Congenital and infantile nephrotic syndrome

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INTRODUCTION — The term congenital nephrotic syndrome refers to disease that is present at birth or within the first three months of life. Later onset, between three months and one year of age, is called infantile nephrotic syndrome. Most of these children have a genetic basis for the renal disease and a poor outcome. The precise diagnosis of the glomerular lesion is based on clinical, laboratory, and histological criteria.

The causes of congenital and infantile nephrotic syndrome will be discussed here.

ETIOLOGY — In a review of 89 Central European and Turkish children (from 80 families) who presented with nephrotic syndrome in the first year of life, two-thirds overall and as many as 85 percent of cases that occurred during the first three months of life could be explained by mutations in the following four genes [1]:

- NPHS1, which encodes nephrin (a key component of the podocyte slit diaphragm) and is responsible for the Finnish-type congenital nephrotic syndrome. (See 'CNS of Finnish type' below.)

- NPHS2, which encodes podocin (a protein that interacts with nephrin at the slit diaphragm) and is responsible for familial focal segmental glomerulosclerosis. (See 'CNS and NPHS2 mutations' below.)

- WT1, which encodes the transcription tumor suppressor (a protein involved in kidney and gonad development) and is responsible for the Denys-Drash syndrome. (See 'Diffuse mesangial sclerosis with Drash syndrome' below.)

- LAMB2, which encodes laminin beta 2 (a component of the glomerular basement membrane) and is responsible for the Pierson syndrome. (See 'Pierson syndrome' below.)

NPHS2 and NPHS1 were the most common, accounting for approximately 95 percent of cases [1]. None of 28 patients with a mutation who were treated with glucocorticoids responded.

In addition to the above defects, mutations in the PLCE1 gene, which encodes phospholipase C epsilon, are responsible for the early onset of isolated diffuse mesangial sclerosis [2]. (See 'Diffuse mesangial sclerosis' below.)

Nongenetic causes are often secondary and possibly curable disorders. They include infections, such as congenital nephrotic syndrome induced by syphilis or toxoplasmosis (table 1), and toxins such as mercury exposure. (See 'Infectious causes' below and 'Other causes' below.)

CNS OF FINNISH TYPE — Congenital nephrotic syndrome (CNS) of the Finnish type (CNF) is most frequent in Finland, with initial studies suggesting an incidence of 1.2 per 10,000 births [3,4]. With prenatal screening, the incidence has fallen to 0.9 per 10,000 births [5]. CNF has also been described in various ethnic groups throughout the world [6-8].

CNF is inherited as an autosomal recessive trait, with both sexes being involved equally. There are no manifestations of the disease in heterozygous individuals.

Pathology — Light microscopic studies of renal biopsy specimens obtained early in the course of the disease show mild mesangial hypercellularity and increased mesangial matrix in the glomeruli [6,9]. No immune deposits are detected by immunofluorescence studies. Over time, there is an increase in mesangial matrix accompanied by progressive glomerulosclerosis.

Tubulointerstitial changes are also prominent in CNF. Irregular microcystic dilatation of proximal tubules is the most striking feature (picture 1); however, this change is not specific and is not seen in all patients [10]. Later in the course, interstitial fibrosis, lymphocytic and plasma cell infiltration, tubular atrophy, and periglomerular fibrosis develop in parallel with sclerosis of the glomeruli.

Pathogenesis — It had been proposed that proteinuria in CNF results from an inherited error in the structure of the glomerular capillary filter. The abnormal gene was subsequently localized to the long arm of chromosome 19 in both Finnish and non-Finnish families [11-13].

The defective gene in CNF has been cloned and is named NPHS1 [14,15]. The gene encodes for a transmembrane protein, named **nephrin**, which is a member of the immunoglobulin family of cell adhesion molecules and is phosphorylated by Src family kinases [16]. Nephrin is specifically located at the slit diaphragm of the glomerular podocytes; this could explain the absence of slit diaphragms and foot processes in patients with CNF who have a mutant nephrin protein [17,18] and in mice with nephrin gene disruption [19].

In the original report, four different mutations in this gene were found to segregate with the disorder in affected Finnish families [14]. However, the two most common mutations, Fin-major (nt121delCT) and Fin-minor (R1109X), account for nearly 90 percent of all affected Finnish patients and are associated with severe early onset of disease [14,20,21].

