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## Neurological complications in subjects with sickle cell disease or trait in Mali

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### Abstract

**Background**—Sickle cell disease (SCD) is the most common inherited disorder in the world.

Although more common in Africa, the clinical care of patients with this disease is still a problem in this part of the world. Sickle cell disease is characterized by a wide range of complications, but neurological features are not understood by health practitioners.

**Objectives**—The goal of this study is to clinically characterize patients with SCD or trait (SCT) who presented neurological complications and to explore the underlying causes.

**Methods**—Patients with SCD or SCT who presented neurological features were seen in our neurology clinic. Brain CT-scans were performed to confirm cerebral lesions. EEG and EMG were also performed where needed. Blood cell count and CK levels were done.

**Results**—Eight patients with SCD or SCT presented neurological symptoms. Stroke was the most seen neurological complications with six cases (85%), and the remaining patients had myopathy. Two of the patients with stroke presented with seizures later in the disease course. The diagnosis of stroke was based on clinical findings and/or brain imaging, and for myopathy on the presence of proximal weakness and high CK levels. When available, patients always had low hemoglobin levels (8–11 g/dl). In addition, patients with myopathy had high CK levels.

**Conclusion**—complications of SCD or SCT are frequent, especially in Africa because of limited access to specialized care. Although stroke is the most reported neurological complication, myopathy needs more attention. This study sets the field for larger cohort studies that may come up with standardized approaches to prevent complications in resource limited countries.

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## Keywords

Sickle cell disease; sickle cell trait; stroke; myopathy; Mali

## Introduction

Sickle cell disease is the most common inherited single gene disorder in world, and Africa houses the majority of the patients. In fact, in 2010, 79% of newborns with SCD were in Africa, and this number is expected to increase to 88% by 2050.(1)

Although known to be inheritable before the age of technology, the first molecular diagnosis of SCD goes back to the early 1900. Despite its high frequency and disabling complications, SCD was recognized by World Health Organization as public health concern only in 2006 (Fifty-ninth World Health Assembly: resolutions and decisions, annexes.

WHA59/2006/REC/1. Geneva: World Health Organization). Since then, resolutions were taken for its prevention and management. But still, while countries with low SCD incidence are seeing their numbers drop, the prevalence and complications of SCD in sub-Saharan Africa in general, and Mali in particular will increase because of the high birth rate but yet poor access to public health infrastructures.

Complications occurring in SCD or SCT are diverse and include vaso-occlusive episodes, hyperhaemolysis, acute chest syndrome, and, less frequently, neurological complications. The improvement in screening and prevention in high income countries have reduced the incidence of those complications.(2) However, the lack of infrastructure and the poor understanding of the disease and its complications have increased the burden of SCD and SCT in Africa.(3, 4)

While stroke is the major neurological complication reported worldwide, few cases of muscle involvement are reported, and consisted mostly of exertional rhabmyolysis and muscle necrosis.(5) The genetic risk in the occurrence of stroke in SCD patients has been documented.(6–8) In addition, it is known that epilepsy is 2 to 3 times more common in individuals with SCD than in the general population.(9)

Recent studies have shown the impact of effective screening and prophylaxis such as transcranial Doppler (TCD) and regular blood transfusion in preventing complications. For example, it is expected that 11% of children without effective screening and prophylaxis will have ischemic stroke. This number drops to 1% for children with effective follow-up. However, access to TCD is still limited in Africa.(10)

Mali has pioneered a center for research and against SCD (CRLD) which has improved the clinical management of SCD.(11) Yet, many cases are missed because of the high demand and not all patients of the center benefit an effective screening and prophylactic care to prevent complications. Therefore, many of these patients may present neurological complications and are admitted in our clinic. We present here a preliminary survey of patients with SCD or SCT who presented a wide range of neurological symptoms.

## Methods

Individuals with SCA or SCT and neurological symptoms were enrolled in this study. All patients were seen by a neurologist and went through a thorough neurological examination. Brain CT-scan was performed in patients with stroke-like symptoms and EEG in patients with seizures. EMG was also performed on patient with myopathic features. Blood cell count was done for all patients to check for anemia. CK levels were assessed in patients with myopathy. Where not available, sickle cell anemia was tested by hemoglobin gel electrophoresis.

