Congenital nephrotic syndrome, Finnish type

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Abstract
The congenital nephrotic syndrome of the Finnish type is a hereditary disease with autosomal recessive inheritance. The gene frequency is approximately 1/200 in Finland. The disease is caused by mutations in the gene for nephrin, which is a key component of the glomerular ultrafilter, the podocyte slit diaphragm. The first symptom is fetal proteinuria, which leads to a more than 10-fold increase of the alpha-fetoprotein concentration in amniotic fluid and a parallel but smaller rise in the maternal serum level. At birth, one notes a large placenta, whose weight exceeds by 25% the birth weight of the often-premature child. The nephrotic syndrome starts very early and is severe. Histologically, microcytic dilatations of the tubules are seen while glomeruli are only slightly modified. The nephrotic syndrome is resistant to corticosteroids and immunosuppressants. Infectious and nutritional complications are common, due to the massive protein loss. If the child survives, renal function deteriorates justifying initiation of dialysis/transplantation between the ages of 5 and 8 years. The disease does not recur in the graft.

Keywords
Congenital nephrotic syndrome of the Finnish type, autosomal recessive disease, renal failure, corticoresistance.

Disease name and synonyms

Congenital nephrotic syndrome of the Finnish type (CNF)

Definition

The term congenital nephrotic syndrome refers to disease which is present at birth or within the first 3 months of life. Later onset, between three months and 1 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 congenital nephrotic syndrome of Finnish type (CNF) is an autosomal recessive disease responsible for severe nephrotic syndrome with proteinuria beginning *in utero*.

Incidence

CNF is most common in Finland, with an incidence of 1.2 per 10,000 live births [1,2]. It has, however, been described in various ethnic groups throughout the world [3,4].

Clinical description

Most infants with CNF are born prematurely (35-38 weeks), with a low birth weight for gestational age. The placenta is enlarged, being representing than 25% 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 half of the cases. Severe nephrotic syndrome with marked ascites is always present by 3 months. The proteinuria is highly selective early during 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 filtering selectivity as the disease progresses. As a result of these changes, nutritional status and 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 due to urinary losses of thyroxine-binding proteins is also common.
The blood urea nitrogen and creatinine concentrations are initially normal. Renal ultrasonography shows enlarged, hyperechogenic kidneys without normal corticomedullary differentiation.
End-stage renal failure invariably occurs between 3 and 8 years of age. Prolonged survival is possible with aggressive supportive treatment, including dialysis and renal transplantation.

Histology
Light microscopy studies of renal biopsy specimens obtained early duting the course of the disease show mild mesangial hypercellularity and increased mesangial matrix in the glomeruli [3,5]. No immune deposits are detected by immunofluorescence studies. Over time, the mesangial matrix increases, accompanied by progressive glomerulosclerosis.
Tubulointerstitial changes are prominent in CNF. Irregular microcystic dilatation of proximal tubules is the most striking feature; however, this change is not specific and is not seen in all patients [6]. Later, interstitial fibrosis, lymphocyte and plasma cell infiltrations, tubular atrophy, and periglomerular fibrosis develop in parallel with sclerosis of the glomeruli.

Treatment
The nephrotic syndrome in CNF is always resistant to corticosteroids and immunosuppressive drugs, since this is not an immune disease. Furthermore these drugs may be harmful due to the already high susceptibility to infection, as confirmed by a retrospective study on 21 infants with CNF, who suffered of (63 verified and 62 suspected) septic episodes over a mean follow-up period of 1 year [7].
Standard conservative treatment includes daily or every other day albumin infusion, gamma globulin replacement, nutrition with a high-protein, low-salt diet, vitamin supplement and thyroxine replacement, and prevention of infections and thrombotic complications. Nutrients are given by tube feeding or by parenteral alimentation.
However, the rate of intercurrent complications remains high; growth and development are usually retarded. As a result, some patients may require bilateral nephrectomy to prevent continued massive protein losses even before renal failure develops. Dialysis is then performed until the patient reaches a weight of 8-9 kg, at which time, renal transplantation can be considered [8,9]. No recurrence of the nephrotic syndrome has been observed after transplantation.
A possible medical alternative to nephrectomy has been described in two children. The combination of an angiotensin-converting enzyme inhibitor and indomethacin therapy, both of which should lower intraglomerular pressure, markedly reduced and led to striking improvement of nutritional status and growth [10].

Etiology
CNF is inherited as an autosomal recessive trait, with both sexes being equally involved. Heterozygous individuals have no manifestations of the disease.
It has been advanced that proteinuria in CNF results from an inherited error in the structure of the glomerular capillary filter. The abnormal gene has been localized to the long arm of chromosome 19 in both Finnish and non-Finnish families [11-13].
The defective gene responsible for CNF, *NPHS1* was recently cloned [14]. The gene encodes for a transmembrane protein, named nephrin, which is a member of the immunoglobulin family of cell-adhesion molecules. Nephrin is specifically located at the slit diaphragm of the glomerular podocytes; which could explain the absence of slit diaphragms and foot processes in patients with CNF who have a mutant nephrin protein [15,16].
In the original report, four different mutations in this gene were found to segregate with the disorder in affected Finnish families [14]. 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) [17]. These patients may have mutations elsewhere in the promoter, intron areas, or a gene encoding

another protein that interacts with nephrin [18]. These results may indicate genetic heterogeneity in the disease.
Mutations in the *NPHS2* gene, encoding the podocyte protein, podocin, have been shown to be associated with steroid-resistant nephrotic syndrome (SRN). Mutations in the *NPHS1* gene, encoding the slit diaphragm protein, nephrin, have been shown to be associated with congenital nephrotic syndrome of the Finnish type (CNF). However, recent evidence shows that *NPHS2* alterations are sometimes found in CNF patients who lack *NPHS1* mutations. In addition, patients with a unique phenotype have been identified with mutations in both *NPHS1* and *NPHS2*. These findings emphasise the importance of screening for both *NPHS1* and *NPHS2* mutations in CNF, especially when no *NPHS1* mutation is apparent. [22-24]

Antenatal diagnosis
The CNF becomes manifest during early fetal life, beginning at the gestational age of 15-16 weeks. The initial symptom is fetal proteinuria, which leads to a more than a 10-fold increase of the alpha-fetoprotein (AFP) concentration in the amniotic fluid. A parallel, but less marked increase in the maternal plasma AFP level is also observed. These changes are not specific, but they permit the antenatal diagnosis of CNF in high-risk families in which termination of the pregnancy might be considered [19]. Measurement of maternal plasma AFP levels is currently the only method available for general screening. However, false-positive results do occur, often leading to abortion of healthy fetuses. Preliminary studies suggest that genetic linkage and haplotype analyses may diminish the risk of false positive results in families with previously identified mutation(s) [20]. The four major haplotypes, which cover 90% of the *NPHS1* alleles in Finland, have been identified, resulting in a test with up to 95 % accuracy. Analysis of the *NPHS1* gene is now the method of choice for antenatal diagnosis in families with an affected child whose mutation has been identified [21].

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