and those with steroid-responsive nephrotic syndrome, representing the majority of cases. They often have serious side effects due to corticosteroids and treatment with other agents is recommended in order to maintain remission while reducing corticosteroid dosing. The purpose of treatment of steroid-resistant cases is to decrease proteinuria and to preserve kidney function. Treatment strategies include immunosuppressive and non-immunosuppressive measures. A kidney biopsy should be done in these children in order to reveal the underlying histology. In patients with a strong suspicion for a genetic cause genetic testing should be done as well. Congenital nephrotic syndrome is a nephrotic syndrome that presents at birth or during the first three months of life while infantile nephrotic syndrome presents between three and twelve months of age. In majority of these children there is a genetic basis for the disease and poor outcome with no indication for immunosuppressive treatment. A new way of possible treatment of this type of nephrotic syndrome in the future is presented.

Keywords: Nephrotic syndrome; Children; Steroid-resistance; Steroid-responsiveness; Genetics; Treatment

INTRODUCTION

The nephrotic syndrome is characterized by increased permeability across the glomerular filtration barrier. Several mechanisms of glomerular injury are responsible for pathogenesis, such as circulating factor, circulating immune factors in immune-mediated disorders and mutations in podocyte or slit diaphragm proteins. Children with nephrotic syndrome are classified as primary, secondary and congenital / infantile nephrotic syndrome. Children with idiopathic nephrotic syndrome, the most common form, can be divided into those with steroid-resistant nephrotic syndrome, who are at increased risk for developing end-stage renal disease, and those with steroid-responsive nephrotic syndrome, representing the majority of cases. They often have serious side effects due to corticosteroids and treatment with other agents is recommended in order to maintain remission while reducing corticosteroid dosing. The purpose of treatment of steroid-resistant cases is to decrease proteinuria and to preserve kidney function. Treatment strategies include immunosuppressive and non-immunosuppressive measures. A kidney biopsy should be done in these children in order to reveal the underlying histology. In patients with a strong suspicion for a genetic cause genetic testing should be done as well. Congenital nephrotic syndrome is a nephrotic syndrome that presents at birth or during the first three months of life while infantile nephrotic syndrome presents between three and twelve months of age. In majority of these children there is a genetic basis for the disease and poor outcome with no indication for immunosuppressive treatment. A new way of possible treatment of this type of nephrotic syndrome in the future is presented.

Keywords: Nephrotic syndrome; Children; Steroid-resistance; Steroid-responsiveness; Genetics; Treatment

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ABSTRACT

The nephrotic syndrome is characterized by increased permeability across the glomerular filtration barrier. Several mechanisms of glomerular injury are responsible for pathogenesis, such as circulating factor, circulating immune factors in immune-mediated disorders and mutations in podocyte or slit diaphragm proteins. Children with nephrotic syndrome are classified as primary, secondary and congenital / infantile nephrotic syndrome. Children with idiopathic nephrotic syndrome, the most common form, can be divided into those with steroid-resistant nephrotic syndrome, who are at increased risk for developing end-stage renal disease, and those with steroid-responsive nephrotic syndrome, representing the majority of cases. They often have serious side effects due to corticosteroids and treatment with other agents is recommended in order to maintain remission while reducing corticosteroid dosing. The purpose of treatment of steroid-resistant cases is to decrease proteinuria and to preserve kidney function. Treatment strategies include immunosuppressive and non-immunosuppressive measures. A kidney biopsy should be done in these children in order to reveal the underlying histology. In patients with a strong suspicion for a genetic cause genetic testing should be done as well. Congenital nephrotic syndrome is a nephrotic syndrome that presents at birth or during the first three months of life while infantile nephrotic syndrome presents between three and twelve months of age. In majority of these children there is a genetic basis for the disease and poor outcome with no indication for immunosuppressive treatment. A new way of possible treatment of this type of nephrotic syndrome in the future is presented.

