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Research Article

Impact of Haplotypes on the Frequency of Morbid Complications in Homozygous SSFA2 Sickle Cell Disease in Cote D'ivoire

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Abstract

Background: Sickle cell disease is a constitutional hemoglobin disease witch poses a public health problem in Côte d'Ivoire due to its prevalence and complications. The homozygous form (SSFA2) is the most severe. The proportion of hemoglobin F by its property determines the haplotype. Authors wanted to determine the impact of these haplotypes on the frequency of morbid complications.

Methods: Our study was a transversal type and analytical aims, occurred in the clinical hematology department of the University Hospital of Yopougon over a 3 months period. Our study included 150 SSFA2 patients with complications. The statistical test used was the student.

Results: The mean age was 11 years, (6 months to 42 years). The sex ratio was 1.05. The mean rate of hemoglobin S was 86%, of which 17% had severe haplotype, 37% intermediate haplotype, and 45% benign haplotype. Infectious complications were the most frequent (58.72%) (Malaria 53.47%; bronchial pneumonia: 28.22%), followed by anemic complications (36.92%) and ischemic complications (4.36%). Deglobulization crisis was the major acute anemic complication (97.5%) followed by splenic sequestration (2.5%). Chronic anemic complications were dominated by leg ulcers (57.14%) followed by biliary lithiasis (42.86%). Aseptic necrosis of the femoral head was the most frequent ischemic complication (46.66%), followed by retinopathy (33.33%), and then stroke (20%). The severe haplotype was associated with a high frequency of complications in general and infectious complications in particular. (P=0.005)

Conclusion: The clinical expression of the SSFA2 homozygous form and the occurrence of complications is closely related to the haplotype.

Keywords: Complications; SSFA2; Sickle cell disease; Haplotypes

Abbreviations

RBC-SS: Red Blood Cell - SS; Hb: Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; RR: Relative Risk; CI: Confidence Interval

Introduction

Sickle cell disease is a hereditary disease related to an abnormality in the structure of hemoglobin (Hb). It is characterized by the substitution of Glutamic acid (Glu) at position 6 on the β-chain by valine (val), resulting in the synthesis of an abnormal hemoglobin called HbS. Genetically, the GAG codon is substituted by GTG. In Côte d'Ivoire, this disease affects 12% of the population, of which 2% are severe according to a study by Cabannes [1]. It represents a real public health problem due to its frequency and potential severity. It is a disease whose evolution is marked by iterative, hemolytic, and/or ischemic vascular occlusive painful crises, but especially by the occurrence of anemic, ischemic and infectious complications.

During the last three decades, the therapeutic management of patients has improved considerably, allowing an increase in life expectancy and consequently an increase of the population with sickle cell disease, which has been associated with a parallel increase in the incidence of complications. In contrast to hemoglobin S, hemoglobin F (HbF) does not bind 2-3 DPG, hence its hyper affinity for oxygen (O_2), which gives it the property to inhibit the polymerization of hemoglobin and therefore the sickling of the SS red blood cell. The proportion of hemoglobin F in the SS red blood cell over and above the MCHC, hematocrit, blood viscosity, mechanical properties, and the surface/volume ratio of the SS RBC; determines the haplotypes of the SSFA2 phenotype. The severity of the SS haplotype should therefore be inversely proportional to the level of hemoglobin F in the RBC-SS [2]. Considering by definition that in the homozygous form, the proportions vary between: 2 and 20% (HbF); between 77% and 96% (HbS), and 2 to 3% (HbA2), the Haplotype is said to be severe if HbF <5%; intermediate Haplotype if HbF >10% and <5% and benign Haplotype if HbF >10%) [3].

The authors wanted to determine their impact on the frequency of morbid complications in SSFA2 sickle cell disease in the clinical hematology department of the University Hospital of Yopougon.

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Study Material and Methods

Our study occurred in the clinical hematology department of the University Hospital Center of Yopougon in Abidjan, Ivory Coast. It was a prospective cross-sectional study with a descriptive and analytical aim on SSFA2 homozygous sickle cell patients with morbid complications. Our study took place from November, 2015 to March, 2017, i.e., 3 months or approximately 100 days.

