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Homozygous Hemoglobinosis CC: A Series of 3 Cases and a Review of the Literature

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Abstract

Hemoglobinosis C occurs mainly in Africa and America with a high frequency in West Africa. In Senegal, homozygous hemoglobinopathy CC constitutes a very rare profile of which only 3 cases are followed in the clinical hematology department of Dakar. The 1st case is a 49-year-old female patient, with notion of 1st degree consanguinity, and a long history of abdominal pain who presented a poorly tolerated anemic syndrome and splenomegaly. The biological assessment showed moderate anemia (7.6 g/dL) with microcytic hypochromia and a CC profile (HbC = 99.2%; HbA2 = 0.8%) on hemoglobin electrophoresis. The second case was a 22-year-old female patient with a notion of 2nd degree consanguinity who presented a Chauffard triad. The haemogram showed mild anaemia (11 g/dL), microcytic and hypochromic. Hemoglobin electrophoresis confirmed a CC profile (HbC = 95.3%; HbA2 = 4.7%). The third patient was 27 years old, with a history of diffuse abdominal pain and 2nd degree consanguinity. The haemogram and haemoglobin electrophoresis confirmed the CC profile (HbC = 94.6%; HbA2 = 5.4%). The negativity of the Emmel test in front of this presentation suggestive of sickle cell disease means that this type of hemoglobinopathy is diagnosed late in our regions. We therefore recommend the systematic performance of hemoglobin electrophoresis in the presence of any chronic hemolytic anemia.

Keywords

Hemoglobinopathy Homozygous CC, Abdominal Pain, Hemoglobin Electrophoresis, Chauffard Triad

1. Introduction

Hemoglobinosis C results from a point mutation in codon 7 of the β-globin gene

(HBB: c.19G>A) leading to the substitution of amino acids at position 7 of the β-globin chain (HBB: p.Glu7Lys). It has a reduced solubility and thus an increased tendency to aggregate [1] [2]. Hemoglobinopathy C occurs mainly in Africa, South and North America, and more rarely in the Mediterranean region. Very high genetic frequencies are known in West Africa (up to 20% heterozygous carriage); in African-Americans, it is about 2% [3].

Heterozygous forms are usually asymptomatic. Homozygous forms present with moderate chronic hemolytic anemia and often splenomegaly of variable size. Bone and abdominal pain are possible as in homozygous sickle cell disease SS but painful attacks are rare. On blood smear, target cells predominate (30% - 100%), much more than in other types of hemoglobinopathy such as thalassemia, as well as microspherocytes. Electrophoretic techniques confirm the diagnosis and show the following profile HbC = 60% - 98% and HbA2 = 2% - 3% [3] [4].

In Senegal, hemoglobin S carriage is 8% - 10% in the population while major forms of hemoglobinopathies represent 0.5% of births with more than 95% of cases for the homozygous SS form, 3.6% for double heterozygosity SC and 1% for Sβ thalassemia. Double heterozygosity SC is the most common major form after the SS form [5].

In our country, few published studies have focused on the heterozygous SC forms [6]. The reasons are related to the rarity of CC forms, but also to a relatively less important clinical expression than in the SS or SC form. The objective of this work was to report a series of 3 cases of homozygous CC hemoglobinopathy followed in the clinical hematology department of Dakar (Senegal).

2. Case Description

The 1st case is a 49-year-old female patient, without any particular pathological history, with a notion of oral phytotherapy and a long history of swimming in freshwater. She presented a notion of 1st degree consanguinity and had two brothers who had died following chronic abdominal pains without any other precision. She was seen in 1st consultation for exploration of splenomegaly associated with abdominal pain. The Emmel test was negative and the diagnosis of splenic bilharziasis was evoked given her history. She was referred to a hematology consultation three months later. The examination showed a poorly tolerated anemic syndrome and splenomegaly (12 cm overhang). The biological examination showed an anemia of 7.6 g/dL microcytic hypochromia and a CC profile on hemoglobin electrophoresis (HbC = 99.2% and HbA2 = 0.8%). At diagnosis, she already had non-symptomatic gallbladder lithiasis which was treated by cholecystectomy. She was put on a long-term folic acid and transfusion program with regular follow-up and a clear improvement in her quality of life.

The second case was a 22-year-old female patient from Guinea Conakry, who was seen in a hematological consultation in the context of an evolving pregnancy of 25 weeks' gestation with a notion of second-degree consanguinity. She had a

history of two miscarriages and a history of hemolytic anemia. The examination showed pale skin and mucous membranes, subicterus and splenomegaly (5 cm overflow). The blood count showed an anemia of 11 g/dL, microcytic, and hypochromic. Hemoglobin electrophoresis showed a CC profile with an HbC level of 95.3% and an HbA2 level of 4.7%. The pregnancy went well with good hematological and gynecological follow-up. She gave birth at term by vaginal delivery and returned to Guinea for further care.

The third patient was a 27-year-old from the Ivory Coast, with a notion of second degree consanguinity. He did not report any particular pathological history and did not present any notion of herbal medicine or exposure to toxins. He was seen in a hematological consultation in a context of diffuse abdominal pain. Questioning revealed a long history of abdominal pain since childhood, but no investigations were performed. The clinical examination revealed only diffuse abdominal tenderness without splenomegaly or other signs of orientation. The haemogram showed an Hb level of 12.1 g/dL and microcytosis with a GMV of 76 fl without hypochromia. Hemoglobin electrophoresis showed HbC at 94.6% and HbA2 at 5.4%. He had a good hematological follow-up every 3 months with a clear regression of his abdominal pain frequency.

