

Characteristics and Predictive Factors of Chronic Complications in a Cohort of Hemoglobin Sc Disease Patients from Dakar, Senegal

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Abstract: Hemoglobin SC disease is characterized by less severe morbidity than in homozygous form. Nevertheless vaso-occlusive crisis was reported to be less frequent, some chronic complications are more frequent, such as retinopathy and osteonecrosis of femoral head. This study aimed to describe the chronic complications of Hb SC disease patients and to identify associated predictive factors. This cohort included 132 Hb SC patients followed between 1995 and 2015 with a mean of 6.2 patients/year. Patients were monitored with at least two medical visits per year. Screening for chronic complications was performed every two years by biological and radiological analyzes. Bivariate analysis was carried out to evaluate the predictive factors of chronic complications. Medium age was 42 years (4-73). Median number of follow-up was 14 years (3-21). Sex ratio (M/F) was 0.85. Circumstances of discovery were bone pain (73.5%), fortuitous discovery (12.9%) or chronic complications (5.3%). Mean number of vaso-occlusive crisis/year was 1 (0 - 5). Twenty seven patients (19.4%) had chronic complications including osteonecrosis of femoral head (11.3%), retinopathy (9.8%) and chronic osteomyelitis (3%). Risks factors identified were age ($p = 0.0006$), irregular follow-up ($p = 0.007$) and high white blood cell count ($p = 0.002$). This study confirms that Hb SC disease is associated with a recrudescence of chronic complications. Osteonecrosis of the femoral head and retinopathy are more frequently described. Two predictive factors of these chronic complications that are rarely described have been identified in our patients: irregular follow-up and high number of white blood cells count.

Key words: Hb SC disease, retinopathy, osteonecrosis of femoral head, Senegal

INTRODUCTION

Hb SC disease is the most common major sickle cell syndrome in West Africa after the homozygous form (1,2), characterized by the presence of two abnormal hemoglobins due to two distinct mutations in β -globin chain: S hemoglobin and C hemoglobin (3).

Hemoglobin C in the red blood cell leads to intracellular dehydration by activation of K-Cl transporter. This causes the polymerization of hemoglobin S to cause acute or chronic manifestations of Hb SC disease patients (4,5).

Hb SC disease morbidity is moderate, characterized by less frequent or less severe complications than SS sickle cell anemia (6,7). Nevertheless vaso-occlusive crisis (VOC) have been reported to be less frequent, some chronic complications are more frequent, such as retinopathy and osteonecrosis of femoral head (8,9,10).

Improved management of patients with major sickle cell syndromes has resulted in an increase in life expectancy in both developed and developing countries (1,11). Thus, more frequent are the chronic complications which occur towards the 3rd - 4th decade of evolution of the disease. These chronic complications correspond to irreversible damage to several organs including bone, kidney, retina, lung, brain etc (1,5).

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In Senegal, there are no studies evaluating clinical features or chronic complications of Hb SC disease patients. There is a need to study morbidity and outcome aspects of these patients. Having predictive factors for the occurrence of these chronic complications would make it possible to carry out their early diagnosis, propose targeted treatment and thus have an impact on the cost of care and on the quality and life expectancy of patients. This study aims to determine the socio demographic, clinical and biological characteristics, and to look for chronic complications and their predictive factors. The recognition of such factors would better target screening for these complications and improve the early diagnosis and management.

PATIENTS AND METHODS

Patients

The study included 132 Hb SC disease patients among 1376 patients followed for a major sickle cell syndrome (9.5%). Diagnosis of Hb SC disease was confirmed by alkaline hemoglobin electrophoresis. All patients regularly followed had at least two medical visits per year and any patient had a medical record listing socio-demographic, clinical and biological and outcome data.

Methods

This cohort study was started in 1995 and patients were progressively unrolled and followed until 2015.

