non-blanching, burning in character, last for more than 24 hours and leaves with residual dyspigmentation and scar formation. Whereas urticaria occurring as the result of dermal edema and subcutaneous edema will lead to the clinical picture of angioedema. Angioedema is non-pitting edema occurs alone or in combination with urticaria, including urticarial vasculitis and the physical urticarias.[4] Sites of involvement include the eyelids, lips, tongue, larynx, and gastrointestinal tract as well as the subcutaneous tissue. Angioedema without urticaria is unusual and affects approximately 10 percent of patients and involves non-central regions such as face, tongue, throat, extremities and genitals.[5]

Symptomatic treatment with medication may not completely suppress all the symptoms in all patients. Sometimes the poor response of the symptomatic treatment and the inability of the physician to explain the cause and prognosis of condition may put the parents at immense stress and lead to various costly and unwanted investigations. Large clinical studies have shown that frequency of severe underlying diseases in patients with urticaria is low. In the literature it has been suggested that too much money and time are spent on routine investigations and that more time should be spent on history taking. Despite these recommendations, extensive routine screening procedures are still used in urticaria cases.

Most of the studies were done in western countries and Indian studies are very few. In this context we did this study to know the clinicoetiological profile of urticaria in children aged 1 month to 15 years who are attending the OPD, IP and emergency room of Department of Pediatrics in KIMS Hospital, Trivandrum.

AIMS & OBJECTIVES

Clinicoetiological profile and outcome of urticaria in children aged 1 month to 15 years in a tertiary care center.

1) Primary Objective

To study the clinicoetiological profile of urticaria in children aged 1 month to 15 years in a tertiary care center.

2) Secondary Objective

To study the prognosis of urticaria in children aged 1 month to 15 years in terms of duration of illness and UAS scoring in a tertiary care center.

REVIEW OF LITERATURE

Burden of disease in India

Urticaria is a worldwide disease which can present at any age of life. The life time incidence of urticaria in general population is around 15 to 25% .[1]

Clinical features of Urticaria

Classification of urticaria is most often based upon clinical characteristics rather than etiology. Unfortunately, it is often difficult to determine the etiology or pathogenesis of individual cases of urticaria and many cases remain idiopathic. Urticaria is considered acute if symptoms are present for less than 6 weeks duration and chronic if they are present for more than 6 weeks. If the duration of symptom free periods between urticaria episodes is longer than 6 weeks and if episodes last less than 6 weeks, urticaria is considered to be recurrent.[6]The distinction is important because the mechanism of urticaria formation and the therapeutic approaches are different in each instance.

Acute Urticaria is defined as lesions last less than 6 weeks and individual lesions usually resolve in 24 hours, occur more commonly in pediatric population. Etiological data suggest that around 50% of patient cause is idiopathic and due to upper respiratory tract infection in 40%, drugs in 9 % and to food in 1%[7]. Acute urticaria is caused by foods (peanut, shellfish, egg, meat) medications (like B lactam

antibiotics), insect bite (Honey bee, yellow jacket, hornet, wasp, fire ant), contact with an external agent (latex, animal hair, nettle plant and pollen), infections (bacterial, viral, fungal) and idiopathic cause.[3]

Chronic urticaria is defined as the development of cutaneous wheals that occur on a regular basis for >6 weeks with individual lesion lasting from 4 to 36 hours. The symptoms can be severe and can impair health-related quality of life.[8] Etiology of chronic urticaria of most cases is idiopathic rest include physical (dermatographism, cold, pressure, solar, aquagenic, vibration), rheumatologic (SLE, Juvenile rheumatoid arthritis), endocrine (hypo/hyperthyroidism),neoplasia(lypmphocytosis,mastocytosis,leukemia),Angioedema(hereditary angioedema, ACE inhibitor, acquired angioedema).[3]

Pathogenesis of Urticaria

The mast cell is the principal effecter cell of urticaria. Mast cells are distributed throughout the body but vary in their response to stimuli. All mast cells express high affinity IgE receptors on their cell surface which enables their involvement in IgE dependent allergic reactions. The key mediator in the pathway is Histamine along with-it TNF (tumor necrosis factor), various interleukins IL-3,4,5,6,8,13 plays a role. Histamine, TNF and IL-8 up regulates the expression of adhesion molecules on the endothelial cells and encourage migration of circulating inflammatory cells from the blood in to the urticarial lesion. IL-4 promotes further IgE production that causes the positive feedback.[7]

Etiology of Urticaria

Due to the acute nature of the illness, first episode of urticaria /angioedema may occur without an identifiable stimulus. Hives that occur within several minutes to a few hours after ingestion of a food or medication or occurring during an illness allow the causative agents to be identified from a detailed history taking. The treating physician must focus on clinical history, in particular on medication, dietary supplements, foods, contact exposure, insect bites and any associated comorbid illness. Etiology of urticaria is difficult to establish even after extensive investigation and follow up. [3] In children, reports of success in identifying a cause for the urticaria range from 21% to 83%.[9] Common causes of acute urticaria include foods, drugs, insect bite etc. In many children we can find out a recent or intercurrent history of a

viral infection as a likely trigger. Infection, not allergy, appears to be the most common cause of acute urticaria in children. In some cases of food allergy, serum IgE levels have been used as a positive predictor for food challenge test.[10, 11, 12] Parents are advised to keep a food diary, recording the foods eaten during the day and symptoms. These are retrospectively analyzed and suspected food items are avoided from the diet and reintroduced in a systematic fashion. Despite of all the efforts no etiology is evident and management of the episode is mainly based on symptom control.

Table 1: Etiology of Acute Urticaria [3]

1. Foods	Egg, milk, wheat, peanuts, tree nuts, soy , shell fish ,fish , strawberries.
2. Medications	Suspect all medications.
3. Insect bite	Hymenoptera (honey bee, yellow jacket, hornet, wasp, fire ants), biting insects.
4. Infections	Bacterial, viral, parasitic, fungal infections.
5. Contact allergy	Latex, pollen, animal saliva, nettle plants, caterpillars.
6.Transfusion reactions	Blood, blood products, IV immunoglobulin.

