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(CASE REPORT)

Incidental discovery of SC heterozygosity: A case report

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Abstract

Composite heterozygous sickle cell syndrome (SC) is a distinct entity, very different from homozygous sickle cell disease, characterized by less severe and less debilitating systemic disease. The milder clinical symptoms and subtle hematological abnormalities often lead to a delayed diagnosis in adulthood.

Hemoglobin electrophoresis and high-performance liquid chromatography remain highly useful and valuable methods for detecting hemoglobin abnormalities.

We report the case of a young patient with a dual hemoglobin variant (HbS and HbC) that was incidentally discovered during a routine workup.

Keywords: Sickle Cell Syndromes; Hemoglobin Electrophoresis; HPLC; Detection of SC Heterozygosity

1. Introduction

SC heterozygosity, along with SS sickle cell disease and B-thalassemia-sickle cell disease, constitutes the sickle cell syndromes [1].

SC composite sickle cell syndrome accounts for 20% to 30% of major sickle cell syndromes. It is particularly common in certain West African countries such as Ghana, Burkina Faso, and Nigeria [2].

We report a case of incidental discovery of SC composite heterozygous sickle cell disease.

The objective of this study is to review the role of techniques such as HPLC and hemoglobin electrophoresis in the detection of SC heterozygosity.

2. Clinical Case

We report the case of a 22-year-old male from Sidi Slimane, born to non-consanguineous parents, the youngest of eight siblings, unmarried, and from a low socioeconomic background; he has no personal medical history or history of similar cases in his family.

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As part of routine medical follow-up, a standard battery of tests was performed, including a complete blood count (CBC) and platelet count, an electrolyte panel, a lipid profile, liver function tests, and viral serology (hepatitis B and C, syphilis, and HIV) … (Table 1).

The complete blood count revealed hypochromic (Hb 10.7 g/dL), microcytic (MCV 70.4 fl) anemia (MCH 25.4 pg), and the white blood cell differential was assessed via a blood smear, which showed no immature or atypical cells and the presence of globular anisopoikilocytosis consisting of annulocytes and a few target cells, along with a few macroplatelets.

Biochemical testing revealed a slight increase in CRP (16.4 mg/L) and uric acid (494.2 µmol/L).

Our patient also underwent testing for hemolysis and iron deficiency, which were found to be normal.

Table 1 Results of the blood chemistry panel

Parameters	**Patient Results**	**Reference Values**
-Hemoglobin (Hb) (g/dL)	10.7	13—18
Red blood cells ($\times 10^6/\mu L$)	4.22	4.28—6
Mean corpuscular volume (fl)	70.4	78—98
- Hematocrit (Hct) (%)	29.7	39—53
-Mean corpuscular hemoglobin concentration (MCH) (%)	36	31—36.5
-Mean corpuscular Hb content (MCH) (pg)	25.4	26—34
-Reticulocytes ($\times 10^6/\mu L$)	0.1756	0.11—1.10
-Platelets ($\times 10^3/\mu L$) 120	164	150—450
-White blood cells ($\times 10^3/\mu L$)	9.25	4—11
-Total bilirubin (µmol/L)	27.3	< 17
-Conjugated bilirubin (µmol/L)	10	< 4
-ALT (IU/L)	17	<65
-GGT (IU/L)	26	8—61
-Alkaline phosphatase (IU/L)	58	40—150
-Urea (mmol/L)	4	2.5—7.5
-Creatinine (µmol/L)	82.6	60—120
-Fasting blood glucose (mmol/L)	4.7	3.9—5.8
-Cholesterol (mmol/L)	2.5	0—5.2
-Triglycerides (mmol/L)	0.8	0—2.3
-Uric acid (µmol/L)	494.2	210—420
-Albumin (g/L)	44	35—50
-Potassium (mmol/L)	4.40	3.5—4.6
-Sodium (mmol/L)	142	136—145
-C-reactive protein (mg/L)	16.4	<5
-LDH (IU/L)	211	135—225
-Serum iron (µmol/L)	13.3	10—28

-Ferritin (ng/mL)	107.44	30—400
-Folate (ng/mL)	4.5	4.8—37.2
-HBcAb (-) HBsAb (+) HBsAg (-)	Vaccine-induced immunity with a protective HBsAg titer (16.64 mIU/mL)	
-Hepatitis C serology	Negative	
-HIV serology	Negative	
-Syphilis serology	Negative	

Consequently, a thorough medical history was taken, revealing episodes of generalized joint pain, severe fatigue, and paroxysmal abdominal pain. On physical examination, pallor of the skin and mucous membranes was observed, along with a palpable, painless splenomegaly. An initial hemoglobin electrophoresis was performed using 3octa capillaries (SEBIA) and revealed a heterozygous hemoglobin variant with 50% HbS and 40% HbC.

