Neurological Complications in Subjects With Sickle Cell Disease or Trait

Genetic Results From Mali

Guida Landouré*, Lassana Cissé*, Boubacar A. Touré†, Abdoulaye Yalcouyé*, Toumany Coulibaly*, Mamadou Karambé*, Adama S. Sissoko*, Thomas Coulibaly*, Ambroise Wonkam‡, Cheick O. Guinto*, The H3Africa Consortium

Bamako, Mali; and Cape Town, South Africa

Sickle cell disease (SCD) 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 the World Health Organization as a public health concern only in 2006 [2]. 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 and poor access to public health infrastructures.

Complications occurring in SCD or sickle cell traits (SCT) are diverse and include vaso-occlusive episodes, hyperhemolysis, 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 [3]. 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 [4,5].

Whereas stroke is the major neurological complication reported worldwide, few cases of muscle involvement were reported, and they consisted mostly of exertional rhabdomyolysis and muscle necrosis [6]. The genetic risk in the occurrence of stroke in SCD patients has been documented [7-9]. In addition, it is known that epilepsy is 2× to 3× more common in individuals with SCD than in the general population [10].

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 an ischemic stroke. This number drops to 1% for children with effective follow-up. However, access to TCD is still limited in Africa [11].

Mali has pioneered a center for research and against SCD (Centre de Recherche et de Lutte contre la Drepanocytose, or CRLD) that has improved the clinical management of SCD [12]. Yet, many cases are missed because of the high demand and not all patients of the center benefit from 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.

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

Seven patients with SCD or SCT presented neurological symptoms. The age at diagnosis ranged from 7 to 47 years with a mean age of 21.43 years. The sex ratio, 1.33, was in favor of men. Among them, 6 presented with stroke or stroke-like features and 1 had myopathy. In 2 cases (28.6%), neurological complications were the presenting features of SCD.

Six patients (86%) had stroke or stroke-like features. In 3 cases, brain imaging showed lesions consistent with ischemic stroke. The first case, a 14-year-old girl with homozygous SS, was seen for an acute left-side hemiplegia. She had a history of ischemic stroke with right-side hemiplegia of which she kept some sequelae 3 months prior to the present episode. On examination, she had tetraparesis with brisk reflexes on right and bilateral plantar extensor. Brain CT scan showed 2 ischemic lesions, 1 in the right anterior cerebral artery (Fig. 1) and another in the left Sylvian artery. Hemoglobin level was at 8 g/dl. He received blood transfusions and fluids but could not recover from weakness after 3 months. The second case was a 20-year-old man with homozygous SS admitted for acute right-side weakness. He was diagnosed with SCD at age 12 with recurring vaso-occlusive crises. Brain CT scan showed an ischemic stroke of the left Sylvian artery. His hemoglobin levels were

The authors report no relationships that could be construed as a conflict of interest.
This work is supported by Grant U01HG007044 administered by the National Human Genome Research Institute as part of the National Institutes of Health Common Fund H3Africa Initiative and the Teaching Hospital of Point "G."
From the *Service de Neurologie, Centre Hospitalier Universitaire du Point G, Bamako, Mali; †Centre de Recherche et de Lutte contre la Drépanocytose, Bamako, Mali; and the ‡Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa. Correspondence: G. Landouré (landoureg@ninds.nih.gov).

GLOBAL HEART
Published by Elsevier Ltd. on behalf of World Heart Federation (Geneva).
VOL. 12, NO. 2, 2017
ISSN 2211-8160/$36.00.
http://dx.doi.org/10.1016/j.gheart.2017.01.014

