Hipopotasemia genética refractaria en la edad adulta

Refractory genetic hypokalemia in adulthood

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ABSTRACT

Hypokalemia, despite its potential seriousness, is frequently encountered in clinical practice; with the majority of cases occurring in adulthood being rationalized by examining the triad losses: diuretics, vomiting and diarrhea, as inherited causes of hypokalemia with later onset are uncommon.

Below we report a case of chronic and recurrent mild hypokalemia, in an adult patient with idiopathic congenital deafness. Early clinical and analytical findings pointed to a hereditary syndrome with augmented potassium renal excretion. Suspicion of a likely molecular basis motivated the analysis of the barttin's gene, revealing a G47R mutation in heterozygosity as well as a second mutation within an usually unaltered area. G47R mutation when in homozygosity is associated with an attenuated BSND (Bartter syndrome accompanied by sensorineural deafness) phenotype, questioning the clinical significance of the second mutation discovered.

Keywords: Bartter Syndrome; Hypokalemia; BSND.

Palabras clave: Síndrome de Bartter; Hipopotasemia; BSND.

INTRODUCTION

Renal tubular disorders manifesting as hypokalemic metabolic alkalosis, such as Gitelman and Bartter Syndrome (BS) previously considered unrelated diseases, are now considered inherited cognate disorders, all conditioning defects in the handling of electrolytes at different sites of the nephron; differentiated clinically mainly by the allocation of the patient within a spectrum of phenotype severity, as laboratory testing may not be sufficient to distinguish between them[1]. Therefore, the determination of the associated gene/mutation by genetic analysis and the assessment of genotype-phenotype correlation are required to establish the final diagnosis.

BS type IV is a rare subtype of Bartter first described in 1995, characterized mainly by antenatal onset and sensorineural hearing loss[2]. Linked to the BSND gene, which encodes an essential membranous protein (termed barttin) acting as a beta subunit for ClC-Ka and ClC-Kb chloride channels located in the basolateral membranes of renal tubes and epithelia of the inner ear[3]. Several mutations in the BSND have been identified as causes for barttin's loss of function[4], and, as both channels are affected, the symptoms, though variable, are usually severe. However, BDSN patients have been described with a milder phenotype – probably correlated with a low level barttin dysfunction - associated with G47R mutation being present in homozygosity[5].

CLINICAL CASE

A 35-year-old female patient has been referred to an in-hospital Internal Medicine consultation due to recurrent "chest tightness", palpitations, headaches and fatigue. Patient also described a history of polyuria and polydipsia.

Medical records revealed history of preterm birth (no maternal polyhydramnios was described), sensorineural congenital deafness, orthostatic dizziness and multiple emergency room admissions during a 5-year span mainly due to headache and/or palpitations. On all ER admissions blood was drawn and hypokalemia was revealed (K+ 2.7-3.0 mmol/L) as well as flattened T waves on EKG, and treated with potassium supplements. Patient denied alcohol or drug abuse, as well as use of over the counter medications (including laxatives). When questioned patient mentioned a second cousin with congenital deafness, denying other relevant family history. There was no relevant dietary history.

During the physical observation pertinent findings included normal blood pressure and pain upon palpation of the epicranial insertion of the cervical muscles suggesting cervicogenic headache. Patient presented with height and weight within a healthy range and denied a history of growth retardation.

In order to assess orthostatic dizziness, the patient was referred to an otolaryngologist and videonystagmography revealed no vestibular deficit, confirming sensorineural deafness as auditory brainstem response audiometry shown an absent response.

Renal ultrasonography revealed kidneys of usual topography, with dimensions within the limits of normality and regular contours, with good parenchymal-sinusal differentiation and no evidence of parenchymal thickness decrease, without signs of lithiasis or hydronephrosis bilaterally, doppler evaluation showed bilateral permeability of the renal arteries with no signs of turbulence or spectral changes suggestive of hemodynamic stenosis, as well as permeable renal veins. CT scan of the abdominal area excluded any adrenal gland abnor-

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Table 1: Blood biochemistry results