150 patients with well-documented records of SSFA2 homozygous major sickle cell disease with at least one complication were analyzed according to systematic random sampling. They were divided into benign, intermediate, and severe haplotypes forming 26; 56 and 68 patients, respectively. Epidemiological, clinical, and paraclinical data were collected.

After separating the patients according to the different haplotypes that we have defined, we performed a comparative analysis using the Epi-Info 6.04 b statistical software. The statistical test used was the Student test. For the P value, the significance level was 0.05. The adjusted Relative Risk (RR) and 95% Confidence Interval (CI) were used to assess the significance of the observed differences.

Results

The mean age in the present study was 11 years, with extremes ranging from 6 months to 42 years. The diagnosis was made for the majority after 1 year old for an average of 4 years and extremes from 6 months to 13 years. There was a predominance of subjects from 0 to 10 years old with a percentage of 53.3% of cases with a peak of frequency for patients over 15 years (36.66%) and the sex ratio was 1.05 (Table 1).

The number of annual vaso occlusive crises was lower than 3 for 26.66% of our patients (n=40) and between 3 and 6 for 63.33% (N=95) and higher than 6 for 10% (N=15). The frequency of crisis varied from one series to another.

We counted 344 cases of progressive complications. Infectious complications represented 58.72% (N=202) of cases, followed by anemic complications (36.92%) (N=127) and ischemic complications (4.36%) (Table 4).

Of the 127 cases of anemic complications, acute complications predominated with 120 cases including Deglobulization crisis with 97.5% (N=117) against 2.5% of splenic sequestration. We observed 7 cases of chronic anemic complications with a clear predominance of leg ulcer (57.14%; N=4) against 42.86% of pigment lithiasis. In all 344 cases, the overall prevalence of leg ulcers was 1.16% compared to 0.8% for the overall prevalence of pigment lithiasis. The mean rate of hemoglobin S was 6.5 with extremes of 2.3 to 10.5 g/dl.

Three types of ischemic complications were found: aseptic osteonecrosis (46.66%, N=7), ocular complications (33.33%, N=5) and stroke (20%, N=3). Of the 344 cases, osteonecrosis accounted for 2.03% of these complications. Ocular complications and stroke accounted for 1.45% and 0.87%, respectively.

A total of 202 cases of infectious complications were reported: the major infectious complication was malaria (53.47%), which was followed by the most frequent sites: pulmonary (28.22%; N=57), skin (3.47%; N=7), ear, nose and throat (ENT) (2.97%; N=6), osteomyelitis (1.49%; N=3) and urinary tract infections (0.5%; N=1), but also without a focus (9.9%; N=20).

Depending on the phenotype, hemoglobin S ranged from 75 to 98% with a mean rate of 86%. Hemoglobin F was less than 5% in 17% of the patients, between 5 and 10% in 37% of the patients, and more than 10% in 45% of the patients (Table 2). Hemoglobin F percentage ranged from 2 to 15% with a mean of 9.5%.

The analysis of the results (Table 3) showed no statistically significant relationship between the haplotypes and the number of annual infectious episodes (P=0.16); the number of annual vaso occlusive crises (P=0.63); the number of annual hospitalizations (P=0.07), the number of transfusions (p=0.05), the hemoglobin level (p=0.05) and the number of white blood cells. (p=0.05).

On the other hand, there was a statistically significant relationship between the haplotypes and the occurrence of complications in general and infectious complications in particular (p=0.005) (Table 3).

Table 1: Distribution by age and gender.

	Effective	Percentage (%)
Sex (sex-ratio = 1.05)		
Male	77	51.3
Female	73	48.7
Age (years old) (Mean = 11; Min = 6 months; Max = 42 years old)		
0-5	45	30
6-10	35	23.3
11-15	15	10
>15	55	36.66
Discovery age (Mean = 4 years; Min = 6 years; Max = 13 years)		
6 months	8	5.33%
1 year	10	6.66%
>1 year	132	88%

Table 2: Distribution according to the Hb fraction of the red blood cell.

