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CHALLENGING INFANTILE NEPHROTIC SYNDROME – MANAGEMENT AND DIAGNOSTIC ISSUES

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ABSTRACT

Infantile nephrotic syndrome (INS) is a kidney disorder characterized by nephrotic syndrome presenting between 4 and 12 months of age with hypoalbuminemia, (<2.5 mg/dl), proteinuria(> 40 mg/m^2) and edema. Children with infantile nephrotic syndrome appear normal at birth, proteinuria with a bland urine sediment develops postnatally, increasing progressively during the first or the second year of life. From the point of view of etiology, nephrotic syndrome may be idiopathic, genetic or secondary. Renal histopathology is not anymore a key criterion for diagnostic and prognostic in children with SRNS (steroid resistant nephrotic syndrome), having limited value in distinguishing genetic from nongenetic etiologies. Genetic podocytopathies changed diagnostic, prognostic judgment and therapeutic approaches in early onset SRNS. Therapeutic decisions are based on the underlying etiology.

Keywords: infantile nephrotic syndrome, genetic basis, genetic podocytopathies

INTRODUCTION

Infantile nephrotic syndrome (INS) is a kidney disorder characterized by nephrotic syndrome presenting between 4 and 12 months of age with hypoalbuminemia (<2.5 mg/dl), proteinuria (> 40 mg/m2) and edema. Most of these children have a genetic basis for the renal disease and a poor outcome.

Nephrotic syndrome (NS) appearing later is called childhood NS and NS manifesting soon after birth in the first three months of life is defined congenital (1).

NS can be classified as idiopathic, genetic, and secondary (autoimmune, toxic, infectious diseases, medication) based on the underlying causes.

According to the PodoNet registry cohort (1,655 patients from 67 centers in 21 countries) Trautmann et all reported resistant nephrotic syndrome manifested in the first 5 years of life in 64% of the patients. Early infantile nephrotic syndrome (onset age of 3-12 months) accounted for 7% of all patients (17).

PATHOGENESIS AND GENETICS

PodoNet registry proved that the proportion of patients with a genetic disease cause decreased with increasing manifestation age: from 69.4% in congenital nephrotic syndrome and 49.7% in infantile NS to 15-16% in school children and adolescents (17).

Proteinuria in most cases is caused by defects in the components of the glomerular filtration barrier which consists of the vascular endothelium, the glomerular basement membrane and the epithelial cell (podocyte) (2).

The proteinuria is highly selective early in the course of the disease and hematuria is uncommon,

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reflecting the lack of inflammation in the glomeruli.

The main components of the slit diaphragm are nephrin, the product of NPHS1 gene and podocin (a protein that interacts with nephrin), the product of NPHS2 gene.

Clasically mutations in NPHS1 lead to congenital nephrotic syndrome of the Finnish type (CNF) within the first 3 mo of life (3) whereas NPHS2 mutations are responsible for familial focal segmental glomerulosclerosis (FSGS) developing steroid-resistant nephrotic syndrome later.

Currently, close to 100 mutations in the *NPHS1* gene have been identified (4).

The NPHS1 mutation detection rate approaches 98% in Finland and is 39-80% outside Finland. This mutation rate was found as 39% in Europeans (5).

Compound heterozygous mutations in the *NPHS1* gene present with later onset of nephrotic syndrome (mean age 3 years, range 6 months to 8 years) (6).

Recently, *NPHS2* mutations have been identified in children with congenital nephrotic syndrome and *NPHS1* mutations similarly accounted for some cases of childhood and one case of adulthood steroid-resistant nephrotic syndrome, broadening the phenotypic spectrum of renal disease associated with mutations in the *NPHS1* (6).

Early-onset NS (CNS and INS) is less commonly caused by mutations in WT1, PLCE1, LAMB2, NPHS2I, *TRPC6* or LMX1B: *WT1* encodes the transcription tumor suppressor (a protein involved in kidney and gonad development) and is responsible for the Denys-Drash syndrome, *LAMB2* gene encodes laminin beta 2 (a component of the glomerular basement membrane) is responsible for the Pierson syndrome with diffuse mesangial sclerosis , *NPHS3* (*PLCE1*) which encodes phospholipase C epsilon (a signaling protein of many G protein-coupled receptors) is responsible for early onset nephrotic syndrome whereas *TRPC6* gene which encodes a transient receptor potential 6 ion channel, is incriminated in the appearance of GSFS with late onset (adult type), and the mutation in the LAMX1B gene in Nail-Patella syndrome (7,8).

