

Brief Report

Serum Immunoglobulin E and Interleukin-13 Levels in Children with Idiopathic Nephrotic Syndrome

by Om P. Mishra,¹ Akkatai S. Teli,¹ Usha Singh,² Abhishek Abhinay,¹ and Rajniti Prasad¹

¹Department of Pediatrics, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

²Department of Pathology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

Correspondence: Om P. Mishra, Department of Pediatrics, Institute of Medical Sciences, Banaras Hindu University, Varanasi 221005, India. Tel: +91-542-2317111. Fax: + 91-542-2367568. E-mail <opmpedia@yahoo.co.uk>.

Summary

Serum IgE and IL-13 levels were estimated in 40 idiopathic nephrotic syndrome and 16 controls. There were 15 first episode nephrotic syndrome (FENS), 15 infrequent relapsing nephrotic syndrome (IRNS) and 10 patients belonged to frequent relapsing nephrotic syndrome (FRNS). Serum IgE and IL-13 levels were significantly increased in active nephrotic syndrome and its sub-groups as compared to controls and remission ($p < 0.001$). IgE levels did not differ significantly among different subgroups, while IL-13 was significantly higher in FRNS in comparison with FENS ($p = 0.041$). Both IgE and IL-13 levels were comparable in nephrotic patients with and without bronchial asthma. Serum IL-13 had significant positive correlation with IgE ($r = 0.605$, $p < 0.001$). Thus, raised levels of IgE and IL-13 are found in nephrotic syndrome and could have a role in the pathogenesis of disease.

Key words: IgE, interleukin 13, nephrotic syndrome.

Introduction

Nephrotic syndrome in children can have association with allergic disorders [1–3]. Immunological alterations have been demonstrated by abnormalities in the immunoglobulins [4, 5] and defective cell-mediated immunity [6, 7]. Raised serum immunoglobulin E (IgE) has been reported in active phase [4, 8], as type-2 T-helper lymphocytes (Th 2) secrete interleukin-13 (IL-13), which in turn can lead to increased IgE production by B cells [9]. The overexpression of IL-13 has been shown by Lai *et al.* [10],

and it lead to glomerular injury causing fusion of foot processes of podocytes. As such the relapsers have more cell-mediated immune dysfunction than the first episode [9], and this can affect the IgE and IL-13 levels. However, it is not known whether IL-13 levels differ in relapsers from the first episode or not? Therefore, the present study was undertaken to estimate the serum IgE and IL-13 levels simultaneously among the first episode, infrequent and frequent relapsers during active and remission period, and also to find out the levels in cases with and without other Th 2-mediated atopic disorder such as bronchial asthma.

Acknowledgements

The authors are thankful to Prof. T.B. Singh, Division of Biostatistics, Department of Community Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, for his help in data analysis.

Funding

The present study was supported by the Department of Science and Technology (DST) Purse Grant, Government of India through Institute of Medical Sciences, Banaras Hindu University, Varanasi, India.

Materials and Methods

Forty children with steroid-responsive idiopathic nephrotic syndrome (27 males), aged 1–14 years, reporting to Pediatric Nephrology Clinic of Department of Pediatrics during the period of January 2011 to August 2013 were included. They had generalized edema, proteinuria (urine protein/creatinine ratio >2 mg/mg), hypoalbuminemia (serum albumin <2.5 g/dl), hypercholesterolemia (serum cholesterol >200 mg/dl), normal glomerular filtration rate and absence of any systemic disease known to produce nephrotic syndrome. None of

the patients had received prednisolone or any other immunosuppressive drugs (cyclosporine, mycophenolate mofetil or rituximab) at least 4 weeks before inclusion in the study. Eighteen cases had concomitant bronchial asthma. Another 16 age- and gender-matched normal healthy children (11 males) without any atopic disorders were included as controls. The protocol of the study was approved by Institute Ethics Committee, and informed consent was taken from each parent.

