Case Report

Familial hypomagnesemia with hypercalciuria with nephrocalcinosis: a rare case report

Amaresh Roy*, Sumanta Laha, Susama Saren

Paediatric Medicine, Burdwan Medical College and Hospital, Burdwan, West Bengal, India

Received: 19 December 2021

Revised: 11 January 2022

Accepted: 17 January 2022

*Correspondence:

Amaresh Roy,

E-mail: ashesroy481@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

A 4 years old girl child was presented with generalised body ache with carpopedal spasm and episodes of fever since last 5-6 days with intermittent abdominal pain since last 3 months and progressive deformity of both upper and lower limbs over months and poor growth. Examination showed short stature with bowing of both legs and arms with widening of wrist. USG revealed bilateral medullary nephrocalcinosis, serum parathyroid and 25-VitD and calcium were very low and urine calcium excretion and serum creatinine were high with urine culture was positive for *E. coli*. She was finally diagnosed as a case of familial hypomagnesemia with hypercalciuria with nephrocalcinosis.

Keywords: Carpopedal spasm, Short stature, Serum parathyroid, Medullary nephrocalcinosis

INTRODUCTION

Familial hypomagnesemia with hypercalciuria with nephrocalcinosis (FHHNC, Michellis-Castrillo syndrome) is a rare autosomal recessive renal tubular disorder characterised by excessive urinary losses of magnesium and calcium, bilateral medullary nephrocalcinosis and progressive chronic renal failure with prevalence <1/1000000.¹ Using a positional cloning method, Simon et al analysed 12 families with FHHNC and identified a gene, PCLN1 (now described as CLDN16), associated with the disorder.² A few year later, Konrad et al studied a group of FHHNC patients, also suffered with severe ocular defects and lacking mutation in CLDN 16 and identified a second gene, CLDN19.³ During the last decade there have been significant advances in the pathophysiology of FHHNC. We reported this case of FHHNC from Burdwan, West Bengal in a 4 years old girl who presented with symptomatic hypocalcemic episode and bilateral medullary nephrocalcinosis, for its distinct rachitic

changes and poor linear growth with normal serum magnesium.

CASE REPORT

A 4 years old girl child from Purba Burdwan born at term as the 2nd child of their parents with 2nd degree consanguineous marriage presented with painful spasm of the hands and fingers since last 2 days with complains of fever and generalised body ache since last 5-6 days. The child was having intermittent episodes of fever with abdominal pain and vomiting lasting for a few days subsiding with antibiotics and antipyretics prescribed by local physician since last 3 months. Parents noticed bowing of the shin bones and forearms of the child over last 7-8 months (as shown in the Figure 1 and 2). According to the mother the child was exclusively breastfeed till the age of 1 year followed initiation of supplementary diet and feeding of cow milk. Immunisation was till date and all developmental goals were achieved as per peer group. Siblings (1 elder sister and younger brother) were apparently well. On

examination the child had short stature (height 88 cm, less than 3rd percentile for age) normal weight for age with increased US and LS ratio, Chvostek sign was positive, skin, nail and eyes were normal, mild pallor was present, all deciduous teeth erupted and some caries tooth was there, chest circumference was more than head circumference and no chest wall deformity was present, respiratory rate was 28 /min, heart rate was 96 bpm and temp was 36.8 degree Celcius, abdomen was soft, no hepatosplenomegaly was present and other systemic examinations were within normal limit.

Figure 1: Widening of the wrist joints of upper limbs.

Figure 2: Bowing of both the legs and arm.

Figure 3: Radiological changes of upper limbs in the child showing cupping with widening of metaphysis with relative osteopenia and bowing of both the humerus and radius.

Initial laboratory work up showed serum calcium 5.8 mg/dl, RA factor was negative, anti CCP Ab was negative, serum parathyroid was 8 Pg/ml, total protein 7.5 gm/dl (serum albumin 3.9gm/dl), 25 OH vitamin D was 15 ng/ml, alkaline phosphatase 330 IU/Lt, early morning serum cortisol 7.23 microgram/dl, serum Mg^{+2} was 1.65 meq/l, serum phosphate 6.31 mg/dl, 24 hours urine calcium excretion was 326.4 mg/24 hours (25 mg/kg/day), 24 hours urine phosphate 88.4 mg/24 hours, urine RE revealed plenty of pus cells with 1 (+) proteinuria with 5-8 RBC/hpf, urine culture revealed *E. coli* growth, Hb 16.5 gm/dl, TLC 25,000 /mm³ (neutrophil 74 percent), platelet 1,88,000 /mm³, arterial blood gas was normal, urea 22 mg/dl, creatinine 0.7 mg/dl (eGFR using modified Schwartz formula 69.14 ml/1.73 m²/min). USG revealed B/L medullary nephrocalcinosis as shown in the Figure 5 with normal renal cortico medullary differentiation and sizes of the kidneys (right kidney-7.12 cm, left kidney-7.82 cm), USGs of the parents were normal, X-ray of the wrist joints, knee joints, elbow joints were done showing cupping with widening of metaphysis with relative osteopenia, bowing of both femur and tibia, humerus, radius (as shown in the Figures 3-4). NCCT brain was normal. Eye evaluation was normal. Clinical exome sequencing done to confirm the diagnosis (next generation sequence of clinically relevant exome gene panel))-CLDN16 mutated gene (homozygous). Variants: exonic, rs:NA, Phe125Ser, Chromosome 3.

