

# Clinical difference between identical twins with sickle cell anemia

## *Diferenças clínicas entre gêmeas idênticas com anemia falciforme*

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### ABSTRACT

Sickle cell anemia (SCA) is a genetic disease that causes important clinical manifestations due to chronic hemolysis and vascular occlusion. The aim of this study was to report a rare case of monozygotic twins diagnosed with SCA, presenting a different clinical characteristic. An interview with the patients was carried out and the medical records were consulted. One patient has a history of malleolar ulcer in the left back, while the other does not. Both patients used hydroxyurea at the same dosage. This study shows that SCA presents, in addition to genetic factors, non-genetic factors involved in the severity of the disease and its clinical manifestations. Studies are needed that may contribute to the understanding of the clinical heterogeneity of SCA.

**Key words:** sickle cell anemia; leg ulcer; monozygotic twins; genetics; hydroxyurea.

### RESUMO

*A anemia falciforme (AF) é uma doença genética que causa importantes manifestações clínicas devido à hemólise crônica e à oclusão vascular. O objetivo deste estudo foi relatar um caso raro de gêmeas univitelinas com diagnóstico de AF, apresentando uma característica clínica diferente. Uma entrevista com as pacientes foi realizada, e os prontuários foram consultados. Uma paciente tem história de úlcera maleolar na região esquerda, enquanto a outra não. Ambas as pacientes faziam tratamento com hidroxiureia na mesma dosagem. Este estudo mostra que a AF apresenta, além de fatores genéticos, fatores não genéticos envolvidos na gravidade da doença e suas manifestações clínicas, sendo necessários estudos que possam contribuir para o entendimento da heterogeneidade clínica da AF.*

*Unitermos:* anemia falciforme; úlcera da perna; gêmeos monozigóticos; genética; hidroxiureia.

### RESUMEN

*La anemia de células falciformes (ACF) es una enfermedad genética que causa importantes manifestaciones clínicas debido a la anemia hemolítica crónica y a la oclusión vascular. El objetivo de este estudio fue reportar un caso raro de gemelas monocigóticas con diagnóstico de ACF, presentando una característica clínica diferente. Se realizó una entrevista con las pacientes, consultándose sus fichas médicas. Una paciente tiene historia de úlcera maleolar en la región izquierda, mientras la otra no. Ambas hacían tratamiento con hidroxiurea en la misma dosis. Este estudio demuestra que la ACF presenta, además de factores genéticos, factores no genéticos involucrados en la severidad de la enfermedad y sus manifestaciones clínicas. Son necesarios estudios que contribuyan para la comprensión de la heterogeneidad clínica de la ACF.*

*Palabras clave:* anemia de células falciformes; úlcera de la pierna; gemelos monocigóticos; genética; hidroxiurea.

## INTRODUCTION

Sickle cell anemia (SCA) is a genetic disease caused by a point mutation in the beta-globin S gene. The fetal hemoglobin concentration (HbF), beta-globin S gene haplotypes and coexistence with alpha-thalassemia are known factors involved in the clinical modulation of the disease. However, SCA presents other clinical manifestations that depend not only on these factors, but also on environmental and genetic interaction<sup>(1)</sup>. In this study, we show the rare case of two monozygotic twins with SCA (HbSS) with different clinical presentation.

## CASE REPORT

Female patients, 22 years old, identical twins, born in Ceará, Brazil, students, diagnosed with SCA (HbSS) since the age of 5 months, they have been followed up at an outpatient clinic. In childhood, they underwent various hospitalizations due to painful crises, receiving more than 10 blood transfusions both, until 18 they were years old. Both present hepatomegaly and reduced spleen (functional auto-splenectomy) and both underwent cholecystectomy five years ago. The patients started treatment with hydroxyurea (HU) four years ago (mean dose of 750 mg/day) and both continued treatment, currently with an average dose of 1250 mg/day.

They presented the same clinical evolution, except for a left lower limb malleolar ulcer in patient 2, presenting fibrotic appearance, with regular pain, yellowish exudate and adjacent dry skin (**Figure**). Cleansing, physical debridement and topical use of drugs were performed and the ulcer healed after seven months. Three years later, it recurred and was treated during four months, until complete resolution. Patient 1 never had any severe clinical manifestation.

Patients presented similar changes in blood count parameters, with elevated HbF as measured with HU (**Table 1**). The differences observed were at levels above the reference value of aspartate aminotransferase (AST) in patient 1 and indirect bilirubin in patient 2, although without clinical repercussion (**Table 2**).