Currently, over 45 recessive or dominant genes have been associated with SRNS and/or hereditary NS in humans; the known podocyte genes explain not more than 20-30% of hereditary NS. However, they explain 57-100% of familial and infant-onset NS, as compared with 10-20% of sporadic cases (9).

Besides nephrin there are some other recently identified podocyte proteins, such as Neph1, Neph2, FAT1, FAT2, and dendrin. They associate with each other extracellularly and interact with the adapter proteins, such as podocin, CD2AP, ZO-1, CASK, and MAGI-1, localized in the cytosolic part of the podocyte (10).

MAGI2 interacts with nephrin and regulates podocyte cytoskeleton and slit diaphragm dynamics. Disease-causing mutations in membrane-associated guanylate kinase MAGI2 (MAG, WW and PDZ domain-containing 2) have been reported in a cohort of patients with congenital and childhood–onset SRNS (11).

An early-onset nephrotic syndrome has been described in children with mutations in coenzyme Q10 biosynthesis genes (*COQ2*, *PDSS2*, *COQ6*, *ADCK4*). All affected individuals with CoQ2 mutations presented with nephrotic syndrome in the first year of life (12).

Renal histopathology is not anymore a key criterion for diagnostic and prognostic in children with SRNS,having limited value in distinguishing genetic from nongenetic etiologies.

The most common histologic patterns of glomerular injury in PodoNet registry cohort were FSGS (56%), minimal change nephropathy (21%), and mesangioproliferative GN (12%) (17).

Histopathologic associations with specific genetic disorders were limited to diffuse mesangial sclerosis-DMS (WT1 and PLCE1 nephropathies) and microcystic dilation of the proximal tubules-nephrotic syndrome of the Finnish type (CNF) (NPHS1 disease) (21).

CLINICAL FEATURES

Mutations in different genes as well as different mutations in the same gene manifest with NS onset at different ages (13).

There is significant phenotypic variability associated with defects in NS-related genes. Recessive mutations in NPHS1, NPHS2, LAMB2, and PLCE1 cause severe clinical features of early-onset NS. Hereditary, autosomal-dominant NS is rare, occurring mostly in juvenile and adult familial cases (14).

Children with infantile nephrotic syndrome appear normal at birth, proteinuria with a bland urine sediment develops postnatally, increasing progressively during the first or the second year of life. The degree of proteinuria is typically less severe than in CNF, but specific supplemental therapy is often required. They usually present with white, soft, and pitting edema often occuring after an event, such as an upper respiratory infection or an insect bite. Edema is gravity dependent and increases gradual-

ly, becoming detectable when fluid retention exceeds 3 to 5 percent of body weight.

Nutritional status and statural growth are poor, and affected infants are highly susceptible to bacterial infections (peritonitis, respiratory infections) and to thromboembolic complications due to the severity of the nephrotic syndrome. Hypothyroidism because of urinary losses of thyroxine-binding proteins is also common.

Genetic NS may present as a syndromic disorder with extrarenal manifestations. Pierson syndrome includes congenital nephrotic syndrome (CNS) ocular malformations and neurologic symptoms (hypotonia, psychomotor retardation). Wilms' tumor may be the first clinical manifestation of the Denys and Drash syndrome (the triad of progressive renal disease, male pseudohermaphroditism, and Wilms' tumor). Children with LMX1B mutations usually present with Nail-Patella syndrome. INF2 mutations can lead to isolated Charcot-Marie-Tooth disease. MYH9 is a disease-causing gene in the rare giant-platelet disorders, including May-Hegglin anomaly, Epstein-Fechtner, or Sebastian syndrome (15).

THERAPY

Therapeutic decisions are based on the underlying etiology (17,18).

Treatment goals are to achieve complete resolution of proteinuria, thereby reducing the complications associated with NS, and preservation of kidney function.

Conservative treatment is supportive and includes maintenance of electrolyte and water balance, albumin infusion, gamma globulin replacement, nutrition with a high-protein, low-salt diet, vitamin and thyroxine substitution, prevention of infections and thrombotic complications.

