

Hyponatremic Seizures—Presenting Symptom of Helix Syndrome.

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Research Article

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Abstract

Genetic causes of renal tubular dyselectrolytemia are primarily associated with urinary sodium loss, with secondary hypokalemic metabolic alkalosis. They may be associated with or without hypercalciuria and hypermagnesuria. HELIX syndrome (OMIM 617671) is one condition associated with hypermagnesemia and hypomagnesuria in contrast to Gitleman syndrome. The diagnosis is made if dyselectrolytemia and hypermagnesemia is accompanied with physical findings of hypohidrosis, lacrimal gland dysfunction, ichthyosis and xerostomia. This is the first case in our limited experience of a genotype of HELIX syndrome presenting as hyponatremic seizures with unreported hypomagnesemia, hypermagnesuria and hypercalciuria due to defect of para-cellular ion transport in the thicker limb of ascending Henle's loop (TAL).

What is new

An adult female, with childhood SSNS, genetically and phenotypically identified as HELIX syndrome presented with unusual features of recurrent seizures associated with hyponatremia, hypomagnesemia, hypermagnesuria and hypercalciuria

Introduction

Genetically mediated renal transport of electrolytes and minerals is attributed to specific transport proteins on the tubular epithelial and basolateral borders. Additionally, considerable amount of electrolytes and minerals pass through para cellular pathway. This permeability is controlled by intercellular adhesion molecules called tight junctions (TJs). The integral part of these TJs are a group of membrane spanning proteins called Claudins. We are presenting a case of HELIX syndrome with a rare abnormal Claudin 10b protein. Hypohydrosis, imbalances of electrolytes, abnormal function of the lacrimal gland, ichthyosis, and xerostomia are features of this uncommon condition which is brought about by biallelic mutation of CLDN 10 gene located on chromosome 13q31-q34(OMIM 617671). This is the first case in our limited experience of a phenotype with salt loosing hypokalemic alkalosis with unreported hypomagnesemia, hypermagnesuria and hypercalciuria due to defective paracellular ion transport in the thicker limb of ascending Henle's loop (TAL)

Background

The Na/K/ATPase pump on the basolateral membrane of the epithelial cells in TAL mediate around 40% of the total Na⁺ absorbed. Three Na⁺ ions are pumped out and two K⁺ ions are pumped in, creating a low Na⁺ intracellular concentration. Because of this, the intracellular environment becomes negatively charged, and an electrochemical gradient is established. Through the luminal Na/K/2Cl cotransporter, the Na⁺ and K⁺ are co-transported from the tubular lumen into the cell. The apically situated ROMK channel returns the intracellular K⁺ back into the lumen. Briefly, it is this recycling of K⁺ back into the lumen that creates, a transepithelial potential difference, which is positive on the luminal side that drives the cation transport via the paracellular route. The cations like Ca⁺⁺, Mg⁺⁺, and Na⁺ from the luminal side of the tubule pass through the TJs and find their way back into the interstitial space and the vascular compartment. Functionally, the TJs serve as a barrier and aid in the selective permeability of water and solute through the paracellular space laterally. The two additional functions they perform are maintaining polarity of the cell and maintaining fence function, which is a mechanism for signal transduction. The Claudins form a major constituent of the of the TJs located on the apical side of the tubular cell membrane. The word Claudin originates from the Latin verb claudere, which means 'to close'. The CLDN10 gene by alternative splicing during gene expression codes for two distinct isoforms of Claudin 10, 10a and 10b. Isoform Claudin10a is limited to the kidney, confines its expression to the proximal tubule and mediates paracellular Cl⁻ reabsorption in the proximal tubule. Isoform10b is expressed in both inner and outer stripes of outer medulla and cortical segment of TAL, salivary glands, skin, sweat glands, brain, lungs and pancreas. In TAL, Claudin 10b mediates about 40 percent of the paracellular Na⁺ passage in addition to pre existing transcellular route. Due to the defective paracellular reabsorption of Na⁺ in TAL there are major kidney function implications. One, the large delivery of Na⁺ with the concomitantly increased K⁺ secretion in the distal nephron. Two, the Na⁺ deficit effectively reduces the arteriolar blood volume and activates RAAS, there by promoting K⁺ deficit and metabolic alkalosis. Third, it reduces the buildup of interstitial osmolality, causing hyposthenuria. Four, Claudin16 and 19 has enhanced paracellular reabsorption of Ca⁺⁺, Mg⁺⁺ and leads to hypermagnesemia and nephrocalcinosis, hypercalciuria¹.

