PIEZ01-related Hereditary Xerocytosis in a boy with cardiac arrhythmia

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Abstract

Hematological evaluation to explain indirect hyperbilirubinemia in a boy with cardiac arrhythmia showed the presence of PIEZ01-related hereditary xerocytosis (HX) [c.6008C>A (p.Ala2003Asp) variant] presenting with compensated hemolytic anemia and splenomegaly. PIEZ01 expression is not limited to erythrocytes and can also be found in other types of cells. It has been shown very recently that PIEZ01 is expressed in cardiomyocytes and chemically prolonging PIEZ01 activation results in cardiac arrhythmias. Since no other causative variants were detected in genes previously associated with cardiac arrhythmias, the arrhythmia was attributed to the PIEZ01 variant underlying HX. Arrhythmias can be fatal and we recommend that cardiac evaluation be part of the examination in patients with PIEZ01-related HX.

PIEZ01-related Hereditary Xerocytosis in a boy with cardiac arrhythmia

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Abbreviation table

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<tr>
<td>HX</td>
<td>Hereditary xerocytosis</td>
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<td>MCHC</td>
<td>Mean corpuscular hemoglobin concentration</td>
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<td>WES</td>
<td>Whole exome sequencing</td>
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Hematological evaluation to explain indirect hyperbilirubinemia in a boy with cardiac arrhythmia showed the presence of PIEZO1-related hereditary xerocytosis (HX) [c.6008C>A (p.Ala2003Asp) variant] presenting with compensated hemolytic anemia and splenomegaly. PIEZO1 expression is not limited to erythrocytes and can also be found in other types of cells. It has been shown very recently that PIEZO1 is expressed in cardiomyocytes and chemically prolonging PIEZO1 activation results in cardiac arrhythmias. Since no other causative variants were detected in genes previously associated with cardiac arrhythmias, the arrhythmia was attributed to the PIEZO1 variant underlying HX. Arrhythmias can be fatal and we recommend that cardiac evaluation be part of the examination in patients with PIEZO1-related HX.

Introduction

Hereditary xerocytosis (HX) (MIM:194380) is a non-immune congenital hemolytic disorder characterized by red blood cell dehydration and lysis (1). The genetic description of this disease, which was first described in 1971 (2), was made in 2012-2013 almost simultaneously by three groups (3-5). In most patients, mutations in the PIEZO1 gene encoding the large transmembrane PIEZO1 cation channel cause this disease. To date, less than 200 cases have been reported. PIEZO1 is expressed in other mechanoeelastic cells and tissues (e.g., macrophages, platelets, and endothelial, lymphatic, and hepatic cells) besides erythrocytes and may therefore be responsible for non-hematological disorders (6, 7). It has been shown very recently that PIEZO1 is expressed in cardiomyocytes (8). Mechanosensitive ion channels are the electrophysiological background of the cardiac conduction system and mutations in these channels have been shown to cause arrhythmia (9). We herein report a young patient with a c.6008C>A (p.Ala2003Asp) variant in PIEZO1 presenting with HX and cardiac arrhythmia. Although hemolytic anemia is fully compensated in this disease, cardiac arrhythmia may be life-threatening. We recommend that evaluation for cardiac arrhythmias be part of the examination of patients with PIEZO1-related HX.

Case presentation and methods

A 13-year-old boy was referred to the hematology department due to indirect hyperbilirubinemia. He was second child of nonconsanguineous Turkish parents, born at term with normal anthropometric measurements. There was no perinatal complications including edema. His developmental milestones were compatible with his peers. Mild scleral jaundice was noticed at the first year of age and continued throughout childhood. He was otherwise healthy until the age of 8 when he was admitted to the hospital with palpitation and was diagnosed with supraventricular tachycardia requiring ablation. In his follow-up visits persistent indirect hyperbilirubinemia was detected.

On admission, his anthropometric measurements were normal. Physical examination was unremarkable but scleral jaundice and dullness to percussion over Traube’s space. There was no medical history regarding anemia or transfusion. Family history was uneventful regarding hematological disorders or rhythm abnormalities.

In laboratory workup, complete blood count revealed macrocytosis, elevated MCHC, and reticulocytosis (Hb 12.7 g/dl [11.5-13.5], Hct 37.2 % [35-40], MCV 97.5 fl [77-86], MCH 30.5 pg [25-29], MCHC 36.6 g/dl [31-34], RBC 3.8 x10^{12}/l [4-6], RDW 17.8 % [12.5-13], reticulocyte ratio 9.2 % [0.9-1.5], leukocytes 6100 /mm3 [3880-9800] with an absolute neutrophil count of 3600, platelets 338000 /mm3 [175000-350000]). A peripheral blood smear was unremarkable. Plasma routine biochemistry tests revealed increased indirect bilirubin (5.1 mg/dl [0.2-1.0]) and high normal potassium levels (5.4 mEq/L [3.9-5.4]). Haptoglobin was reduced (0.29 g/l [0.3-2]) and direct coombs test was negative. Hb variant analysis was normal and osmotic fragility was reduced. Erythrocyte enzymes of glucose-6-phosphate dehydrogenase and pyruvate kinase were within normal range. Serum iron parameters were elevated (iron 275 μg/dl [14-150], transferrin saturation

