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VASCULITIS IN CHILDREN WITH ACUTE URTICARIA*

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Urticaria is a clinical syndrome with a wide spectrum of pathogenesis. Many different stimuli, both immunologic and non-immunologic, can cause urticaria. Anaphylatoxins, which are products of complement activation, can cause urticaria-like skin lesions[1]. In view of this relationship, several investigators have studied complement and immunoglobulin levels in patients with urticaria[2-5].

Recently, immune complexes have been shown to play a role in the pathogenesis of many systemic diseases[6]. In the past few years, leukocytoclastic vasculitis has been described in adults with chronic urticaria[7,8]. Immune complexes have also been investigated in patients with chronic urticaria[9-12]. Since there is no similar report on acute urticaria in the literature, we investigated the incidence of circulating immune complexes and vasculitis in children with acute urticaria.

Material and Methods

This study included 37 cases. The patient group was composed of 20 children with acute urticaria aged 4-17 years. The control group consisted of 17 cases, aged 2-17 years, hospitalized for surgical reasons, but with no skin lesions. The mean age of both groups was 9 years.

Some allergic, microbiological and serological examinations such as total eosinophil count, total and differential peripheral white blood cell count, throat culture, urinalysis, stool examinations for ova and parasites, liver function tests, antinuclear antibodies and hepatitis B surface antigen determinations and latex fixation tests were performed. Chest and paranasal sinus radiograms were made.

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Punch biopsies were obtained from a fully developed urticarial lesion of each patient. Half of the tissue samples were fixed in 10% buffered formalin for routine histologic examinations. The other half were frozen and stored at −70 °C for immunofluorescent studies. In the control group, biopsies of clinically normal skin were similarly studied.

Direct immunofluorescent technique[13] was performed on a 4 μ cryostat section of skin samples using commercial rabbit antiserum monospecific to IgA, IgG, IgE, and C_3 (Behringwerke).

The histological and immunological criteria that we used for the diagnosis of vasculitis are as follows[8]: swelling and proliferation of vascular endothelial cells, extravasation of erythrocytes, leukocytoclasis, cellular infiltrate consisting mainly of neutrophils, eosinophils, and/or lymphocytes and plasmocytes within and/or around the vessel walls, vascular deposition of immunoglobulins and/or C_3. Due to there being insufficient commercial monospecific antiserum in our laboratory, the presence of fibrinogen and fibrin related products in the dermal vessel wall was not evaluated.

Blood samples were obtained at the same time as the biopsy. Circulating immune complexes were determined by the EA (Fc) rosette inhibition method of Sandilands *et al*[14]. The results were expressed as percentages of EA rosette inhibition with the patient's serum.

The total serum IgE level was measured by the paper radioimmunosorbent test (PRIST) (Pharmacia Diagnostics). Concentrations of immunoglobulins and C_3 were quantitated by single radial immunodiffusion (Behringwerke). The total eosinophil count was determined by the method of Dacie and Lewis[15]. Laboratory data were compared by the Student t test, the Mann-Whitney U test and Fisher's X^2 test.

Findings and Discussion

The serum immunoglobulin and C_3 levels and total eosinophil counts of the patients are shown in Table I.

There was no statistical difference between the serum IgE levels of the control and the patient groups. Serum IgG, IgA, IgM, and C_3 levels of children with acute urticaria were within normal limits when compared with age-matched controls.

The differences between the mean percentages of EA (Fc) rosette inhibition of the control and patient groups were statistically significant ($p \leq 0.001$). It was shown that 12 of the children with acute urticaria (60%) had circulating immune complexes (Table II, Figure 1).

