International Journal of Contemporary Pediatrics
Abhinay A et al. Int J Contemp Pediatr. 2024 Jun;11(6):858-861
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20241380

Case Report

Multiple gene mutations in cytomegalovirus positive infantile nephrotic syndrome: a case report

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Received: 03 April 2024
Revised: 04 May 2024
Accepted: 09 May 2024

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ABSTRACT

The term "infantile" is used for those cases of nephrotic syndrome (NS) that manifest from 3 months to 1 year of age. These are rare diseases attributable to both genetic and certain congenital infections. The prognosis depends on the type of mutation and whether remission occurs with specific therapy in the latter. However, multiple other gene mutations may be found associated with these that hold individual significance. Here, we report a case of an 11-month-old child with infantile NS having novel gene mutations NPHS 2 gene and the gut-associated lymphoid tissues (GALT) on Exon 4 and Exon 5 gene respectively. The presence of hepatomegaly and poor nutritional status instigated us to investigate congenital infections. Positive IgM and IgG values of cytomegalovirus (CMV) in the TORCH profile and a positive urinary polymerase chain reaction confirmed CMV infection, though we were unable to establish whether it was congenital or acquired postnatally. The child was managed with injectable gancyclovir along with supportive therapy which showed partial remission after a period of 10 days and discharge on angiotensin converting enzyme (ACE) inhibitor and diuretic. The coexistence of the multiple gene mutations might have caused the severity of the phenotype. Also, identification and treatment at earlier notice might have an impact on the outcome of the disease. The authors emphasize the importance of performing a genetic test in cases of infantile NS and also working up for acquired causes on an individualized basis.

Keywords: Congenital nephrotic syndrome, Cytomegalovirus infection, Finnish type, ganciclovir, NPHS 1

INTRODUCTION

Infantile nephrotic syndrome manifests from 3 months to 1 year of age. Infantile NS is mainly due to mutations in genes that code for the framework proteins forming the glomerular filtration barrier, i.e., NPHS 1, NPHS 2, NPHS 3, WT1, and LAMB2. Some of them occur secondary to acquired causes that disrupt the podocytes, such as infections with congenital syphilis, congenital toxoplasmosis, or cytomegalovirus (CMV) infection. However, the exact pathophysiology behind CMV-associated glomerulopathies is still not clear.[1] Very few cases of CMV IgM-positive congenital NS have been reported from India in a literature search. The presence of other gene mutations in association with infantile NS is, however, very rare, and very few to negligible studies have shown such significance.[2] Infantile NS type 2 occurs due to a "podocin" gene mutation associated with NPHS2 gene deletion. In this report, we describe an infant with infantile NS due to a novel mutation that was complicated by a co-existing CMV infection as well as other gene mutations. We share the challenges that we faced in establishing diagnosis and management.

CASE REPORT

An 11-month-old boy presented with generalised body swelling for 7 days and fever, loose stools, and decreased urine output for 2 days. The baby is a product of a non-consanguineous marriage. Antenatal ultrasonogram identified oligohydramnios however no renal or other organ anomalies were present with no significant past

history. There was no history of similar complaints or infantile deaths in the family. The development of the patient is appropriate for the age, and the child is immunised until age as per the national immunisation schedule.

On examination, the child was irritable, had a heart rate of 112/min, a respiratory rate of 20/min, and a saturation of 97%. The blood pressure was 82/46 mmHg (50th-90th centile), all peripheral pulses were palpable, bilaterally symmetrical, and the patient had a temperature of 102.1°F. and having mild pallor, periorbital, and facial oedema with no clubbing, cyanosis, and significant lymphadenopathy. The weight was 9.7 kg (weight for age -1 to -2 SD), length was 80 cm (length for age -1 to -2 SD, weight for length median to -1 SD), and head circumference was 51 cm (-2 SD), indicative of poor head growth. The abdomen was grossly distended with an enlarged liver (3 cm below the right costal margin) but with no palpable spleen. Chest, cardiovascular, and nervous system examination within normal limits.