In another study, 32 novel mutations in the nephrin gene were discovered in patients elsewhere in Europe and North America, but no abnormalities were found in seven affected individuals (including the 5' flanking region) [12]. These patients may have mutations elsewhere in the promoter or in intron areas, or in a gene encoding another protein that interacts with nephrin [22]. (See "Epidemiology, classification, and pathogenesis of focal segmental glomerulosclerosis".)

A case report of two siblings with a milder form of CNF (ie, alternating periods of proteinuria and remission) showed that the two children were compound heterozygotes for two novel, nonconserved missense mutations [23]. Additional studies from renal biopsy samples demonstrated expression of nephrin, but with impaired function.

Clinical features — Most infants with the CNF are born prematurely (35 to 38 weeks), with a low birth weight for gestational age. The placenta is enlarged, being more than 25 percent of the total birth weight. Fetal distress is common and the cranial sutures are widely separated due to delayed ossification. Infants often have a small nose and low ears. Flexion deformities of the hips, knees, and elbows are thought to be secondary to the large placenta.

Edema is present at birth or appears during the first week of life in one-half of cases. Severe nephrotic syndrome with marked ascites is always present by three months. The proteinuria is highly selective early in the course of the disease and hematuria is uncommon, reflecting the lack of inflammation in the glomeruli. The urinary protein losses are accompanied by profound hypoalbuminemia and severe hypogammaglobulinemia due in part to loss of selectivity as the disease progresses. As a result of these changes, 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. (See "Renal vein thrombosis and hypercoagulable state in nephrotic syndrome".)

The blood urea nitrogen and creatinine concentrations are initially normal. Renal ultrasonography shows enlarged, hyperechogenic kidneys without normal corticomedullary differentiation.

End-stage renal disease usually occurs between three and eight years of age. Several studies, however, have reported that some NPHS1 mutations are associated with end-stage renal disease occurring after the age of 20 years [20,24,25]. As an example, a case series from New Zealand reported that Maori children with CNS have prolonged renal survival with medical therapy, including with indomethacin and angiotensin converting enzyme inhibitor [26]. Genetic evaluation detected a common founder mutation, a missense mutation at codon location 2131, in all of the affected Maori children.

Treatment — The nephrotic syndrome in CNF is always resistant to glucocorticoids and immunosuppressive drugs, since this is not an immunologic disease. Furthermore, these drugs may be harmful due to the already high susceptibility to infection. A retrospective study of 21 infants with CNF, for example, found that 63 verified and 62 suspected septic episodes occurred over a mean follow-up period of one year [27].

Standard conservative treatment includes daily or every other day albumin infusion, gamma globulin replacement, nutrition with a high-protein, low-salt diet, vitamin and thyroxine substitution, and prevention of infections and thrombotic complications. The diet is provided by tube feeding or by parenteral alimentation.

However, the rate of intercurrent complications remains high, and growth and development are usually retarded. As a result, some patients may require bilateral nephrectomy to prevent continued massive protein losses before the development of renal failure.

A possible medical alternative to nephrectomy has been described in three children. The combination of an angiotensin converting enzyme inhibitor and indomethacin therapy, both of which should lower intraglomerular pressure, led to a marked fall in protein excretion and striking improvement in nutritional status and growth [28,29].

If nephrectomy is performed, dialysis is provided until the patient reaches a weight of 8 to 9 kg. At this stage, renal transplantation can be considered [30,31].

Nephrotic syndrome can develop in the transplanted kidney. In one case series of 65 patients who received 77 kidney transplants, 23 episodes of recurrent nephrotic syndrome occurred in 13 patients with 19 grafts [32]. All 13 affected patients had the Fin-major/Fin-major genotype, which is associated with the absence of nephrin. Eight (of 11 patients tested) had circulating antinephrin antibodies. Recurrence of disease is associated with graft loss. Plasma exchange combined with cyclophosphamide and anti-CD20 antibodies has been successful in treating recurrence of nephrosis due to antinephrin antibodies [33].

Antenatal diagnosis — The CNF becomes manifest during early fetal life, beginning at the gestational age of 15 to 16 weeks. The initial symptom is fetal proteinuria, which leads to a more than 10-fold increase in the amniotic fluid alpha-fetoprotein (AFP) concentration. A parallel, but less important increase in the maternal plasma AFP level is observed. These changes are not specific, but they may permit the antenatal diagnosis of CNF in high-risk families in which termination of the pregnancy might be considered [34].

However, false positive results do occur, often leading to abortion of healthy fetuses. In one study of 21 pregnancies that had been terminated because of increased AFP levels in amniotic fluid, only 12 fetuses were homozygous for nephrin gene mutations as determined by DNA sequencing [35]. The remaining nine were heterozygous carriers and would therefore not have developed CNF. The kidneys of both groups had a similar reduction in podocyte foot processes and slit pores.