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presence or absence of signs of systemic disease: primary nephrotic syndrome, such as idiopathic nephrotic syndrome (with absence of a systemic disease), secondary nephrotic syndrome (with presence of a systemic disease) and congenital and infantile nephrotic syndrome (in children in the first year of life). The latter can be either secondary (due to infection, for example) or primary, with majority of them having a genetic cause\(^1\).

**PATHOGENESIS**

Several different mechanisms of glomerular injury have been described: circulating factors, especially in primary focal segmental glomerulosclerosis (FSGS), circulating immune factors in immune-mediated disorders (poststreptococcal glomerulonephritis, lupus nephritis,…) and mutations in podocyte or slit diaphragm proteins (podocin, nephrin,…), mainly in congenital and infantile nephrotic syndrome. The glomerular capillary wall consists of the glomerular basement membrane (GBM), the fenestrated endothelial cell and the epithelial cell foot processes, the pores between them being closed by the slit diaphragm\(^1\).

Another factor, important in the pathogenesis of nephrotic syndrome, is proteinuria. It is caused by increased filtration of macromolecules (mainly albumin) across the glomerular capillary wall. This is regulated by a net negative charge (due to polyanions such as heparan sulfate proteoglycans) of the endothelial cells and the GBM that creates a charge barrier to the filtration of large anions such as albumin. In addition, the glomerular capillary wall is size-selective with functional pores of a radius that is slightly larger than the radius of albumin. In minimal change disease (MCD), the most common cause of nephrotic syndrome in children, there is a loss of anionic charge without any structural damage to the glomerular filtration unit (observed by light microscopy) but with visible epithelial podocyte effacement, seen by electron microscopy. But in other glomerular diseases, structural injury to the glomerulus (seen by light microscopy) results in an increased number of large pores in the GBM with a consequent movement of proteins of varying sizes across the filtration barrier\(^1\).

Recently, the pathogenesis of MCD as a two-hit model podocyte immune disorder was proposed: the initial hit is the induction of CD80 on the podocyte with alteration in shape with actin rearrangement, with a consequent increased glomerular permeability causing proteinuria. CD80 is expressed due to direct binding of cytokines from activated T cells or due to activation of podocyte toll-like receptors by viral products. Normally, CD80 expression is just transiently expressed with minimal proteinuria due to rapid autoregulatory responses by circulating T cells or by the podocyte itself. On the other hand, there is a defect in CD80 podocyte autoregulation in MCD with persistent CD80 expression and persistent proteinuria\(^1\).

**IDIOPATHIC NEPHROTIC SYNDROME**

Idiopathic nephrotic syndrome is the most common form of childhood nephrotic syndrome. It is a cause of nephrotic syndrome in over 90% of children between 1 and 10 years of age and in 50% above 10 years of age\(^1\). In idiopathic nephrotic syndrome, there is the association of a nephrotic syndrome with diffuse foot process effacement on electron microscopy and minimal changes (in MCD), FSGS, or mesangial proliferation on light microscopy, revealed at renal biopsy. These light microscopic patterns may represent separate diseases or are a spectrum of a single disease\(^1\).

The results from the International Study of Kidney Disease in Children (ISKDc) revealed that certain clinical findings at disease presentation, such as young age (less than six years), absence of hypertension and hematuria, normal renal function and complement levels can reliably differentiate children with MCD from those with other glomerular disorders. It also revealed MCD to be the most common cause of childhood nephrotic syndrome, representing about three quarters of these patients, and FSGS to be the second most common cause with 7% of cases. Other causes are much more rare (membranoproliferative glomerulonephritis, membranous nephropathy,…)\(^1\).

Children with idiopathic nephrotic syndrome can be, according to their response to empiric therapy with corticosteroids, divided into patients with steroid-responsive (or steroid-sensitive) nephrotic syndrome (SSNS), representing the majority of these children (with MCD as the most common histologic lesion) and patients with steroid-resistant nephrotic syndrome (SRNS), representing about 20% of these children. The latter have a bad prognosis regarding renal survival, estimated to be up to 50% at 10 years, depending on ethnicity of children. In this group of patients, some of them have genetic mutations of podocyte proteins, such as NPHS2, NPHS1 or other genes\(^1\).