The lack of an identifiable cause in chronic urticaria is difficult for both parents and treating physician to accept. This will eventually lead in to many unnecessary and invasive procedures and test in children.[5,13,14] A thorough medical history and diet history must be taken in chronic urticaria including any herbal item exposure must be obtained since some herbal items like cranberry, honey bee royal jelly, hypericum, garlic, ginger, glucosamine, horseradish, phytoestrogen, propolis as well as herbal soaps are associated with etiology.[15] Medication and foods are much less frequently implicated as causal for chronic urticaria than for acute urticaria. In case of cold induced urticaria an ice cube placed on patient's skin for 5 minutes will cause hives to appear.[16] Aquagenic urticaria can be evoked by application of room-temperature water compress directly to the skin. The diagnosis of aquagenic urticaria can only made if all other causes of physical urticaria are ruled out.

Table 2: Etiology of Chronic urticaria[3]

1.Idiopathic	60-70 % of chronic urticaria.
2.Physical	Dermatographism, cholinergic urticaria, cold urticaria, solar pressure, vibratory urticaria, aquagenic urticaria.

3. Autoimmune diseases	SLE, JIA, thyroid diseases, celiac disease, IBD.
4. Autoinflammatory/periodic fever syndromes	Neonatal onset multisystem inflammatory disease, Familial cold autoinflammatory syndrome.
5. Neoplastic	Lymphoma, Leukemia
6. Angioedema	Hereditary angioedema, acquired angioedema, angiotensin-converting enzyme inhibitors

Urticaria Activity Scoring (UAS) [17]

The 2009 EAACI/GA2LEN/EDF/WAO diagnosis guideline recommends using a direct well-established scale, urticaria activity score (UAS) which evaluates the main disease characteristics (itch, presence, and number of wheals) on a Likert-type symptom intensity scale (0 to 3) (Table III) to measure disease severity and monitor treatment results. The UAS assigns a score from 0 (no disease activity) to 3(intense activity) for each of the two key urticaria symptoms, wheals and pruritus. The sum of the scores represents disease severity on a scale from 0(minimum) to 6(maximum). The UAS has been used in numerous controlled activities and daily clinical practice worldwide.[18] Since the UAS can change from one day to another, various authors recommend using the sum of the UAS scores over 4 consecutive days (UAS 4) or over 7 days to compensate for these fluctuations. In this study UAS scoring at the time of presentation is taken for follow up.

Table 3: Urticaria Activity Score (UAS) [17]

Score	Wheals	Pruritus
0	None	None
1	Mild (<20 wheals /24 hours)	Mild (present but not annoying or troublesome)
2	Moderate (20-50 wheals/24 hours)	Moderate (troublesome but doesn't interfere with normal daily activity or sleep)
3	INTENSE (>50 wheals /24 hours or large confluent areas of wheals)	INTENSE (severe pruritus, which is troublesome to interfere with normal daily activity or sleep.)

Treatment of Urticaria

The main aim of treatment in urticaria is symptom control. This usually includes identification and elimination of the cause of urticaria and medication therapy to control symptom and attain relief to the child and follow up in OP basis. Mild cases of urticaria are treated on OP basis with oral medication and planned home based management. Parents were counselled about the clinical condition of the child and danger signs are properly explained before sending home. They are also counselled to keep a symptom diary and daily diet list, and these are reviewed in op on follow.

In acute urticaria according to 2013 EAACI/GA2LEN/EDF/WAO management guideline, due to the fluctuating nature of the disease and chances of spontaneous remission at any time during the disease period continued or alternative drug therapy should be done and should be revaluated.

H1 Antihistamines

Antihistamines are the primary agents used in the treatment of acute urticaria. They are divided into older, first-generation agents and newer, second-generation agents. Second line antihistamines have got less blood brain barrier penetration, less sedation and side effects than the first-generation ones. So, they are considered as first line therapy. Most of the first-generation antihistamines (eg: Diphenhydramine, Chlorpheniramine, Hydroxyzine) has got side effects and should be avoided if possible. They can be used if the second-generation medications (eg. Cetirizine, Loratadine, Fexofenadine) are not available or the benefits outweigh the side effects of first-generation ones.

H2 Antihistamines

Nearly 15 percentage of histamine receptors in skin are histamine type 2 receptors. Thus the addition of a histamine type 2 receptor blocking medication is a rational adjunct that may provide benefit. H2 antihistamines include ranitidine, famotidine, cimetidine. Caution should be used with cimetidine since it increases the level of other drugs in the serum. The combination therapy with H1 and H2 antihistamines may be more effective than H1 antihistamines in treatment for urticaria.

Glucocorticoids

A brief course of systemic corticosteroids (usually a week or less) may be added to the antihistamine therapy to control the persistent and severe symptoms.[19,16] They good in reducing the itch and helps in faster resolution of urticarial rashes but not recommended for long term therapy. Glucocorticoids will not inhibit the mast cell degranulation but they probably act by suppressing a variety of contributing inflammatory cascade. A short course of prednisolone 2 mg/kg/day is used in addition to anti histamines. Anti histamine therapy should be continued during and after the course of glucocorticoid therapy because of chance of exacerbation while steroids are tapered or stopped.

Leukotriene receptor antagonists

Patients who are resistant to antihistamine therapy can be given a trail of 3-4 weeks of lekotriene receptor antagonist (eg. Montelukast 4-10 mg once daily) therapy. Evidences are less in favour of these agents.

Avoidance of known triggers and Prevention

Another aspect of the management of chronic urticaria involves prevention.[19, 16] For patients with physical urticaria, avoidance of triggers or minimization of trigger exposure is important. Parents were counselled to remove a known trigger if present in daily activity. Certain cases of drug allergy they are advised to avoid using them in future life also. They should be mentioned in hospital data base and discharge summary for future reference. In known case of food allergy parents are advised to restrain from those items. For the patients with urticaria due to underlying systemic illness, the treatment of the underlying illness will produce the resolution of the symptoms.