Genetic linkage and haplotype analyses may diminish the risk of false positive results in informed families [36]. The four major haplotypes, which cover 90 percent of the CNF alleles in Finland, have been identified, resulting in a test with up to 95 percent accuracy. Commercial tests are also available to detect NPHS1 mutations.

CNS AND NPHS2 MUTATIONS — NPHS2 encodes an integral membrane protein, podocin, which is found exclusively in glomerular podocytes and is the causative gene for an autosomal recessive form of familial focal segmental glomerulosclerosis (FSGS). A few patients with the typical clinical picture of congenital nephrotic syndrome (CNS) were found to lack NPHS1 mutations:

- One study found homozygous NPHS2 mutations in two of five such patients [24].

- These findings were confirmed in a second report that described 11 patients with two recessive NPHS2 mutations who presented initially with congenital nephrotic syndrome [25].

- Two additional cases with similar findings in terms of mutations in NPHS2, but not NPHS1, were also reported in a study of 13 unrelated patients from Japan [37].

Some patients also have both NPHS1 and NPHS2 mutations, resulting in a triallelic abnormality (homozygous mutations in one gene and a heterozygous mutation in the other) [24,25,38]. These findings demonstrate the genetic heterogeneity of congenital nephrotic syndrome and the absence of clear genotype/phenotype correlations.

Although affected individuals typically present in early childhood, some have milder disease and present in adolescence or young adulthood. Issues related to treatment of FSGS associated with NPHS2 mutations are discussed separately. (See "Epidemiology, classification, and pathogenesis of focal segmental glomerulosclerosis", section on 'NPHS2 gene' and "Steroid-resistant idiopathic nephrotic syndrome in children", section on 'NPHS2 mutations'.)

DIFFUSE MESANGIAL SCLEROSIS — Diffuse mesangial sclerosis is a second hereditary cause of infantile nephrotic syndrome associated with glomerular injury and rapid progression to end-stage renal disease. The same glomerular lesions are observed in the Denys-Drash syndrome, which is characterized by the combination of nephropathy, male pseudohermaphroditism, and Wilms' tumor.

Diffuse mesangial sclerosis is seen exclusively in infancy [6,39-43] and appears to be transmitted in some families as an autosomal recessive trait [44]. The defective gene has not been identified.

Pathology — The glomerular lesions are characterized in the early stages by a fibrillar increase in mesangial matrix without mesangial cell proliferation [42-44]. The capillary walls are lined by hypertrophied podocytes (picture 2). The fully developed lesion consists of the combination of thickening of the glomerular basement membranes and massive enlargement of mesangial areas, leading to reduction of the capillary lumens. The mesangial sclerosis eventually contracts the glomerular tuft into a sclerotic mass within a dilated urinary space (picture 3). There is usually a corticomedullary gradient of involvement, with the deepest glomeruli being less affected. Tubules are severely damaged, especially in the deeper cortex where they are markedly dilated and often contain hyaline casts.

Electron microscopy reveals hypertrophic mesangial cells surrounded by an abundant mesangial matrix, which often contains collagen fibrils. The podocytes are hypertrophied and contain many vacuoles. There is also irregular effacement of foot processes with focal detachment of the epithelial cell from the glomerular basement membrane.

Immunofluorescence shows mesangial deposits of IgM, C3, and C1q in the least affected glomeruli, while deposits of IgM and C3 outline the periphery of the sclerosed glomeruli. These immune deposits are probably nonspecific, occurring in areas of previous injury.

The same glomerular lesion is observed in the Denys-Drash syndrome. As a result, all patients with diffuse mesangial sclerosis should be screened for the Denys-Drash syndrome. This consists of karyotyping in phenotypic females, looking for male pseudohermaphroditism with a 46 XY genotype, and ultrasonography in all patients, looking for Wilms' tumor and abnormal gonadal development. Some investigators also suggest that an assessment for mutations in the Wilms' tumor predisposing gene, WT1, should be performed to help identify individuals at risk for the tumor [45,46]. As an example, among 10 patients presenting with isolated diffuse mesangial sclerosis, four had mutations in the WT1 gene [46]. (See 'Diffuse mesangial sclerosis with Drash syndrome' below.)

