Hemoglobin SC disease complications: a clinical study of 179 cases

by Francois Lionnet, Nadjib Hammoudi, Katia Stankovic Stojanovic, Virginie Avellino, Gilles Gradeau, Robert Girot, and Jean-Philippe Haymann

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Hemoglobin SC disease complications: a clinical study of 179 cases

Running title: Hemoglobin SC disease; F. Lionnet et al

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Abstract

Background. Hemoglobin SC disease is one of the most frequent hemoglobinopathy. Surprisingly, few studies were dedicated to this disease, currently considered as a mild variant of homozygous sickle cell disease. The aim of this study was to update our knowledge about hemoglobin SC disease.

Design and Methods. We conducted this study in a monocentric series of 179 patients. Clinical and biological data were collected, with a special concern for the assessment of pulmonary arterial hypertension and nephropathy.

Results. Hemoglobin SC diagnosis was delayed and performed in adulthood in 29% of cases. Hospitalized painful vasoocclusive crisis, acute chest syndrome and priapism had a prevalence of 36%, 20% and 20% respectively. The most common chronic organ complications were retinopathy and sensorineural otologic disorders occurring in 70% and 29% of cases. Indeed, prevalence of complications reported in homozygous sickle cell 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 level: 11.5 g/dL), prevented acute events recurrence 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 genuine disease with a special emphasis on viscosity-associated otologic and ophthalmologic disorders and with a low prevalence of vasculopathy (strokes, pulmonary hypertension, ulcers and nephropathy). Phlebotomy was useful to reduce acute events and a wider use of this procedure should be further investigated.
INTRODUCTION

Hemoglobin (Hb) SC disease is the second most frequent hemoglobinopathy after homozygous SS sickle cell disease also called sickle cell anemia (SCA). HbSC disease is encountered with an estimated 54.736 annual birth count worldwide. Most of our knowledge in HbSC disease pathophysiology stems from studies performed in SCA that have focused a great matter of interest for decades. The primary event in the pathogenesis of SCA is 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% HbC. The main reason why HbSC is accompanied by significant clinical abnormalities, while separately HbS and HbC trait have no clinical consequence, is that HbC enhances the formation of intracellular polymer of HbS by dehydrating red cells.

The major acute features of SCA are recurrent painful vaso-occlusive crisis (VOC) and acute chest syndrome (ACS), priapism and anemia. Chronic organ dysfunctions are a rising 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 raised a special focus. Sickle cell anemia-associated nephropathy was reported as the most frequent chronic organic feature in SCA with a prevalence of approximately 80%, 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.

Curiously, whereas SCA clinical features have been extensively studied, very few studies were dedicated to HbSC disease specifically. Indeed, HbSC disease is generally considered as a SCA variant, sharing similar clinical complications though with a milder severity and a lower frequency.

Thus, the aim of our study was to lay a special emphasis on the specific clinical and biological features of HbSC disease from a single centre cohort of patients.
DESIGN AND METHODS

Patients

One hundred-seventy nine adult HbSC patients (age ≥ 18 yr) who consecutively attended the sickle cell disease centre of Tenon’s 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 the renal involvement was made with the population of SCA patients treated in the same centre and described elsewhere.4

Data collection

Epidemiological and clinical data such as geographic origin, birth location, age, disease onset, comorbidity, obstetrical history, 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 3 years before the inclusion in this study. Acute chest syndrome was recorded according to the current criteria: new infiltrate visible on chest radiograph 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 the presence of retinopathy, avascular bone necrosis, glomerulopathy, stroke, priapism, leg ulcers, gallblader disease, vertigo and hypoacousia and/or pulmonary arterial hypertension were carefully recorded. Sensorineural otologic disorders (requiring hospitalization or not) were recorded on the following criteria: (i) prolonged vertigo with clinical vestibular syndrome confirmed by video-oculography and/or (ii) fluctuating or permanent hearing loss confirmed by audiometry.