The patients were treated as per guidelines of Indian Pediatric Nephrology Group [11]. Thereafter, they were observed for remission (proteinuria 0/trace by heat precipitation method and/or spot urine protein/creatinine <0.2 mg/mg for consecutive three days). Serum IgE and IL-13 levels were done in active phase and repeated during remission after 4 weeks of stoppage of prednisolone in the first episode nephrotic syndrome (FENS) and infrequent relapsing nephrotic syndrome (IRNS), and in frequent relapsing nephrotic syndrome (FRNS) when the patients were on low dose alternate days therapy. Renal biopsy was not done in any patients, as all were steroid responsive.

Biochemical investigations

The blood urea, serum creatinine, total protein, albumin and cholesterol were estimated at presentation. Patients were screened for HIV, HbsAg, tuberculin test and X-ray chest to exclude associated infections. The ANA, C3, C4 and anti-dsDNA levels were assayed, wherever indicated.

Serum IgE and IL-13 estimations

Serum IgE and IL-13 estimations were done by ELISA method using kits manufactured by Demeditec Dignostics, GmbH, Germany, for IgE and Immunotech by France for IL-13 levels.

Statistical analysis

Data were analyzed using SPSS version 16.0 software (Chicago, IL, USA). Student's *t*-test was used for comparisons of data showing normal and Mann-Whitney U test for non-Gaussian distributions. Analysis of variance (ANOVA) was applied for comparisons among groups showing normal, and Kruskal-Wallis test for non-Gaussian distributions. Wilcoxon signed-rank test was applied for paired sample observations for IL-13 and paired Student's *t*-test for serum IgE. Spearman's correlation coefficients were calculated among different parameters. A *p* value of <0.05 was considered as statistically significant.

Results

Basic characteristics of controls and active nephrotic syndrome (ANS) are presented in Table 1.

The different parameters were comparable between controls and ANS, whereas serum cholesterol, urinary protein/creatinine ratios, total serum protein and albumin levels were significantly different from each other ($p < 0.001$).

IgE and IL-13 levels were significantly increased in nephrotic syndrome and in its subgroups as compared with controls ($p < 0.001$). Mean serum IgE values were comparable among different subgroups of patients. The FRNS had significantly raised median level of IL-13 than FENS. Both parameters showed significant reductions in remission (Table 2, $p < 0.001$), and became comparable with that of controls (Fig. 1A and B). Mean serum IgE (158.1 ± 2.4 vs. 150.8 ± 13.0 , $p = 0.99$) and median IL-13 (11 vs. 13.4, $p = 0.43$) levels did not differ significantly in nephrotic patients with ($n = 18$) and without ($n = 22$) bronchial asthma, respectively. The urinary protein/creatinine ratio had no significant correlations with IgE and IL-13 levels. Serum IL-13 had a significant positive relationship with IgE ($r = 0.605$, $p < 0.001$).

Discussion

Raised serum IgE in ANS has been reported earlier [8, 12, 13]. The normalization during remission is similar to the findings of Cheung *et al.* [12]. Conversely, our previous observation [8] and Youn *et al.* [13] showed that raised serum IgE persisted during remission, and authors concluded that it reflected abnormal immune status even in the disease-free state.

We observed raised serum IL-13 in active phase and normalization in remission. Kimata *et al.* [14] reported higher level of urinary IL-13 in untreated nephrotic syndrome in comparison to normal controls or membranoproliferative glomerulonephritis or atopic dermatitis patients. Cheung *et al.* [12] found that percentage of CD₃⁺ IL-13-producing cells was significantly higher in relapsing nephrotics and decreased during remission. Yap *et al.* [15] demonstrated that IL-13 mRNA expression was increased in CD₄⁺ and CD₈⁺ in nephrotic relapse than remission.

Median IL-13 level was significantly raised in FRNS in comparison with FENS. IRNS should have had higher value than FENS also, but we did not find so, and it could be possibly due to shorter duration of illness in infrequent relapsers, which becomes more abnormal in frequent relapsers due to repeated relapses and longer duration of the disease.

