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Case Report

Recurrent hypomagnesemia: an uncommon presentation in congenital nephrotic syndrome caused by NPHS-1 mutation

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ABSTRACT

Congenital nephrotic syndrome (CNS) is a rare inherited disorder arising from defects in the proteins of the cells in the glomerular basement membrane and develops either in utero or at birth. The clinical presentation is the result of massive proteinuria. Here we report an interesting clinical case of boy, with history of multiple admissions with involuntary movements found to have recurrent hypocalcaemia and hypomagnesaemia during each admission. Genetic evaluation (clinical exome sequencing) revealed homozygous deletion at exon 23-25 of NPHS1 (NM_004646.4) gene CNS (Finnish type). Child did not have anasarca. CNS presenting as recurrent hypomagnesaemia with absence of anasarca is very rare occurrence in literature.

Keywords: Congenital nephrotic syndrome, NPHS1 gene, Hypocalcaemia, Hypomagnesaemia

INTRODUCTION

Congenital nephrotic syndrome (CNS), term first coined by Gautier and Miville in 1942, is characterized by triad of nephrotic range proteinuria (>200 mg/mmol creatinine), hypoalbuminaemia and edema, which especially occurs in the first three months of life.[1] It is Inherited in autosomal recessive mode with approximate incidence of 1–3 per 100,000 live births.

CNS is caused by inherited defects in one of the three components of the glomerular basement barrier which consists of fenestrated endothelium, glomerular basement membrane and podocytes.[2-4] NPHS1 gene mutations account for almost all cases of CNS of the Finnish variety. The NPHS1 gene plays a vital role in giving direction to produce a protein called “nephrin”. Nephrin protein is located at the cell surface in the area between two podocytes which is known as slit diaphragm. Approximately more than 200 mutations in the NPHS1 gene have been found to cause CNS till date. CNS is a kidney disorder which begins in early months of infancy and leads to growth failure and end-stage renal disease by early childhood.

CASE REPORT

A 1 month old exclusively breast fed boy, born of 3rd degree consanguineous marriage, came with generalized tonic clonic convulsions. His weight was 3.7 kg with length of 52 cm. He was found to have low serum total calcium 5.3mg/dl (normal range 8.5-10.2 mg/dl)/ionic calcium 0.75 mmol/l (1.15-1.33 mmol/l) with low vitamin D 13.8 ng/ml (normal range 20-100 ng/ml), for which he was treated with intravenous calcium gluconate for 72 hours and active vitamin D.

Even after of treatment for 4 days there was not much improvement in ionic calcium levels hence serum Mg sent which was found to be on the lower side 1.3 mg/dl (normal range-1.5-2.3 mg/dl) hence was treated with IV magnesium sulphate with dose of 25 mg/kg TID. Child was discharged after 2 weeks with normalization of calcium and magnesium levels. He was discharged with oral calcium carbonate (100 mg/kg/day) along with vitamin D drops (800 IU/day).

Child got readmitted for similar complaints of convulsion after 2 weeks and again found to have hypocalcaemia (6.1 mg/dl) normal 8.5-10.2 mg/dl and hypomagnesaemia 1.0 mg/dl (normal 1.5-2.3 mg/dl). Child was again started with IV calcium gluconate and magnesium sulphate. Child was investigated for recurrent hypocalcaemia. His parathyroid hormone (PTH) levels were high, serum PTH- 221 pg/ml (normal range-15-65 pg/ml) indicative of secondary hyperparathyroidism secondary to low levels of vitamin D.

2D echo was done to rule out Di-George syndrome, which came out to be normal, urine calcium: creatinine ratio was 0.02 (normal range <0.14) found to be normal. Child got readmitted with fever and excessive crying. He found to have urinary tract infection (UTI) with urine culture showing *Enterococcus* species. He had another episode in a span of 2-3 weeks of UTI with *E. coli* and was treated with sensitive antibiotics during each admission. During these admissions with UTI child continued to have hypocalcaemia and hypomagnesaemia despite oral treatment. Child ultrasonography kidney, ureter and bladder (USG KUB) was normal without any evidence of renal parenchymal disease.

He had similar episodes of hypocalcaemia and hypomagnesaemia after 1 month (Table 1). In view of multiple and recurrent episodes of hypocalcaemia and hypomagnesaemia, genetic evaluation was sent to rule out genetic variety of hypomagnesemia.

However whole clinical exome sequencing revealed homozygous deletion at exon 23-25 of NPHS1 (NM_004646.4) gene suggestive of autosomal recessive Finnish type of CNS (Figure 1).

