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Case Report

Congenital Nephrotic Syndrome: A Cases Report

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ABSTRACT

Congenital nephrotic syndrome (CNS) can be caused by neonatal infections and renal diseases that usually occur in early infancy. The most common CNS is the Finnish type, which is an autosomal recessively inherited disease characterized by intrauterine onset of massive proteinuria. In this study, we presented a preterm neonate confirmed as the first case of CNS in Iran by genetic study, who was admitted to the Neonatal Intensive Care Unit of Imam Reza Hospital, Mashhad, Iran. The patient's mother had gestational diabetes mellitus and a history of intrahepatic cholestasis of pregnancy. The newborn was hospitalized at birth because of hypoglycemia. Upon admission, repeat seizure, intraventricular hemorrhage, intracerebral hemorrhage, and edema (specific gravity of more than 58 and sever protein urea) were detected. Furthermore, hypoalbuminemia was observed. The result of the blood culture and cerebral spinal fluid culture were negative. In addition, TORCH and venereal disease research laboratory tests were negative. Finally, genetic study showed a mutation in C3250 DUPG.

Keywords: Albumin, Congenital nephrotic syndrome, Hypoalbuminemia

Introduction

Renal diseases associated with nephrotic syndrome (NS) in newborns are uncommon, consisting of a heterogeneous group of disorders. Congenital nephrotic syndrome (CNS) is a very rare form of nephrotic syndrome. The CNS is defined as proteinuria manifesting in the first three months of life. The NS appearing later during the first year of life (i.e., 4-12 months) is referred as infantile NS, and if it manifests thereafter, it is called childhood NS.

The leakage of plasma proteins into urine is the main feature of this syndrome, which results from mutations in genes encoding for structural or regulatory proteins of the kidney filtration barrier placed in the glomerular capillary wall (1, 2). Hypoproteinemia, oliguria, edema, thrombotic complications, and infections are the main side effects of CNS. Moreover, this condition can also lead to hyperlipidemia and hypothyreosis as a result of severe protein loss (2).

The neonates with CNS have a uniform clinical course characterized by failure to thrive, frequent infections, and declining renal function. Recently, molecular genetics research has improved the identification of mutant genes in many renal disorders. Accordingly, *NPHS1* and *NPHS2* mutations account for about 75% of CNS cases (3). This indicates that a particular gene defect can be responsible for NS, which can manifest at different ages. However, the term of childhood NS is still applied due to the different etiology, clinical features, and management of CNS (4).

The prognosis in CNS is poor as the majority of cases die within six months of life. However, intravenous albumin supplementation, nutritional management, complication treatment, dialysis, and renal transplantation have been shown to improve the growth and development of the affected children (5, 6). Herein, we reported a neonate confirmed as the first case of CNS in Iran by genetic study. The neonate with gestational age of 37 weeks was admitted to the Neonatal Intensive Care Unit (NICU) of Imam Reza Hospital affiliated to Mashhad University of Medical

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Sciences, Mashhad, Iran, with hypoglycemia, protoienura, and hypoalbomineia. Based on genetic finings, she was diagnosed with CNS, probably the Finish type.

Case report

Our case was a female newborn with the gestational age of 37 weeks with CNS, who was admitted to the NICU of Imam Reza Hospital. The neonate was the third child of a 37-year-old woman with gestational diabetes mellitus and a history of intrahepatic cholestasis of pregnancy. The patient was hospitalized at birth due to hypoglycemia. The neonate had the birth weight, height, and head circumference of 2,500 g, 47 cm, and 36 cm, respectively. Furthermore, the Apgar score was reported as 8-9.

Intrahepatic cholestasis of pregnancy and thyroid abnormality were observed after the assessment of the mother's family history. Also, high alpha-fetoprotein and high risk of neural tube defects were reported in the prenatal screening. On the ninth day of birth, the patient was admitted due to poor feeding and irritability.

After hospitalization, the newborn underwent sepsis workup and received cefotaxime in combination with vancomycin injection. Seizure attacks were reported during hospitalization. Therefore, the neonate was subjected to ultrasound revealing intraventricular hemorrhage and intracerebral hemorrhage, which were controlled by phenobarbital. Then, lumbar puncture was performed. The test results indicted the white blood cell of 400, lymphocyte of 80%, protein of 98 mg/dL, and glucose of 44 mg/dL.

Also, edema (specific gravity of more than 58 and protein of 3+) was reported. Upon admission, the newborn was detected with hypoalbuminemia. Blood culture and cerebral spinal fluid culture were negative. In addition, the results of the TORCH and venereal disease research laboratory tests were negative. The genetic study revealed a mutation in *C3250 DUPG* offering the evaluation of parents' genetics.

