

## Exploring neurocognitive deficits among children with sickle cell disease and its impact on their quality of life at the University Teaching Hospital, Lusaka, Zambia

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### Abstract

**Introduction:** Sickle cell disease (SCD) may cause insufficient flow of blood and oxygen to the brain and put children with SCD at risk of cerebral damage that cause neurocognitive deficits functioning in domains such as memory, attention, abnormal fine motor functioning and executive functioning.

**Objective:** The study sought to explore the neurocognitive deficits among children with SCD and its impact on the quality of their live.

**Methodology:** It is a cross-sectional comparative study of thirty (30) children. Fifteen (15) with SCD and a matched control group of fifteen (15) siblings. Neuropsychological assessment tool (NEPSY II) and Pediatric Quality of Life Inventory (PedsQL) were administered to children with SCD and to the control group. Data obtained from the assessments was analyzed using the Statistical Package for Social Science (SPSS). Regression analysis was used to evaluate the relationship between the neurocognitive deficits and the quality of life.

**Results:** The results of the study showed that 50% of children with SCD scored average in clocks and list memory tests while 80% scored below average in the rest of the tests administered. The results indicate that SCD children have neurocognitive deficits which negatively impact their quality of life.

**Conclusion:** The study identified neurocognitive deficits in executive function, attention and memory among children with SCD. To ensure early intervention and management, developmental neuropsychological testing should be done regularly on SCD children. The research findings serve as a foundation and direction for future large-scale research on neurocognitive deficits and quality of life in children with SCD.

**Keywords:** Sickle Cell Disease; SCD; Neurocognitive Deficits; Quality Of Life; Child Neuropsychology

### 1. Introduction and the rationale of the study

Sickle cell disease (SCD) is one of the most common diseases in the world with approximately 300, 000 babies being born each year. It is particularly common among people whose ancestors come from Sub-Sahara Africa, South America, Cuba, Central America, Saudi Arabia, India as well as Mediterranean countries such as Turkey, Greece and Italy [1-2].

Furthermore, in the United States of America, SCD is one of the most common genetic disorders [3]. It is estimated that SCD affects approximately 100,000 Americans. It occurs in about 1 out of every 365 Black or African-American births. SCD occurs in about 1 out of every 16,300 Hispanics-American births and about 1 in 13 Black or African-American

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babies is born with sickle cell trait. What was once a disease of childhood, it is now a chronic health illness that most affected people manage into their fifth decade and beyond. Even though the life expectancy of patients with SCD has increased, adults with SCD face debilitating health problems including multi organ failure, chronic pain and neurocognitive deficits.

Macharia et al [4] state that in Africa sickle cell disease is a major global public health concern of which sub-Saharan Africa bears the greatest load. More than 3 out of 4 of those affected worldwide are born within the region - almost quarter of a million-new birth every year. Patients with sickle cell suffer chronic ill health and reduced survival and even today such that without specific treatment most children born with sickle cell disease die before their fifth birthday.

In Zambia, Nchimba [5] estimates that the prevalence of sickle cell disease trait to be 18% in the general population. Furthermore, Macharia et al [4] indicate that in Africa sickle cell disease is a major global public health concern of which sub-Saharan Africa bears the greatest load.

A neurocognitive deficit is a decrease or impairment of cognitive function in mental functioning [6-9]. Children with sickle cell disease SCD are at high risk to deficits in neurocognitive functioning [10]. It has several causes which include genetics, stroke, brain trauma as well as other diseases. When a child with SCD develops neurocognitive deficits he or she has abnormalities in processing speed, verbal memory, memory, attention as well as executive functioning [11]. But if these neurocognitive deficits are identified early the health interventions can help improve the cognitive function of these children through art therapy.

According to Schatz and McClellan [12], the central nervous system (CNS) is one of the organs frequently affected by the disease. Brain disease can begin early in life and often leads to neurocognitive dysfunction. Approximately one-fourth to one-third of children with SCD have some form of central nervous system effects from the disease, which typically manifests as deficits in specific cognitive domains.

Children with SCD experience cognitive deficits across several domains when compared to healthy peers and normative samples [13]. These deficits are known to adversely affect school performance among students with SCD which lead to academic failure, limited career options and for some total disability. This confirms that the neurocognitive deficits in these children result in compromised academic performance. In comparison to healthy children, performance of SCD children with cognitive deficits is usually below average. This may result in repeated grades which may eventually lead dropping out of school. The risk of dropping out of school is higher in SCD children than in the healthy ones.

Executive function is the cognitive process that organizes thoughts and activities, prioritizes tasks, manages time efficiently, and makes decisions [6, 14-16]. It includes self-awareness, inhibition, non-verbal working memory, emotional self-regulation, self-motivation, planning and problem solving. These skills are controlled by an area of the brain called the frontal lobe. The executive function helps individuals manage their time, remember details, plan and organize, multitask, avoid saying or doing the wrong things as well as paying attention. Thus a deficit in the executive function can disrupt the normal function of an individual especially in demanding situations that require rapid and flexible adjustment of behavior to changing demands of the environment [6, 16-19]. Children who have neurocognitive deficits in the executive domain normally struggle to plan, organize, analyze schedules as well as complete tasks at all.

Schatz and McClellan [12] postulate that executive functions deficits in SCD can emerge early in life and may be an important context for other areas of cognitive development. This indicates that executive functioning is poorer in children with SCD than children without simply because the disease is associated with prominent risk for neurological complications. This is supported by a study that was done by Noll et al [20] who wrote that children with SCD without overt strokes demonstrated significant deficits in neurocognitive functioning compared to classroom case controls. These finding highlight the impact of SCD on general cognitive functioning.

