Int J Clin Exp Med 2018;11(12):13913-13919
www.ijcem.com /ISSN:1940-5901/IJCEM0073842

Case Report

Congenital nephrotic syndrome: a case report and literature review

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Received February 1, 2018; Accepted September 13, 2018; Epub December 15, 2018; Published December 30, 2018

Abstract: The purpose of this study is to report the clinical characteristics and etiology of congenital nephrotic syndrome (CNS) in China by retrospectively analyzing one CNS case from the First Affiliated Hospital of Nanjing Medical University together with a total of 17 reported CNS cases from available Chinese literature. Most of the 17 cases originated in the eastern and central region of China. The male-to-female ratio was 8:9 and the onset age of 9 CNS cases was under 1 month. Genetic mutation and infection are the main causes of CNS, and mutations of NHPS1 have been verified in 12 cases. α-fetoprotein (AFP) level in amniotic fluid and maternal serum reflects fetal proteinuria, which may be a potential antenatal diagnostic marker of CNS. Symptomatic treatment was the most common used therapy for CNS. However, the prognoses of most patients were not satisfactory.

Keywords: Congenital nephrotic syndrome, gene mutation, NHPS1, infection, China

Introduction

Congenital nephrotic syndrome (CNS), a rare disease, has been defined as nephrotic syndrome which occurs within the first three months of life [1]. Typical clinical manifestations characterized by edema, massive proteinuria, low serum albumin and hyperlipemia often present within a few weeks after birth. In addition, hypothyroidism, hypoferric anemia and even some thrombotic complications can also be observed in the patients with CNS. Shi et al [2], who reported the first case of CNS in China, once discovered three heterozygous in NPHS1 genes. One of which was a deletion mutation (1893-1900del8) and the other two were the missense mutation (G928A and G2869C). In this study, one CNS case from our center is reported. Furthermore, for the first time, all available CNS cases in China were collected and analyzed to illuminate characteristics and mechanisms of CNS.

Materials and methods

This study obtained the ethic committee approval from the Institutional Review Board of the First Affiliated Hospital of Nanjing Medical University in 2016. The informed consent was also received from the parents before data collection. The CNS case from the First Affiliated Hospital of Nanjing Medical University together with other 16 CNS cases reported from previous studies in China were all involved into this study. We browsed Pubmed (https://www.ncbi.nlm.nih.gov/), Wanfang Data (http://www.wanfangdata.com/), and Cqvip (http://www.cqvip.com/) for previous studies by using keywords 'congenital nephritic syndrome'. Finally, 22 reports were found, after carefully reviewing and extracting data from the publications, eight cases were excluded ultimately because of non-coincidence with diagnostic criteria or an absence of relevant clinical data. Clinical features, laboratory data, and gene information were analyzed retrospectively.

Results

The CNS case from first affiliated hospital of Nanjing medical university

A girl, 17 days old, was admitted to First Affiliated Hospital of Nanjing Medical University

Table 1. Genetic analysis of one case from First Affiliated Hospital of Nanjing Medical University

Gene	Sub Region	Nucleotide Change	Amino acid change	Hom/ Het	Chromosomal Position
NPSH1	VS14	c.1930 + 2T > C	-	Het	Chr19:36336268
	EX11	c.1409delG	p.Gly470Alafs* 16	Het	Chr19:36338974

Hom: homozygote, Het: heterozygote.

due to moaning and shortness of breath for three hours. The baby was born of 38 weeks and 4 days of gestational age with a birth weight of 3100 g. Apgar score was 10 to 10 at 1 and 5 min, respectively. The baby vomited twice a day before admission. By physical examination, she showed abdominal distension and mild edema in face and legs. She has normal female external genitalia. Routine prenatal examinations showed that the level of her mother's α-fetoprotein (AFP) was high. The parents and her older brother are all healthy.

