

Elevated Levels of Immunoglobulin E May Indicate Steroid Resistance or Relapse in Adult Primary Nephrotic Syndrome, Especially in Minimal Change Nephrotic Syndrome

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Immunoglobulin E (IgE) antibodies may play a role in the development of kidney diseases that are related to hypersensitivity reactions. Patients with idiopathic nephrotic syndrome often exhibit increased serum IgE levels and this may be related to sensitivity to steroid treatment. In the present study, the serum IgE levels in 120 patients with different types of primary nephrotic syndrome (PNS) were analysed and found to be significantly elevated in cases of minimal change nephrotic syndrome (MCNS) compared with membranous nephropathy or membrano-

proliferative glomerulonephritis. No difference in serum IgE level was observed between cases of steroid-sensitive nephrotic syndrome (SSNS) or steroid-resistant nephrotic syndrome, although the serum IgE level was significantly elevated in SSNS patients in relapse compared with SSNS patients in remission. In MCNS patients, 73.6% exhibited SSNS regardless of their serum IgE level at diagnosis. It is concluded that elevated levels of IgE may be a feature of steroid resistance or relapse, indicating prognostic significance in adult PNS, particularly in MCNS.

KEY WORDS: IMMUNOGLOBULIN E; PRIMARY NEPHROTIC SYNDROME; MINIMAL CHANGE NEPHROTIC SYNDROME; STEROID-SENSITIVE NEPHROTIC SYNDROME; STEROID-RESISTANT NEPHROTIC SYNDROME; NEPHROTIC SYNDROME RELAPSE

Introduction

Immunoglobulin E (IgE) is associated with allergic reactions and increased IgE levels are detected in patients with atopic diseases. The highest levels of IgE are often associated with atopic dermatitis, followed by atopic asthma, perennial allergic rhinitis and seasonal allergic rhinitis. Measurement of

total IgE levels in patients with allergic bronchopulmonary aspergillosis can be used to monitor disease activity and response to therapy. IgE may also play a role in immediate hypersensitivity reactions, as is suggested by the association of allergic reactions with nephrotic syndromes,^{1,2} and elevated serum IgE levels have been noted in

glomerular diseases,³ such as minimal change nephrotic syndrome (MCNS).⁴ High serum IgE levels may be related to poor disease prognosis and frequent relapses,⁵ or poor responses to steroid therapy⁶ in nephrotic children. Serum IgE levels may not only reflect disease activity, but may also predict disease outcome in childhood nephrotic syndrome.⁷

Primary nephrotic syndrome (PNS) is a glomerulopathy of unknown aetiology that is characterized by marked oedema, proteinuria, hypoalbuminaemia and, often, hyperlipidaemia. There are five distinct histological variants of idiopathic PNS: (i) MCNS; (ii) focal segmental glomerulosclerosis (FSGS); (iii) membranous nephropathy; (iv) immunoglobulin A (IgA) nephropathy; and (v) membranoproliferative glomerulonephritis. A close relationship exists between these histological variants and degree of disease progression, as well as therapy outcomes. Thus, different histological variants and clinical manifestations have different treatments and prognoses.⁸

A strong association has been demonstrated between steroid-resistant nephrotic syndrome (SRNS), atopy and elevated serum levels of IgE.⁹ In contrast there has been little investigation of the relationship between serum IgE levels, the histological variants of PNS and therapeutic outcomes. The present study attempted, therefore, to identify whether IgE levels were related to the histological variants of idiopathic PNS, whether IgE could be used to predict the histological variants of idiopathic PNS before renal biopsy and whether IgE could be a good predictor of steroid resistance or susceptibility to relapse.

Patients and methods

STUDY POPULATION

Adult Chinese patients (≥ 18 years of age)

with idiopathic PNS, admitted sequentially to the Kidney Disease Centre at The First Affiliated Hospital of Zhejiang University, Hangzhou, China between May 2009 and February 2011, were enrolled into the study. Patients were diagnosed with PNS according to the 1995 World Health Organization (WHO) guidelines¹⁰ and the 2001 domestic renal biopsy diagnostic criteria,¹¹ and the diagnoses were recorded in registered hospital records. The results of percutaneous renal biopsies were available for all patients before treatment. All renal specimens were analysed by light microscopy, immunofluorescence and electronic microscopy. Patients with infection, systemic lupus erythematosus, positive antinuclear antibody, gross haematuria, allergic disorders, elevated blood urea and serum creatinine levels, as well as those who received prednisolone or any other immunosuppressive agent within 4 weeks prior to the study were excluded.

The study was approved by the Ethics Committee of The First Affiliated Hospital, College of Medicine, Zhejiang University, China and written informed consent was obtained from all participants at the time of enrolment.

