

# Neurological Manifestations of Sickle Cell Anaemia among Sudanese patients

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## Research Article

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# Abstract

## Introduction:

Central nervous system involvement is one of the most devastating aspects of sickle cell disease.

**Objectives:** The aim of this review is to document the range of neurological complications of sickle cell disease.

## Methods and materials:

This is a descriptive cross-sectional Hospital based study. One hundred Sudanese patients with Sickle cell anemia were included in the study during the period from March to July 2018.

**Results:** The most common age group affected was below 20 years, Male to female ratio was almost equal; irritability & headache were the most common symptoms 41%, 40% respectively. Numbness was observed in 25%, hemiplegia in 24%, seizure in 19%, recurrence of hemiplegia occurred in 8%, gait was found to be spastic in 14%, limping gait (due to non-neurological causes) in 7%, while inability to walk in 6% and cerebellar manifestation in 2%.

## Conclusion:

The study revealed high incidence of irritability and headache followed by numbness then hemiplegia. Hemiplegia is usually ischemic in children and hemorrhagic in adults. Silent brain infarcts occur in 17% of patients. Convulsions occur as an isolated event but frequently associated with stroke.

# Introduction

Sickle cell anemia is a hemolytic anemia due to haemoglobinopathy characterized by abnormal shaped (sickled) RBCs that are removed from the circulation and destroyed, leading to anemia.[1,2] Vascular occlusion, one of the most important presentations, caused by the sickled RBCs leads to tissue ischemia and infarction result in variable clinical presentations.[3,4,5,6] Neurological complications were the most serious complications because they results in debilitating symptoms and may end by permanent disability. Stroke, atrophy and cognitive decline are the main sequelae of SCA. Approximately 25% of SCA patients will experience lifelong neurological complications; 11% of these complications occur before the age of 20.[7,8,9] Hemiplegia secondary to cerebral vascular ischemia occurs with high frequency in children with sickle syndromes. The onset may be in the first year of life and 80% occurs before the age of twenty. There is a very high recurrence rate approaching 85% in the three years after the first episode. [10,11] Other neurological presentations such as seizures, transient ischemic attacks, coma, and sensory loss may occur. Treatment is with chronic blood transfusion to maintain the Hb S level at less than 30% to prevent recurrences.[12,13] Current evidence suggests that the need for blood transfusion may be lifelong, and complications such as alloimmunization, iron overload, and infectious diseases may be

common complications.. Bone marrow transplantation may, in the future, offer these children the best chances for a more normal life.[14,15]

## Objectives

The aim of this study is to document the range of neurological manifestations of sickle cell disease among our studied group.

### METHODS and materials:

**Study design:** This is a descriptive cross-sectional hospital based study.Total coverage in a time frame was done from March-July 2018 and 100 patients were included. **Study area:** Sudan is one of the largest countries in Africa, extending from north to south, having a diverse environment due to different climatic zones, from the great desert to equatorial rain forests. The study was conducted in Khartoum state with a surface area of 20140 Km and a population of 10,000,000. The central location of the state subjects the state to continuous population influx from other states almost on a daily basis for work, education, health services, marketing, and some for residence. It is a heterogeneous state that presents people of different socio-cultural backgrounds who also are living in environments completely different from each other. The study was conducted in Jaafar Ibn Aof Pediatric Hospital ,it is located in the center of Khartoum , it had 281 bed and 16 units, all have referral clinic one of them sickle cell clinic which was established 1996 It provide care, follow up, education and drug supplementation for all patients with sickle cell disease . The clinic is a focus for research on SCD and it offers training for the medical staff.

**Study population:** One hundred Sudanese patients with sickle cell disease.

**Inclusion criteria :**( 1) Sudanese patients with sickle cell disease age  $\geq 6$ years (2) Those who agreed to participate in the study. **Exclusion criteria:** (1) Non Sudanese. (2) Those who refused to participate in the study. (3) Those who are less than 6 years.

**Sample size:** Total of 100 patients. **Sampling technique:** Patients were seen personally. A full detailed history and neurological examination were done for each patient. Lists of investigations were done including: 1- Complete haemogram,urine general,blood urea and electrolyte,LFT.2- Neurological investigation such as brain MRI.

### Ethical consideration:

Ethical consent was obtained from all patients (or relatives), only patients who agreed to participate were included in this study. Consent was also obtained from the local ethical committee.

**Data collection tools:** This was done through a highly confidential, well structured, close ended and Validated questionnaire. It was checked by the authors and subsequently coded to ease analysis, and then coded data was moved to the prepared data sheets then into the computer. Data was collected in the

field. The patients responded to the instructed questionnaire, no names written in the questionnaire but a code known only to the interviewer for identification if needed. **Data Analysis:** The data collected was analyzed by a computer using Statistical Package for Social Science (SPSS 26). The results were obtained and presented in tables and figures. The level of significance was taken as  $p < 0.05$ .

