Idiopathic Nephrotic Syndrome and Atopy: Is There a Common Link?

Maher Abdel-Hafez, MD,[1] Michiko Shimada, MD,[2] Pui Y. Lee, MS,[3] Richard J. Johnson, MD,[2] and Eduardo H. Garin, MD[1]

Numerous reports during the last 60 years have reported a strong association between idiopathic nephrotic syndrome and atopic disorders. Idiopathic nephrotic syndrome can be precipitated by allergic reactions and has been associated with both aeroallergens (pollens, mold, and dust) and food allergies. Patients with idiopathic nephrotic syndrome also may show increased serum immunoglobulin E (IgE) levels. A review of the literature suggests that although some idiopathic nephrotic syndrome cases may be associated with allergies, evidence that it is a type of allergic disorder or can be induced by a specific allergen is weak. Rather, it is likely that the proteinuria and increased IgE levels in patients with idiopathic nephrotic syndrome are caused by increased levels of interleukin 13 observed in these patients. Recent studies suggest that interleukin 13, a known stimulator of IgE response, may mediate proteinuria in patients with minimal change disease because of its ability to directly induce CD80 expression on the podocyte.

Am J Kidney Dis 54:945-953.

INDEX WORDS: Atopy; nephrotic syndrome; minimal change disease.

Idiopathic nephrotic syndrome in children is a clinical syndrome associated with a variety of glomerular lesions. Minimal change disease (MCD) is the most common cause of idiopathic nephrotic syndrome. MCD is often abrupt in onset. It can be dramatic in presentation, yet is one of the most rewarding diseases for a physician to manage because response to corticosteroids often is rapid and complete**.** Because kidney biopsy usually is not performed when the disease responds to corticosteroid therapy, the term MCD has become synonymous with steroid-sensitive nephrotic syndrome.

The mechanism(s) underlying the MCD pathogenesis are unknown, although it is believed to be immunologically mediated.[1] Strong evidence suggests that it may be caused by a circulating factor, possibly T-cell related, that causes podocyte dysfunction resulting in massive proteinuria.[2] However, there also have been numerous reports linking MCD with atopic disorders and increases in serum immunoglobulin E (IgE) levels. In this review, we discuss the evidence supporting the association of atopy and whether there may be a common underlying immune disorder that may predispose patients to both conditions.

ATOPY

Atopy is a term used to describe IgE-mediated diseases. Persons with atopy have a hereditary predisposition to produce IgE antibodies to common allergens and often manifest with 1 or more atopic diseases (asthma, allergic rhinitis, and atopic eczema). Atopic patients mount an exaggerated immunologic response characterized by production of allergen-specific IgE antibodies and positive reactions to extracts of common aeroallergens on skin-prick tests. Type 2 helper T cells (T_H2) from patients with atopy respond to allergens in vitro by expressing such cytokines as interleukin 4 (IL-4) and IL-13[3] (Fig 1A and B).

Early Reports of Atopy With MCD

In 1951, Fanconi et al[4] were among of the first to associate atopy and nephrotic syndrome. Forty-three percent of their nephrotic patients showed signs of an "allergic diathesis." They suggested that allergy could have a role in the pathogenesis of nephrotic syndrome. Since then, several studies have been reported linking atopy and nephrotic syndrome. In nephrotic patients, relapses have been described after exposure to allergens, including pollens,[5-7] mold,[8] poison oak,[9] bee

From the [1]Division of Pediatric Nephrology, University of Florida, Gainesville, FL; [2]Division of Renal Diseases and Hypertension, University of Colorado, Denver, CO; and [3]Division of Renal Diseases and Hypertension, University of Florida, Gainesville, FL.

Received December 10, 2008. Accepted in revised form March 20, 2009. Originally published online as doi: 10.1053/j.ajkd.2009.03.019 on June 26, 2009.

Address correspondence to Eduardo H. Garin, MD, 1600 SW Archer Rd, Gainesville, FL 32610. E-mail: garineh@peds.ufl.edu

