# Histopathologic and Clinical Findings of Congenital Nephrotic Syndrome in Iranian Children

## A Study of Two Centers

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**Introduction.** Congenital nephrotic syndrome (CNS), an uncommon form of kidney disease, presents during the first year of life and is a diagnostic and therapeutic challenge for the pediatricians as well as pediatric nephrologists. Our study is the first study of Iranian children with CNS in two pediatric nephrology centers in Tehran, Iran.

**Materials and Methods.** We reviewed medical charts of 30 infants diagnosed with CNS from 1990 to 2005.

**Results.** There were 15 boys and 15 girls with CNS (mean age, 1.7 months). The presentation of the disease was nephrotic syndrome in 96.6% of the patients. Eighty percent of the patients presented within 3 months of life and 16 in the neonatal period. The Finnish type of CNS was seen in 43.3% and diffuse mesangial sclerosis in 50%. Preterm labor and low birth weight was seen in 20%. A family history of nephrotic syndrome in infancy was noted for 8 children (26.7%). Numerous complications of nephrotic syndrome occurred in 73.3%. Seventy percent of the patients had 27 episodes of infections. Sepsis was seen in 43.3% of the children, of which 61.5% were caused by gram-negative bacteria and 38.6% were caused by *Staphylococcus aureus*. Thrombotic complications and hypertension developed in 6.6% and 23.3% of the patients, respectively. The mortality rate of patients was 86.6%.

**Conclusions.** Diffuse mesangial sclerosis is an important cause of CNS. The outcome of our patients was poor and most of our patients died before reaching the age of 5 years old.

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## INTRODUCTION

Kidney diseases associated with nephrotic syndrome in the first year of life are uncommon.[1] They make up a heterogeneous group of disorders with different causes, courses, and prognoses. These disorders can affect only the kidneys or can be inherited as a part of a malformation syndrome. The designation of congenital nephrotic syndrome (CNS) identifies infants with onset of the nephrotic syndrome, usually in the first three months of life. The CNS of Finnish type (CNF) and diffuse mesangial sclerosis (DMS) are the two main causes.[2]

Most of patients with CNF and DMS have a genetic basis for the kidney disease. In recent years, molecular genetics research has led to the identification of genes mutated in several renal disorders that lead to proteinuria and CNS. Mutations in *NPHS1*, which encodes nephrin, are

the main causes of CNS in Finnish patients, whereas mutations in *NPHS2*, which encodes podocin, are typically responsible for infantile or childhood-onset of steroid-resistant nephrotic syndrome (SRNS) in non-Finnish populations. Among non-Finnish cases with a CNF phenotype, the *NPHS1* deletion remains to be the leading cause of CNS in the first 3 months of life. The *NPHS1* and *NPHS2* mutations are found in most of the severe isolated cases of CNS whereas, *LAMB2* (Pierson syndrome) and *WT1* (Denys-Drash and Frasier syndromes) are often associated with syndromic CNS.[3-7] In the presence of DMS, it is generally said that looking for mutations in at least 2 genes (*WT1* and *LAMB2*) should be performed.[6,8-10]

Expansion of glomerular mesangium and cystic dilatation in proximal and distal tubules are the most characteristic findings in *NPHS1* mutations. Renal histology in *NPHS2* mutations reveals either minimal glomerular changes or focal segmental glomerular sclerosis (FSGS). Effacement of podocytes foot processes and disappearance of the filamentous image of slit diaphragm are seen in electron microscopy. However, no single histological finding is pathognomic for either Finnish (*NPHS1*) or non-Finnish type of CNS (*NPHP2*).

Identification of mutations in CNS is important, as it may enable the treating physicians to avoid prescribing immunosuppressive therapy for these patients. Thus, analysis of *NPHS1* and *NPHS2* mutations are warranted in the isolated CNS patients. Prenatal diagnosis in families with a known risk for CNS should be based on genetic testing whenever possible.

