Hemoglobin SC disease complications: a clinical study of 179 cases

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ABSTRACT

Background
Hemoglobin SC disease is one of the most frequent hemoglobinopathies. Surprisingly, few studies have been dedicated to this disease, currently considered to be a mild variant of homozygous SS disease. The aim of this study was to update our knowledge about hemoglobin SC disease.

Design and Methods
The study involved a single center series of 179 patients. Clinical and biological data were collected with special attention to the assessment of pulmonary arterial hypertension and nephropathy.

Results
Hemoglobin SC diagnosis was delayed and performed in adulthood in 29% of cases. Prevalence of hospitalized painful vasoocclusive crisis, acute chest syndrome and priapism was 36%, 20% and 20%, respectively. The most common chronic organ complications were retinopathy and sensorineural otological disorders in 70% and 29% of cases. Indeed, prevalence of complications reported in homozygous SS disease, such as nephropathy, suspicion of pulmonary hypertension, strokes and leg ulcers was rather low (13%, 4% and 1%, respectively). Phlebotomy performed in 36% of this population (baseline hemoglobin 11.5 g/dL) prevented recurrence of acute events in 71% of cases.

Conclusions
Our data suggest that hemoglobin SC disease should not be considered as a mild form of sickle cell anemia but as a separate disease with a special emphasis on viscosity-associated otological and ophthalmological disorders, and with a low prevalence of vasculopathy (strokes, pulmonary hypertension, ulcers and nephropathy). Phlebotomy was useful in reducing acute events and a wider use of this procedure should be further investigated.

Key words: hemoglobin SC disease, sickle cell anemia, nephropathy, pulmonary arterial hypertention, retinopathy, hyperviscosity, otologic disorders, anemia, phlebotomy.

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Introduction

Hemoglobin sickle cell disease (HbSC) is the second most frequent hemoglobinopathy after homozygous sickle cell disease, also called sickle cell anemia (SCA).[1] There are an estimated 54,736 babies born with HbSC disease each year worldwide.[1] Most of our knowledge about HbSC disease pathophysiology comes from studies performed in SCA that has been the focus of great interest for decades. The primary event in the pathogenesis of SCA is hemoglobin "sickle" (HbS) polymerization occurring in deoxygenated erythrocytes. The sickled erythrocytes obstruct vessels and have a reduced red cell life span, leading to hyperhemolysis, diffuse vasculopathy and to tissue damage in various target organs. Hemoglobin composition in HbSC erythrocytes is approximately 50% HbS and 50% hemoglobin C (HbC). While individually HbS and HbC trait have no clinical consequence, HbSC is accompanied by significant clinical abnormalities. The main reason is that HbC enhances the formation of intracellular polymer of HbS by dehydrating red cells.[2,3]

The major acute features of SCA are recurrent painful vasoocclusive crisis (VOC) and acute chest syndrome (ACS), priapism and anemia. Chronic organ dysfunctions are of increasing concern in adult patients leading to life-threatening end-stage organ failures. They include cerebral vasculopathy leading to stroke, leg ulcers, retinopathy and osteonecrosis. Recently, sickle cell anemia-associated nephropathy (SCAN) and pulmonary arterial hypertension have received special attention. Sickle cell anemia-associated nephropathy was reported to be the most frequent chronic organic feature in SCA with a prevalence of approximately 80%,[4] whereas suspected pulmonary arterial hypertension (assessed by a tricuspid regurgitant jet velocity (TRJV) of at least 2.5 m per second in Doppler ultrasound) is found in 30% of SCA patients and has been associated with a worse prognosis.[5]

Curiously, whereas SCA clinical features have been extensively studied, very few studies have been dedicated specifically to HbSC disease.[3,6-9] Indeed, HbSC disease is generally considered to be a variant of SCA, sharing similar clinical complications though with a milder severity and a lower frequency.[7] Therefore, the aim of our study was to examine the specific clinical and biological features of HbSC disease in a single center patient cohort.