Based on the laboratory tests, the level of albumin was low, and the presence of protein in the urine sample was reported. Therefore, the patient was treated with albumin serum. Also, total parenteral nutrition was performed during the treatment process. Considering that the patient was suspicious for CNS, she was assessed for TORCH syndrome. According to endocrine consultation, LEVBEL was prescribed for controlling seizure. Furthermore, the treatment of hypothyroidism was performed based on the high level of thyroid-stimulating hormone.

Finally, the patient was discharged from the hospital with parental consent. She was prescribed with oral albumin, vitamin D, levothyroxine, captopril, levothyroxine, and levetiracetam. However, she was re-referred after eight days.

Discussion

We reported a patient with CNS, who presented with edema, proteinuria, and hypoalbuminemia with irritability. In the majority of CNS cases, genetic defects are observed in different components of the glomerular filtration barrier, which is caused by mutations in nephrin and podocin genes. The other forms of CNS are caused by treatable infections, such as congenital syphilis, toxoplasmosis, and malaria (7).

In our case, the mutations in nephrin (considered as *NPHS1*, NS type I) gene was identified. The *NPHS1* gene is 26 kb in size and has 29 exons. It codes a transmembrane protein named 'nephrin'. The mutation detection rate of this gene varies among different ethnic groups (8). It approaches 98% in the Finish children with CNS, but is lower outside Finland (9).

The treatment of CNS is very challenging. Renal transplantation is considered as the curative treatment of only primary forms of CN, resulting in excellent outcomes without recurrence. Intensive therapy with frequent albumin infusions and nutritional and vitamin supplementation, together with early bilateral nephrectomy, followed by dialysis is the other standard treatment (10). Hypothyroidism develops secondary to loss of thyroid binding globulin, thyroid hormone, and iodine; therefore, thyroxine supplements are needed (11).

In this study, the management of treatment was performed based on the total parenteral nutrition principle. The control of edema and uremia during the first month is the main target of therapy in patients with CNS. Moreover, several possible complications, such as infections and thrombosis, should be inhibited. Furthermore, it is important to provide an optimal diet for optimal child growth (4).

One of the main issues in the management of CNS is the rate of proteinuria. Proteinuria inhibition (10-100 g/L) is an issue of fundamental significance considering its important role in the incidence of life-threatening edema, growth retardation, and malnutrition. Therefore, protein

substitution is essential in these cases.

Although the treatment with anti-proteinuric medication is essential, several patients with severe *NPHS* mutations do not respond to this therapy due to the inhibition of nephrin and podocin expression. In our study, oral albumin was prescribed to the patient. Furthermore, the children with CNS have low levels of thyroxine-binding globulin and thyroxine hormone due to the protein excretion. Since thyroid stimulating hormone increases during the first month, thyroid substitution is recommended in these patients (4).

The conventional treatment for the neonates with severe CNS include a high-energy and high-protein diet. Excess protein and vitamin D_2 (400 IU/day) is normally prescribed and multivitamin and supplementary magnesium and calcium are also recommended to keep serum levels within the normal range (4).

However, kidney transplantation is the only curative treatment in most of the patients. One of the main problems of renal transplantation is the increased risk of thrombotic and ureteral complications due to using adult-sized kidneys. Overall, the outcome of kidney transplantation in CNS patients is quite good, and its recurrence is rare and can be controlled with cyclophosphamide and plasmapheresis (12).

Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II type-1 receptor blockers (ARB) have been demonstrated to delay the progression of chronic renal diseases (13). Furthermore, children with NS and other glomerular diseases showed decreased urinary protein excretion when treated with ACEi or ARB (14). Kovacevic et al. reported a successful management of CNS with captopril and indomethacin in combination with unilateral nephrectomy, which might serve as an alternative medicine, allowing a delay for transplantation until the third year of life or longer (15).

However, the lack of possibility for neonatal dialysis in Iran overcame the risk of undergoing nephrectomy and obligated us to transfer the patient to a more specialized center outside the country. This case was reported to highlight the diagnostic and therapeutic difficulties in developing countries when facing rare congenital problems and call clinicians' attention to consider prenatal diagnosis through elevated maternal serum alpha fetoprotein and large placental size.

Conclusion

Genetic factors and molecular basis are known as the main factors in the incidence of CNS. In this regard, glomerular sieving by podocyte proteins, and mutations in genes encoding for nephrin, podocin, *WT1*, and lamininβ2 play an important role in most of the CNS cases. The management of CNS is possible by medical and dietary therapies.

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Conflicts of interests

The authors declare no conflicts of interest.

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