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90% [15-45] and ferritin 284 ng/ml [11-135]). Ultrasound showed splenomegaly and accessory spleen. Laboratory findings were not suggestive for common causes of non-immune hemolytic anemias. Bone marrow examination was not indicated due to fully compensated hemolysis.

In solo whole exome sequencing (WES) analysis, the PIEZO1 (NM_001142864.4) c.6008C>A (p.Ala2003Asp) heterozygous variant was detected. This variant results from a substitution of alanin for aspartic acid in the 2003 position of the protein. In silico analysis confirmed that this variant affected the protein (REVEL: 0.58, addAF score: 0.25). The variant was classified as likely pathogenic according to ACGS and ClinGen guidelines. No other causative variants were detected in genes previously associated with cardiac arrhythmias. The subsequent family study revealed negative WES results in the mother and father.

Discussion

Hereditary anemias (HAs) is a rare, heterogenous group of diseases including hyporegenerative or hemolytic anemias. Hemolytic anemias develop due to erythrocyte membrane defects or enzymatic defects. The most common diseases that develop due to membrane defects are hereditary spherocytosis and hereditary stomatocytosis (hereditary xerocytosis [HX]). Next Generation Sequencing technologies have been shown to help identify new genes and multiple disease-causing genotypes of HAs (10).

HX develops due to genetic alterations in the PIEZO1 gene in most patients (for the rest KCNN4 mutations are responsible). The PIEZO1 is a nonselective mechanosensitive channel that allows permeation of cations such as Na⁺, K⁺, Mg²⁺, and Ca²⁺. The channel is activated by pressure or stretch of the cell membrane that erythrocytes are repeatedly exposed to. The PIEZO1 mutations in patients with HX result in a gain of function that leads to delayed inactivation of the ion channel. During the extended opening, K⁺ efflux is promoted leading to the net loss of total cations and dehydration. The dehydrated cells are less deformable and therefore more vulnerable to lysis. Hemolysis is fully compensated, but the disease shows complications such as iron overload, thrombosis after splenectomy, perinatal edema and hydrops fetalis. Recognition of the HX diagnosis is crucial for acknowledgement of immediate and future complications, for advisable and contraindicated management, and for planning of adequate follow-up (1).

Other than erythrocytes, PIEZO1 is expressed in different cell types and tissues that respond to mechanical stress and non-hematological findings may be observed in the mutant cases (6, 7). It is thought that its expression in non-erythrocyte cells may be responsible for unexplained complications (6). Due to its broad expression, cases presenting with both hematological and non-hematological findings are expected. It has been shown very recently that the mechanosensitive ion channel PIEZO1 is expressed in zebrafish cardiomyocytes (8). Furthermore, chemically prolonging PIEZO1 activation in zebrafish studies has been shown to result in significant cardiac arrhythmias. Of note, zebrafish have proven to be a useful model to study cardiac development and disease. Indeed, compared to mice, zebrafish cardiac electrophysiology and heart rate are more similar to humans. Based on this, it was speculated that PIEZO1 gain of function mutations could be linked to hereditary cardiac arrhythmias in humans (8). The presence of cardiac arrhythmia in this case suffering from PIEZO1-related HX may be an example of this hypothesis. The analysis of inheritance pattern in the family demonstrated that variant c.6008C>A(p.Ala2003Asp) is ade novo event occurring in the proband. PIEZO1 is a large and highly polymorphic gene in which de novo variants have previously been shown (11, 12). The lack of hematological disorders or rhythm abnormalities in the family is compatible with the variant detected in the patient being de novo. Since no other causative variants were detected in genes previously associated with cardiac arrhythmias, it is highly likely that the detected variant is responsible for the arrhythmia. Further cases will be helpful for certainty of this critical relationship. Cardiac arrhythmias are frequent (1.5-5% in the general population) with a high mortality (13). For these reasons, we encourage investigating patients with PIEZO1-related HX for cardiac arrhythmia.

In conclusion, with this article we present a boy with PIEZO1-related HX and cardiac arrhythmia, and suggest that cases with PIEZO1-related HX should be examined in terms of cardiac arrhythmias. We recommend direct WES in HAs with unusual form. WES will not only help in the correct diagnosis but also in establishing the correct relationship between comorbid conditions and HA for a better care of these rare
patients.

The author has no conflict of interest to declare.

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References


