



A review of nephrotic syndrome and atopic diseases in children

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Abstract: Pediatric nephrotic syndrome (NS) is a common and recurrent glomerular disease in childhood. Furthermore, 50–70% of children with NS have increased total IgE in peripheral blood and a variety of clinical manifestations of atopic diseases. Hence, NS has many similarities with atopic diseases. However, no study has revealed a clear link between these two diseases. The present review discusses the correlation between pediatric NS and atopic diseases in children from three aspects: pathogenesis, cytokine change, and treatment. There are similar changes in T cells in terms of pathogenesis, with Th1/Th2 dysfunction and Treg cell function downregulation. Cytokine changes are similar and manifest as an increase in Th2 cytokines, TNF- α and TGF- β 1, and a decrease in IL-10. Glucocorticoids, immunosuppressants and biological agents are used for the treatment of these two diseases. Therefore, it was speculated that NS and atopic diseases may be the same kind of disease, have a similar pathogenesis, and only exhibit different clinical manifestations due to different affected parts of the disease.

Keywords: Pediatric; nephrotic syndrome (NS); atopic diseases; clinical manifestations; review

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Introduction

Pediatric nephrotic syndrome (NS) is a group of clinical syndromes, including severe proteinuria, hypoalbuminemia, hyperlipidemia, and edema. These are caused by the highly increased permeability of glomerular filtration barrier to plasma protein, and severe loss of a large amount of plasma protein from urine. The pathogenesis of this disease is not clear. However, in recent years, with the improvement of medical technology and more in-depth research, it was found that 50–70% of children with NS have increased total IgE in peripheral blood, and have clinical manifestations, such as airway hyperresponsiveness, skin pruritus, repeated eczema, and skin allergy. Hence, NS has many similarities with atopic diseases. However, no study has revealed a clear link between NS and atopic disease in children. This review discusses the correlation between NS and atopic diseases

in children from three aspects (pathogenesis, cytokine change, and treatment) in order to identify the similarities between NS and atopic diseases in children and provide new clues and methods for the treatment of NS in children.

An overview and pathogenesis of NS and atopic disease

An overview and pathogenesis of NS in children

The most common pathological type of NS in children is a disorder with minimal changes. Most children are sensitive to steroid therapy, while some children have hormone dependence. The pathogenesis of minimal changes in NS children is not clear. To date, no single theory can completely explain its entire pathophysiological process. At present, it is considered that NS is mainly correlated to

immune dysfunction, especially T cell dysfunction, which leads to the abnormal secretion of osmotic factors, such as cytokines or specific antibodies, and attacks podocytes, resulting in glomerular filtration membrane damage (1,2).

According to the different cytokines secreted, helper T cells (Th) can be divided into three types: Th0, Th1, and Th2 cells. A previous study revealed that the pathogenesis of NS might be correlated to Th2 activation. Furthermore, NS patients commonly exhibit the downregulation of Th1 cells and the upregulation of Th2 cells, resulting in a Th1/Th2 imbalance, and this may be one of the important mechanisms of NS occurrence and development (3,4). After undergoing further research, Dong *et al.* (5,6) reported that Th17 cells may be correlated to renal tubular epithelial and renal interstitial damage, chronic inflammatory damage to the kidney, and renal fibrosis. Th17 cells are a subset of T cells, which mainly secretes interleukin (IL)-17. In addition, as important immunoregulatory cells, Treg also plays an important role in autoimmune diseases, transplant rejection, and tumors (7). Normally, Treg cells and Th17 cells maintain a balance between them. In NS, Treg expression decreases, and Th17 expression increases, and the Th17/Treg imbalance is involved in the development of NS (8).

Cellular immunity also plays an important role in the occurrence and development of NS. Humoral immunity, namely, the immune response involved in B cells and their secreted immunoglobulins, may also be involved in the process of immune regulation in NS. Peripheral blood IgE is significantly increased in NS children, especially in children with frequent relapses (9), and activated B cells are the main cells that produce antibodies. Hence, it could be speculated that B cells are involved in the pathogenesis of NS. This is also one of the bases for the conjecture that NS and atopic diseases are correlated.

