

BMJ Open Neurological complications of sickle cell disease in Africa: protocol for a systematic review

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ABSTRACT

Introduction: Sickle cell disease (SCD) is highly prevalent in Africa. Considered as a public health problem, it is associated with high morbidity and mortality. Neurological complications of SCD can cause significant disability with important socioeconomic and psychological impact on the patients and their families, and can even lead to death if not properly managed. There are important knowledge gaps regarding the burden of neurological complications of SCD in African populations. We propose to conduct the first systematic review to summarise the epidemiological data available on neurological complications of SCD in Africa.

Methods and analysis: We will search PubMed, MEDLINE, EMBASE and the African Index Medicus from 1 January 1950 to 31 May 2016 for studies of neurological complications of SCD in Africa. After study selection, full-text paper acquisition, data extraction and synthesis, we will assess all studies for quality, risk of bias and heterogeneity. Appropriate methods of meta-analysis will be used to pool prevalence estimates from studies with similar features, globally and in major subgroups. This protocol complies with the 2015 Preferred Reporting Items for Systematic reviews and Meta-Analysis protocols (PRISMA-P) guidelines.

Ethics and dissemination: The proposed study will use published data. Therefore, there is no requirement for ethical approval. This review is expected to provide relevant data to help quantify the burden of neurological complications of SCD in African populations, inform policymakers and identify further research topics. The final report of the systematic review will be published in a peer-reviewed journal and presented at conferences.

Review registration number: CRD42016039574.

INTRODUCTION

Rationale

Sickle cell disease (SCD) is a well-known genetic haematological disorder with variable severity.¹ It is characterised by the presence of a pathological haemoglobin S that differs

from the normal one by the presence of the amino acid Valine at position 6 of the β -globin subunit rather than glutamic acid (Glu6Val mutation). Haemoglobin S is poorly soluble when deoxygenated and its precipitation in red blood cells is the *primum movens* of all the acute manifestations and long-term complications of SCD.²

SCD affects millions of people worldwide.³ It is associated with severe complications that have a negative impact on their quality of life and survival.^{3–4} The incidence and the prevalence of SCD in Africa have kept increasing over the past decades. It is estimated that 240 000 children are born with SCD annually in sub-Saharan Africa (SSA) and 50–80% of these children die before the age of 5 years.^{5–7} The prevalence is highly variable across Africa. It is as high as 45% in Uganda,⁸ 20–30% in Cameroon, Republic of Congo, Gabon, Ghana and Nigeria,^{9–12} 1–2% in Northern Africa and <1% in southern Africa.⁸ SCD remains a major public health challenge in African countries because of the lack of national health coverage systems, the lack of basic healthcare facilities, the low population awareness of the disease and its complications and the inadequate access to screening and diagnostic procedures.⁶ This inadequate access to proper healthcare explains the increased vulnerability of children affected with SCD to exacerbations and complications with resulting major psychological and socioeconomic consequences for them and their families.^{6–8}

Vaso-occlusive crises and haemolysis are the clinical hallmarks of SCD.² The polymerisation of deoxy-haemoglobin S leads to the formation of non-flexible sickle-shaped red blood cells that occlude terminal vessels.² Repeated vaso-occlusive crises in various organs could result in a wide range of complications classified as locomotor (chronic pain, aseptic osteonecrosis), renal (renal



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infarction with papillary necrosis, medullary fibrosis with focal segmental glomerulosclerosis, glomerular hyperfiltration and tubular dysfunction), neurological (ischaemic or haemorrhagic strokes, silent brain infarcts) and cardiorespiratory (acute chest syndrome).^{12–14} Regarding haemolysis, it refers to the continuous destruction of sickled red blood cells within the blood vessels or the spleen (following splenic sequestration). This could result in chronic anaemia, aplastic crises and eventually heart failure in some cases. Patients with SCD are also susceptible to severe and often multifocal infections as a result of several factors, including functional asplenia, micronutrient deficiencies and tissue ischaemia.^{14 15} Neurological manifestations of SCD are common and include chronic headache, epilepsy, ischaemic or haemorrhagic stroke, cognitive impairment due to chronic anaemia, hypoxia and silent infarcts.^{12–14}

So far, most studies have focused on cerebrovascular complications that are the most debilitating and need urgent implementation of prevention and management strategies. However, the majority of these studies have involved patients from outside the African continent which currently has the highest burden of disease. In the African context, the relative proportion of vascular and non-vascular neurological complications might be different. Most studies in Africa have included small samples and putting their findings together in a systematic review might help to better estimate the prevalence of the various neurological complications of SCD, thus providing useful data for policymakers.