**SECONDARY NEPHROTIC SYNDROME**

Secondary nephrotic syndrome is defined as nephrotic syndrome associated with systemic diseases or is secondary to another disease, causing glomerular injury. There are disorders without signs of glomerular inflammation on renal biopsy, such as membranous nephropathy (due to chronic hepatitis B infection) or secondary FSGS (due to renal scarring or hypoplasia, for example) and disorders, presenting with nephritic syndrome (with red cells and cellular casts in urine sediment) and with signs of glomerular inflammation on renal biopsy, such as postinfectious glomerulonephritis, systemic lupus erythematosus, various forms of vasculitis, Alport syndrome and hemolytic-uremic syndrome\(^1\).

**CLINICAL MANIFESTATIONS**

Idiopathic nephrotic syndrome in children often follows a triggering event, usually an upper respiratory infection. Edema is the main clinical feature and usually appears in periorbital region first but can later appear in the lower extremities and other dependent areas, such as the scrotum, labia and sacral area due to gravity dependence. Edema is soft and pitting to palpation. Pronounced generalized edema (anasarca) with abdominal distension (due to ascites) can appear in some patients. Signs of a decreased effective circulating volume, such as peripheral vasoconstriction, tachycardia, oliguria or decreased glomerular filtration rate (GFR) can develop in some children with nephrotic syndrome (especially those with MCD) even though the extracellular fluid volume is increased. In these cases, additional noxious events, such as sepsis, diarrhea or diuretic therapy, can cause hypotension and even shock. Other clinical manifestations can be present, such as hernias (umbilical, inguinal), abdominal pain (due to peritonitis, for example), dyspnea (due to pleural effusions or pronounced ascites) and various nonspecific complaints, such as headache, fatigue and irritability. Blood pressure is usually normal\(^1\). Microhematuria can present in 20% of cases while macrohematuria is rare in idiopathic nephrotic syndrome\(^1\).

**DIAGNOSTIC EVALUATION**

The diagnosis of nephrotic syndrome is confirmed by the presence of nephrotic range proteinuria (urinary protein excretion above 50 mg/kg per day or 40 mg/m$^2$ per hour in timed urine collection) and hypoalbuminemia (serum albumin concentration below 30 g/L) while
edema may not be present in all patients\textsuperscript{(11)}. Initial evaluation includes:

1. Urinalysis: a screening test (followed by confirmation with quantitative protein excretion studies), urine sediment is usually inactive, there are hyaline casts and just a few red cells and no red cell or other cellular casts, but their presence suggests nephritis and demands evaluation for glomerulonephritis rather than primary nephrotic syndrome.

2. Protein to creatinine ratio in first morning void, especially when timed urine collection is difficult to obtain (in small children): ratio greater than 3 mg protein/mg creatinine means nephrotic range proteinuria.

3. Blood tests: complete blood count (hemoglobin and hematocrit may be increased due to plasma volume contraction and thrombocytosis is common), electrolytes (hypotension can occur due to decreased free water excretion), creatinine (usually normal), blood urea nitrogen (often elevated due to hypovolemia), cholesterol (typically elevated), complement studies (to exclude other diseases that present with nephrotic syndrome) and albumin. Hypoalbuminemia is one of main findings and serum albumin concentration is typically below 30 g/L while total globulins are relatively preserved with normal or slightly decreased serum alpha-1 globulin, increased alpha-2 and beta globulin concentrations and varying concentrations of gamma globulin.

4. Additional blood tests according to clinical situation: antinuclear antibody level in patients ≥10 years of age (or with signs of systemic lupus erythematosus), serology for hepatitis B and C.

