Commentary

The US3 study: a first step towards large scale epidemiology for sickle cell disease in Africa

Brigitte Ranque

Internal Medicine Unit, European Georges Pompidou Hospital, Assistance Publique des Hôpitaux de Paris, UMR_S970, Inserm, Paris Descartes University, Paris Descartes University, Paris, France

Correspondence to: Prof. Brigitte Ranque, MD, PhD. Internal Medicine Unit, European Georges Pompidou Hospital, Assistance Publique des Hôpitaux de Paris, 20 rue Leblanc, 75015 Paris, France. Email: brigitte.ranque@aphp.fr.

Comment on: 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 Glob Health 2016;4:e195-200.

Received: 26 September 2016; Accepted: 29 October 2016; Published: 09 January 2017.

doi: 10.21037/jphe.2016.12.19

View this article at: http://dx.doi.org/10.21037/jphe.2016.12.19

It is currently estimated that 230,000 babies are born each year in sub-Saharan Africa with the sickle cell disease (SCD), compared to 10,000 in the USA and 3,000 in Europe. However, these estimations are based on very scarce and outdated data that even the most sophisticated geostatistical methods cannot make more accurate (1). Moreover, despite the obvious high frequency of the disease in sub-Saharan Africa, there is no comprehensive study on the natural history of SCD in this region. Previous surveys suffer from small sample size and many methodological biases (2).

African physicians who are expert in the field of SCD have repeatedly expressed the need to get accurate figures of the SCD prevalence, morbidity and mortality in Africa (3-5), in order to draw attention of the African governments to the enormous burden of SCD in their countries. Increasing the awareness of SCD disease in the general population and the health policy makers is viewed as the best way of obtaining nationwide comprehensive programs of improvement of SCD care and prevention. However, even though WHO has described SCD as a public health priority for sub-Saharan Africa since 2006 (6) and the United Nations has declared SCD a world healthcare priority in 2009, African governments have not modified their health policy.

Therefore, describing the prevalence of the disease and estimating survival and complication rates with greater precision should be one of the priorities for African medical research in the next few years. Collecting the results of systematic neonatal screening would have been the best method for estimating the accurate prevalence of SCD in Africa, but unfortunately no African country has implemented newborn screening at the nationwide level, although some countries have reported efficacy and good acceptability of pilot neonatal screening programs, as in Benin (7), Nigeria (8), the Democratic Republic of Congo (9), Ghana (10) or Liberia (11). However, when not based on an existing health care network, population based epidemiological studies are very expensive both in terms of financial and human resources. Thus, African public health departments cannot afford implementing such studies on their own.

In that respect, the US3 study recently published by Dr. Ndeezi and colleagues in *The Lancet Global Health* (12) is reporting precious data, since it is the first epidemiological study of sickle cell trait and disease prevalence on a large scale in Africa. The authors used residual dried blood spots collected for a national programme of HIV diagnosis in infants of HIV-infected women in Uganda and isoelectric focusing analysis of hemoglobin to screen sickle cell trait and disease. With such screening performed in almost 100,000 infants, the US3 study confirms the high burden of SCD at the nationwide level in Uganda (the overall prevalence was 0.7%), but also the heterogeneity of the SCD prevalence across the ten regions and 112 districts (from 0.2% to 1.5%). This heterogeneity could result both from population movement history and environmental factors. The interaction between sickle cell red cells and environment is likely to be a major determinant of the prevalence of the disease, especially through the relative

protection against malaria conferred by the sickle cell trait, as suggested by the geostatistical correlation between SCD and Malaria prevalence observed in US3 study.

Although the evidence is less straightforward, the study also suggests high childhood mortality, based on the difference between the observed prevalence of SCD in newborns (0.6%) and infants aged more than 12 months (0.8%), which is small but statistically significant. Because of the high prevalence of HIV infection in these infants, it would have been interesting to have more data about the interaction between HIV infection and the age of screening effect on the prevalence. A prospective follow up of the neonates diagnosed with SCD is warranted to validate the estimation of early mortality in this population.

The US3 study has resulted from a collaboration between the public health department of a sub-Saharan African country with limited financial resources and an internationally known American research team. The investigators have cleverly taken advantage of the already existing network deployed in the whole country for HIV infection screening to build a large epidemiological study at the lowest cost. Indeed, many efforts have been made for the development of medical research and care in the field on malaria, tuberculosis and HIV in Africa, not only by building scientific facilities and gathering data and biological samples in the field but also by training and educating local staffs so that they can be able to work independently (13). Therefore, lessons have certainly to be taken from the history of transmissible diseases epidemiology in Africa.

The US3 study will certainly have long term benefit effect in Uganda, not only by paving the way for a nationwide newborn screening of SCD, but also by giving an impetus to medical research in the field of SCD. It indeed allowed the establishment of an infrastructure that was lacking so far and repeatedly trained laboratory staff to perform the screening procedures correctly.

However, the US3 study has some limitations, as any non-population-based epidemiological study. In particular, the blood samples were collected from children of HIV-infected mothers, which could potentially bias the SCD prevalence. Indeed, women with SCD children are often struggling with very hard social conditions: they are commonly repudiated by their husbands and sometimes bound to prostitute themselves to be able to pay for their children's health care. One can hypothesize that these women (who carry either the AS or SS genotype) are more exposed to HIV infection and thus that the prevalence of SCT is over estimated in this population. Conversely, a few studies have described a lower prevalence of HIV-infection in SCD patients, but a selection bias cannot be ruled out (14).