Current literature

Kozel *et al*[20] in his study conducted in Netherlands 1994 among 220 patients of a secondary and tertiary care centre tried to assess the value of extensive laboratory screening for the identification of causes in patients with chronic urticaria and angioedema. With a questionnaire and the limited laboratory tests, a cause was found in 45.9% of the patients compared with 52.7% with the questionnaire and the extended screening program. Conclusion of the study was that disease history is the most useful tool in finding the underlying cause of urticaria, and the investigations

should be so guided. These patients were followed up 1 year, after 1 year each patient was re interviewed and asked about any remaining or new complaints and if indicated repeated lab tests were performed. Each item of the history can be considered as a diagnostic test that either increases or decreases the probability of an etiology. By combining several questions, the probability that certain underlying disease or factors are present can be reduced to nearly zero or nearly 100%.

Mortureux *et al*[21] in their study done in Bordeaux University Pediatric Hospital, France 1992 tried to establish the clinicoetiological and prognostic features of acute urticaria in infancy and tried to define its optimal management. Fifty seven consecutive infants aged 1 to 36 month are taken and followed up for 2 years. In the study with the conjunction of clinical and laboratory criteria, a cause was identified or suspected in 91% of cases. It showed infection was the most common cause in 81% and foods were the cause in 11%. Leukocytosis was more in consistently associated with possible or probable infection. Parasitic infestations were non contributory. Atopy in patients or family was associated in 58%. They also noted discordance between clinical criteria and IgE serum levels. The increase in total IgE levels in acute urticaria may represent only a non specific marker of immune mechanism rather than a sign of underlying atopy. They concluded that in most of the cases laboratory investigations are not required and 20% to 30% of the cases evolve in to chronic or recurrent urticaria. In patients with atopic dermatitis , food allergy should also be investigated.

Sackesen *et al*[6] in 2002 conducted a study in Anarka, Turkey about the etiology of different forms of urticaria in childhood. Fifty four children with various forms of urticaria were included in the study. Thirty-seven of 54 children (68%) were classified as having acute urticaria and the remaining 17 (31%) were classified as having chronic urticaria. In the acute urticaria group, 35% of patients described a recurrence and were classified as recurrent acute urticaria. Detailed lab investigations were conducted to reveal the probable aetiologies. In acute urticaria infections was the most frequently associated cause 48.6% followed by drugs 5.4% and food allergies 2.7% whereas in chronic urticaria, physical factors are the leading cause 52.94%. Most frequently documented infection was urinary tract infections, followed by serologically determined infections of Chlamydia pneumoniae and Helicobacter pylori. Total IgE levels are elevated in majority of patients (74%). There were no

significant differences between those with acute, recurrent, or chronic urticaria concerning IgE levels. They also evaluated cases of chronic urticaria for autoimmune problems but all came as negative.

Yan-Re *et* al[22] conducted a study in Taiwan in 2002 to 2010 to determine the predictive factors of the duration of first attack acute urticaria in children. Sample sizes of 1075 children were taken and followed up on OPD and information on the duration of urticaria were obtained according to the descriptions of the physicians. The etiologies of acute urticaria were divided in to 7 major categories and the relationships between these etiologies and first attack acute urticaria were determined by peer review of medical history and clinical assessments. The etiology of acute urticaria was determined based on statements made by the patients and or their family members about special events or exposure to certain environmental stressors. The conclusion was that aetiologies and personal allergy history were the most important predictors of the duration of a first attack of acute urticaria. In this study they found out that child without a personal allergic history has got a shorter duration of illness when compared to other group. So they recommended including personal allergy in history taking to denote the duration of the illness. Those 7 categories of etiology were analysed and longest mean duration was associated with inhalants (8.7 ± 4.6 days) followed by idiopathic (8.1 ± 5.7 days), food (6.2 ± 4.4 days), medications (5.5 ± 3.6 days) and contact materials (3.7 ± 0.9 days).

Supramanium *et al* [19] in his study explained artificial food additive intolerance in patients with angioedema and urticaria. Study group of 43 children were taken and were challenged with artificial food additives. 24 out of the 43 children reacted to the food additive with urticaria and angioedema and 18 children remained normal during the study. Atopy was less common in these patients than the general population. He concluded that ingestion of a number of artificial food additives has been shown to provoke urticaria and asthma in some individuals.

Le´aute *et al*[23] in his study discussed the diagnosis and treatment of urticaria. He concluded that proper diagnosis and treatment should be done in initial periods of presentation since the prevalence of the disease is more than expected. About one third of patients with chronic urticaria will continue to experience symptoms after 5 years of follow up. Consequently, it is important to provide early treatment in order to

improve patient's quality of life. Reduction of the exposure to precipitating and aggravating factors is also important, especially in patients with physical urticaria.

Vonakis *et al*[24] in his study conducted in 2008 introduced new concepts in chronic urticaria. Chronic urticaria is affecting the quality of life and vast majority are without and etiological agent. The presence of serum IgG autoantibodies against IgE antibodies and IgE receptors are noted and support the theory of autoimmunity in this condition. So the arrival of therapies targeting IgE and IgE receptors has got a promising future in treatment of chronic idiopathic urticaria. He also concluded due to the increased prevelance of the condition and lack of definite understanding of the pathology, further more studies are needed in this area about the treatment plans.

MATERIALS AND METHODS

This study was done among children came with clinical features suggestive of urticaria at OPD, IP and emergency room of Department of Pediatrics at Kerala Institute of Medical Science (KIMS), Trivandrum a tertiary care center in South Kerala. As per the department statistics we catered to a population of 150-200 children per day. Children aged from 1 month to 15 years attended the Pediatric OPD,IP and emergency room of Kerala Institute of Medical Science (KIMS), Trivandrum with clinical features suggestive of urticaria. All children aged 1 month to 15 years came to outpatient, inpatient department and emergency department of KIMS Hospital, Trivandrum with clinical features of urticaria.

STUDY DURATION

2 year (April 2015 to March 2017)

SAMPLE SIZE[25,26]

$$n = \frac{Z_{\infty}^2 p(1-p)}{d^2}$$

Where n= Sample size

Z_{∞} = Z statistics for a level of confidence

P = Estimated proportion of an attribute present in the population

d = Level of precision

In the present study: -

p = 0.48 (Proportion of major etiological factor of Urticaria) [25, 26]

d = 0.081

Z_{∞} = 1.96 for ∞ = 0.05

$$N = \frac{(1.96)^2 \times (0.48) \times (0.52)}{(0.081)^2}$$

= 144

Final sample size of the study was 144.

