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Case Report

A Report of Claudin-19 Mutation Causing Nephrocalcinosis and End-Stage Kidney Disease from Iran

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Abstract

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is an autosomal recessive disorder that affect children and young adults. Mutation in gene that coding the tight junction proteins Claudin-16 and Claudin-19(CLDN19) is responsible of this rare disorder. Hypomagnesemia, hypercalciuria, kidney failure and visual impairment (in CLDN 19 gene mutation) are the most common presentations of FHHNC. Here we present a 31-year-old woman with end-stage kidney disease (ESKD) on routine hemodialysis for the past eight years and was referred to Firoozgar nephrology clinic for kidney transplantation. Her past medical history included recurrent kidney stones. Although FHHNC is a rare disease, genetic evaluation recommended in patients with ESKD and concomitant nephrocalcinosis.

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Key words: kidney stone; end stage kidney disease; hypomagnesemia; claudin-19; nephrocalcinosis

Introduction

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is an autosomal recessive condition that affect children and young adults. It is characterized by the excessive loss of magnesium and calcium through the kidneys, nephrocalcinosis, and kidney failure.1,2 Nephrolithiasis and recurrent urinary tract infections, are the most presentation of FHHNC.3,4,5 Approximately half of these patients need renal replacement therapy during their second or third decade of life.6 Extra-renal involvements of this syndrome include seizure, muscular spasms and eye involvement such as macular coloboma, nystagmus, retinopathy, and visual loss .5 Mutation in gene that codes the tight junction Claudin-16 and Claudin-19 (CLDN19) proteins is responsible of this rare disorder.1,7 To the best of our knowledge we report the first report of the Claudin -19 mutation with end-stage kidney disease (ESKD) and recurrent kidney stones in Iran.

Case Report

A 31-year-old woman with ESKD was referred to Firoozgar nephrology clinic for a kidney transplant workup. She was on Hemodialysis for the past eight years and had a history of recurrent kidney stones that required surgical intervention and extracorporeal shock wave lithotripsy. The patient 's brother had recurrent kidney stones and never followed kidney evaluation.

There was no history of bone fractures, or visual or hearing loss. On physical examination, she had short stature, pigmented skin, and nystagmus with no skeletal deformity. Demographic data consisted of the height of 147 Cm, weight of 44 kg, body mass index of 20.4 kg/m2, and blood pressure of 130/75 mm/Hg. Lab tests have shown in Table 1. Ophthalmologic study showed a bilateral macular scar, nystagmus, and cataract. An echocardiogram revealed an ejection fraction of 55%, mild left ventricular diastolic dysfunction, mild to moderate tricuspid regurgitation, and normal pulmonary arterial pressure. Ultrasound study showed bilateral small size kidneys, an eight mm stone in the inferior calyx of the right kidney, and a simple cyst in the superior pole of the left kidney. Whole A Report of Claudin-19 Mutation Causing Nephrocalcinosis—Savaj et al exome sequencing (WES) was performed to rule out of hyperoxaluria. Whole exome sequencing and variant data analysis revealed a homozygote variant defined as c.364G > A (p. Gly122Arg) in exon 2 of CLDN19 gene (NM_148960.3) which compatible with FHNCC. AGXT, GRHPR, HOGA1 genes for hyperoxaluria showed no mutation.

Demographic	Patient
Gender	Female
Age at diagnosis (Yrs)	31
Hemoglobin gr/dl	11.6
White Blood Cell count mm^3	5200
Platelet count mm_3	156000
Serum Albumin gr/dl	4.7
Serum Phosphorus mg/dl	5
Serum Magnesium mg/dl	2.5
Vit D ng/ml	22
Uric Acid mg/dl	6.8
Intact Parathyroid Hormone pg/ml	284
Ph	7.38
HCO_3 meq/L	23
PCO_2 mmHg	43
Urine tests	Anuric

Table 1: Demographic Characteristics and Laboratory Results

Discussion

Most of the filtered Magnesium is reabsorbed by a passive paracellular mechanism in the thick ascending limb of Henle (TAL).8 Claudins are tight junction proteins, in thick ascending loop of Henle (TAL) and distal convoluted tubules (DCT) that regulate the paracellular cation transport.9,10 Impaired functions of either claudin-16 or claudin-19 result in renal magnesium and calcium wasting.11 FHHNC is an autosomal recessive disorder resulting from mutations in the CLDN16 or CLDN19 genes.12 It presents with hypercalciuria, magnesuria, hypomagnesemia and nephrocalcinosis. Additional symptoms include nephrolithiasis, urinary tract infections, polyuria, polydipsia, hypocitraturia, muscle spasms and convulsions.3,6 Patients with cludin19 mutation also have eye involvement as same as severe myopia, nystagmus, and chorioretinitis.5 Our patient had nephrolithiasis, ESKD, mild ocular abnormalities and, a missense mutation with a homozygote variant defined as c.364G > A (p.Gly122Arg) in exon 2 of CLDN19 gene (NM_148960.3). Amar et al, described three children in one family with a homozygous missense mutation in CLDN19 (c.241C > T, p.Arg 81Cys) with severe ocular involvement and retinal changes. 13 Another presentation is a report of a 33-year-old Chinese woman with a history of recurrent acute pyelonephritis who developed ESKD after three years with a homozygous mutation (c.346C > G, p. Leu116Val) in the 115G-L-W117 motif of CLDN 16 gene.12 In one study, 31 patients with four pathogenic mutations (p. G122R, p.I41T, p.G75C, and p.G75S) of the CLDN19 gene were presented. They had the age range of 6.8-48, and ocular manifestation, such as nystagmus, myopia, and macular coloboma were observed in 87% of the patients.14 Malakoutian et al. reported a pathogenic variant of a missense mutation (c.338G > A: p.C113Y) in exon 2 of the CLDN-16 gene in a 35 years-old-man with ESKD on routine hemodialysis and his two siblings. 15 To the best of our knowledge, our patient is the first reported case of the CLDN19 gene mutation in Iran. We should consider FHNCC as a possible differential diagnosis of recurrent nephrolithiasis with hypomagnesemia in patients with nephrocalcinosis.

Statement of Ethics

The study was approved by Iran University of Medical Sciences ethics committee IR.IUMS.FMD. REC. 1402.329. The patient's written informed consent was secured including the permission to publish anonymously.

Conflict of Interest

The authors declare no conflict of interest.

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