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STATE OF THE ART

Correlation Between Idiopathic Nephrotic Syndrome and Atopy in Children – Short Review

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ABSTRACT

The idiopathic nephrotic syndrome is a common chronic kidney diseases in children defined by the association of massive proteinuria and hypoalbuminemia in a relapsing/remission course, with histological aspect of minimal changes (also called minimal change disease) in the majority of the cases, but its pathogenesis remains not very well known. Clinical and immunological studies have consistently shown a relationship between atopic diathesis, immunoglobulin E and cytokines involved in immunoglobulin E synthesis and idiopathic nephrotic syndrome. Additional research is necessary to clarify this relationship and to explore the contribution of allergic disease to the development of nephrotic syndrome and to identify potential new strategies of diagnosis and treatment.

Keywords: idiopathic nephrotic syndrome, atopy, immunoglobulin E, children

INTRODUCTION

The idiopathic nephrotic syndrome (INS) is a common chronic kidney diseases in children, representing more than 90% of cases of nephrotic syndrome between 1 and 10 years of age and 50% after 10 years of age (1, 2). INS is defined by the association of the clinical features of NS (massive proteinuria and hypoalbuminemia in a relapsing/remission course) with renal biopsy findings of diffuse foot process effacement on electron microscopy and in majority of cases, aspect of minimal changes (also called minimal change disease – MCD) on light microscopy, but its pathogenesis remains not very well known (2, 3). The association of this disease with atopy has been extensively discussed. There are reported cases of INS induced or precipitated by allergy to foods, aeroallergens or insect venom and many of the children with INS show an elevated level of immunoglobulin E (IgE), the immunoglobulin with a central role in allergic inflammation (1).

The purpose of this article is to review clinical and experimental findings showing the involvement of the immune response and of immunoglobulin E in INS pathogenesis.

INS pathogenesis

INS is currently classified as steroid-sensitive idiopathic nephrotic syndrome (SSNS) and steroid-resistant idiopathic nephrotic syndrome (SRNS) depending on the response to corticoste-

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roids. There are now two hypotheses concerning the mechanisms of INS. One of them is that the proteinuria is induced by a primary glomerular defect due to a mutation of a gene coding for podocyte structures or for glomerular basement membrane proteins resulting in podocyte effacement. The older one is that INS results from a disorder of T-cell function resulting in increased plasma levels of lymphocyte-derived permeability factor affecting podocyte shape and function (2).

Podocyte disorder

In 1998 a mutations in the gene NPHS1, which encodes the podocyte-expressed immunoglobulin superfamily protein nephrin, was identified as a cause of congenital nephrotic syndrome in humans (4). Mutations of genes encoding several other podocyte proteins can explain cases of inherited nephrotic syndrome.

In addition, it was shown that podocytes express a T-cell costimulatory, known as CD80 or B7.1, that can be induced by direct activation of podocytes, independent of T cells action, or by cytokines such as interleukin (IL)-13 (5) and is associated with proteinuria (6). The underlying mechanism is unknown but it is believed that the increased expression of CD80 on podocytes leads to shape change and proteinuria. MCD is associated with pronounced expression of CD80 on podocytes, and increased urinary excretion of CD80 (7, 8). The expression of CD80 is regulated by cytokines such as CTLA-4, IL-10, and TGF-β, all produced by Tregs cells. Disfunctional Tregs in INS unable to produce these cytokines, induce persistent expression of CD80 and persistent proteinuria (6).

T-cell disfunction and lymphocyte-derived permeability factors

The pathophysiological role of a circulating factor affecting the podocyte structure and function was suggested by cases of massive proteinuria in patients with nephrotic syndrome after transplantation of a kidney from a healthy donor, by the successful treatment of some of those patients by plasma exchange (9), by the disappearance of nephrotic syndrome when kidneys affected by MCD were transplanted into patients without nephrotic syndrome (10) or the development of neonatal nephrotic syndrome by placental transfer of proinflammatory cytokines from a mother to her newborn (11).