STUDY DESIGN AND INTERVENTION

This was a Prospective Descriptive study. The study population was selected as per inclusion criteria. All children aged 1 month to 15 years presented to the OPD, IP and emergency room of Kerala Institute of Medical Science (KIMS), Trivandrum with clinical features of urticaria were enrolled into the study after taking the informed consent (annexure 4) from parents/patient. The general condition of the child was assessed. The clinicoetiological profile of urticaria were determined based on the statements made by the parents or their family members about special life events or exposure to certain environmental stressors and from relevant investigations done. A patient who presented with urticaria after a recent bacterial or viral infection was surveyed for the source of infection. Food or medications were suspected to be the etiology when patients or family members stated that they had rashes after eating a particular food or taking a particular medication. Past history of similar illness, associated other allergic conditions like atopy, allergic rhinitis, asthma was noted, details of other family members having allergic history were also noted and relevant physical examination was done by the principal investigator and confirmed by the guide and co-guide. Laboratory investigations like CBC, CRP, URE, AST were done. Total IgE was done according to patient's financial status and willingness. Children were scored according to UAS scoring system at the time of presentation.[8]Their final outcome in terms of duration of illness was noted on review and confirmed by telephone enquiry by the principle investigator on follow up. The total duration of urticaria was defined as the period from the onset of the rash to the time of subsidence of symptoms in hours. All details were recorded using a proforma (Annexure 1). Children were followed up till the date of their discharge from the hospital by the principle investigator.

METHOD OF MEASUREMENT OF OUTCOME OF INTEREST

Primary outcome

Clinicoetiological profile of urticaria in children aged 1 month to 15 years in a tertiary care center**.**

Secondary outcome

Prognosis of urticaria in terms of duration of illness and UAS scoring.

DATA COLLECTION METHODS

There was a structured proforma which was filled by the principal investigator. This proforma contained data regarding personal details, clinical features, family history of allergy, possible etiological agents, UAS scoring of urticaria, relevant investigations and duration of disease to measure the outcome of this study.

STATISTICAL METHODS

The statistical data was entered in excel sheets and analyzed using the statistical software SPSS version 16. All the numerical data were expressed as mean ±standard deviation. Categorical data were expressed as frequency and percentage. Correlation between duration and UAS score were analyzed with spearman correlation. A p-value <0.05 was considered as significance.

OBSERVATIONS AND RESULTS

Total children enrolled in the study -144

Total children analyzed – 144

A. Baseline characteristics of the study population

Table 4: Baseline characteristics of the study population

Characteristics		Number	Frequency (%)
Age	0-2	17	11.8
	2-4	54	37.5
	4-6	22	15.2
	6-10	34	23.6
	10-12	14	9.7
	12-15	3	2.8
Gender	Males	80	55.6
	Females	64	44.4
Rural / Urban	Urban	125	86.8
	Rural	19	13.19
Type of urticaria	Acute	108	75.0
	Chronic	8	5.6
	Acute on chronic	14	9.7
	Acute on recurrent	14	9.7
First episode of urticaria		110	76
Family history of urticaria		33	22.9

In our study population males and females were almost equally distributed. Most of the study population belonged to urban population (86.8%) than rural population (13.19%). Majority of the children had a positive family history of allergy and urticaria in the family. Around 110 patients (76%) came with first episode of urticaria. Age distribution showed increased incidence of urticaria between 2 to 4 years of age.

B. MAIN RESULTS

1. PRIMARY OUTCOME

Table 5: Clinical profile of urticaria in children

Type of urticarial lesion	Number	Percentage
Acute	108	75
Chronic	8	5.6
Acute on chronic	14	9.7
Acute on recurrent	14	9.7

Acute urticaria was having increase in incidence (75%) followed by chronic (5.6%) and recurrent urticaria (9.7%).

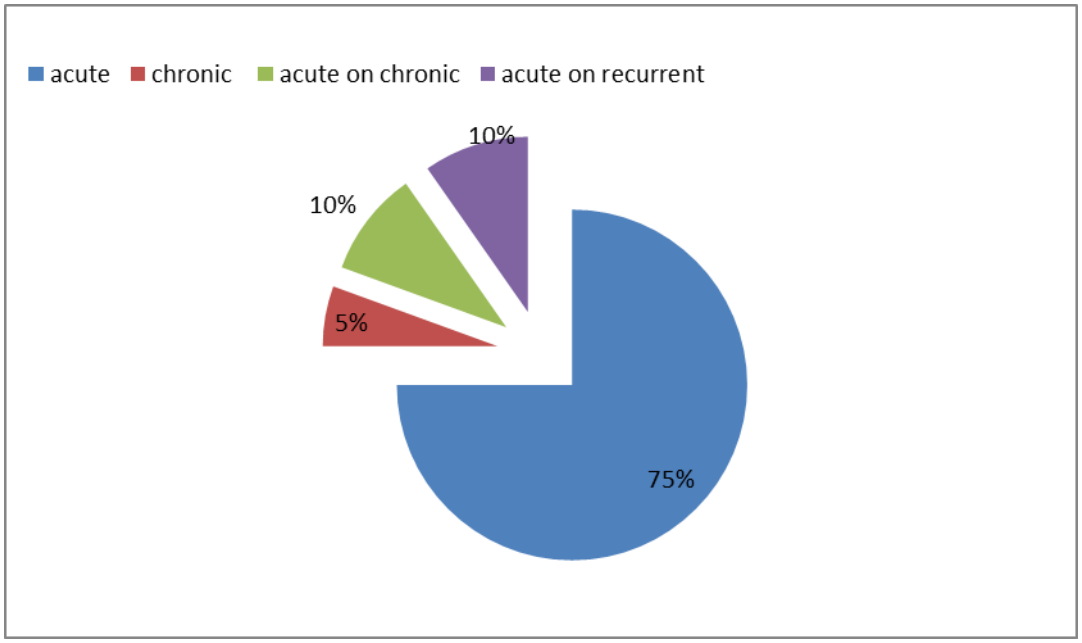

Figure 1: Clinical profile of urticaria in children

Table 6: Etiological profile of urticaria

Etiology	Number	Percentage
Infection	33	22.9
Food	33	22.9
Drugs	17	11.8
Insect bite	10	6.9
Contact	6	4.2
Dental carries	4	2.8
Idiopathic	40	27.8
Aquagenic	1	0.7
Cold induced	0	0
Solar urticaria	0	0
exercise	0	0
psychosomatic	0	0

