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Congenital nephrotic syndrome

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Abstract. Congentital nephrotic syndrome (CNS) is an uncommon disorder. Several different diseases may cause the syndrome. These may be inherited, sporadic, acquired or part of a general malformation syndrome. The problems associated with nephrotic syndrome in early infancy are divided into three parts: diagnosis, treatment and prenatal diagnosis. Accurate diagnosis is essential for the treatment, genetic counselling and prenatal diagnosis. The ultimate curative treatment of CNS is renal transplantation. The supportive treatment before the transplantation is of utmost importance in order to maintain a reasonable clinical condition and prepare the child for the dialysis and renal transplantation. Prenatal diagnosis is possible in some types of CNS by determination of the maternal serum and amniotic fluid alpha-fetoprotein (AFP). Increased AFP indicates fetal proteinuria, and thereby nephrotic syndrome before birth. In some cases with the onset of proteinuria after birth prenatal AFP measurement does not detect the disease.

Key words: Congenital nephrotic syndrome – Finnish type – Drash syndrome – Diffuse mesangial sclerosis – Renal transplantation – Prenatal diagnosis

Introduction

Nephrotic syndrome in the neonatal period and in infancy is an uncommon disorder. In spite of its rarity, nephrotic syndrome in the first months of life is caused by a heterogeneous group of renal diseases with variable etiology and natural history. Nephrotic syndrome with onset in the 1st year of life is conventionally divided into congenital and infantile types, the arbitrary age limit being 3 months of age. This division is, however, of limited diagnostic value since some disorders, even in the same family, may become manifest right after birth or several months later. A current classification of congenital and infantile nephrotic syndrome is presented in Table 1.

Although the infants with congenital nephrotic syndrome (CNS) may superficially be all alike, the underlying renal disease causes significant differences in the clinical course and response to treatment of the patients. The possibilities of the genetic counselling and prenatal diagnosis are also dependent on the type of disease causing CNS. The major current problems of CNS concern the diagnosis of the disease, treatment and possibilities of prenatal diagnosis.

Diagnosis of congenital nephrotic syndrome

Of the diseases presented in Table 1, the Finnish type of CNS, known as CNF, has often been considered as the prototype of idiopathic congenital nephrosis. Since 1956, when Hallman et al. [1] discovered that the disorder is unusually common in the Finnish population, more than 200 cases have been recorded in this country. The heredity, clinical picture and pathology of CNF have been thoroughly reviewed [2–5]. The major features of the disease are presented in Table 2. It has to be emphasized that there is no single clinical or pathological feature pathognomonic for CNF. The diagnosis has to be based on all available informa-

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Table 1. Classification of congenital and infantile nephrotic syndrome

Idiopathic types
– Congenital nephrotic syndrome of Finnish type
– Diffuse mesangial sclerosis
– Other glomerular diseases
Secondary types
– Congenital syphilis
– Other perinatal infections
Syndromic congenital nephrotic syndrome
– Drash syndrome
– Nephropathy associated with brain malformations
– Nail-Patella syndrome

Table 2. Features of congenital nephrotic syndrome of the Finnish type

Genetics	Autosomal – recessive
Perinatal findings	Birth asphyxia, prematurity, "small for dates", large placenta (> 25% of birth weight)
Onset of proteinuria	Detected by alpha-fetoprotein in amniotic fluid or early after birth
Onset of edema	At birth to 1 month
Phenotypic features	Talipes, wide sutures of the skull, umbilical hernia, distended abdomen
Growth and development	Growth failure, psychomotor retardation
Course of the disease	No remission of proteinuria at development of renal failure. Normal blood pressure
Renal pathology	Glomerular mesangial proliferation. Obsolete glomeruli late feature. Microcystic dilation of (proximal) tubules

tion, including family history, obstetric and perinatal findings, size of the placenta, clinical features, laboratory data and renal pathology. In the diagnostic evaluation of a patient with CNS several acquired and idiopathic disorders must be considered, as well as disorders forming part of a syndrome.

Neonatal syphilis is the most common cause of acquired CNS [6, 7]. Congenital toxoplasmosis, rubella and cytomegalovirus infections have rarely been implicated in the etiology of CNS [8–10].

