Arch Argent Pediatr. 2026;e202510777

Clinical clues to recognizing hereditary dehydrated stomatocytosis (DHSt) in children

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SUMMARY

Dehydrated hereditary stomatocytosis (DHSt) is a heterogeneous group of rare hemolytic disorders with autosomal dominant inheritance. A series of 20 cases demonstrates that early identification of DHSt can prevent unnecessary interventions and improve the management of anemia, iron overload, and other complications in pediatric and adult patients.

The presence of elevated mean corpuscular hemoglobin concentration (MCHC) with resistant erythrocytes suggested a possible association with variants in *PIEZO1*. Patients with *KCNN4* variants showed no clear signs of erythrocyte dehydration, but, as with *PIEZO1*, macrocytosis, hemolytic anemia, and iron overload were common manifestations.

Keywords: *abnormal erythrocytes; iron overload; hemolytic anemia; fetal hydrops.*

doi: http://dx.doi.org/10.5546/aap.2025-10777.eng

To cite: Rossetti E, Eansi Eberle S, Aguirre F, Nieto L, Fernández D, Mininni MF, et al. Clinical clues to recognizing hereditary dehydrated stomatocytosis (DHSt) in children. *Arch Argent Pediatr.* 2026;e202510777. Online ahead of print 19-MAR-2026

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Funding*: None.*

Conflict of interest*: None.*

Received*: 6-2-2025*
Accepted*: 1-2-2026*

INTRODUCTION

Dehydrated hereditary spherocytosis (DHSt) encompasses a diverse group of syndromic and non-syndromic hemolytic anemias characterized by increased cation permeability of the erythrocyte membrane. Cation leakage alters red blood cell morphology and leads to premature destruction. Although the clinical presentation is variable, most cases are characterized by varying degrees of anemia, hemolysis, and iron overload, along with complications arising from these conditions.[1-4] While the estimated prevalence in the general population was described as 1:50 000, this prevalence is currently being revised. Studies show that many oligosymptomatic cases go unnoticed, and it is currently estimated that the prevalence could be as high as 1:8000.[5,6]

DHSt is caused by missense mutations in the *PIEZO1* and *KCNN4* genes. *PIEZO1*, located on chromosome 16, is a selective cation channel with various functions, including regulation of urinary osmolarity, blood pressure control, and blood and lymphatic vessel formation. Gain-of-function variants in *PIEZO1* have been shown to modify the channel, causing it to remain open and increasing the concentration of Ca^{2+} in red blood cells. This increase in calcium can activate the Gardos channel, allowing the loss of K^{+} and, with it, water. This phenomenon is known as the Gardos effect.[1-4]

In this study, we analyzed a cohort of 20 patients diagnosed with DHSt between 1991 and 2025 at a tertiary center in Argentina.

POPULATION AND METHODS

We conducted a retrospective observational study at the Hospital de Pediatría Dr. Juan P. Garrahan (Autonomous City of Buenos Aires) from 1991 to 2025. A total of 529 individuals were diagnosed with erythrocyte membrane disorders. Twenty of the 529 patients belonging to four unrelated families were diagnosed with DHSt. Laboratory evaluation included a complete blood count with peripheral blood smear (PBS), reticulocyte production index (RPI), iron profile, osmotic fragility test (OFT), and eosin-5'-maleimide (5'EMA) binding test.

Sanger sequencing of exon 51 of *PIEZO1* and the 8 coding exons of *KCNN4*, including flanking intronic regions, was performed when DHSt was suspected. Variants were named according to HGVS (Human Genome Variation Society) recommendations, using the most clinically relevant transcripts, NM_001142864.2 (*PIEZO1*) and NM_002250.3 (*KCNQ4*). They were classified according to ACMG (American College of Medical Genetics and Genomics) guidelines and ClinGen SVI Working Group recommendations.

For categorical variables, absolute frequencies are presented. Numerical variables are presented as median and interquartile range (p25-p75).

Case descriptions

Sixteen patients had variants in *PIEZO1,* and four patients had variants in *KCNN4*. Six of the 16 patients with variants in *PIEZO1* had fetal hydrops at birth; none of the patients with *KCNN4* did. Fourteen of the 20 patients with DHSt required phototherapy, and two patients required exchange transfusion for severe jaundice.