Both IgE and IL-13 levels were comparable between patients with and without bronchial asthma. Cheung *et al.* [12] reported no difference in serum IgE between nephrotic relapse with and without atopy. Serum IL-13 had significant positive correlation with IgE. The positive relationship between

TABLE 1
Basic characteristics of study groups

Parameters	Controls <i>n</i> = 16	Active nephrotic syndrome <i>n</i> = 40	<i>p</i> value
Age (months) ^a	60 (48, 72)	72 (48, 108)	0.126 ^b
History of bronchial asthma	0 (0%)	18 (45%)	–
Weight (kg) ^c	18.3 ± 4.6 (10.0, 26.0)	18.9 ± 7.6 (7.0–40.0)	0.360 ^d
Height (cm) ^c	104.2 ± 10.7 (89.0–130.0)	107.0 ± 17.6 (76.0–145.0)	0.235 ^d
Body mass index (kg/m ²) ^c	16.7 ± 2.9 (11.6–21.8)	16.0 ± 3.1 (9.5–22.5)	0.786 ^d
Blood urea (mg/dl) ^c	26.4 ± 7.7 (13.0–40.0)	27.9 ± 16.7 (9.0–92.0)	0.325 ^d
Serum creatinine (mg/dl) ^c	0.6 ± 0.2 (0.3–1.0)	0.6 ± 0.2 (0.4–1.0)	1.00 ^d
Total serum protein (g/dl) ^c	7.0 ± 1.1 (5.0–8.0)	4.9 ± 1.1 (3.0–6.0)	<0.001 ^d
Serum albumin (g/dl) ^c	3.6 ± 1.0 (2.5–4.8.)	2.0 ± 0.6 (1.0–3.0)	<0.001 ^d
Serum cholesterol (mg/dl) ^c	142.6 ± 15.8 (118.0–175.0)	420.2 ± 143.3 (226.0–877.0)	<0.001 ^d
Urinary protein/creatinine (mg/mg) ^c	0.16 ± 0.02 (0.13–0.21)	11.4 ± 3.9 (5.0–26.0)	<0.001 ^d

n: Number of cases.

^aMedian, interquartile range.

^bMann–Whitney U test.

^cMean ± SD and range.

^dStudent's *t*-test.

TABLE 2
Serum IgE and IL-13 levels in controls and active nephrotic syndrome

Parameters	Controls <i>n</i> = 16	Active nephrotic syndrome <i>n</i> = 40	FENS <i>n</i> = 15	IRNS <i>n</i> = 15	FRNS <i>n</i> = 10	Remission <i>n</i> = 40	<i>p</i> value among groups
Serum IgE (IU/ml) ^a	86.1 ± 31.9 16.0–124.0 (92.0)	154.1* ± 10.3 112.0–160.0 (158.1)	153.2* ± 9.1 136.0–160.0 (158.2)	152.1* ± 14.0 112.0–160.0 (158.0)	158.3* ± 1.3 156.0–160.0 (158.0)	55.9 ± 24.7 ^b 11.0–99.0 (57.0)	<0.001 ^c
Serum IL-13 (pg/ml) ^d	3.4 2.2, 4.4	12.5* 7.5, 21.9	12.5* 6.3, 17.5	9.4* 7.5, 29.6	21.9* 9.4, 52.5	3.1 ^c 2.2, 4.2	<0.001 ^f

n: Number of cases.

P values between groups (Mann–Whitney U test):

IgE: FENS vs. IRNS 0.802, FENS vs. FRNS 0.051, IRNS vs. FRNS 0.111;

IL-13: FENS vs. IRNS 0.533, FENS vs. FRNS 0.041, IRNS vs. FRNS 0.160.

**P* as compared with controls: <0.001.

^amean ± SD, range and median in parentheses.