CNS may be a part of a few general malformation syndromes, the most common of which is the syndrome combining a glomerulopathy, male pseudohermaphroditism and a Wilms' tumor. The syndrome is also known as Drash syndrome [11]. Recent reports indicate that the syndrome may not be as rare as previously assumed [12, 13]. Any infant with CNS and the slightest suspicion of ambiguous genital development should be subjected to chromosomal analysis. The syndrome may also be present in chromosomally and phenotypically normal female infants and become manifest by the development of a nephroblastoma in infants with a glomerular disorder [13].

The difficulties in separating Drash syndrome from other types of CNS are exemplified by the following case from our institution. A phenotypically normal girl was born at term to young, healthy and nonconsanguineous parents. The placenta was very large and the newborn infant showed heavy proteinuria at birth. She showed laboratory signs of renal insufficiency in the 2nd week of life, a feature inconsistent with CNF. The only sign of genital abnormality was a slight clitorimegaly. This led to routine sex chromatin determination. Subsequent chromosomal analysis revealed a genotype 46,XY. Her disorder was characterized by rapid progression of renal insufficiency, and the Drash syndrome was confirmed by renal biopsy and later at autopsy.

Renal pathology of Drash syndrome is characterized by tubular atrophy and diffuse mesangial sclerosis of the glomeruli. Subcortical nephrons are atrophic and there is a decreasing degree of severity of the lesions from superficial to deep cortex [13].

Another rare malformation syndrome with CNS consists of microcephaly, hiatus hernia and nephropathy [14–16]. Nail-Patella syndrome has also been occasionally associated with postnatal nephrotic syndrome [17].

After exclusion of the acquired and syndromic forms of CNS, a group of patients having a disease other than CNF remains. The best known of them is congenital or infantile nephrotic syndrome associated with diffuse mesangial sclerosis (DMS) of the glomeruli [18] (Fig. 1). Besides the characteristic glomerular pathology, identical to that seen in the Drash syndrome, DMS differs from CNF in several respects. The perinatal period is usually uneventful and there is no placentamegaly. The onset of proteinuria may be as early as in CNF, but in many cases it becomes manifest later in infancy [19, 20]. The clinical course of DMS is characterized by early and progressive insufficiency, leading to renal failure 1–2 years later. This is the major difference from the CNF which is characterized by continuous heavy proteinuria without signs of renal insufficiency in the 1st year of life. Before the era of contemporary active treatment of CNS, no cases of renal failure were recorded in the Finnish CNF series.