Design and Methods

Patients

One hundred and seventy-nine adult HbSC patients (age ≥ 18 years) who consecutively attended the sickle cell disease center at Tenon Hospital between January 2007 and November 2010 were included in this observational study. All enrolled patients gave their oral consent. The study was conducted in accordance with French ethical laws and was approved by the local ethical committee. The comparison between HbSC disease and SCA related to renal involvement was made with the population of SCA patients treated in the same center and described elsewhere.[4]

Data collection

Epidemiological and clinical data relating to geographical origin, place of birth, age, disease onset, comorbidity, obstetrical history, and past and ongoing treatments were collected. Hospital admissions were also recorded, especially for painful VOC, ACS, bone marrow embolism, spleen infarcts, and severe infectious complications. We recorded painful VOC that required at least a consultation at the emergency department and/or hospitalization within the last three years before inclusion in this study. Acute chest syndrome was recorded according to the current criteria: new infiltrate visible on chest X-ray associated with one or more symptoms, such as fever, cough, tachypnea, breathing difficulties or new-onset hypoxia. All sickle related organ involvements, in particular a history or presence of retinopathy, avascular bone necrosis, glomerulopathy, stroke, priapism, leg ulcers, gallbladder disease, vertigo, and hypoacousia and/or pulmonary arterial hypertension were carefully recorded. Sensorineural otological disorders (whether these required hospitalization or not) were recorded according to the following criteria: i) prolonged vertigo with clinical vestibular syndrome confirmed by video-oculography; and/or ii) fluctuating or permanent hearing loss confirmed by audiometric tests.

Laboratory methods

Laboratory tests were performed as part of a routine diagnostic and therapeutic evaluation. Albumin excretion rate (AER) was defined as normoalbuminuria (AER < 5 mg/mmol creatinine), microalbuminuria (AER from 5-30 mg/mmol creatinine), or macroalbuminuria (AER > 30 mg/mmol creatinine). We defined renal insufficiency as an estimated glomerular filtration rate (eGFR) (calculated according to the MDRD formula) below 60 mL/min per 1.73 m^2 and renal hyperfiltration as an eGFR above 130 mL/min per 1.73 m^2 for women and above 140 mL/min per 1.73 m^2 for men.[4] All patients were systematically screened for pulmonary arterial hypertension by echocardiography performed by an experienced physician. Peak tricuspid regurgitation jet velocity assessed by Doppler ultrasound was recorded in multiple views and the highest level of velocity was selected. To define a suspected pulmonary arterial hypertension, a threshold of 2.5 m/s is usually used. However, this value was recently increased to 2.9 m/s.[10] When TRJV was not measurable, peak velocities of pulmonary regurgitation and pulmonary acceleration time were recorded. One patient with severe mitral and severe aortic rheumatic regurgitations was excluded from the analysis. Routine ophthalmological visit included visual acuity, direct and indirect ophthalmoscopy and, when indicated, fluorescein angiography and laser photocoagulations. Audiometric tests were only performed in subjects complaining of hearing disturbances or vertigo. Similarly, X-rays for osteonecrosis were only performed in subjects complaining of bone pain at steady-state. Cerebral imaging was only performed in patients complaining of neurological symptoms (e.g. transient stoke, persistent headheaches) in accordance with the current guidelines.

Phlebotomy

Therapeutic phlebotomy was routinely proposed for patients with hemoglobin concentration values above 10.5 g/dL experiencing at least one of the following complications: ACS, one painful VOC requiring a consultation at the emergency department or hospitalization, more than 3 ambulatory VOC requiring bed rest in the previous year. Phlebotomy was also proposed for priapism, otological disorders (hypoacousia or vestibular syndrome), spleen infarct or arterial thrombosis (cerebral or myocardial). The phlebotomy program included weekly venesection until a hemoglobin target of 9.5 g/dL was reached. Thereafter, phlebotomy was performed to maintain hemoglobin between 9.5 and 10.5 g/dL, with a 2-3 month monitoring schedule. Good clinical results were defined as the absence of pain requiring unplanned health care, a 50% decrease in ambulatory acute VOC or priapism episodes, no vestibular syndrome recurrence and/or no hypoacousia aggrava-

tion, and no spleen infarct or recurrence of arterial thrombosis. Patient data were considered not to be evaluable if the patient discontinued the program before the target hemoglobin level was reached.

