Epidemiology in sickle cell disease. Lessons learned from the CADRE cohort in Africa

Brigitte Ranque
Paris Descartes University, Paris, France

**Take Home Messages**
- CADRE is the first multinational cohort of sickle cell disease (SCD) in Africa, where SCD is a public health issue.
- This study provides valuable data on the history and prognosis factors of SCD patients living in sub-Saharan Africa and will help to focus further research and care on the most important concerns in this region.
- The management of such study is particularly challenging and reveals the need for financial and methodological support of the international scientific community, as well as an increased local governments’ awareness of the disease.

**Introduction**

Annually, more than 230,000 children with SCD are born in sub-Saharan African, compared to only 3000 in Europe in 2010. The African setting displays many particularities including a high infectious burden, very poor socioeconomic conditions and underdeveloped health care system. The current average life expectancy of SCD patients is believed to be less than 10 years in sub-Saharan Africa, compared to more than 50 years in the United States. Likewise, the acute and chronic complications of SCD are most likely different in Africa and in high-income countries. However, the natural history of SCD patients living in sub-Saharan Africa is practically unknown.

Although primarily a blood disorder, SCD may also be regarded as a vascular disease, since its main chronic complications are stroke, heart failure, pulmonary hypertension, kidney disease, retinopathy, bone infarcts and leg ulcers. Many analytic studies on SCD-related vascular complications display conflicting results, probably because of strong interactions between clinical and biological parameters that lead to many biases. To assess the prevalence and the determinants of SCD vasculopathy, we set up a large cohort of SCD patients in five sub-Saharan African countries. The CADRE study (Coeur Artères et DREpanocytose, i.e. Heart Arteries and Sickle cell disease) has become the world largest ongoing cohort of SCD and fulfills the requested criteria for the multivariable analyses of clinical, functional or biological phenotypes.

**The CADRE cohort**

SCD patients were recruited through outpatient clinics in Yaoundé (Cameroon), Abidjan (Ivory Coast), Bamako (Mali), Libreville (Gabon) and Dakar (Senegal). All SCD patients aged three years and older were invited to participate in the study. SCD-free controls from the same area were recruited to ensure good comparison for functional tests. The medical visits were performed at steady state, i.e. at least 15 days after the last vaso-occlusive crisis, eight days after infectious disease, and three months after the last transfusion. SCD vascular complications (pulmonary arterial hypertension, microalbuminuria, leg ulcers, priapism, stroke and osteonecrosis) were assessed using the clinical examination, blood and urine laboratory exams, and echocardiography performed by a trained cardiologist. Pulse wave analysis was performed using applanation tonometry.

Between February 2011 and December 2013, 3627 SCD patients and 943 controls were recruited. The median age of the patients was 15 years. The distribution of hemoglobin phenotypes varied by country: more than 90% of the patients from Cameroon, Gabon and Senegal were SS, whereas SC and S thal patients were common in Ivory Coast and Mali (42-48%). The inclusion data have provided insights on the characteristics of SCD patients referring to these West and Central African hospitals (Table 1). We have been able to describe the prevalence of vascular complications in children and adults with different types of SCD, and look for their clinical, biological and cardiovascular functional correlates. Overall, we observed significant differences in disease severity (for example: growth retardation, hemoglobin level, frequency of VOC or chronic organ complications) among the five countries, regardless of the age and hemoglobin phenotype. In particular, we studied microalbuminuria, an early marker of SCD nephropathy, and showed a very high prevalence globally, including in infants, but also a high heterogeneity across the countries (three times higher prevalence in Cameroon, compared to Ivory Coast) partially explained by an association with the SCD genotype and the level of hemolysis. We studied the properties of large arteries in SCD patients using pulse wave velocity measure and showed that arterial stiffness is highly reduced in SCD patients independently of blood pressure and age; and that the augmentation index, which reflects both arterial stiffness and the reflection of the pulse wave on the capillary bed, is correlated with several vascular complications. We also challenged the paradigm stating that SCD patients with
hyperhemolysis are more prone to develop certain vascular complications such as pulmonary hypertension and leg ulcers, whereas other ‘hyperviscous’ patients develop more VOC and osteonecrosis. We showed that, after adjustment for confounding variables, such a dichotomy is not clinically relevant in the African population when the level of hemolysis is determined using indirect blood markers of hemolysis (LDH and bilirubin). Conversely, hemoglobin alone has a much better discriminative value.6

Since June 2016, patients are recalled for a 5 year-follow up visit. The same clinical, biological and cardio-echographical parameters are collected again. Due to many logistic and staff problems, the center of Gabon has been replaced by another center in central Africa: 1000 new patients are being recruited in Kinshasa (Democratic Republic of Congo).

