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A novel type 1b pseudohypoparathyroidism gene mutation in an adult with dilated cardiomyopathy and massive pericardial effusion

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Introduction

Pseudohypoparathyroidism (PHP) is a medical condition that affects calcium-mediated myocardial membrane depolarization [1] and cardiac contractility. Hypocalcemic ventricular dysfunction secondary to parathyroid dysfunction is a rare event in adults [2] that responds promptly to restoration of normocalcemia. There are three types of PHP according to the specific alteration detected in the Paratohormone (PTH)-induced signaling pathways [3]; type 1 is further subdivided in subtypes 1a and 1c that affect the alpha-subunit of the stimulatory G protein leading to PTH-resistant hypocalcemia and hyperphosphatemia as well as resistance to other hormones [4] and subtype 1b which exhibit normal G-protein activity, rarely present resistance to other hormones [5] and is characterized by PTH resistance in the proximal renal tubules [6] with no other endocrine alteration and normal Gsa activity. Subtype 1b is caused by maternal mutations [7] at the GNAS locus [8] most frequently STX16 deletions that lead to loss of methylation restricted to GNAS exon A/B [4,9].

Pericardial effusions are cataloged as inflammatory and non-inflammatory according to the cause [10]. Although hypocalcemia cardiomyopathy due to idiopathic hypoparathyroidism rarely leads to pericardial effusion [11], there is only one case reported with massive pericardial effusion [12].

We report a rare case of subtype 1b pseudohypoparathyroidism with massive pericardial effusion secondary to hypocalcemia due to a newly described mutation.

Case presentation

A 43 year-old woman with a five-year history of cardiac insufficiency treated with ACE inhibitor, beta-blocker, mineralocorticoid receptor antagonist and diuretic. The week previous to hospital admission se developed a sudden severe grade III (NYHA) heart failure. The ECG showed sinus rhythm with right branch complete blockade, left auricular and right ventricular hyperthrophy (Figure 1). The transthoracic echocardiogram showed dilated ventricles, a 35% ventricular ejection fraction, and massive pericardial effusion with systolic and diastolic heart compression. Magnetic resonance demonstrated right auricle collapse secondary to the pericardial effusion and lobulated left pleural effusion (Figure 2). Angiotomography did not show significant lesions. Brain computed tomography showed hyperdense lesions in basal ganglia and a decrease in the cortico-subcortical region (Figure 3). An emergency open-heart pericardiectomy (8 mm thick pericardium), pericardial and pleural effusions drainage (400 ml and 1 lt, respectively) and left lung decortication were performed. Histopathology results confirmed chronic pericarditis with mesothelial cells hyperplasia.

The post-surgery evaluation of the patient showed severe hypocalcemia (5.4 mg/dl), hypomagnesemia (1.92 mg/dl) and hyperphosphatemia (7.1 mg/dl) as well as low levels of parathyroid hormone (<3 pg/ml), and vitamin D (15 ng/dl) and elevated urine calcium values (368 mg/dl/24 h). A cranial tomography showed calcification of basal ganglia and the ECH showed a prolonged (535 ms) QT interval.

The most frequent causes of dilated myocardiopathy (autoimmune, infiltrative, infectious, neoplastic, ischemic) were considered in this patient but after exhaustive analysis and testing they were all eliminated so ventricular dysfunction secondary to hypocalcemia due to parathyroid dysfunction and/or pseudohypoparathyroidism, which are rare events in adults, were considered.

The result of a genetic analysis performed in a whole blood EDTA sample by NCGM, Inc. (Raleigh, NC, USA) showed a GNAS mutation in exon 1 (variant nomenclature: c.119_1120insA (p.Pro374ThrfsTer603) that was interpreted as a "heterozygous likely probably pathogenic variant consistent with phenotype detected". Calcium and magnesium supplementation therapy was initiated, and transthoracic echocardiography performed 3 weeks after showed a 45% ventricular ejection fraction value, an improved ventricular contraction, absence of pleural or pericardial effusions, and a grade II NYHA value.

