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Original Research Article

Etiology and immediate drug hypersensitivity in acute urticaria: a retrospective study

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ABSTRACT

Background: Acute urticaria is an immune mediated or non-immune reaction lasting for less than 6 weeks. This can be caused by food, drugs, infections, physical contact, insect bite but majority are reported to be idiopathic. Theoretically, almost any drug can cause urticaria especially antibiotics like penicillin. We carried out this study to assess the various etiologial factors and to assess the immediate hypersensitivity reaction to various drugs in acute urticaria.
Methods: We reviewed the medical records of patients with acute urticaria in dermatology department from 2016 to 2018 (2 years) and recorded the demographic details, history of suspected cause, medications and intradermal drug test report in a standard proforma.
Results: There were 154 cases of acute urticaria. Mean age of these cases were 36.48±11.37 years. 13.6% had associated angioedema. Mean duration of urticaria was 21.74±7.92 days. 40.9% cases were labelled idiopathic. Food accounted for 29.2% of the cases, drugs for 23.4% and infection for 5.2%. The rest 1.3% were due to insect bite. Intradermal drug test report showed the following frequency of positive reaction: diclofenac>ciprofloxacin= piroxicam>paracetamol=ketamine=diazepam>promethazine=atracurium.
Conclusions: Most cases of acute urticaria were idiopathic whereas food, drugs, infections and insect bite were the specific causes. Fish among food, acetaminophen among drugs and streptococci among infections were most responsible agents. Immediate hypersensitivity to drugs in intradermal test were maximum for NSAIDs especially diclofenac and piroxicam followed by antibiotic namely ciprofloxacin in patients with acute urticaria.

Keywords: Acute urticaria, Etiology, Skin test, Immediate drug hypersensitivity

INTRODUCTION

Acute urticaria is defined as spontaneous urticaria lasting for less than six weeks. This can be immune mediated due to type 1 or 3 hypersensitivity or non-immune. There are many etiological factors like food, drugs, recent infections, physical contact, insect bites etc. but the majority being idiopathic. Theoretically, almost any drug can cause urticaria especially antibiotics like penicillin.[1] No reliable in vitro tests are available to determine probability of drug reaction and elective challenge testing has been recommended in this setting.[2] But since this requires inpatient stay and takes about 2 weeks, many patients opt for intradermal drug testing (IDT) for immediate hypersensitivity reaction with a standard drug panel which gives faster results. We carried out this study to assess the various etiologial factors and to assess the immediate hypersensitivity reaction to various drugs in acute urticaria.

METHODS

This was a 2 year retrospective descriptive study conducted in the dermatology department in Sree Gokulam Medical College from 2016 to 2018. This study was started after ethical clearance and conducted in accordance with Declaration of Helsinki principles. We reviewed the medical records of the patients with the clinical diagnosis of acute urticaria (defined as urticaria lasting for less than 6 weeks) and episodic urticaria (defined as intermittent urticaria, recurrent over months or years but not as frequent as in chronic urticaria). We excluded cases of chronic urticaria i.e. continuous urticaria occurring at least twice a week off treatment for more than six weeks. Demographic details, history of urticaria, suspected cause, medications, IDT reports were recorded in a standard proforma.

Statistical analysis

Descriptive statistics were used for data analysis using SPSS version 20. Categorical data was expressed as frequencies and percentages.

RESULTS

There were 154 cases of acute urticaria (117 females: 37 males) who attended outpatient dermatology department between 2016 to 2018. Mean age of these cases were 34.48±14.37 years. 21 cases (13.6%) had associated angioedema. Mean duration of urticaria was 21.74±7.92 days. Majority of the cases i.e. 63 (40.9%) cases were labelled idiopathic. Infection accounted for 8 (5.2%) cases with 5 (3.2%) for *Streptocoocal* pharyngitis, 2 (1.3%) for urinary tract infection, 1 (0.6%) for herpes simplex virus 1 infection. Food accounted for 45 (29.2%) cases with 16 (10.4%) for fish especially tuna and mackerel, 9 (5.8%) for beef, 8 (5.2%) for food additives, 7 (4.5%) for poultry, 5 (3.2%) for seafood like crab and prawns. 2 cases (1.3%) were due to insect bite (Figure 1). Drugs accounted for 36 (23.4%) cases with 14 (9.1%) cases for acetaminophen, 14 (9.1%) for NSAIDs including 8 (5.2%) for diclofenac, 4 (2.6%) for piroxicam and 2 (1.3%)for mefenamic acid and 8 (5.2%) for antibiotics namely 3 (1.9%) for ceftriaxone, 3 (1.9%) for cefotaxime, 1 (0.6%) for cotrimoxazole and 1 (0.6%) for ciprofloxacin (Figure 1) (Table 1).