Objective

The objective of this study is to summarise the epidemiological data available on the prevalence of neurological complications in patients with SCD in Africa.

METHODS

This review protocol has been prepared according to the 2015 Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines.¹⁶ It has been registered in the PROSPERO International Prospective Register of Systematic Reviews (<http://www.crd.york.ac.uk/PROSPERO>), registration number CRD42014015376.

Criteria for considering studies for the review

Inclusion criteria

All observational studies and clinical trials conducted in Africa from 1 January 1950 to 31 May 2016, and reporting epidemiological data on the neurological complications of SCD will be included without any restriction of language.

Exclusion criteria

1. Studies conducted outside of Africa.
2. Case series with small sample size (<30 participants), letters, reviews, commentaries and editorials.

3. Duplicates; for studies published in more than one report, the most comprehensive and up-to-date version will be used.
4. Studies whose full data will not be accessible even after request from the authors.

Search strategy for the identification of relevant studies

The search strategy will be implemented in two steps.

Search in bibliographic databases

We will search PubMed MEDLINE, EMBASE, and the African Index Medicus from 1 January 1950 to 31 May 2016, for observational studies and clinical trials reporting data on the neurological complications of SCD in Africa. As summarised in [table 1](#), the search strategy will be built by combining relevant terms related to SCD and its possible neurological complications with the names of the 54 African countries.

Forwards and backwards citation searching

Forwards and backwards citation searching will be performed to identify additional sources of data that were missed during the search in bibliographic databases.

Selection of studies for inclusion in the review

Two investigators (NN and MKM) will independently perform the literature search. Titles and abstracts will be screened and the full texts of all relevant articles will be retrieved. These full texts will be screened using a pre-tested standardised form to include eligible studies. Disagreements will be resolved by consensus, with consultation of a third author (JKT). Authors of publications reporting unclear data that may be subject to multiple interpretations will be contacted by email for clarification or to request supplemental information. If a study is excluded, the reasons will be documented. The PRISMA flow chart¹⁶ will be used to summarise the entire selection process ([figure 1](#)).

Assessment of the methodological quality and risk of bias

The Risk of Bias Tool for Prevalence Studies established by Hoy *et al*¹⁷ ([table 2](#)) and the Cochrane guidelines available in Review Manager V.5.3 (<http://tech.cochrane.org/revman>) will be used to evaluate the methodological quality and risk of bias for each study. The STROBE checklist¹⁸ will be used to evaluate the quality of reporting in each paper.

Data extraction

A data extraction sheet will be used to collect information about the country, the year of publication, the language of publication, the type of publication, the study design, the number of participants, the mean age of the population, the diagnostic criteria for SCD and the prevalence of the various neurological complications of SCD. Where prevalence rates or information for calculating them (eg, sample size, frequency of outcomes) are lacking, we will contact the corresponding author to request the

