

Serum IgE in patients with minimal-change nephrotic syndrome

Serum levels of IgE were studied in 53 children; 17 children had minimal-change nephrotic syndrome, 9 had probable MCNS, and 27 had other renal diseases. These studies showed higher levels of IgE in patients with MCNS and probable MCNS than in the renal control subjects or in the general population. Patients with MCNS who received therapy with cyclophosphamide had lower levels of IgE than those who did not.

Ted Groshong,[†] Lieutenant Commander (MC), USNR, Louis Mendelson, M.D., Stanley Mendoza, M.D., Michael Bazaral, Ph.D., Robert Hamburger, M.D.,* San Diego, Calif., and Bruce Tune, M.D., Stanford, Calif.

THE NEPHROTIC SYNDROME with minimal change in renal histology is one of the more common chronic renal diseases in children. With increasing knowledge of immunologic mechanisms, the pathogenesis of some forms of renal disease has been elucidated.^{1,2} The pathogenesis of minimal-change nephrotic syndrome (MCNS), however, has remained obscure. For many years investigators have noted an association between al-

lergic diseases and nephrotic syndrome in children.³⁻⁵ These observations, and a recent report of characteristic localization of IgE in the glomeruli of some patients with minimal-change nephrotic syndrome,⁶ prompted an investigation of serum IgE levels in children with various renal diseases.

MATERIALS AND METHODS

Fifty-three patients from the pediatric renal clinics of Naval Hospital and University Hospital, San Diego, California; Stanford University Medical Center, Palo Alto, California; and Children's Memorial Hospital, Chicago, Illinois, were studied. They were divided into three groups: patients with MCNS, patients with probable MCNS, and renal control subjects.

Minimal-change nephrotic syndrome. Seventeen patients were diagnosed as having MCNS by both clinical findings and renal

From the Department of Pediatrics and the Clinical Investigation Center, Naval Hospital; Department of Pediatrics, Divisions of Immunology-Allergy, Nephrology, University of California, San Diego School of Medicine; and Department of Pediatrics, Stanford University School of Medicine.

The opinions or assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the Navy Department.

**Reprint address: Department of Pediatrics, UCSD School of Medicine-San Diego, Box 109, La Jolla, Calif. 92037.*

Table I. Number and ages of patients by diagnostic category

Study groups	No. of patients	Age (yr.)	
		Mean	Range
MCNS	17	10	4-16
Probable MCNS	9	6	3-10
Renal control subjects	27	10	2-19

Table II. Diagnosis of patients who had a disease other than minimal-change nephrotic syndrome

Diagnosis	No. of patients	Biopsy	Nephrotic syndrome
Acute glomerulonephritis	8	0	0
Membranoproliferative glomerulonephritis	5	5	3
Chronic pyelonephritis	4	1	0
Focal sclerotic glomerulonephritis	2	2	2
Lupus nephritis	3	3	2
Chronic glomerulonephritis	3	3	2
Hemolytic-uremic syndrome	1	0	0
Bartter's syndrome	1	1	0
Total	27	15	9

biopsy. Clinical criteria included significant proteinuria, hypoalbuminemia (serum albumin concentration below 2.5 Gm. per 100 ml.), edema, and hypercholesterolemia. Ages are noted in Table I. The duration of illness prior to study ranged from 2 months to 14 years. Only one patient was steroid resistant. Eleven patients had received therapy with cyclophosphamide (Cytoxan) prior to this study.

The results of renal biopsies were classified as MCNS if they were normal or showed minimal focal proliferation with normal basement membranes.⁷

Probable minimal-change nephrotic syndrome. Nine patients were examined who fulfilled all the clinical criteria of MCNS, but biopsies were not performed. All of these children had an early onset of disease (before 5 years of age) and absence of hypertension or azotemia at any time. At least 90 per cent

of these patients would be expected to have MCNS on biopsy.⁸ Clinically, they were similar to the patients with MCNS who were not treated with cyclophosphamide because they had a relatively short period of illness, were generally younger when studied (Table I), and were steroid responsive. None had received cyclophosphamide. Four of the nine children were in prolonged remission after steroid withdrawal.