Results

Demographic findings

In our study cohort, 97 (54%) patients were women and 82 (46%) were men. Median age was 29 years (mean 31.1 years, range 18-68). Patients came from 17 different African (n=122) or West Indian (n=57) countries (*Online Supplementary Table S1*). Sixty-nine percent of patients were been born abroad and 31% were first generation born in France. Among the 69% of foreign born patients, the mean duration of residence in France was 13.8 years and the mean duration of follow up at the center was 5.1 years. Fifty-eight percent of female patients had been pregnant with a mean of 1.9 children per woman and 32 spontaneous abortions were reported in 12 females (5 multiple abortions, range 2-11). High body mass index (≥25kg/m^2) and blood hypertension (> 130/80 mmHg) were reported in 33% and 14% of HbSC patients, respectively. Body weight was in the normal range in 63% of cases, and below normal in 4%. Six patients (3.3%) were treated for diabetes mellitus.

Diagnosis in adulthood

In most patients, HbSC was diagnosed during infancy. However, HbSC diagnosis was delayed after the age of 18 years in 29% of cases (n=52), with the oldest patient diagnosed at 68 years of age. In adults, diagnosis was made: i) following painful VOC (n=20); ii) during pregnancy (n=14); iii) after an acute complication such as acute visual loss due to vitreous hemorrhage or retinal detachment related to proliferative retinopathy (n=7); arterial thrombosis (2 stroke, one myocardial infarction) or acute multiorgan failure syndrome (n=1); iv) incidental diagnosis (n=7).

Table 1. Prevalence of acute complications and therapeutical management.

Condition	N. patients (%)
Acute complications:	
Painful vaso-occlusive crisis	64 (36)
Acute chest syndrome	35 (20)
Priapism (% males)	16 (20)
Thrombosis:	23 (13)
Papillary necrosis	8 (4)
Venous thrombo-embolic disease	12 (7)
Arterial thrombotic accident	3 (2)
Infections:	17 (9)
Osteomyelitis	2
Salmonella Typhi	2
Tuberculosis	3
Pneumococcal disease	1
Chronic viral infection (HIV, HCV, HBV)	10
Treatment:	
Program of phlebotomy	64 (36)
Transfusion in the past	50 (28)
Cholecystectomy	25 (14)
Hydroxycarbamide	1 (0.6)

HIV: human immunodeficiency virus; HCV: hepatitis C virus; HBV: hepatitis B virus.

Clinical characteristics

Complications occurred frequently in our population: 90.5% presented at least once either acute or chronic organic clinical characteristics (Tables 1 and 2). Painful VOC were the more frequent acute complications with a prevalence of 36%. Spleen infarcts occurred in 3 patients aged 13, 18 and 20 years, whereas spleen enlargement was found in 52 patients (29%). In our series, only one patient underwent splenectomy; for the 2 remaining patients, no recurrence of spleen infarct was reported following a phlebotomy program. No patient experienced stroke during childhood. Acute arterial thrombotic events occurred in 3 patients with no underlying associated vasculopathy: 2 patients (51 and 68 years of age) had transient ischemic stroke with normal cerebral angiography and one 28-year old man had a myocardial necrosis (coronary thrombus detected by angiography at admission with normal coronary vessels after thromboaspiration). All 3 patients had an uneventful follow up (mean 40.3 months) under a phlebotomy program. Two patients died during the course of this study: a 25-year old man died from a massive pulmonary embolism one week after recovering from an ACS, and a 35-year old HIV positive man died of unknown causes at home.

Prevalence of chronic organic complications in our population was also high as only 17% (i.e. 31 patients) had no retinopathy, otological disorders, glomerulopathy, osteonecrosis or leg ulcers (Table 2). Retinopathy and sensorineural otological disorders were the two main complications reported. Retinopathy was presented in 71% of our study cohort, reaching a prevalence of 85% in patients with otological disorders (P<0.0001). Sensorineural disorders were diagnosed at a mean age of 34.4 years and consisted of vestibular syndrome (n=22), hearing loss (n=23) and both these in 7 cases. Interestingly, there was a greater prevalence of otological disorders in patients over the age of 40 years (56%) with hearing loss in 39% of this group of patients.