	Effective =150	Percentage
Proportion of S fraction: Med: 86% Mean: 84% (Min = 75% - Max = 98%)		
75-80%	21	14%
80-85%	36	24%
85-90%	55	37%
90-95%	29	19%
>95%	9	6%
Proportion of F fraction: (Med = 8.2%; Mean = 9.5%; Min = 2% - Max = 15%)		
<5% (Severe haplotype)	26	17.33%
5-10% (Intermediate haplotype)	56	37.33%
>10% (Benign haplotype)	68	45.33%
Proportion of A2 fraction: (Med = 1.83%; Mean = 1.5%; Min = 1% - Max = 7%)		
1-5%	110	73%
>5%	40	27%

Table 3: Distribution of complications according to haplotype.

	Haplotype						P-Value
	Severe		Intermediate		Benign		
	N=26	%	N=56	%	N=68	%	
Annual number of hospitalizations							
<3	7	26.92%	22	39.29%	24	35.29%	P=0.07
3-6	5	19.23%	23	5.36%	0	0	
Annual number of vaso-occlusive crises							
1-3	7	26.92%	16	28.57%	17	25%	P=0.06
3-6	18	69.23%	35	62.50%	42	61.76%	P=0.07
≥6	1	3.85%	5	8.93%	9	13.24%	P=0.05
Hb rate (g/dl) (Med = 6.87; Mean = 6.5; Min = 2.3; Max = 10.5)							
<6	13	50%	26	46.43%	35	51.47%	P=0.05
6-9	9	34.62%	17	30.36%	23	33.82%	P=0.06
>9	4	15.38%	13	23.21%	10	14.71%	P=0.06
Annual Blood Transfusion Number							
1-3	5	19.23%	10	17.86%	17	25%	P=0.05
3-6	1	3.85%	0	0	6	8.82%	

Table 4: Distribution of the nature of the evolutionary complications according to haplotypes.

Evolving Complications	Phenotype			P-value	Total N(%)
	Benign N(%)	Intermediate N(%)	Severe N(%)		
Infectious	42(20.8)	76(37.6)	84(41.58)	P=0.005	202(58.72)
Ischemic	3(20%)	6(40)	6(40)		15(4.36)
Anemic	23(18.1%)	51(40.50)	53(41.73)		127(36.92)
Total	68(19.76)	133(38.66)	143(41.56)		344(100)

Discussion

There seemed to be a male predominance with a sex ratio of 1.05, but sickle cell disease is not a sexually transmitted disease, so the differences in the results observed between different series could be explained by a recruitment bias. In fact, local work from previous theses in 2002 [4], also found a male predominance with a sex ratio that was higher up to 1.53. In Revenge, in the West African region [5], more recently in 2019 a female predominance was evoked with a sex ratio of 0.81.

The average age of patients with sickle cell disease is increasing with the improvement of management. In our study, it was 11 years, with extremes ranging from 6 months to 42 years, with nearly 37% of patients over 15 years old (Table 1). From a relatively low average of around 11 years in the 1980s [6], then 14.5 (2 to 38 years) between 1990 and 2000 [7]; it is nowadays around 21 years (06 months and 62) [8]. Nevertheless, there is a variability in the average age due to the heterogeneity of the different series in relation to the selection criteria.

The proportion of hemoglobin S ranging from 75 to 98% with a mean of 86% was inversely proportional to the level of hemoglobin F, which ranged from 2 to 15% with a mean of 9.5%. In contrast to hemoglobin S, hemoglobin F does not bind 2-3 DPG, hence its high affinity for O_2, which gives it the property of inhibiting hemoglobin polymerization and therefore sickling of SS red blood cells. The proportion of hemoglobin F in the red blood cell determines the haplotypes of the SSFA2 phenotype [3] in addition to the MCHC, hematocrit, blood viscosity, mechanical properties and surface/volume ratio of SS-RBC.

