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Evaluation of Clinical and Follow-up Results of Patients with Congenital Nephrotic Syndrome

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Abstract

Congenital nephrotic syndrome (CNS) is characterized by severe proteinuria, hypoalbuminemia, and edema within the first three months of life. Congenital nephrotic syndrome can occur due to perinatal infections or mutation of genes encoding structural or regulatory proteins of the glomerular filtration barrier. Treatment includes albumin infusions, nephrectomy, dialysis, and transplantation. In this study, we aimed to evaluate the demographic, clinical, and follow-up results of patients with CNS followed up in our center between 2010 and 2020. Demographic, clinical, laboratory values of 8 patients diagnosed with CNS between 2010 and 2020, kidney biopsy results, genetic examinations, and follow-up results were retrospectively evaluated. A total of 8 patients (4 girls) were included in this study. The median age at diagnosis was 36 days (3 days-8 months) and the follow-up period was 34 months (7-114 months). There was a history of prematurity and consanguinity in 5 patients. Edema was detected at the admission of all patients. Albumin infusion and captopril therapy were started from the diagnosis. No pathology was seen in the tests for perinatal infection, and ultrasonographic examinations were normal. In the genetic analysis, NPHS1 (Nephrin) homozygous mutation was detected in six patients, and coenzyme Q2 mutation was detected in one patient. Peritoneal dialysis treatment was performed in four patients during the follow-up, and unilateral nephrectomy was completed in one patient. During the follow-up, four of eight patients (three due to sepsis while on dialysis, one on the postoperative after the first day of transplantation) died. Three patients are followed up with kidney transplantation and one with supportive treatment. According to our results, most CNS cases are genetic, and nephrin mutation is the most common cause. Management of complications in CNS is crucial for patient survival.

Keywords: Congenital nephrotic syndrome, nephrin mutation, dialysis, transplantation, pediatric

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Introduction

Congenital nephrotic syndrome (CNS) is a rare kidney disease characterized by severe proteinuria, hypoalbuminemia, and edema that manifests after birth.[1] It is a genetic disorder caused by the disruption of the glomerular filtration barrier, mainly due to mutations in the genes called Nephrin and Podocin. Also, CNS may result from perinatal infections or may be part of various syndromes as Galloway–Mowat syndrome.[2] Genetic analysis is the definitive diagnosis of congenital nephrotic syndrome, and it is recommended to be done in all of these patients.

Highlights

- The nephrotic syndrome occurring in the first three months of life is defined as congenital NS. Nephrin mutation is the most common cause.
- The management should plan on a case by case basis, depending on the severity of nephrosis, complications, the response of antiproteinuric therapy.

Immunosuppressive therapy is ineffective in CNS of genetic origin, but kidney transplantation provides the curative treatment. In many cases, daily infusion of albumin is required to prevent life-threatening edema in the first months. In addition, a high-calorie diet, thyroxine, and mineral support are applied. Prevention of thromboembolic complications and opportunistic infections that may develop due to immune deficiency is required. Unilateral nephrectomy is an effective alternative to bilateral nephrectomy for patients with NS.[3,4]

This study aimed to evaluate the demographic, clinical, and follow-up results of patients with CNS who were followed up in our center between 2010 and 2020.

Material and Method

Ondokuz Mayıs University, Faculty of Medicine Ethics Committee was obtained for this study (Date: 12.11.2021, Number: 2021/493). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Eight patients with a diagnosis of CNS were included in this study and analyzed retrospectively. CNS was defined as the onset of NS within three months of birth.

Patients were classified according to the following definitions of nephrotic syndrome: the presence of profound proteinuria (random urine protein creatinine ratio >2 or greater than 40/mg/m2/hour), hypoalbuminemia (serum albumin <2.5 g/dl), and edema.

The data for individual patients, including demographic details and clinical information about the age of onset, syndromic features, a workup for infective etiology, genetic mutation study, and clinical outcomes, were recorded for each patient.

Statistical Analysis

Analyses were done using Statistical Package for the Social Sciences 22.0 (SPSS IBM Corp, Armonk, New York, USA). The characteristics of patients were determined using descriptive statistics. The data were expressed as number, percentage and range.