Phenotypes associated with mutations in these genes display significant variability. Recent reports reveal that CNS is not a distinct clinical entity in either CNF patients (*NPHS1* mutations) or in non-Finnish populations (*NPHS2* mutations), but rather a clinically heterogeneous group of disorders.[6,11-13] Most patients with NPHS1 are born prematurely with low birth weight and the placental weight is usually over 25% of the newborn weight. Microscopic hematuria is present. These may be seen in other forms of CNS. Infants with *NPHS1* genotype do not have extrarenal manifestations. Kidney function remains normal for the first 2 to 3 months. Blood pressure may be low due to hypoalbuminemia or elevated if kidney failure is present. Compared with *NPHS1* mutations, patients with *NPHS2* mutations have milder clinical manifestations of CNS and they slowly progress to the end-stage renal disease. Mutation in *NPHS1* can be also suspected prenatally based on elevated α-fetoprotein levels in maternal serum and amniotic fluid if fetal ultrasonography does not show CNS anomalies or other malformations. There are, however, rare secondary and possibly curable disorders, such as congenital nephrotic syndrome induced by syphilis or toxoplasmosis

This study is the first report of Iranian children with CNS in two pediatric nephrology centers in Tehran, Iran. A major limitation of this study is the absence of molecular determination of the probable mutations and we hope that in future reporting the genetic characteristics of Iranian patients. We assessed the clinical and pathologic findings and also outcome of these patients.

## MATERIALS AND METHODS

We reviewed the medical records and pathologic specimens of 30 patients (15 boys and 15 girls) who presented with edema, hypoalbuminemia, hyperlipidemia, and significant proteinuria within the first 6 months of life. The clinical features, family history, and laboratory data at the time of presentation and during the course of the disease were evaluated for each child. None of the patients had evidence of a congenitally acquired infection. These cases would be excluded on the basis of lack of clinical manifestations, and by testing for specific immunoglobulin antibodies against cytomegalovirus, rubella, herpes simplex virus, hepatitis B, human immunodeficiency virus, syphilis, and toxoplasma.

Kidney biopsy was performed in 28 of 30 children (93.3%) at 3 to 8 months of birth. The light microscopy and immunofluorescence was assessed in all biopsies. The diagnosis of CNF and DMS were based on clinical and pathological findings as recommended in the literature.[2] We did not have genetic analysis for diagnosis in our patients.

The management of each infant was supervised by a nephrologist, and included careful historical and laboratory evaluation at presentation, at follow-up visits, and during hospital stays. Infants received oral diuretics, angiotensin-converting enzyme inhibitors, prostaglandin inhibitors, 20% albumin (to minimize proteinuria and edema), and antibiotics for the treatment of infections. Albumin

infusion was used according to the clinical needs from daily infusion to once per week.

The Student *t* test and chi-square test were used for evaluating the quantitative and qualitative variables, respectively. *P* values less than .05 were regarded as being statistically significant.

## RESULTS

Thirty children with CNS at Ali-Asghar Children Hospital and Markaz-e-Tebbi Children Hospital in Tehran, Iran from 1990 to 2005 were included. They were 15 boys and 15 girls with a mean age of 1.7 ± 2.2 months. The median follow-up duration was 1.5 years (range, 1 month to 3.5 years). Fifteen patients were involved with DMS and 13 had the Finish type CNS. The mean birth weight was 2.7 kg (range, 1 kg to 3.7 kg). Preterm labor and low birth weight was seen in 6 of 30 children (20.0%).

The presentation was edema in 29 of 30 subjects (96.6%). Sixteen patients (53.3%) presented with nephrotic syndrome in the neonatal period. A family history of nephrotic syndrome in infancy was noted for 8 children (26.7%), of whom 5 (62.5%) were involved with DMS and 3 (37.5%) with the CNS, but consanguinity between parents was seen in only 5 patients. All the patients had failure to thrive and 24 of them (80%) showed psychomotor delay.