The challenges of an Africa multinational study on SCD

Many logistic and human difficulties have been encountered from the beginning of the cohort, and still make the follow-up particularly challenging. The technical limitations are numerous in sub-Saharan Africa: medical and scientific equipment is often lacking or outdated, frequent power blackouts jeopardize the safety of biological samples stored in a freezer, poor road infrastructure makes any transportation extremely complicated, etc. Health care providers work in hard conditions, especially in public hospitals. Because of extremely low salaries, they usually need to have several occupations to increase their income and often lack motivation to participate to academic research studies. In addition, their clinical research practice is usually far from the methodological standards and need strong methodological support. Administrative or hierarchical freezing and corrosive habits are frequent, which can delay or end the studies despite enormous diplomatic and financial means. Finally, many cultural misunderstandings can occur between North and South collaborators. Because there are many social, political, cultural and environmental issues that are specific to the African context and cannot be embraced correctly by strangers, it is fundamental that African physicians determine their own research priorities.7 Besides, North supervisors have to travel to the site to be able to understand the difficulties encountered.

Future perspectives

Despite these pitfalls, CADRE and other large epidemiological studies or clinical trials on SCD have been successfully conducted in Africa with the help of international teams.8,9 Because of a global ignorance or disregard of the African governments for SCD, further studies need to be supported, both financially and methodologically by the international scientific community, in order to increase the local awareness of this public health problem, describe the peculiarities of SCD in Africa and help driving research and care on the most appropriate issues in this setting.

Acknowledgments

The author thanks her collaborators in Africa for their dedication to their patients, their engagement in the CADRE study and the sound discussions they had together.

| Table 1.  Main features of SCD patients included in the CADRE study. |
| All SCD patients | Sβ0 | SS | Sβ+ | SC |
|------------------|-----|----|-----|-----|
| N=3627           | N=148| N=2308| N=171| N=580 |
| Age (median [IQR], mg/g) | 16 [10;24] | 13 [8;19] | 15 [9;23] | 20 [13;30] | 21 [14;30] |
| Female n (%)     | 1943 (54%) | 84 (57%) | 1240 (54%) | 97 (67%) | 306 (53%) |
| Body mass index (mean ± SD, kg/m²) | 17.4±4.3 | 16.2±3.6 | 17±4.2 | 19±4.3 | 19.6±4.7 |
| Mean blood pressure (mean ± SD, mmHg) | 77±10 | 75±9 | 76±9 | 81±10 | 82±11 |

| Country          | Cameroon | Gabon | Ivory Coast | Mali | Senegal |
|------------------|----------|-------|-------------|-----|---------|
|                  | 973 (27%) | 376 (10%) | 648 (18%) | 896 (25%) | 734 (20%) |

| Biological parameters | All SCD patients | Sβ0 | SS | Sβ+ | SC |
|-----------------------|------------------|-----|----|-----|-----|
| Age (median [IQR], g/dl) | 8.8±2.1 | 8.8±1.7 | 8.2±1.6 | 11.2±1.7 | 11.4±1.5 |
| Leukocyte count (mean ± SD, 10³/mm³) | 11±5 | 10±3.5 | 12.3±4.7 | 6.6±3 | 7.8±2.7 |
| LDH level (mean ± SD, IU/l) | 804±583 | 624±344 | 1025±621 | 454±374 | 458±282 |
| Bilirubin level (mean ± SD, mg/d) | 27±19 | 23±14 | 33±20 | 15±14 | 14±9 |
| Hemoglobin (mean ± SD, g/d) | 121 [95;158] | 140 [113;182] | 123 [97;162] | 115 [94;141] | 106 [89;141] |