Results

Eight patients with CNS were included in this study between 2010 and 2020. Baseline demographic and clinical characteristics of children with congenital nephrotic syndrome are reported in **Table 1**.

The median duration of follow-up was 34 months (7months -9.5 years). The sex ratio (female/male) was one, and consanguinity concerned 62.5 % of families. The median age of initial diagnosis was 36 days (3 days- 8 months). Two of our patients were siblings. The patient was admitted when he was eight months old (his sibling died due to CNS complication), although the family noticed the swelling in the first three months, but admitted in the 8th month. He had less edema compared to other patients on the first visit. There was a history of prematurity in 5 patients. Edema was detected at the admission of all patients.

Perinatal infections or extra-renal findings were not detected in any of the patients. Ultrasonographic examinations were normal. In the genetic analysis, NPHS1 (Nephrin) homozygous mutation was detected in six patients, and coenzyme Q2 mutation was detected in one patient. This child had no extra-renal symptoms. He progressed to the end-stage renal disease shortly after the diagnosis of CNS and died due to sepsis during the peritoneal dialysis. No mutation was found in one patient, but his sibling had a nephrin mutation who was admitted at eight months.

Table 1
Baseline demographic and clinical characteristics of children with congenital nephrotic syndrome

Clinical characteristic	Results
Number of patients	8
Gender (m/f), number (n)	4/4
Prematurity, n (%)	5 (62.5)
Consanguinity, n (%)	5 (62.5)
Age at initial diagnosis, days, median (IQR)	36 (3 days-8 months)
Follow-up time, months, median (IQR)	34 months (7months -9.5 year)
Edema at admission, n (%)	8 (100)
Genetic testing, n	
	6 patient : NPHS1 (Nephrin) homozygous mutation
	1 patient : coenzyme Q2 mutation
	1 patient : no mutation
Extrarenal symptoms	None
Treatment, n (%)	
Antiproteinuric therapy, n (%)	8(100)
Unilateral Nephrectomy, n (%)	1 (12.5)
Peritoneal Dialysis, n (%)	4 (50)
Transplantation, n (%)	3 (37.5)
Complications, n (%)	4 (50)
Sepsis	3 patient (on dialysis , ex) 1 patient ,ex (first day of postoperative transplantation)

All patients were hospitalized at the diagnosis of CNS. Daily albumin infusions, angiotensin-converting enzyme inhibitor (ACEi), a high caloric diet, and mineral support were started. Four patients eventually progressed to end-stage, and peritoneal dialysis treatment was started during the follow-up. Unilateral nephrectomy was completed in one patient due to severe edema. During the follow-up, four of eight patients (three due to sepsis while on dialysis, one on the postoperative after the first day of transplantation) died. Three patients are followed up with kidney transplantation and one with supportive treatment.

Discussion

Congenital nephrotic syndrome (CNS) consists of heavy proteinuria, edema, hypoalbuminemia defined within the three months of birth. Management is very challenging as patients are prone to complications such as infection, thrombosis, and failure to thrive. CNS has a low incidence and a poor prognosis; end-stage renal disease (ESRD) often develops, requiring dialysis and renal transplantation therapy.[4-6] This is the largest series in our tertiary center that analyzed CNS.

Congenital Nephrotic syndrome is mainly caused by mutations in genes encoding structural or regulatory proteins of the glomerular filtration barrier. NPHS1, NPHS2, NPHS3 (PLCε1), WT1, and LAMB2 mutations are responsible for more than 80% of cases. Mutations in the NPHS1, NPHS2 genes are responsible for 95% of the cases. Genetic causes do not respond to glucocorticoid and other immunosuppression treatments.[4,7]