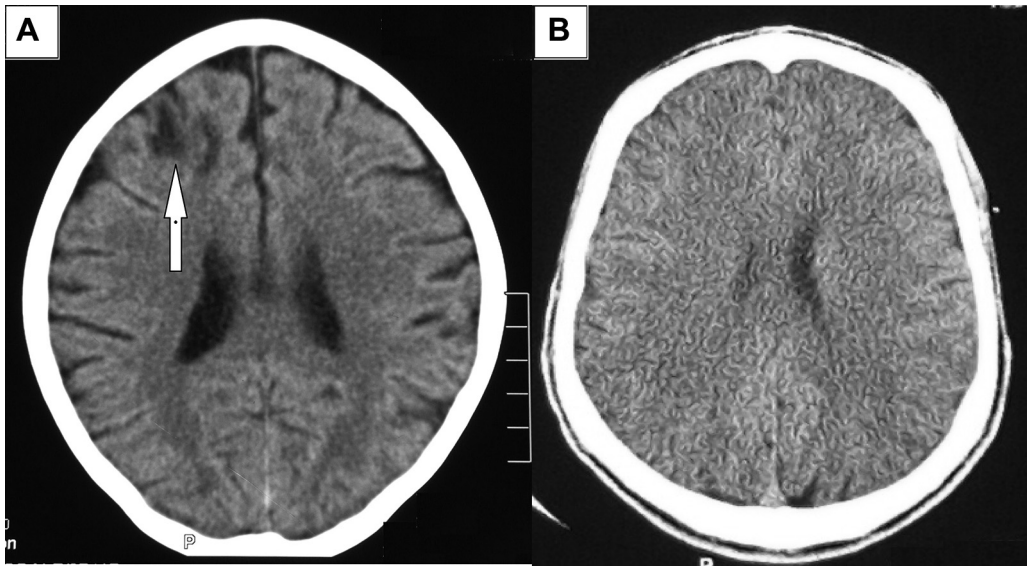

FIGURE 1. Brain imaging of ischemic stroke. (A) Brain computed tomography (CT)-scan of a patient with anterior cerebral artery ischemia, shown by the white arrow, associated with cortical atrophy compared to (B) normal brain CT-scan of same age.

10.2 g/dl. Despite blood transfusion, he did not recover from weakness. The third case, an 8-year-old boy with 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 3 cases, brain imaging was normal or unavailable but patients had symptoms consistent with stroke. The first patient, a 47-year-old woman with homozygous SS, had symptoms suggesting brain stem involvement. Symptoms included problems with swallowing and hypophonia. On examination, she had hemiparesis and sensory decrease on the left side of her body, 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 with 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 electroencephalography showed multiple focal spike waves consistent with focal generalized seizures. Her hemoglobin levels were at 8.8 g/dl. The third patient, a 46-year-old man with heterozygous AS, was seen for seizures. He had a history of stroke with hemiparesis on the left about 1 year prior to seizures. Brain CT scan showed ischemic infarct in the Sylvian artery. No other risk factor was identified.

One patient presented with muscular disease. An 8-year-old boy with heterozygous SC, was seen for proximal weakness that he developed over 3 months. No other risk factor was identified. Chest examination and x-rays were consistent with pulmonary infection. His hemoglobin levels were at 11.5 g/dl. His CK levels were high at 2,900 and electromyography showed myopathic features. TCD was normal. After blood transfusion and antibiotic treatment, he recovered partially.

Clinical and laboratory features of all patients are summarized in Table 1.

DISCUSSION

SCD is very devastating, especially in sub-Saharan Africa where it afflicts several thousand 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 [13]. 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 developed countries. Complications arise in general during young age, with some occurring before the first birthday. The mean age in our study is 21.43 years. This may due by the fact that our clinic focuses on adult neurology, thus missing all pediatric cases. Sex was evenly distributed in our study. Although the small number of cases in our cohort limits conclusions, a study with a similar number of cases has reported a predominance of female patients [14]. Whereas 5 patients

TABLE 1. Summary of clinical and laboratory findings

	Age (yrs)	Sex	Status	Type	Major Signs	Hb (g/dl)	Brain Imaging	CK	EEG	EMG
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	—	Myogenic
Patient 5	7	F	SS	Stroke	S, L H	8.8	Normal	—	FGS	—
Patient 6	46	M	AS	Stroke	L H, S	N/A	MCA I	—	FS	—
Patient 7	8	M	SS	Stroke	VL	9.2	PCA I	—	—	—

—, not done; AS, hemoglobin AS; 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; SC, hemoglobin SC; SS, hemoglobin SS; VFP, vocal folds paralysis; VL, visual loss.