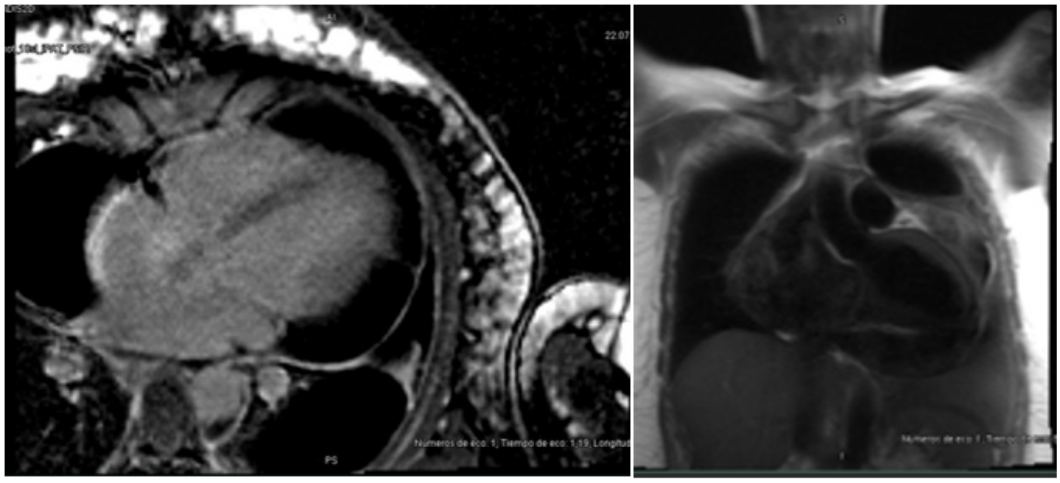

Figure 1: Cardiac magnetic resonance imaging showing cardiac chamber diameter and wall thickness within normal parameters, left ventricular systolic dysfunction, LVEF 38%, poor basal anterior intramyocardial (non-ischemic) late enhancement, pericarditis with significant pericardial effusion, loculated at the apical level, left pleural effusion.

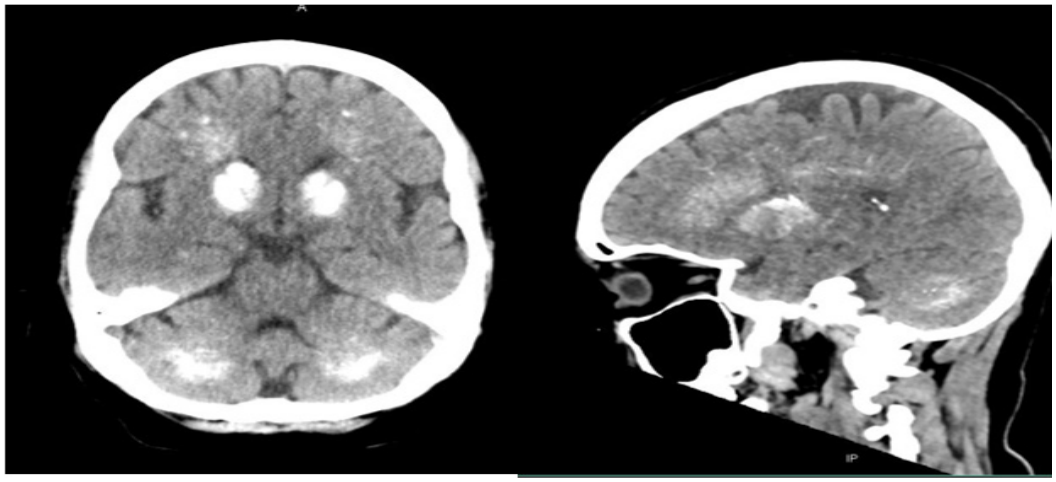

Figure 2: Computed tomography of the skull showing a decrease in the cortico-subcortical region, hyperdense lesions are evident in the basal ganglia suggestive of calcifications at this level.

