Paediatrica Indonesiana

VOLUME 45 March - April • 2005 NUMBER 3-4

Original Article

Serum immunoglobulin E levels in children with idiopathic nephrotic syndrome

Ninik Asmaningsih, MD; Windhu Poernomo, MD, MS, PhD; M Sjaifullah Noer, MD

Abstract

Background Children with idiopathic nephrotic syndrome (INS) have been known to have T-cell dysfunction and an impairment of the cytokine network that may alter glomerular permeability and the glomerular filtration barrier. This disorder may contribute to the presence of urinary protein loss in children with INS. The elevation of serum IgE levels has been noted in some cases, but its association with steroid-responsive nephrotic syndrome has not been fully elucidated.

Objective This study was done to investigate the association between serum IgE levels prior to prednisone treatment in children with INS and the outcome of treatment.

Methods A prospective observational study has been conducted on 22 children with INS. Prednisone therapy was given with a dose of 60 mg/m^2 body surface area (BSA) for four weeks followed by a single dose of 40 mg/m^2 BSA every other day for another four weeks. This protocol was applied for steroid-responsive INS children. Children with steroid resistance were given oral cyclophosphamide 2 mg/kg for eight weeks. IgE level measurements were performed prior to prednisone therapy and at remission. Data were analyzed using one-way ANOVA and multiple regression.

Results Twenty-two children were enrolled in this study. High levels of serum IgE were found in 95.5% of children, with a mean of 2002.5 (SD 2172.1) IU/ml. The serum IgE levels of INS children with history of allergy were significantly higher than those of nephrotic children without history of allergy (P<0.05). However, there was no significant correlation between the serum IgE levels and the outcome of treatment in children with INS.

Conclusion The high serum IgE levels in children with INS seem to be associated with humoral immune disorder and did not have any association with the outcome of therapy. Even though the serum IgE levels were significantly higher in INS children with history of allergy, other factors that may influence serum IgE levels must be considered **[Paediatr Indones 2005;45:55-59].**

Keywords*: idiopathic nephrotic syndrome, prednisone, IgE, allergy*

Idiopathic childhood nephrotic syndrome (INS) represents a heterogeneous set of glomerular disorders. Data accumulated suggest that patients with INS have T-cell dysfunction and an impaired cytokine network that may alter the glomerular permeability and glomerular filtration barrier, contributing to protein loss.[1,2] This disease is usually divided into two entities based on the response to steroid therapy, i.e. steroid-sensitive nephrotic syndrome and steroid-resistant nephrotic syndrome. Children with steroid-resistant nephrotic syndrome tend to develop end-stage renal failure.[3,4,5]

IgE is mostly known for its association with hypersensitivity. In addition, elevated serum IgE levels have been noted in glomerular diseases. Higher levels of serum IgE in nephrotic children have been related to poor outcomes with frequent relapses or poor responses to steroid therapy.[1]

The purpose of the study was to investigate the association between IgE levels prior to prednisone treatment and the outcome of treatment in children with idiopathic nephrotic syndrome.

From the Department of Child Health, Medical School, Airlangga University, Surabaya, Indonesia (NA, MSN) and the Department of Biostatistics, School of Public Health, Airlangga University, Surabaya, Indonesia (WP).

Reprint requests to: Ninik Asmaningsih, MD, Department of Child Health, Medical School, Airlangga University, Soetomo Hospital, Jl. Prof. Moestopo 6-8, Surabaya 60286. Tel/Fax: 62-31-5501748; E-mail: ninikas@hotmail.com.

Methods

This was a prospective observational study on children with initial attack of idiopathic nephrotic syndrome in the Pediatric Nephrology Division, Dr Soetomo Hospital, from January 2002 to December 2003. Parents signed informed consent prior to the enrollment.

Children with initial attack of idiopathic nephrotic syndrome who had never received prednisone therapy were included in this study. Sample size was determined using a formula to fulfill normal distribution with α of 95%. Children with initial attack of INS who had received prior prednisone therapy, had not completed the treatment, and were lost to follow up, were excluded.