5. Renal biopsy in children above 12 years of age\textsuperscript{(1, 2)}.

**TREATMENT**

Children, likely to have nephrotic syndrome due to MCD, are treated empirically with corticosteroids (usually with prednisone at a dose of 60 mg/m\textsuperscript{2} per day) without need for kidney biopsy. After achieving remission, defined as negative proteinuria (urinary protein excretion less than 4 mg/m\textsuperscript{2} per hour), corticosteroids are continued at the same daily dose for 30 days, followed by alternate-day therapy that is tapered over four to eight weeks\textsuperscript{(9)}. Another approach is treatment with prednisone of 2 mg/kg per day for six weeks, followed by alternate-day dosing of 1.5 mg/kg for the next six weeks\textsuperscript{(2)}. According to KDIGO (Kidney Disease: Improving Global Outcomes) guidelines, initial treatment with prednisone (60 mg/m\textsuperscript{2} or 2 mg/kg per day, with maximal dose being 60 mg/day) for four to six weeks is followed by alternate-day prednisone (40 mg/m\textsuperscript{2} or 1.5 mg/kg, with maximal dose being 40 mg/day) with gradual tapering of the dose for two to five months\textsuperscript{(3)}. According to recent findings, treatment duration of two or three months is enough for the first episode of steroid-sensitive nephrotic syndrome. However, it is worth mentioning that spontaneous remission can occur in approximately 5% of cases within one or two weeks\textsuperscript{(4)}.

Most children with idiopathic nephrotic syndrome will respond to corticosteroid therapy. However, 40 – 50% of them will have frequent relapses (defined as four or more relapses per year, FRNS) or will be steroid-dependent (defined as relapsing during taper or within two weeks of treatment discontinuation with corticosteroids, SDNS)\textsuperscript{(5, 6, 7, 10)}. Treatment with prednisone of 2 mg/kg per day or 60 mg/m\textsuperscript{2} until the remission, followed by alternate-day dosing of 1.5 mg/kg or 40 mg/m\textsuperscript{2} for four weeks is suggested for children with a first relapse or infrequent relapses\textsuperscript{(2, 3, 10)}. For children with frequent relapses, daily treatment with prednisone until remission is followed by alternate-day dosing of 1.5 mg/kg for four weeks and then by taper over two months by 0.5 mg/kg every other day\textsuperscript{(2)}.

For children with frequent relapses or steroid-dependence, suggested treatment consists of prednisone (2 mg/kg per day or 60 mg/m\textsuperscript{2}) until remission, followed by alternate-day prednisone for at least three months with the lowest dose of alternate-day prednisone (or the lowest dose of daily prednisone in patients with ineffective alternate-day therapy), needed to maintain remission without side effects. In order to prevent a relapse, daily prednisone administration of maintenance doses for one week should be given to patients during respiratory and other infections, known to cause relapses\textsuperscript{(2, 3, 10)}.

Children, who respond to treatment with corticosteroids, especially frequent relapsers and steroid-dependent patients, often have serious side effects due to corticosteroid therapy, such as: growth impairment, excessive weight gain, cataracts, decreased bone mineral density, suppression of the hypothalamic-pituitary-adrenal axis and some others\textsuperscript{(8)}. Therapy with other agents is recommended in these patients in order to maintain remission while reducing corticosteroid dosing and side effects. These agents are:

1. Levamisole (if available, which is not the case in all countries): it can cause reversible neutropenia, therefore regular monitoring of complete blood count is mandatory\textsuperscript{(5, 6)}.

2. Mycophenolate mofetil (MMF): it can cause gastrointestinal disturbances (such as abdominal pain and diarrhea) and hematological abnormalities\textsuperscript{(6, 7)}.

3. Cyclophosphamide: it can have several side effects, but a 12-week course (with maximum cumulative dose of 168 mg/kg) seems to induce minimal long-term complications; it is reported to be more useful in patients with frequent relapses\textsuperscript{(6, 7)} compared to steroid-dependent patients\textsuperscript{(9)}.

4. Calcineurin inhibitors ( cyclosporine and tacrolimus) are effective in inducing or maintaining remission in patients with frequently relapsing or steroid-dependent course\textsuperscript{(6, 7)}; however, prolonged treatment is necessary in order to achieve a sustained remission thus increasing the risk of nephrotoxicity; therefore, it is only suggested in patients who fail to maintain remission after treatment with other agents, such as MMF or cyclophosphamide\textsuperscript{(9)}.