Pathogenesis — Abnormalities in the PLCE1 gene, which encodes phospholipase C epsilon, appear to cause isolated diffuse mesangial sclerosis. In one study of 12 children from six families with the disease, homozygous truncating gene mutations in PLCE1 were found in eight children [2]. By comparison, missense mutations found in two siblings were only associated with focal segmental changes.

Phospholipase C epsilon is a member of the phospholipase family of enzymes that catalyzes the hydrolysis of polyphosphoinositides resulting in generation of second messengers (eg, inositol-1,4,5-triphosphate), which are involved in cell growth and differentiation. A pathogenetic role for PLCE1 in glomerular development was supported by findings of disruption of the glomerular filtration barrier and edema in a PLCE1 knockout zebrafish model.

How a PLCE1 gene defect results in changes in the glomerular nephrotic syndrome is unknown. One possible explanation is that phospholipase C epsilon interacts with GTPase-activating protein, which is known to interact with the slit diaphragm protein, nephrin. Perturbations of this normal interaction would have a downstream effect including

the subsequent interaction of GTPase-activating protein with nephrin.

Clinical and laboratory features — As opposed to the congenital nephrotic syndrome of the Finnish type (CNF), children with diffuse mesangial sclerosis appear normal at birth, with a normal birth weight and without placental enlargement. The nephrotic syndrome may be present at birth or even suspected in utero by the finding of an elevated plasma alpha-fetoprotein level in the mother or the discovery of large hyperechogenic kidneys [47]. More commonly, however, proteinuria with a bland urine sediment develops postnatally, increasing progressively during the first or the second year of life. Various types of extrarenal signs have been reported in isolated patients including nystagmus, cataract, intellectual disability (mental retardation), microcephaly, severe myopia, and muscular dystrophy. (See "Cataract in children".)

All children progress to end-stage renal disease, frequently in association with hypertension. This usually occurs before age three, within a few months after the discovery of renal symptoms [43].

Treatment — Diffuse mesangial sclerosis is reportedly resistant to corticosteroids and immunosuppressive drugs. In the previously mentioned report, however, there was a clinical response to immunosuppressive therapy in two of the eight children with diffuse mesangial sclerosis due to a genetic mutation in PLCE1 [2]. In one child, remission was achieved with steroids, and the second patient responded to cyclosporine therapy after failing initial steroid therapy. These cases are the first reported cases of successful remission in patients with congenital nephrotic syndrome due to genetic defect.

The degree of proteinuria is typically less severe than in the CNF, and specific supplemental therapy is usually not required.

Treatment is supportive and consists of maintenance of electrolyte and water balance and adequate nutrition, prevention and treatment of infectious complications, and management of renal failure. Bilateral nephrectomy has been considered at the time of transplantation because of the theoretical risk of developing a Wilms' tumor. This issue remains unresolved, although some investigators have not found Wilms' tumor in the kidneys from 14 children with renal failure [43]. Recurrent disease does not develop in the transplant.

The combination of an angiotensin converting enzyme inhibitor and indomethacin therapy was used to treat one child with diffuse mesangial sclerosis [29]. The child had a sustained clinical response, normal growth pattern, and suffered no adverse effects.

DIFFUSE MESANGIAL SCLEROSIS WITH DRASH SYNDROME — Denys and Drash first reported the triad of progressive renal disease, male pseudohermaphroditism, and Wilms' tumor [48,49]. All of the patients were infants with heavy proteinuria progressing rapidly to renal failure. Incomplete forms of the syndrome were described and the glomerulopathy was identified as diffuse mesangial sclerosis [50].

Epidemiology and genetics — A number of cases of Denys-Drash syndrome have been reported [48-52]. The Denys-Drash syndrome is usually sporadic, although occurrence in two kindreds has been reported. However, constitutional mutations occur in the Wilms' tumor predisposing gene, WT1 [53].

Wilms' tumor is an embryonic kidney tumor thought to arise from aberrant mesenchymal stem cell differentiation secondary to the loss of a tumor suppressor gene or genes [54,55]. The WT1 gene lies at chromosomal position 11p13; it appears to encode a zinc finger protein, which is probably a transcription factor [56-59]. WT1 is also expressed in the gonads, suggesting that the genital abnormalities in the Denys-Drash syndrome may result from pleiotropic effects of mutations in the WT1 gene itself. This hypothesis was first confirmed in a report, which identified constitutional heterozygous mutations within the WT1 gene in some individuals with the Denys-Drash syndrome [60].

Subsequently, mutations of WT1 have been found in most patients with this syndrome. Most abnormalities are missense changes either in exon 9, which encodes for zinc finger 3 (with a mutational hot spot at an arginine residue thought to interact with the consensus DNA sequence), or in exon 8, which encodes for zinc finger 2 [61].