Laboratory methods

The 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 to 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 m² and renal hyperfiltration as an eGFR above 130 ml/min per 1.73 m² for women.
and above 140 ml/min per 1.73 m$^2$ for men. 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. When TRJV was not measurable, peak velocities of pulmonary regurgitation and pulmonary acceleration time were recorded in place. One patient with severe mitral and severe aortic rheumatic regurgitations has been excluded from the analysis. Routine ophthalmological visit included visual acuity, direct and indirect ophthalmoscopy, and when indicated fluorescein angiography and laser photocoagulations. Audiometry tests were only performed in subjects complaining for hearing disturbances or vertigo. Similarly, radiographic examinations for osteonecrosis were performed only for subjects complaining for bone pain at steady-state. Cerebral imaging was performed only in patients complaining for neurological symptoms (transient stoke, persistent headaches...) 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 a hospitalization, more than 3 ambulatory VOC requiring bed rest in the precedent year. Phlebotomy was also proposed for priapism, otologic disorders (hypoacusia or vestibular syndrome), spleen infarct or arterial thrombosis (cerebral or myocardial). Phlebotomy program included weekly venesection until a hemoglobin level target of 9.5 g/dL. Thereafter, phlebotomy was performed to maintain hemoglobin between 9.5 and 10.5 g/dL, with a 2 to 3 months monitoring schedule. A clinical success was defined as the absence of pain requiring unplanned health care utilization, a 50% decrease of ambulatory acute VOC or priapism episodes, the lack of vestibular syndrome recurrence, and/or hypoacusia aggravation and the lack of spleen infarct or arterial thrombosis recurrence. It was considered as non evaluable if the program was discontinued by the patient before hemoglobin target level was reached.
RESULTS

Demographic findings
Among our population, 97 (54%) were women and 82 (46%) were men. The median age was 29 years (mean, 31.1 yr), with a range of 18–68 years. The patients originated from 17 different countries all belonging to Africa (n=122) or West Indies (n=57) (see Supplementary Table 1). Sixty-nine percent was foreign-born and 31% appertained to the first generation born in France. Among the 69% of patients foreign born, the mean duration of residence in France was 13.8 years and the mean duration of follow-up in the centre was 5.1 years. Pregnancy was encountered in 58% of females with a mean of 1.9 children per woman and 32 spontaneous abortions were reported in twelve females (multiple abortions in 5 cases, ranging from 2 to 11). High body mass index (≥ 25kg/m²) and blood hypertension (> 130/80 mmHg) were encountered in 33% and 14% of HbSC patients respectively. Body weight was in the normal range in 63% of cases, and decreased in 4%. Six patients (3.3%) were treated for diabetes mellitus.

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

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

The prevalence of chronic organic complications in our population was also high, as only 17% (i.e. 31 patients) were devoided of retinopathy, otologic disorders, glomerulopathy, osteonecrosis or leg ulcers (Table 2). Retinopathy and sensorineural otologic disorders were the two main complications. Retinopathy was encountered in 71% of our population, reaching a prevalence of 85% in patients with otologic disorders (p<0.0001). The sensorineural disorders were diagnosed at a mean age of 34.4 years and consisted in: vestibular syndrome in 22 cases, hearing loss in 23 cases and both in 7 cases. Interestingly, the prevalence of otologic disorders was increased in patients above 40 years of age, rising up to 56%, with hearing loss present in 39% of this population.

The nature and prevalence of renal involvement in HbSC patients were very different from SCA population (Table 3), while the two populations had a similar age (mean age of respectively 31 and 26 years). Median eGFR was 106 and 93 ml/min/1.73m² for males and females (versus 148 and 126 ml/min/1.73m2 for SCA males and females respectively). Hyperfiltration was detected in 9 patients with a mean eGFR of 156 ml/min/1.73m² in this group and only 3 patients above 150 ml/min/1.73m². Hyperfiltration was associated to albuminuria only in 1 patient in contrast with SCA population where the magnitude of eGFR value were higher (reaching 300 ml/min/1.73m²) and albuminuria occurring in 51% of patients with hyperfiltration. 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 two cases. Of notice, median systolic arterial blood pressure was in the normal range (116.5 mmHg) in the whole population.

The median value of TRJV was 2.25 m/s (mean, 2.27 m/s). Six patients had a TRJV between 2.5 and 2.9 m/s and none was above 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 catheterisation was performed.
Median hemoglobin level was relatively high in the whole population (11.5 g/dL), and hemoglobin below 10 g/dL was detected only in 10% of patients (n=17) (Figure 1). Anemia was found in 72% of patients (61% males and 80% 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 versus 438 UI/L respectively). The prevalence of α-thalassemia in the cohort was 27%.

**Treatment**

Sixty-four patients (36% of the cohort) underwent a phlebotomy program. Phlebotomy criteria were (one patient can meet several criteria): repeated acute VOC (n=40), sensorineural otologic 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, for a mean total blood volume drawn of 3087 ml. A good clinical response as assessed in material and methods section was present in 71% of patients, a failure was noted in 11% and 18% were not evaluable. No side effect was reported, except 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), mostly during pregnancy or in post-partum period (20/35). Only one patient was on a regular program of erythropheresis, because of recurrent choroidal infarctions despite the achievement of targeted hemoglobin level by regular phlebotomies. Only one patient received briefly hydroxyurea for painful vaso-occlusive crisis, then replaced by phlebotomy, with a good clinical efficacy.