Nephrotic syndrome was defined as the presence of edema, plasma albumin <25 g/l, and proteinuria >40 mg/m^2 body surface area (BSA)/hour or protein:creatinin ratio >200 mg/mmol. Relapse was defined as increased urinary protein excretion >40 mg/m^2 BSA/hour or albustix ++ or more for three consecutive days, having previously been in remission. Remission was defined as urinary protein excretion <4 mg/hr/m^2 BSA or albustix negative or trace for three consecutive days.[6] A patient was classified as steroid responsive when remission could be achieved with steroid therapy alone. Steroid resistance was defined as failure to achieve response after four weeks of 60 mg/m^2 BSA/day of prednisone. Frequent relapses were two or more relapses within six months after initial response or more than four relapses within any 12-month period. Steroid dependence was two consecutive relapses occurring during corticosteroid treatment or within 14 days of its cessation.[6]

Prednisone therapy was commenced based on the protocol of The International Study of Kidney Diseases in Children. Prednisone therapy was given with a dose of 60 mg/m^2 BSA for four weeks, followed by a single dose of 40 mg/m^2 BSA every other day for another four weeks.[7] This protocol was applied for INS children with steroid response. For INS children with steroid resistance, oral cyclophosphamide was commenced with the dose of 2 mg/kg for 8–12 weeks.[6] Serum IgE level measurements were performed prior to prednisone treatment and at remission.

Based on the outcome of the prednisone treatment, children were stratified into steroid responsive nephrotic syndrome (i.e., infrequent relapses, frequent relapses, steroid-dependent) and steroid-resistant nephrotic syndrome. Association of serum IgE levels with the outcome of treatment was analyzed using one-way ANOVA and multiple regressions. The difference of serum IgE levels between children with history of allergy and children without allergy was analyzed using independent t-test.

The Ethical Committee of Dr. Soetomo hospital Surabaya gave ethical clearance for this study.

Results

During the study period, 23 children with initial attack INS were enrolled. None of them had ever received prednisone therapy. One child was excluded since he did not complete the treatment and was lost to follow up. The final set of subjects consisted of 5 females and 17 males. The average age of children in this study (mean $\pm$ SD) was 6.8 $\pm$ 3.1 years. According to response towards prednisone therapy, the majority of children (21/22) were steroid-sensitive, while 1/22 was steroid-resistant. Among the children with steroid-sensitive nephrotic syndrome, 1/22 children had frequent relapse nephrotic syndrome, 3/22 children were steroid dependent, and 17/22 had infrequent relapse nephrotic syndrome (**Figure 1**). Five of 22 children had history of allergy.

Prior to prednisone therapy, high levels of serum IgE was found in 22 children, while one child had

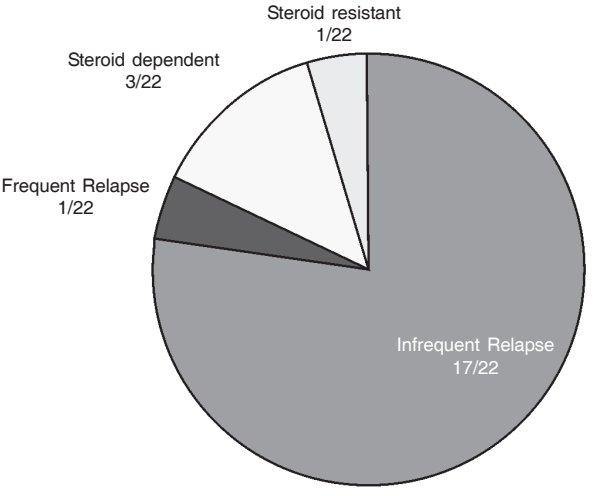

Figure 1. Outcome of prednisone therapy in children with idiopathic nephrotic syndrome.

normal IgE level. The average serum IgE level was (mean ± SD) 2002.5 ± 2172.1 IU/ml. The average serum IgE level of five children with a history of allergy was (mean ± SD) 3013.7 ± 3805.4 IU/ml, while that of 17 children without history of allergy was 1704.3 ± 1468.9 IU/ml. This difference was statistically significant (P<0.05) (**Figure 2**). The highest serum IgE level (9618 IU/ml) was found in a child with infrequent relapse nephrotic syndrome. This child also had a history of allergic rhinitis. The lowest serum IgE level (55.2 IU/ml) was also found in a child with infrequent relapse nephrotic syndrome; however, this child had no history of allergy.

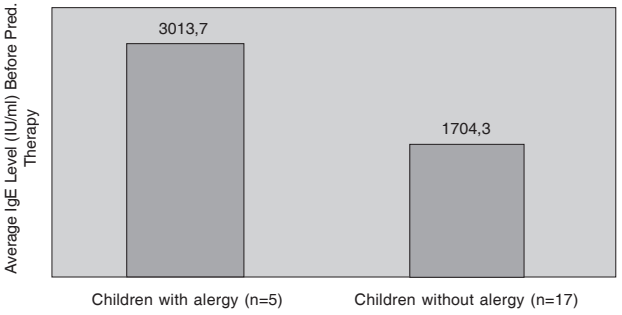

FIGURE 2. MEAN IGE LEVELS PRIOR TO PREDNISONE THERAPY IN CHILDREN WITH IDIOPATHIC NEPHROTIC SYNDROME, WITH AND WITHOUT HISTORY OF ALLERGY (P<0.05)

Statistical analysis using logistic regression showed no correlation between IgE levels and outcome of prednisone treatment in children with idiopathic nephrotic syndrome (P>0.05).