DEFINITIONS

The following terms commonly used in the management of nephrotic syndrome were applied in the present study.¹² Remission described a urinary protein/creatinine ratio (UP/Cr) < 0.2 , or the continued detection of trace levels of UP/Cr over a 3-day period. Relapse described an increase of UP/Cr to ≥ 2 following a period of remission. Steroid resistance was defined as the inability to induce remission following 4 weeks of daily steroid therapy.

All patients, including those with MCNS, were divided into two groups according to

the definition of their response to steroids: (i) steroid-sensitive nephrotic syndrome (SSNS) was defined as being free of proteinuria following 4 weeks of steroid treatment; and (ii) SRNS (steroid-resistant nephrotic syndrome) was defined as failure to achieve a therapeutic response despite 4 weeks of steroid treatment.

STUDY ASSESSMENTS

Total serum IgE levels were measured using the UniCAP 100 system (Pharmacia & Upjohn Diagnostics, Uppsala, Sweden) automated IgE-specific assay. Levels of IgA, IgM and IgG were measured by an automated quantitative immunochemical reaction using the BNTMII system (Siemens, Erlangen, Germany). All fluoroenzyme immunoassay reagents were purchased from Phadia Diagnostics, Uppsala, Sweden. Urinary protein was measured by the Tina-Quant albumin assay, blood urea nitrogen (BUN) was measured by kinetic ultraviolet assay, blood and urinary creatinine were measured by standard enzymatic assay, and serum albumin was measured by the bromocresol green method. All parameters were measured on an Abbott AerosetTM clinical chemistry analyser (Abbott Laboratories, Abbott Park, IL, USA) using commercially available reagents from Roche Diagnostics (Indianapolis, IN, USA).

STATISTICAL ANALYSES

All data were analysed using the SPSS[®] statistical package, version 13.0 (SPSS Inc., Chicago, IL, USA) for Windows[®]. Unless otherwise stated, all data are presented as the mean $\pm$ SD. The IgG, IgM, IgA, serum albumin, creatinine, BUN and urinary protein results were normally distributed. The IgE levels were not normally distributed and were, therefore, reported as the median and 25th – 75th percentile distribution. The

IgE levels between groups were analysed using a one-way analysis of variance and those between patients with SSNS and SRNS were analysed using the Student's *t*-test. A *P*-value < 0.05 was considered to be statistically significant.

Results

A total of 126 adult patients (86 males, 40 females; median age 26 years; range 14 – 75 years) were diagnosed with idiopathic PNS and accepted percutaneous renal biopsy. Among them, 53 cases (42.1%) were diagnosed with MCNS; 27 (21.4%) with membranous nephropathy; 15 (11.9%) with membranoproliferative glomerulonephritis; 25 (19.8%) with IgA nephropathy; four (3.2%) with FSGS; and two (1.6%) with primary amyloidosis. The four patients with FSGS and the two with primary amyloidosis were excluded from further analyses.

The demographic data and clinical characteristics of the 120 idiopathic PNS patients who were included in the analyses are shown in Table 1 according to histological variant. Age at MCNS presentation ranged from 16 to 75 years (mean $\pm$ SD 28.0 $\pm$ 15.4 years), although the proportion of young adults with MCNS was relatively high, with 66.0% (35/53 patients) being < 40 years old. All patients manifested features typical of PNS at the time of presentation or renal biopsy. In the active nephrotic stage, a lower than normal serum IgG level was found in 86.7% (104/120 patients) of cases, with a mean level of 475 mg/dl (normal range 700 – 1600 mg/dl; Clinical Laboratory, The First Affiliated Hospital, College of Medicine, Zhejiang University) and a raised serum IgE level was found in 75.0% (90/120 patients) of cases, with a mean level of 616 kU/l (normal range 0 – 100 kU/l; Clinical Laboratory, The First Affiliated Hospital, College of Medicine, Zhejiang University).

TABLE 1:

Demographic and clinical characteristics of the adult Chinese patients with idiopathic primary nephrotic syndrome who were included in the analyses, according to histological variant