**DISCUSSION**

Our findings underline three acute frequent complications in young adult HbSC patients: painful VOC, ACS and priapism (with a prevalence of 36%, 20% and 20% respectively); and four main chronic disorders: retinopathy, sensorineural otologic disorders, nephropathy and avascular necrosis (in 70%, 29%, 13% and 12% of cases respectively). However, the population described is young (mean age 31.1 years) and the prevalence of most complications is expected to increase with the age of patients. Prevalence of specific HbSC morbidities has been poorly investigated on large cohorts. Most of the knowledge in the field of HbSC disease comes from the Cooperative Study of Sickle Cell Disease which was conducted both in HbSC disease...
and SCA in the eighties. In accordance with previous reports, we found a very low rate of leg ulcers\textsuperscript{11} and a rate of osteonecrosis and retinopathy within the same order of magnitude.\textsuperscript{12,13} Surprisingly, in our cohort sensorineural otologic disorders were the second most frequent chronic complication, while this feature was not recorded previously as a specific HbSC morbidity in the main series.\textsuperscript{3,6,8,9} Nevertheless, some studies including small populations have pinpointed specifically hearing loss,\textsuperscript{14,15} with a prevalence of 27.9\% in a cohort of 43 patients\textsuperscript{16} reaching 69\% in a series of 13 patients.\textsuperscript{17} Pathophysiology of inner ear damages may be linked to an increased blood viscosity which compromises blood oxygen delivery by terminal arteries to cochlea’s fragile structures.\textsuperscript{14,17} Moreover, our finding that otologic disorders are associated in 85\% of cases with retinopathy, thus forming an ophtalmologic-otologic “sensorial phenotype” raises the issue of potential similar pathophysiological mechanisms, as retinopathy is also known to be linked to hyperviscosity.\textsuperscript{18} Of notice, we may have underestimated otologic disorders prevalence as no routine otologic screening was performed in subjects with no complain. Hearing loss may represent a major health problem in senior HbSC patients as more than one third of them were affected after 40 years of age. Thus these data raise the issue of routine and repeated audiometry in order to provide an early support when necessary.

Sickle cell anemia-associated nephropathy has been recently a great matter of interest in SCA patients due to a high prevalence.\textsuperscript{4,19} Glomerular hyperfiltration with low filtration fraction appears as a hallmark of SCAN\textsuperscript{20} at an early stage altogether with microalbuminuria.\textsuperscript{19,21} Whereas hyperfiltration seems related to increased cardiac output and a hemolytic phenotype,\textsuperscript{4} the mechanisms leading to the onset of albuminuria remain to be elucidated. Conversely, in HbSC patients, nephropathy is far less frequent (13\% vs 84\%). Hyperfiltration assessed by estimated GFR is encountered in only 5\%, albuminuria in 7\% and chronic renal failure in 2\% in young HbSC patients (versus respectively 51\%, 59\% and 7\% in SCA patients) and seems frequently related to comorbidities (such as HIV infection and microangiopathy in our series). In contrast to SCA, sickle cell-associated glomerulopathy is thus rarely encountered in HbSC patients but further data are warranted to address the issue whether HbSC may be an additional risk factor for other-cause chronic kidney diseases, as recently suggested for the patients with sickle cell trait.\textsuperscript{22} Prevalence of high blood pressure was 14\% in our young HbSC population, a high figure compared to SCA patients who have a low blood pressure despite a high prevalence of kidney disease.\textsuperscript{4,23,24} The TRJV threshold beyond which the existence of pulmonary arterial hypertension is suspected was recently increased by the American Society of Echocardiography guidelines from 2.5 to 2.9 m/s as the lower cut-off
value resulted in too much false positive when right-heart catheterization was performed. Our results show that whatever the threshold chosen, pulmonary arterial hypertension is not obviously a concern in HbSC disease, as we experienced no patient with a TRJV above 2.9 m/s and only 4% above 2.5 m/s (versus 10% and 30% respectively in SCA). Consequently, the screening of pulmonary hypertension by routine use of echocardiography appears unnecessary in non-symptomatic HbSC patients.

Life survival is much higher in HbSC than SCA patients (64 vs 45 years), 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 happen such as pulmonary embolism, extensive medullary necrosis with acute multiorgan failure syndrome and myocardial or cerebral infarction. In a recent autopsy study, pulmonary thromboembolisms mortality was found more frequently in HbSC disease than in SCA. Of notice, none of the life-threatening complications happened in female patients in our series, possibly because the lower hemoglobin levels linked to menstrual blood losses decreased blood viscosity related morbidity in females.