Discussion

Minimal change nephrotic syndrome (MCNS) is the most common form of nephrotic syndrome in childhood that characteristically responds well to steroid therapy. It has a well-recognized association with atopy. Hardwicke *et al* in 1959 found the correlation of pollen hypersensitivity with seasonal protein loss. Subsequently, various studies have described higher incidences of allergic disorders such as asthma, allergic rhinitis, and atopic eczema in children with steroid-sensitive nephrotic syndrome.[8]

IgE is mostly known for its association with hypersensitivity. In addition, elevated serum IgE has been reported in glomerular diseases. Higher levels of serum IgE in nephrotic syndrome was related to poor outcome with frequent relapse or poor response to steroid therapy. Serum IgE levels increase during an acute stage and recover in remission. This implies that IgE production reflects immunological regulation, which might play a pathogenic role in nephrotic syndrome. However, it was necessary that IgE in the host had direct relation to specific atopic diseases.[9,10]

Our study shows that the majority of children with INS prior to prednisone therapy had high levels of serum IgE. Only one of 22 children had normal serum IgE level. This child had no history of allergy and was included in a group of children with infrequent-relapse nephrotic syndrome. The highest serum IgE level was also found in a child with infrequent-relapse nephrotic syndrome who had history of allergy. The cause of the increase of serum IgE levels in children with idiopathic nephrotic syndrome remains unclear; it seems to be influenced by several factors.

The increased serum IgE level in children with INS was probably the result of primary immune disturbances. Many studies have been conducted to investigate lymphocyte abnormalities in INS. However, the results have been conflicting. Increased T suppressor cell activity has been described in some children with INS which return to normal after steroid

TABLE 1. ASSOCIATION OF SERUM IGE LEVELS WITH THE OUTCOME OF PREDNISONE THERAPY

Outcome of prednisone therapy	N (22)	Age (Year) Mean (SD)	IgE (IU/ml) Mean (SD)	P
Infrequent relapse	17	6.8 (3.2)	2038.9 (2433.4)	>0.05
Frequent relapse	1	6.0	2433.6	>0.05
Steroid dependent	3	5 ± 1	1248.0 ± 685.8	>0.05
Steroid resistance	1	12	3216.2	>0.05

treatment. An increase in Tγ cells was associated with suppressor activity. Meanwhile, another study showed a decrease of both Tγ and Tμ cells.[2,12] IgE synthesis is modulated by several factors. Activation of Th2 lymphocytes play a key role in IgE-mediated inflammation in atopic diseases and parasite infections.[1] The possible link between abnormal T cell response and glomerular diseases was postulated 30 years ago. Logrue *et al* found that systemic infusion of supernatant T lymphocytes from patients with MCNS relapse induced proteinuria in rats. These observations have suggested that peripheral immune cells produce a circulating factor which impairs the glomerular filtration barrier.[13]

Th1 cytokine (interferon IFN–α) and Th2 cytokine (IL-13 and IL-4) are also known to have regulatory effects on IgE synthesis. CD4+ and CD8+ T cell interleukin (IL-13 mRNA expression) was significantly increased in children with steroid-sensitive nephrotic syndrome.[6,14 ,15]

T lymphocytes from MCNS display a down-regulation of the IL-12 receptor ß2 subunit (IL-12Rb2) during relapse, while the second component of IL-12R, the ß1 chain, was normally expressed. The IL-12Rß2 is selectively expressed by Th1 cells and plays a key role in the transduction of IL-12 signaling through the Jak/Stat pathway. The down regulation of the IL-12Rß2 was compatible with a lack of IL-12 production during relapse as reported by Stefanovic *et al*. They suggested that activated T cells of MCNS were early driven toward Th2 phenotype. Valanciute *et al* also supported the finding that there was an increased Th2 specific factor (c-maf) during relapse. These results were in agreement with early reports by Kimata *et al* and Yap *et al*. They found an increasing production of IL-13 Th2 cytokine during relapse. [13]

Yap (1999) also studied both CD4+ and CD8+ cells in patients with SRNS. During relapse, the level of IL-13 mRNA expression was significantly increased compared to that in normal children, children with viral infection, and nephrotic children in remission. The results showed no significant difference of IL12, IFN-y, and IL-4 mRNA expression comparing to CD4+ and CD8+ cells in nephrotic patients, during relapse and remission phases with normal controls.[11] The increase in IgE production reflects immunological regulation that might play a pathogenic role in nephrotic syndrome but is not necessarily related directly to specific atopic diseases.