were homozygous SS, 1 patient was heterozygous SC and 2 patients were heterozygous AS. Although most cases of neurological complications were reported in SCD cases, few cases were reported in SCT patients, and most were reported after exertional myopathy [6]. It is possible that the heterozygous cases may be β-thalassemia or misdiagnosed cases. The most reported neurological complication in SCD, in general, is stroke, especially ischemic stroke. However, cases of muscle injury were also reported [15,16]. In our cohort, the majority of neurological complications were stroke, and ischemic infarct was the main cerebral lesion. Although brain imaging was normal in 2 patients and unavailable for another patient, they had symptoms consistent with stroke. Moreover, CT scan can appear normal, especially within the first hours of stroke, and magnetic resonance imaging (MRI) was not available at the time of the disease. The most affected cerebral artery was the Sylvian artery. This prevalence is in concordance with what was found in the published reports. In 1 case, the patient presented with symptoms consistent with brain stem involvement. CT scan was normal but the patient presented with hypophonia, dysphagia, right vocal cords paralysis, and left-side hemiparesis. In addition to the fact that brain stem ischemia is difficult to see in some cases, MRI is the gold-standard diagnostic tool. In another case, the CT scan was normal but the 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. One patient presented with myopathy. Although previously reported cases were secondary to pain crisis and involved only 1 side [15,16], in the case presented here, the patient 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, confirming muscle injury. In addition, no other risk factor was found to explain the disease. The patient was from a nonconsanguineous marriage and no other familial case was reported, reducing the possibility of a genetic cause. The patient improved with repetitive blood transfusions, raising the role of SCD in his disease. In general, stroke was associated with low hemoglobin levels around 8 to 10 g/dl. None of our patients with stroke underwent TCD around the time of complications. However, in 1 patient with myopathy, TCD was done about a month after disease onset and it was normal. In 28.6% of cases, neurological complications were the presenting SCD symptoms, and 57% of patients were followed up in the CRLD center. No TCD was performed until the time of the complication in 1 patient only. 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. Whereas some studies have found some protective variants, others have instead found variants with increased risk of stroke.

CONCLUSIONS

Our study confirms the high frequency of neurological complications in SCD and SCT patients. Scientists are increasingly studying the possible pathogenesis of SCT; however, to date, there is no mechanistic explanation. Studying larger cohorts may shed light on 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 sets the field for more accurate and multidisciplinary cohort studies that will set guidelines for a better prevention and management of complications linked to SCD and SCT in Africa.

REFERENCES

1. Piel FB, Patil AP, Howes RE, et al. Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. Lancet 2013;381:142–51.
2. World Health Organization. Fifty-Ninth World Health Assembly: Resolutions and Decisions, Annexes. WHA59/2006/REC/1. Geneva, Switzerland: World Health Organization.

3. Piel FB, Hay SI, Gupta S, Weatherall DJ, Williams TN. Global burden of sickle cell anaemia in children under five, 2010—2050: modelling based on demographics, excess mortality, and interventions. PLoS Med 2013;10:e1001484.
4. Sidibe T, Sangho H, Keita HD, et al. Management of sickle cell disease by health professional in Bamako. Mali Med 2008;23:1–4.
5. Sangho H, Keita HD, Keita AS, et al. Management of sickle cells disease by households in Bamako. Mali Med 2009;24:53–6.
6. Nelson DA, Deuster PA, Carter R 3rd, Hill OT, Wolcott VL, Kurina LM. Sickle cell trait, rhabdomyolysis, and mortality among U.S. Army soldiers. N Engl J Med 2016;375:435–42.
7. Flanagan JM, Frohlich DM, Howard TA, et al. Genetic predictors for stroke in children with sickle cell anemia. Blood 2011;117:6681–4.
8. Flanagan JM, Sheehan V, Linder H, et al. Genetic mapping and exome sequencing identify 2 mutations associated with stroke protection in pediatric patients with sickle cell anemia. Blood 2013; 121:3237–45.
9. Belisario AR, Sales RR, Toledo NE, Velloso-Rodrigues C, Silva CM, Viana MB. Association between ENPP1 K173Q and stroke in a newborn cohort of 395 Brazilian children with sickle cell anemia. Blood 2015;126:1259–60.
10. Ali SB, Reid M, Fraser R, MooSang M, Ali A. Seizures in the Jamaica cohort study of sickle cell disease. Br J Haematol 2010;151:265–72.
11. DeBaun MR, Kirkham FJ. Central nervous system complications and management in sickle cell disease. Blood 2016;127:829–38.
12. Diallo DA. The Research Center and the Fight Against Sickle Cell Anemia of Bamako: an example of a North-South public private partnership. Bull Acad Natl Med 2013;197:1221–3.
13. Diallo D, Tchernia G. Sickle cell disease in Africa. Curr Opin Hematol 2002;9:111–6.
14. Oliveira CC, Ciasca SM, Moura-Ribeiro MV. Stroke in patients with sickle cell disease: clinical and neurological aspects. Arq Neuropsiquiatr 2008;66:30–3.
15. Schumacher HR Jr, Murray WM, Dalinka MK. Acute muscle injury complicating sickle cell crisis. Semin Arthritis Rheum 1990;19:243–7.
16. Tageja N, Racovan M, Valent J, Zonder J. Myonecrosis in sickle cell anemia-overlooked and underdiagnosed. Case Rep Med 2010;2010: 659031.