Neurocognitive deficits in children with SCD are caused by central nervous system abnormalities where total white matter brain volume is decreased [21]. Globally grey matter volume may not different but white matter volume may be lower in the right hemisphere in the SCD patients compared with controls. It is suggested that there are diffuse white matter abnormalities in SCD patients especially in the frontal, parietal and temporal lobes that are associated with low hemoglobin levels and mean platelets volume. Therefore, children with SCD have lower full scale, verbal and performance IQ as compared to children without SCD this is because of abnormalities of the central nervous system. This is supported by a study done by Hijmans et al [13] which showed that SCD was clearly associated with lower IQ scores. More than one in three children with SCD had a full-scale IQ below 75. Furthermore, children with SCD showed deficits in visual-motor functioning; they displayed poor visual-spatial working members. This is supported by

Berkelhammer et al [10] who show that overall neurocognitive compromise was revealed to be related to the level of neurological injury therefore executive dysfunction is prevalent and related to frontal lobe abnormalities.

SCD has been associated with deficits in specific areas of neurocognitive functioning as well as visual-motor function. Deficits in these two areas are expected given that silent infarcts commonly occur in the frontal lobe white matter within the border zone, the middle and the anterior cerebral artery distribution. According to Hijmans et al [22], this basically means that, these deficits that take place in the frontal lobe of children with SCD significantly affect other areas of neurocognitive functions and are normally strongly associated to behavioral and academic difficulties. For example, they cannot regulate their emotions and they have difficulties starting tasks, expressing themselves verbally and in writing.

Chronic brain hypoxia which is as a result of severe anemia also causes neurocognitive deficits because the brain does not receive sufficient oxygen even when blood is still circulating. This results in the brain cells dying after 5 minutes due to lack of oxygen. Which in turn causes neurocognitive deficits such as executive dysfunction, memory as well as attention impairments. Furthermore, several studies began reporting differences in global cognitive function, particularly for children with sickle cell disease as well as patterns of specific difficulties in processing speed, executive functioning and academic difficulties in reading and math [23]. At the same time, The Cooperative Study of Sickle Cell Disease (CSSCD) began examining neurocognitive function and neuroimaging of children with SCD. The CSSCD found that nearly 22% of children with sickle cell disease had experienced a clinical stroke or silent cerebral infarct prior the age of 15 years and that there were measurable differences in global cognitive function associated with these events. In addition, the CSSCD found that children who had no evidence of brain abnormality on MRI still had a decline in IQ points. This strongly suggested that something besides vascular occlusion/infarction placed children with SCD at risk and mechanisms involving chronic anemia, hypoxia or interference with oxygen perfusion and diffusion have to be considered [24].

Children with SCD including those without evidence for cerebral infarcts are at high risk of cognitive deficits because chronic inflammatory processes are common to SCD and cytokines facilitating the inflammatory processes that can impact SCD patient's cognition. This is supported by a study done by Andreotti et al [25] which examined the relationship between plasma levels of cytokines in 25 children with SCD with normal MRI studies of the brain. Children with SCD performed significantly below the normative mean on tests of cognitive function. Similarly, it was noted that children with SCD may suffer from neurocognitive deficits as a result of the inflammatory processes that they experience as part of their illness.

Research has consistently demonstrated an increased risk for neurological deficits in sickle cell disease. Neurocognitive deficits are associated with the severity of anemia, indicating reduced oxygen delivery to the brain as an etiological mechanism possibly affecting their academic development and the full participation in society. This implies that since the brain uses great amount of oxygen to function if the amount of oxygen that is available to the brain is temporarily reduced due to anemia in sickle cell, then vulnerable brain structures can become injured. For example, if the hippocampus is damaged it affects the child's ability to remember past events and learn new information causing neurocognitive deficits in memory. According to Hijmans et al [13], hemoglobin was associated with a decrease in verbal short term memory.

Frontal brain regions are thought to facilitate planned processes that enhance memory. According to Brandling-Bennett et al [27], children with frontal cerebral infarcts related to SCD performed poorly in terms of free recall but there was intact encoding with impaired retrieval. This simply means that because of these infarctions there are disruptions in planned processing which causes memory impairment in these children. Furthermore, according to the study which was done in the United States of America, it was concluded that SCD is associated with cognitive effects even in the absence of cerebral infarction. The causes of this cognitive decrement may include direct effects of SCD on the brain function or indirect effects of chronic illness. SCD is a chronic disease and dehydration occurs among children as well as adults with chronic illness. Dehydration occurs when the body has lost too much water which affects the transportation of nutrients and oxygen to tissues and the ability to maintain appropriate electrolyte levels (chemicals that are critical for nerve and muscle function such as sodium and potassium). Severe dehydration can cause confusion which resembles dementia. In addition, since patients with SCD are prone to infections, these same infections can cause cognitive problems by affecting the brain's ability to function correctly. Common cognitive symptoms caused by infections include confusion difficulty in concentrating (attention) or forgetfulness (memory).