The median age at diagnosis for the entire series was 14.9 years (6.2-35.2), although symptoms were observed from birth in many cases. The median hemoglobin (Hb) (g/dL) was 12.9 (11.3-13.8) in patients with *PIEZO1* variants and 10.4 (9.6-12.0) in *KCNN4*, with a non-significant *p-value* (0.0588). The median mean corpuscular volume (MCV) (fL) was 94.5 (85.9-97.3) for *PIEZO1* and 98.4 (88.0-101.9) for *KCNN4*, with *a* non-significant *p-value* (0.3847). Only 2 patients had an RPI <2. All others had regenerative anemia with an RPI >3.

Laboratory parameters in patients with variants in *PIEZO1* showed elevated CHCM (g/dL) with a median of 37.4 (36.8-38.5), while patients with variants in *KCNN4* had a median CHCM of 34.8 (34.2-35.5), with a statistically significant *p-value* (0.0250). Stomatocytes in the FSP were observed in only 2 patients. The osmotic fragility curve showed resistant erythrocytes in patients with *PIEZO1* but fragile erythrocytes in all family members with *KCNN4* variants.

The median ferritin (ng/mL) was 243.8 (163.0-386.5) in *PIEZO1* and 216.0 (186.5-898.0) in *KCNN4*, with a statistically non-significant *p-value* (0.9635). Hepatic iron overload was documented by T2* (T2 star) nuclear magnetic resonance (NMR) in 6 of 16 patients with *PIEZO1* and in 3 of 4 patients with *KCNN4*. All patients with documented overload began oral chelation with deferasirox.

The clinical and biochemical characteristics and molecular biology results are shown in *Tables 1* and *2*.[7,8]

DISCUSSION

DHSs encompass a diverse spectrum of hemolytic disorders whose defining characteristic

is increased cation permeability of the erythrocyte membrane. Most are inherited in an autosomal dominant manner. The resulting cation leakage disrupts cell volume regulation, leading to morphological alterations in red blood cells.

Although clinical manifestations are variable, hemolysis and anemia are common, with varying degrees of severity. Perinatal edema of varying severity has been described in patients with *PIEZO1* variants, consistent with its role in lymphatic vessel formation. In the series described by Picard *et al.*, more than 20% of families had a history of perinatal ascites. In our series, 9 of 20 patients had perinatal edema. However, hereditary anemia was not suspected in any of them, highlighting the importance of including these disorders in the differential diagnosis and avoiding unnecessary studies or procedures.[4,9]

When the body absorbs and stores more iron than it can eliminate, iron overload occurs, with iron deposits in various tissues. Iron overload is a key feature of this condition, which is often underdiagnosed. Iron deposited in tissues can lead to multiple complications, including liver complications (cirrhosis and liver failure), endocrine complications (hypogonadism, glucose intolerance, diabetes, growth disorders, osteopenia, osteoporosis), and cardiac complications (arrhythmias, heart failure). Although red blood cell transfusions contribute to iron overload in severe forms of DHSt, even in the absence of transfusions, chronic hemolysis, increased erythropoiesis, and abnormal iron regulation can promote overload. In our series, 7 of 16 patients with *PIEZO1* variants and 3 of 4 with *KCNN4* variants had MRI-detected overload. Iron overload can develop over time, so regular

Table 1. Clinical variants and laboratory parameters of patients according to molecular variants (n = 20)

	PIEZO1 **(n = 16)**	***KCNN4*** (n = 4)
Gender		
Female	8	2
Male	8	2
Age at diagnosis (years)	15.1 (5.6-38.1)	12.6 (5.5-26.7)
Red blood cells, 10^6/uL	3.7 (3.4-3.8)	3.2 (3.1-3.7)
Hemoglobin, g/dL	12.9 (11.3-13.8)	10.4 (9.6-12.0)
Hematocrit, %	34.6 (29.2-36.4)	30.0 (27.5-34.6)
MCV, fL	94.5 (85.9-97.3)	98.4 (88.0-101.9)
MCHC, g/dL	37.4 (36.8-38.5)	34.8 (34.2-35.5)
RPI	5.9 (3.5-7.0)	4.3 (2.7-5.5)
Presence of stomatocytes in PBS	1	1
Total bilirubin, mg/dL	1.8 (1.0-2.5)	6.1 (3.1-28.3)
Ferritin, ng/mL	243.8 (163.0-386.5)	216.0 (186.5-898.0)
Lactate dehydrogenase, U/L	261 (163-373)	511 (424-857)
Osmotic fragility curve		
Resistant	16	0
Fragile	0	4
Phototherapy	13	1
Exsanguination transfusion	1	1
Fetal hydrops	6	0
Transfusion requirement	7	2
Splenomegaly	5	3
Splenectomy	0	0

Categorical variables are presented as absolute frequencies, and continuous variables are presented as median and interquartile range. MCV (mean corpuscular volume), MCHC (mean corpuscular hemoglobin concentration), RPI (reticulocyte production index), PBS (peripheral blood smear).