Socio-demographic data were age, sex, profession, scolarity status, sibling size, number of Hb SC disease patients in the family, regularity of follow-up (follow-up is considered regular if the patient had at least two medical visits per year).

Clinical data were circumstances of discovery, age of first symptoms, age at diagnosis, history of transfusion, history of hospitalizations and number of VOC.

Chronic complications screening were osteonecrosis, retinopathy, leg ulcer, biliary lithiasis, renal and cardiac failure. The screening for these chronic complications was performed every two years by a medical imaging exams or laboratory tests. This assessment included abdominal ultrasound, electrocardiogram, echocardiography, pelvis X-ray, retinal angiography, micro albuminuria.

Full blood count was carried out of vaso occlusive crisis. The diagnosis of Hb SC disease was established using hemoglobin electrophoresis on cellulose acetate and agar gel electrophoresis using a sodium citrate buffer solution and sickle cell test if needed.

STATISTIC ANALYSIS

Data collection was done according to a survey sheet. Data was entered into the computer with Epi info version 6 and analyzed with statistical analysis system (SAS). Descriptive analysis was realized with a quantitative study (mean and standard deviation: SD) and a qualitative study (proportions, confidence interval). Bivariate analysis was carried out by comparing the proportion of two qualitative variables using chi-square test or Fisher test and the comparison of the means by Anova test and Student's t test. These tests were performed according to their condition of applicability and significance p (probability of error) was fixed: $p \leq 0.05$.

RESULTS

Socio-demographic, clinical and biological characteristics

Mean age of our patients was 26.3 years (4 – 73 years) and median number of follow-up was 14 years (3 – 21 years). Sex ratio (M/F) was 0.85. Thirty-five patients (26.5%) were not in school. Mean number of Hb SC disease patients in the family was 1.5 (1 - 3). Average number of siblings was 4.7 (1-11) (Table I).

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Mean age of first painful symptoms was 8.5 years (1 - 31). Mean age at diagnosis was 19.2 years (1 - 47). The circumstances of diagnosis consisted on bone pain (73.5%), fortuitous discovery (12.9%) during family screening, pregnancy or health check, or chronic complications (5.3%). Mean number of VOC per year was 1 (0 - 5), 58 patients (43.9%) had never VOC, 57 patients (43.2%) had 1 to 2 VOC/year and 17 patients (12.9%) had a number of VOC/year \geq 3. Mean number of hospitalization per patient was 1.8 (0 - 6). Five patients (3.8%) had a history of blood transfusion. Twenty-five patients (18.9%) were regularly follow-up (Table I). Twenty seven patients (19.4%) had chronic complications such as osteonecrosis of femoral head (11.36%), sickle cell retinopathy (9.84%) and chronic osteomyelitis (2.27%). Four patients had both osteonecrosis and retinopathy (table I).

Table I. Baseline characteristics of patients

Parameters	Value (Number/%)
Sex (Male, Female)	62/46.9, 70/53.1
Scolarity	97/73.5
No vaso-occlusive crisis	58/43.9
History of hospitalization	39/28.6
History of transfusion	5/3.8
Irregular follow-up	107/18.9
Osteonecrosis of femoral head	15/11.3
Retinopathy	13/9.8
Chronic osteomyelitis	3/2.3

According to biological data, mean hemoglobin S was 50.8% (13 - 60.5), mean hemoglobin C was 42.2% (13 - 58.5), mean hemoglobin F and hemoglobin A2 were respectively 2.1% (0 - 7) and 1.54% (0 - 2.7), mean HGB level was 10.5 g/dl (7 - 14), mean HCT level was 32.1% (23 - 52.1), mean WBC count was 6,9 G/l (1 - 18), MCV was 74.8 fl (28 - 96), MCH was 26.2 pg (20 - 32) and mean PLT counts was 311,9 G/L (28 - 803).