TABLE I

Serum Immunoglobulin, Complement Levels and Eosinophil Count of the Patients with Acute Urticaria

Case no.	Serum immunoglobulins (mg/dl) IgG	IgA	IgM	IgE (U/ml)	Complement (C_3) mg/dl	Eosinophil count /mm^3
1	660	65	71	20	81	450
2	870	65	135	4000 ↗	72	2000
3	830	82	123	90	72	300
4	700	132	82	75	72	500
5	840	140	86	33	89	150
6	860	100	95	36	73	500
7	670	80	73	360	73	600
8	560	43	71	148	62	550
9	760	126	97	74	81	200
10	770	67	95	10	93	375
11	930	113	100	5 ↘	87	300
12	1030	55	100	190	83	500
13	860	58	73	160	53	500
14	930	95	100	65	85	650
15	1100	113	120	3400	93	2200
16	760	98	110	85	88	600
17	970	65	93	110	72	750
18	980	126	95	55	57	500
19	980	95	95	4000 ↗	73	500
20	800	70	73	320	63	450

Control values:

IgG (mg/dl)	1191.3 ± 282.6
IgA (mg/dl)	130.1 ± 27.6
IgM (mg/dl)	133.3 ± 39.3
IgE (U/ml)	0-200
Complement (C_3)	91.1 ± 13.0
Eosinophil count	300/mm^3

TABLE II

EA (F_c) Inhibition Percentages of the Patient and Control Groups

Case no.	EA (F_c) Inhibition Percentages	
	Patient	Control
1	23.80	14.28
2	0	0
3	23.80	14.28
4	38.09	0
5	28.57	0
6	4.76	0
7	57.14	0
8	28.57	4.76
9	33.33	14.28
10	19.04	19.04
11	0	4.76
12	0	0
13	28.57	0
14	38.09	0
15	33.33	0
16	0	0
17	0	4.76
18	4.76	
19	4.76	
20	19.04	

