SURVEY OF THE CAUSES OF URTICARIA

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Summary

Analysis of 493 consecutive cases of urticaria investigated over a period of 2 years revealed that the cause of urticaria was cholinergic in 51 (10.3%) cases, cold in 46 (9.3%), dermographism in 20 (4.1%), pressure in 3 (0.6%), drugs in 17 (3.4%), inhalants in 38 (7.7%), foods in 34 (6.9%), infestations in 7 (1.4%) and bacterial foci in 27 (5.5%). This accounts for 49.2% of the total cases. A large majority of the remaining cases did not report the outcome of the investigative procedures advised, but there were 13 cases who could not be classified in spite of all the tests being currently employed by us.

This is a retrospective study of cases of urticaria seen in the Allergy Clinic, Department of Dermatology, All India Institute of Medical Sciences, New Delhi during the years 1975 and 1976. An attempt is being made to report the outcome of the investigative procedures currently being employed by us to find out the causative factors.

Material and Methods

Every case of urticaria was thoroughly interviewed to record the circumstances noticed by the patient to precipitate the attacks. This was largely done on the basis of a detailed proforma being employed for this purpose.

A patient was considered to be having cold urticaria if there was association of the attacks with at least 3 of the following stimuli, (1) winter season, (2) cold winds, (3) cold water bath or washing hands in cold water, (4) drenching in the rain, (5) sitting under a fan while sweating, (6) entering an air-conditioned room, (7) visit to a hill station, (8) taking an ice-cold food or a drink, and (9) changing clothes. The diagnosis in these cases was confirmed by the Cryo-Stimulation test[1].

The diagnosis of cholinergic urticaria was considered if the patient developed urticaria on exposure to (1) sunlight, (2) heat from other sources such as ovens, fire-place, room heaters, (3) physical exertion sufficient to stimulate sweating, and (4) emotional upsets. These cases were tested by giving an intradermal injection of 0.1 ml (0.025 mg) carbachol on the forearm skin and recording the size of the wheal and erythema that followed.

Dermographic urticaria was considered when the wheals were linear and occurred only on those areas which had been scratched. These cases were confirmed by performing dermographism as detailed elsewhere[2].

The diagnosis of pressure urticaria was made when the lesions occurred only at those sites which had been subjected to pressure for several hours, as from a tight belt, elastic band of socks, strap of a brassiere, watch strap or other similar objects.

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Drugs were considered responsible for urticaria if there was a clear-cut and/or repeated history of recurrences following administration of some drug.

The urticaria was considered to be due to an inhalant if the symptoms occurred only during a particular period of the year, or if the occurrence of symptoms was related to a particular place, the patient showing improvement on moving to a different place. The diagnosis in these cases was confirmed by asking a patient to breathe through a cloth mask worn on the nose and mouth for 48 hours and seeing if the symptoms disappeared without taking any drugs.

Food urticaria was suspected when the patient had repeatedly noticed aggravations of symptoms following ingestion of certain foods or if the symptoms were occurring at a regular frequency following meals. These patients were subjected to the diet elimination and provocation test[9] or advised to prepare diet charts (food diaries) to pick up the suspected items of food. The diagnosis of food urticaria was considered valid only if the diet elimination and provocation test produced some positive results.

In the remaining cases where a detailed history did not provide any clue to the possible aetiological factor, the following procedures were adopted one after the other, (1) complete diet elimination or diet substitution for 48 hours, (2) breathing through a mask for 48 hours, and (3) examination of 3 consecutive specimens of stools by the concentration method for the presence of ova or cysts. In case there was improvement following diet elimination/substitution, the patient was classified as food urticaria and investigated accordingly. In case the patient improved on breathing through a mask, he was diagnosed as a case of inhalant allergy and recommended the nasal filter[8]. If the stools showed the presence of some parasite, appropriate treatment was given for elimination of these parasites and examination of the stools was repeated to confirm their eradication. In case there was no improvement on any of the above mentioned procedures, the patient was given a 7 day course of treatment with some antibiotic in its usual therapeutic dose. If the patient improved during this week, he was continued on the same antibiotic for another week, while those who showed no improvement were given a 7 day course of a second antibiotic. Patients who improved following antibiotic therapy were classified as cases of infective urticaria.

Results

The total number of patients seen in 2 years was 493. There were 286 males and 207 females, ranging in age from 2 years to 71 years.

Forty six patients were diagnosed as cases of cold urticaria. These cases included 26 males and 20 females ranging in age from 10 to 70 years. Various factors recorded to precipitate the attacks included cold water bath in 41 cases, cold winds in 34 cases, drenching in the rain or sitting under the fan in 20 cases and ice cold drinks in 26 cases. In 24 cases, the attacks occurred in the winter season only. The cryo-stimulation test was positive in 39 cases and negative in 7 cases.