Laboratory data revealed a total serum protein level of 20.9 g/L, albumin 6.9 g/L, total cholesterol 6.61 mmol/L, and serum creatinine 18.2 μmol/L. Her electrolytes were out of the normal range such as hyponatremia and hypocalcemia. Hypothyroidism was also found in this child. There was no evidence of congenital infection. Screening of blood serum from the baby excluded the presence of antibodies for toxoplasma, rubella virus, cytomegalovirus, herpes simplex virus, syphilis, hepatitis B virus, hepatitis C virus, herpes virus types 1 and 2, and HIV. Urine analysis showed proteinuria of 4 + and hematuria of 3 +. Renal ultrasonography showed the size of the right kidney as 61 × 32 × 30 mm and that of the left kidney at 64 × 34 × 32 mm with increased renal cortex echogenicity. Renal biopsy was not performed due to the parents' rejection.

In all, the child was diagnosed with CNS. She had hypoalbuminemia, massive proteinuria, hyperlipemia, edema and hypothyroidism. Intravenous albumin and diuretics were administered. She was also treated with prednisone and euthyrox. However, facial and lower limbs edema persisted. Unfortunately, deep venous thrombo was found in her left femoral vein, which was the complication of CNS. Clexane was administrated for anti-thrombin treatment. After 11 days of comprehensive treatments including symptomatic, anti-infective, and anti-inflammatory treatment, she was discharged.

Gene mutation analysis

In order to investigate the pathogenesis of CNS in this case, capture of target area and high-throughput sequencing which contained 355 genes (NPHP4, MTR and NPHS1, etc.) were performed by Beijing Genomics Institute. High-throughput sequencing data analysis process BGIv.0.1.0 was applied and UCSC hg19 Feb.2009 was served as Human genome reference. Sequences were analyzed using SOAPsnp software 2.0, and SAM tools v1.4. Data interpretation rules referred to the guidelines of American College of Medical Genetics and Genomics (ACMG).

As shown in **Table 1**, two heterozygous likely pathogenic mutations of NPHS1 were detected in this baby. The mutation c.1930 + 2T > C (**Figure 1**) is a slice site mutation that may lead to a change in the splicing mode of the NPHS1 gene's RNA precursor, which in turn encodes an abnormal protein. The c.1409delG (p.Gly470-Alafs* 16) mutation (**Figure 2**) was a frameshift mutation of the NPHS1 gene. It turned the glycine which located on 470 th encoding protein in NPHS1 gene into alanine and had an early termination at 485 th amino acids (normal protein is made of 1241 amino acids). There was no record of these two mutations in the normal population genome sequencing database (ESP6500 genome database and Huada genome database). There was no c.1930 + 2T > C mutation reported previously, but the same type of slice site mutation has been identified [3]. CNS associated with the NPHS1 mutation is an autosomal recessive disorder [4]. Homozygous or heterozygous mutations can lead to CNS.

Literature review

The clinical features of the 17 cases summarized in **Tables 2** and **3**. The ages of patients ranged from 1 to 89 days, and about a half were under the age of 30 days. Two patients had pathogen detected infection, and one was suffering from syphilis infection. The other patient, detected of cytomegalovirus (CMV) infection, was also found genetic mutation in