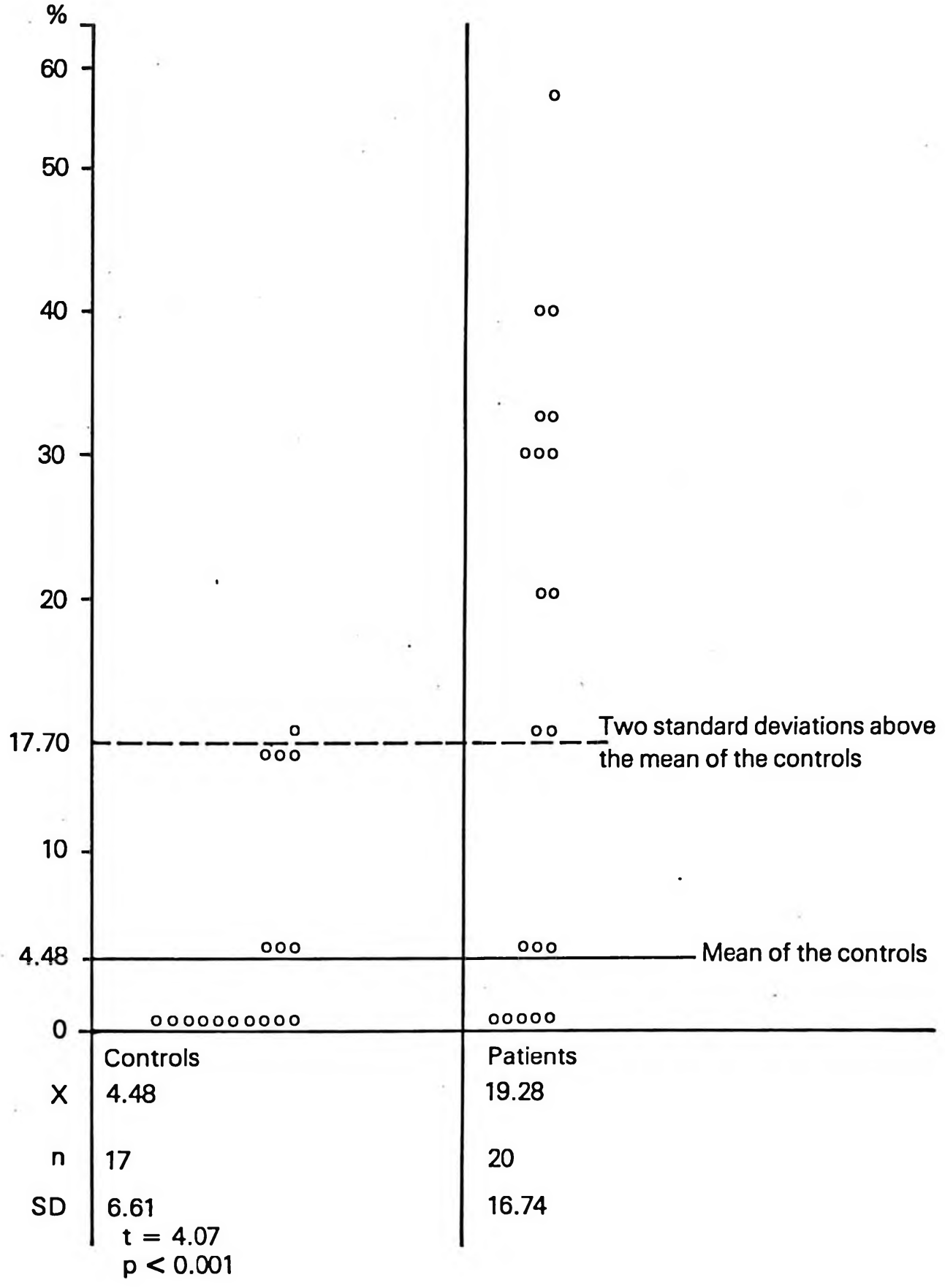

Figure 1.

Circulating immune complexes in patients and controls

TABLE III

The Percentage of Immune Complexes and Vasculitis in Cases with Acute Urticaria

Case no.	Circulating immune complexes	Vasculitis
1	+	–
2	–	–
3	+	–
4	+	–
5	+	–
6	–	–
7	+	–
8	+	–
9	+	–
10	+	–
11	–	–
12	–	+
13	+	+
14	+	–
15	+	+
16	–	–
17	–	+
18	–	–
19	–	+
20	+	–
Total	**12**	**5**
100%	**60%**	**25%**

Vasculitis was diagnosed in 5 patients (25%) according to histopathologic criteria. All of the patients with vasculitis had vascular deposits of immunoreactants, and two of them had circulating immune complexes (Table III, Figure 2). Various combinations of immunoglobulins and/or C_3 were seen in the dermal vessel walls of the urticarial lesions in 14 children (70%) by direct immunofluorescent technique (Table