Cholinergic urticaria was diagnosed in 51 cases, out of whom 36 cases were males and 15 cases were females. The youngest patient was 16 years and the eldest 58 years. Urticarial attacks in these cases were noticed to have been precipitated by exposure to sunlight in 43 cases, heat from other sources such as ovens and room heaters in 46 cases, hot food or drinks in 8 cases, physical exertion in 48 cases and emotional upsets in 14 cases. In 14 cases the attacks were worse in the summer season.

Dermographic urticaria was diagnosed in 20 cases, out of whom 17 cases were males and 3 were females. Their ages ranged between 16 and 63 years. The duration of the disease varied from 1½ months to 10 years. The lesions in all these were linear and limited to the scratched areas only. Experimental dermographism was positive in all of them.

Pressure urticaria was seen only in 3 cases all of whom were males. The lesions were recurrent on the abdomen in the belt region and occasionally on other parts of the body.

Drugs were considered responsible for urticaria in 17 cases (8 males and 9 females). In each case, exacerbations had been noticed to follow administration of some drug. In 8 cases the total duration of the disease was longer, but recurrences were infrequent. The incriminated drugs were analgin in 6 cases, aspirin in 3 cases, crocin, terramycin and sulphadiazine in 2 cases each and penicillin, orisul, unienzyme, isonex, mexaform, anacin and some homeopathic drug in 1 case each. Provocation test was not done in any of these cases.

Inhalants were considered responsible for urticaria in 36 cases. In 26 cases the attacks of urticaria were seasonal, and in 11 of these cases the patient had also noticed improvement on going to a different place. In 10 cases the attacks did not show any relationship with the seasons, but there was history of remissions on going to a different place and recurrences on return to the original place.

Foods were clinically considered responsible in 155 cases because the attacks of urticaria were occurring with a regular frequency after meals. By diet elimination procedure, 30 cases showed improvement, 38 cases showed no relief, while 87 cases did not report for further follow up. The actual provocating foods could be discovered in 17 cases only and these included milk and its products in 7 cases, moong dal in 5 cases, raj mah, grams, urad dal and tea in 2 cases each, potato, dalda ghee, wheat, rice, sweet potato, and brinjal in 1 case each. Some cases were allergic to more than one food.

In 182 cases, the history did not provide any clue to the aetiologic agent. Diet elimination was done in 94 of these, out of whom 33 patients did not report for follow up, 57 patients showed no relief, while the remaining 4 cases were relieved by this procedure and thus subjected to provocation with various foods. Mask was advised in 70 cases out of whom 2 patients showed relief and were considered as cases of inhalant allergy, 38 cases showed no relief and 30 patients did not report for follow up. Testing 3 consecutive specimens of stools revealed the presence of gastro-intestinal parasites in 34 cases, but deworming led to regression of urticaria in only 7 of these patients. The parasites discovered in these 7 patients included **Entamoeba histolytica** in 4 cases, **Giardia lamblia** in 2 cases, hook worm in 3 cases and **Ascaris lumbricoides** in 2 cases. Eighty one cases were given a course of antibiotics which included tetracyclines, ampicillins and sulphonamides. Twenty six cases did not report for follow up, 28 patients showed no improvement while 27 patients were relieved by this treatment.

Thus the cause of urticaria was found to be cold in 46 (9.3 per cent), cholinergic in 51 (10.3 per cent), dermographism in 20 (4.1 per cent), pressure in 3 (0.6 per cent), drugs in 17 (3.4 per cent), inhalants in 38 (7.7 per cent), foods in 34 (6.9 per cent), infestations in 7 (1.4 per cent) and bacterial foci in 27 (5.5 cent) cases (table I), accounting for 49.2 per cent of the cases. A large number of the remaining cases did not report the outcome of the investigative procedures, while in 13 cases the cause of urticaria could not be ascertained in spite of all these investigations.

TABLE 1

Aetiologic classification of cases of urticaria

Cause	Number of cases	Percentage
Cold	46	9.3
Cholinergic	51	10.3
Dermographic	20	4.1
Pressure	3	0.6
Drugs	17	3.4
Inhalant	38	7.7
Food	34	6.9
Infestations	7	1.4
Bacterial foci	27	5.5
Total	243	49.2

Discussion

Various factors reported to precipitate urticaria include physical agents such as heat, cold, sunlight, friction and pressure; drugs; foods; inhalants such as pollens, fungal spores, animal and human dander and fragments of household insects; emotional stimuli; gastro-intestinal parasites; infective foci and biting or stinging insects. Sometimes urticaria can occur as a manifestation of serum sickness when it may be associated with fever, joint pains and even albuminuria and still rarely it may be a manifestation of systemic lupus erythematosus, internal malignancies or other similar diseases when the patient will show other manifestations of the disease as well.