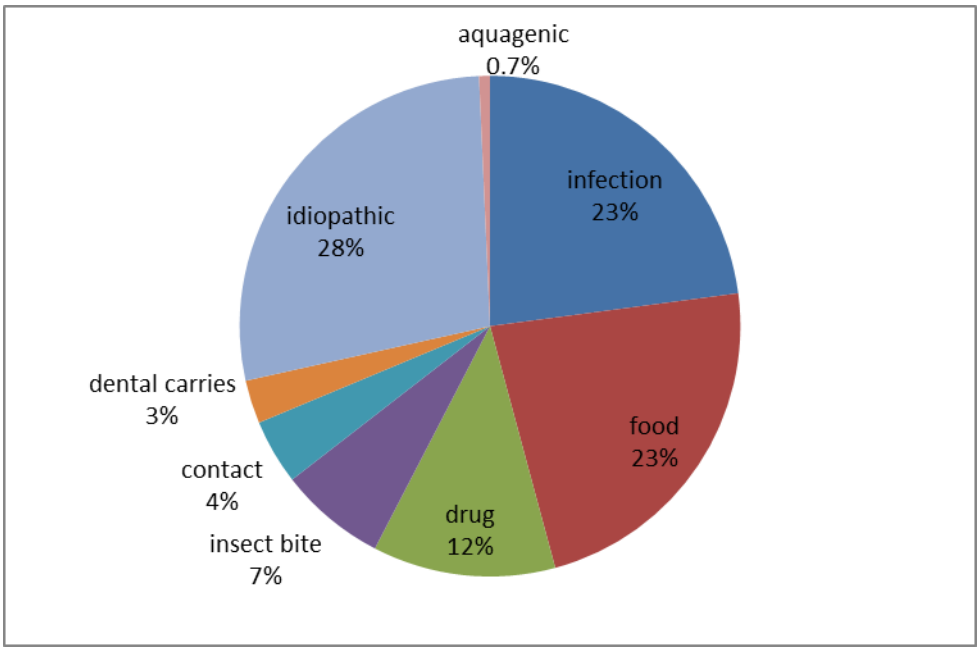

Fig 2: Etiological profile of urticaria.

Infection (22.9%) and food allergy (22.9 %) were the most common etiological agent identified in the study population. Followed by drug allergy (11.8%). Incidence of idiopathic urticaria was 27.8%. 4 patients had dental carries as etiology (2.8%). Insect bite induced urticaria occurred in 10 patients (6.9%).

2. SECONDARY OUTCOME

Table 6: duration of illness and UAS[17] score

UAS score	Mean duration of illness in hours
1	23.33
2	34.18
3	73.14
4	79.23
5	126.17
6	110.5

Mean duration of urticaria was highest with UAS score 5.

Table 7: Correlation between duration of illness and UAS scoring

	UAS score	**duration**
Correlation coefficient (r^2)	1.0	0.569
P value	<0.001	

Duration of illness and UAS score was found to be statistically significant with p value <0.001 and correlation coefficient 0.569.

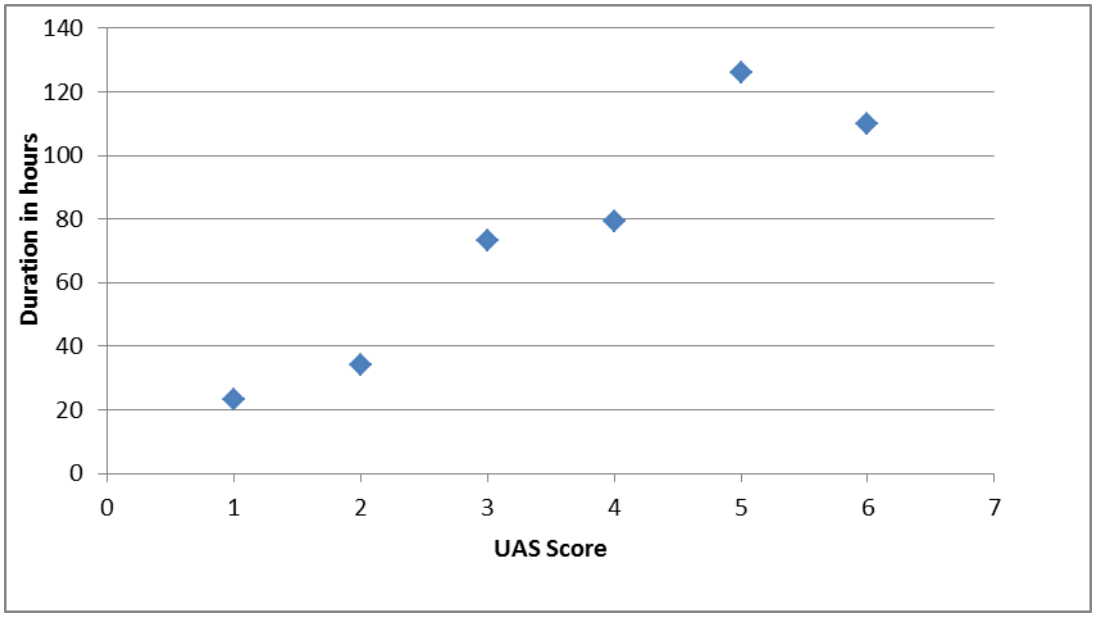

Fig 3: Correlation curve between UAS score and duration of illness

3. OTHER RELEVANT FINDINGS

Table 8: Duration of illness

	Median	Inter Quartile Range
Duration of illness	66.5 hours	47

Mean duration of illness was 66.5 hours in the study population.