^bPaired Student's *t*-test (*p* < 0.001).

^cANOVA.

^dmedian, interquartile range.

^eWilcoxon signed-rank test (*p* < 0.001).

^fKruskal–Wallis test.

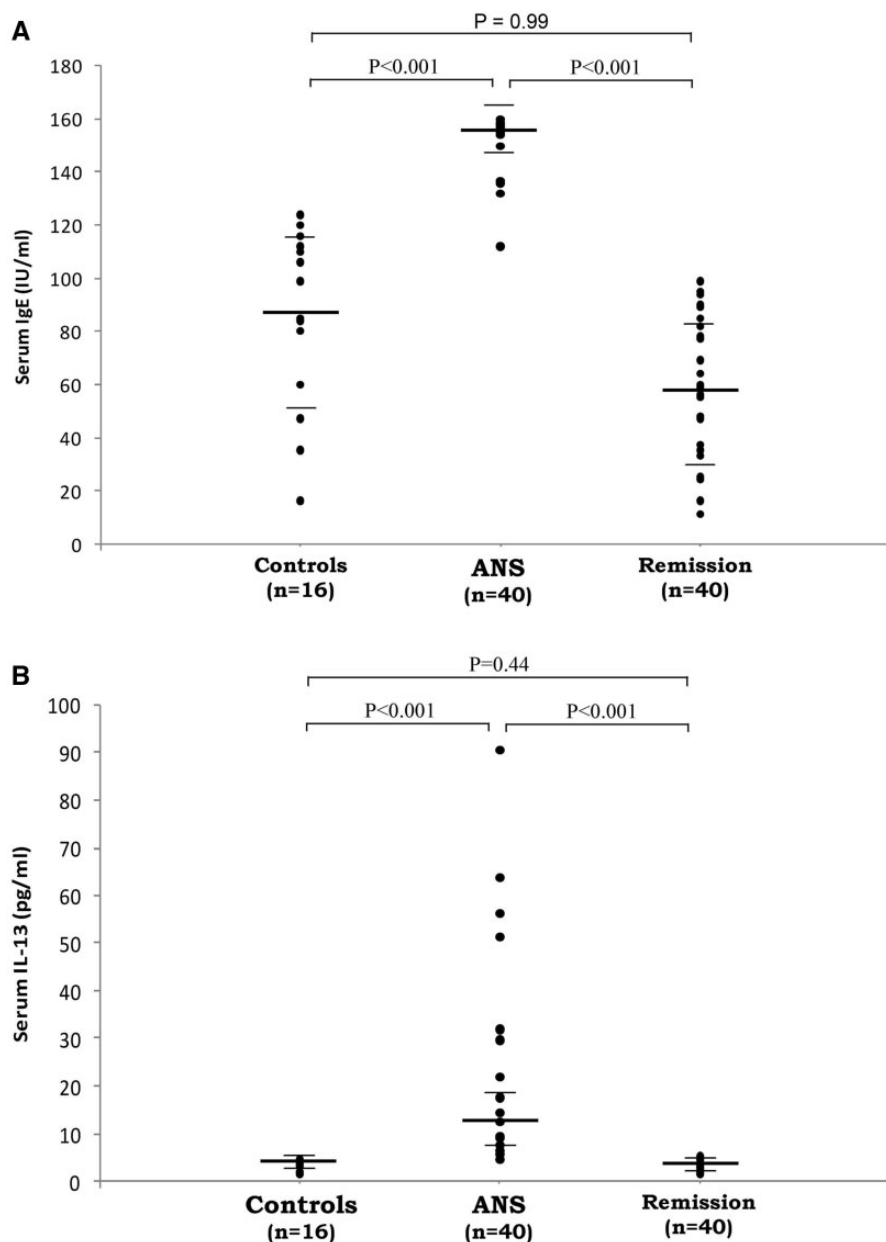


FIG. 1. (A) Serum IgE levels in controls, ANS and remission (n=number of cases, ANS—active nephrotic syndrome, long horizontal lines indicate mean, short horizontal lines $\pm$ SD). (B) Serum IL-13 levels in controls, ANS and remission (n=number of cases, ANS—active nephrotic syndrome, long horizontal lines indicate median, short horizontal lines interquartile range).

percentage of CD₃⁺ IL-13-producing cells and serum IgE has been reported earlier and it was a reflection of upregulation of IgE synthesis [12].