| History of SCD complications | All SCD patients | Sβ0 | SS | Sβ+ | SC |
|-----------------------------|------------------|-----|----|-----|-----|
| At least one VOC >48h in the previous year (n, %) | 2463 (70%) | 86 (61%) | 1595 (70%) | 99 (61%) | 396 (71%) |
| Acute chest syndrome, lifetime (n, %) | 733 (21%) | 21 (16%) | 574 (26%) | 32 (20%) | 44 (8%) |
| Stroke, lifetime (n, %) | 49 (1.4%) | 1 (0.7%) | 38 (1.6%) | 0 (0%) | 2 (0.3%) |
| Pulmonary hypertension (TRV >2.5 m/s) (n, %) | 167 (28%) | 2 (14%) | 136 (30%) | 4 (21%) | 22 (23%) |
| Osteonecrosis, lifetime (n, %) | 350 (10%) | 8 (5%) | 244 (11%) | 21 (12%) | 54 (9%) |
| At least one VOC >48h in the previous year (n, %) | 2463 (70%) | 86 (61%) | 1595 (70%) | 99 (61%) | 396 (71%) |
References

1. Piel FB, Patil AP, Howes RE, et al. Global distribution of the sickle cell gene and geographical confirmation of the malaria hypothesis. Nat Commun. 2010; 1: 104.

This article reports on the worldwide distribution of sickle cell anemia, as inferred by sophisticated statistical methods, within the limits of uncertain incidence data in some regions, including sub-Saharan Africa.

2. Williams TN. Sickle cell disease in Sub-Saharan Africa. Hematology/oncology clinics of North America. 2016;30:343-58.

3. Diop S, Diallo D, Tolo A, et al. The Cadre (Coeur Artères et Drépanocytose) study. Blood Adv 2017;1:32-5.

4. Sokal A, Dubert M, Sanogo I, et al. African sickle zero beta thalassemia patients vs sickle cell anemia patients: similar clinical features but less severe hemolysis. J Hematol Transf 2016;4:1053.

5. Ranque B, Menet A, Diop IB, et al. Early renal damage in patients with sickle cell disease in sub-Saharan Africa: a multinational, prospective, cross-sectional study. Lancet Haematol 2014;1:e64-73.

This is the first study using the inclusion data of the CADRE cohort, it describes the high prevalence and the factors associated with microalbuminuria in African sickle cell disease patients.

6. Ranque B, Menet A, Boutouryie P, et al. Arterial stiffness impairment in sickle cell disease associated with chronic vascular complications: The multinational African CADRE study. Circulation 2016;134:923-33.

This article reports the first large scale study of large arteries properties in sickle cell disease patients of all ages and show significant decrease in arterial rigidity in patients compared to controls of the same age and country.

7. Kato GJ, Gladwin MT, Steinberg MH. Deconstructing sickle cell disease: reappraisal of the role of hemolysis in the development of clinical subphenotypes. Blood Rev 2007;21:37-47.

8. Dubert M, Elion J, Tolo A, et al. Degree of anemia, indirect markers of hemolysis, and vascular complications of sickle cell disease in Africa. Blood 2017;130:2215-23.

In this article we challenge the paradigm of hyperhaemolysis and show that, unlike hemoglobin level, usual indirect markers of hemolysis are not independently associated with vascular complications in sub-Saharan patients with sickle cell disease.

9. Makani J, Williams TN, Marsh K. Sickle cell disease in Africa: burden and research priorities. Ann Trop Med Parasitol 2007;101:3-14.

10. Makani J, Cox SE, Soka D, et al. Mortality in sickle cell anemia in Africa: a prospective cohort study in Tanzania. PloS One 2011;6:e14699.

11. Mtatiro SN, Singh T, Rooks H, et al. Genome wide association study of fetal hemoglobin in sickle cell anemia in Tanzania. PloS One 2014;9:e111464.

12. Ndeezi G, Kiyaga C, Hernandez AG, et al. Burden of sickle cell trait and disease in the Uganda Sickle Surveillance Study (US3): a cross-sectional study. Lancet Global Health 2016;4:e195-200.

This study is the first nationwide neonatal screening study in Africa, cleverly taking advantage of the network created for a national program of HIV diagnosis in infants of HIV-infected women in Uganda.

13. Heeney MM, Hoppe CC, Abboud MR, et al. A Multinational trial of prasugrel for sickle cell vaso-occlusive events. N Engl J Med 2016;374:625-35.

14. McGann PT, Williams TN, Olopout-Oflopout P, et al. Realizing effectiveness across continents with hydroxyurea: Enrollment and baseline characteristics of the multicenter REACH study in Sub-Saharan Africa. Am J Hematol 2018;93:537-45.