Table 9: Symptoms of urticaria

Symptoms	Number	Percentage %
a) fever	70	48.6
b) itching	123	85.4
c) angioedema	23	16.0
d) hypotension	4	2.8
e) vomiting	27	18.8
f) wheezing	22	15.3
g) rhinitis	17	11.8
h) abdomen pain/diarrhoea	38	26.4
i) joint pain	10	6.9
j) dermatographism	2	1.4
k) internal diseases	1	0.7

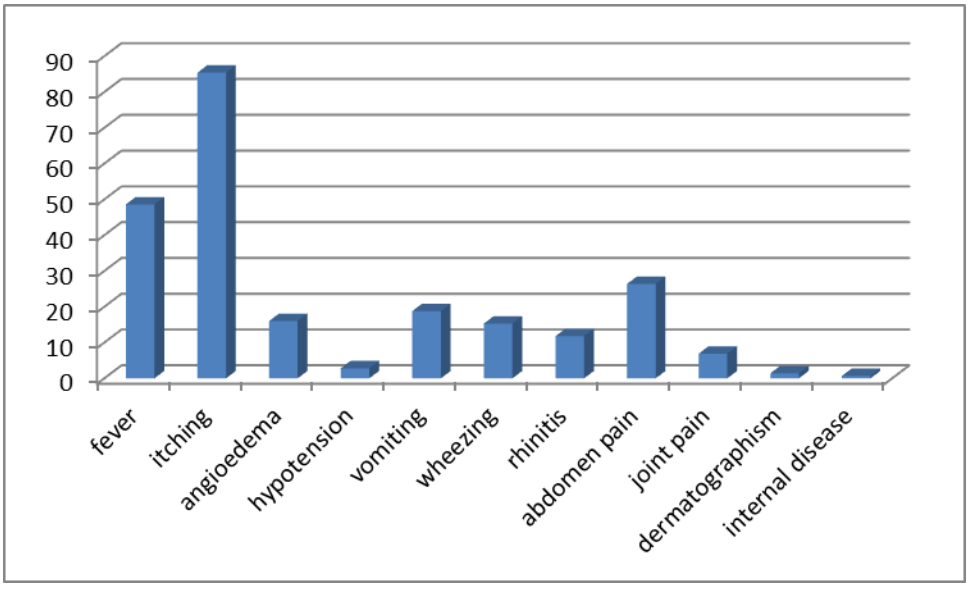

Fig 4: Symptoms of urticaria

Almost half of the children with urticaria presented with fever and about 85 % of children had associated itching. Angioedema was noted in 16 % of the study group. Dermatographism was noted in 2 patients (1.4%).

Table 10: Comorbidities in study population.

Conditions	Frequency	Percentage %
Atopy	38	26.4
Allergic Rhinitis	40	27.8
Asthma	42	29.2
Food allergy	29	20.1
Drug allergy	14	9.7

Associated asthma was the most common comorbidity seen among the study population (29.2 %), followed by allergic rhinitis (27.8 %), atopy (26.4%) and food allergy(20.1%).

Table 11: Family history of associated comorbidities

Condition	Frequency	Percentage %
Atopy	41	28.5
Allergic rhinitis	55	38.2
Asthma	45	31.3
Urticaria	33	22.9

Most common comorbidity in family was allergic rhinitis (38.2%) followed by asthma (31.3 %) and atopy (28.5%) and 22.9% of the family members had urticaria.

Table 12: Atopy association and duration of illness

Atopy	Number	Mean duration in hours	p value
no	106	65.18	0.0072
yes	38	76.50	0.0072

Those children who had associated atopy in personal comorbity, the mean duration of urticaria was found to be more and statistically significant with p value <0.05.

DISCUSSION

Urticaria is a very troublesome disease in all age group. Although the literature on the disease is vast, only few studies are still available on urticaria, especially on the clinical profile and prognosis of the illness. So we took up this descriptive study based on history, clinical examination and relevant investigation to assess the Clinicoetiological profile and outcome in children aged 1 month to 15 years. During the study period of 2 years, a total of 144 children were enrolled.

PATIENT POPULATION AND CHARACTERISTICS

This study included a total of 144 children under the age of 15 years presented with urticaria. The mean age of our study population was 5.6 years (mean age +/- SD age , 5.6 +/- 3.3 years). Of the studies done in India, this study enrolled maximum number of patients till now. All the cases we enrolled in the study were confirmed by our consultant dermatologist and follow up was done on OPD basis. There were 80 (55.6 %) boys and 64 (44.4 %) girls. Gender distribution was almost similar in population with some predominance towards male population. Most of the children were in 2 to 4 years of age group (54%) (Figure 1).

PRIMARY OUTCOME

1. Clinicoetiological profile of urticaria (Table 5 & 6)

The clinical profile of urticaria was evaluated in our study population. Despite the fact that there are very few studies available in India; we found that all forms of urticaria can be observed during the childhood. Of the 144 children evaluated 75% presented with acute urticaria, chronic urticaria 5.6%, acute on chronic urticaria 9.7%, acute on recurrent urticaria 9.7%. That is around 75% of the cases presented as acute urticaria in to our clinics followed by 24.9% of chronic and recurrent cases. This is at par with the studies conducted by **Mortureux *et al*** [21] in 1992 where acute urticaria was 70% and 30 % of chronic and recurrent cases. As we did the study in a tertiary care center which acts as a referral hospital, some severe cases referred from peripheral center were included in the study so that the frequency of chronic and

recurrent urticaria is more. This will not represent the actual prevalence in general population.

In our study with the support of clinical history, examination and relevant lab investigation a cause was identified in 104 cases (60 %). An association between the etiological agent and urticaria is often very difficult to establish since there is no possibility of challenging the patient with the suspected etiological agent. Success of identifying a cause or etiological agent in our study goes in par with study conducted by **Yan-Ren *et al***[22] in 2011 Taiwan of 72.2 %. Etiological profile of urticaria showed infection (22.9%) and food (22.9%) as most common etiological agents. This is in comparison with studies conducted by **Yan-Ren *et al***[22] where food allergy (24%) and infection (45%) accounted for the main etiology. In the study conducted by **Mortureux *et al*** [21] the most common etiological agents identified were also infection (81%) and food allergy (11%). **Sackesen *et al***[6] in his study concluded infection (49% acute, 39% chronic), food (3% acute, 12% chronic) and drugs (5% acute, 17% chronic) as the important causes of urticaria. Infections in our study mainly included viral infection proven by blood counts and CRP. No urinary tract infection was noted in our study population during the study period. In food allergy cases those who can afford were done food allergy panel –Immunocap. In food induced urticaria cases sea food was the most commonly implicated ones, especially prawns. Beef allergy was also noted in 8 cases. One case of chronic urticaria after testing came positive for coconut allergy, excluded from the diet and followed up in OPD. A positive drug intake attributed to 17 patients, especially antibiotics. Out of 17 cases 3 cases were associated with mefenemic acid, 1 case with acetaminophen, 3 cases with vancomycin and 2 cases were due to ceftriazone allergy. Insect bite induced urticaria accounted for 10 (6.9%), this is slightly increased compared to the reference study **Yan-Ren *et al***[22] (1.5%) most probably due to the geographical variation of the comparison groups and types of the insects. Dental carries were identified with 4 cases (2.8%), dental consultation and follow up was done on op basis. Incidence of dental carries was more than the reference study may due to the better socioeconomic standard present among the reference population and improved oral hygiene. Those cases in which an identifiable cause not detected even after a proper history, clinical examination and lab investigations were classified as idiopathic urticaria. In our study etiological factors are not documented in 40 patients (27.8%), includes 25 acute urticaria, 12