Cerebrovascular accidents (CVAs), including silent and overt infarcts, are well recognized as a major cause of neurocognitive impairment [6]. Schatz et al [28] found that 79% of children with a silent cerebral infarct exhibited deficits. Importantly also, they also found that 36% of children without infarct had significant cognitive deficits in at

least one domain, compared with 11% of sibling controls. As for overt strokes the risks for these types of strokes in children with SCD is more than 200 times higher than that of the general population which continues up to adulthood. Stroke sometimes can occur in the first year of life and become more common with increasing age. The risks for strokes in children with SCD is more than 200 times higher than that of the general population which continues up to adulthood. History of stroke has lower intelligence quotient (IQ) scores, alterations are found in attention, executive functioning, language verbal and visual memory, visual-spatial processing and sensory-motor skills. These alterations are found both in children and adolescents with cerebral infarcts. This simply means that children with SCD who experienced cerebrovascular accidents are seen to have lower IQ scores when compared to children without these accidents.

It was concluded that four factors directly caused comprised neurological function in children with sickle cell disease: (1) recurrent micro infarction of the central nervous system, (2) chronic hypoxic damage to the brain or diminished pulmonary function, (3) sub-acute brain damage that occurred during bouts of hypoxia associated with events such as aplastic crisis, acute chest syndrome and obstructive sleep apnea, and (4) chronic nutritional deficiency associated with decreased metabolic demands [29]. It is important to consider the impact of other biomedical factors on patient's cognition. For example, cerebral blood flow and sleep disordered breathing, and anemia severity have also been associated with deficits across a number of domains in children with SCD. It has been suggested that brain damage is the result of recurrent acute hypoxic damage secondary to anemia and diminished pulmonary function.

Attention can be impaired due to different neurological and psychiatric conditions [6, 15-16, 30-32]. Neurocognitive deficits in children among SCD occur because of the significant association between pathological electroencephalogram and lower attention. The acute pain that children with SCD go through is referred to the thalamo-cortical dysrhythmia, it causes increased theta band EEG power in these children which leads to neurocognitive deficits inattention [33].

Sickle cell disease (SCD) is a chronic disease which causes progressive decline in one's quality of life because of complication caused by the illness like the development of neurocognitive deficits. Children with SCD are at high risk of neurocognitive impairment, which has potential implications for overall quality of life (QOL) [27]. This implies that neurocognitive deficits among sickle cell children compromises their QOL. In addition to pain and suffering, this disease can lead to decreased coping ability and difficulty for these people to become productive citizens, which impacts on the life of the patient and reduces their quality of life. However, this review reveals relatively few studies of health related quality of life (HRQL) in children with SCD [34].

Cognitive decrements in children with SCD are significant and progressive [12]. A school aged children often presents with progressive declines in cognitive functioning from early childhood throughout middle and late childhood. This means that because of the neurocognitive deficits that these children develop as a result of SCD they are more likely to struggle at school, have poor social and emotional functioning.

Sickle Cell Disease has an impact on the central nervous system and approximately one-quarter to one-third of children with SCD have CNS effects, which often appear as cognitive impairments and scholastic problems [12]. Because children with SCD might acquire neurocognitive deficiencies, they end up repeating grades and scoring much worse in reading and arithmetic. As a result, intellectually, their quality of life is affected as they cannot progress normally and may sometimes drop out of school. Further, the impact cognitive impairment has is evident in studies documented that children with SCD have high rates of enrollment in special education services relative to peers and are likely to struggle with academic achievement throughout school [28]. Meaning that children with SCD who have neurocognitive deficits are under stress because they do not learn at the same pace as their peers. Again even though these affected children are not in special schools but regular schools they usually score below their peers in school grades and fail to make academic development in school because of neurocognitive deficits. Academic development is hampered by the neurocognitive problems that accompany SCD because sickled cells might clump together in the brain and adolescents with SCD are at risk of cerebral vascular infarcts, or strokes, which may result in cognitive morbidity. The implication is that academic performance is adversely affected by the neurocognitive deficits that impair reading, visual motor processing, memory, language, attention as well as other executive functions which are very critical for learning and educational success. Therefore, there is an increased risk of school dropouts and grade repeating which may lead to academic failure.

Emotional wellbeing is an important part of health. Positive emotional health permits people to realize their full potential. Many sickle cell children have had strokes and silent infarcts before developing neurocognitive deficits in attention and because of this are unable to concentrate for long periods of time. They also have difficulty with completing tasks that require a person without deficits to maintain or shift their attention. As a result, they feel frustrated and they often react with emotional outburst, making it difficult for friends to help them. Others may push

people away in an attempt to isolate themselves. These children develop mental or rather emotional problems like stress, anxieties, depression due to the fact that they feel worthless.

Family remains the, main source of nurturing, socialization and attachment in society. Thus, the impact of neurocognitive deficits among children with SCD are felt by the entire family as it brings about emotional pain because family members always worry about their children's health. These worries cause anxiety, stress, and panic disorders among the family members. Children with SCD are also stressed and this can be seen through their behavioral changes such as mood swings, acting out, changes in sleep while others blame themselves for their parents' stress.

It is believed that evidence from this study has highlighted the importance of assessing patients with sickle cell disease for neurocognitive deficits at an early age. The study has identified areas that need improvement in service delivery to patients. It will enable parents, care givers, guardians and teachers of children with sickle cell disease to be aware of the possible risk of children developing neurocognitive deficits. Furthermore, this study has added to the existing knowledge on the neurocognitive deficits among children with sickle cell disease and the subsequent impact on their quality of life. The aim of the study was to explore the neurocognitive deficits among children with sickle cell disease and its impact on their quality of lives.