Renal control subjects. The renal control group included 27 patients with renal diseases other than MCNS. The ages of these children were similar to those of the children with MCNS (Table I). Diagnosis was established by renal biopsy unless it was definitely established by clinical or radiologic examination alone. Nine of these patients had clinical nephrotic syndrome with definite pathologic changes on renal biopsy (Table II).

IgE assay. Serum IgE levels were measured by using a radioimmunoassay,⁹ and results were expressed in units relative to World Health Organization IgE Standard 68-341.¹⁰ The unit has been estimated to contain 2.4 ng. of IgE.¹¹ Most serum specimens from nephrotic children were obtained while the patients were in remission and receiving corticosteroids. (Serum IgE levels are unchanged by treatment with corticosteroids for as long as 14 days.¹² The effect of more prolonged treatment with corticosteroids on serum IgE levels has not been determined.)

Statistics. The distribution of serum IgE levels in a normal population is not gaussian.^{9, 13} Groups of data were compared by using a Mann-Witney U test for the significance of differences of medians.¹⁴ The relative frequency of allergic diseases in the population was compared using chi square analysis.

RESULTS

Atopic disease. A diagnosis of atopic disease was made only when the diagnosis of seasonal allergic rhinitis, eczema, urticaria, or allergic asthma was unambiguous. A significantly higher incidence of one or more of these diseases was noted in patients with

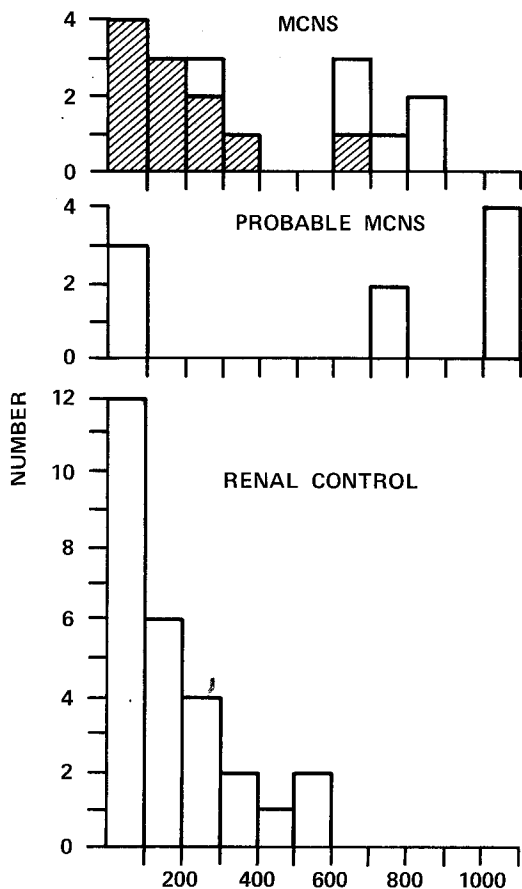


Fig. 1. Serum levels of IgE in patients with MCNS (*Top*), probable MCNS (*Middle*), and other renal diseases (*Bottom*). On the abscissa are the numbers of patients, with IgE values indicated on ordinate. Crosshatched areas indicate patients treated with cyclophosphamide.

MCNS (41 per cent) and probable MCNS (44 per cent) than in the control renal population (22 per cent- $p < 0.02$).

Serum IgE. The IgE levels of children with MCNS (mean 362 units per milliliter) were significantly higher ($p < 0.01$) than the IgE levels of the control renal population (mean 174 units per milliliter, Fig. 1). The distribution of IgE levels in children with MCNS proved on biopsy but who were not treated with cyclophosphamide (mean 650) was similar to that of the group with probable MCNS (mean 617); these two groups combined (all patients with MCNS and probable MCNS) had a significantly higher IgE level ($p < 0.005$) than the renal control