Table 2. Molecular results in the patients studied

	Gene	HGVS classification (coding)	HGVS (protein)	Status	*falta traducción*
Family 1	*PIEZO1*	c.7367G>A	p.(Arg2456His)	Het	Pathogenic (PM2_s, PS4_m, PP3_m, PP1_strong, PM1, PS3_s)
Family 2	*PIEZO1*	c.7483_7488dup	p.(Glu2496_Glu2497insLeuGlu)	Het	Pathogenic (PM2_s, PS4_m, PP1_strong, PM1, PS3_s)
Family 3	*PIEZO1*	c.7483_7488dup	p.(Glu2496_Glu2497insLeuGlu)	Het	Pathogenic (PM2_s, PS4_m, PP1_strong, PM1, PS3_s)
Family 4	*KCNN4*	c.1055 G>A	p.(Arg352His)	Het	Pathogenic (PM2_s, PS4_m, PP1_strong, PM1, PS3_s, PP4, PP2)

*HGVS (*Human Genome Variation Society*) Het (heterozygous) PM2_s: The variant is absent (or below the expected frequency in carriers if it is recessive) in a large general population or control cohort. Applied with supporting evidence for pathogenicity. PS4_m: The prevalence of the variant in affected individuals is significantly increased compared to the prevalence in controls. Applied as moderate evidence for pathogenicity. PP3_m: In silico tools predict a deleterious effect on the gene or gene product (conservation, evolution, impact on* splicing*, etc.). Applied with moderate evidence for pathogenicity. PP1_strong: Co-segregation with the disease in multiple affected members of a family, in a gene known with certainty to cause the disease. Applied as strong evidence for pathogenicity. PM1: Variant located in a "hot spot" region of the gene and/or in a well-established functional domain for the protein. PS3_s: Functional assays determined that the variant has a deleterious effect on the gene or gene product. Applied with strong support for pathogenicity. PP4: The patient's phenotype is highly specific to the disease associated with alterations in the gene. PP2:* Missense *variants in a gene where the occurrence of this type of variant constitutes a mechanism of the disease, and where the occurrence rate of benign missense variants is low.* [7,8]

MRI and laboratory evaluations are recommended for timely detection and treatment.[1-4]

An increased risk of thrombosis has been described in this disease, especially after splenectomy. Picard *et al*. reported thrombosis in all splenectomized patients with *PIEZO1* and in 4 non-splenectomized patients (3 of whom had comorbidities). Although Picard's series did not report thrombotic events in *KCNN4*, Mansour-Hendili *et al*. documented several thromboses in a patient with the Gardos channelopathy after splenectomy, so this procedure is not recommended.[4,10-14] In our series, no patients underwent splenectomy.

Although variants in both genes, *KCNN4* and *PIEZO1,* are associated with hereditary stomatocytosis with erythrocyte dehydration, published data suggest that patients with *KCNN4* variants do not exhibit clear signs of dehydration, and it is proposed to redefine this entity as "Gardos channelopathy". In our series, consistent with these findings, patients with *KCNN4* did not show clear signs of erythrocyte dehydration, with normal CHCM and fragile erythrocytes with normal 5'EMA.[1,4,15]

DHSt is a rare group of disorders that requires a high index of suspicion for diagnosis. Since PBS is inconclusive, elevated MCHC with resistant erythrocytes may suggest an association with variants in *PIEZO1*. Patients with *KCNN4* showed no obvious signs of erythrocyte dehydration, but as with *PIEZO1*, macrocytosis, hemolytic anemia, and iron overload were common. The variants found in our patients have been previously reported and are classified as pathogenic and associated with DHSt. Molecular findings provide the possibility of adequate genetic counseling.

It is essential to consider this hereditary disease as a differential diagnosis in various clinical conditions, such as neonatal jaundice, fetal hydrops, chronic hemolytic anemia, or macrocytic anemia. This will avoid unnecessary tests for patients and facilitate early appropriate management, minimizing the morbidity and mortality associated with this pathology. ■

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