Claudin 10b plays a significant role in glandular physiology like secretion of saliva, sweat and tears². Extrarenally, the mutated Claudin10b is expressed in the epidermis and the eccrine sweat glands. Impaired TJs induce epidermal thickness, ichthyosis, and palmar hyperlinearity.³Claudin 10b is expressed along the basolateral membrane in the acinar cells of the pancreas, salivary and the lacrimal glands, The mutation of Claudin10b causes loss of sodium and water secretion in saliva and tears⁴.Dermatological symptoms include plantar keratoderma, hypohidrosis with heat intolerance and dry skin that primarily affects the arms and knees associated with fine white scaling. Histological analysis shows ichthyosis and more than usual number of sweat glands that are dilated ². Other symptoms are an inability to produce tears or alacrima, xerostomia, a reduction of the watery component of saliva and severe enamel wear in the teeth due to absence of saliva and increased palmar linearity and can also have kidney damage⁵.

Case study

Mrs S aged about 29 years was born of first cousins marriage after an uneventful pregnancy and delivery. An elder male neonate died on the seventh day of life of an unrecognized cause. Her younger two siblings are normal and parents are unaffected.

Her post birth history is interesting. She was born at 6 PM and on the very next day morning she became hot needing oral paracetamol. As an infant and child she was comfortable when in air conditioned room and was dry and hot when outdoors. At the age of 6 years, she complained of poor sweating, sticky feel, inability to tolerate heat and had multiple cold water showers. Her sweating was imperceptible. Tears were one or two drops. Avoided exposure to sun light. Washed face frequently to keep cool. She felt thirsty and drank plenty of water. Played out doors only after sunset. Good scholastic performance. She passed urine 6 to 8 times per day and in large quantity each time. A skin biopsy showed less number of sweat glands and was advised symptomatic management.

At 7 years she was diagnosed as steroid responsive nephrotic syndrome and went into complete remission at 13 years of age. She received multiple doses of prednisolone, nineteen months of T levamisole and two courses of 8 weeks each of T cyclophosphamide with short intermittent periods of T lisinopril. While on T lisinopril her serum K⁺ was 3.8 mEq/L and 4 mEq /L on two occasions. Serum Na⁺ level was not done during this period.

On 26 Sept 2017 at the age of 23 years she developed unprovoked seizures. Her biochemistry on admission showed normal renal function with hyponatremia and hypokalemia (**Table 1 Line 1**). Her biochemistry on discharge showed hyponatremia, hypokalemia, hypomagnesemia and normocalcemia (**Table 1 Line 2**). On 12 Nov 2017 she had a normal serum Na⁺, hypokalemia metabolic alkalosis and hypomagnesemia (**Table 1 Line 3**). She was advised syrup KCl, T CaCO₃ and T MgO. Her compliance was poor. On 20 April 2020 she developed a second episode of seizures. She was managed symptomatically and investigations done are unavailable. She had bilateral lensectomy on 13 July 2021 and 30 Nov 2021 and IOL placed. Both the procedures were uneventful. On 10 March 2022 she had third episode of seizures and biochemistry showed 2+ proteinuria, elevated blood urea and serum creatinine, (AKI), hyponatremia, hypokalemia and hypochloremia (**Table 1 Line 4**). On 16 March 2022 she had similar biochemical features plus hypomagnesemia, hypermagnesuria and hypocalciuria (**Table 1 Line 5**). On 17 March 2022 her biochemistry showed elevated blood urea and serum creatinine, hyponatremia, hypokalemia (**Table 1 Line 6**). She was advised syrup KCl , T CaCO₃ and T MgO. Follow up serial biochemistry showed persistence of elevated S creatinine, hyponatremia, hypokalemia and increased S. bicarbonate (**Table 1 Line 7,8,9**) After two months her serum values of Na⁺,HCO₃⁻ and Mg normalized. (**Table 1 Line 10**). She was continued on syrup KCl , T CaCO₃ and T MgO for a diagnosis of Gitleman syndrome and the biochemistry normalized in most of the parameters including the AKI, except for hypermagnesuria and hypocalciuria (**Table 1 Line 11,12,13,14,15,16,17**). Though the genetic study had a diagnosis of HELIX syndrome, we continued with T MgO for fear of seizures as seizures can occur with severe hypomagnesemia. We believed a combination of hyponatremia and hypomagnesemia can further lower seizure threshold. On 13 May 2023 we took courage to withdraw T MgO after appropriate warning her and her family. A repeat investigation one month later on **14 June 2023** indicated a fall of S.Mg⁺⁺ (1.6 mgs/dL) hypermagnesuria and hypocalciuria (**Table 1 Line 18**). To reassure ourselves that S Mg⁺⁺ does fall on withdrawal of oral supplement, a repeat investigation three weeks later confirmed a low normal S Mg⁺⁺ with hypermagnesuria and hypocalciuria (**Table 1 Line 19**).