Predictive factors associated with chronic complications (table II)

Table II. Predictive factors of chronic complications (Group I: patients with chronic complications, Group II: patients without chronic complications)

Parameters	Group I (n=27)	Group II (n=105)	P
Age (Mean/SD)	33.9/10.7	24.9/12	0.0006
Scolarity (Yes/No)	22/5	75/30	0.89
Size of siblings (Mean/SD)	5.1/2.1	4.6/2.4	0.37
Age of first symptoms (Mean/SD)	9.1/4.4	8.4/6.1	0.57
Hospitalization (Yes/No)	12/15	27/78	0.57
Hemoglobin level (Mean/SD)	10.6/1.5	10.5/1.4	0.75
Hematocrit (Mean/SD)	32.1/2.7	31.1/2.1	0.82
Hemoglobin C level (Mean/SD)	43.8/3.9	45.5/4.9	0.09
Hemoglobin S level (Mean/SD)	45.1/4.1	44.8/4.8	0.08
WBC count (Mean/SD)	8327/2558.6	6575.7/2693.1	0.003
PLT count (Mean/SD)	326.9/139.3	308/155.3	0.56
MCV (Mean/SD)	76.6/7.4	74.3/9.4	0.25

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Socio-demographic factors associated of the occurrence of chronic complications was only age of patient ($p = 0.0006$). The occurrence of complications was not significantly influenced by sex, socio-economic status, educational level, sibling size.

Chronic complications were significantly more frequent in patients who had an irregular follow-up ($p=0.007$). The occurrence of chronic complications was not significantly influenced by age at diagnosis, age of first symptoms, history of transfusions, number of vaso-occlusive crisis per year and history of hospitalizations.

Patients with chronic complications had significantly higher white blood cell counts ($p=0.002$). The occurrence of chronic complications was not significantly influenced by hemoglobin level, platelet count, hemoglobin F, hemoglobin C and MCV.

DISCUSSION

Mean age of our patients was 26.3 years (4 –73 years) and more than half of the patients (53.78%) were over 25 years older. Our results are similar to those described in this study with a mean age of 27.3 years **(14)**, however a higher average age of 35.8 years was reported in Hb SC disease **(10)**. Others studies confirm the hypothesis that Hb SC disease is characterized by longer life expectancy approaching that of the normal population **(8,9,11)**.

The high schooling rate with a high number of patients reaching higher scolarity level can be explained by the lower severity of Hb SC disease with more spaced VOC resulting in a lower scolarity absenteeism rate **(6)**.

Female sex predominated was reported in some studies while in others the distribution is the same in both sexes **(15)**. But we can consider that this female predominance is only related to a random distribution as sickle cell anemia is an autosomal genetic disease whose the defective gene transmission is not related to sex.

The average age of first clinical symptoms dominated by bone pain in our patients was about 9 years and for some patients, symptoms had occurred after 20 years older. Mean number of VOC per year was 1 VOC/year and 44% of patients had never VOC. Indeed, Nagel reported an average of 0.4 VOC/patient/year in Hb SC disease, less than half as much as Hb SS sickle cell anemia **(9)**. Moreover, Poward reported that 60% of Hb SC disease patients had less than one VOC/year **(16)**. In Africa, a study showed an Hb SC disease clinical expression more severe because of 82% of patients presented VOC with a high frequency of infections that are the main trigger **(17)**.

We found that our patients were less transfused (3% of patients). These results are comparable to those found in this study where only 16% of the patients were transfused and confirm that Hb SC disease is a non-anemic form of sickle cell disease **(17)**. Hemogram data outside of any VOC showed an average hemoglobin level of 10.5 g/dl and a mean MCV was 74.8 fl.

It is described in the absence of any aggravating factor, Hb SC disease is characterized by an absence of anemia or a basic hemoglobin near normal associated microcytosis reflecting the lesser severity of hemolysis in this disease **(17)**. In some studies lower basal hemoglobin levels close to those described in the homozygote form have been reported **(17,18)**. The other parameters of blood count had not presented major disruptions as previously described in other studies **(6,18)**.