## Results

Eight patients with SCD or SCT presented neurological symptoms. The age at diagnosis ranged from 7 to 47 years with a mean age of 20 years. Gender was evenly represented with four cases each. Among them six presented with stroke or stroke-like features and two had myopathy. In two cases (25%), neurological complications were the presenting features of SCD.

### Stroke

Six patients had stroke or stroke-like features. In three cases, brain imaging showed lesions consistent with ischemic stroke. The first case, a 14-year-old girl homozygous SS, was seen for an acute left side hemiplegia. She had a history of an ischemic stroke with right side hemiplegia of which she kept some sequelae three prior to the present episode. On examination she had a tetraparesis with brisk reflexes on right and bilateral plantar extensor. Brain CT-scan showed two ischemic lesions, one in the left anterior cerebral artery and another in the right sylvian artery. Hemoglobin level was at 8 g/dl. He received blood transfusions and fluids but could not recover weakness after three months. The second case was a 20-year-old male homozygous SS admitted for acute right side weakness. He was diagnosed with sickle cell disease at age 12 with recurring vaso-occlusive crises. Brain CT-scan showed an ischemic stroke of the left sylvian artery. Hemoglobin levels were 10.2 g/dl. Despite blood transfusion he did not recover weakness. The third case, an 8-year-old boy homozygous SS, was seen for acute vision impairment and vaso-occlusive pain. Brain CT-scan showed cerebral posterior artery ischemia. After iterative blood transfusion he recovered vision progressively but completely. In the remaining three cases brain imaging was normal or unavailable but patients had symptoms consistent with stroke. The first patient, a 47-year-old female with homozygous SS, had symptoms suggesting brain stem involvement. Symptoms included problems with swallowing and hypophonia. On examination she had hemiparesis and sensory decrease in left and laryngoscopy showed right vocal fold paralysis and palate hypotonia. She recovered progressively with no sequelae. Prior to the stroke she had recurring vaso-occlusive pain and coxal femoral joints necrosis and ankyloses. She later developed pulmonary embolism. The second patient, an 8-year-old girl homozygous SS, was seen for relapsing seizures that started at age 5. On examination she had a left hemiparesis with brisk reflexes. Brain CT-scan was normal but EEG showed multiple focal spike waves consistent with focal generalized seizures. Her hemoglobin level was at 8.8 g/dl. The third patient, a 46-year-old male with heterozygous

AS, was seen for seizures. He had a history of stroke with hemiparesis on left about one year prior to seizures. Brain CT-scan showed ischemic infarct in the sylvian artery. No other risk factor was identified.

### Myopathy

Two patients presented with muscular disease. The first patient, an 8-year-old boy heterozygous SC, was seen for proximal weakness he developed over 3 months. No other risk factor was identified. Chest examination and X-rays were consistent with pulmonary involvement. Hemoglobin levels were at 11.1 g/dl. CK levels were high at 2,500 and EMG showed myopathic feature. TCD was normal. After blood transfusion and antibiotic treatment he recovered partially. The second patient, a 24-year-old female heterozygous AS, was admitted for proximal weakness. CK levels were increased at 550 and hemoglobin levels at 10 g/dl.

Clinical and laboratory features are summarized in Table I.

### Discussion

SCD is very devastating disease especially in sub-Saharan Africa where it afflicts several families. Recent progress in the diagnosis and management of this disease has improved the quality of life of patients in developed countries. However, in developing countries where endemic factors such as infectious diseases and malnutrition are prevalent, SCD is associated with complications.(12) In fact, acute infection with fever and other risk factors lead to low oxygen content and to increased cerebral and muscle metabolic demands. This may result in diverse neurological complications such as stroke and myonecrosis. The wide use of TCD has considerably reduced these complications in the developed countries. Complications arise in general during young with some occurring before the first birthday. The mean age in study is 20 years. This may be due to the fact that our clinic is an adult neurology, thus missing all pediatric cases. Gender was evenly distributed in our study. Although the small number of our cohort limit conclusions, a study with similar number of cases has reported a predominance of females.(13) While five patients were homozygous SS, one patient was SC and two patients were AS. Although most cases of neurological complications were reported in SCD cases, few cases were reported in SCT patients, and mostly post exertional myopathy.(5) It is possible that the heterozygous cases may be  $\beta$ -thalassemia or misdiagnosed cases. The most reported neurological complications in SCD are in general stroke, especially ischemic stroke. However, cases of muscle injury were also reported.(14, 15) In our cohort the majority of neurological complications were stroke, and ischemic infarct was the main cerebral lesion. Although brain imaging was normal in two patients and unavailable for another, they had symptoms consistent with stroke. Moreover, CT-scan can appear normal, especially within the first hours of stroke, and MRI was not available at the time of the disease. The most affected artery was the sylvian. This prevalence is in concordance with what was found in the literature. In one case, patient presented symptoms consistent with brain stem involvement. CT-scan was normal but patient presented with hypophonia, dysphagia, left vocal cords paralysis and right side hemiparesis. In addition to the fact that brain stem ischemia are difficult to see in some