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## 2. Methodology

The study utilized a comparative cross sectional study design. This research design is widely used to compare relationship between variables of interest as they exist in a population by using identical methods. Therefore, this design provided a wider method as the researcher was able to examine the neurocognitive deficits among children with SCD by comparing their performance on neuropsychological tests with healthy control group of the same age. The participants were assessed using the NEPSY-II which tests seven domains of cognition (visual episodic domain, verbal episodic, verbal fluency, speed of information processing, executive functioning, working memory, and attention and motor dexterity domains). For this study the NEPSY-II only assessed three domains of cognitive functioning – executive functions, attention and memory. Also the participants were assessed using the PedsQL inventory, an assessment tool that is a brief, standardized, generic assessment instrument that systematically assesses patients' perception of HRQOL overall quality of life in pediatric patients with chronic health conditions.

The study was undertaken at the University Teaching Hospital (UTH), a third level referral center in Zambia. The hospital has a well-established sickle cell clinic which is conducted once a week on Fridays. The aim of the clinic is to offer comprehensive health care to patients with SCD.

The study population comprised of SCD patients aged 8-17 years with a clinical diagnosis SCD attending outpatient clinic for their reviews at UTH. The range was chosen because they belong to the same age group of cognitive development. Apart from that, at this age, children are able to read and write in English (because they are of school going age). Also, the other reason the researcher chose this age range is because that is the age range of patients that attend the SCD clinic. The study also included a healthy control group with the same age, education background and gender. A total of 30 participants were recruited in the study which comprised of 15 SCD patients and 15 healthy controls (siblings to the sickle cell participants); both genders were included.

The purposive sampling technique was used because the researcher was focusing on particular characteristics of a population which would best answer the research question in the study. Also it was used because it one of the most cost effective and time effective sampling methods available.

The participants were recruited at the hospital (UTH). The recruited patients were referred to the researcher by the medical doctors who ascertained the diagnosis of SCD and then the medical staff also got informed consent from participants before referring them to the researcher. Healthy controls were recruited from families of participants with SCD (siblings/relatives). All participants were presented with neuropsychological tool that tested the domains of interest and the pediatric quality of life was also administered to the control group so as to test the quality of life of the participants.

The data collected in this study was statistically analyzed using the statistical package for social sciences (SPSS) version 21. The version was well suited in this study because it is one of the latest version and could therefore, perform a variety of data analyses and presentation of functions. Regression analysis was used to evaluate the relationship between the neurocognitive deficits and the quality of life. While the T test was used to compare differences in performance between the children with SCD and the control group. Then descriptive analysis was utilized to obtain mean and deviation for

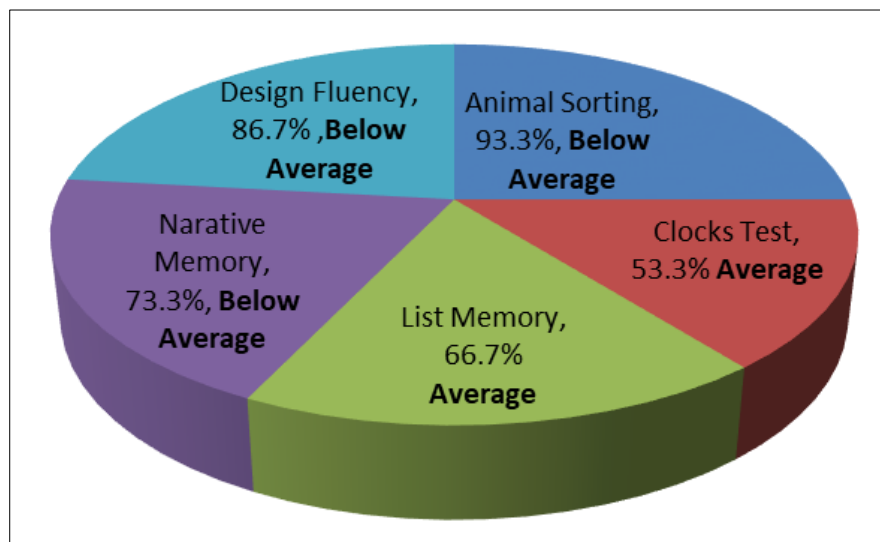
the independent and dependent variables. The descriptive study was also used to determine the amount of variability and association between sickle cell disease and neurocognitive deficits and its impact on the quality of life.

### 3. Results

The characteristics considered were age, gender and grade for both groups. The number of participants with SCD was 15 and their age ranged from 8 to 16 years. Six (6) of the participants were aged between 8-10 years old accounting for 40%; two (2) participants were aged between 11-12 years accounting for 13.3% and seven (7) participants were above 12 years old. The years that the participants had spent in school ranged from 1 to 12. Out of this number 60% were at primary school; 6.7% at junior secondary school whilst 33.3% were at senior secondary school.

The characteristics considered for the control group were the same as for those with SCD. The ages for both male and female control participants that were recruited in the study ranged from 8 to 16 years. Five participants were aged between 8-10 years old accounting for 33.3%; two (2) participants were aged 10-12 accounting for 13.3% and 8 participants were above 12 years old accounting for 53.3%. The number of years the participants had spent in school were 2 to 12 with about 46.7% at primary school; while 2 participants were at junior secondary school translating into 13.3% and about 6 participants accounting for 40% attended senior secondary school.

Neuropsychological tests to test neurocognitive deficits: tests were done to determine whether SCD causes neurocognitive deficits among children with SCD and also to compare the neurocognitive deficits among children with SCD and the matched control. Tests were done to test three domains which are executive functioning, attention as well as memory functioning. Figure 1 illustrates scores from different tests of children with SCD. The results indicate that clocks and list memory had more than 50% scoring average.