An overview of atopic disease and its pathogenesis

Atopic disease is a chronic inflammatory immune disease mainly mediated by IgE and characterized by positive results of skin allergen tests or serum specific IgE, which include atopic dermatitis, allergic rhinitis, and asthma. Atopic disease is closely correlated to genetic and environmental factors. Therefore, an allergic constitution's tendency to produce IgE antibodies in response to common antigens in the environment is the basis of atopic diseases (10,11).

Under the stimulation of allergens (such as dust mites, pollens, molds, etc.), the immune response mediated by

Th2 is enhanced in individuals with atopic constitutions, causing an imbalance in the proportion and function of THL/Th2. Th2 cells secrete a variety of cytokines (such as IL-4, IL-5, IL-6, IL-13, etc.) to promote the synthesis and secretion of IgE through B cells, and this results in the occurrence of allergic diseases (12). In addition, Treg can reduce IgE production by inhibiting Th2 cells and regulating antibody subtypes produced by B cells (13,14). However, the immunosuppressive function of Treg cells in patients with allergic constitutions remains defective. Therefore, the excessive release of IgE through B cells binds to a large number of IgE receptors on the surfaces of the nasal cavity, skin, and airway mucosa, which accordingly activate mast cells to release inflammatory mediators that mainly comprise of leukotrienes and histamines. These inflammatory mediators act on the nasal cavity, skin, and airway and other mucosae, and cause the corresponding symptoms (15,16).

Similarities of pathogenesis between NS and atopic disease in children

As early as 1951, Fanconi *et al.* (17) reported that the occurrence of NS is correlated to an atopic constitution. Subsequently, there have been reports on the occurrence and recurrence of NS induced by exposure to pollen (18), mold (19), mosquito bites (20), and vaccination (21). Therefore, exposure to allergens may lead to the occurrence and recurrence of NS.

IgE is synthesized by B cells, which plays an important role in the occurrence and development of atopic diseases in children, such as asthma, allergic rhinitis, and atopic asthma. Furthermore, it has been considered that IgE is the basis of the pathogenesis of atopic diseases (22,23). Many studies have revealed that the serum IgE level is significantly higher in NS children than in healthy age-matched children (24). In children with recurrent NS, the IgE level significantly increases, and there is a higher relapse rate when compared to the remission stage (1,25). A study also revealed that the IgE level increased with the prolongation of NS development (26). This suggests that the atopic process is also involved in the development of NS.

In addition, by summarizing the pathogenesis of the two diseases, it was found that there are some similarities in T cell changes between NS and atopic diseases. Both have THL/Th2 dysfunction (that is, Th2-mediated immune enhancement and Th1-mediated immune weakening), which is accompanied by Treg cell function downregulation. Therefore, it was speculated that NS and atopic disease

might have a similar immunological mechanism.

Changes in cytokines in NS and atopic diseases

Changes in cytokines in NS

As a small molecular weight-secreted protein with important physiological and pathological functions, cytokines can mediate many biological processes, and participate in the occurrence and development of many diseases.

Th1 cells mainly secrete interferon- γ (INF- γ), tumor necrosis factor- α (TNF- α), IL-2, IL-12, and IL-23, and its function is primarily to play a role in inflammatory responses by activating phagocytes and neutrophils. Th2 cells mainly secrete IL-4, IL-5, IL-6, IL-10, and IL-13, and its function is to play an anti-inflammatory role by inducing the activation of eosinophils and B cells to synthesize and secrete IgE and antibodies (27-29). The inflammatory response and anti-inflammatory effects are maintained in a balanced state in normal subjects. For the NS children mentioned in the above study, there was an over-activation of Th2, TH1/Th2 dysfunction, and changes in cytokine levels. In NS, Th2 cells are upregulated, and the levels of cytokines secreted by these, as well as IL-4 (30), IL-5 (31), IL-6 (32), and IL-13 (33,34), all increased. However, there was no significant increase in Th1 cytokines, such as IL-2 and IFN- γ , in NS (33).