Presently her skin, palms and soles are thick, dry , rough with palmar hyper linearity. The nails and hair are normal. Mouth and tongue are dry with practically no saliva secretion. Dental examination showed severe enamel wear . (Fig.1a,1b,1c). Sadly, we paid no heed to these clinical features until the genetic study done for a possible Gitleman syndrome turned out to be HELIX syndrome . Genetic Report: Disease: Homozygous, Autosomal Recessive, HELIX Syndrome ,Genetic transcript: CLDN10(+) (ENST00000299009.3), Location: Exon 1, Variant: c.151A>G(p.Lys51Glu) .

In summary

We present a child with steroid responsive NS and later as an adult with seizures associated with hyponatremia, hypomagnesemia, hypermagnesuria and hypocalciuria with extra renal symptoms of hypohidrosis, ichthyosis, xerostomia and lacrimal gland dysfunction. The unusual findings in this genetically identified case of HELIX are seizures associated with hyponatremia, hypomagnesemia, hypermagnesuria and hypocalciuria.

Declarations

Written informed consent for publication of clinical details and images was obtained from the subject of study.

Conflict of interest: Nil

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Contributions All the authors were involved in the care of the patient and in preparing the manuscript.

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Table

Table 1. Serial kidney urine and blood workup

No.	Date	B.Urea (mg/dl)	S.Creatinine (mg/dl)	S.Na ⁺ (mEq/L)	S.K ⁺ (mEq/L)	S.Cl ⁻ (mEq/L)	HCO ₃ ⁻ (mEq/L)	S.Ca ⁺⁺ (mg/dl)	S.Mg ⁺⁺ (mg/dl)	Urine Protein	Fe Mg ⁺⁺	Fe Ca ⁺⁺
1	26/9/17	30	0.8	129	2.5	ND	ND	ND	ND	-		
2	30/9/17	ND	ND	131	1.7	-	ND	8.0	1.1	-		
3	12/11/17	ND	0.9	140	3.2	100	30	9.9	1.6	-		
4	10/3/22	57	2.3	117	1.5	83	ND	8.6	ND	2+		
5	16/3/22	50	2.2	134	2.9	ND	20	9.5	1.3	-	8.04	0.004
6	17/3/22	ND	1.95	129	2.75	86.7	18	9.2	ND	ND		
7	28/3/22	ND	1.5	123	2.4	87	34	8.9	ND	ND		
8	23/4/22	ND	1.2	127	2.3`	89	31	8.9	ND	Nil		
9	26/5/22	ND	1.36	135	2.9	94	22.9	8.9	ND	ND		0.003
10	8/7/22	15.8	1.18	134.9	3.1	92	27.9	9.4	2.1	NIL		
11	6/1/23	27.7	1.03	133.7	4.5	94.5	27.9	9.6	2.5	ND	12.8	0.021
12	20/1/23	ND	ND	134.1	3.3	97.5	21.5	9.6	2.5	ND		
13	6/2/23	ND	ND	132	3.2	94.7	22.6	ND	2.2	ND		
14	14/2/12	ND	ND	132	3.2	94.7	22.6	ND	2.2	ND		
15	24/2/23	ND	ND	133	3.3	93.5	24.4	ND	2.2	ND		
16	10/4/23	ND	0.9	133	3.0	100.9	19.2	ND	2.2	ND		
17	13/5/23	ND	0.76	139.3	3.0	100.8	19.5	ND	2.1	ND		
18	14/6/23	23.1	0.81	137.1	2.9	100.4	18.5	9.8	1.6	Nil	11.0	0.012
19	7/7/23	17.1	0.8	138.8	3.1	103.4	19.2	9.7	1.7	1+	9.87	0.0096

ND Not done. S.Na+:Serum Sodium, S.K+:Serum potassium, S.Cl⁻:Serum chloride, S HCO₃⁻: Serum bicarbonate, S.Ca⁺⁺:Serum calcium, S.Mg⁺⁺: Serum magnesium, Fe Mg⁺⁺: Fractional excretion of magnesium, Fe Ca⁺⁺:Fractional excretion of calcium. B Ur :Blood urea S Cr:Serum creatinine Urine Pr : urine protein.