Table 1 Search strategy for MEDLINE and adaptability to regional databases

Search	Search terms
1	Sickle cell disease OR sickle cell anemia OR sickle cell hemoglobinopathy OR drepanocytosis
2	Headache OR seizure OR epilepsy OR cognitive deficit OR intellectual disability OR intellectual impairment OR cognitive impairment OR neuropsychologic* deficit OR cerebral infarct OR white matter lesions OR subcortical infarct OR cortical infarct OR stroke OR ischemic stroke OR hemorrhagic stroke OR ischaemic stroke OR haemorrhagic stroke OR intraventricular hemorrhage OR aneurysm OR parenchymal hemorrhage OR fat embolism OR subarachnoid hemorrhage OR arterial stenosis OR intracranial stenosis OR carotid stenosis OR moya moya OR moya* OR epidural hematoma OR borderline infarct OR watershed infarct OR fat embolism OR cerebral venous thrombosis OR hemiparesis OR hemiplegia OR quadriplegia OR paraparesis OR paraplegia OR cranial nerve palsy OR cerebral vasoconstriction OR leukoencephalopathy OR encephalopathy OR encephalitis OR meningitis OR brain* OR spine OR spinal cord OR neurologic* complications OR central nervous system OR peripheral nervous system OR neuropathy OR polyneuropathy OR cortical atrophy OR brain atrophy OR posterior reversible encephalopathy syndrome
3	Africa* OR Algeria OR Angola OR Benin OR Botswana OR "Burkina Faso" OR Burundi OR Cameroon OR "Canary Islands" OR "Cape Verde" OR "Central African Republic" OR Chad OR Comoros OR Congo OR "Democratic Republic of Congo" OR Djibouti OR Egypt OR "Equatorial Guinea" OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR "Guinea Bissau" OR "Ivory Coast" OR "Cote d'Ivoire" OR Jamahiriya OR Kenya OR Lesotho OR Liberia OR Libya OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mayotte OR Morocco OR Mozambique OR Namibia OR Niger OR Nigeria OR Principe OR Reunion OR Rwanda OR "Sao Tome" OR Senegal OR Seychelles OR "Sierra Leone" OR Somalia OR "South Africa" OR "St Helena" OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR "Western Sahara" OR Zaire OR Zambia OR Zimbabwe OR "Central Africa" OR "Central African" OR "West Africa" OR "West African" OR "Western Africa" OR "Western African" OR "East Africa" OR "East African" OR "Eastern Africa" OR "Eastern African" OR "North Africa" OR "North African" OR "Northern Africa" OR "Northern African" OR "South African" OR "Southern Africa" OR "Southern African" OR "sub Saharan Africa" OR "sub Saharan African" OR "subSaharan Africa" OR "subSaharan African)" NOT ("guinea pig" OR "guinea pigs" OR "aspergillus niger")
4	# 1 AND # 2 AND # 3
5	#4 Limits: 1986/01/01 to 2016/05/31

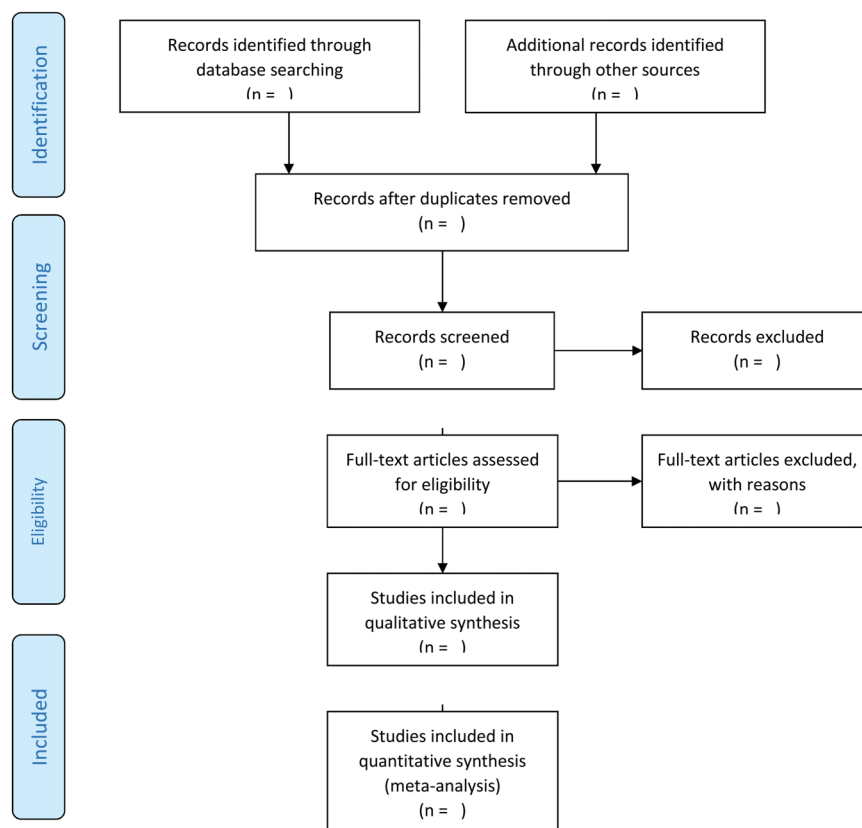
Figure 1 PRISMA flow diagram.