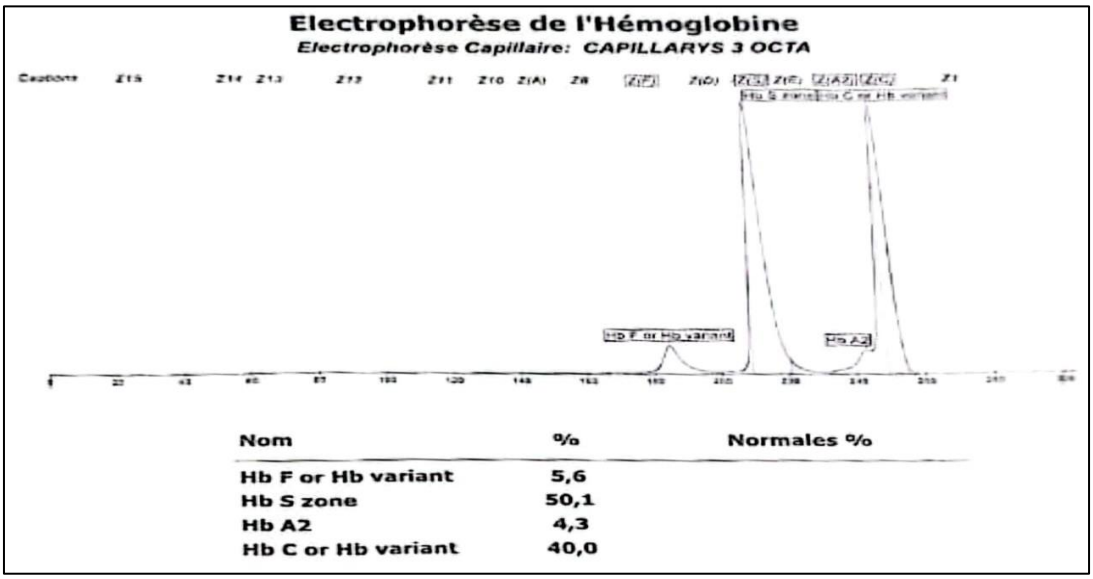

Figure 1 Electrophoretic profile of hemoglobin showing the presence of the HbS and HbC variants

The same sample was subsequently analyzed using a second technique, high-performance liquid chromatography on the Bio-RAD Variant II, which yielded the same results.