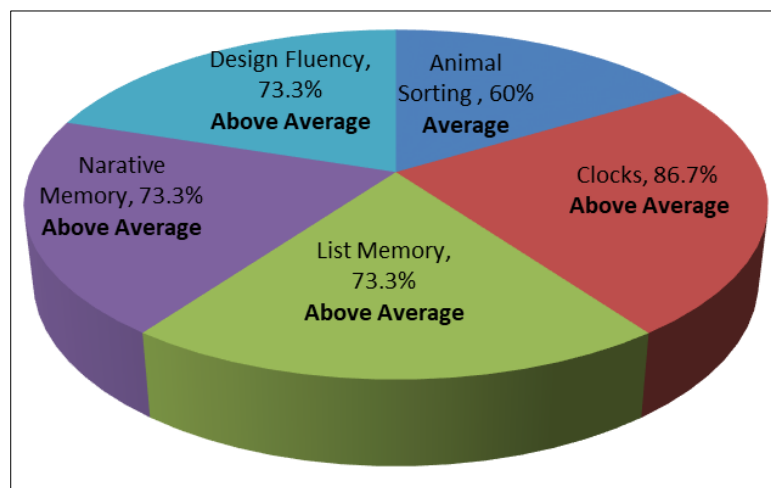
**Figure 1** Children with SCD showing scores from different tests

The analysis of the table 1 below indicates that children with SCD on the animal sorting test reviewed the mean was 1.1 and the standard deviation was 0.26. Under clocks test the sample mean score was 1.7 and the standard deviation was 0.62. On design fluency test reviewed that the score mean was 1.2 and standard deviation was 0.56. Under narrative memory test reviewed that the mean score was 1.2 and standard 0.59 while list memory test reviewed a mean score of 1.9 and standard deviation of 0.59. The results indicate that children with SCD had neurocognitive deficits in executive functioning, attention and memory.

**Table 1** T-scores of mean and SD of SCD group test results

<b>One-Sample Statistics- SCD group results</b>				
	<b>N</b>	<b>Mean</b>	<b>Std. Deviation</b>	<b>Std. Error Mean</b>
Animal Sorting	15	1.0667	0.25820	0.06667
Clocks	15	1.6667	0.61721	0.15936
Design Fluency	15	1.2000	0.56061	0.14475
Narrative Memory	15	1.2667	0.45774	0.11819
List Memory	15	1.9333	0.59362	0.15327

Control assessment results are presented as a figure 2 below.



**Figure 2** Assessment results from the tests of the control respondents

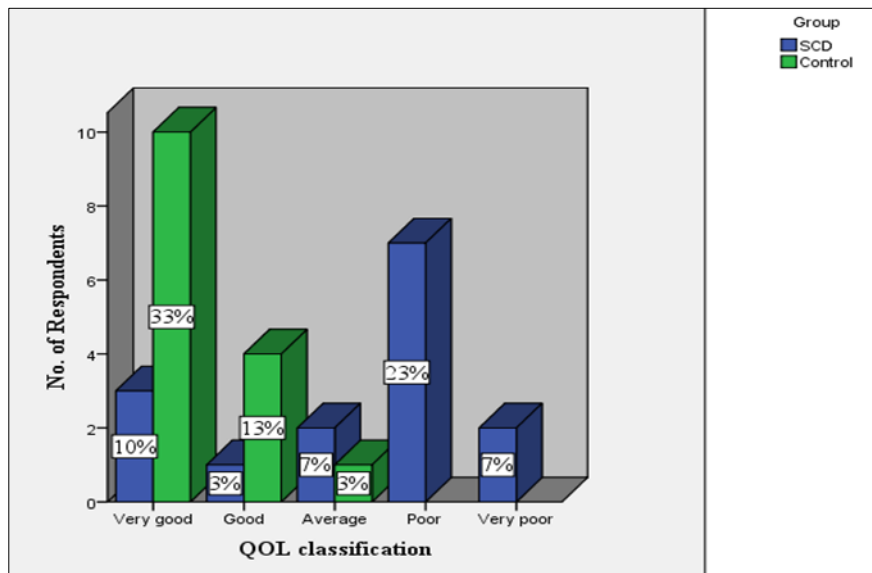
The analysis of the table 2 above indicate that the control group on Animal Sorting reviewed mean was 2.4 and the standard deviation was 0.51. Under Clocks Test the sample mean score was 2.9 and the standard deviation was 0.35. On design fluency test reviewed that the score mean was 2.7 and standard deviation was 0.46. Under narrative memory test reviewed that the mean score was 2.4 and standard deviation 0.74 while list memory test reviewed a mean score of 2.7 and standard deviation of 0.62. These results indicate that the controls had no neurocognitive deficit.

**Table 2** T- scores of mean and SD of the control group of test results

<b>One-Sample Statistics control group result</b>				
	<b>N</b>	<b>Mean</b>	<b>Std. Deviation</b>	<b>Std. Error Mean</b>
Animal Sorting	15	2.4000	0.50709	0.13093
Clocks	15	2.8667	0.35187	0.09085
Design Fluency	15	2.7333	0.45774	0.11819
Narrative Memory	15	2.4000	0.73679	0.19024
List Memory	15	2.6667	0.61721	0.15936

Effects of neurocognitive deficits on quality of life: a cross tabulation was conducted in order to come up with QOL classification. Figure 3 below shows the results. The graph shows that children with SCD had low quality of life scoring

10% for very good QOL, 23% for poor QOL and 7% for very poor QOL out of the 50%. While the matched control scored 33% for very good QOL, 13% for good QOL and 3% for average QOL.