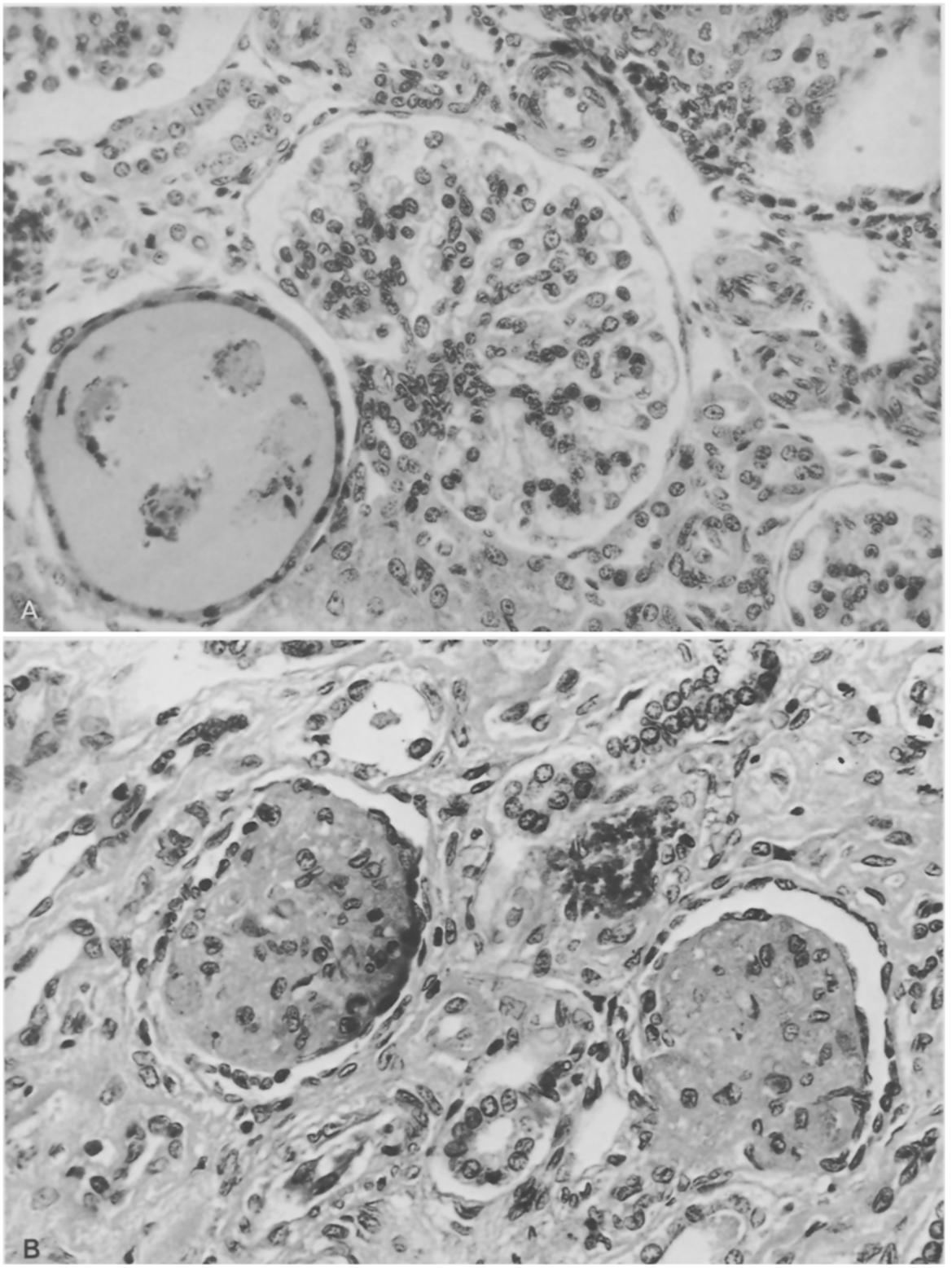

Fig. 1A, B. Comparison of the glomerular pathology in congenital nephrotic syndrome of the Finnish type (CNF) and diffuse mesangial sclerosis (DMS). **A** Glomerulus from the kidney of a CNF patient. Note mesangial hypercellularity and open capillaries of the glomerulus. A dilated tubulus is also present. **B** Renal cortex from a case of DMS. The glomeruli are sclerotic globules without patent capillaries and the interstitium is fibrotic. H&E, x240

The last very heterogeneous group of idiopathic congenital or infantile nephrotic syndrome is often associated with minimal glomerular changes or focal segmental glomerular sclerosis in biopsy specimens [18, 21, 22]. Their overall prognosis is variable, but often less severe than that of CNF and DMS. In rare patients remissions have been recorded [23, 24] and a few patients respond favorably to steroid treatment [25].

Treatment

In the older series of CNS the prognosis was extremely poor. The vast majority of the patients did not benefit from any medical treatment, including steroids and cytostatic agents. In the Finnish material 50% of the CNF patients died before the age of 6 months and none lived longer than 2 years [26]. Recent achievements in dialysis and renal transplantation among young children have opened a new era in the treatment of CNS [27–30]. Renal transplantation, however, is not possible in the neonatal period or in early infancy.

Very careful supportive treatment is required in order to keep the patients alive and in a reasonable clinical condition before dialysis and transplantation become possible. The aims of the supportive treatment are (1) control of infection, (2) alleviation of edema, (3) maintenance of adequate nutrition, (4) treatment of secondary hypothyroidism and (5) prevention of thrombosis. Detailed schedules for the achievement of these goals have been published [29, 31, 32]. In spite of this therapy, the patients remain proteinuric and growth and psychomotor development are retarded. Severely proteinuric patients need bilateral nephrectomy and hemo- or peritoneal dialysis before transplantation. With the help of pretransplant dialysis treatment, the clinical condition, blood chemistry and growth improve markedly [29]. Renal transplantation in CNS is usually performed only after the age of 2 years is attained [29] but recently children under 1 year of age have been successfully transplanted [30].