Table 2 Risk of bias assessment tool

Risk of bias item	Response: yes (low risk) or no (high risk)
External validity	
Was the study target population a close representation of the national population in relation to relevant variables?	
Was the sampling frame a true or close representation of the target population?	
Was some form of random selection used to select the sample, OR, was a census undertaken?	
Was the likelihood of non-participation bias minimal?	
Internal Validity	
Were data collected directly from the participants (as opposed to medical records)?	
Were acceptable case definitions of sickle cell disease and the assessed neurologic complications used?	
Were reliable and accepted diagnostic methods for sickle cell disease and the assessed neurologic complications utilized?	
Was the same mode of data collection used for all participants?	
Was the length of the shortest prevalence period for the parameter of interest appropriate?	
Were the numerator(s) and denominator(s) for the calculation of the assessed neurologic complications appropriate?	
Summary item on the overall risk of study bias	
Low Risk of Bias: 8 or more 'yes' answers. Further research is very unlikely to change our confidence in the estimate.	
Moderate Risk of Bias: 6 to 7 'yes' answers. Further research is likely to have an important impact on our confidence in the estimate and may change the estimate.	
High Risk of Bias: 5 or fewer 'yes' answers. Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate.	
The Risk of Bias Tool for Prevalence Studies developed and modified by Hoy <i>et al.</i> ¹⁷	

information. In case of multinational studies, we will separate the results to show the prevalence of the SCD-related neurological complications in each country. In the event that it is not possible to disaggregate the data by country, the study will be presented as one and the countries in which the study was carried out will be shown.

Statistical analysis

Heterogeneity will be evaluated by the χ^2 test on Cochrane's Q statistic¹⁹ and quantified by calculating the I^2 .²⁰ I^2 values of 25%, 50% and 75% will be considered as representing low, medium and high heterogeneity, respectively. Assessment of publication bias and selective reporting will be done by examining articles' abstracts and by using funnel plots and the Egger's test.²¹ If there is no substantial heterogeneity across studies, we will conduct a global meta-analysis. For this purpose, the study-specific estimates will be determined from the point estimate and the appropriate denominators, assuming a binomial (or Poisson for incidence data) distribution. We will pool the study-specific estimates using a random-effects meta-analysis model after stabilising the variance of individual studies with the Freeman-Tukey double arcsine transformation.²² Where substantial heterogeneity is detected, we will perform subgroup analyses to explore the possible sources of heterogeneity using the following grouping variables: age (below vs at or above the median), gender (gender-specific

analysis where possible; and below vs at or above the median proportion of men across study), study setting (rural vs urban; hospital vs community-based), geographical region (central, eastern, northern, southern and western Africa), time when the study was conducted/published (below vs at or above the median) and study quality. If the data are limited or cannot be pooled due to substantial heterogeneity, the findings will be presented in a narrative form.

We will assess inter-rater agreement for study inclusion using Cohen's κ coefficient.²³ Data will be analysed using the statistical software R (V.3.0.3 (2014-03-04), The R Foundation for statistical computing, Vienna, Austria).

Reporting of this review

The proposed systematic review will be reported following the PRISMA guidelines.²³ A PRISMA checklist will be published with the final report.

Potential amendments

We do not intend to make any amendment to this protocol. However, any necessary amendment will be documented and reported transparently.

Ethics and dissemination

The current study will be based on published data. An ethical clearance is therefore not required. The final

report of the systematic review will be published as an original article in a peer-reviewed journal. Findings will be presented at conferences and submitted to relevant health authorities. We also plan to perform regular updates of the review every 5 years.

CONCLUSION

Neurological complications of SCD may be more frequent in Africa than currently reported. The rarity of prevalence studies of these complications makes it difficult to manage them. The most commonly reported neurological complication of SCD is overt stroke. However, the frequency of silent infarcts, intracranial bleeding, leukoencephalopathy, cerebral atrophy and impaired cognition is most often underestimated since these are usually revealed by neuropsychological and neuroimaging screening studies in otherwise asymptomatic patients with SCD. The high prevalence of these findings in young patients with SCD underscores the fact that central nervous system injuries begin early in life. The strength of this review is that it will be the first to quantify the magnitude of neurological complications of SCD across Africa where this haematological condition is highly prevalent. Furthermore, this review might identify specific research challenges to be addressed in future studies of neurological complications of SCD in Africa.

The main possible limitations of this review could be the scarcity of studies on the subject and the predominance of poor quality studies (due to lack of population awareness and inadequate screening or follow-up) that might result in an underestimation of the real prevalence of the neurological complications of SCD in Africa. Regional differences in the standard of care could also lead to significant heterogeneity among studies, thus precluding the meta-analysis and making it difficult to get a global picture of the burden of neurological complications of SCD across Africa.

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