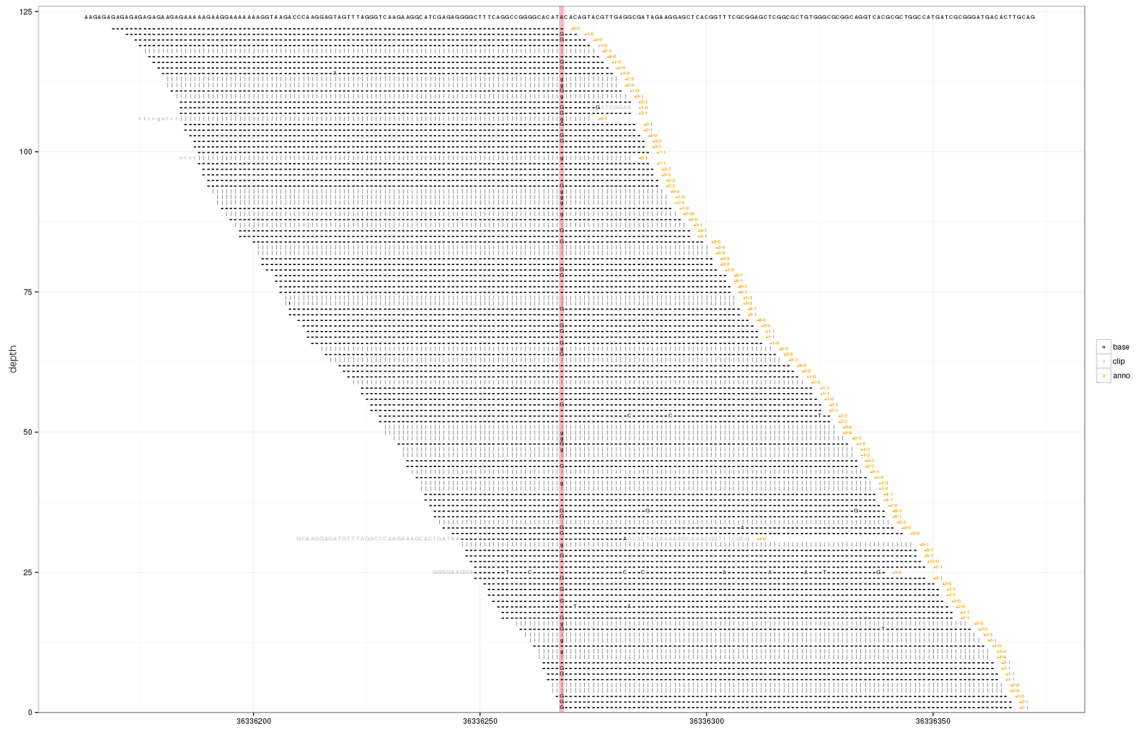

Figure 1. The reads supporting picture of c.1930 + 2T > C mutation in NPHS1 gene. The mutation c.1930 + 2T > C is a slice site mutation.

NPHS1 and the condition wasn't improved after anti-infection therapy, which suggested the mutation of NPHS1 maybe the primary cause of CNS. Edema occurred initially on almost all patients (88.2%). 13 patients had reported genetic analysis. Some patients received the symptomatic supportive treatment. In some cases, the prognoses haven't been fully reported. From the reported cases, patients who detected of infection recovered to normal largely, and others died of various complications eventually.

Discussion

CNS is a clinically and genetically heterogeneous syndrome. It may be caused by perinatal infections, or more importantly, by genetic defects in structural proteins that consist of the glomerular filtration barrier [5]. CMV infection and syphilis were identified respectively in patient no.6 and no.17. From the view of the publications we found, CMV and syphilis were the most frequent infections in China. Other types of infections were reported rarely. In addition, a number of CNS cases are associated with genetic mutation. However, the specific pathogenesis of CNS in China remains unclear. Interestingly, Most CNS cases were located in the eastern and central parts of China, including Hubei, Hunan, Shanghai, Jiangsu, and Fujian provinces. The main reason for this distribution may be economic and social factors, especially different abilities of diagnosis and comprehension of CNS in different areas of China. Accordingly, the all available information on Chinese CNS patients since database established were collected, and the characteristics were analyzed in the present study.

NPHS1 is localized on chromosome 19q13.1 and codes for the nephrin protein which is an important component of the interpodocyte-spanning slit diaphragm. Nephrin is a transmembrane protein of the immunoglobulin (Ig) superfamily and plays a vital role in cell-cell signaling in the slit diaphragm [4]. Mutations of the NPHS1 gene can lead to disruption of the filtration barrier and cause massive protein loss. CNS of Finnish type (CNF), a recessively inherited disorder because of NPHS1 mutations, is most common in Finland with the incidence of 1 in 10,000 births [6]. In our study, 12 cases of CNF have been reported in China,