Red cell lifespan is approximately two folds higher in HbSC than in SCA patients (28.9 days versus 15 days), 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. A high erythrocytes turn over, and its consequences on anemia and high cardiac workload, accounts for increased resting energy expenditure and may be a reason for SCA patients low body mass index, conversely to HbSC population with subnormal hemoglobin levels where a body mass index over 25 kg/m2 is found in one third of patients. Moreover, in HbSC patients, the prevalence of frequent SCA complications such as SCAN, pulmonary hypertension, leg ulcers and stroke is low supporting the view that hemolysis-related vasculopathy is a rare event, and thus favors the view of hyperviscosity and thrombosis related pathological processes. Of notice, priapism encountered both in HbSC and SCA male patients is an intriguing data as priapism was previously associated with a hemolysis phenotype. This finding should deserve further studies to unravel this 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 a striking figure, 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. Thus, hemoglobin target below this level appears as a
rational therapeutical goal that can be easily achieved and sustained using regular phlebotomies. Iron deficiency induced by phlebotomies decreases blood viscosity by: (i) reducing intracellular hemoglobin concentration thus leading to an antisickling effect\textsuperscript{29,36} (ii) decreasing hematocrit level. Phlebotomy efficacy has been previously reported in few case reports\textsuperscript{37-40}. In our series, so far the largest, phlebotomy was performed approximately in 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 the prevention of acute events recurrences. Conversely, phlebotomy efficacy remains an open question in chronic organic complications prevention such as retinopathy or hearing loss as we have no available data. A specific study is warranted to answer this important issue, as no other alternative treatments are currently available, in particular with a marginal interest reported for hydroxyurea\textsuperscript{41}.

To conclude, our data support the view that HbSC disease should not be considered as a mild form of SCA but as a genuine disease and thus the two diseases should no longer be mixed either in a clinical setting or in clinical trials. Viscosity appears as a hallmark of HbSC disease with a special emphasis on increased risk of thrombotic events and otologic disorders which should deserve a 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**

FL was the principal investigator. FL, KS, RG, JPH, NH, GG, took parts in the care of the patients, interpreted data and contributed to the discussion. VA collected the cases and contributed to the discussion. FL, JPH and NH wrote the manuscript. KS, RG, GG, VA revised the manuscript.

The authors reported no potential conflicts of interest.
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41. Ware RE. How I use hydroxyurea to treat young patients with sickle cell anemia. Blood. 2010;115(26):5300-11.
Table 1. Prevalence of acute complications and therapeutical management.

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

HIV, human immunodeficiency virus; HCV, hepatitis C virus; HBV, Hepatitis B virus
Table 2. Prevalence of chronic complications in HbSC and SCA patients.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patients with data available</th>
<th>HbSC No. of patients (%)</th>
<th>SCA* % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy</td>
<td>163</td>
<td>114 (70)</td>
<td>43</td>
</tr>
<tr>
<td>PSR treated by laser</td>
<td>163</td>
<td>81 (50)</td>
<td>ND</td>
</tr>
<tr>
<td>Otologic disorders</td>
<td>179</td>
<td>52 (29)</td>
<td>ND</td>
</tr>
<tr>
<td>Renal involvement</td>
<td>174</td>
<td>23 (13)</td>
<td>84</td>
</tr>
<tr>
<td>Osteonecrosis</td>
<td>179</td>
<td>22 (12)</td>
<td>26</td>
</tr>
<tr>
<td>TRJV &gt; 2.5 m/sec.</td>
<td>159</td>
<td>6 (4)</td>
<td>30</td>
</tr>
<tr>
<td>TRJV ≥ 2.9 m/sec.</td>
<td>159</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Stroke</td>
<td>179</td>
<td>2 (1)</td>
<td>24</td>
</tr>
<tr>
<td>Leg ulcer</td>
<td>179</td>
<td>1 (0.6)</td>
<td>10</td>
</tr>
</tbody>
</table>

* References for sickle cell anemia data: 4, 5, 11, 13, 42.
HbSC, hemoglobin SC disease; ND, not done; PSR, proliferative sickle cell retinopathy; SCA, sickle cell anemia; TRJV, tricuspid regurgitant jet velocity.

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>HbSC No. (%)</th>
<th>SCA* %</th>
</tr>
</thead>
<tbody>
<tr>
<td>No renal involvement</td>
<td>151 (87)</td>
<td>16</td>
</tr>
<tr>
<td>Glomerular hyperfiltration</td>
<td>9 (5)</td>
<td>51</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>9 (5)</td>
<td>40</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>4 (2)</td>
<td>19</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>4 (2)</td>
<td>7</td>
</tr>
</tbody>
</table>

* Reference for sickle cell anemia data: 4.

Abbreviations: HbSC, hemoglobin SC disease; SCA, sickle cell anemia.
Legend to Figure

Figure 1. Distribution of hemoglobin level among HbSC population.