IDT: 33 patients (25 females, 8 males) had undergone IDT under the supervision of an allergist. Mean age of these cases was 48.18±16.98 years. All the patients denied taking any antihistamines or immunosuppressants at the time of drug testing. Drugs were tested intradermally on volar forearm along with saline as control and belonged to the following categories: (1) Antibiotics: benzyl penicillin, ampicillin, amoxicillin, cloxacillin, gentamycin amikacin, ciprofloxacin, ofloxacin, ceftriaxone, cefotaxime, metronidazole. (2) Analgesics: paracetamol, diclofenac, ketorolac, piroxicam, tramadol, pentazocine. (3) Others: scoline, lignocaine, thiopentone, ketamine, vecuronium, pancuronium, propofol, atracurium, buprenorphine, glycopyrrolate, sensorcaine, atropine, morphine, pethidine, fentanyl, metaclopromide, ranitidine, pantoprazole, ondansetron, diazepam, midazolam, neostigmine, mephenteramine, methargin, oxytocin, ephedrine, dopamine, dobutamine, deriphylline, aminophylline, frusemide. The reaction was graded positive if the drug wheal size was more than double the control wheal size which is usually 5 mm × 5 mm or above; doubtful if exactly double the size and negative if less than double the size.

Table 1: Frequency and percentage of specific causes of acute urticaria.

Causes	Number of cases	Percentage of cases (%)
Streptococcal pharyngitis	5	3.2
Urinary tract infection	2	1.3
Herpes simplex virus type 1	1	0.6
Fish	16	10.4
Beef	9	5.8
Food additives	8	5.2
Poultry	7	4.5
Seafood	5	3.2
Acetaminophen	14	9.1
Diclofenac	8	5.2
Piroxicam	4	2.6
Mefenamic acid	2	1.3
Ceftriaxone	3	1.9
Cefotaxime	3	1.9
Cotrimoxazole	1	0.6
Ciprofloxacin	1	0.6

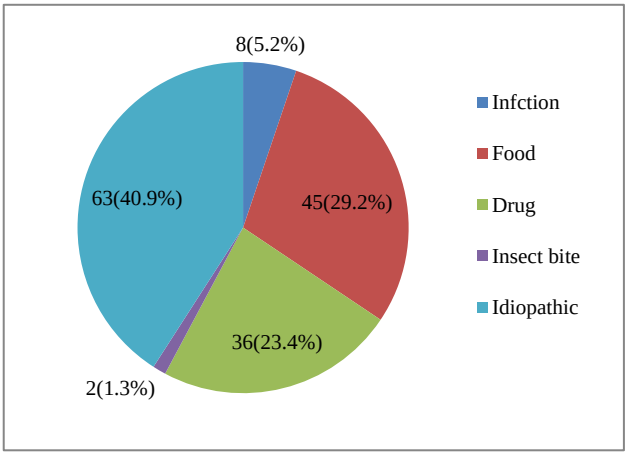

Figure 1: Pie chart showing the causes for acute urticaria.

The frequency of positive reaction is as follows: diclofenac > ciprofloxacin = piroxicam > paracetamol = ketamine = diazepam > promethazine = atracurium.

Frequency of doubtful reaction was less compared to positive reaction with maximum cases for vecuronium and tramadol (Table 2). 2 cases did not have positive reaction to any drug, 1 case had single positive reaction (to piroxicam) but the rest 30 cases had positive reaction to at least 2 drugs all of which were pharmacologically unrelated.

Table 2: Frequency and percentage of positive and doubtful reaction to standard drugs in IDT.

Drugs	Number of positive (%)	Number of doubtful (%)
Benzylpenicillin	1 (3.03)	1 (3.03)
Ampicillin	1 (3.03)	2 (6.06)
Amoxicillin	1 (3.03)	2 (6.06)
Cloxacillin	0 (0)	1 (3.03)
Gentamycin	3 (6.06)	5 (15.15)
Ciprofloxacin	12 (36.36)	4(12.12)
Ofloxacin	3 (6.06)	1 (3.03)
Cefotaxime	1 (3.03)	3 (6.06)
Ceftriaxone	2 (6.06)	0 (0)
Acetaminophen	9 (27.27)	1 (3.03)
Diclofenac	13 (39.39)	5 (15.15)
Ketorolac	6 (18.18)	2 (6.06)
Piroxicam	12 (36.36)	3 (6.06)
Tramadol	3 (6.06)	6 (18.18)
Pentazocine	6 (18.18)	2 (6.06)
Scoline	6 (18.18)	5 (15.15)
Lignocaine	4 (12.12)	0 (0)
Thiopentone	3 (6.06)	0 (0)
Ketamine	9 (27.27)	4 (12.12)
Vecuronium	4 (12.12)	6 (18.18)
Pancuronium	1 (3.03)	1 (3.03)
Atracurium	7 (21.21)	1 (3.03)
Propofol	0 (0)	3 (6.06)
Glycopyrrolate	0 (0)	1 (3.03)
Promethazine	7 (21.21)	4 (12.12)
Atropine	6 (18.18)	3 (6.06)
Morphine	5 (15.15)	1 (3.03)
Pethidine	3 (6.06)	2 (6.06)
Ranitidine	4 (12.12)	3 (6.06)
Pantoprazole	1 (3.03)	0 (0)
Ondansetron	2 (6.06)	0 (0)
Diazepam	9 (27.27)	5 (15.15)
Midazolam	0 (0)	2 (6.06)
Neostigmine	0 (0)	2 (6.06)
Mephenteramine	4 (12.12)	1 (3.03)
Dopamine	2 (6.06)	0 (0)