The NPHS1 mutation is also a major cause of CNS, more represented in the Finnish people, which was associated with Finnish-type CNS.[7-9] Premature birth, increased placental weight (>25% of the newborn weight), fetal edema, are the common findings of Finnish type CNS but there is no specific histopathology. The diagnosis is based on clinic and genetic analysis. In this present study, the disease type was Finnish in 7 patients, non-Finnish without syndrome in 1 patient. The number of male and female patients was similar (4 female and four male respectively). As Finnish-type CNS is inherited in an autosomal recessive manner, the incidence in both sexes tends to be similar.[10,11] Patients with Finnish-type were diagnosed earliest because clinical manifestations of the disease, such as the enlarged placenta and the massive edema, become evident shortly after birth in most patients with Finnish-type CNS. In our study, the earliest diagnosis of age is three days, and the median age of admission was 36 days. Seven patients presented with severe edema. The patient, who had the latest admission, was diagnosed when he was eight months old. The patient had minimal edema at presentation. The first child of the family was diagnosed with CNS and died due to sepsis. In the first three months, there was mild edema that the mother noticed. Or contrast to his other ex-sibling, he did not have severe edema since birth. Homozygous mutation p.Asn1077Ser is detected in the NPHS1 gene. This may be a “mild” mutation that causes a different phenotype other than the common primary mutation or the minor mutation.[11-13] Fin major and minor mutations were severe and presented with early symptoms. To date, more than 200 mutations have been identified all over the world.[10,11]

Patients with NPHS1 mutations do not have extra-renal malformations, but growth retardation was the most common extra-renal symptom.[14] The present study found only short stature as extra-renal symptoms, no other urogenital, mental retardation, eye-ear, or skeletal problems.

Mostly, patients with Finnish-type and non-Finnish-type with CNS do not respond to corticosteroids and immunosuppressive treatments because it is not an immunological disease. In these patients, CNS is progressive, often leading to end-stage renal disease or even death. Supportive treatment such as high caloric sodium-free diet, albumin infusion, mineral supports, unilateral/bilateral nephrectomy, and dialysis is the treatment modalities until kidney transplantation.[4,7,14,15] Early unilateral nephrectomy to reduce proteinuria and decrease the intense albumin infusions or bilateral nephrectomy with the initiation of dialysis followed by kidney transplantation have been reported to be effective in CNS . Recent reports stated that unilateral nephrectomy is more suitable than bilateral nephrectomy in CNS.[3,4,10]

Daily albumin infusion and ACEi, a high-calorie diet, mineral support were given to all patients in this study. Four patients eventually progressed to the end stage, and peritoneal dialysis treatment was started during the follow-up. Unilateral nephrectomy was completed in one patient due to severe edema and severe infections due to catheter-associated sepsis. After the unilateral nephrectomy, the need for albumin infusion decreased to once in 15 days.

Reports suggest unilateral nephrectomy with ACE inhibitor and indomethacin to reduce proteinuria with severe edema and related complications. Patients with mild proteinuria may require unilateral nephrectomy to facilitate proteinuria and albumin replacement, and patients with severe proteinuria may require bilateral nephrectomy.[4,5,15] A recent study by Murakoshi et al.[16] found that unilateral nephrectomy reduced proteinuria and shortened hospitalization with CNS. Recent reports showed that bilateral nephrectomy could cause life-threatening complications such as hypotension, infections and this rate was similar in the conservative approach. The decision for nephrectomy should be considered in the presence of severe complications of the CNS, including growth retardation, thrombosis, and difficulties in maintaining euvolemia despite optimization of conservative therapy.[17,18] During the follow-up, four of eight patients (three due to sepsis while on dialysis, one on the postoperative after the first day of transplantation) died. Three patients are followed up with kidney transplantation and one with supportive treatment with ACEi. Two patients underwent kidney transplantation at the age of 1 and the other patient at two years. Transplantation is the curative treatment for the majority of CNS patients. Early treatment of daily albumin infusions, nutrition, and timely bilateral nephrectomy followed by transplantation at the age of 1–2 years showed dramatic improvement in neurodevelopmental skills.[19]

Conclusion

According to our results, the underlying cause of most CNS cases are genetic, and the nephrin mutation being the most common. Management of complications in CNS is crucial for patient survival. Management of CNS should be individualized case by case in the presence of severe complications, including growth retardation, severe nephrosis, infections, thrombosis, and difficulties in maintaining euvolemia despite conservative therapy.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

Ethics Committee Approval: Ondokuz Mayıs University, Faculty of Medicine Ethics Committee was obtained for this study (Date: 12.11.2021, Number: 2021/493).

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Informed Consent: Informed consent was obtained from the parents of the patients.

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