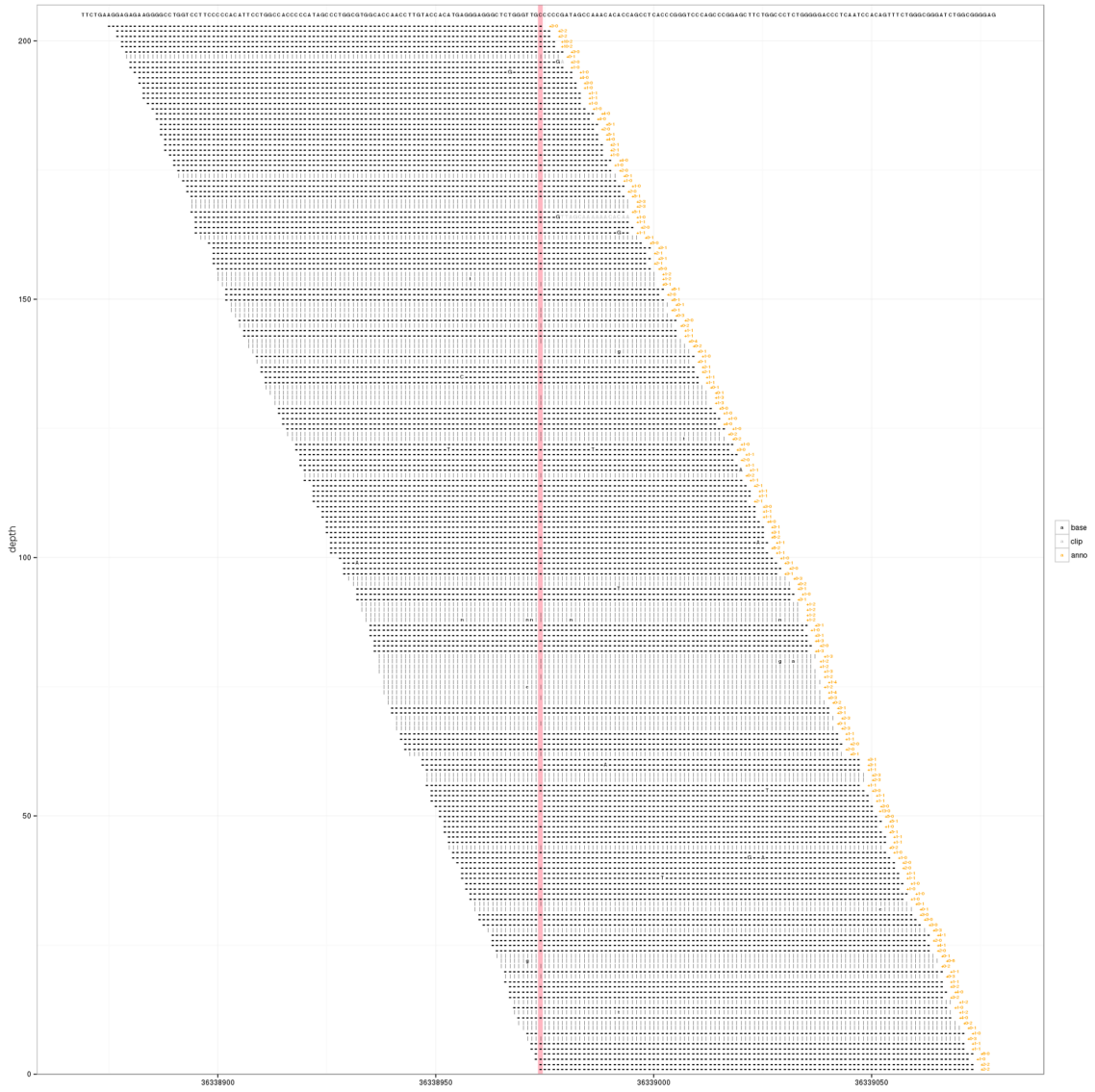

Figure 2. The reads supporting picture of c.1409delG mutation in NPHS1 gene. The c.1409delG mutation is a frameshift mutation of the NPHS1 gene.

including the present one. These observations revealed that loss-of-function mutations in NPHS1 were the main cause of CNS in China. Yoshizawa et al. [7] have discovered compound heterozygous mutations are more frequent than homozygous mutations in CNF among East Asian patients. There is no hot spot mutation reported in East Asia.