The following Table 1 summarizes the characteristics of the 3 patients.

3. Discussion

Hemoglobin C is formed as a result of a point mutation at the first nucleotide of codon 6 (GAG AAG) in the beta-globin gene. This is a substitution of guanine for adenine, resulting in the replacement of glutamic acid (the sixth amino acid in the β-chain) with a lysine: $\alpha 2\beta 2$ 6GluàLys. The presence of lysine (a diamine monoacid) in the polypeptide chain results in the replacement of two negative charges by two positive charges. Thus, hemoglobin C migrates less rapidly than

Table 1. Summary of the 3 cases.

Patient	Age and sex	History	Clinical presentation	Hemogram	Hemoglobin electrophoresis	Complications
No. 1	49 years old, F	• Freshwater swimming • 1st degree consanguinity • Brothers who died of abdominal pain • Long history of abdominal pain	• Splenomegaly • Abdominal pain • Anemic syndrome	Anemia (7.6 g/dL)	HbC: 99.2%; HbA2: 0.8%	Gallbladder lithiasis
No. 2	22 years old, F	• 2 miscarriages • Long history of hemolytic anemia • 2nd degree consanguinity	• Clinical Anemia • Subictere • Splenomegaly • Progressive pregnancy (25SA)	Anemia (11 g/dL)	HbC: 95.3%; HbA2: 4.7%	Normal delivery
No. 3	27 years old, M	• Abdominal pain since childhood • 2nd degree consanguinity	Abdominal sensitivity	Hb: 12.1 g/dL	HbC: 94.6% and HbA2:5.4%.	Good clinical evolution

2nd: second; Hb: hemoglobin.

Hb S, at alkaline pH. Hb C, originally described in the Voltaic Plateau, has spread through human migrations to the Gulf of Guinea and North Africa (Morocco, Algeria, Tunisia). It is especially widespread in the Malaria regions of West Africa (Ghana, Côte d'Ivoire, Burkina Faso, Togo, Benin, Nigeria). The prevalence of Hb C is less than 1% in Central Africa and nil in East Africa. Southern Europe, notably Italy and Turkey, is also affected. Hb C is also found in the French West Indies (about 3%) as well as in populations of African origin living in the United States (prevalence = 2400/100,000 blacks) or in the Caribbean (prevalence = 3.5%). It is occasionally found in the Arabian Peninsula, the Near East, the Balkans and Sicily. Erythrocytes containing hemoglobin C are partially dehydrated (with water loss and K^+ efflux), small in size but with a normal hemoglobin load. As the hemoglobin concentration increases, rhombohedral intraerythrocytic crystals are formed and transmembrane ion exchange is disrupted. This leads to hyperviscosity of the RBC. The mechanical resistance is thus decreased while the osmotic resistance remains good. Hb C has a thrombotic rather than a hemolytic tendency. However, this hemolytic tendency exists with the clinical and biological consequences that follow [1] [7] [8].

Through this case series, we note that CC hemoglobinopathy is a rare and under-diagnosed form of hemoglobinopathy in our West African countries where the largest cohort was reported by Padaro in Lomé and included 90 patients carrying Hb CC [7]. In Morocco, Ouzzif. Z in a retrospective study of 111 cases recorded over 12 years found only 8% homozygous carriage of Hb CC and the rest of the cases were A/C (75%), S/C (9%), C/β^+-thal (6%) and C/O-Arab (2%) [8].

All 3 patients had diagnostic confirmation rather late and this was despite their chronic and persistent symptomatology. This diagnostic delay could be explained by the lack of knowledge of this form of major hemoglobinopathy with a negative Emmel test, which is a source of diagnostic delay or errancy. The 3 cases reported in this work have in common minimal to moderate chronic hemolytic anemia, recurrent abdominal pain and splenomegaly of variable size. These clinical symptoms are consistent with the literature where abdominal discomfort dominated the clinical presentation in contrast to SS sickle cell disease where painful attacks are more frequent [3] [4] [7]. Chronic hemolysis has also been found in several case series and some have been able to identify mitigating factors for this hemolysis in patients [7].

In addition, a study on the protection of trait C against malaria like trait S was conducted in Mali in 2015 and they were able to demonstrate that trait C protected patients against severe malaria and malaria complications [9]. Nevertheless, we did not find any study of this protection conducted in individuals carrying the homozygous form.

Due to the absence of a technical platform, we were not able to identify the corresponding type of Hb C in these 3 patients (Hb C Ziguinchor or Hb C Harlem) [1] [2]. However, given the geographical location and symptomatology of the patients, it is more likely that the type is C Ziguinchor than C Harlem.

Finally, all 3 patients were able to start regular follow-up with a plan to screen and confirm the diagnosis in their 1st and 2nd degree relatives.

4. Conclusion

Homozygous CC hemoglobinopathy is a form of hemoglobinopathy that is rare in sub-Saharan Africa and is diagnosed late because of the negativity of the Emmel test, its lack of recognition by some physicians, and above all, the sometimes-difficult accessibility of confirmatory tests. It is still very important to raise awareness among medical personnel and to systematize hemoglobin electrophoresis in the presence of chronic hemolytic anemia.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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