Clinical presentation — Diffuse mesangial sclerosis is a constant feature of the Denys-Drash syndrome. It is associated with the two other components of the triad in the complete form, but with only one of the two in the incomplete forms.

The clinical course of the nephropathy is not different from that described above in isolated diffuse mesangial sclerosis. However, Wilms' tumor may be the first clinical manifestation of the syndrome. Thus, careful renal ultrasonography should be performed, looking for nephroblastoma, in any patient found to have diffuse mesangial sclerosis. The tumor may be unilateral or bilateral and is associated in a few cases with nodules of nephroblastomatosis [44,53].

Male pseudohermaphroditism, characterized by ambiguous genitalia or female phenotype with dysgenetic testis or streak gonads, is observed in all 46 XY patients. In contrast, all 46 XX children appeared to have a normal female phenotype, with normal ovaries, when the information was available. The finding of a normal male phenotype seems to exclude the diagnosis of Denys-Drash syndrome. (See "Evaluation of the infant with ambiguous genitalia".)

IDIOPATHIC NEPHROTIC SYNDROME — Idiopathic nephrosis rarely occurs at birth, more commonly presenting during the first year of life. All the morphological variants of idiopathic nephrotic syndrome seen in older children can occur at this time including minimal change disease, diffuse mesangial proliferation, and focal segmental glomerulosclerosis.

Establishing the diagnosis of one of these disorders may be important clinically, since steroid-responsiveness with a favorable course can be seen [8,62]. However, most affected infants are resistant to therapy and many progress to end-stage renal disease.

In some cases, particularly those with familial disease, NPHS2 mutations have been detected [21]. NPHS2 encodes for an integral membrane protein, podocin, which is found exclusively in glomerular podocytes. In several case series, NPHS2 mutations have also been detected in infants who present with congenital nephrotic syndrome [24,25,37].

In addition, there are individuals with both NPHS1 and NPHS2 mutations resulting in a triallelic abnormality (homozygous mutations in one gene and a heterozygous mutation in the other).

Other genetic defects associated with infantile nephrotic syndrome include mutations for alpha-actinin-4 gene and mutation at the locus of chromosome 2p. The latter appears to be responsible for some forms of steroid-sensitive idiopathic nephrosis, which is inherited in an autosomal recessive fashion [63]. Some affected families, however, do not display linkage to this locus, suggesting additional genetic heterogeneity.

These findings demonstrate the genetic heterogeneity of congenital and infantile nephrotic syndrome and the absence of specific genotype/phenotype correlations.

MISCELLANEOUS — A number of other disorders are infrequent causes of congenital or infantile nephrotic syndrome.

Pierson syndrome — Pierson syndrome, (also referred to as microcoria-congenital nephrosis syndrome, MIM #6090409) is an autosomal recessive syndrome. Characteristic findings include congenital nephrotic syndrome with histologic lesions of diffuse mesangial sclerosis and ocular malformations (microcoria, abnormal lens with cataracts, and retinal abnormalities) [64-66]. This autosomal recessive disorder is due to mutations in the LAMB2 gene, which encodes laminin beta 2 [64,65]. Laminin beta 2 is abundantly expressed in the glomerular basement membrane, where it plays a role in anchoring and in the development of podocyte foot processes [67]. LAMB2 knockout mice exhibit congenital nephrotic syndrome in association with anomalies of the retina and neuromuscular junction. LAMB2 mutations have also been found in patients with congenital nephrotic syndrome and either no or less severe ocular abnormalities [68].

Galloway-Mowat syndrome — The Galloway-Mowat syndrome is characterized by microcephaly, mental retardation, hiatus hernia, and the nephrotic syndrome [69]. It appears to be transmitted as an autosomal recessive

trait. The nephrotic syndrome presents early with a mean age of onset of three months and is usually severe and resistant to steroid therapy. Renal biopsy reveals minimal changes or focal segmental glomerulosclerosis. The underlying genetic defect is unknown.

Infectious causes

- Congenital syphilis − Congenital syphilis can cause membranous nephropathy [70,71]. Histological examination often shows a mixed pattern with membranous nephropathy and mesangial proliferation. Penicillin treatment leads to the resolution of the syphilis and the renal abnormalities.

- Congenital toxoplasmosis − The nephrotic syndrome may be induced by congenital toxoplasmosis [72]. Proteinuria may be present at birth or may develop during the first three months, in association with ocular or neurologic symptoms. Histological examination often shows mesangial proliferation with or without focal segmental glomerulosclerosis. Treatment of toxoplasmosis or steroid therapy usually leads to remission of the proteinuria.