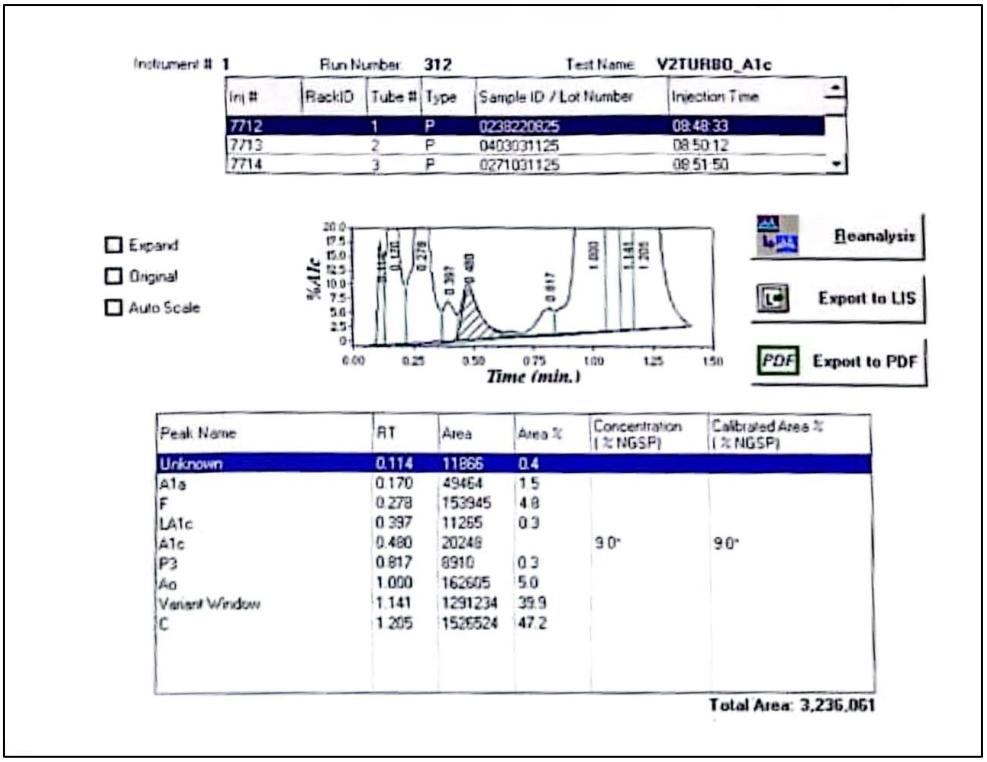

Figure 2 Hemoglobin profile on HPLC showing the presence of HbC and another variant, HbS

The prescribing physician requested a genealogical study for further investigation and potential future management of the patient's ancestors.

Hydroxyurea therapy was initiated to prevent complications, in combination with pain management and lifestyle and dietary measures.

3. Discussion

In Morocco, the full epidemiology of hemoglobinopathies remains unknown. The WHO estimates the carrier rate in Morocco at 6.5%, which would suggest the existence of 30,000 cases of major forms of thalassemia and sickle cell disease [3].

Hb C is the most common abnormal hemoglobin in West Africa, particularly in Burkina Faso, where it originated [4].

Hemoglobinopathies are defined by the presence of qualitative and/or quantitative abnormalities affecting the globin chains. To date, nearly 700 abnormal hemoglobins have been described [5, 6, 7]. Qualitative abnormalities lead to the production of hemoglobin with an abnormal structure. Among these variants, the best known are hemoglobin S (HbS), which causes sickle cell disease, and hemoglobin C (HbC), due to the clinical and/or biological consequences they are likely to cause.

However, the majority of variants are asymptomatic and are therefore discovered incidentally. [8] The coexistence of both variants in the same individual should come as no surprise; indeed, it is in combination with HbS that HbC is truly pathogenic [9].

SC double heterozygosity, along with SS sickle cell disease and β-thalassemia-sickle cell disease, constitutes the sickle cell syndromes [10].

Sickle cell syndromes are genetic hemoglobin (Hb) disorders, inherited in an autosomal recessive manner and characterized by the presence of Hb S. There are different types, the most common of which are homozygosity for Hb S (Hb SS) or sickle cell anemia, composite heterozygosity for Hb S and Hb C, or SC hemoglobinopathy, and composite heterozygosity for Hb S and β-thalassemia [11].

The presence of Hb C in red blood cells (RBCs) is associated with their dehydration due to activation of the K-Cl transporter; this dehydration leads to the polymerization of Hb S. [12].

The pathophysiological basis of SC double heterozygosity is the same as that of SS sickle cell disease: the sickling of red blood cells caused the clinical manifestations. The presence of HbC promotes sickling in SC double heterozygotes. [13]

HbSC patients typically present with moderate sickle cell disease [2]; in fact, regardless of the type of sickle cell disease, in the absence of neonatal screening, the diagnosis is made too late. However, early diagnosis of the disease leads to a significant reduction in mortality rates and the number of complications, particularly infectious ones [14].

Screening for hemoglobin abnormalities requires at least one electrophoresis technique, along with two additional tests tailored to specific needs, to provide a preliminary diagnostic result.

Alkaline pH electrophoresis [15, 16] on agarose or cellulose acetate gel is one of the standard tests for screening for hemoglobinopathies [15–17] and helps guide the diagnosis of homozygous or heterozygous hemoglobin abnormalities. However, this technique, which is widely used in general clinical laboratories, confuses HbC with HbE, HbA2, and HbO-arab. To differentiate these forms, confirmation using other, more advanced techniques for separating the different Hb fractions—including quantification and phenotyping—is necessary. These include HPLC and capillary electrophoresis. Capillary electrophoresis has higher sensitivity compared to agarose gel electrophoresis (95% vs. 91%) [18]

Capillary electrophoresis involves the separation of charged species under the influence of an electric field, generally based on their charge-to-mass ratio.

Capillary electrophoresis performed on our patient revealed the presence of Hb S at 50.1% and Hb C at 40%. Hb A, Hb A2 at 4.3%, and Hb F at 5.6%.

This profile is consistent with those of other Moroccan studies that have demonstrated the presence, in addition to hemoglobin S and C, of Hb A2 (2.7–3.9%) and Hb F (1.2–3.6%) [19, 20, 21].