Test indicator	Result	Normal adult range
Hb (g/dL)	13.5	11.5-16.0
BUN (mmol/L)	5.2	2.8-7.2
Cr (umol/L)	58	45-84
K+ (mmol/L)	3.0	3.5-5.1
Na+ (mmol/L)	139	136-146
Cl- (mmol/L)	101	101-109
Mg2+ (mmol/L)	0.94	0.11-1.03
Plasma aldosterone – standing (µUI/mL)	16.3	2.56-44.5
Plasma renin – standing (µ UI/mL)	334.7	4.4-46.1
Plasma cortisol - morning (µg/dL)	13.3	6.7 – 22.6
Plasma ACTH – morning (pg/mol)	8.08	7.2 – 63.3

Table 2: Urine examination

Test indicator	Result	Normal adult reference range
Urinary sodium (mmol/24h)	357	130-260
Urinary potassium (mmol/24h)	186	25-100
Urinary chloride (mmol/24h)	136	170-250
Urinary calcium (mmol/24h)	3.57	2.5-7-5
Urinary magnesium (mmol/24h)	5.52	2.1-8.2
Urine pH	6.5	4.0-8.0
Urine density	1.009	1.003-1.030

Table 3: Blood gas analysis

Test indicator	Result	Normal adult reference range
pH	7.500	7.350-7.450
Carbon dioxide partial pressure (mmHg)	39.0	35.0-45.0
Oxygen partial pressure (mmHg)	101.0	83.0-108.0
HCO3 (mmol/L)	30	21-28
Base Excess (mmol/L)	6	-3-3

malities. 24-hour Holter monitoring showed base sinus rhythm with average heart rate of 77bpm, absence of significant alterations. The laboratory examination data are shown in Tables 1, 2 and 3; all of the testing was done without potassium supplementation.

Hypokalemia and an urinalysis compatible with augmented potassium and chloride renal excretion, discrete metabolic alkalosis in a normotense patient with hyperreninemia, suggested a BS. Therefore, despite such mild clinical manifestation in an adult patient, without clear family history, the association with congenital deafness was compatible with previously described cases of Bartter Syndrome type IV in adults[5,6]. BSND gene analysis was performed, as it remains the gold standard diagnosis test, detecting the following variants on our patient: c.139G>A p. (Gly47Arg or G47R) described as probably pathogenic, and c.173C>G p.(Pro 58Arg) of unknown significance, both in heterozygosity.

The initial treatment entailed symptom relief and the correction of electrolyte disorders firstly with potassium oral supplementation and a potassium rich diet. During re-examinations, while holding for test results, the maintenance of hypokalemia notwithstanding therapy required the introduction of spironolactone, which was followed by improvement of complaints such as palpitations and fatigue. After confirmation of BDSN diagnosis, in order to maintain stable serum potassium levels, it was prescribed a very low dose of non-steroid anti-inflammatory drugs (firstly with Indomethacin 25mg daily but, due to gastric intolerance, was switched to Ibuprofen 200mg on alternate days).

The patient was referred to a Medical Genetics consult, where it was advised for family members to undergo genetic testing to confirm or exclude the presence of the variants, despite the described low risk of recurrence in her offspring.

DISCUSSION

Although the diagnosis of such monogenetic disorders by gene analysis stands as the gold standard, it is still hampered by several difficulties, one being the lack of assessability mainly due to high costs and delays. It is questionable whether a thyazide test or renal biopsy should have been conducted as there were confounding factors[7], however assuming the sensorineural hearing loss as an integrant part of the clinical picture, adding to a normal magnesemia, no hypercalciuria and no signs of nephrocalcinosis[8], it was not a big leap to assume probable BSND.

As BSND, like the majority of BS, presents as an autosomal recessive heterogeneous disease, the G47R mutation in heterozygosity may appear insufficient to justify the genetic etiology for this clinical presentation due to loss of function of the barttin protein. Consequently, the base substitution of G to C at the 173 nucleic acid position in the barttin cDNA, an usually unaltered area of the gene, resulting in an amino acid substitution of arginine for proline, to this day of unknown significance, may contribute to disease phenotype expression suggesting pathogenicity in the absence of other abnormalities and response to supplementation, sparing potassium diuretics and low dose NSAIDs.

Since in the relevant existing literature there are no reports of variable expression of the BSDN phenotype accompanying the G47R mutation, the question of conditional phenotypic expression of the G47R mutation in heterozygosity while accompanied by a second mutation and its significance should require further study.

CONFLICT OF INTEREST
The authors listed certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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ETHICAL ASPECTS
All participants submitted a consent form to be included in this study.

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