Haplotype was said to be severe if HbF <5%; intermediate haplotype if HbF >10% and <5% and benign haplotype if HbF >10%. It has been shown that a level of hemoglobin F >10% prevents the occurrence of chronic organic complications [2]. In addition, according to several authors, the percentage of hemoglobin F is a modulating factor in the clinical expressiveness of sickle cell disease [9]. In our study, 17% of the patients had a benign haplotype, 37% an intermediate haplotype, and 45% a severe haplotype (Table 2).

Most authors estimate the annual number of attacks to be between 1 and 5 [4,9], thus corroborating the results of our series (Table 3), but the haplotypes did not have a statistically significant influence on the number of annual vaso occlusive attacks (P=0.63). Several authors including Bailet [10] state that it is established that the hemoglobin F level modulates the severity and not the number of sickle cell crises. This mechanism is explained by the fact that fetal hemoglobin interrupts the growth of the hemoglobin F polymer, thus blocking the gelification and sickling phenomenon which are responsible for the vaso occlusive crisis of sickle cell disease.

Our result was in contradiction (Table 3) with those of the literature and Akinsheye [11], who showed a statistically significant

correlation between the level of hemoglobin F and the number of annual hospitalizations. In the same study [11], on the level of Hb F and the clinical severity of the disease in sickle cell patients, a correlation was found between the level of Hb F and the number of transfusions. This difference could be explained by the fact that our sample included only patients with complications. Furthermore, 35% of the patients had a hemoglobin level below 6 grams per deciliter and there was no statistically significant relationship between the hemoglobin level and the haplotype. Except for intolerance, patients were systematically transfused only below 6g/dl

Concerning the different evolving complications, the analysis of our results showed that there was a statistically significant relationship between the haplotypes and the occurrence of complications in general and infectious complications in particular (p=0.005). This was partly explained by the high endemicity of plasmodial infection in our region. Even if the protection against severe forms of malaria is known in sickle cell disease, the malaria attack through fever and rheological disturbances created by the parasite is at the origin of hemolytic crises which can be severe. Most authors have noted a predominance of pulmonary and bone complications [6,13,14]. This susceptibility to infection in sickle cell patients is explained by functional asplenia and the reduced opsonizing power of the serum towards encapsulated germs. It appears from this analysis that patients with a severe haplotype have more complications than others. Our result is in agreement with that of Kueviakoe [12] who observed in his study on the influence of the hemoglobin F level on the progressive profile of sickle cell disease that the complications are less when the Hb S level is high. However, it has also been shown that a hemoglobin F level >10% prevents the occurrence of chronic organic complications [15]. Indeed, previous studies had already described the protective effect of Hb F against ischemic complications such as osteonecrosis [16], retinopathy [17], and leg ulcers [18]. Similarly, the effect of the β globin gene haplotype has been studied, finding an increasing severity of the following haplotypes: Senegal, Arab-Indian, Benin and Bantu. In the latter case, the baseline HbF level is lower, which would explain more organ damage [19].

Conclusion

The prospective transversal study, which took place in the clinical hematology department of the University Hospital of Yopougon on 150 patients had the general objective of evaluating the impact of haplotypes on the frequency of morbid complications in homozygous sickle cell disease (SSFA2).

Analysis of the results showed no statistically significant relationship between the haplotypes and the number of annual infectious episodes; the number of annual vaso-occlusive crises; the number of annual hospitalizations; and the number of transfusions, hemoglobin levels and white blood cell counts. (p=0.05). However, there was a statistically significant relationship between the haplotypes and the occurrence of complications in general and infectious complications in particular.

The clinical expression of the SSFA2 homozygous form and the occurrence of complications is closely related to the haplotype.

Limitation

The main limits of this study were related to its retrospective nature.

Declarations

Consent to participate: The informed consent obtained from study participants was written.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Data availability: The data sets used and/or analyzed during the current study are available from the corresponding author on request.

Authors' contributions: Silue and Koffi collected data from files of patients. K-KG: Designed the study. S-D: A wrote the manuscript. KKG: Supervised this work. All authors reviewed the final manuscript and agreed for submission.