- Other organisms − Congenital or infantile nephrotic syndrome has been reported in association with cytomegalovirus, rubeola virus, and human immunodeficiency virus.

Other causes

- Nail-patella syndrome. (See "Nail-patella syndrome".)

- Mercury exposure.

- Neonatal nephrotic syndrome due to membranous nephropathy has been diagnosed antenatally in infants with mothers who have mutations in the metallomembrane endopeptidase gene, which encodes the podocyte protein neutral endopeptidase (NEP) [73]. During pregnancy, the presence of fetal NEP protein induces a maternal alloimmune response. Maternal antibody to NEP fetal protein results in fetal podocyte injury, which may lead to chronic renal failure. The mothers' IgG response to the expression of fetal NEP determines the severity of the neonatal disease.

Congenital nephrotic syndrome has been observed in case reports of mitochondrial cytopathy [74], type I carbohydrate-deficient glycoprotein syndrome [75], and Herlitz junctional epidermolysis bullosa [76].

DIAGNOSIS — Because most cases of congenital and infantile nephrotic syndrome are caused by genetic mutations and fail to respond to immunosuppressive therapy, genetic screening should be performed before starting treatment. In addition, extrarenal manifestations can be helpful in the diagnosis. As an example, genital abnormalities in an affected male infant suggest a WT1 mutation and the diagnosis of Denys-Drash syndrome.

SUMMARY — Nephrotic syndrome that presents at birth or within the first three months of life is defined as congenital nephrotic syndrome. Later onset, between three months and one year of age, is called infantile nephrotic syndrome. Most children with congenital or infantile nephrotic syndrome have a genetic basis for the renal disease and a poor outcome.

Mutations of the following genes are responsible for the majority of cases of congenital and infantile nephrotic syndrome:

- NPHS1, which encodes nephrin (a key component of the podocyte slit diaphragm) and is responsible for the Finnish-type congenital nephrotic syndrome. (See 'CNS of Finnish type' above.)

- NPHS2, which encodes podocin (a protein that interacts with nephrin at the slit diaphragm) and is responsible for familial focal segmental glomerulosclerosis. (See 'CNS and NPHS2 mutations' above.)

- WT1, which encodes the transcription tumor suppressor (a protein involved in kidney and gonad development) and is responsible for the Denys-Drash syndrome. (See 'Diffuse mesangial sclerosis with Drash syndrome' above.)

- LAMB2, which encodes laminin beta 2 (a component of the glomerular basement membrane) and is responsible for the Pierson syndrome. (See 'Pierson syndrome' above.)

- PLCE1 gene, which encodes phospholipase C epsilon, is responsible for the early onset of isolated diffuse mesangial sclerosis. (See 'Diffuse mesangial sclerosis' above.)

Other etiologies of congenital or infantile nephrotic syndrome include secondary causes such as infections (eg, syphilis or toxoplasmosis) (table 1), toxins such as mercury exposure, and genetic disorders. (See 'Infectious causes' above and 'Other causes' above.)

Because most cases of congenital and infantile nephrotic syndrome are caused by genetic mutations and fail to respond to immunosuppressive therapy, we suggest genetic screening be performed before starting such treatment (**Grade 2C**).