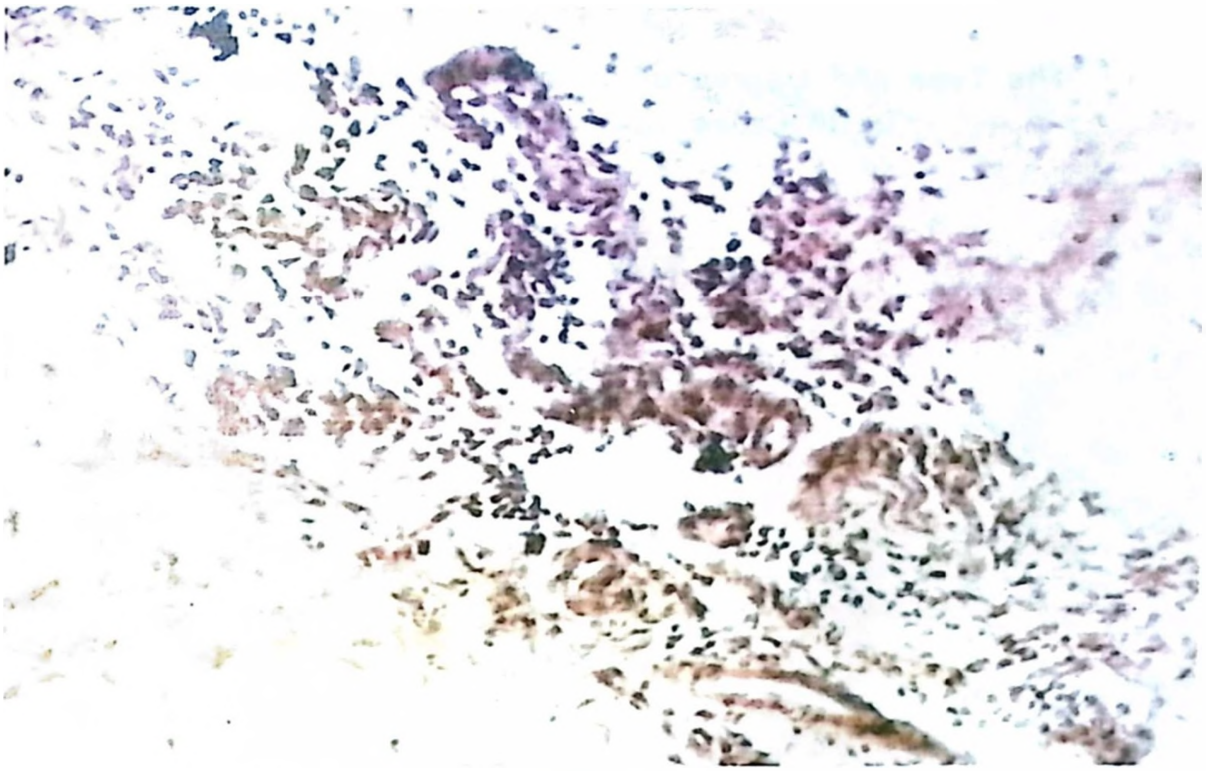

Figure 2.

(Patient No. 13) Neutrophilic, eosinophilic, and lymphomonocytic cellular filtration within and around the vessel walls (Hematoxylin-eosin × 250).