Demographic or clinical characteristic	Membranous nephropathy (n = 27)	MCNS (n = 53)	IgA nephropathy (n = 25)	Membranoproliferative glomerulonephritis (n = 15)
Age, years	43.3 ± 17.8	28.0 ± 15.4	33.2 ± 16.6	35.3 ± 18.4
Females/males	7/20	16/37	10/15	6/9
Serum albumin, g/l	20.7 ± 7.7	19.0 ± 7.8	17.1 ± 4.8	20.4 ± 6.5
Creatinine, µmol/l	73.0 ± 19.5	73.1 ± 19.2	70.3 ± 17.3	89.2 ± 33.0
BUN, mmol/l	5.4 ± 2.6	6.9 ± 4.0	5.1 ± 1.1	7.6 ± 3.3
UP/Cr, g/g	9.6 ± 7.9	8.7 ± 5.8	8.7 ± 6.9	10.7 ± 7.1
Proteinuria, g/day	9.3 ± 7.8	8.5 ± 5.3	8.7 ± 8.4	10.7 ± 5.5
IgG, mg/dl	474.9 ± 238.1	459.2 ± 288.2	448.4 ± 181.7	484.4 ± 277.9
IgM, mg/dl	129.2 ± 56.2	161.8 ± 84.4	157.5 ± 79.2	179.2 ± 64.0
IgA, mg/dl	223.6 ± 98.9	225.6 ± 84.4	224.8 ± 63.8	206.1 ± 74.7
IgE, kU/l	112 (31 – 341)	709 (200 – 1288)	333 (137 – 827)	290 (64 – 467)

Data presented as mean ± SD, number of patients or median (25th – 75th percentile).

Between-group statistical analysis not undertaken.

MCNS, minimal change nephrotic syndrome; BUN, blood urea nitrogen; UP/Cr, urinary protein/creatinine ratio; Ig, immunoglobulin.

The serum IgE levels in the four analysed histological variants of idiopathic PNS are shown in Fig. 1. The IgE levels were significantly elevated in patients with MCNS (median, 25th – 75th percentile 709 kU/l, 200 – 1288 kU/l) compared with those with membranous nephropathy (median, 25th – 75th percentile 112 kU/l, 31 – 341 kU/l; $P < 0.001$) and membranoproliferative glomerulonephritis (median, 25th – 75th percentile 290 kU/l, 64 – 467 kU/l; $P < 0.05$). There was no difference in IgE levels between patients with MCNS and IgA nephropathy (median, 25th – 75th percentile 333 kU/l, 137 – 827 kU/l), and patients with IgA nephropathy and membranous nephropathy or membranoproliferative glomerulonephritis.

Of the 120 PNS patients, 72 were steroid-sensitive (SSNS group) and 48 were steroid-resistant (SRNS group). No difference in serum IgE levels was observed when the SSNS

group was compared to the SRNS group (median, 25th – 75th percentile 223 kU/l, 72 – 826 kU/l, versus 376 kU/l, 101 – 778 kU/l). A total of 38.9% (28/72 patients) of the SSNS group relapsed and they had significantly elevated serum IgE levels compared with 61.1% (44/72 patients) in the SSNS group in remission (median, 25th – 75th percentile 767 kU/l, 481 – 1215 kU/l, versus 189 kU/l, 63 – 442 kU/l; $P < 0.001$). Among the MCNS patients, 26.4% (14/53 patients) exhibited SRNS and 73.6% (39/53 patients) exhibited SSNS regardless of their serum IgE levels at diagnosis. Levels of IgE were significantly higher in the MCNS patients with SRNS than the MCNS patients with SSNS (median, 25th – 75th percentile, 1530 kU/l, 706 – 2709 kU/l versus 516 kU/l, 159 – 799 kU/l; $P < 0.05$). In the SSNS group of MCNS patients a total of 48.7% (19/39 patients) were in relapse compared with 51.3% (20/39 patients) who were in