Researchers have tried to identify the circulating factors released from T-cells that increase the glomerular permeability to serum proteins. Because cytokines are small proteins that function as inflammatory mediators in a paracrine and autocrine mode, they were believed to be the most likely pathogenic soluble factors (6). Increased levels of IL-2 (12), soluble IL-2 receptor (13), interferon-gamma (12, 13), IL-4 (14, 15), IL-12 (16), IL-13 (17), IL-18 (17), tumor necrosis factor (TNF)-α (18), and vascular endothelial growth factor (VEGF) (19) were associated with MCD relapse (6). The specific effect of a cytokine on the development of proteinuria was not studied extensively. However, it was shown that IL-13 can experimentaly induce nephrotic proteinuria in IL-13 transfected rats, but the role of IL-13 in the pathogenesis of the nephrotic syndrome is not yet clarified (20). There are other diseases like asthma and psoriazis, associated with high levels of IL-13, and not with proteinuria (6). Remission of renal lesions after treatment with infliximab, a monoclonal antibody anti-TNF-α, suggests a role for this cytokine in nephrotic syndrome (21). However, due to the complex interactions among cytokines, it is very difficult to determine the role of each cytokine.

Another molecule proposed by the investigators as circulating factor that increases glomerular permeability is the nuclear transcription factor called NF-κB, that controls the expression of several cytokines and cellular adhesion molecules and it was shown that its activity is higher in patients with INS (22). Another factor involved in INS pathogenesis is an imbalance of subtypes of T lymphocytes. Here are some suggestive data: remission of INS after treatment with cyclosporin-A due to reduction of IL-2 levels, a cytokine produced by T lymphocytes (23), association of INS, severity with decreased activity of regulatory T cells (24), INS worsening after TCD4+ cells depletion (25), high expression of mRNA for IL-13 on TCD4+ and TCD8+ lymphocytes of children with INS and overexpression of receptors for IL-4 and IL-13 in glomeruli of mice transfected with IL-13 (26), although it has not been definitively established that MCD was a Th2-dependent disorder (27).

Association with atopy

Atopy is defined as a personal and/or familial tendency, usually in childhood or adolescence, to

become sensitized and produce IgE antibodies in response to ordinary exposure to allergens, usually proteins (28). MCD is frequently associated with allergic symptoms and an elevated serum IgE level (29). Some authors mentioned that higher serum IgE levels can be related to poor outcome with frequent relapses or poor response to corticosteroids of INS in children (30, 31). There are data showing that, in atopic children with INS, serum IgE levels are higher when they were in remission than in non-atopic patients. Both atopic and non-atopic nephrotic children develop high levels of IgE during relapses compared with remission (29). Very early information about specific sensitization to an allergen and its impact on nephrotic syndrome dates from 1959, when Hardwicke *et al*. (27, 32) reported seasonal proteinuria in patients with pollen hypersensitivity. Subsequent studies have shown a higher incidence of allergic diseases in children with nephrotic syndrome, but the exact correlation between IgE specific sensitization and the pathogenesis of proteinuria is not understood. It is debatable whether the very frequent association between high levels of IgE and INS is indicative for atopic state or just uncover pathogenetic mechanism affecting lymphocyte regulation of immunoglobulin synthesis during nephrotic relapses, similar to those found in atopy (27). Some authors suggest that a humoral immune perturbation seen in patients with INS relapses is responsible for the increased IgE synthesis (33).

Evidence suggesting common pathways include: increased expression of IL-13 mRNA on T cells CD4+, CD8+ în children with INS relapses (35), IL-13 experimentally induced proteinuria (26), a significantly higher expression of CD23, the type II IgE receptor, on B cells from active MCD patients (34), correlated with greater IL-4 activity. IL-4 and IL-13 are known regulators of B cell IgE production in atopic patients. It was shown that in MCD patients, IL-13 can spontaneusly induce IgE synthesis, in contrast to atopic patients in whom the major role in IgE synthesis it is accomplished by IL-4 (27). Serum levels of IL-5 (cyotkine important în eosinophilic inflammation characteristic for asthma and allergic disesases) and IL-13 are higher in patients with steroid-sensitive NS before compared with after treatment (29).