This study supported Cheung's study that children with history of allergy had higher serum IgE levels than those without history of allergy.[8] The significant difference of IgE levels in INS children with and without history of allergy indicated that humoral immune disorder takes into account an increasing serum IgE level. However, we have to consider that other factors may be influential in increasing serum IgE levels in children with INS.

Some studies have also argued that there was no correlation between nephrotic relapses and history of allergy. It has already been known that patients with steroid-sensitive nephrotic syndrome have elevated serum IgE levels, especially in the active relapse phase. Because of the intense association between MCNS and atopy, the high serum IgE levels were thought to be predictive of the atopic stage in these children.[8] Cheung *et al* (2004) found that serum IgE levels were higher in atopic children with steroid-sensitive nephrotic syndrome when they were in remission than in non atopic patients. However, in both atopic and non-atopic nephrotic children, serum IgE levels were significantly elevated during relapses compared to remission. Additionally, in a cohort study of those patients there was no correlation between the elevation of serum IgE level during nephrotic relapses and history of atopy. This implies that the increase of serum IgE levels during nephrotic relapse was most likely a result of the humoral immune perturbation seen in patients in this phase of the disease rather than playing a direct role in the pathogenesis of protein loss.[8] Our study found no correlation between the level of IgE before prednisone therapy and the outcome of treatment ($P>0.05$). These results supported the view that the increase of IgE level is the result of humoral immune disorder and does not correlate directly with the course of the disease.

In conclusion, our data suggested that many factors influence the elevation of serum IgE level in children with INS and that there is no direct association between serum IgE level prior to prednisone therapy and the outcome of treatment. Further investigation is needed to understand the influence of IL-13 mRNA on the increase of IgE level in children with INS.

References

1. Tai YL, Chen TY, Yang KD. Implication of serum IgE in childhood nephrotic syndrome. Pediatr Nephrol 2003;18:1211-5.
2. Cunard R, Kelly CJ. T cells and minimal change disease. J Am Soc Nephrol 2002;13:1409-11.
3. Haycock G. The child with idiopathic nephrotic syndrome. In: Nicholas JA, editor. Clinical paediatric nephrology. 3rd edition. Postlethwaite: Oxford University Press; 2003. p. 341-66.
4. Niaudet P. Steroid-sensitive idiopathic nephrotic syndrome in children. In: Avner ED, Harmon WE, Niaudet P, editors. Pediatric nephrology. 5th edition. Philadelphia: Lippincott William & Wilkins; 2004. p. 543-56.
5. Niaudet P. Steroid-resistant idiopathic nephrotic syndrome in children. In: Avner ED, Harmon WE, Niaudet P, editors. Pediatric nephrology. 5th edition. Philadelphia: Lippincott William & Wilkins; 2004. p. 558-73.
6. Clark AG, Barratt TM. Steroid-responsive nephrotic syndrome. In: Barratt TM, Avner ED, Harmon WE, editors. Pediatric nephrology. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 1999. p. 731-47.
7. International Study of Kidney Diseases in Children. The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisone. J Pediatr 1981;98:561-4.
8. Cheung W, Wei CL, Seah CC. Atopy, serum IgE, and interleukin-13 in steroid-responsive nephrotic syndrome. Pediatr Nephrol 2004;19:627-32.
9. Schulte-Wissermann H, Gortz W, Straub E. IgE in patients with glomerulonephritis and minimal-change nephrotic syndrome. Eur J Pediatr 1979; 131:105-11.
10. Meadow SR, Sarsfield JK, Scott DG, Rajah SM. Steroid-responsive nephrotic syndrome and allergy: immunological studies. Arch Dis Child 1981;56:517-24.
11. Durkan A, Hodson E, Willis N, Craig J. Non-corticosteroid treatment for nephrotic syndrome in children [abstract]. Cochrane Database Syst Rev 2001;(4):CD002290.
12. Yap HK, Cheung W, Murugasu B, Sim SK, Seah CC, Jourdan SC. Th1 and Th2 cytokine mRNA profiles in childhood nephrotic syndrome. J Am Soc Nephrol 1999;10:529-37.
13. Grimbert P, Audard V, Remy P, Lang P, Sahali D. Recent approaches to the pathogenesis of minimal-change nephrotic syndrome. Nephrol Dial Transplant 2003;18:245-8.
14. Gudmundsson KO, Sigurjonsson OE, Gudmundsson S, Goldblatt D, Weemaes CMR, Haraldsson A. Increase expression of interleukin-13 but not interleukin-4 in CD4+ cells from patients with the hyper-IgE syndrome. Clin Exp Immunol 2002;128:532-7.
15. Yanagihara Y. Molecular regulation of human IgE synthesis. Allergology International 1999;48:111-9.