Besides NHPS1, few mutations in other genes can also lead to CNS. In the present review, 1 out of 17 cases had confirmed the mutations in LAMB2. LAMB2 gene, located on chromosome 3, encodes lamininβ2 which includes 1798 amino acids and 32 exons. Laminin is expressed in a significant role in adhesion, proliferation, differentiation, and migration of cells, especially in glomerular basement membrane, iris and synapses [8]. Therefore, mutations in LAMB2 gene can lead to diffuse mesangial sclerosis, as well as microcoria and mental retardation, which is called Pierson syndrome [9]. Interestingly, patient no.2 had obvious clinical manifestations of nephrotic syndrome without any ocular or nervous syndromes. What's more, Hinkes et al. [10] reported that in Europe the detection rates of genetic mutations in NPHS1, NPHS2, WT1 and LAMB2 were respectively

Table 2. Information of 17 CNS Chinese case

Reported by	Case no.	Gender	Age (days)	Etiology	Onset		
					Edema	Abdominal distention	Other symptom
The First Affiliated Hospital of Nanjing Medical University	1	F	17	Genetic mutation	Y	Y	Shortness of breath, groaning, vomit
Qiu et al. [12] (Hubei)	2	F	34	Genetic mutation	Y	Y	N
Yu et al. [13] (Fujian)	3	M	37	Genetic mutation	Y	N	N
Li et al. [14] (Shanghai)	4	F	32	Genetic mutation	Y	Y	N
	5	M	8	Genetic mutation	Y	N	Jaundice
Mi et al. [15] (Beijing)	6	F	37	Genetic mutation, CMV infection	Y	Y	Diarrhoea, convulsion
Zhang et al. [16] (Shandong)	7	F	1	NR	Y	Y	Hypermyotonia, drowsiness
Fu et al. [17] (Henan)	8	M	77	Genetic mutation	Y	Y	N
Hu et al. [18] (Jiangsu)	9	M	10	Genetic mutation	Y	Y	Umbilical hernia, hyperspasmia
Zhang et al. [19] (Jilin)	10	M	3	Genetic mutation	Y	N	N
Guan et al. [20] (Guangdong)	11	F	17	NR	Y	N	N
Ke et al. [21] (Shanxi)	12	F	32	NR	Y	N	N
Wang et al. [22] (Fujian)	13	M	37	Genetic mutation	Y	N	N
Wu et al. [23] (Hunan)	14	M	10	Genetic mutation	N	Y	Myasthenia of limbs
	15	F	20	Genetic mutation	N	Y	Myasthenia of limbs
Yang et al. [24] (Hubei)	16	F	15	Genetic mutation	Y	N	N
Zheng et al. [25] (Hebei)	17	M	62	Syphilis infection	Y	Y	Anemia, herpetiform rash