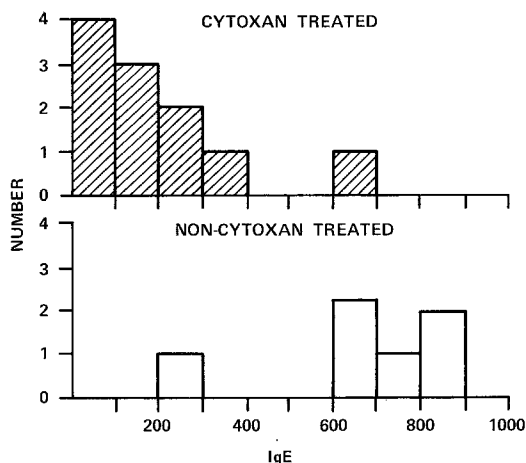


Fig. 2. Serum IgE levels in patients with MCNS treated with cyclophosphamide (crosshatched) and in those treated only with corticosteroids (clear).

subjects. The values of patients with MCNS who were treated and of those who were not treated with cyclophosphamide are shown in Fig. 2; the IgE levels in the cyclophosphamide-treated patients (mean 206 units per milliliter) were significantly lower ($p < 0.005$) than those not treated.

Nine children with nephrotic syndrome who had pathologic changes on renal biopsy had a mean serum IgE value of 102 units per milliliter. The distribution of values was similar to that of the rest of the control renal population.

DISCUSSION

For many years observers have noted an association between allergic diseases and nephrotic syndrome, both in affected individuals and in family members.^{3, 15, 16} Indeed, several persons have undergone spontaneous remission of both renal and respiratory symptoms with hyposensitization therapy.^{5, 17} Appropriate controlled studies, however, have not been performed.^{3, 16}

In 1971, Gerber and Paronetto⁶ found that patients with MCNS, during relapse, have IgE detectable in glomeruli by immunofluorescence. This was not present in patients with MCNS during remission, or in the same configuration in patients with other renal diseases. No comment was made, however,

concerning allergic symptoms or serum IgE values in these patients. In the present series IgE localization was not found in the small number of biopsies from patients with MCNS in which IgE immunofluorescence was performed. This was not unexpected, since all patients were in remission at the time of biopsy. Barratt and associates¹⁸ studied plasma and urinary IgE levels in children with heavy proteinuria and a variety of findings on renal biopsy. They found that the excretion of IgE in the urine was not increased in spite of a 100-fold increase in excretion of albumin. Plasma IgE levels were also normal. Only two of the patients studied had MCNS.

In this study, patients with MCNS and presumed MCNS had high mean values of IgE in their sera, with a wide range of values. This distribution is similar to that seen in an allergic population.^{13, 17, 19} The highest IgE values were in children with MCNS not treated with immunosuppressive agents and in children with probable MCNS. Less than 7 per cent of the normal adult population have IgE values above 500 units per milliliter,²⁰ yet five of six children with MCNS who were not treated with cyclophosphamide and six of nine patients with probable MCNS had values above that level. Only 2 of the 27 renal control subjects and one of the 11 cyclophosphamide-treated patients with MCNS had IgE values above 500 units per milliliter.

In our clinics patients with nephrotic syndrome have had renal biopsies performed either because they are older children (and might be likely to have a renal disease other than MCNS⁸) or because they were being considered for therapy with cyclophosphamide. Patients in the probable MCNS group, therefore, either are in prolonged remission after steroid withdrawal or are relatively early in the course of their disease. Those patients who have had biopsies, but were not treated with immunosuppressive agents, are also generally early in the course of their disease. Conversely, cyclophosphamide-treated children had had their disease relatively longer, were older, and had a higher

incidence of steroid dependency. It is not clear whether the difference between the cyclophosphamide-treated patients and the untreated group represents a response of the IgE levels to the drug, a change in the IgE level with time, or a difference in the basic disease process.

It is highly unlikely, however, that serum IgE elevation is a nonspecific response similar to the myriad of metabolic derangements characterizing the nephrotic syndrome. Nine children with clinical manifestations of the nephrotic syndrome, but with abnormal renal biopsies, had a distribution of serum IgE values identical to the rest of the renal control population and markedly different from that of the MCNS and probable MCNS groups.

There is good evidence that the presence of IgE is required for the occurrence of allergy.²¹ The remarkably high mean IgE levels in patients with MCNS noted above, along with the previously reported presence of IgE in glomeruli of patients with MCNS,⁶ suggest that IgE may play a role in the pathogenesis of this disease. The mechanism by which this might occur is unknown. Continuing studies of children with nephrotic syndrome will be necessary to clarify this relationship.