The study also raised a thorny ethical issue, shared by many epidemiological studies performed in Africa, because no optimum clinical care could be assured for the children who were diagnosed with SCD, not only because most families cannot afford the simple preventive measures that are recommended such as vaccinations, folic acid supplementation or penicillin prophylaxis, but also because the medical infrastructure and staff are not ready to inform, educate and take care of all screened patients. However, as we said earlier, describing the prevalence of the disease and estimating survival and complication rates with greater precision is one of the priorities for African medical research and the inescapable step to climb for persuading the governments that it is essential to move towards the establishment of a comprehensive care program for SCD patients. On the other hand, the improvement of research and care in SCD could have paradoxical consequences because it will turn SCD from a condition that is fatal early in life to a chronic condition that necessitates lifelong expensive care, requiring many financial resources and competing with other diseases for the use of health care services, especially for blood transfusion. Therefore, ethics are not always as obvious as they appear at a first glance in such a context of restricted medical means.

That is why it is fundamental that African physicians determine themselves their own research priorities. There are many social, cultural and environmental issues that are specific to the African context and cannot be embraced correctly by strangers. Nevertheless, epidemiological research on SCD is particularly tricky in Africa for many reasons. The lack of financial resources is certainly the most evident. Unlike research on HIV, tuberculosis and malaria, which have been boosted by the funds gathered by many international associations, SCD is practically unknown in high-income countries populations and very few charitable associations and governmental organizations are collecting funds for it. But money is not the only shortcoming. Road infrastructure is terribly poor, which makes any trip or transportation extremely long and complicated, especially if biological samples need freezing or cool storage. Likewise, even in scientific facilities, the equipment is often outdated, internet connection is absent or slow and unstable, and frequent power blackouts make it difficult to guaranty the safety of biological samples stored in a freezer. Point of care

testing will certainly make these epidemiological studies on SCD easier and less expensive.

There are also many human limitations to epidemiological research in Africa. Patients often feel like "guinea pigs" for the pharmacological industry or commodity for medical publications since they have no direct advantage of participating to the study. This feeling has been reinforced by the "post colonialist" behavior of some US or European scientists during certain medical studies conducted in Africa. Sometimes, the patients were just "used" to provide clinical data and biological samples for the research, and the health care facilities or supplies used during the study were discarded after the study had ended. Moreover, the daily work of health care providers in public hospitals is particularly hard, whereas their income is extremely low, so they usually need to have several occupations to earn enough money for a decent life. Therefore, they lack motivation to do more than their essential clinical duty and are often reluctant to participate to research studies for free. Moreover, most physicians have never received any research education, even in university hospitals, so their clinical research practice is usually far from the methodological standards required in high-income countries. Therefore, they often need methodological support as much as financial one.

However, North-South research collaboration is not always easy, because cultural misunderstandings are extremely frequent, even when the same language is used by both parts (mostly English or French depending on the African regions). Administrative or hierarchical freezing is also frequent, as well as corruptive habits, which can stop the studies for many months or end them forever, despite enormous diplomatic and financial means. Therefore, both parts need to make considerable efforts to understand each other's point of view, and the supervisors from the North need to make the trip to the field to be able to understand the difficulties encountered, that cannot even be imagined from their privileged positions. Fortunately, many African physicians and researchers are extremely motivated to move towards high quality epidemiological research in SCD. The US3 study is one example of successful North-South collaboration that should pave the way for future nationwide epidemiological studies of SCD in sub-Saharan Africa.

Acknowledgments

The author thanks Prof. Leon Tshilolo for careful reading of the manuscript and helpful discussions.
Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Public Health and Emergency*. The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jphe.2016.12.19). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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.
2. Williams TN. Sickle Cell Disease in Sub-Saharan Africa. Hematol Oncol Clin North Am 2016;30:343-58.
3. Makani J, Williams TN, Marsh K. Sickle cell disease in Africa: burden and research priorities. Ann Trop Med Parasitol 2007;101:3-14.
4. Tshilolo L, Kafando E, Sawadogo M, et al. Neonatal screening and clinical care programmes for sickle cell disorders in sub-Saharan Africa: lessons from pilot studies. Public Health 2008;122:933-41.
5. Aygun B, Odame I. A global perspective on sickle cell disease. Pediatr Blood Cancer 2012;59:386-90.
6. World Health Organization. Sickle-cell anaemia: report by the Secretariat. Geneva: World Health Organization, 2006.

7. Rahimy MC, Gangbo A, Ahouignan G, et al. Newborn screening for sickle cell disease in the Republic of Benin. J Clin Pathol 2009;62:46-8.
8. Odunvbun ME, Okolo AA, Rahimy CM. Newborn screening for sickle cell disease in a Nigerian hospital. Public Health 2008;122:1111-6.
9. Tshilolo L, Aissi LM, Lukusa D, et al. Neonatal screening for sickle cell anaemia in the Democratic Republic of the Congo: experience from a pioneer project on 31 204 newborns. J Clin Pathol 2009;62:35-8.
10. Ohene-Frempong K. Selected testing of newborns for sickle cell disease. Pediatrics 1989;83:879-80.
11. Tubman VN, Marshall R, Jallah W, et al. Newborn Screening for Sickle Cell Disease in Liberia: A Pilot Study. Pediatr Blood Cancer 2016;63:671-6.
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 Glob Health 2016;4:e195-200.
13. Lopera-Mesa TM, Doumbia S, Konaté D, et al. Effect of red blood cell variants on childhood malaria in Mali: a prospective cohort study. Lancet Haematol 2015;2:e140-9.
14. Owusu ED, Visser BJ, Nagel IM, et al. The interaction between sickle cell disease and HIV infection: a systematic review. Clin Infect Dis 2015;60:612-26.

doi: 10.21037/jphe.2016.12.19
Cite this article as: Ranque B. The US3 study: a first step towards large scale epidemiology for sickle cell disease in Africa. J Public Health Emerg 2017;1:13.