5. Rituximab (a chimeric anti-CD20 monoclonal antibody) should be considered only in children with ineffective combination therapy of prednisone and other corticosteroid-sparing agents because of the risk of severe and potentially life-threatening complications and because the long-term efficacy and safety is unknown\textsuperscript{(4, 8, 9, 10)}. However, a recent study showed that rituximab is an effective and safe treatment for childhood-onset nephrotic syndrome that presents with frequent relapses or steroid-dependence. The median relapse-free period was significantly longer in patients treated with this drug than in those treated with placebo but the difference in occurrence rate of serious adverse events between these two groups was not statistically significant. But the follow-up period was 1 year which is relatively short\textsuperscript{(4, 8, 9, 10, 11)}. In addition, another study demonstrated that rituximab can directly affect glomerular podocytes and decrease proteinuria in adriamycin-induced nephrotic syndrome in laboratory animals through B-lymphocyte independent mechanisms of podocyte protection, mediated by direct modulation of a sphingomyelin phosphodiesterase, acid-like 3b-dependent mechanisms\textsuperscript{(12, 13)}.

Agent selection is based upon the clinician’s assessment of the ratio between risk and benefit since there is no evidence, obtained from randomized clinical trials, that any of the above mentioned agents provide long-term efficacy without significant side effects\textsuperscript{(5, 6)}.

Regarding the duration of corticosteroid therapy in childhood SSNS, a recent multicenter randomized trial revealed that initial prednisolone therapy for two months is not inferior to six months of initial therapy in terms of clinical outcome: time to onset of FRNS,
time to first relapse and the number of relapses. In addition, frequency and severity of adverse events were similar in both groups. This is not in accordance with previous findings, suggesting that long-term corticosteroid therapy (up to 7 months) leads to a longer lasting remission.

If four weeks of daily treatment with corticosteroids do not lead to remission, three pulses of methylprednisolone (1000 mg/1.73 m²) every other day should be given. If proteinuria persists one week later despite of that, steroid-resistance is confirmed. In this case a renal biopsy must be done because of increased likelihood of presence of another glomerular disease. However, other approaches may be used, such as renal biopsy without treatment with three pulses of methylprednisolone or prolongation of daily corticosteroid treatment for another four weeks.

Regarding the prognosis of children with steroid sensitive nephrotic syndrome, renal function remains normal in adulthood and long-term sequelae are usually consequences of side effects of the drugs that were used.

**Steroid-Resistant Nephrotic Syndrome**

A minority of children with idiopathic nephrotic syndrome (10-20%) do not respond to initial treatment with corticosteroids, a condition named steroid-resistant nephrotic syndrome (SRNS). These children are at increased risk for developing end-stage renal disease (ESRD). Genetic mutations can cause SRNS in a significant proportion of children and mutations of the NPHS1, NPHS2, and WT1 genes are the most common among them. However, often no underlying cause is detected. The most common histological diagnoses, revealed by kidney biopsy, are FSGS and MCD. Children with SRNS had decreased corticosteroid receptor expression in peripheral blood mononuclear cells (which may be genetically based) before the start of treatment compared to children, who responded to corticosteroids, according to a recently published study, and this may explain steroid resistance in children.

The purpose of SRNS treatment is to decrease protein excretion with a consequent decrease of complications and preservation of kidney function. Treatment strategies include immunosuppressive and non-immunosuppressive measures for reducing proteinuria. Immunosuppressive treatment options in these children are calcineurin inhibitors, mycophenolate and rituximab. They are usually not considered first-line agents, MMF or rituximab is not suggested in these cases due to lack of efficacy and safety.

Galactose was proposed recently as a novel treatment for nephrotic syndrome in FSGS due to its binding to the FSGS permeability factor and decreasing its activity. There were some reports of sporadic cases, resistant to various other treatment options, where partial or complete remission was achieved with this agent while a study on several children failed to prove an effect on proteinuria even though there was a reduction of the plasma FSGS permeability factor activity.