**Figure 3** Classification of respondents QOL

Table 3 presented below illustrates T scores of mean and SD between SCD group and control group. The SCD group had a lower mean in all the domains and the overall QOL compared to the control group. Parents to SCD report also indicated a lower mean compared to parents to control group.

**Table 3** T scores comparison of mean and SD between SCD group and control group

Group		Physical Functioning	Social Functioning	Emotional Functioning	School Functioning	Quality of life
SCD	Mean	28.33	43.33	51.67	35.00	44.13
	N	15	15	15	15	15
	Std. Deviation	22.89	29.07	19.97	24.64	23.07
Parent to SCD	Mean	16.67	46.67	45.00	30.00	34.67
	N	15	15	15	15	15
	Std. Deviation	24.398	22.887	21.547	31.623	21.356
Control	Mean	95.00	85.00	80.00	75.00	83.67
	N	15	15	15	15	15
	Std. Deviation	10.351	15.811	16.903	23.146	13.372
Parent to Control	Mean	93.33	88.33	83.33	78.33	85.73
	N	15	15	15	15	15
	Std. Deviation	11.443	15.999	15.430	20.845	12.881

There was statistical difference in all the QOL domains and the overall QOL between the SCD group and the control group with the SCD group showing compromised functioning in all the QOL domains.

The results presented in the table 4 indicate that there was statistical significance between poor performance on neuropsychological tests and QOL. This implied that neurocognitive deficits in SCD group had an adverse effect on their



quality of life. Pearson Chi-Square Asymp. Sig. (2-sided) of 0.005 indicates that there is statistical significance between neurocognitive deficits and QOL.

**Table 4** Regression analysis to determine the relationship between neurocognitive deficits and the QOL

Model		Sum of Squares	DF	Mean Square	F	Sig.
1	Regression	10468.861	5	2093.772	4.484	0.005
	Residual	11207.839	24	466.993		
	Total	21676.700	29			

Predictors: (Constant), Narrative memory, List memory, Clock, Design fluency, Animal sorting; Dependent Variable: Quality of life.

#### 4. Discussion

The findings from this study reveal that children with SCD had neurocognitive deficits in executive functioning, attention and memory. There are statistically significant differences that were observed in the neuropsychological tests that were administered: Animal sorting and clocks tests. SCD children performed significantly poorly ( $M=1.1$ ,  $SD=0.26$ ;  $M=1.7$ ,  $SD=0.62$ ) on both tests than their healthy control ( $M=2.4$ ,  $SD=0.51$ ;  $M=2.9$ ,  $SD=0.35$ ). Design fluency SCD children performed significantly poorly ( $M=1.2$ ,  $SD=0.56$ ) than their health control ( $M=2.7$ ,  $SD=0.46$ ). Narrative Memory and List Memory SCD children performed significantly poorly ( $M=1.2$ ,  $SD=0.46$ ;  $M=1.9$ ,  $SD=0.59$ ) on both tests than their healthy control ( $M=2.4$ ,  $SD=0.74$ ;  $M=2.7$ ,  $SD=0.62$ ). Further, regression analysis was used to evaluate the relationship between the neurocognitive deficits and the quality of life. The results indicate that there is statistical significance with a P-value of 0.005. The quality of life of SCD participants with neurocognitive deficits was significantly poor as measured by PedsQL.

The first objective was to examine the neurocognitive deficits among children with SCD. Both descriptive and inferential statistics illustrated children with SCD developed neurocognitive impairments in the three domains that were examined which are executive functioning, attention and memory. Hijmans et al [13] highlighted that, throughout development, patients continue to be at risk of cognitive impairment across a range of domains including executive function and memory. This implies that SCD facilitates the development of neurocognitive impairment due to multiple disease processes. SCD is associated with neurocognitive impairments across executive functioning, attention, and working memory either in relation to or independent of a known cerebral infarct.

During the study children with SCD completed the following neuropsychological tests. Animal sorting, clocks and design fluency within the executive and attention domain and they also completed narrative memory and list memory for memory domain. Children with SCD scored worse than their health sibling (control group) in neurocognitive tests.

Executive function is one of the major areas of deficits found in SCD-related morbidity [10]. It is a higher-order cognitive ability that enables children to appropriately plan, organize, and initiate action in order to solve problems across contexts. It spans verbal and non-verbal processes, and relies on specific cognitive abilities including fluid reasoning, working memory and attention which are often affected in pediatric SCD [27]. In children with SCD, there is a wealth of evidence that executive abilities are impaired, but very little research has been conducted in which academic achievement has been examined within the context of specific cognitive domains including executive function [10].

Animal sorting and clocks were done so as to test the executive functioning of children with SCD. Animal sorting test required the participants to sort the cards in categories; plan and shift sets between concepts, this test assessed cognitive flexibility, reasoning skills and inhibition. The results in this test show that 93% of the children with SCD scored below average, the mean  $\pm$  standard deviation was  $1.1 \pm 0.26$ , displaying poor reasoning, poor inhibitory control and planning when completing the tests and again switching was a weak area for them as most of them showed signs of preservation since they got stuck on one idea showing difficulty moving on to another idea. In addition, clocks test was administered to test executive and attention domain and 53% scored average, the mean  $\pm$  standard deviation was  $1.7 \pm 0.62$ , while the rest scored below average showing poor planning, poor visual-spatial/drawing poor time concept.