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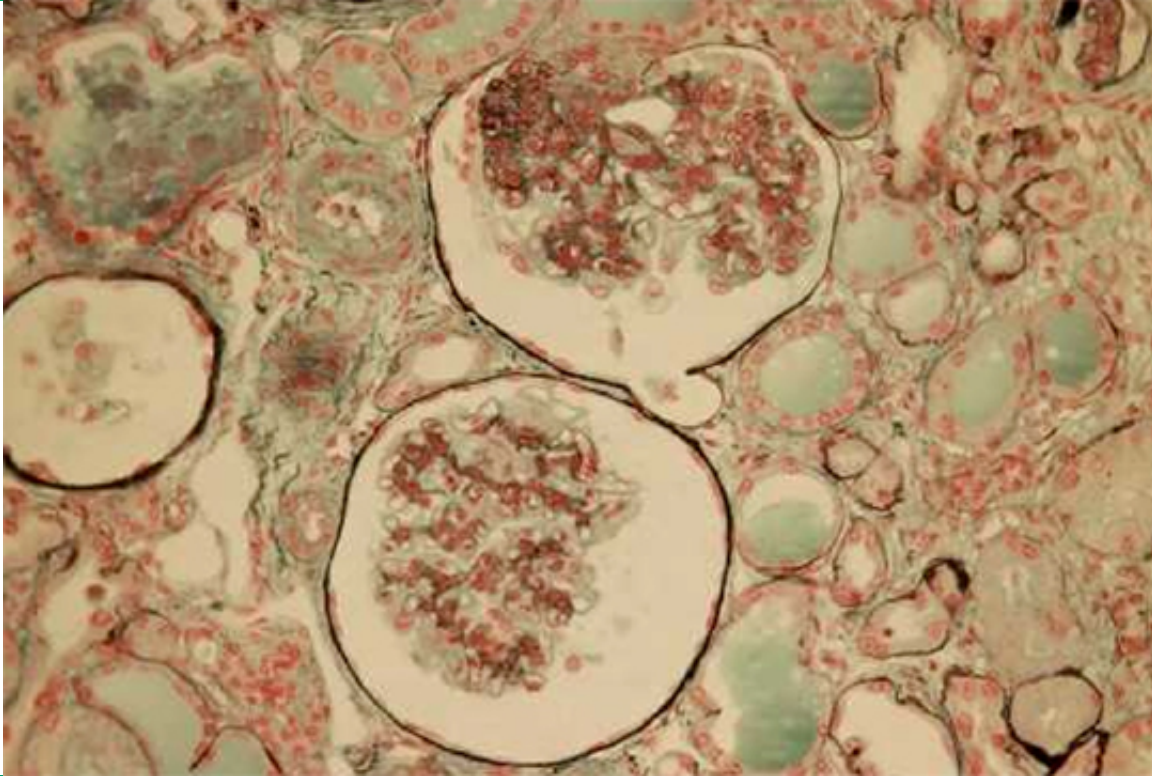
Topic 6137 Version 10.0

GRAPHICS

Major causes of congenital nephrotic syndrome

| |
|---|
| Congenital nephrotic syndrome of Finnish type |
| Diffuse mesangial sclerosis |
| Diffuse mesangial sclerosis with Drash syndrome |
| Idiopathic nephrotic syndrome |
| Other |
| Congenital syphilis |
| Congenital toxoplasmosis |
| Certain viral infections |
| Galloway syndrome |

Graphic 80781 Version 1.0

Renal Bx - congenital NS of the Finnish type

Renal biopsy from an infant with congenital nephrotic syndrome (NS) of the Finnish type due to mutations in the NPSH 1 gene that encodes nephrin, a transmembrane protein located at the slit diaphragm of the glomerular podocytes. Histologic changes include the characteristic findings of mild mesangial hypercellularity and increased mesangial matrix in the glomeruli, and irregular microcystic dilatation of proximal tubules.
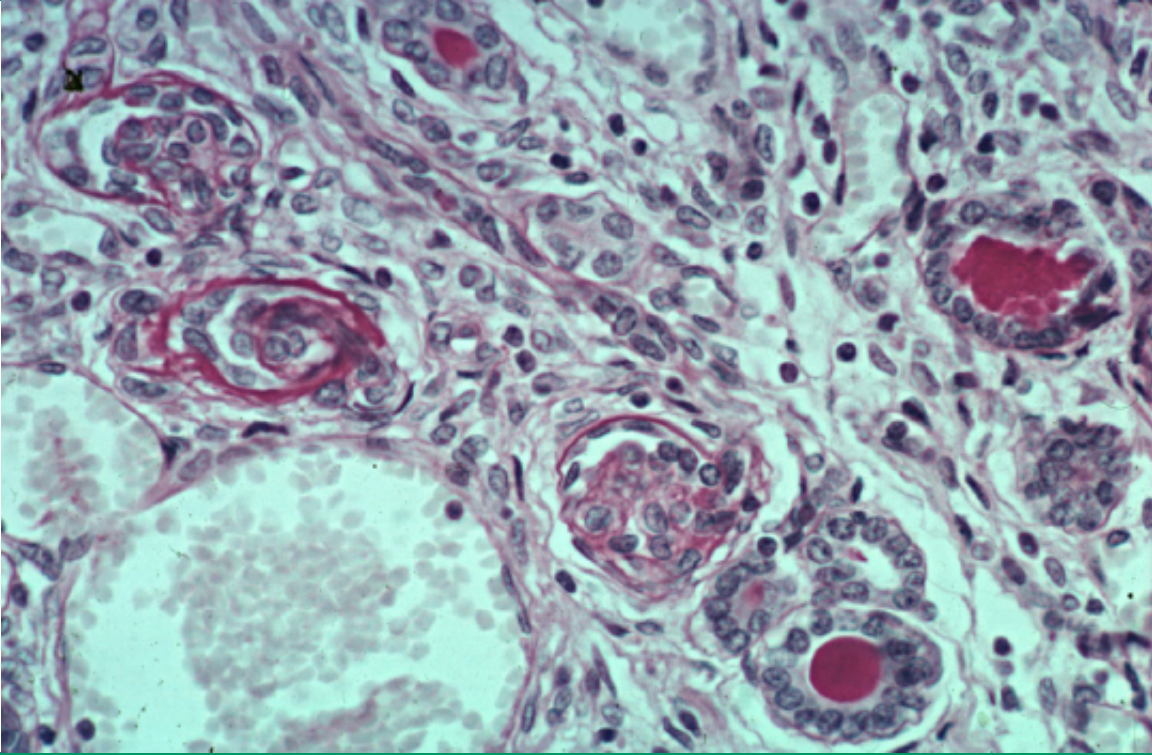
Graphic 69624 Version 3.0