Therefore, galactose is recommended no more as a treatment option for children with SRNS. SRNS usually presents histologically as FSGS. Identification of single-gene (monogenic) causes of SRNS revealed podocytes as crucial in the pathogenesis. In the last years, mutations in over 30 recessive or dominant genes were identified as causes of monogenic forms of SRNS, thus revealing the encoded proteins as very important for glomerular function. It was discovered recently that in about one third of young patients (children and adults under the age of 25) with SRNS, a causative mutation can be detected in one of the above mentioned genes. Mutation analysis should therefore be done in all young patients with SRNS in order to provide the patients and their families with a precise molecular genetic diagnosis, to reveal a form of SRNS that is amenable to treatment (mutation in the coenzyme Q₁₀ biosynthesis pathway, for example), to define genotype-phenotype correlations, to avoid renal biopsy in some cases and to permit personalised treatment options, based on a genetic cause.

Recent technological advances in high throughput sequencing have enabled genetic panel testing for patients with SRNS. Significant phenotypic variability of monogenic SRNS combined with the availability of genetic testing is challenging in clinical practice when faced with a patient in need of a genetic testing. Therefore, clear clinical guidelines are needed, providing a systematic approach for mutational screening in SRNS. Young age at disease onset, the presence of family history and extra-renal manifestations, congenital and infantile nephrotic syndrome and consanguinity are associated with increased probability of identifying a causative mutation. Therefore, these situations represent clinical indications for genetic testing in SRNS. The precise molecular diagnosis could enable a personalised treatment approach with avoidance of immunosuppressive drugs that can have serious side effects. Linkage analysis and next generation sequencing have allowed the identification of over 50 genes, responsible for SRNS, with the majority of encoded proteins mapping to structural protein complexes and signalling pathways within the podocyte. Their detailed listing and description is beyond the scope of this article and can be found in the literature. Identification of known and novel pathogenic variants involved in monogenic SRNS can help to better define genotype-phenotype correlations and increase our knowledge about glomerular filtration barrier. Renal histology has been considered as a key diagnostic and prognostic criterion in cases of SRNS for a long time but new evidence does not confirm a strong correlation between kidney biopsy findings and genetic results. The cost-effectiveness of next-generation sequencing...
Congenital nephrotic syndrome is a nephrotic syndrome that presents at birth or during the first three months of life while infantile nephrotic syndrome presents between three and twelve months of age. There is a genetic basis for the nephrotic syndrome in majority of these children and consequently a poor outcome. Mutations, responsible for the majority (more than 80%) of cases of congenital and infantile nephrotic syndrome, are NPHS1, NPHS2 (it encodes podocin, a protein interacting with nephrin at the slit diaphragm), NPHS3 (it encodes phospholipase C epsilon, a signaling protein of many G protein-coupled receptors), LAMB2 and WT1. These cases do not respond to immuno-suppressive treatment. Therefore, genetic screening is recommended to confirm a diagnosis before starting such treatment. Congenital or infantile nephrotic syndrome may occur due to other causes as well, such as other genetic disorders, idiopathic nephrotic syndrome, certain infections and toxins, as presented in table 1 [25].

Congenital nephrotic syndrome of the Finnish type is the most frequent in Finland, with an incidence of 1.2 per 10 000 births but has been described in other parts of the world as well. It is inherited as an autosomal recessive trait, with both sexes affected equally. Edema is present at birth or during the first week of life in 50% of cases and severe nephrotic syndrome appears by three months of age. Severe proteinuria is accompanied by marked hypoalbuminemia, hypothyroidism and hypogammaglobulinemia with a consequent malnutrition, impaired growth and high susceptibility for various bacterial infections and thromboembolic complications. The GFR is normal initially and ESRD usually occurs between three and eight years of age. It is resistant to immuno-suppressive treatment, and therefore, treatment is supportive: regular albumin, gamma globulin, vitamin and mineral supplementation and treatment with an ACE inhibitor and indomethacin, which lowers intraglomerular pressure, has been described with resultant fall in proteinuria and improvement in general condition of affected children [29].