	Initial Examination				Genetic analysis	Treatment			
	Albumin (g/L)	Total cholesterol (mmol/L)	Proteinuria (±)	Hematuria (±)		Corticosteroids	Intravenous albumin	Diuretic	ACEI
The First Affiliated Hospital of Nanjing Medical University	6.9	6.61	4+	3+	Mutation in NPHS1	Oral prednisone	Y	Y	-
Qiu et al. (Hubei)	16.1	2.72	3+	3+	Mutation in LAMB2	-	Y	Y	-
Yu et al. (Fujian)	4.6	5.01	3+	-	Mutation in NPHS1	Oral prednisone	-	-	-
Li et al. (Shanghai)	8.26	12.3	3+	2+	Mutation in NPHS1	Oral prednisone	Y	-	Y
	11.5	5.77	3+	2+	Mutation in NPHS1	Oral prednisone	Y	-	Y
Mi et al. (Beijing)	11.0	8.07	4+	2+	Mutation in NPHS1	-	Y	Y	Y
Zhang et al. (Shandong)	13.1	6.7	3+	2+	NR	-	Y	Y	-
Fu et al. (Henan)	10.9	6.66	3+	-	Mutation in NPHS1	-	-	-	Y
Hu et al. (Jiangsu)	18.2	9.0	3+	-	Mutation in NPHS1	-	-	-	-
Zhang et al. (Jilin)	13.7	9.16	3+	3+	Mutation in NPHS1	-	Y	Y	-
Guan et al. (Guangdong)	32.9	5.9	3+	+	NR	-	-	-	-
Ke et al. (Shanxi)	23.1	-	3+	3+	NR	-	Y	Y	Y
Wang et al. (Fujian)	4.6	5.01	3+	-	Mutation in NPHS1	Y	-	-	-
Wu et al. (Hunan)	-	-	3+	-	Mutation in NPHS1	-	-	-	-
	18.2	9.0	3+	-	Mutation in NPHS1	-	Y	-	-
Yang et al. (Hubei)	10.0	6.06	3+	3+	Mutation in NPHS1	-	-	-	-
Zheng et al. (Hebei)	10.0	-	4+	+	NR	Dexamethasone, prednisone acetate	Y	Y	-

F female, M male, NR not reported, N normal, CMV cytomegalovirus.

Table 3. Summary of clinical manifestations of the 17 CNS cases

Category	n (%)
Gender	
Female	9 (52.9%)
Male	8 (47.1%)
Age	
≤ 30 days	9 (52.9%)
> 30 days	8 (47.1%)
Etiology	
Genetic mutation	13 (76.5%)
Infection	2 (11.8%)
Onset	
Edema	15 (88.2%)
Abdominal distention	10 (58.8%)
Therapy	
Corticosteroids	6 (35.3%)
Intravenous albumin	10 (58.8%)
Diuretic	7 (41.2%)
ACEI	5 (29.4%)
Genetic analysis	
Mutation in NPHS1	12 (70.6%)
Mutation in LAMB2	1 (5.9%)

39.1%, 39.1%, 2.2% and 4.4% within 46 patients with nephrotic syndrome in the first year of life. Thus far, NPHS2 and WT1 gene mutations haven't been reported in China.

The treatment for CNS is still very difficult. Anti-infective treatment must be conducted on patients with perinatal infection. The diagnosis of Secondary nephrotic syndrome can't be confirmed just because of the detection of injection. The etiology of CNS can be identified by the result of anti-infective treatment and genetic analysis. In this study, many patients received symptomatic and supportive treatments including intravenous albumin, diuresis, corticosteroids and ACEI. ACEI is recommended to use because it can lowers intraglomerular pressure and decreases the excretion of urinary protein. Except patients no.7 who was detected of syphilis infection recovered completely, the prognoses of other patients with CNS were not satisfactory. A variety of symptomatic treatments can alleviate the symptoms temporarily, but death is inevitable ultimately for renal failure or other complications. Therefore, renal transplantation is the only promising treatment. Recent developments suggest that edema and other symptoms must be controlled before transplantation.

In conclusion, mutation in NPHS1 was the main cause of CNS in China. Prevention and prenatal diagnosis are more important than therapy. It was reported that AFP levels in amniotic fluid and maternal serum reflects fetal proteinuria and may be used as a antenatal diagnostic marker of CNF [11]. The family which had a CNS baby before or had a higher risk of CNS should take genetic analysis early after pregnancy.

Acknowledgements

The present study was supported by the Six peak talent pro2016, China (grant no. 2016-WSN-090), National Natural Scientific fund of China (81871195) and Health research project of maternal and child health of Jiangsu Province Hospital (F201745).

Disclosure of conflict of interest

None.

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