Neurological Complications in Subjects With Sickle Cell Disease or Trait

An Observational Study From Mali

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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

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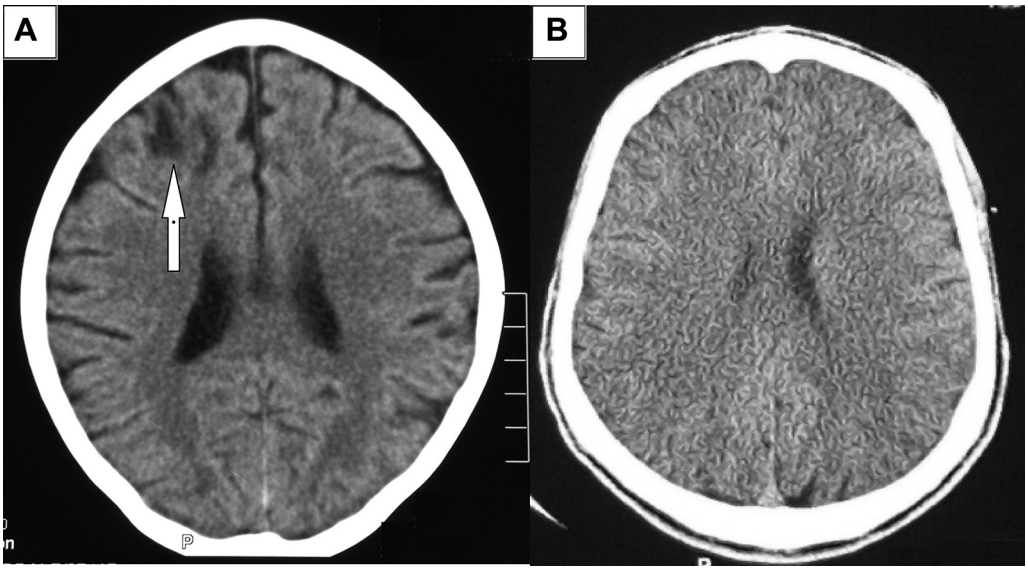

FIGURE 1. Brain imaging of ischemic stroke. (A) Brain computed tomography (CT)-scan of a patient with anterior cerebral artery ischemia, shown by the white arrow, associated with cortical atrophy compared to (B) normal brain CT-scan of same age.

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