Biopsy was performed in 28 of 30 patients (93.3%) and revealed mesangial cellularity, contracted glomeruli, radiated tubular dilatation, microcyst formation, tubular atrophy, interstitial fibrosis, and inflammatory cells infiltration in different degrees in a scoring system from zero to 3+. The authors had a good experience in this type of scoring system in other kidney diseases.[16] Although immunofluorescent studies are classically negative in congenital nephrosis, a few of the biopsies (5 of 28; 17.8%) had deposits of immunoglobulins A, G, and M, and complement C3 in variable combinations and intensities.

The CNF was seen in 13 of 30 patients (43.3%) and DMS in 15 of 30 (50%). All of the patients with the CNF presented in the neonatal period. The age at presentation in patients with DMS was between neonatal period and 6 months. The characteristics of patients in these two groups are shown in the Table.

Numerous complications of nephrotic syndrome occurred in 22 patients (73.3%). Infections were the most common complications; 27 episodes of infections were seen in 21 patients (70%) and included septicemia with gram-negative microorganisms (*Klebsiella*, *Escherichia coli*, *Salmonella*, and *Enterobacter*) in 8 of 13 patients (61.5%) and with *Staphylococcus aureus* in 5 of 13 patients (38.6%), pneumonia (4 patients), spontaneous bacterial peritonitis (4 patients), cellulitis (4 patients), gastroenteritis, epidural abscess, and urinary tract infection (2 patients). Thrombotic complications developed in 2 patients (6.6%). These included bilateral vein thrombosis and central vein thrombosis. Hypertension was seen in 7 patients (23.3%).

Comaprison of Characteristics of Children With Diffuse Mesengial Sclerosis (DMS) and Congenital Nephrotic Finnish Type (CNF)

| Characteristic | Patient Group | | *P* |
|---|---|---|---|
| | DMS | CNF | |
| Mean age, mo | 2.8 | 1.1 | > .05 |
| Male/female ratio | 8/7 | 6/7 | > .05 |
| Birth weight, kg | 2.9 | 2.6 | > .05 |
| Hypertension | 6 (40.0) | 1 (7.7) | .04 |
| Familial history | 5 (33.3) | 3 (23.1) | > .05 |
| Death | 12 (80.0) | 13 (100) | > .05 |
| Thrombotic complications | 1 (6.7) | 0 | > .05 |
| Bacterial infection episodes (total, 27) | 16 | 11 | > .05 |

The mean age of the patients at death was 1.3 years old (range, 1 months to 3 years). Of patients who died (n = 26), 12 were on peritoneal dialysis for 6 months to 1 year before death. Four of the patients were alive at the latest follow-up visits, 2 with functioning kidney (2 girls aged 6 months and 18 months old) and 2 were on peritoneal dialysis awaiting transplantation (12 months old and 14 months old).

## DISCUSSION

Congenital nephrotic syndrome was defined as proteinuria leading to clinical symptoms soon after birth (first 3 months). Infantile nephrotic syndrome was defined as nephrotic syndrome manifesting later in the first year (3 months to 1 year). Although uncommon, CNS continues to be a diagnostic and therapeutic challenge for the pediatrician as well as pediatric nephrologists. The CNS of Finnish type and DMS are the two main causes. The most common feature in CNF is focal dilatation of proximal tubules forming microcysts

and there are no pathogonomonic glomerular findings. Glomeruli often appear normal but may show mesangial hypercellularity or increased matrix. In DMS, glomeruli display diffuse mesangial matrix increase and then sclerosis, with or without increased mesangial hypercellularity. As the disease progresses tubular atrophy, interstitial fibrosis and inflammation become more prominent.[15]

With the rapidly increasing number of genes known to be implicated in CNS and the significant phenotypic variability observed, genetic testing is now the method of choice for precise CNS diagnosis, which needs to be based on different clinical information, including the type of renal histological lesions.[7] The CNF is most frequent in Finland, with initial studies suggesting an incidence of 1.2 per 10 000 births.[1,16] Diffuse mesangial sclerosis is a second hereditary cause of congenital or infantile nephrotic syndrome associated with glomerular injury and rapid progression to end-stage renal failure.