chronic urticaria, and 3 cases of recurrent urticaria. This was in agreement with the study conducted by **Sackesen *et al***[6] in 2002 where idiopathic cases were 46% (20 cases of acute and 8 cases of chronic urticaria). Our study we were able to identify an etiology in 76.8% (83 cases) of acute and 45.5% (10 cases) of chronic urticaria which was in par with **Sackesen *et al***[6] where success rate was 56% in acute and 53% in chronic cases.

SECONDARY OUTCOME

1. Outcome based on duration of illness and UAS score (Table 6 & 7)

In our study duration of illness was taken as the time period from the first appearance of the symptoms till resolution. This was measured in hours and compared with the initial UAS score at the time of presentation[17]. The mean duration of the illness was 66.0 hours (2.75 days) and the duration of illness in hours was plotted against UAS score and correlation curve obtained. There was a significant positive correlation with statistical significance (p value <0.001) and correlation coefficient (r^2) was (0.569). However, we found out that those children who had urticaria with high UAS score at presentation i.e, UAS score 6 had a shorter duration of illness than the rest of the group. This result might be due to the difference in methods used to treat those cases with increased severity.

Other relevant findings

1. Associated symptoms of children presented with urticaria in our study were evaluated (Table 9). Fever was associated with 70 cases (48.6 %), followed by itching (85%), angioedema (16 %), vomiting (18.8%) wheezing (15.3), rhinitis (11.8%), abdomen symptoms(26.4%) and joint pain (6.9%). This was almost similar in study done by **Kozel *et al***[20] and **Yan-Ren *et al***[22] in their studies in 1998. In their study association of asthma (15%), allergic rhinitis (17%), atopic dermatitis (5%) were documented with the clinical presentation. In study conducted by **Montreuax *et al***[21] in 1992 the association of atopy with family members was 58%, particularly atopic dermatitis which is similar with our study, they also noted itching (89%), fever (50%), rhinitis in 30 cases. These findings are similar with our study. Fever was seen in 70 cases but was not always due to the underlying infection. This may be due to a part of generalised

inflammatory response seen with urticaria rather than denoting the underlying infection.

2. Association of comorbidities. (Table 10) Our study evaluated various personal allergies associated with urticaria. Asthma was the most common one, accounting for 29%, followed by allergic rhinitis (27.8%) and atopy (26.4%), this is in par with study conducted by **Sackesen *et al***[6] which showed atopy 29% and study by **Yan-Ren *et al***[22] which showed allergic rhinitis 23.8 % in their study population. Family history of allergy showed allergic rhinitis (38.2%) as the most common comorbidity followed by asthma (31.3%) and atopy (28.5%). **Sackesen *et al***[6] study showed family allergy association as 25% but didn't classified in to subgroups. In **Montreuax *et al***[21] study association of atopy in personal or family members was 58% which is much higher than our results.
3. Association of atopy and duration of illness in urticaria. (Table 12) Mean duration of the illness was 66.5 hours in our study population. Then the duration of illness in children with a positive history of atpoy (personal or family history) was compared with the rest of the study population, it showed a significant increase in duration of illness. The mean duration in atopy associated cases was 76.5 hours, where as it was 65.18 hours in the rest of population. This was significantly high with P value <0.01. This is in comparison with study done by **Yan-Ren *et al***[22] which showed longer duration of urticaria associated with positive atopic history.
4. Another important result seen in our study was the absence of urinary tract infection as etiology. A number of investigators have found that antibiotics used for urinary tract infection caused the development of urticaria, the infection itself not being a factor in the development of the disease as such.[27, 28] Our result can be compared with the above mentioned findings.

Table 13: Comparison of main variables of various studies in a nutshell

Studies	Study period	Sample size	Sample population	Clinical profile	Etiology	Correlation of duration of illness and UAS score
Our study	2015-17	**144**	Children (1 month- 15 years)	Acute (75%) Chronic (5.6%) Acute on chronic (9.7%) Acute on recurrent (9.7%)	Infection (22.9%) Food (22.9%) Idiopathic (27.8%)	Positive correlation (P<0.001)
Sackesen *et al*	2001	44	Children (1-19 years)	Acute (68%) Chronic (31%) Recurrent (24%)	Infection (49%) Drugs (5%) Food (3%)	------
Montreuax *et al*	1992-94	57	1month -3 years	Acute (70%) Chronic and recurrent (30%)	Infection ± drugs (81%) Food (11%)	-------
Kozel *et al*	1992-94	220	Age >15 years	-------	Food (6.8%) Idiopathic (35.5%) Drugs (9.1%)	-------
Yan-Ren *et al*[22]	2010	1075	Age 1 to 18 years	-------	Infection (45%) Food (24%) Idiopathic (15.3%)	-------

Strength of our study

1. This is the pioneering study in South India till now regarding the Clinicoetiological profile of Urticaria and outcome based on UAS score in children.
2. This study included maximum number of subjects when compared with other reference studies available.

Limitation of our study

- Most of our study population belonged to middle and high socioeconomic class. So it may not represent the general population. It would better to include IgE, TSH, ANA test in investigation profile to increase the yield of etiological agents.