Prenatal diagnosis

In CNF proteinuria is already present in the fetus and may be demonstrated by measuring the alpha-fetoprotein (AFP) in amniotic fluid at 16–20 weeks of pregnancy [33–36]. AFP is also elevated in the maternal serum in the presence of a nephrotic fetus [37], facilitating the initial investigation of risk pregnancies. The crucial question is whether the amniotic fluid AFP is increased in all types of CNS. Negative results have been reported for fetuses in cases in which nephrotic syndrome developed after birth [38, 39]. It seems most probable that the elevated amniotic fluid AFP is nothing more than an indication of fetal proteinuria. If AFP is increased in high-risk pregnancies or in screening studies, the following investigations should be undertaken. The fetus has to be checked by ultrasonography and chromosome analysis for neural tube defects, exomphalos, twin pregnancy, fetal death, Turner's syndrome and other fetal disorders known to be associated with elevated amniotic fluid AFP. If these investigations are negative, it must be concluded that the fetus has CNS. The kidneys of the CNF fetus show dilated tubules 80–300 μm in diameter in the deep cortex. They are filled with an eosinophilic colloid-like substance (Fig. 2). The most mature glomeruli of the fetal kidney show loss of foot processes on electron microscopy. These changes confirm the CNS in the fetus, but they are merely the morphological counterparts of the fetal proteinuria and hardly specific for any particular type of CNS [40]. If, however, the AFP concentration of the

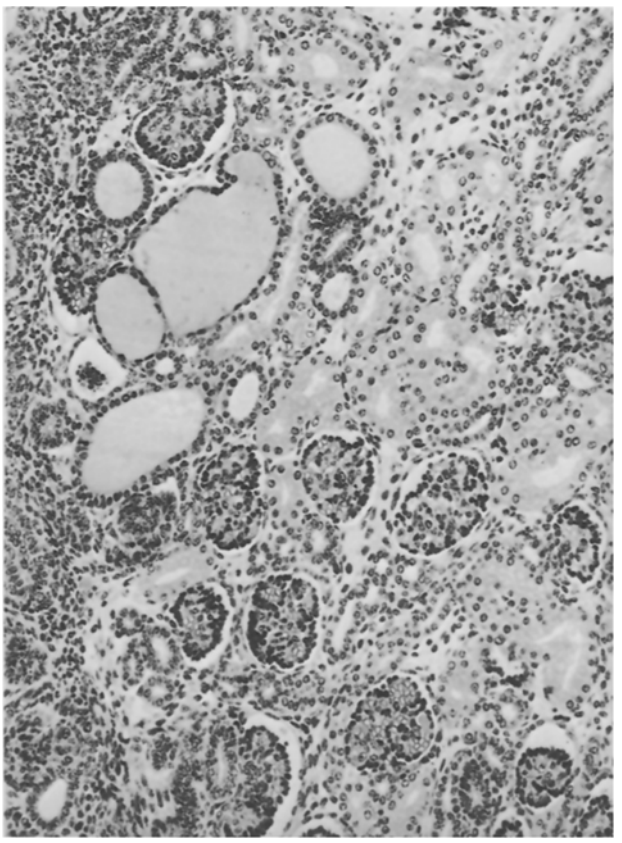

Fig. 2. Renal cortex from an 18-week-old CNF fetus. Note the dilated, colloid-like substance containing tubules in the deep cortex. H&E, x240

amniotic fluid is normal, fetal proteinuria can be excluded. A negative finding does not exclude the possibility of nephrotic syndrome developing postnatally.

At this stage it appears that CNF is the only type of CNS with constantly elevated amniotic fluid AFP, i.e., with fetal proteinuria, although a recent report of a syndromic familial type of CNS with a malformation of the central nervous system also showed increased amniotic fluid AFP [16]. The renal pathology of this fetus was identical with that of CNF [40].

Discussion

Although uncommon, CNS remains a diagnostic and therapeutic challenge for the pediatrician. It may result from different etiologies and has different clinical courses. In spite of the therapeutic advances made by dialysis and renal transplantation, many patients will still succumb or remain severely handicapped. Knowledge of the pathogenesis of the renal lesion in CNS is limited. Recently it was reported that the concentration of heparan sulfate in the glomerular basement membrane is decreased [41]. Further studies will be necessary on the glycoprotein metabolism of glomerular basement membrane.

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