We showed that DMS was more common than CNS, and this is in contrast to other studies.[17,18] A family history of nephrotic syndrome in infancy was noted for 8 children (26.7%) in our study. In contrast, in a study in Arab children, a family history of nephrotic syndrome in infancy was noted for 83% of children.[17] The distribution of causes of CNS in our study and this study was different; DMS was not seen in the Arab children, but was seen in 50% of our patients. This is probably because of differences in genetic background in these two races. We do not know what the exact predominant mutations in our patients are. Few studies showed that the prevalence of *NPHS2* mutations is higher in Europeans and Turkish patients than in Asian children.[3,19]

The mean birth weight was 2.7 kg. Preterm labor and low birth weight was seen in 20% of patients and this is similar to other studies such as Mahan and colleagues' (24%).[20] In contrast, prematurity was much higher in Hamed and colleagues' study (83%).[17] This can also be attributed to the higher frequency of DMS in our patients in relation to this study.

In CNF, 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. Diffuse mesangial sclerosis is seen exclusively in infancy.[21-25] Although nephrotic syndrome may be present at birth or even suspected in utero by the finding of an elevated plasma α-fetoprotein level in the mother or the discovery of large hyperechogenic kidneys.[26] In our study, all patients with CNF presented with edema in neonatal period and the patients with DMS, proteinuria was started in mean age of 3 months. All our patients had failure to thrive despite aggressive medical management. Most of patients had psychomotor delay.

Thrombotic complications have developed in 6.6% and this is similar to early reports from Finland. Some authors believe that the incidence of asymptomatic thrombotic complications is high in patients with Finnish type.[27] In our patients with thrombosis one patient had CNF, and renal biopsy was not performed for another.

Infection is a major problem in this study. The majority of our patients suffered severe bacterial infections (70%). Sepsis was seen in 13 (43.3%), of which 8 (61.5%) were gram-negative sepsis and 5 (38.6%) were *Staphyloccucus aureus* sepsis. The high incidence of gram-negative infections (61.5%) is similar to other studies.[17,27] One patient in our study was involved by epidural abscess. Holmberg believes that the reduction in mortality secondary to Finnish CNS is related directly to the introduction of aggressive interventional treatment in the past decade.[28] The mortality rate of patients in this study was 86.6%. The mean age at death was 1.4 years old.

We must emphasize that the renal biopsy does not reveal the etiology of CNS, because the histological findings may overlap in different entities. In addition, if the lesions are focal the biopsy finding may be misleading. Thus, the diagnostic indications for renal biopsy are not quite clear. Absent or altered glomerular nephrin immunostaining, while characteristic, has also been described in other proteinuric glomerular disease and is therefore not specific for CNF.[15]

As we mentioned previously, for the management of CNS, the combined therapy with indometacin and ACE inhibitors are found to be efficient with partial response in about 20% of patients with CNS.[30] Because of urinary losses of plasma gamma globulin and complement factors these patients are prone to bacterial infections. Prophylactic use of antibiotics and immunoglobulin may reduce the incidence of bacterial infections. Surgical or

chemical nephrectomy and start of peritoneal dialysis indicated in the severe form of CNS complicated by heavy proteinuria and malnutrition to avoid the complications associated during the nephrotic stage.[31,32]

## CONCLUSIONS

We showed that DMS is an important cause of congenital nephrotic syndrome in our patients. These patients were not different from CNF in relation to complications and outcome. The outcome of our patients with congenital or infantile type of nephrotic syndrome was poor in our study.

## CONFLICT OF INTEREST

None declared.

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