Burden of sickle cell trait and disease in the Uganda Sickle Surveillance Study (US3): a cross-sectional study

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Summary

Background **Sickle cell disease contributes substantially to mortality in children younger than 5 years in sub-Saharan Africa. In Uganda, 20 000 babies per year are thought to be born with sickle cell disease, but accurate data are not available. We did the cross-sectional Uganda Sickle Surveillance Study to assess the burden of disease.**

Methods **The primary objective of the study was to calculate prevalence of sickle cell trait and disease. We obtained punch samples from dried blood spots routinely collected from HIV-exposed infants in ten regions and 112 districts across Uganda for the national Early Infant Diagnosis programme. Haemoglobin electrophoresis by isoelectric focusing was done on all samples to identify those from babies with sickle trait or disease.**

Findings **Between February, 2014, and March, 2015, 99 243 dried blood spots were analysed and results were available for 97 631. The overall number of children with sickle cell trait was 12 979 (13·3%) and with disease was 716 (0·7%). Sickle cell numbers ranged from 631 (4·6%) for trait and 23 (0·2%) for disease of 13 649 in the South Western region to 1306 (19·8%) for trait and 96 (1·5%) for disease of 6581 in the East Central region. Sickle cell trait was seen in all districts. The lowest prevalence was less than 3·0% in two districts. Eight districts had prevalence greater than 20·0%, with the highest being 23·9%. Sickle cell disease was less common in children older than 12 months or who were HIV positive, which is consistent with comorbidity and early mortality.**

Interpretation **Prevalence of sickle cell trait and disease were high in Uganda, with notable variation between regions and districts. The data will help to inform national strategies for sickle cell disease, including neonatal screening.**

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Introduction

Sickle cell disease refers to a group of inherited haemoglobin disorders characterised by a predominance of abnormal sickle haemoglobin in erythrocytes.[1] Sickle cell anaemia, which results from homozygous inheritance of sickle haemoglobin from both parents, is the most common and severe form of sickle cell disease. On deoxygenation, sickle haemoglobin undergoes a conformational change that promotes intracellular polymerisation, which leads to distortion of the normal biconcave erythrocyte disc into the distinctive and pathological crescent shape. The resulting haemolytic anaemia manifests as recurrent vaso-occlusion and organ damage that together cause substantial morbidity and early mortality.[1]

Worldwide, sickle haemoglobinopathies lead to a substantial burden of disease that is not adequately addressed.[2–4] Accurate data are lacking, but the worldwide estimate for neonates born with sickle cell disease each year is 400 000, including 300 000 with sickle cell anaemia.[5] The greatest burden is seen in sub-Saharan Africa, where more than 75% of all sickle cell disease occurs, with this proportion projected to increase by 2050.[6] In Africa, sickle cell disease contributes substantially to mortality in children younger than 5 years and, therefore, limits progress towards achieving UN Sustainable Development Goal 3, Good Health and Well-Being, which includes the reduction of childhood mortality.[7,8]

In 2006, WHO issued an important report on sickle cell disease in the African region, which described the overall prevalence and provided guidelines on care and management strategies.[9] WHO also publicised the need to improve sickle cell awareness, disease prevention, and early detection.[10] Countries in sub-Saharan Africa have been challenged by WHO to formulate national strategies for sickle cell disease that address specific aims, targets, and objectives. Despite this charge, ministries of health are hindered from creating meaningful interventions by many obstacles, including lack of accurate data about the burden and distribution of disease within their countries.[11]

Uganda was among the first countries in Africa with a documented large burden of sickle cell disease. In 1949, substantial differences in the prevalence of sickle cell trait were reported between different tribes, ranging from less than 5% for Hamites in the southwest to more than 20% for the northern Nilotices (Lango and Acholi). Some Bantu tribes had even higher rates, including 45% among Bamba living in the western region.[12] A later study, however, has suggested lower values.[13] Of note,

Research in context

Evidence before this study

Decades have passed since the initial descriptions of sickle cell trait in different regions of Uganda, but accurate data on prevalence are unavailable. We searched PubMed for articles published in English up to May, 2015, with the search terms "sickle cell", "screening", "Uganda", "Africa", and "haemoglobin electrophoresis". We identified four articles published before 1960 that described ethnic origin and distribution of sickle cell trait and disease in Uganda. We found one paper from 2010 that described the distribution of sickle cell trait in several regions of Uganda and seven reports since 2005 that provided pilot neonatal screening data in other sub-Saharan African locations, but could find no comprehensive surveillance data at the national level.