A thorough clinical history can reveal the actual cause of urticaria in cases of allergy due to physical causes, drugs, emotional stimuli and in some cases of inhalant or food urticaria. The diagnostic criteria have, however, to be very strict and accurate.

Cold urticaria is generally considered to be rare[4] but in our experience[5], it constitutes one of the largest groups among the known causes of urticaria. Although it is possible that cold urticaria is especially more frequent in our region, it seems more probable that the diagnosis is missed because of lack of awareness. This is further complicated by the fact that the commonly employed tests for the diagnosis of cold urticaria often give a negative result[6,7]. We recommend the use of clinical criteria as detailed out earlier for the diagnosis of cold urticaria, and the use of cryo-stimulation test for confirmation. The ice cube method and the cold water immersion test fail to confirm the diagnosis in a large number of clinically classical cases. The causes of false positive and false negative results to the cryo-stimulation test are few and can be easily taken care of[1].

Cholinergic urticaria has constituted the largest group of cases in our series. The diagnosis in these cases has to be based almost entirely on clinical criteria. The chief stimulus responsible for the attacks seems to be the liberation of acetylcholine at the cutaneous nerve endings and since the sweat glands are cholinergic in innervation, any stimulus which stimulates the sweat glands also leads to an attack of cholinergic urticaria. Thus heat from sunlight, oven or any other source, physical exertion sufficient to stimulate the sweat glands or emotional stimuli which stimulate sympathetic fibres innervating the sweat glands can all precipitate an attack. While diagnosing cholinergic urticaria however, it is important to distinguish these cases from (1) heat urticaria which occurs on exposure to sunlight as well as heat from other sources, but is not precipitated by physical exertion or emotional stimuli, (2) solar urticaria which is limited to only those areas of the body which are exposed to sunlight and is not precipitated by heat from other sources, and (3) functional urticaria in which the urticarial attacks occur only during periods of emotional tension. Thus only those cases of urticaria which are precipitated by physical exertion alone, or the other two stimuli viz. heat and emotional stimuli can be diagnosed as cholinergic urticaria. The belief that the wheals in cholinergic urticaria are

small[8] and resemble papules is not correct because small papule-like wheals have been seen by us in cases caused by other agents also and typical cases of cholinergic urticaria have been seen to produce large irregular wheals. The only laboratory procedure to confirm the diagnosis of cholinergic urticaria consists of injecting 0. 1 ml (0.025 mg) carbachol or an equivalent dose of some other cholinergic drug, intradermally into the forearm skin of the patient. The wheal and erythema that follow in the patients are larger than those seen in the controls. For comparison however, one has to have figures for the normal population belonging to the same community. Appearance of pseudopodia or satellite lesions around the wheal is a more definite indication of the exaggerated response. Sometimes, it may also be possible to precipitate an attack of cholinergic urticaria by a subcutaneous injection of 0.5 ml (0.125 mg) carbachol. We did not come across any patient with solar urticaria, heat urticaria or functional urticaria during this period, though cases of each of these types have been seen by us outside the period of this study. Such cases are far less common as compared to other types.

Dermographism is essentially an exaggerated 'Triple response of Lewis', but the reason for this abnormal state of reactivity is not known. Since dermographism is also positive in cases of mastocytosis, it was considered that like mastocytosis, the patients with dermographism may also be having increased number of mast cells in their skin. However, this possibility was not substantiated by a study of the cutaneous mast cells in which the number and the sizes of cutaneous mast cells in patients having dermographism were found to be similar to those seen in urticaria cases due to other causes[9]. It seems that the defect in these cases probably lies in the increased susceptibility of the cutaneous mast cells to degranulate in response to mechanical stimuli. Dermographism has been demonstrated in a small percentage of urticaria cases due to other causes as well[8], but the label of dermographic urticaria should be used only when all the lesions are linear and they are limited to the scratched areas only and the patient does not develop the usual irregularly shaped wheals.

Pressure urticaria is to be distinguished from dermographic urticaria, because pressure urticaria occurs when the skin has been under pressure for several hours and the lesions develop only after that pressure has been released. A common example is an individual who wears a pant with a tight belt and develops urticaria around the waist on removing the pant in the evening. Instances of urticaria developing on the forearm which had been held tightly by another individual for a few minutes are actually cases of dermographic urticaria where the act of holding the forearm leads to friction on the skin while the essential feature of prolonged pressure characteristic of pressure urticaria is missing.

Drugs should be considered as a probable cause either when the urticaria is of a short duration or if the attacks occur at infrequent and irregular intervals. Sometimes the patient may give a clear cut history of attacks following administration of some drug. Almost any drug can cause urticaria but penicillin and salicylates are frequently responsible. As a rule the lesions do not recur unless the drug is readministered, but in case of penicillin, ampicillin and salicylates, the attacks may continue to recur for 3–4 weeks even if the drug is not readministered.