This baby was admitted to the renal care unit. The routine investigation showed haemoglobin levels of 9.74 g/dl, lymphocytic leukocytosis, and a peripheral smear with microcytic hypochromic anaemia and anisocytosis with no evidence of any schistocytes serum albumin was 1.9 g/dl. Spot urinary protein/creatinine (UPCR) 7.8 gm/gm along with 4+, proteinuria by urinary dipstick, indicative of high proteinuria. Cholesterol level (319 mg/dl), serum sodium (141 mmol/l), potassium (3.8 mmol/l), blood urea (18 mg/dl), and serum creatinine (0.36 mg/dl) were normal. Liver enzymes and serum bilirubin were within normal limits. Keeping the clinical picture in mind and the investigations in mind, a provisional diagnosis of infantile nephrotic syndrome was made. The child was given supportive treatment with 20% albumin infusions with furosemide. Ultrasonography of the abdomen showed normal-sized, hyperechoic kidneys with loss of corticomedullary differentiation, mild ascites, and confirmed hepatomegaly. A congenital infection was suspected because of the hepatomegaly. Thus, we performed serological tests for *Toxoplasmosis*, *Rubella*, CMV, and herpes virus infections, which showed CMV IgM positivity. The urine sample of the child was processed using polymerase chain reaction (PCR). A positive cytomegalovirus (CMV) test result in urine samples was later obtained. Ophthalmological examination revealed no evidence of chorioretinitis. Echocardiograms were normal. Later, magnetic resonance imaging of the brain was done in follow up which demonstrated ventriculomegaly as shown in Figure 1. Brainstem-evoked response audiometry and fundoscopy were planned in further follow-ups. Clinical exome sequencing was sent, which suggested multiple gene mutations, including NPHS2(-) (c.522dup), GALT (+) (c.442C>T), and ADAMTS13 (+) (c.3839G>A). The classification of the variants is done based on American College of Medical Genetics suggested autosomal recessive disorder caused by bi-allelic (homozygous or compound heterozygous) pathogenic/likely pathogenic variants in the GALT and ADAMTS13 gene along with the NPHS2 variation is classified as a pathogenic variant.

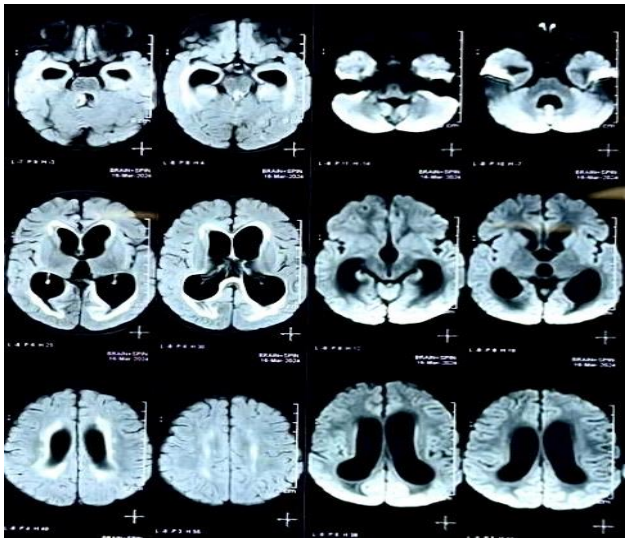

Figure 1: Magnetic resonance imaging of the brain shows bilaterally dilated ventricles.

A clinical diagnosis of infantile NS was made, probably due to a CMV infection with multiple gene mutations. Renal biopsy was deferred as infantile onset nephrotic syndrome is no longer an indication for biopsy. The child was treated with intravenous ganciclovir (12 mg/kg/day) for 2 weeks, and the proteinuria improved. At the end of the intravenous antiviral therapy, serum albumin (2.2 g/dl), UPCR (1.4 gm/gm) and edema improved and the baby attained a state of partial remission. after which oral valganciclovir (32 mg/kg/day) was given for 6 months. Complete blood count (CBC) for neutropenia and liver function test (LFT) were monitored every week.