The child was treated with IV calcium following admission followed by oral calcitriol, calcium, thiazide and weekly oral vitamin D (60,000IU) supplementation for 6 weeks. IV antibiotics were given for 7 days for UTI

and subsequent culture revealed no growth. The child was followed after 2 weeks with clinical improvements of the presenting symptoms and serum calcium.

Figure 4 (a and b): Bowing of both the femur and tibia with osteopenia and widening of metaphysis.

Figure 5: USG showing bilateral medullary nephrocalcinosis with normal sized of both the kidneys.

DISCUSSION

Presentation with FHHNC occurs early in the childhood or before adolescent. This rare disease is caused by mutations in CLDN16, chromosome 3q or CLDN19 genes, chromosome 1p34.2.^{4,10} These genes encode tight junction proteins claudin-16 (paracellin-1) and claudin-19 in the thick ascending limb of Henle's loop and forms an essential complex for the paracellular reabsorption of magnesium and calcium.^{5,6} FHHNC with ophthalmologic disease indicates potential claudin-19 mutation.⁷ A recent finding had established that another member of Claudin family, Claudin 14, played a key regulatory role in paracellular cation reabsorption by inhibiting Claudin 16-Claudin 19 complex. To date, >50 CLDN16 pathogenic mutations have been reported including mainly missense mutations, splice site mutations and small deletions and these mutations were found in either a homozygous or compound heterozygous state and were spread over the five exons of the CLDN16 gene.² Although no comprehensive studies have addressed the actual incidence of hypomagnesemia stratified by age group, neonates may be more predisposed to develop this condition. Blood levels of magnesium may be variable, even between affected siblings and fractional excretion of magnesium helps demonstrate tubular wasting as in our case.⁸ Hypomagnesemia may disappear with the deterioration of the glomerular filtration rate (GFR) due to decline in the filtered magnesium.⁹ Progression to ESRD was frequent (50% of patients at 20 years). No treatment seemed to have a significant effect on the levels on serum calcium, magnesium, urinary calcium or regression of renal function.¹⁰ However the condition does not recur after renal transplant.

CONCLUSION

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis is a rare form of tubulopathy in paediatric age group causing medullary nephrocalcinosis with progression to ESRD which may present with rachitic changes and often remain underdiagnosed and must be investigated as one of the important causes even with normal serum magnesium level.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

REFERENCES

1. Available at: https://www.orpha.net/consor/cgi-bin/OC_EXP.php?Ing=en&Expert=306516
2. Simon DB, Lu Y, Choate KA, Velazquez H, Al-Sabban E, Praga M, et al. Paracellin-1, a renal tight Junction protein required for paracellular Mg²⁺ resorption. *Science*. 1999;285(5424):103-6.
3. Konrad M, Schaller A, Seelow D, Pandey AV, Waldegger S, Lesslauer A, et al. Mutation in the tight junction gene claudin 19 (CLDN19) are associated with renal magnesium wasting, renal failure, severe ocular involvement. *Am J Hum Genet*. 2006;79(5):949-57.
4. Al-Haggar M, Bakr A, Tajima T, Fujieda K, Hammad A, Soliman O, et al. Familial hypomagnesemia with hypercalciuria and nephrocalcinosis: unusual clinical associations and novel claudin16 mutation in an Egyptian family. *Clin Exp Nephrol*. 2009;13(4):288-94.
5. Kausalya PJ, Amasheh S, Günzel D, Wurps H, Müller D, Fromm M, et al. Disease-associated mutations affect intracellular traffic and paracellular Mg²⁺ transport function of Claudin-16. *J Clin Invest*. 2006;116(4):878-91.
6. Blanchard A, Jeunemaitre X, Coudol P, Dechaux M, Froissart M, May A, et al. Paracellin-1 is critical for magnesium and calcium reabsorption in the human thick ascending limb of Henle. *Kidney Int*. 2001;59(6):2206-15.
7. Ekinci Z, Karabas L, Konrad M. Hypomagnesemia-hypercalciuria-nephrocalcinosis and ocular findings: a new claudin-19 mutation. *Turk J Pediatr*. 2012;54(2):168-70.
8. Mathew G, Khandelwal P, Thergaonkar R, Sinha A, Hari P, Bagga A. Novel pathogenic variant causing familial hypomagnesemia with hypercalciuria and nephrocalcinosis. *Asian J Paediatr Nephrol*. 2020;3:31-3.
9. Praga M, Vara J, Gonzalez-Parra E, Alamo C, Araque A, Ortiz A, et al. Familial hypomagnesemia with hypercalciuria and nephrocalcinosis. *Kidney Int*. 1995;47(5):1419-25.
10. Claverie-Martin F. Familial hypomagnesemia with hypercalciuria and nephrocalcinosis: clinical and molecular characteristics. *Clin Kidney J*. 2015;8(6):656-64.

Cite this article as: Roy A, Laha S, Saren S. Familial hypomagnesemia with hypercalciuria with nephrocalcinosis: a rare case report. *Int J Res Med Sci* 2022;10:533-6.