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Hypomagnesemia Revealing A Rare Familial Hereditary Tubulopathy: A Case Study Of A Family

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Abstract:
Introduction: *Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is a rare autosomal recessive tubular disease that eventually progresses to renal failure, depending on the extent of nephrocalcinosis. Its fundamental pathogenesis involves impaired tubular reabsorption of magnesium and calcium in the thick ascending limb of the loop of Henle due to a genetic defect of paracellin-1 (a tight junction protein expressed at the thick ascending limb). Mutations in the claudin-16 (CLDN16) gene, formerly known as the paracellin-1 (PCLN-1) gene, have been linked to FHHNC.*
Methods: *An extended Algerian family with more than one member affected by nephrocalcinosis was included and studied in this report after obtaining informed consent. Detailed medical history was obtained, and a clinical examination focusing on anthropometric measurements and radiological evaluation of the kidneys and bones was performed. Laboratory investigations for the differential diagnosis of nephrocalcinosis included complete urine analysis, urinary calcium excretion, pH, and electrolytes, arterial blood gas analysis, serum electrolytes (sodium, potassium, calcium, magnesium, and phosphorus), renal function, parathyroid hormone levels, and genetic testing in a single proband.*
Results: *Two brothers from a consanguineous marriage were affected by nephrocalcinosis, presenting with persistent hypomagnesemia, hypercalciuria, nephrocalcinosis with persistent alkaline urine, and ocular manifestations such as strabismus. The elder brother had stage 3a chronic kidney disease (CKD), whereas the younger brother had normal renal function. Homozygous variation in intron 2 of the CLDN16 gene (c.427 + 5G > A) responsible for an exon skipping was found in the younger brother.*
Conclusion: *Clinical data in the two affected brothers associated with nephrocalcinosis and myopia suggest a diagnosis of FHHNC, which was confirmed for the first time in an Algerian family by a novel mutation in intron 2 of the CLDN16 gene.*
Keywords: *hypomagnesemia with hypercalciuria and nephrocalcinosis, Paracellin-1, CLDN16.*

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I. Introduction

Renal hypomagnesemia with hypercalciuria and nephrocalcinosis is a renal disease that progresses to renal failure between the second and fourth decades of life. It is caused by a defect in the reabsorption of magnesium and calcium in the thick ascending limb of the loop of Henle. Clinical manifestations include urinary tract infections, manifestations associated with hypercalciuria, and polyuria. From a biological standpoint, hypomagnesemia, hypercalciuria, and nephrocalcinosis are consistent findings. Hyperparathyroidism is also observed, which is not correlated with the degree of renal insufficiency. This condition is transmitted in an autosomal recessive manner and is caused by mutations in the CLDN16 gene located on 3q28-3q29 and the CLDN19 gene located on 1p34.2 (MIM#248250 and MIM#248190). These genes encode for claudin-16 (initially known as paracellin-1) and claudin-19 proteins. These proteins are located in tight junctions and regulate the paracellular reabsorption of cations. Claudin-19 is also expressed in the retina, and severe and constant ocular anomalies are associated with it (strabismus, nystagmus, myopia, and chorioretinitis). Although the expression of claudin-16 in the eye has not been confirmed, less severe ocular anomalies are present in 25% of cases.

Materials and Methods: We report the case of two brothers aged 13 and 22 years from a second-degree consanguineous marriage. During a preoperative assessment for "ascender" testicles in 13-year-old AA, nephrocalcinosis was incidentally discovered, triggering an etiological investigation including renal function tests, urinary electrolytes and pH, complete blood count, serum electrolytes (sodium, potassium, calcium, magnesium, and phosphorus), PTH, Vit D, urine chemistry, and urine culture.

II. Results:

Young B.A., aged 13, had a clinical examination without anomalies. His personal history included a few urinary tract infections in early childhood with strabismus, and family history included episodes of nephrolithiasis in the father and astigmatism and hyperopia in the mother. BA's assessment showed chronic kidney disease CKD1A1, no anemia, normal calcium levels, hypercalciuria, hypomagnesemia, vitamin D deficiency, elevated PTH, alkaline pH, and albumin-to-creatinine ratio (ACR): A1. Urinary system ultrasound revealed decreased kidney size with nephrocalcinosis. The clinical examination did not show any delay in growth or weight, and the rest of the biological and radiological assessment was unremarkable. Given the unusual biology for his age, the parents consulted a specialized center for childhood diseases at Necker Hospital. The diagnosis was confirmed, and due to the major diagnostic criteria of a genetic pathology in the patient: hypomagnesemia, hypercalciuria, and its complications "nephrocalcinosis," genetic analysis was initiated at the specialized MARHEA center at Necker Hospital. The genetic study concluded a homozygous variation in intron 2 of the CLDN16 gene (c.427 + 5G > A), which is highly likely to be responsible for an exon skipping and is likely very pathogenic.