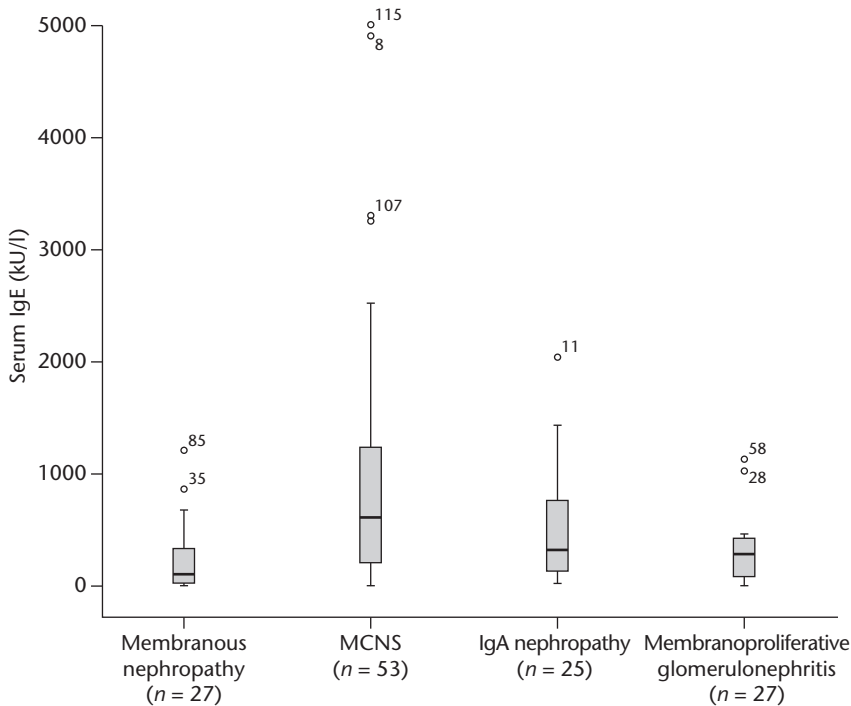


FIGURE 1: Box and whisker plots showing serum immunoglobulin (IgE) levels in patients with membranous nephropathy, minimal change nephrotic syndrome (MCNS), IgA nephropathy or membranoproliferative glomerulonephritis. The IgE level was significantly elevated in patients with MCNS compared with membranous nephropathy ($P < 0.001$) and membranoproliferative glomerulonephritis ($P < 0.05$) but not compared with those with IgA nephropathy; one-way analysis of variance (black horizontal lines represent median values, the extremities of the box are the 25th and 75th percentiles, 'whiskers' represent minimum and maximum outliers, and the circles above the bars represent extreme outliers, with the numbers being the specimen numbers)

remission. The IgE levels were significantly elevated in the patients in relapse compared with those in remission (median, 25th – 75th percentile 709 kU/l, 516 – 1230 kU/l, versus 164 kU/l, 39 – 526 kU/l; $P < 0.001$).

Discussion

The present study of idiopathic PNS in Chinese adults showed MCNS to be the most common cause of adult-onset idiopathic PNS in this patient cohort and that MCNS predominantly affected young adults. Membranous nephropathy was the second most common cause and FSGS was rarely seen. The Chinese adults with MCNS in the

present study were less responsive to steroid treatment (73.6%) than has previously been found for children (95%),¹³ non-Chinese Asian adults (83 – 94%),¹⁴ or Western groups (80 – 92%).¹⁵

No difference was observed in serum IgE levels between the SSNS or SRNS groups in the present study. The IgE levels in the SSNS group were, however, significantly elevated in patients in relapse compared with those in remission. Among patients with the MCNS histological variant, patients with SRNS had significantly higher serum IgE levels than those with SSNS. Moreover, also in the MCNS variant, IgE levels were significantly elevated

in patient in relapse compared with those in remission. Thus, it was concluded that elevated levels of IgE may be a feature of steroid resistance or relapse, indicating prognostic significance in adult PNS, particularly in MCNS. The present study, therefore, confirmed the results of previous studies that had demonstrated increased serum IgE levels in glomerulonephritis, particularly MCNS.¹⁶ Previously, serum IgE level has been shown to be excellent as a predictor of MCNS¹⁶ and has been shown to be increased not only in patients with active nephrotic syndrome, but also in patients who experience infrequent or frequent relapses compared with healthy control subjects.³ It can be concluded, therefore, that elevated levels of IgE may be a feature of steroid resistance, indicating prognostic significance.

Immunoglobulin E is not readily found in renal tissues and no experimental model of IgE-mediated nephropathy has been reported. Thus, proving the role of IgE in nephropathy may be difficult. Increased IgE may, however, reflect immune dysfunction. The increased IgE levels seen in MCNS may indicate B- and T-cell activation.^{17,18} Studies have revealed that patients with membranous glomerulonephritis, MCNS and IgA nephropathy have a predominant ongoing T-helper cell type 2 (Th2) immune response. MCNS may, therefore, be an example of a Th2-dependent glomerular disease, which have frequently been linked with elevated levels IgE,⁹ atopy,³ elevation of interleukin (IL)-4 in peripheral T-cells,^{19,20} and IL-13 secretion during relapse episodes; IL-13 regulates immunoglobulin isotype switching towards IgE.²¹ T-lymphocytes from

patients with MCNS down-regulate the IL-12 receptor β_2 subunit (IL-12R β_2) during relapse, which is important because IL-12R β_2 is selectively expressed by Th1 cells and plays a critical role in IL-12 signal transduction.^{22,23}

Despite encouraging results, there were several limitations to the present study. First, the number of patients was small, which limited the predictive accuracy. Secondly, as only one institution was involved in the study, the results may not be directly extrapolated to other patient populations. Thirdly, patients with elevated serum creatinine levels were excluded from the study, although this also had the benefit of making the study population more homogeneous. Finally, the lack of follow-up data, including missing IgE levels during remission or relapse episodes, limited the attempt to draw a correlation between serum IgE levels and treatment response.

In summary, significantly higher serum IgE levels were shown to be associated with disease activity and outcome in adults with PMS. Measurement of serum IgE levels may improve clinical decision making and management in homogeneous subsets of these patients, particularly those with contraindications to renal biopsy.

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Conflicts of interest

The authors had no conflicts of interest to declare in relation to this article.

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