Treg cells also secrete cytokines. TGF- β is a cytokine with many biological functions, and its interaction with Treg cells is complex. Treg can secrete TGF- β , and while in a stable body state, TGF- β can promote the production of Treg to inhibit inflammatory responses. However, in the presence of infection, TGF- β inhibits the differentiation of CD4⁺ T cells into Treg cells and induces Th17 cell differentiation. This results in glomerulosclerosis, renal interstitial fibrosis, and increased permeability of the glomerular filtration membrane, which leads to the occurrence of NS. It is possible that in the presence of infection, the high levels of produced IL-6 have a synergistic effect with TGF- β (35,36). Both Th2 cells and Treg cells can secrete IL-10. IL-10 has a negative immunomodulatory effect and is also a protective factor for NS. Furthermore, the level of IL-10 in NS patients is lower than in other subjects (31).

In addition, Th and Treg cells can secrete cytokines, monocyte-macrophages, epithelial cells, and mesangial cells in the kidneys and secrete TNF- α . These cannot only induce damage to glomerular vascular endothelial cells and glomerular basement membrane epithelial cells but also destroy the charge barrier of the glomerular basement

membrane, leading to protein loss (37). TNF- α levels increase in NS children (33,38).

Changes in cytokines in atopic diseases

There are IgE-dependent immediate hypersensitivity reactions in all atopic diseases. For example, Th2 cytokines are dominantly expressed, and the levels of IL-4, IL-5, IL-6, and IL-13 increase in children with asthma and allergic rhinitis (39-42). Studies have revealed that the TGF- β 1 level in the airway of asthma is higher than that in healthy subjects (43), and this is the main regulatory factor of airway remodeling in asthma (44). Similarly, animal experiments have also confirmed that the TGF- β 1 level in allergic rhinitis rats is higher than in the control group, which can not only inhibit the inflammatory reaction but also remodel the airway tissue of the nasal mucosa (45). IL-10 can inhibit the production of inflammatory cells and IgE and protect the airway. Furthermore, IL-10 levels in peripheral blood are low in patients with asthmatic and allergic rhinitis (46). In addition, TNF- α can cause eosinophils to accumulate and adhere to vascular endothelial cells, and release cytotoxic substances to increase vascular permeability, resulting in local mucosal edema and damage. Its level in atopic diseases is significantly higher than that in normal subjects (47,48).

Similarities of cytokines between NS and atopic diseases

IL-13 is a cytokine secreted by Th2 cells. A large number of studies have revealed that IL-13 levels significantly increased in NS children, especially in children with frequent relapses. Animal experiments have also confirmed that rats with a high expression of IL-13 may have NS. The mechanism may be that IL-13 receptors are present on the podocyte surface. Hence, IL-13 can directly act on podocytes, resulting in the rearrangement of the actin cytoskeleton of podocytes, the disappearance of the foot process, and the occurrence of proteinuria (49). Furthermore, IL-13 has also been proven to regulate the rearrangement of actin cytoskeletons in human nasal epithelial cells (50), which can remodel the nasal mucosa airway. Similarly, in the development of asthma, IL-13 can regulate the proliferation of bronchial fibroblasts, myofibroblasts, and airway smooth muscle cells, resulting in airway remodeling (51). Therefore, in both NS and atopic diseases, such as asthma and allergic rhinitis, IL-13 has a direct effect on target organs and can cause functional disorder and even disease by changing the target organ structure.

IL-4 can also remodel the target organ structure (51,52). Similar to IL-13, and in addition to its direct effects, IL-4 is an important transmission factor in the synthesis of IgE through B cells. Furthermore, the serum levels of IL-4, IL-13, and IgE are significantly elevated in NS and atopic diseases. Therefore, IL-4 and IL-13 may also be involved in the production of IgE in NS and atopic diseases.

The above-mentioned summaries reveal similarities between NS and atopic diseases in terms of cytokines (pediatric asthma, allergic rhinitis, and the acute stage of atopic dermatitis). All manifest as an increase in Th2 cytokines, TNF- α and TGF- β 1, and a decrease in IL-10. Therefore, it was speculated that there were some similarities in the nature of these two diseases.

Comparison of treatment schemes between NS and atopic disease in children

Summary of NS treatment

Glucocorticoid is the first-line drug for NS (53,54). However, for patients with refractory NS, immunosuppressants should be added in clinical practice.