Diffuse mesangial sclerosis is another hereditary cause of infantile nephrotic syndrome associated with glomerular injury and rapid progression to ESRD. It can be caused by abnormalities in the PLCE1 gene, which encodes phospholipase C epsilon, a phospholipase enzyme that catalyzes the hydrolysis of polyphosphoinositides resulting in generation of second messengers, which are involved in cell growth and differentiation. Its mutation leads to disruption of the glomerular filtration barrier and edema, proved in a PLCE1 knockout zebrafish model [29]. A study on children with isolated diffuse mesangial sclerosis from different countries revealed truncating PLCE1 mutations in 10 of 35 families [29]. Precise mechanism of PLCE1 gene mutation on development of nephrotic syndrome is not yet explained but probably involves disturbed interaction of phospholipase C epsilon with GTPase-activating protein, which interacts with nephrin [29].

**Table 1** Main causes of congenital and infantile nephrotic syndrome [25].

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Congenital nephrotic syndrome of Finnish type</strong></td>
<td>Due to mutation of NPHS1, that encodes nephrin, a transmembrane protein that is a crucial component of the podocyte slit diaphragm; this results in disruption of the glomerular capillary filter structure</td>
</tr>
<tr>
<td><strong>Diffuse mesangial sclerosis</strong></td>
<td>Due to WT1 mutation, encoding the transcription tumor suppressor, a protein involved in kidney and gonad development; it is associated with Wilms’ tumor and male pseudohermaphroditism in 46 XY patients and a normal female phenotype in 46 XX children</td>
</tr>
<tr>
<td><strong>Diffuse mesangial sclerosis with Denys Drash syndrome</strong></td>
<td>Due to WT1 mutation, encoding the transcription tumor suppressor, a protein involved in kidney and gonad development; it is associated with Wilms’ tumor and male pseudohermaphroditism in 46 XY patients and a normal female phenotype in 46 XX children</td>
</tr>
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</table>

**Figure 1** (A) Schematic representation of disturbed interaction of mutated phospholipase C epsilon (PLCE1) with GTPase-activating protein, which interacts with nephrin, leading to development of nephrotic syndrome [25,29,30]. Legend: 1 - nephrin, 2-6 - other podocyte and slit diaphragm proteins [29]. (B) Schematic representation of theoretical concept of possible new treatment of nephrotic syndrome due to PLCE1 gene mutation with a recombinant enzyme phospholipase C epsilon 1 (PLCE1), administered parenterally. In this way, the function of inactive native enzyme (due to gene defect) could be replaced, with a consequent restoration of glomerular filtration barrier and amelioration of clinical features of nephrotic syndrome.
a clinical response to cyclosporine after unsuccessful treatment with corticosteroids in one child with diffuse mesangial sclerosis due to PLCE1 gene defect[29].

Figure 1. b) presents a schematic representation of theoretical concept of a possible new way of treatment of nephrotic syndrome due to PLCE1 gene mutation with a recombinant enzyme phospholipase C epsilon 1 (PLCE1), administered parenterally (with intravenous infusion, for example). In this way, the function of inactive native enzyme (due to gene defect) could be replaced, with a consequent restoration of glomerular filtration barrier and amelioration of clinical features of nephrotic syndrome. Similarly, a recombinant nephrin could be theoretically used to treat congenital nephrotic syndrome of the Finnish type. Further studies in laboratory and in animal models are, of course, needed to prove this. This could be regarded as a way of personalised treatment. If this proves to be effective and safe in the future, this kind of treatment, if started early enough, may prevent progression to chronic kidney disease and the need for renal replacement therapy. This could lead to a significant decrease of the burden of these diseases on patients and the entire health care systems.

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30. Phospholipase C Epsilon 1 (PLCe1) (scheme of enzyme)


Peer Reviewers: Hiroshi Tanaka; Laura Espinosa