Renal pathology of early diffuse mesangial sclerosis
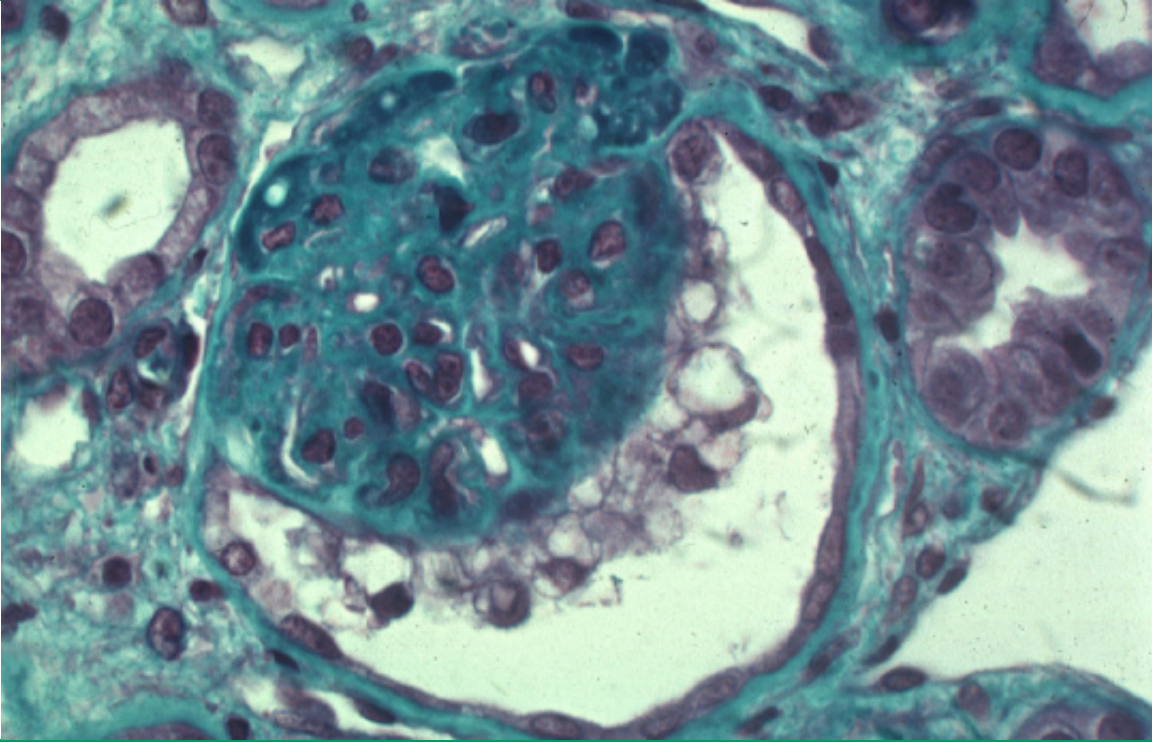
Pathologic specimen from a patient with diffuse mesangial sclerosis demonstrating the fibrillar increase in mesangial matrix. The capillary walls are lined by hypertrophied podocytes.

Graphic 77219 Version 2.0

Renal pathology of late diffuse mesangial sclerosis

Pathologic specimen from a patient with diffuse mesangial sclerosis demonstrating the characteristic contraction of the glomerular tuft into sclerotic masses.

Graphic 56256 Version 2.0

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