The parents were provided with a prenatal diagnosis and counseled regarding the risk of recurrence in future pregnancies. The child was discharged on oral valganciclovir, angiotensin-converting enzyme inhibitor, and oral calcium and was asked to come in to follow up with regular monitoring of complete blood count, liver function test along with a nephrotic diary.

DISCUSSION

This patient exhibited features of infantile NS due to a homozygous NPHS-2 pathogenic variant, complicated by a CMV infection and other gene mutations, including GALT and ADAMTS13. The baby had microcephaly and hepatomegaly, which were strongly in favor of CMV infection. CMV infection is the most common congenital infection reported in low- and middle-income countries, with prevalence rates of 1–6%.[3] The presence of other genetic mutations may have complicated the present scenario.

Prompt and early detection of CMV infection in an NS led to the initiation of gancyclovir, which showed improvement in the patient's condition. However, the effects of other gene mutations in this child in the future are still a long path to trace and monitor. A thorough literature search of the cases of CMV-associated congenital or infantile NS that we identified in PubMed and Google Scholar is depicted in Table 1.

Table 1: Clinical and genetic profile of young infants with cytomegalovirus infection.

Author, year	Age/gender	Mutations	Presenting features	Management
Qiu et al, 2016[4]	34 days/F	LAMB2, NPHP1	Mild ascites and edema in the face, legs, and periorbital area	Genetic counselling and prenatal diagnosis
Lotfi et al, 2018[5]	3 days/F	NPHS1	Seizures, intraventricular hemorrhage, intracerebral hemorrhage, and edema	Oral albumin, vitamin D, levothyroxine, captopril, levothyroxine, and levetiracetam
Li et al, 2019[6]	6 days/F	NPHS1 c.3286+5G> A	Hypertelorism, palpebral edema, broad nose bridge, upturned nose, dysmorphic auricle, long philtrum, and a thin upper lip	Steroid induction, genetic counselling, and prenatal diagnosis
Alwabariet al, 2020[7]	2 months/M	-	Generalized body edema, difficulty in breathing, fever, and decreased feeding and activity	Levothyroxine, ARB, regular albumin transfusions
Han et al, 2021[8]	1 month 20 days/F	NPHS1	Abdominal distension and palpebral edema	Glucocorticoid therapy (methylprednisolone, 1.6 mg/kg, once daily). Intermittent albumin and furosemide injections

It is important to perform genetic testing to establish a diagnosis, provide genetic counselling, and be able to offer prenatal diagnosis in subsequent pregnancies. Also, it affects the prognosis in these cases and leads us to a better understanding of the possible outcomes.

Multiple studies have been conducted documenting various gene mutations associated with congenital and infantile nephrotic syndrome. Most of them had a similar clinical picture of generalised swelling and periorbital edema.

However, not much in the literature is present about the involvement of multiple gene mutations in a single child of NS. however certain studies like Qiu and Zhou et al document the involvement of both LAMB2 and NPHP1 in a single child with nephrotic syndrome.[4] The involvement of multiple genes does play a huge role in determining prognosis and outcome.

CONCLUSION

The coexistence of the multiple gene variations might have caused the severity of the phenotype. Also, identification and treatment at earlier notice might have an impact on the outcome of the disease. The authors emphasize the importance of performing a genetic test in cases of infantile NS and also working up for acquired causes on an individualized basis. Although genetic causes are the most common etiology of congenital NS, if there is the slightest suspicion of an acquired cause, it should be thoroughly investigated as the remission of symptoms has been reported in some cases with specific therapy.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Abhinay A, Swetketu, Kumar D, Prasad R, Singh A, Kumar N. Multiple gene mutations in cytomegalovirus positive infantile nephrotic syndrome: a case report. Int J Contemp Pediatr 2024;11:858-61.