There was a great difference in the nature and prevalence of renal involvement between HbSC and SCA patients (Table 3) while the two populations were of a similar age (mean 31 and 26 years, respectively).[4] Median eGFR was 106 and 93 mL/min/1.73m^2 for males and females (*vs.* 148 and 126 mL/min/1.73m^2 for SCA males

Table 2. Prevalence of chronic complications in HbSC and SCA patients.

Condition	Patients with data available	HbSC N. patients (%)	SCA* % patients
Retinopathy	163	114 (70)	43
PSR treated by laser	163	81 (50)	ND
Otological disorders	179	52 (29)	ND
Renal involvement	174	23 (13)	84
Osteonecrosis	179	22 (12)	26
TRJV > 2.5 m/sec.	159	6 (4)	30
TRJV ≥ 2.9 m/sec.	159	0	9
Stroke	179	2 (1)	24
Leg ulcer	179	1 (0.6)	10

**References for sickle cell anemia data: 4, 5, 11, 13. HbSC, hemoglobin SC disease; ND: not done; PSR: proliferative sickle cell retinopathy; SCA: sickle cell anemia; TRJV: tricuspid regurgitant jet velocity.*

and females, respectively).[4] Hyperfiltration was observed in 9 patients with a mean eGFR of 156 mL/min/1.73m^2 in this group and only 3 patients above 150 mL/min/1.73m^2. Hyperfiltration was associated to albuminuria in only one patient compared with the SCA population in whom eGFR values were higher (< 300 mL/min/1.73m^2) and albuminuria was observed in 51% of patients with hyperfiltration.[4] In our series, renal failure was due to HIV-associated nephropathy in one case, thrombotic thrombocytopenic purpura in one case and undetermined vascular nephropathy in 2 cases. Interestingly, median systolic arterial blood pressure was in the normal range (116.5 mmHg) for the whole study cohort.

Median TRJV was 2.25 m/s (mean 2.27 m/s). Six patients had a TRJV between 2.5 and 2.9 m/s; none had values over 2.9 m/s. All patients without tricuspid regurgitation had a measurable pulmonary regurgitation velocity or pulmonary acceleration time; none of these patients had pulmonary hypertension. No right heart catheterization was performed.

Median hemoglobin was relatively high in the whole population (11.5g/dL), and hemoglobin below 10g/dL was observed in only 10% of patients (n=17) (Figure 1). Anemia was observed in 72% of patients (61% of males, 80% of females). As expected, the intensity of hemolysis assessed by plasma LDH level was lower in HbSC than in SCA patients (mean level of plasma LDH was 261 *vs*. 438 UI/L, respectively).[4] The prevalence of α-thalassemia in the study cohort was 27%.

Treatment

Sixty-four patients (36% of the cohort) followed a phlebotomy program. Phlebotomy criteria (one patient can meet several criteria) were: repeated acute VOC (n=40), sensorineural otological disorders (n=27), priapism (n=11), ACS (n=4), splenic infarct (n=2), stroke and myocardial infarction (n=3). During the first year of this program, the patients underwent a mean number of 9.1 venesections; mean total blood volume drawn was 3087 mL. A good clinical response as defined in the *Design and Methods* section was seen in 71% of patients, a failure was reported in 11% and 18% were not evaluable. No side-effect was reported except for 3 cases of reversible hypotension. Venous access was the main recurrent problem encountered in daily practice.

Fifty patients received at least one transfusion with a higher prevalence for females compared to males (35% *vs*. 18%, respectively); these were mostly given during pregnancy or in the post-partum period (20 of 35). Only one patient was on a regular program of erythrapheresis because of recurrent choroidal infarctions, despite achieving targeted hemoglobin levels by regular phlebotomies.

Table 3. Prevalence of renal involvement in HbSC and SCA patients.

Condition	Hemoglobin SC disease N. (%)	Sickle cell anemia* %
No renal involvement	151 (87)	16
Glomerular hyperfiltration	9 (5)	51
Microalbuminuria	9 (5)	40
Macroalbuminuria	4 (2)	19
Renal insufficiency	4 (2)	7

**Reference for sickle cell anemia data:4.*

Only one patient received short-term hydroxyurea for a painful vaso-occlusive crisis; this was then replaced by phlebotomy with good clinical efficacy.