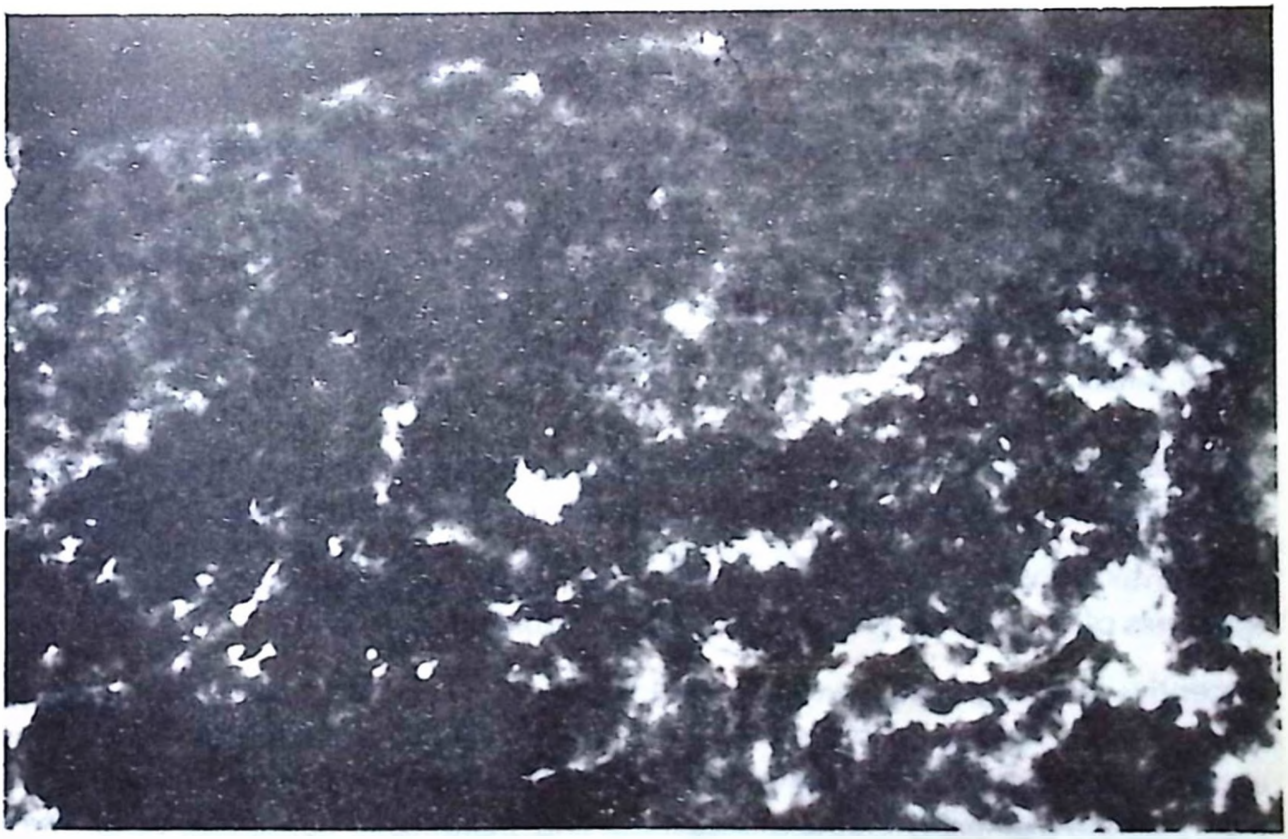

Figure 3.

(Patient No. 16) Granular deposits of IgG in the dermal vessel walls (Immunofluorescence × 320).

TABLE IV

The Type and Degree of Vascular Immune Deposition in 14 Cases with Acute Urticaria

Case no.	Immune reactants				
	IgG	IgA	IgM	C_3	IgE
1	+				
3	±	±		+ +	+
4	+	+			±
5					+
6		+ +	+ +		
7				+ +	
9					+
12	+ +				+
13					+
15			+		+
16	+			+	+
17				+ +	+
19			+	+	
20					+

± minimal
\+ slight
\+ + medium
\+ + + severe

IV, Figure 3). No vascular deposit was observed in the other 6 patients or in any of the controls. No staining could be observed along the dermal-epidermal junction.

There was a positive correlation between the total eosinophil counts and the serum IgE levels of the children with acute urticaria (Table I, Figure 4).

Recently, several groups have described vasculitis in selected patients with chronic urticaria[7,12]. These patients were young women with arthralgia or arthritis, elevated erythrocyte sedimentation rate and hypocomplementemia. They occasionally had fever, abdominal pain, glomerulonephritis and hepatitis. Phanuphak *et al*[8] have shown that 52% of 42 patients with chronic urticaria revealed vasculitis on biopsy, but vascular deposits of immunoreactants were found in only four (18%) of those