In conclusion, IgE and IL-13 levels were abnormal during active phase, and frequent relapsers showed

more pronounced changes in IL-13 levels. The IRNS did not show much alteration than first episode or frequent relapsers. Raised levels are reflection of immune dysregulation and may have a role in the pathogenesis of disease.

References

1. Meadow SR, Sarsfield JK, Scott DG, Rajah SM. Steroid-responsive nephrotic syndrome and allergy: immunological studies. *Arch Dis Child* 1981;56:517–24.
2. Yap HK, Yip WC, Lee BW, *et al.* The incidence of atopy in steroid-responsive nephrotic syndrome: clinical and immunological parameters. *Ann Allergy* 1983;51: 590–4.
3. Lin CY, Lee BH, Lin CC, Chen WP. A study of the relationship between childhood nephrotic syndrome and allergic diseases. *Chest* 1990;47:1408–11.
4. Giangiacomo J, Cleary TG, Cole BR, *et al.* Serum immunoglobulins in the nephrotic syndrome. A possible cause of minimal-change nephrotic syndrome. *N Eng J Med* 1975;293:8–12.
5. Mishra OP, Garg R, Usha *et al.* Immunoglobulins and circulating immune complexes in nephrotic syndrome. *J Trop Pediatr* 1997;43:93–7.
6. Shalhoub RJ. Pathogenesis of lipoid nephrosis: a disorder of T-cell function. *Lancet* 1974;2:556–60.
7. Mishra OP, Ghosh J, Ali Z, *et al.* Lymphocyte adenosine deaminase activity in children with idiopathic nephrotic syndrome. *Pediatr Nephrol* 2005;20:1426–9.
8. Mishra OP, Ibrahim N, Usha Das BK. Serum immunoglobulin E in idiopathic nephrotic syndrome. *J Trop Pediatr* 2004;50:149–52.
9. Levy F, Kristofic C, Heusser C, Brinkmann V. Role of IL-13 in CD4 T cell- dependent IgE production in atopy. *Int Arch Allergy Immunol* 1997;112:49–58.
10. Lai KW, Wei CL, Tan LK, *et al.* Overexpression of interleukin-13 induces minimal -change -like nephropathy in rats. *J Am Soc Nephrol* 2007;18:1476–85.
11. Bagga A, Ali U, Banerjee S, *et al.* Indian Pediatric Nephrology Group, Indian Academy of Pediatrics. Management of steroid sensitive nephrotic syndrome: revised guidelines. *Indian Pediatr* 2008;45:203–14.
12. Cheung W, Wei CL, Seah CC, *et al.* Atopy, serum IgE, and interleukin-13 in steroid-responsive nephrotic syndrome. *Pediatr Nephrol* 2004;19:627–32.
13. Youn YS, Lim HH, Lee JH. The clinical characteristics of steroid responsive nephrotic syndrome of children according to the serum immunoglobulin E levels and cytokines. *Yonsei Med J* 2012;53:715–22.
14. Kimata H, Fujimoto M, Furusho K. Involvement of interleukin (IL)-13, but not IL-4, in spontaneous IgE and IgG4 production in nephrotic syndrome. *Eur J Immunol* 1995;25:1497–501.
15. Yap KM, Cheung W, Murugasu B, *et al.* Th1 and Th 2 cytokine mRNA profiles in childhood nephrotic syndrome: evidence for increased IL-13 mRNA expression in relapse. *J Am Soc Nephrol* 1999;10: 529–37.