DISCUSSION

Urticaria is a vascular skin reaction characterised by wheals associated with severe pruritus. It can be acute if the episodes last for less than 6 weeks and chronic if longer than 6 weeks. This may be immune mediated or non-immune mediated. Kulthanan et al reported that more than half of the patients were idiopathic, 36.7% due to infections, followed by drugs, food and insect bite reactions.[3] Our study showed most cases to be idiopathic followed by food, drugs, infections, insect bite in decreasing order. Any food protein can trigger an allergic response but the most often implicated foods are egg, milk, peanuts, soy, fish, shellfish, tree nuts and wheat. Chung et al reported the most common food considered allergenic by Korean patients with chronic urticaria was pork which was also most commonly showing a positive result with the serum food-specific Immunoglobulin (Ig) E test as well as in oral food challenge test.[4] In our study, among food, fish especially mackerel and tuna was considered the most allergenic. Urticaria has also been associated with infectious diseases including viral infections like acute viral syndromes, hepatitis A, B and C, Epstein-Barr virus and herpes simplex virus. Streptococcal infection has been reported as the cause of 17% of acute urticaria cases in children.[5] Our study showed streptococci to be responsible for 3.2% cases, majority being children. Mareri et al reported 11% of patients with acute urticaria had HSV1 infection.[6] But we observed only 0.6% of cases had HSV1. Kulthanan et al had 16% cases with coexisting angioedema whereas Kaplan et al observed 50% cases had both chronic urticaria and angioedema.[3,7] Our study showed 14% of our cases had associated angioedema. We also observed a female preponderance over male (3:1 ratio) in acute urticaria as previously described in literature. Allergic reaction to a wide variety of drugs can occur. Certain drugs like opioids, vecuronium, succinylcholine and antibiotics e.g. vancomycin, rifampicin, polymixin, ciprofloxacin, some beta-lactams cause urticaria due to mast cell degranulation through non IgE mediated mechanism. NSAID induced urticaria can be IgE mediated or due to mast cell degranulation. In a study by Rutnin et al, the most frequent drug groups were antibiotics namely cephalosporins and among NSAIDS, diclofenac.[8] We observed that acetaminophen followed by NSAIDs especially diclofenac accounted for most cases of drug urticaria among our patients. Specific IgE maybe a mechanism underlying paracetamol (acetaminophen) hypersensitivity as reported by Rutkowski in 18.8% of their patients.[9] We noted that intradermal drug test showed high positivity to anti-inflammatory drugs especially diclofenac followed by antibiotic namely ciprofloxacin. We observed that a few cases of cephalosporin induced urticaria were excluded from intradermal cephalosporin injection test probably due to high risk of angioedema and anaphylaxis. Fluoroquinolones have been shown to induce false positive reactions probably because of their capacity to directly induce histamine release.[10-15] This mechanism probably also accounts for high frequency of positivity to neuromuscular blockers like atracurium. Majority of our case who underwent skin test fell under multiple drug hypersensitivity or multiple drug allergy syndrome defined as allergy to two or more structurally or pharmacologically unrelated drugs.[16] Halevy et al in their study supported the role of a T- cell mediated mechanism

in the pathogenesis of multiple drug allergy and suggested in vitro drug induced IFN gamma as a laboratory tool to identify the culprit drug associated with this allergy.[17] IDT has the advantage of identifying immediate hypersensitivity reaction to drugs in short span of time. But it fails to differentiate between true IgE mediated immune and nonimmune urticarial reactions which needs measurement of drug-specific IgE in the serum. But unfortunately, the latter is available only for reactions to limited number of drugs like beta-lactam antibiotics, neuromuscular blocking agents and morphine and their predictive value is not per se absolute.[18] There may be high cases of false positivity in IDT unless compared to results in control subjects.[19] Elective oral challenge testing has been recommended due to lack of reliable in vitro testing for various type of drug reactions [16,20]though this takes about two weeks time and needs admission. While there is general agreement that these drug provocation tests have the highest sensitivity among the available diagnostic tools and may improve patient management, its use as gold standard to establish rather than to exclude diagnosis of drug hypersensitivity is not unanimously accepted due to reactions it may trigger requiring appropriate medical facilities and trained personnel.[21]

To conclude, most cases of acute urticaria were idiopathic. Food, drugs, infections and insect bite were the other reported causes. Fish was the most implicated food. Streptococcus was the most frequent pathogen for infection induced urticaria. The major culprit drug for acute urticaria was acetaminophen. There was high immediate hypersensitivity to NSAIDs like diclofenac in patients with acute urticaria.

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