These results indicate that 70% of participants with SCD have impaired executive functioning. For that reason, these participants were not able to inhibit impulses, plan, organize their thoughts, initiate new tasks, and remember newly presented information as well as to organize materials in order to complete a task.

Furthermore, the design fluency test was done to test attention domain and 86.7% of the children with SCD scored below average the mean  $\pm$  standard deviation was  $1.2 \pm 0.56$ . The results of SCD participants showed that they have impaired initiation and productivity, poor cognitive flexibility, poor non-verbal fluency and working memory since the recall of rules for a drawing throughout the task is required. This means that they have poor performance on the less structured stimuli.

Similarly, narrative memory and list memory were administered to the SCD children so as to test the memory domain which is necessary for the proper functioning of the other cognitive skills which is why alteration in any of the intentional processes may make it more complicated to complete. Neurocognitive tests showed that 53% of children with SCD had neurocognitive deficits with the mean  $\pm$  standard deviations of  $1.3 \pm 0.46$  and  $1.9 \pm 0.59$ . This is also consistent with the study done by Brandling-Bennett et al (2003), which indicates that children with frontal cerebral infarcts related to SCD performed poorly in terms of free recall but there was intact encoding with impaired retrieval [26].

The second objective was to compare the neurocognitive deficits among children with SCD and the matched control (siblings). Comparison with siblings is essential because it allows for better evaluation of the disease's impact on cognitive functioning as the siblings essentially act as a control for early environment and genetics. According to the results of this study there were significant statistical differences observed in the neuropsychological tests that were administered in animal sorting, clocks, design fluency, narrative memory and list memory in that children with SCD performed notably poorly in most tests.

In animal sorting test 93.3% had severe cognitive deficits while in narrative memory test, 73.3% had severe cognitive deficits. In design fluency 86.7% had severe cognitive deficits while the matched control group performed better than the children with SCD in - animal sorting - 60% scored average, narrative memory - 73.3% scored above average and design fluency - 73.3% scored above average as revealed by an independent sample of neuropsychological test. These results indicate that children with SCD performed poorly in executive functioning as their ability to they inhibit impulses was difficult, plan and also had problems in working memory as well as cognitive flexibility than their matched control. These deficits may be linked to the hypoxia and severe anemia that children with SCD experience. This is because children with SCD usually suffer insufficient delivery of oxygen and glucose to the brain resulting in impaired brain function without observable structural damage on clinical imaging studies.

Children with SCD performed worse in all the neuropsychological tests in comparison with the healthy controls which indicated that children with SCD had deficits in executive function, attention as well as memory. Berkelhammer et al [10] highlighted that, domains of attention, executive function and working memory are particularly impacted, which may reflect insult to the frontal lobe. This clearly signifies that SCD is associated with neurocognitive deficits. Hijmans et al [13] agrees that, children with SCD are at higher risk of neurocognitive deficits that are related to strokes or micro vascular infarcts that contribute to functional impairments across academic domains.

Research particularly examining quality of life in children with SCD begun in the late 1990s and has slowly increased since then. Indeed, a more recent review of the literature available on Medline indicates that there have been approximately 30 studies published regarding quality of life in pediatric SCD [22]. Regardless of the fact that most studies on quality of life was done in early stages it has a lot of potential to help us understand the magnitude of this disease on the physical and mental wellbeing of these children. These studies also provide clinicians with another clinically important outcome variable which assesses a child's health status and functional impairment. Therefore, assessing whether neurocognitive deficits in children with SCD have an impact on the quality of life helps provide a more comprehensive assessment of a child's needs which can be addressed by clinicians and other health providers.

Regression analysis was used to evaluate the relationship between the neurocognitive deficits and the quality of life. The results indicate that there is statistical significance with a P-value of 0.005. The quality of life of SCD participants with neurocognitive deficits was significantly poor as measured by PedsQL. The results indicated that the overall quality of life of children with SCD is low which are Mean=44.1 and SD=23.1 while the overall quality of life of the control is higher which are Mean=83.7 and SD=13.4. These results apply for both the PedsQL total score and all of the four subscales. This is consistent with the research question outcomes; the current results suggest that neurocognitive deficits have a significant impact on the subjective reports of overall well-being in children with SCD; more specifically executive and attention impairments contribute to the lower levels of their quality of life.

A comprehensive studies published in 2006 and 2007 done by Schatz et al found that 11 out of 13 studies showed that executive functioning and attention were impaired in children with SCD in domains such as sustained attention, cognitive flexibility and working memory [12, 35]. In the current study children with SCD performed poorer than the control group because about 70% of these did not reach the average performance level in executive functioning. Abilities in executive functioning are very important for social interactions such as attending to social cues and responding appropriately, school functioning (the ability to concentrate during lessons in class as well as complete class and homework) and emotional functioning (the ability to be familiar with emotions and cope in the face of emotionally challenging situations). As a result, the SCD children (participants) displayed poor social, emotional, and school functioning which are central aspects of good quality of life. Indeed, this theoretical account is consistent with the findings in which children reported poor quality of life in the context of weaker executive functioning. This can be seen in the studies that were done by Crosby et al [36] which indicated that, academic progress is hindered by the neurocognitive complications that accompany SCD because sickled cells can clump together in the brain and adolescents with SCD are at risk of cerebral vascular infarcts, or strokes, which may result in cognitive morbidity. Schatz et al [27] found out that children with SCD are at high risk of neurocognitive impairment, which has potential implications for overall QOL.