Cyclophosphamide (CTX) is the oldest cytotoxic drug that inhibits cell division and proliferation by inhibiting DNA synthesis. It affects both B cells and T cells, but particularly B cells. Cyclosporine A (CsA) can inhibit IL-2 production by inhibiting the activity of calcineurin and interfering with T cell activation. Tacrolimus is a macrolide antibiotic, and its molecular structure and immune mechanism are the same as CsA, but the effect is better than CsA. Mycophenolate mofetil (MMF) inhibits lymphocyte proliferation by inhibiting the activity of hypoxanthine nucleoside monophosphate dehydrogenase. Therefore, it affects T and B cells (55,56).

In recent years, there have been successive reports on the treatment of steroid dependence in refractory NS using a human-mouse chimeric monoclonal antibody (rituximab) specifically for B cell surface antigen CD20. The mechanism may be that the production of some pathogenic cytokines affected by B cells can be activated by eliminating B cells (57-59), in order to maintain the normal function of the filtration barrier.

Treatment of atopic diseases

Summary of treatment of atopic dermatitis

In addition to basic treatments such as phototherapy,

moisturizing, and cleaning, glucocorticoid remains the first-line treatment for atopic dermatitis. Calcineurin inhibitors, such as tacrolimus ointment, are chosen when the effect of glucocorticoids is not enough. At present, the systemic medication of atopic dermatitis is mainly antihistamines (60). However, for severe cases, glucocorticoids or other immunosuppressants such as cyclosporine, MMF, and azathioprine can be applied (61-63). The guidelines for the 2018 European consensus consider that systemic immunosuppressants, such as cyclosporin, methotrexate, azathioprine, and MMF, are the first choice for treating refractory atopic dermatitis.

In addition, it has been recently found that monoclonal anti-IgE antibody omalizumab (64), human-mouse chimeric monoclonal anti-CD20 antibody rituximab, and anti-IL-4/IL-13 antibody dupilumab (65) can also achieve a good therapeutic effect.

A summary of the treatment of asthma in children (66)

The treatment of asthma in children is mainly divided into acute stage treatment and maintenance treatment. Glucocorticoid is one of the most important drugs in the treatment of asthma in children. Furthermore, the most effective long-term treatment for asthma in children under six years old is the inhalation of glucocorticoids, and low-dose inhaled corticosteroids (ICS) are recommended as the initial control therapy (67). The systemic application of glucocorticoids is the first-line drug for the treatment of severe asthma attacks in children, and its early application can effectively alleviate these conditions and reduce the fatality rate (68). An inhaled β 2 receptor agonist is a widely used bronchodilator in clinics that can reduce the release of inflammatory mediators, reduce microvascular permeability, and enhance the ciliary function of epithelial cells. Furthermore, this can be used for the long-term maintenance treatment of children with acute asthma attacks and moderate-severe asthma. Leukotriene regulator is a new kind of non-hormone anti-inflammatory drug, which can inhibit leukotriene activity in airway smooth muscles, reduces vascular permeability and bronchospasm, and can be used on its own to treat light asthma attacks, especially in patients with ICS contraindications. In addition, anticholinergic drugs, magnesium sulfate, theophylline, and other drugs also have an apparent effect in achieving remission in the acute stage. In recent years, the monoclonal anti-IgE antibody omalizumab has been used in the maintenance period of asthma, which can effectively reduce asthma attacks (69,70). Furthermore, anti-IL-4

and anti-IL-13 monoclonal antibodies would come out in succession.

Similarities in treatments between NS and atopic disease in children

The above-mentioned analysis revealed that glucocorticoids, immunosuppressants, and biological agents are all used in the treatment of both NS and atopic diseases. Therefore, it was speculated that NS and atopic diseases may be the same kind of disease, have a similar pathogenesis, and only exhibit different clinical manifestations due to the different affected parts of the disease.

Conclusions

Although NS and atopic diseases in children have different pathological positions and clinical manifestations, these are very similar in pathogenesis and cytokine changes. Furthermore, these have some common points in the treatment. In clinics, some children suffer from NS and atopic disease at the same time or have one of these diseases after the onset of the other. Therefore, the investigators propose that NS in children and other atopic diseases may have the same process in different organs and that NS children may also have atopic dermatitis or allergic rhinitis. In summary, it could be necessary to explore the correlation between these two further. This may provide a new method for the treatment of NS children.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tau-20-665>). The authors have no conflicts of interest to declare.

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