SUMMARY

1. The concentration of IgE was measured in the serum of children with a variety of renal diseases.
2. Those children with MCNS and probable MCNS had significantly higher IgE levels than children with other forms of renal diseases.
3. The elevated levels of IgE were not a reflection of the nephrotic syndrome as such, since children with nephrotic syndrome and histologic abnormalities determined by biopsy had lower levels of IgE than children with MCNS.
4. Children with MCNS who were previously treated with cyclophosphamide had considerably lower levels of IgE than those not treated with immunosuppressive drugs.

We thank Eva Lydick for technical assistance, Captain J. E. Schanberger (MC), USN, for his thoughtful review, and Gwen Bacilla for secretarial help.

REFERENCES

1. Dixon, F.: The pathogenesis of glomerulonephritis, *Am. J. Med.* **44**: 493, 1968.
2. Cochrane, C. G.: Mediation of immunologic glomerular injury, *Transplant. Proc.* **1**: 949, 1969.
3. Fontana, V. J., Spain, W. C., and Desanctis, A.: The role of allergy in nephrosis, *N. Y. State J. Med.* **3907**, 1956.
4. Hardwicke, J., Soothill, J. F., Squire, J. R., and Holt, I. G.: Nephrotic syndrome with pollen hypersensitivity, *Lancet* **1**: 500, 1959.
5. Wittig, H. J., and Goldman, A.: Nephrotic syndrome associated with inhaled allergens, *Lancet* **1**: 542, 1970.
6. Gerber, M. A., and Paronetto, F.: IgE in glomeruli of patients with nephrotic syndrome, *Lancet* **1**: 1097, 1971.
7. Chung, J., Habib, R., and White, R. H. R.: Pathology of the nephrotic syndrome in children, *Lancet* **1**: 4299, 1970.
8. White, R. H. R., Glosow, E. F., and Mills, R. J.: Clinicopathological study of nephrotic syndrome in childhood, *Lancet* **1**: 1353, 1970.
9. Bazaral, M., Orgel, H. A., and Hamburger, R. N.: IgE levels in normal infants and mothers and an inheritance hypothesis, *J. Immunol.* **107**: 794, 1971.
10. Rowe, D. S., Tackett, L., Bennich, H., Ishizaka, K., Johansson, S. G. O., and Anderson, S. G.: A research standard for human serum immunoglobulin E, *Bull. W.H.O.* **43**: 609, 1970.
11. Bazaral, M., and Hamburger, R. N.: Standardization and stability of immunoglobulin E (IgE), *J. Allergy Clin. Immunol.* **49**: 189, 1972.
12. Johansson, S. G. O., and Julian, L.: Immunoglobulin E in "healed" atopic dermatitis and after treatment with corticosteroids and azathioprine, *Br. J. Dermatol.* **82**: 10, 1970.
13. Arbesman, C. E., Ita, A., Wypych, J. I., and Wicker, K.: Measurement of serum IgE by a one-step single radial radio-diffusion method, *J. Allergy Clin. Immunol.* **49**: 72, 1972.
14. Hoel, P. G.: Introduction to mathematical statistics, ed. 2, New York, 1954, John Wiley & Sons, Inc., pp. 291-293.
15. Black, W. M., Jackson, R. L., Stearns, G., and Butsch, M. P.: Lipoid nephrosis, *Pediatrics* **1**: 733, 1948.
16. Barness, L. A., Moll, G. H., and Janeway, C. A.: Nephrotic syndrome. I. Natural history of the disease, *Pediatrics* **5**: 486, 1950.
17. Williamson, D. A. J.: Nephrotic syndrome associated with inhaled allergens, *Lancet* **1**: 778, 1970.
18. Barratt, T. M., Turner, M. W., and Johansson, S. G. O.: Urinary excretion of immunoglobulin E in the nephrotic syndrome and atopic eczema, *Lancet* **2**: 402, 1971.
19. Johansson, S. G. O.: Raised levels of a new immunoglobulin class (IgND) in asthma, *Lancet* **2**: 951, 1967.
20. Unpublished observations.
21. Bennich, H., and Johansson, S. G. O.: Structure and function of human immunoglobulin E, *Adv. Immunol.* **13**: 1, 1971.