References

1. Cabanne R, Bonhomme J, Sendrail A. La Drépanocytose, problème de santé publique. Ann Univ ABJ Série B. 1970; 4: 141-147.
2. Powars DR, Weiss JN, Chan LS, Schroeder WA. Is there a threshold level of fetal hemoglobin that ameliorates morbidity in sickle cell anemia? Blood. 1984; 63: 921-926.
3. Platt OS, Thorington BD, Brambilla DJ, Milner PF, Rosse WF, Vichinsky E, et al. Pain in sickle cell disease. Rates and risk factors. N Engl J Med. 1991; 325: 11-16.
4. Sekongo YM. Prévalence des complications et facteurs de risque dans les drépanocytoses majeures. Thèse Médc Abidjan, UFR Sc Med. 2002; 3051.
5. Kueviakoe MD, Padaro E, Magnang H, Mawussi K, Womey KMC, Layibo Y, et al. Complications Chroniques de la Drépanocytose dans une Population de 893 Patients, Adultes Suivis au CHU Campus de Lomé. European Scientific Journal. 2019; 15: 12.
6. Cabannes R, Sangare A, Kple-faget P, Bassimbie J. Prise en charge de la drépanocytose: Expérience ivoirienne. Ann Univ Abidjan Série B (Méd.) Tome. 2021; XXI: 176-185.
7. Tolo A, Touré A, N'dhatz , Nanho D C, Kouakou B, Sanogo I. et al. Profil évolutif de la drépanocytose homozygote suivie: expérience du service d'hématologie clinique du CHU de Yopougon. Med Afr Noire. 2006; 53: 5-10.
8. Konate BI, Sangare A. Profil hématologique de la drépanocytose homozygote en Côte d'Ivoire expérience du service d hématologie clinique du chu de Yopougon. Thèse Méd. Abidjan, UFR Sc. Med. 2006; 4305.
9. Kouehion P. Influence de l'hémoglobine F dans la drépanocytose Homozygote Thèse Méd. Abidjan. 1994: N°1543.
10. Bailey K, Morris JS, Thomas P, Serjeant GR. Fetal haemoglobin and early manifestations of homozygous sickle cell disease. Arch Dis Child. 1992; 67: 517-520.
11. Akinsheye I, Alsultan A, Solovieff N, Nadia Solovieff, Ngo D, Baldwin TC, et al. Fetal hemoglobin in sickle cell anemia. Blood. 2011; 118: 19-27.
12. Kueviakoe N'zouonta V, Agbetiafa K, Padaro E, VovorA, SegbenaA Y. Influence du taux d'hémoglobine F sur le profil évolutif de la drépanocytose homozygote au Togo. J. Rech. Sci. Univ. Lom (Togo). 2010; 12: 243-248.
13. Elira-dokekias A. Etude analytique des facteurs d'aggravation de la maladie drépanocytaire au Congo Pub. Méd. Afr. 1994; 131: 12-16.
14. Pegelow CH, Colangelo L, Steinberg M, Wright EC, Smith J, Phillips G. Natural history of blood pressure in sickle cell disease: risks for stroke and death associated with relative hypertension in sickle cell anemia. Am J Med. 1997; 102: 171-177.
15. Powars DR, Weiss JN, Chan LS, Schroeder WA. Is there a threshold level of fetal hemoglobin that ameliorates morbidity in sickle cell anemia? Blood. 1984; 63: 921-926.
16. Hawker H, Neilson H, Hayes RJ, Serjeant GR. Haematological factors

associated with avascular necrosis of the femoral head in homozygous sickle cell disease. Br J Haematol. 1982; 50: 29-34.

17. Fox PD, Dunn DT, Morris JS, Serjeant GR. Risk factors for proliferative sickle retinopathy. Br J Ophtalmol. 1990; 74: 172-176.

18. Koshy M, Entsuah R, Koranda A, Kraus AP, Johnson R, Bellvue R, et al. Leg ulcers in patients with sickle cell disease. Blood. 1989; 74: 1403-1408.

19. Nagel RL, Rao SK, Dunda-belkhodja O, Connolly MM, Fabry ME, Georgesand A, et al. The hematologic characteristics of sickle cell anemia bearing the Bantu haplotype: the relationship between Gγ and hemoglobine F level. Blood. 1987; 69: 1026-1030.