Furthermore, chromatographic methods offer the advantage of allowing the quantification of different hemoglobin fractions. In some cases, HPLC can be used to confirm results obtained after alkaline pH electrophoresis. For example, HbC can be distinguished from HbA2, HbE, and HbO-arab. It is a valuable tool for clarifying, quantifying, and confirming the identification of abnormal hemoglobins [22, 23]. The only technique allowed for precise measurement of HbF and HbA2 [9].

Ion exchange HPLC separates hemoglobin fractions based on the difference in charge between HbA1c and other hemoglobins (HbA1a and HbA1b). The presence of any of the aforementioned variants affects the ionic charge of the hemoglobin molecule, causing interference with this method, depending on how the Hb variants are separated from HbA.

Analyzers using this principle, such as the BIORAD Variant automated analyzer used in this study, can detect the most common variants, such as HbC. Other variants are generally indicated as a separate but unidentified extra peak, the presence of which must always be taken into account: further identification is required [24, 25].

HPLC and capillary electrophoresis [26, 27] are the more sensitive techniques for separating the various fractions of normal or abnormal hemoglobin and allow researchers to overcome the limitations of agarose gel electrophoresis at alkaline or acidic pH levels. While the strategies depend on the laboratory's equipment, current clinical laboratory guidelines specify "screening for Hb abnormalities using at least one electrophoresis technique and two additional tests, as needed, to provide a preliminary diagnostic result" [28]

The major manifestations of these conditions are chronic hemolytic anemia, painful vaso-occlusive crises, and increased susceptibility to infections, particularly from encapsulated bacteria and Salmonella.

Indeed, affected individuals generally experience fewer acute painful crises than SS sickle cell patients, and their life expectancy is about 20 years longer; however, complications may arise around the age of 50 [29,30], the most serious of which include: thrombosis, avascular necrosis, and sepsis [1-4].

The treatment for SC compound heterozygosity is identical to that for SS homozygous sickle cell disease [10].

Treatment of vaso-occlusive crises involves hyperhydration, analgesics (acetaminophen, NSAIDs, opioid derivatives), oxygen therapy, and hydroxyurea; infectious complications are treated with antibiotics; acute anemia with blood transfusions (Hb level < 5 to 6 g/dL); severe vaso-occlusive events (strokes, acute chest syndromes, priapism) require the initiation of a transfusion regimen (transfusions, exchange transfusions).

Prevention "ideally" includes:

- Vaccinations: EPI + hepatitis B, Haemophilus influenzae, typhoid bacillus, pneumococcus,
- Antibiotic prophylaxis with oral penicillin in children < 5 years of age (pneumococcus)
- Antimalarial chemoprophylaxis (children < 5 years of age, pregnant women),
- Routine deworming for intestinal parasites,
- Folic acid and iron supplementation.

As for the use of hydroxyurea, which promotes the synthesis of Hb F, it faces challenges due to the long-term consequences of "lifelong" use of a cytotoxic drug.

Prevention of post-transfusion viral infections relies on the rational use of transfusions and, above all, on systematic screening of blood donors for HIV and hepatitis B and C.

Improving the prognosis for sickle cell syndromes requires:

- Public education and awareness,
- The implementation of a screening program (Emmel test, agarose gel isoelectric focusing of hemoglobin, or cellulose acetate electrophoresis),
- The establishment of centers for the care of patients with sickle cell disease [10, 13].

4. Conclusion

Our findings underscore that methods such as HPLC and electrophoresis remain useful for diagnosing this condition. The wide clinical variability of sickle cell disease necessitates early screening of at-risk patients with appropriate clinical monitoring to prevent the development of complications.

Key points

- Heterozygous compound sickle cell anemia (HbSC) is less common than the HbSS type and is usually less painful; however, complications may arise in adulthood.
- The most common form of sickle cell anemia is seen in homozygous SS patients; however, it also occurs in individuals who are SC heterozygotes.
- Techniques such as hemoglobin electrophoresis and HPLC remain highly valuable in the detection of hemoglobinopathies, especially in asymptomatic patients.
- The most serious complications of HbSC include thrombosis, avascular necrosis, and sepsis; it is important to administer promptly intravenous antibiotic therapy to patients presenting with fever.

Compliance with ethical standards

Disclosure of conflict of interest

There is no conflict of interest

Statement of informed consent

Informed consent was obtained from all individual participants included in the study by signing the Free and Informed Consent Form.

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