Discussion

Our findings highlight some specific clinical characteristics in young adult HbSC patients. There were three frequent acute complications: painful VOC, ACS and priapism (with a prevalence of 36%, 20% and 20%, respectively); and four main chronic disorders: retinopathy, sensorineural otological disorders, nephropathy and avascular necrosis (70%, 29%, 13% and 12%, respectively). However, our patients were young (mean age 31.1 years) and prevalence of most complications is expected to increase with age. Investigations into large cohorts of patients have not paid much attention to the prevalence of specific HbSC morbidities. Most of our knowledge in the field of HbSC disease comes from the Cooperative Study of Sickle Cell Disease which was conducted in both HbSC disease and SCA in the 1980s. In accordance with previous reports, we found a very low rate of leg ulcers,[11] and similar rates of osteonecrosis and retinopathy.[12,13]

Surprisingly, in our cohort, sensorineural otological disorders were the second most frequent chronic complication; this had not previously been recorded as a specific HbSC morbidity in the main series.[3,6,8,9] Nevertheless, some studies including small patient populations have specifically pinpointed hearing loss,[14,15] with a prevalence of 27.9% in a cohort of 43 patients[16] and reaching 69% in a series of 13 patients.[17] Pathophysiology of inner ear damage may be linked to increased blood viscosity which compromises blood oxygen delivery by terminal arteries to the cochlea's fragile structures.[14,17] Furthermore, 85% of cases in our study presented otological disorders associated with retinopathy, thus forming an ophthalmological-otological 'sensorial phenotype'. This raises the possibility of similar pathophysiological mechanisms, since retinopathy is also known to be linked to hyperviscosity.[18] Interestingly, we may have underestimated the prevalance of otological disorders since no routine otological screening was performed in subjects who did not complain of any symptoms. Hearing loss may represent a major health problem in older HbSC patients as more than one-third of them were affected after 40 years of age. Therefore, these

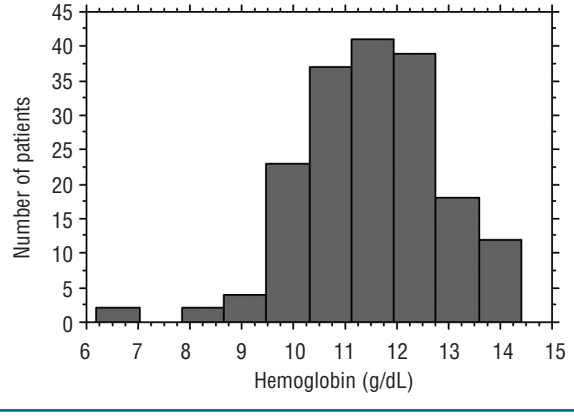

Figure 1. Distribution of hemoglobin level among HbSC population.

data raise the question whether routine and repeated audiometric tests should be carried out in order to provide early support when necessary.

Sickle cell anemia-associated nephropathy (SCAN) has recently been the subject of great interest in SCA patients due to its high prevalence.[4,19] Glomerular hyperfiltration with low filtration fraction appears to be a hallmark of SCAN[20] at an early stage together with microalbuminuria.[19,21] Whereas hyperfiltration seems to be related to increased cardiac output and a hemolytic phenotype,[4] the mechanisms leading to the onset of albuminuria have not yet been defined. On the other hand, nephropathy is far less frequent (13% *vs.* 84%) in HbSC patients. Hyperfiltration assessed by estimated GFR is found in only 5%, albuminuria in 7% and chronic renal failure in 2% of young HbSC patients compared with 51%, 59% and 7%, repesctively, in SCA patients. Hyperfiltration frequently seems to be related to comorbidities; in our series these were HIV infection and microangiopathy. In contrast to SCA, sickle cell-associated glomerulopathy is, therefore, rarely encountered in HbSC patients. However, further data are needed to address the issue as to whether HbSC may be an additional risk factor for chronic kidney diseases from other causes, as recently suggested for the patients with sickle cell trait.[22] Prevalence of high blood pressure was 14% in our young HbSC population; this figure is high compared to SCA patients who have low blood pressure despite a high prevalence of kidney disease.[4,23,24]

In recent changes to their guidelines, the American Society of Echocardiography increased the TRJV threshold beyond which pulmonary arterial hypertension is suspected from 2.5 to 2.9 m/s because the lower cut-off value resulted in too many false positive results when right-heart catheterization was performed.[10,25] Our results show that, whatever the threshold chosen, pulmonary arterial hypertension is not a particular concern in HbSC disease as in our study cohort no patient had TRJV above 2.9 m/s and only 4% had values above 2.5 m/s compared to 10% and 30%, respectively, in SCA.[10] Consequently, routine echocardiograph screening of pulmonary hypertension does not seem to be necessary in non-symptomatic HbSC patients.