0272-6386/09/5405-0020$36.00/0
doi:10.1053/j.ajkd.2009.03.019

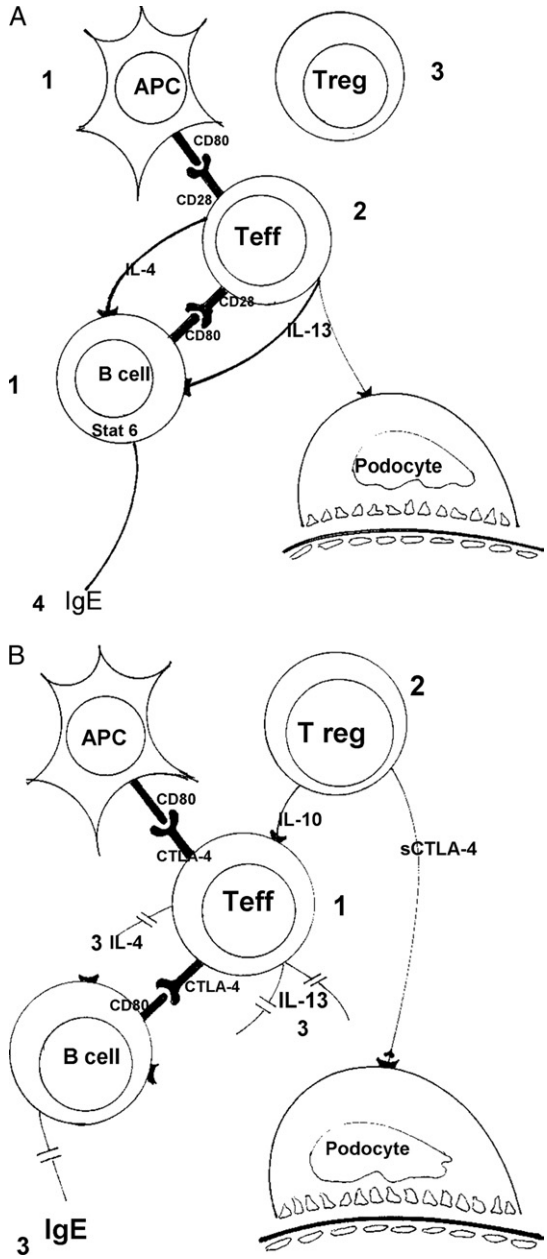

Figure 1. (A) (1) Antigen-presenting cells (APCs) and activated B cells express CD80, which binds to CD28 on the (2) T effector (Teff) cellular membrane. In the absence of suppression by (3) T regulatory (Treg) cells, T effector cells release interleukin 4 (IL-4) and IL-13. These 2 cytokines trigger (4) the switch from immunoglobulin M (IgM) to IgE in the B cell. (B) T effector cells express cytotoxic T-lymphocyte antigen-4 (CTLA-4), which will compete with CD28 for CD80, resulting in (1) decreased activation of T effector cells. In addition, (2) T regulatory cells suppress T effector activation by releasing IL-10 and soluble CTLA-4. These combined events result in decreased production of IL-4, IL-13, and (3) IgE.

stings,[10] and vaccinations. Serum IgE, which also occurs commonly in atopic patients, also commonly has increased levels in patients with MCD as opposed to other glomerular diseases.[11] These findings have raised the possibility that atopy may have a role in the pathogenesis of MCD and allergens could be the triggering factor in the development of proteinuria. Is there evidence from controlled trials that atopic disorders are more common than expected in children with MCD?

Atopic Diseases in Children With MCD and Their Families

Findings of atopic disorders in patients with MCD have varied widely (Table 1). In 1 of the first reported series, Thomson et al[19] reported that 38% (15 of 40) of children with steroid-responsive nephrotic syndrome had asthma, eczema, or hay fever compared with 18% (7 of 40) of age-matched controls. Since then, other series have been reported, and most have confirmed an increase in prevalence of atopic disorders in patients with steroid-sensitive nephrotic syndrome compared with controls.[12-15,17,18,20-22] However, the frequency has varied dramatically (from 10% to 50%), although most series suggest that 30% to 40% of children with steroid-sensitive nephrotic syndrome have some type of allergic disorder (hay fever, asthma, or atopic dermatitis). Interestingly, in some series, the prevalence of atopic diseases also was increased in first-degree relatives, with similar prevalence rates.[12,18] Fewer studies have been performed in patients with biopsy-proven MCD, but a tendency for a greater prevalence of atopic disorders also was observed.[17]

IgE in Atopy and MCD

Many advances have been made in recent years for the pathogenesis of atopy. IgE synthesis by B cells requires 2 signals. The first signal is delivered by the cytokines IL-4 or IL-13 released by T_H2 cells, which target the Cε gene for switch recombination. The second signal is delivered by interaction of the B-cell surface antigen CD40 with its ligand expressed on activated T cells.[23] Therefore, patients with atopy typically present with increased serum IgE and serum IL-4 and IL-13 levels, although on repeated exposure to