Following this genetic diagnosis, a family investigation was launched with assessments for the parents and the 19-year-old sister, all of whom were unaffected. However, brother B.Z. had chronic kidney disease CKD3aA2 with hypomagnesemia, hypercalciuria, hyperparathyroidism, vitamin D deficiency, and small kidneys with nephrocalcinosis on renal ultrasound, without ocular involvement. Both brothers were placed on conventional treatment for hypomagnesemia with hypercalciuria and nephrocalcinosis.

After 5 years of follow-up, patient B.A., now 18 years old, remains stable with a CKD1A1 glomerular filtration rate (GFR), whereas brother B.Z., aged 27, has deteriorated renal function from CKD3aA1 to CKD4.

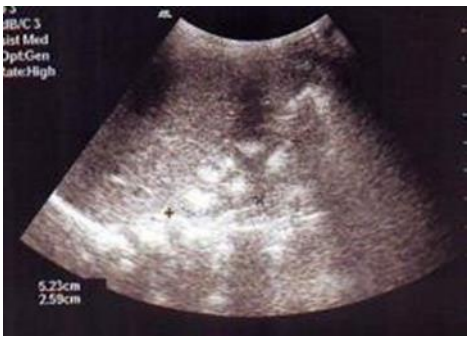

Figure 1: Nephrocalcinosis on renal ultrasound

III. Discussion

Familial primary hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is a rare autosomal recessive renal disorder, first described in 1972[1]; its cardinal features include renal loss of magnesium and calcium associated with the development of nephrocalcinosis and/or kidney stones in early childhood. In any patient with renal calcium leak, there will be secondary hyperparathyroidism, so serum PTH levels are likely to be elevated in FHHNC patients. Typical features of this disorder include polyuria, excessive thirst, tetanic seizures, muscle cramps, and muscle weakness due to magnesium deficiency. Additional manifestations include growth retardation, recurrent urinary tract infections, rickets, kidney stones, abdominal colic, and incomplete distal renal tubular acidosis [2]. Increased urinary calcium excretion, magnesium deficiency, and urinary acidification defects account for the tendency toward nephrocalcinosis and nephrolithiasis in FHHNC [3].

A spectrum of extra-renal associations has been reported with FHHNC; these include ocular manifestations in nearly half of cases and hearing impairment in about 10% [2]. This is not the case in our patients except forsimple myopia.

Parental consanguinity was noted in 6 out of 35 families; none of the parents exhibited a complete clinical picture; however, renal abnormalities such as isolated hypercalciuria or kidney stones were found in 16 out of 23 families [4]. In the present study, the parents did not show clinical or biological signs of renal transport abnormality. Most FHHNC patients progress to ESRD; renal failure often occurs during the 2nd or 3rd decade of life. The severity of nephrocalcinosis is usually correlated with rapid progression to ESRD, but this association has been challenged in some publications[5,6,7,8]. Tubulopathies accompanied by nephrocalcinosis do not invariably progress to renal failure; for example, in distal renal tubular acidosis and Bartter syndrome, GFR is generally not impaired despite severe nephrocalcinosis. Therefore, other unidentified factors appear to be important for the development of renal failure in FHHNC [7]. In our study, patient B.A still has normal renal function, perhaps due to his young age, while B.Z has already progressed to stage 4 CKD at the age of 27. They

were put on conventional treatment with continuous administration of magnesium supplements and thiazides to reduce hypercalciuria; however, serum magnesium remains below normal and renal calcium leak persists. Theoretically, these measures do not impact the ultimate development of renal failure, and kidney transplantation should be the only definitive treatment [1].

To our knowledge, these are the first reported cases of FHHNC in Algerian families diagnosed at the molecular level.

IV. Conclusion

The severity of the FHHNC phenotype depends on the residual function of the mutated claudin-16 protein. Despite the rarity and intriguing nature of FHHNC, it still deserves consideration in any patient presenting with nephrocalcinosis and hypercalciuria even before the development of renal failure, especially in the pediatric age group.

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