Hemostasis factors influencing HbSC morbidity have been described. Protein C and free Protein S are reduced in crisis with lower numbers of platelet microparticles and higher percentage of markers of endothelial damage and of red cell origin. During chest crisis, adrenomedullin and endothelin-1 were elevated suggesting a role for therapy inhibiting endothelin-1 in chest crisis **(19)**.

The frequency of chronic complications of Hb SC disease is differently assessed according to the series. We found in our study a prevalence of 19.4% of patients who had sickle cell chronic complications such as osteonecrosis of femoral head, retinopathy and chronic osteomyelitis. We also find a delay in the diagnosis of these chronic

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complications with an average age of 33 years. This delay can be explained by the advanced age of patients at diagnosis in part related to the delay of onset of clinical symptoms. This confirms the relatively good tolerance of Hb SC disease (6,7) because 44% of our patients had never VOC. This lower clinical expression may explain why Hb SC disease patients were not regularly monitored, which can also be responsible for the delay observed in the diagnosis of chronic complications.

The high incidence of chronic complications of the femoral head and ocular in Hb SC disease is already reported in several studies (1,12). However, the frequency of osteonecrosis of femoral and humeral heads according to the genotype is often debated and varies according to the studies. In some studies comparing the homozygous form, the prevalence of osteonecrosis was not higher in SC sickle cell disease than in SS sickle cell anemia (12).

Proliferative and non-proliferative retinopathy is a frequent complication in major sickle cell syndromes. It is secondary to peripheral retinal capillary occlusion related to the sickling of red blood cells with lesions generally affecting the temporal. Hb SC phenotype is found in all series as the major risk factor for development of neovascular vessels responsible for sickle cell retinopathy (13,14). Proliferative retinopathy is more frequently described in SC sickle cell patients with a high prevalence affecting about half of patients (10,14).

Systematic screening for these two ischemic complications is required at least every two years by pelvic X-ray and retinal angiography.

The other type of chronic complication found in our study is chronic osteomyelitis which is not usually described in Hb SC disease patients.

Risk factors associated with these chronic complications in our study were age, irregular follow-up and high white blood cell counts. Irregular follow-up and high white blood cells counts are rarely reported (17). However, other risk factors were frequently described such as low hemoglobin F level, low mean corpuscular volume, high hemoglobin level and hand-foot syndrome (20,21).

The incidence of sickle cell retinopathy increases with age from about 2.5 cases/year/100 subjects in SC sickle cell disease (22,23). Factors influencing the occurrence of osteonecrosis of femoral head are mainly hemorheologic in response to high hemoglobin or high hematocrit level (24,25). The increase in blood viscosity is accompanied by rheological disorders responsible for sickling and vaso-occlusion especially of the sinusoids of the femoral head (26). Therefore the absence of anemia in Hb SC disease may explain why this complication is frequent. A prospective study researching the existence of a threshold value of hemoglobin levels beyond which the risk of developing osteonecrosis is substantial necessary.

The rarity of painful manifestations in SC sickle cell patients may explain why patients are irregularly monitored, which exposes them to chronic complications. Moreover, the authors had already shown that a regular medical follow-up could explain the significant decrease in the frequency of osteonecrosis of femoral head (20). The interest of regular follow-up is the regular assessment of patient's clinical health but also in screening for chronic complications.

CONCLUSION

This study allowed us to confirm that SC sickle cell disease is associated with a recrudescence of chronic complications such as osteonecrosis of femoral head and retinopathy. Two risk factors for the occurrence of these chronic complications rarely described have been identified in our patients: irregular follow-up and high white blood cell count. These factors should allow to better target patients for whom screening for complications should be more systematic. This strategy could be evaluated in prospective studies, especially in countries with limited resources where chronic complications are often diagnosed at later stages of their development.

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