CONCLUSION

Of the 144 children presented to us clinical profile was acute urticaria 75%, chronic urticaria 5.6%, acute on chronic urticaria 9.7%, acute on recurrent urticaria 9.7%. That is around 75% of the cases presented as acute urticaria in to our clinics followed by 24.9% of chronic and recurrent cases. Etiological profile of urticaria showed idiopathic (27.8%) followed by infection (22.9%) and food (22.9%) as most common etiological agents. There was statistically significant positive correlation between duration of illness and UAS scoring.

REFERENCES

1. Kanwar AJ, Greaves MW. Approach to the patient with chronic urticaria. Hosp Pract. 1996;31(3):175-89,183-4,187-9.

2. Gupta R, Sheikh A, Strachan D, Anderson HR. Increasing hospital admissions for systemic allergic disorders in England: analysis of national admissions data. BMJ. 2003;327:1142-1143.

3. Leung DY, Dreskin SC. Urticaria(Hives) and Angioedema.In: Kliegman R, Behrman R, Jenson H, Stanton B, editors. Nelson Textbook of Pediatrics. 18thedition .vol.1. Newdelhi: Elsevier.2008;p. 979-982.

4. Lawley TJ, Yancey KB.Approach to the patient with skin disorder.In :Fausi AS, Kasper DL, Longo DL, Braunwald E, Hauser SL, Jameson JL, Loscalzo J, editors. Harrison's Principles of Internal Medicine.17th edition.vol.1.New York : MacGrawHill.2008 ;p.330-331.

5. Powell RJ, Du Toit GL, Siddique N, et al. BSACI guidelines for the management of chronic urticaria and angioedema. Clin Exp Allergy.2007; 37(50): 631-50.

6. Sackesen C, Sekerel BE, Orhan FO, Kocabas CN, Tuncer A, Adalioglu G, *et al*.The etiology of different forms of urticaria. Pediatr Dermatol. 2004; 21(2):102-108.

7. Grattan CE, Black AK. Urticaria and Angioedema.In:Bolognia JL, Jorrizo JL, Rapini RP, editors.Dermatology. Vol.1.London:Elsevier.2003;287-302.

8. Grob JJ, Revuz J, Ortonne JP, Auquier P, Lorette G. Comparative study of the impact of chronic urticaria, psoriasis and atopic dermatitis on the quality of life. Br J Dermatol. 2005;152(2): 289-95.

9. Ghosh S, Kanwar AJ, Kaur S. Urticaria in children. Pediatr Dermatol.1993;10:107-110.

10. Wainstein BK, Yee A, Jelley D, Ziegler M, Ziegler JB. Combining skin prick, immediate skin application and specific-IgE testing in diagnosis of peanut allergy in children. Pediatr Allergy Immunol.2007; 18(3): 231-9.

11. Maloney JM, Rudengren M, Ahlstedt S, Bock SA, Sampson HA. The use of serum-specific IgE measurements for the diagnosis of peanut, tree nut and seed allergy. J allergy Clin Immunol.2008; 122(1): 145-51.

12. Lin J, Sampson HA. The role of immunoglobulin E-binding epitopes in the characterization of food allergy. Curr Opin Allergy Clin Immunol.2009; 9(4): 357-363.

13. Grattan CE, Humphreys F. Guidelines for evaluation and management of urticaria in adult and children. Br J Dermatol.2007; 157(6): 1116-1123.

14. Zitelli KB, Cordoro KM. Evidence-based evaluation and management of chronic urticaria in children. Pediatr Dermatol.2011; 28(6): 629-39.

15. Dibbern DA.Urticaria: selected highlights and recent advances. Med Clin North Am.2006; 90(1): 187-209.

16. Kaplan AP.Urticaria and Angioedema. In:Adkinson NF, Bochner BS,Buess WW,Holgate ST,Lemanske Jr RF, Simons FER.Middleton's Allergy:Principles & Practice. 7th ed.Mosby:Elsevier;2009.p. 1063-81.

17. ZuberbierT, Asero R, Bindslev J C, Walter CG, Church MK, Gimenez AA, *et al*. EAACI/GA(2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. Allergy.Oct 2009;64(10):1417-26.

18. Supramanium G, Warner JO. Artificial food additive intolerance in patients with angio-edema and urticaria. Lancet 1986 Oct 18;2(8512) :907-9.

19. Dreskin SC, Patel OP. 2012. Urticaria and Angioedema. In: Vedanthan PK, Nelson H, Agashe SN, Mahesh PA, Katial R,editors. Textbook of Allergy for the clinician. New York:CRC press;2014.p.268-288.

20. Kozel MM, Mekkes JR, Bossuyt PM, Boss JD. The effectiveness of a history-based diagnostic approach in chronic urticaria and angioedema. Arch Dermatol.1998;134(12):1575 1580.

21. Mortureux P, Leaute-Labreze C, Legrain-Lifermann V, Lamireau T, Sarlangue J, Taïeb A, *et al*. Acute urticaria in infancy and early childhood: a prospective study. Arch Dermatol.1998;134(3):319-23.

22. Lin YR, Liu TH, Wu TK, Chang YJ, Chou CC, Wu HP. Predictive factors of the duration of a first attack acute urticaria in children. American Journal of Emergency Medicine 2011Oct;29(8):883-889.

23. Le´aute´-Labre`ze C. Childhood versus adult urticaria. Dermatology from young to old.symposium 12–15/6 2003 in Rotterdam: Isala, 2003.

24. Vonakis BM, Saini SS. New concepts in chronic urticaria. Curr Opin Immunol. 2008; 20(6):709-716.

25. Daniel WW (1999). Biostatistics: A Foundation for Analysis in the Health Sciences. 7th edition. New York: John Wiley & Sons.

26. Yamane, T. (1967). Statistics, An Introductory Analysis (2nd Ed). New York: Harper and Row.p.58.

27. Bilbao A, Garcia JM, Pocheville I , Gutiérrez C, Corral JM, Samper A, *et al*. Round table: urticaria in relation to infections. Allergol Immunopathol. 1999;27(2):73–85.

28. Sakurai M, Oba M, Matsumoto K, Tokura Y, Furukawa F, Takigawa M, *et al*. Acute infectious urticaria: Clinical and laboratory analysis in nineteen patients. J Dermatol 2000;27(2):87–93.