## Results

A total number of 100 patients who had sickle cell anemia presented to Jaafar Ibn Aof pediatric hospital, sickle cell clinic From March 2016 – July 2018, were included in the study. Male to female ratio was found to be 49 to 51. Age groups were as follows (6-10 years 36%, 11-20 years 53% and <20 years 11%). It did appear that 71% of the total patients originated from the western Sudan, 19% from the central part, 7% from the east, 2% from the south and 1% from the north. Those who did not go for schooling were 9%, 2% studying Quran, 4% in pre schooling level, 11% in the primary school, 58% in the secondary school, 12% graduated from university and 4% post graduate studies. Positive family history with similar diseases was seen in 58% of the patients.

### Non neurological clinical history:

The study showed that 53% of the patients had abdominal pain, which occurred more frequently in the age group 6-10 years ( $n = 29$ ). It was found that 73% had extremities pain. 37(50.7%) of them were distributed in the age group 11-20 years ( $P$  value 0.677). Epistaxis occurred in 30%, enuresis in 14% and priapism occurred in 2%. Cardiac examination was normal in 48%, while 35% had systolic murmur, 9% had loud S2, 5% had gallop rhythm and 3% had diastolic murmur. Almost 78% of patients had pallor, 37% had jaundice, 32% had hepatomegaly, 2% had splenomegaly and chest crepitations were observed 8% of the patients.

The neurological clinical symptoms were found as follows: 41% of the patients had irritability, 40% had headache and 25% had numbness. Hemiplegia occurred in 24%, seizure in 19%, drowsiness in 13%, photophobia in 8%, neck stiffness in 7%, deafness in 3%. History of head trauma, night blindness, diplopia and delirium all presented by 2%. Other symptoms presented as 4% (monoplegia, vertigo +clumsiness, CN palsy +  $\uparrow$ ICP). Hemiplegia occurred in 11 patients (age group 6-10 and 11-20 years). Only 5 patients (20.8%) from the hemiplegic group had abnormal speech ( $P$  value 0.000). Seizure associated with hemiplegia in 11 patients (45.8%)  $P$  value 0.000. Recurrent hemiplegia was found in 8 patients. Regarding higher function and cranial nerves assessment, 8% of patients had impaired mental status, 7% had impaired recent and remote memory and only 5% had abnormal speech (3% had motor aphasia, 1% global aphasia and 1% had dysarthria). Optic atrophy was observed in 6% of patients and evidence of laser therapy in 1%. Facial nerve palsy was found in 9% and 12th cranial nerve palsy was detected in 8% of the patients. Regarding the distribution of the side of the weakness 12% had bilateral hemiplegia (2 patients of them had cerebellar involvement), 7% had right sided hemiplegia and 4% had left sided hemiplegia. The study showed that 14% of the patients had spastic gait (6% unable to walk, 7% with limping gait (6 of them were due to hip bone osteonecrosis and 1 due to bilateral legs ulcer). It was found

that 74 patients receive blood transfusion(18 of them (24.3%) had hemiplegia.HB level 4-6 gm was found in 13 patients, 6.1-8gm in 56 patients, 8-11gm in 30 patients and more than 11grams was found in 1 patient. Folic acid was taken by 94% of patients, osteocare (Ca + vit D + zinc) by 73% of the patients, multi-vit. by 68%, NSAID by 62% , hydroxyurea by 55%, omega 3 by 26%, zinc sulphate alone by 3%, iron chelating agent by 2%, and urodoxycholic acid by 1% of the patients.

## Discussion

Sickle cell anemia is a hemolytic anemia due to haemoglobinopathy that had variable clinical presentation because it affects all body organs, all age groups but mainly younger age leading to considerable morbidity & mortality, as well as financial burden on health service and economy.[16,17,18] The pathologic lesions in the brains of patients with sickle cell disease who have neurological manifestations are varied and widespread. However, the principal changes are due to intravascular occlusion of blood vessels.[19,20]

The study was conducted in 100 Sudanese patients seen in the sickle cell clinic in Jaafar Ibn Aof pediatric hospital. Male to female ratio was 50:50 almost equally (1-1), this similar to what was mentioned in the literature by Ariel.[21] Age groups 11-20 years 53% resembling the bulk number of the patients. Geographical distribution of the patients revealed 71% of the total patients originated from the western Sudan, that was almost similar to what was mention in study done in Sudan 1996-2000 (Relationship of the sickle cell gene to the ethnic and geographic groups populating the Sudan).[9] SCA was found to be predominant among the Afro-Asiatic-speaking groups (68.4%) It includes nomadic groups of Arab and non-Arab descent who immigrated to Sudan at different times in history.Those patients clustered in western Sudan (Kordofan and Darfur) from where 73% of all cases originate.[9] About educational level, those who did not go for schooling either because of their illness or because of financial problem. Those who were studying at different educational levels, most of them had a delay in schooling because of their illness. Because of endogamy and the disease has an autosomal recessive inheritance, 58% of our patients had a positive family history of sickle cell anemia.