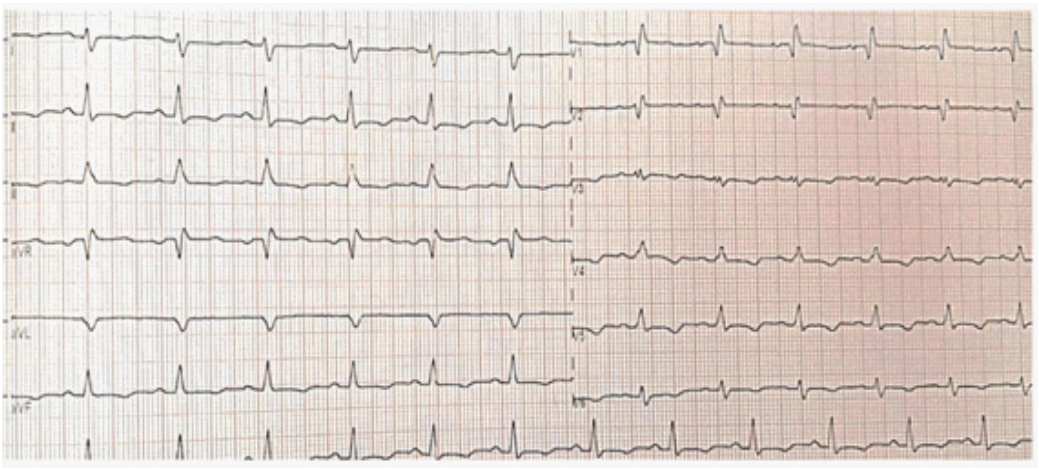

Figure 3: Electrocardiogram showing sinus rhythm with complete right bundle branch block, left atrial and right ventricular enlargement with QTc prolongation 530 ms by Bazzet.

Discussion

Hypoparathyroidism, is a rare disorder, caused by insufficient parathyroid hormone secretion that affects its major target organs: the skeleton and the kidney. The major clinical manifestations in the latter, a consequence of the loss of the calcium-conserving actions of PTH, are hypocalcemia, and low levels of 1,25-dihydroxy vitamin D. Pseudohypoparathyroidism (PHP) is an entity originated by resistance against PTH action in target tissues caused by mutations and/or epigenetic changes at the complex GNAS locus on chromosome 20q13.3 that encodes the a subunit of the stimulatory G protein [13].

PHP subtype 1a is caused by heterozygous inactivating mutations in the maternal exons that cause PTH-resistant hypocalcemia and hyperphosphatemia because paternal Gsa expression is suppressed in certain organs [14]. PHP subtype 1b is caused by heterozygous maternal deletions within GNAS or STX16, this type of PHP is clearly associated with PTH resistance in renal proximal tubules and some resistance to thyrotropin [15]. The patient we report seems to correspond to a sporadic case where epigenetics defects are explained by disruption of the remethylation events during oocyte development [16].

The frame shift c.1119_1120insA (p.Pro374ThrfsTer603) variant in GNAS gene has not been reported previously as a pathogenic variant nor as a benign variant [17]. This novel variant creates a premature Stop codon at position 603 of the new reading frame and has an allele frequency of 0.002% in gnomAD exomes database. This variant is predicted to cause loss of normal protein function through protein truncation. Loss of protein function in c.1141 and c1117 variants have been previously reported to be disease causing [18,19].

Despite all the information available regarding molecular definitions of PHP [4,20] the report of massive pericardial and pleural effusion is rare [11,12,21] and the allegedly origin has been hypocalcemia due to idiopathic hypoparathyroidism, but the cause remains unknown. Dilated cardiomyopathy due to severe maternal vitamin D deficiency accompanied by compensatory hyperparathyroidism has been reported in infants [22]. In adults hypocalcemic cardiomyopathy is usually the result of hypoparathyroidism, with or without vitamin D deficiency [23]. Among the many endocrine causes of heart failure [24] resistance to thyrotropin [15] is rarely considered although haploinsufficiency for GNAS1 also explains the resistance to TSH as the TSH receptor is a G-protein coupled receptor [25]. The most likely cause of the severe pericardial effusion in this patient was congestive heart failure secondary to hypocalcemia cardiomyopathy possibly associated to TSH resistance [12,26]. Nevertheless, the possible implication of an abnormal Gsa consequence of the GNAS gene mutation has to be considered. Gsa polymorphisms are known to influence blood pressure variation [27,28] and pericardial effusion is the result of hemodynamic compromise [29].

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