As the rate of intercurrent complications remains high, and growth and development are usually retarded, bilateral nephrectomy have to be considered to prevent massive protein losses before the development of renal failure and at the time of transplantation at patients presenting diffuse mesangial sclerosis because of the theoretical risk of developing a Wilms' tumor.

A possible alternative to nephrectomy could be lowering intraglomerular pressure with a combination of an angiotensin converting enzyme inhibitor and indomethacin therapy. Marked fall in protein excretion and improvement in nutritional status and growth has been described. The combination of an angiotensin converting enzyme inhibitor and indomethacin therapy also proved to be effective in one case with diffuse mesangial sclerosis (16).

Although studies reported rituximab and calcineurin inhibitors CNI equally effective therapeutic option for patients with SRNS 40-50% achieving complete remission of proteinuria, patients with single gene mutations that affect glomerular podocyte differentiation and function (quarter to a third of all pediatric cases of isolated and syndromic SRNS) are usually unresponsive to immunosuppressive therapy (17,18). A patient with SRNS with a homozygous ADCK4 mutation presented partial remission following CoQ10 treatment (15 to 30 mg/kg per day) suggesting the ubiquinone benefit for these children (14).

Screening for *NPHS2* mutations all children with a first episode of the NS prior to initiation of steroid therapy it is not recommended, given that less than 5 percent of all cases with NS would have a genetic basis (over 85 percent of children with idiopathic NS are steroid-sensitive, and only approximately one-third of steroid-resistant patients have a genetic mutation) (19). The order of testing is suggested by the probability of involvement of a specific mutation as follows:

- age of presentation: patients older than 3 months screening should begin with identifying *NPHS2* mutations.
- presence of extrarenal abnormalities – *LAMB2* screening for patients with ocular abnormalities, and *WT1* screening for those with ambiguous genitalia
- type of histologic lesions – *WT1* or *LAMB2* screening for patients with a histologic diagnosis of DMS.

A genetic diagnosis is far superior to histopathologic disease classification in predicting IIT (Intensified immunosuppressive therapy) responsiveness and post-transplant disease recurrence (17).

The only curative treatment for most cases of infantile nephrotic syndrome caused by genetic defects in glomerular podocyte proteins remains renal transplantation. Post-transplant disease recurrence was noted in 4.5% of PodoNet patients with a genetic diagnosis (17).

Most of the children with homozygous truncating NPHS1 mutation have a complete absence of the major podocyte protein, nephrin, developing proteinuria after renal transplantation due to anti-nephrin antibodies. Plasma exchange with cyclophosphamide and anti-CD20 antibodies has proved to be a successful therapy for these episodes. Few patients with NPHS2 mutation developed post-RTx proteinuria with different pathophysiologic mecha-

nism and no anti-podocin antibodies detectable (20).

Timing of renal replacement therapy does not influence survival and growth in children with congenital nephrotic syndrome caused by mutations in *NPHS1* (17).

DISCUSSION

Genetic podocytopathies changed diagnostic, prognostic judgment and therapeutic approaches in early onset SRNS.

Although the analysis of multiple genes is time-consuming and expensive, the identification of pathogenic mutations can help avoid adverse effects of steroid/immunosuppressive treatment.

The phenotypic spectrum caused by mutations in genes expressed by glomerular podocytes is wider than initially expected.

An appropriate genetic approach for patients with hereditary NS could be determined based on inheritance, age at onset, renal histology, and presence of extrarenal malformations (15). Genetic negative results virtually exclude the common genetic causes of SRNS, however due to the heterogeneity of this syndrome a genetic aetiology cannot be completely excluded.

Although most histological lesions in genetic NS are unspecific, FSGS is more prevalent than other histologic types. Therefore, genetic NS is difficult to treat, has poor prognosis, and often.

Of the non genetic causes of INS, the majority are likely to be immune-mediated and caused by the presence of a still-unknown circulating factor or factors, and whether there is a third (or more) mechanistic group or groups remains to be discovered (22).

One recent study reported 2 cases of INS with complet remission after subsequent infection with Zyka virus. It might be be random, but also possible that future studies will discover that infection has some effect on the cellular immune system (23).

Therapies directed specifically towards the target cell, the podocyte, are in their infancy but hold considerable promise for the near future (22).

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