cases, MRI is the gold-standard diagnostic tool. In another case, CT-scan was normal but patient presented with recurring seizures. On examination she had left side hemiparesis suggesting silent stroke. However, this can also be secondary to seizures as she has always been seen after spells. Two cases presented with myopathy. Although previously reported cases were secondary to pain crisis and involved only one side, in the cases presented here patients had typical bilateral symmetrical myopathy. MRI was not available during the time of our study to check for possible muscle necrosis. Moreover, muscle biopsy was not done. However, CK levels were very high in both patients, confirming muscle injury. In addition, no other risk factor was found to explain the disease. Patients were from non-consanguineous marriage and no other familial case was reported; reducing the possibility of a genetic cause. While one patient improved with repetitive blood transfusion the other did not improve well after a month of treatment. Her SCT status was discovered towards the end of her hospital stay and no further assessment was possible as she had to leave because of social concerns. In general, stroke was associated with low hemoglobin levels around 8–10 g/dl. None of our patients with stroke underwent TCD around the time of complications. However, TCD of one patient with myopathy done about a month after disease onset was normal. In 25% of cases neurological complications were the presenting SCD symptoms, and 50% of patients were followed up in the CRLD center. But no TCD was performed until the time of the complication. This shows the limited access to diagnosis resources and poor management of SCD patients. Previous studies have shown the association of stroke with some genetic factors in SCA children. While some studies have found some protective variants, others have instead found variants with increased risk of stroke.

## Conclusion

Our study confirms the high frequency of neurological complications in SCD and SCT patients. Scientists are increasingly studying the possible pathogenesis of SCT, however, there is today no mechanistic explanation. Studying larger cohorts may shed light into the contribution of SCT in the occurrence of some symptoms. The genetic contribution in complications in SCD has been raised, and sub-Saharan Africa has much to contribute in this endeavor because of the high prevalence of the disease in this part of the world but also the high fertility rate allowing more comprehensive genetic studies. Far from being an exhaustive study, this work set the field for a more accurate and multidisciplinary cohort studies which will set guidelines for a better prevention and management of complications linked SCD and SCT in Africa.

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Summary of clinical and laboratory findings

TABLE 1

	Age (yrs)	Sex	Status	Type	Major Signs	Hb (g/dl)	Brain Imaging	CK
Patient 1	14	F	SS	Stroke	L, R H	8	ACA, MCA I	—
Patient 2	20	M	SS	Stroke	R H	10.2	MCA I	—
Patient 3	47	F	SS	Stroke	R VFP, L H	N/A	Normal	—
Patient 4	8	M	SC	Myopathy	PW	11.5	—	2,900
Patient 5	7	F	SS	Stroke	S, L H	8.8	Normal	—
Patient 6	46	M	AS	Stroke	L H, S	N/A	MCA I	—
Patient 7	8	M	SS	Stroke	VL	9.2	PCA I	—

—, not done; ACA, anterior cerebral artery; CK, creatine kinase; EEG, electroencephalography; EMG, electromyography; F, female; FGS, focal generalized seizures; FS, focal seizures; H, hemiparesis/hemiplegia; Hb, hemoglobin; I, ischemia; M, male; MCA, middle cerebral artery; N/A, not available; PCA, posterior cerebral artery; PW, proximal weakness; L, left; R, right; S, seizure; VFP, vocal folds paroxysms; VL, visual loss.