Added value of this study

The primary study objective of the Uganda Sickle Surveillance Study was to generate critical data on the prevalence of sickle cell trait and disease. Comorbidities that might be associated with early mortality in people with sickle cell disease were also explored. This national-level surveillance study in sub-Saharan Africa documents a high burden in Uganda, with wide distribution of sickle cell trait and disease in every region and district. These national data will inform the Ministry of Health about next steps, including the launch of neonatal screening and development of a national sickle cell strategy. We also found that frequency of sickle cell disease declined in children older than 12 months or with HIV, which was consistent with comorbidity and early mortality.

Implications of all the available evidence

The Ugandan Ministry of Health needed accurate data on the prevalence and distribution of sickle cell trait and disease to help the country follow the WHO guidelines for clinical management. In view of our results, targeted neonatal screening for sickle cell disease is now warranted in the districts with the highest burden, along with efforts to improve education of health-care providers and awareness among the public and the government. Similar studies can be done in other sub-Saharan countries to help the development of national strategies for the management of sickle cell disease.

though, both studies were based on small samples and were not representative of the whole country.

The Ugandan Ministry of Health recognised the need for accurate, up-to-date data on the burden of sickle cell trait and disease to inform its efforts to pilot neonatal screening, begin early education and preventive measures, and eventually create a national strategy. We hypothesised that there is a large burden of sickle cell trait and disease across Uganda, but with substantial geographical variability. A partnership was established between Cincinnati Children's Hospital, Cincinnati, OH, USA, and Makerere University, Kampala, Uganda, to enable the Ministry of Health to do a large cross-sectional research study, the Uganda Sickle Surveillance Study (US3), to generate such data.

Methods

Programme development

The Ugandan Ministry of Health has an active programme for prevention of mother-to-child transmission of HIV that identifies and treats infected mothers and their exposed infants. Infected mothers receive antiretroviral drug therapy during pregnancy and exposed babies receive 6 weeks of treatment after birth, followed by testing with viral PCR for acquired HIV infection, typically before age 6 months. Around 100 000 HIV-exposed infants are tested each year through the Early Infant Diagnosis programme, which includes a national sample transport system.[14] Dried blood spots (DBS) are collected from exposed infants at health-care facilities across the country, carried by motorcycle to laboratory hubs at the subdistrict level, and shipped by courier to the Central Public Health Laboratories in the capital, Kampala.[14] Sample testing is completed within 3 weeks of collection, after which DBS are stored at –20° C for about 1 year then discarded. The DBS collected between February, 2014, and March, 2015, were shared with the newly created sickle cell laboratory in the Central Public Health Laboratories within 1 week of HIV testing, to test for normal and abnormal haemoglobins.

The study protocol was approved with a waiver for informed consent by the School of Medicine Research Ethics Committee at Makerere University and the Uganda National Council for Science and Technology in Kampala. The study was also formally approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board.

Haemoglobin testing

The laboratory methods for haemoglobin testing were based on those previously described for a pilot neonatal haemoglobinopathy screening programme in Angola.[15] DBS were eluted and analysed by isoelectric focusing for the presence of normal and abnormal haemoglobins. Isoelectric focusing readily distinguishes between normal and sickle haemoglobin even in the presence of fetal haemoglobin. Staff at the Central Public Health Laboratories received on-site training by a technical team from Cincinnati Children's Hospital on the study protocol, isoelectric focusing procedures, and interpretation of results. Additional sessions were provided remotely for further training, troubleshooting, and overal technical laboratory support.

The gel bands were independently compared with a standard control by two laboratory technicians and reviewed by the laboratory technologist to derive the final