Urticaria caused by inhalants constitutes a significant group. In case the urticaria is being caused by the pollen of some plant, the symptoms will occur only when that plant develops flowers and sheds its pollen in the air and it

will continue as long as that plant continues to develop flowers. Thus the urticaria tends to recur every year during the same period. Secondly, if the patient moves to a different place where the causative antigen does not exist, the symptoms would subside spontaneously. Any of these two criteria is sufficient to diagnose inhalant allergy but there will still be some patients who are allergic to some inhalant which is present all round the year. These patients would continue to have their symptoms all round the year and if they had no occasion to go to a different place or the antigen was presen at the second place also, the only way to confirm their diagnosis would be to ask them to breathe through a cloth mask for at least 2 days and look for the improvement. The 'mask test' can, however, be undertaken only when the patient is having recurrent attacks at frequent intervals. As a treatment also, the mask can be a useful device, but since it cannot be used all through the day, the nasal filter[3] can be a useful alternative.

Foods which can cause urticaria include mostly those which contain significant amounts of proteins. Sometimes, other foods also can give rise to allergy because of the smaller molecules acting as haptens. Allergy to non-vegetarian foods such as fish, eggs and meat is more frequent but since this is easily discovered by the patient himself he does not report to the hospital. Allergy to other foods such as milk, pulses, wheat, rice etc. forms the bulk of hospital patients. Rarely other foods are also responsible. It is well known that intradermal tests with food antigens are not reliable, because frequently they give rise to wrong results. Diet elimination and provocation test is a far more reliable method because its results show a direct correlation with the allergic symptoms. It has however, to be conducted properly, otherwise its results can also be fallacious. While provoking with a particular food it is essential to administer it in a boiled form only and test the cooking fats and condiments separately, because occasionally even fats and condiments have been seen to cause the allergic symptoms. It is also necessary to give a sufficient quantity of the food item to provide enough antigen and to confirm the association of urticaria with the food by at least one repetition. The only drawback of the diet elimination and provocation test is that it takes a lot of time. We usually keep the patient under observation for a week or two, during which the patient gets trained to continue provocation at home. After the food(s) responsible for the symptoms have been found, the patient can make a choice whether to avoid the food or undergo a course of specific desensitization.

Gastro-intestinal parasites as a cause of urticaria have often been mentioned in the literature[8]. A controlled study[10] however, showed that in the Indian subjects, gastro-intestinal parasites were found with almost the same high frequency in the stools of normal controls as in the patients having urticaria and elimination of the parasites in urticaria patients had no significant effect on the course of urticaria in most of these cases. In the present study also, there were only 7(1.4 per cent) cases in whom elimination of the parasites had resulted in relief from urticaria. Both our studies however, do not account for the urticaria caused by allergy to the larvae of **Ascaris lumbricoides** and hookworm as they traverse various tissues before reaching the gastro-intestinal tract. Such cases of urticaria are likely to be of a short duration only, because once the larvae reach the gastro-intestinal tract and mature into adults, the antigenic stimulus disappears.

Hypersensitivity to bacterial antigens has also been mentioned as a cause of allergic disorders[8] and many tonsils

and/or teeth have been sacrificed with the hope of alleviating the allergic symptoms but without any success. This has created an impression that bacteria are not probably responsible. There are however, some patients who have observed aggravation of the allergic symptoms following infection in some part of the body and disappearance of the symptoms following eradication of the focus of infection. Since bacterial foci can be located at many sites such as tonsils, teeth, kidneys, gall bladder, intestines, paranasal sinuses and so on, it is understandable that many times it may not be even possible to detect this focus because the focus may not be in an active state. Nevertheless, even in an inactive state such a focus can release bacterial antigens into the circulation at irregular and varying intervals. Thus in cases where the history does not provide any clue to the aetiologic agent and complete diet elimination and the mask test are negative, it is worthwhile to treat such a case with a course of antibiotics with the presumption that this antibiotic will eradicate the infection wherever it is. In case the patient improves, the treatment can be prolonged suitably to completely eradicate the focus, but if there is no improvement, either the allergic symptoms are not being caused by a bacterial focus or the bacteria are not susceptible to the antibiotic used. To cover the latter possibility it is preferable to try a second antibiotic during the second week and if still the patient does not show any improvement, most likely the symptoms are not being caused by a bacterial focus.

In the present analysis, we have been able to aetiologically classify approximately 50 per cent of the patients. Out of the remaining cases a large majority failed to complete the investigations and thus could not be classified, but still there were several examples where all these tests showed a negative response indicating that urticaria was being caused by some other agent.

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