Survival is much higher in HbSC than SCA patients (64 *vs.* 45 years)[26] probably because pathologies such as cerebral vasculopathy, pulmonary hypertension and chronic kidney disease, which are recognized risk factors for mortality in SCA, are rare in HbSC disease. However, HbSC disease should not be considered as a benign disease because unpredictable life-threatening complications related to arterial or venous thrombosis can nevertheless occur, such as pulmonary embolism,[27] extensive medullary necrosis with acute multiorgan failure syndrome,[28] and myocardial or cerebral infarction. In a recent autopsy study, pulmonary thrombo-embolism mortality was found more frequently in HbSC disease than in SCA.[27] Interestingly, in our series, no life-threatening complications were observed in female patients, possibly because the lower hemoglobin levels linked to menstrual blood losses[29,30] decreased their blood viscosity-related morbidity.

Red cell lifespan is approximately 2-fold higher in HbSC than in SCA patients (28.9 days *vs.* 15 days),[31,32] indicating a less severe level of hemolysis. Several pathophysiological explanations have been proposed for the different phenotypes encountered in sickle cell disease, involving noteworthy viscosity or hemolysis mechanisms.[18,33,34] A high erythrocyte turnover, and its consequences on anemia and high cardiac workload, account for increased resting energy expenditure and may be a reason for the low body mass index found in SCA patients.[35] This is in contrast to HbSC populations with subnormal hemoglobin levels in whom a body mass index over 25 kg/m^2 is found in one-third of patients. Furthermore, in HbSC patients, there is a low prevalence of the most frequent SCA complications, such as SCAN, pulmonary hypertension, leg ulcers and stroke. This supports the view that hemolysis-related vasculopathy is a rare event and that pathological processes could involve hyperviscosity and thrombosis. Interestingly, priapism observed both in HbSC and SCA male patients, is intriguing as this was previously associated with a hemolysis phenotype.[18,33] This merits further study to unravel the complex interplay between hemolytic and non-hemolytic related endothelial dysfunction and potentially also factors related to viscosity.

The higher level of hemoglobin in HbSC compared to SCA patients is striking since 90% of HbSC patients had hemoglobin levels above 10 g/dL (Figure 1) with a general agreement that 10-11g/dL would represent a threshold for vaso-occlusive outcomes.[24] Therefore, a hemoglobin target below this level seems to be a rational therapeutical goal that can be easily achieved and sustained by regular phlebotomies. Iron deficiency induced by phlebotomies decreases blood viscosity by: i) reducing intracellular hemoglobin concentration, thus leading to an antisickling effect;[29,36] ii) reducing the hematocrit level. Phlebotomy efficacy has been previously reported in a few case reports.[37-40] In our series, so far phlebotomy has been performed in approximately one-third of the patients. Although this study was not designed to assess the efficacy of phlebotomy, our data support the view that this procedure is safe, easy-to-perform and effective in preventing recurrence of acute events. In contrast, phlebotomy efficacy remains a question open to debate regarding the prevention of chronic organic complications such as retinopathy or hearing loss as no data are available. Specific studies are warranted to deal with this important issue as no other alternative treatments are currently available and, in particular, interest in hydroxyurea has only been marginal.[41]

To conclude, our data support the view that HbSC disease should not be considered a mild form of SCA but as a separate disease and, therefore, the two diseases should no longer be dealt with together either in a clinical setting or in clinical trials. Viscosity appears to be a hallmark of HbSC disease with a special emphasis on increased risk of thrombotic events and otological disorders which deserve specific systematic evaluation. Given the specific clinical features of this hemoglobinopathy and its high prevalence worldwide, specific guidelines for hemoglobin SC disease management are needed.

Authorship and Disclosures

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