FIGURE – Evolution of malleolar ulcer in the left lower limb

TABLE 1 – Blood count parameters of SCA patients during treatment

Variables	2014, Jul*		2016, Sep		2017, Dec		References
	(without HU)		(HU 1000 mg/day)		(HU 1250 mg/day)		
	Patient 1	Patient 2	Patient 1	Patient 2	Patient 1	Patient 2	
Hemoglobin (g/dl)	7.352	7.529	7.082	7.564	5.8	6.1	12.3-15.3
Hematocrit (%)	21.14	21.86	19.23	22.22	17.5	17.5	36-45
MCV (fl)	112.6	92.51	107.7	110.4	136.9	133.1	80-96.1
MCHC (%)	34.77	34.4	36.84	34.05	33.3	34.6	33.4-35.5
Leucocytes × 10 <sup>3</sup> (/mm <sup>3</sup> )	12570	14790	12780	6895	8200	7000	4.5-11
Platelets × 10 <sup>3</sup> (/mm <sup>3</sup> )	262,800	438,400	258,000	330,500	279,000	286,900	172-450
Hemoglobin electrophoresis (%)	HbF: 1 HbA2: 4.5 HbS: 94.5	HbF: 0 HbA2: 3.8 HbS: 95.2	HbF: 1.3 HbA2: 3.4 HbS: 93.2	HbF: 1.7 HbA2: 3.3 HbS: 93.1	HbF: 8.4 HbA2: 2.6 HbS: 85.3	HbF: 7.4 HbA2: 2.6 HbS: 87.7	HbF: 0-1.5 HbA2: 2-3.7 HbA: 96-98
Reticulocytes (/mm <sup>3</sup> )	407,200	342,900	324,300	331,400	173,900	125,400	25,000-75,000

SCA: sickle cell anemia; MCV: mean corpuscular volume; MCHC: mean corpuscular hemoglobin concentration; HU: hydroxyurea; \*date of first clinical visit.

TABLE 2 – Physical, clinical and biochemical parameters of patients with SCA

	Patient 1	Patient 2	References
Height (m)	1.53	1.55	–
Weight (kg)	41.7	43.2	–
AST (U/l)	38	19	< 32
ALT (U/l)	26	17	< 31
Alkaline phosphatase (U/l)	244	144	65-300
Indirect bilirubin (mg/dl)	1.88	2.73	< 0.8
Lactate dehydrogenase (U/l)	764	524	230-460
Leg ulcer	No	Yes	–

SCA: sickle cell anemia; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

## DISCUSSION

It is known that SCA is a genetic disease that presents great variability in clinical and laboratory aspects, being influenced by genetic factors, such as haplotype types, polymorphisms in HbF-related regions and non-genetic factors<sup>(1)</sup>. Studies with monozygotic twins are important to exemplify the clinical heterogeneity of the disease, showing that even genetically identical individuals can present different clinical manifestations, emphasizing the importance of environmental factors and their influence on the phenotype and, consequently, on the clinical course of SCA.

The identical twin patients with SCA had a similar clinical course, with sporadic headaches and no serious clinical manifestations of the disease. However, at age 18, patient 2 had a leg ulcer in the lower left limb. Leg ulcer is the most common cutaneous manifestation of SCA, occurring in 8% to 10% of homozygous patients, and is frequently associated with a worse

clinical course. Generally, leg ulcers present a chronic and debilitating character that affects patients in a physical and emotional way, having potential to influence an individual's quality of life<sup>(2)</sup>. The presence of intravascular hemolysis has been implicated in the pathogenesis of ulcers. However, several other factors such as vaso-occlusion, venous insufficiency, infections, decreased nitric oxide (NO) bioavailability and inflammation may be involved in its genesis<sup>(3)</sup>.

Table 1 shows the HbF concentrations of the patients with SCA before and during treatment with HU. Both patients had similar levels of HbF at different time points, indicating that HbF levels and determinants of response to treatment can be controlled by genetic factors. Although important, genetic factors do not explain all the clinical variability found in patients with SCA, suggesting that other factors may be involved in the onset of clinical manifestations. Previous reports have shown that the environmental factor can affect the clinical course of the disease, culminating in the appearance of some complications. Some factors such as temperature, wind speed, humidity, air quality, elevated altitude, home environment, socioeconomic factors and physical activity may influence clinical manifestations<sup>(4)</sup>. About the twins in question, we hypothesized that some of these factors may have favored the appearance of the leg ulcer in patient 2 and not in patient 1.

Clinical differences between twins with hemoglobinopathies have been described in previous studies, suggesting that although they have the same genetic component, external factors may play a major role in the clinical expression of the disease and may contribute to the risk of seizures and complications<sup>(5, 6)</sup>. In the study by Weatherall<sup>(7)</sup>, only one of the twins with HbSS had leg ulcer, attributed to genetic and environmental contributions, although the author cites trauma as an environmental factor clearly involved.

Some of these external factors, such as temperature, are well documented<sup>(4)</sup>. However, medical research and guidance at the time of consultation may be of great importance in preventing complications. Despite the difficulty of identifying and establishing a relationship between a specific environmental factor and the onset of clinical manifestations, the investigation of these components may contribute to improve our understanding of the factors influencing and/or precipitating complications.

## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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