Attention function is best described as the continuous focus of cognitive resources on information while filtering or overlooking extraneous information. Neurocognitive deficits in attention domain among children with SCD has been seen to have a negative impact on the children with SCD's quality of life in that it increases low self-esteem, poor academic functioning (they have poor results and are very behind in terms of grades as compared to their health counterparts), family and peer relationships problems (they exhibit problems making friends and socializing as a result they usually keep to themselves) as compared to the healthy control.

In addition, memory is also one of the domains that is necessary for proper functioning of other cognitive skills and that is why any alteration of the memory processes may disturb the ability to complete given tasks. The neurocognitive tests administered to the SCD participants showed that children with SCD were within average results under memory domain with 66.7% scoring average while 73.3% of the control scored below average. This indicates that neurocognitive deficits have a negative impact on the SCD children's social life such as changes in social roles as they display embarrassment, shame, and frustration because of memory problems resulting in low self-esteem and poor academic performance.

Allen [37] postulates that children with SCD face multiple risk factors for neurocognitive impairment, which can have a lifelong impact and are theoretically relevant to overall HROL. Both the parents and child reports of QOL correlated strongly in assessment of the impact of neurocognitive deficits on QOL. Indeed, this theoretical account is consistent with the current findings, in which both parents and children reported poor quality of life in the context of weaker executive, attention and memory skills.

The impact of neurocognitive deficits on overall quality of life in children with SCD is expected to persist into adulthood. Evidence suggests that adult suffering from SCD have significant difficulty pursuing and maintain occupational goals [38-39]. One study of adult adjustment in SCD reported that less than 50% of patients were employed full-or part-time [40]. This finding may to a degree be attributed to neurocognitive deficits with low academic achievement, which collectively prevents individuals from acquiring the skills needed for vocational achievement. Therefore, it is imperative that interventions address underlying neurocognitive deficits. This will help to facilitate educational and occupational pursuits, which will ultimately improve their quality of life.

The results of the present study seem to be consistent with many other study findings that overwhelmingly show that children with SCD experience cognitive deficits across several domains when compared to healthy peers and normative samples [13]. Also Noll et al [20], stipulates that, children with SCD without overt stroke demonstrated significant deficits in neurocognitive functioning compared to classroom case controls. Furthermore, Schatz et al [27] stated that children with SCD are at high risk of neurocognitive impairment, which has potential implications for overall QOL. These studies reveal that children with SCD develop neurocognitive deficits and it impacts on their quality of their lives.

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## 5. Conclusion

The aim of this study was to explore the neurocognitive deficits among children with sickle cell disease and its impact on their quality of life. The study identified neurocognitive deficits among children with SCD and the correlation between the neurocognitive deficits among children with SCD and the quality of life. Using a comparative cross sectional design and purposive sampling method, 30 child participants (15 children with SCD and 15 matched control group) were enrolled in the study. The participants were assessed using the NEPSY-II in three domains - executive functioning, attention and memory. Also the participants were assessed using the PedsQL assessment tool that systematically

assesses patients' perception of overall quality of life in pediatric patients with chronic health conditions. Overall, results from the NEPSY-II revealed that children with SCD scored worse than their health sibling (control group) in neurocognitive tests. Further regression analysis was used to evaluate the relationship between the neurocognitive deficits and the quality of life. The results indicate that there is statistical significance with a P-value of 0.005. The quality of life of SCD participants with neurocognitive deficits was significantly poor. The results indicated that the overall quality of life of children with SCD is low (Mean=44.1 and SD=23.1), while the overall quality of life of the control is higher (Mean=83.7 and SD=13.4). These results apply for both the PedsQL total score and all of the four subscales. This study concludes that children with SCD develop the neurocognitive deficits because of the nature of the disease. In addition, it was concluded that these neurocognitive deficits ultimately affect the quality of life of these children physically, socially, emotionally and academically. Therefore, these results provide a basis and guidance for future large scale research of neurocognitive impairments among children with SCD and quality of life.

### *Recommendations*

Based on the study findings, the following recommendations have been made:

- Future research studies are needed with larger samples of people with SCD and not just children but adults as well;
- Patients with SCD should be assessed on a regular basis for neurocognitive deficit because early diagnosis will enable the patients to get required support, information and medication;
- Neurocognitive rehabilitation programs for children with SCD should be developed in community healthcare facilities; this is important for their ongoing learning and development;
- Improving service delivery to patients with SCD as well as parents, caregivers, guardians and teachers is necessary as all of the interested parts should be well-informed about the children's possible risk of developing neurocognitive deficits;
- Improving awareness on SCD and its clinical manifestations to parents, care givers, guardians and teachers, would help to improve their QOL.

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### **Compliance with ethical standards**

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#### *Disclosure of conflict of interest*

The authors declare that there is no conflict of interest.

#### *Statement of ethical approval*

This research was approved by biomedical research ethics committee, the "Excellence in Research and Science Converge Institution" (ERES Converge) (ref. # 2019-Mar-009). The permission to conduct this research was also granted by the administration (the Head Clinical Care) of the University Teaching Hospital (UTH) on the 12<sup>th</sup> June, 2019

#### *Statement of informed consent*

Only the participants who met eligibility criteria, expressed willingness to participate, and provide written informed consent were enrolled into the study. The consent processes were done in English since the researcher only chose participants who were able to read and write. The potential participants were given a chance to answer all questions. A copy of the information sheet and consent form was offered to the study participants who were required to read and sign which the researcher counter signed. Appropriate informed consent was obtained from all individual participants included in the study.

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