Recently, were published the results of a population-based cohort study having as topic the incidence and risk of INS in children with atopic dermatitis (AD) compared with non-AD controls in Chinese population (1). AD is a chronic and relapsing inflammatory skin disease whith onset in first months or years of life, that precedes other allergic disorders in early childhood (35). The results obtained by the authors support the relationship between pre-existing AD and the subsequent risk for INS. The incidence of INS was two-fold higher in the AD cohort than in the non-AD cohort, and the risk increased with the severity of AD symptoms (1). ❑

CONCLUSION

Idiopathic nephrotic syndrome is a complex disease with more than one causal factor. Clinical and immunological studies have consistently shown a relationship between atopic diathesis and INS (1), and according to older data, atopy is associated with up 30% of INS cases (36). The significantly increased risk of INS development in children with AD supports an important correlation between allergic diseases and INS pathogenesis. In the future, additional research is needed into both the factors that are known to modulate IgE synthesis and the cytokine-regulating network of serum IgE in order to clarify the relationship between IgE production and INS, explore the contribution of allergic disease to the development of nephrotic syndrome and identify potential new strategies of diagnosis and treatment. ❑

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References

1. **Wei CC, Tsai JD, Lin CL, et al.** Increased risk of idiopathic nephrotic syndrome in children with atopic dermatitis. *Pediatr Nephrol* 2014;29:2157.
2. **Davin JC.** The glomerular permeability factors in idiopathic nephrotic syndrome. *Pediatr Nephrol* 2016;31:207.
3. **Ikeuchi Y, Kobayashi Y, Arakawa H, et al.** Polymorphisms in interleukin-4-related genes in patients with minimal change nephrotic syndrome. *Pediatr Nephrol* 2009;24:489.
4. **Kestila M, Lenkkeri U, Männikkö M, Lamerdin J, McCready P, Putaala H, et al.** Positionally cloned gene for a novel