Non neurological clinical history and examination revealed that abdominal pain occurred more frequently in the age group 6-10 years (54.7% of the total number of the patients in this study), this is due to the fact that abdominal crisis is a well-known manifestations of the disease, this similar to what was mentioned in previous studies.[22,23] Abdominal pain is often so severe that the patient is thought to have an acute surgical emergency.[24] Extremities pain distributed mainly in the age group 11-20 years, similar to what was mentioned in the literature.[25,26] Mistaken diagnosis of acute poliomyelitis, scurvy or injury are made frequently because of pain in the muscles of the neck, back and legs. Unlike what was mentioned in the literature, priapism occurred only in 2% only, because it's often under diagnosed.[27,28,29] Almost 74% of our patients receive blood, because of the crisis or severe anemia. Systolic murmur was found in 35%, it had correlation with occurrence of low HB level. Abdominal examination showed that 32% of our studied group had hepatomegaly whereas only 2% had splenomegaly that indicate either splenic crisis or combination with other hemoglobinopathy.

It is important to recognize the fact that severe neurological disturbances in sickle cell disease may exist without anemia. This indicates that hemolysis of erythrocytes with subsequent anemia is not always the principal underlying process in sickle cell disease. Similar to what was mentioned in the literature the most common neurological symptoms was irritability which was distributed mainly in the age group 11-20 years, followed by headache.[30,31,32,33] Neurological manifestations observed included facial weakness, stiffness of the legs, nystagmus, transitory blindness, ptosis, generalized rigidity, dysphagia, anesthesia and analgesia of right side of body, nasal regurgitation, marked salivation, numbness, limbs weakness, seizure, drowsiness, photophobia, neck stiffness, deafness, night blindness, diplopia and delirium were similar to what was observed in a study which was conducted in John Gaston Children's Hospital.[34] The presence of S-hemoglobin appears to be a definite predisposing factor to the development of cerebral vascular disease, particularly in children. The types of cerebral vascular lesions that may occur with sickle cell disease include ischemic and/or hemorrhagic infarction, intracerebral hemorrhage, cortical venous and/or sinus thrombosis, and subarachnoid hemorrhage. Cerebral infarction is the most common cerebral vascular lesion. It also should be emphasized that not only can ischemic lesions occur in the brain and brainstem, they can also develop in the spinal cord. An alarming aspect of our study is younger age of presentation with neurological problems with major disability and tendency to recurrence hemiplegia. Many of the patients with recurrent strokes developed pseudo bulbar palsy-like picture associated with difficulty in speaking, swallowing, and ambulation, this is near to what was mentioned in Cooperative study, having high incidence in young age group below 20 years and reduce incidence above 20 year.[35] In the Cooperative Study of Sickle Cell Disease, the incidence per 100 patient years of a first cerebral infarct in a series from the United States was 0.70 between ages two and five years, 0.51 between ages six and nine years, 0.24 between 10 and 19 years of age, and then fell to 0.04 between the ages of 20 and 29.[35] In many instances, however, the only manifestation of a crisis maybe the sudden development of a focal neurological deficit with or without seizures. A considerable number of sickle cell patients presenting with a stroke in our series had generalized or focal seizures at the onset. Subsequently, the majority of these patients developed a chronic seizure disorder requiring long-term anticonvulsant therapy. Seizure associated with hemiplegia in 11 patients (45.8%) P. value = 0.000, this may be due to post stroke seizure or due to sickling process per se, bilateral involvement indicating high risk of recurrence as mention in the literature.[36,37,38] Plantar reflex was up going in 13% resembling (54.2%) of the total hemiplegic. The rest of hemiplegic patient 11 patient (45.8%) had down going planter P. value = 0.000. This result suggesting that it is not a good indicator for neurological assessment. The gait was spastic in 14% of our patients. There is no correlation between blood transfusion & occurrence of hemiplegia, this opposite to what was mention by STOP 1 trial that is because it was an episodic blood transfusion not a prophylactic chronic blood transfusion program due to screening program. [39] HB level was found to be low in most of our patients. This low readings not because of the disease alone but nutritional & financial factors had a role similar to what was mention in study done by Bayoumi (sickle cell disease in Sudan).[40]

## Declarations

## Consent for publication

Not applicable.

## Availability of data and materials

The materials datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

## Competing interests

The authors declare that they have no competing interests.

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## Authors' contributions

All authors participated in planning the study, data collection, results and discussion sections.

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