Other lab reports: S. Aldosterone 1626.10 pg/ml (30–160 supine), Renin (Direct) >500 uLU/mL (Supine 2.8-39.9), Urine Osmolality 161mOsm/Kg Serum Osmolality 281 mOsm/Kg.

Figures

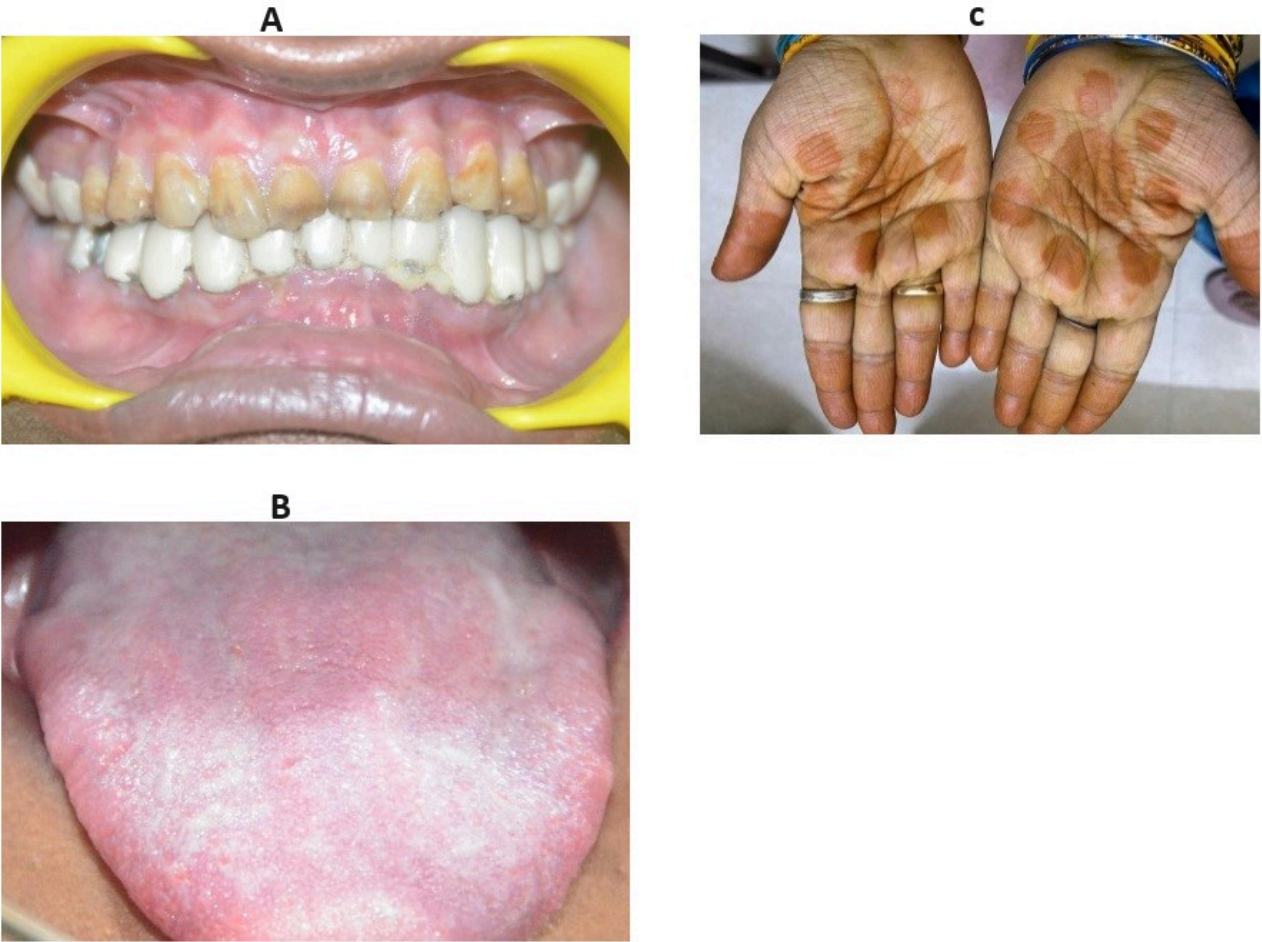


Figure 1

Legend not included with this version