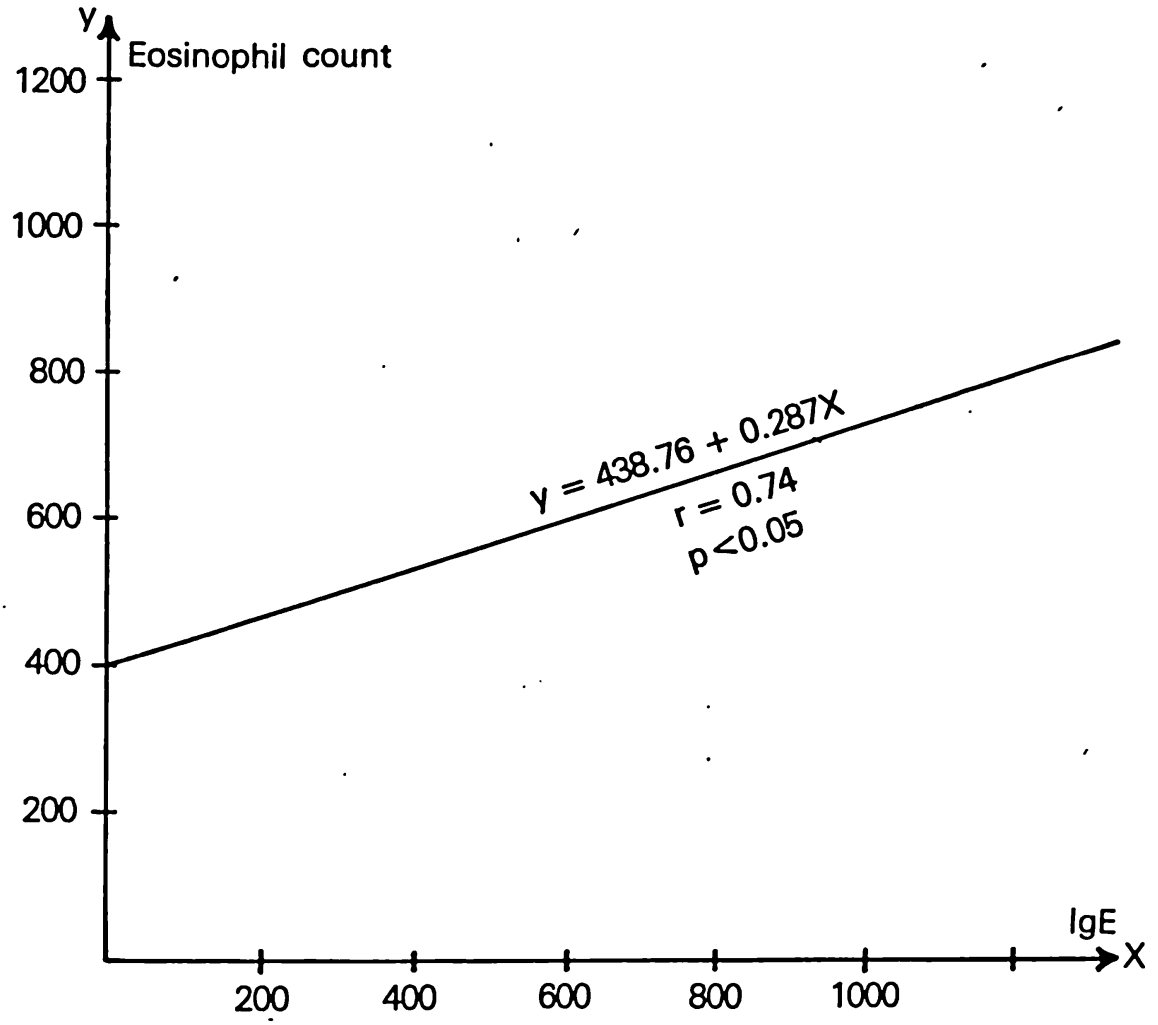

Figure 4.

The correlation between the serum IgE level and the eosinophil count of the patients.

patients. There was no compelling evidence for there being circulating immune complexes in the vasculitis group in their study as opposed to the nonvasculitis group[8]. The presence of vasculitis in patients with chronic urticaria has also been studied in our pediatric allergy and pathology units, and a report is being prepared for publication.

To our knowledge, our investigation is the first clinical, immunological and morphological study on acute urticaria in childhood. This study suggests that vasculitis may occur and circulating immune complexes may be detected in children with acute urticaria. Further investigation is needed to confirm these findings.

Summary

Circulating immune complexes and vasculitis in patients with acute urticaria have been investigated in this study. Twelve of the 20 patients with acute urticaria had circulating immune complexes (60%). Vasculitis was found to be present in 5 patients (25%).

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