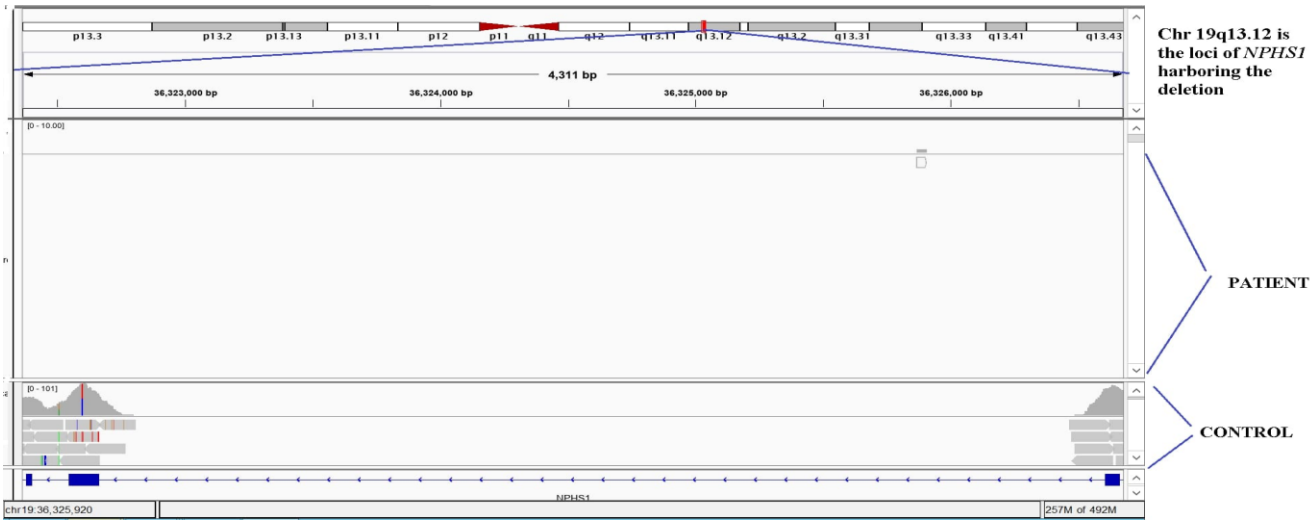

Figure 1: Depicting large deletion in patient at loci of NPHS gene Chr 19q13.12 as compared to normal pattern in control.

Table 1: Investigation profile of a child during each admission.

Date	1st admission	2nd admission	3rd admission	4th admission
Sr. calcium (8.5-10.2 mg/dl)	5.3	6.1	6.7	7.2
Sr. phosphorus (4.3-9.3 mg/dl)	8	6.8	7.4	5.9
Alk. phosphatase (122-469 U/l)	562	627	349	350
Sr. Ionic Ca (1.15-1.33 mmol/l)	0.75	0.8	0.87	0.57
Creatinine (0.3-0.7 mg/dl)	0.34	0.2	0.4	0.3
Vitamin D (20-100 ng/ml)	13.85	17.5	28	36
Sr. PTH (15-65 pg/ml)	28.9	221	48	52
Sr. magnesium (1.5-2.3 mg/dl)	1.3	1.0	0.9	1.1
CRP (2-5 mg/l)	1.3			
Sr. albumin (3.4-5.4 gm/dl)				1.3
Urine calcium creatinine ratio (<0.14)		0.02		
24 hour urine Mg (<1.17)		0.04		
Urine albumin creatinine ratio (<30)				50

The hypocalcaemia and hypomagnesaemia in this case was secondary to urinary loss of these metabolites .This was unique case of CNS since child did not have nephrotic range proteinuria (urine proteins 2+). Child did have haypoalbuminemia. Serum albumin 1.3 (nomal 3.4-5.4 gm/dl) but interestingly there was no anasarca or localized edema pointing towards CNS. In this patient anasarca was not there so diuretics were not used. Child received 20% albumin infusions, additional protein supplementation along with vitamin supplements and oral calcium and magnesium. He was also started on enalapril 0.5 mg/kg/day and indomethacin 3 mg/kg/day for their antiproteinuric action. Child is under regular follow up with nephrology unit and doing well.

DISCUSSION

CNS is a rare autosomal recessive disorder caused by different genetic mutations. In CNS Infections with gram negative encapsulated bacteria is a major cause of concern and the primary cause of mortality. Predominant cause for infections with encapsulated bacteria such as *Pneumococci* and *Enterococci* is because of urinary losses of immunoglobulin G, complement and opsonins. However as per current recommendations prophylactic antibiotics should not be prescribed routinely in these children.[5] CNS is a difficult condition to treat and generally children are resistant to steroids and immunosuppressive drugs. Standard treatment consists of renin–angiotensin system inhibitors, albumin infusion, gamma globulin replacement, high-protein, low-salt diet, vitamin D and thyroxine substitution, and prevention of secondary bacterial infections and thrombotic complications. The frequency of recurrent complications remains high with most of them having retarded physical growth and development. CNS is rapidly progressive condition, which often leads to end-stage renal disease or even death during early childhood.[6] Our child had recurrent hypocalcaemia and hypomagnesaemia even after treating with injectable calcium gluconate and magnesium sulphate. Genetic evaluation was done to find out the exact cause of this metabolite derangement which was suggestive of CNS. Currently as per most recent recommendations by European reference network for kidney diseases (ERKNet) and the European society for paediatric nephrology (ESPN) 2021, genetic screening should be performed in all cases with CNS along with genetic counselling of their families and unless for sporadic and non-syndromic CNS disease routine kidney biopsy is not recommended.[7]

Though proven CNS, cause for hypomagnesaemia still largely unknown. From exome sequencing we have ruled out Gitelman syndrome. In nephrotic syndrome hypocalcaemia is generally caused due to decreased albumin levels, which results in reduced bound and ionized calcium in 50 to 80% of CNS cases.[8] Hypocalciuria seen in CNS is attributed to decreased gastrointestinal absorption and increased renal tubular reabsorption of calcium. Vitamin D abnormalities seen in CNS are due to increased filtration of vitamin D metabolites bound to vitamin D-binding globulin.[9] Decreased ionic calcium and high levels of serum PTH warrants vitamin D and calcium supplementation in these children and it usually corrects vitamin D deficiency in CNS.[10,11]

Though previously there are few reports in with normal serum calcium levels in NS patients.[12] The final out-come of CNS varies from end-stage renal disease or even death. Appropriate treatment to control proteinuria and hypervolemia for CNS is essential to maintain the normal integrity of the glomerular barrier. At times aggressive and more radical treatment option like nephrectomy is required for life saving purpose.

CONCLUSION

CNS may present rarely as a recurrent hypocalcaemia with hypomagnesaemia. Genetic testing immensely helps to identify cause of CNS, establishes etiology, informs about management and particularly with regard to future potential development of Wilm's tumour and it also enables genetic counselling of the family.

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