glomerular protein--nephrin--is mutated in congenital nephrotic syndrome. *Mol Cell* 1998;1:575-582.
5. **Yap HK, Cheung W, Murugasu B, Sim SK, Seah CC, Jordan SC.** Th1 and Th2 cytokine mRNA profiles in childhood nephrotic syndrome: evidence for increased IL-13 mRNA expression in relapse. *J Am Soc Nephrol* 1999;10:529-537.
6. **Kaneko K, Tsuji S, Kimata T, et al.** Pathogenesis of childhood idiopathic nephrotic syndrome: a paradigm shift from T-cells to podocytes. *World J Pediatr* 2015;11:21.
7. **Garin EH, Diaz LN, Mu W, Wasserfall C, Araya C, Segal M, et al.** Urinary CD80 excretion increases in idiopathic minimalchange disease. *J Am Soc Nephrol* 2009;20:260-266.
8. **Garin EH, Mu W, Arthur JM, Rivard CJ, Araya CE, Shimada M, et al.** Urinary CD80 is elevated in minimal change disease but not in focal segmental glomerulosclerosis. *Kidney Int* 2010;78:296-302.
9. **Fine RN.** Recurrence of nephrotic syndrome/focal segmental glomerulosclerosis following renal transplantation in children. *Pediatr Nephrol* 2007; 22:496–502.
10. **Ali AA, Wilson E, Moorhead JF, Amlot P, Abdulla A, Fernando ON, et al.** Minimal-change glomerular nephritis. Normal kidneys in an abnormal environment? *Transplantation* 1994;58:849-852.
11. **Assadi F**. Neonatal nephrotic syndrome associated with placenta transmission of proinflammatory cytokines. *Pediatr Nephrol* 2011;26:469-471.
12. **Daniel V, Trautmann Y, Konrad M, Nayir A, Schärer K.** T-lymphocyte populations, cytokines and other growth factors in serum and urine of children with idiopathic nephrotic syndrome. *Clin Nephrol* 1997;47:289-297.
13. **Kemper MJ, Meyer-Jark T, Lilova M, Muller-Wiefel DE.** Combined T- and B-cell activation in childhood steroid-sensitive nephrotic syndrome. *Clin Nephrol* 2003;60:242-247.
14. **Neuhaus TJ, Wadhwa M, Callard R, Barratt TM.** Increased IL-2, IL-4 and interferon-gamma (IFN-gamma) in steroid-sensitive nephrotic syndrome. *Clin Exp Immunol* 1995;100:475-479.
15. **Cho BS, Yoon SR, Jang JY, Pyun KH, Lee CE.** Up-regulation of interleukin-4 and CD23/FcepsilonRII in minimal change nephrotic syndrome. *Pediatr Nephrol* 1999;13:199-204.
16. **Lin CY, Chien JW.** Increased interleukin-12 release from peripheral blood mononuclear cells in nephrotic phase of minimal change nephrotic syndrome. *Acta Paediatr Taiwan* 2004;45:77-80.
17. **Matsumoto K, Kanmatsuse K.** Elevated interleukin-18 levels in the urine of nephrotic patients. *Nephron* 2001;88:334-339.
18. **Suranyi MG, Guasch A, Hall BM, Myers BD.** Elevated levels of tumor necrosis factor-alpha in the nephrotic syndrome in humans. *Am J Kidney Dis* 1993;21:251-259.
19. **Matsumoto K, Kanmatsuse K.** Elevated vascular endothelial growth factor levels in the urine of patients with minimal-change nephrotic syndrome. *Clin Nephrol* 2001;55:269-274.
20. **Lai KW, Wei CL, Tan LK, Tan PH, Chiang GS, Lee CG, et al.** Overexpression of interleukin-13 induces minimal-change-like nephropathy in rats. *J Am Soc Nephrol* 2007;18:1476-1485.
21. **Raveh D, Shemesh O, Ashkenazi YJ, Winkler R, Barak V.** Tumor necrosis factor-alpha blocking agent as a treatment for nephrotic syndrome. *Pediatr Nephrol* 2004;19:1281-1284.
22. **Valanciuté A Le SG, Solhonne B, Pawlak A, Grimbert P, Lyonnet L, et al.** NF-kappa-B p65 antagonizes IL-4 induction by c-maf in minimal change nephrotic syndrome. *J Immunol* 2004;172:688–698.
23. **Tejani AT, Butt K, Trachtman H, Suthanthiran M, Rosenthal CJ, Khawar MR.** Cyclosporine-A induced remission of relapsing nephrotic syndrome in children. *Kidney Int* 1988;33:729–734.
24. **de Fátima Pereira W, Brito-Melo GEA, Guimarães FTL, et al.** The role of the immune system in idiopathic nephrotic syndrome: a review of clinical and experimental studies. *Inflamm Res* 2014,63: 1.
25. **Wang Y, Feng X, Bao S, Yi S, Kairaitis L, et al.** Depletion of CD4 T cells aggravates glomerular and interstitial injury in murine adriamycin nephropathy. *Kidney Int* 2001;59:975–984.
26. **Lai K-W, Wei Ch-L, Tan L-K, Tan P-H, Chiang GSC, Lee CGL, et al.** Overexpression of interleukin 13 induces minimal-change-like nephropathy in rats. *J Am Soc Nephrol* 2007;18:1476–1485.
27. **Cheung W, Wei CL, Seah CC, et al.** Atopy, serum IgE, and interleukin-13 in steroid-responsive nephrotic syndrome. *Pediatr Nephrol* 2004;19:627.
28. **Johansson SGO, Bieber T, Dahl R, Friedmann PS, Lanier BQ, et al.** Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004;113:832-836.
29. **Salsano ME, Graziano L, Luongo I, Pilla P, Giordano M, Lama G.** Atopy in childhood idiopathic nephrotic syndrome. *Acta Paediatr* 2007;96:561–566.
30. **Yap HK, Yip WC, Lee BW, Ho TF, Teo J, Aw SE, et al** . The incidence of atopy in steroid-responsive nephrotic syndrome: clinical and immunological parameters. *Ann All* 1983;51:590–594.
31. **Hu JF, Liu YZ.** Elevated serum IgE levels in children with nephrotic syndrome, a steroid-resistant sign? *Nephron* 1990;54:275.
32. **Hardwicke J, Soothill JF, Squire JR, Holti G.** Nephrotic syndrome and pollen hypersensitivity. *Lancet* 1959;I:499–502.
33. **Tain YL, Chen TY, Yang KD.** Implication of serum TNF-β and IL-13 in the treatment response of childhood nephrotic syndome. *Cytokine* 2003;21:155–159.
34. **Cho BS, Yoon SR, Jang JY, Pyun KH, Lee CE.** Up-regulation of IL-4 and CD23/FcεRII in minimal change nephrotic syndrome. *Pediatr Nephrol* 1999; 13: 199–204
35. **Boguniewicz M, Leung DYM.** Atopic dermatitis: a disease of altered skin barrier and immune dysregulation. *Immunol Rev* 2011;242:233–246.
36. **Meadow SR, Sarsfield JK, Scott DG, Rajah SM.** Steroid-responsive nephrotic syndrome and allergy: immunological studies. *Arch Dis Child* 1981;56:51.