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## Neuropsychiatric Impairment among Patients with Sickle Cell Anemia

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# Neuropsychiatric Impairment among Patients with Sickle Cell Anemia

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**Abstract**
Sickle cell anemia (SCA) is an inherited disorder of hemoglobin. Each year over 150,000 children in Africa are born with SCA. Cognitive impairment is a common complication of SCA. This case-control study evaluated cognitive function in 41 adolescents and adults with SCA and an equal number of healthy demographically matched controls using the community screening interview for dementia (CSID), Trail Making Test A (TMTA), Saint Louis University Mental Status examination (SLUMS), and Mini Mental State Examination (MMSE). Mood (anxiety and depression) was assessed using the Hospital Anxiety and Depression Scale (HADS). The controls had better total scores on all screening instruments; however, the difference between their performance and that of the SCA adults was not statistically significant; SLUM ($p = 0.179$), TMTA ($p = 0.359$), MMSE ($p = 0.241$), and CSID (0.494). On specific task, the controls performed significantly better based on SLUM (naming), $p = 0.016$; SLUM (repetition), $p = 0.015$; SLUM (recall), $p = 0.003$; and CSID (language expression), $p = 0.001$. The systolic blood pressure (SPB) was inversely correlated with the MMSE scores ($p = 0.009$). In addition, there was direct linear correlation between the creatinine levels and the MMSE scores ($p = 0.009$). The proportion of SCA patients compared with the controls that had abnormal mood were anxiety (7.3% vs. 4.9%), borderline anxiety (17.1% vs. 4.9%), depression (2.4% vs. 2.4%), and borderline depression (14.6% vs. 2.4%). SCA was associated with an increased prevalence of cognitive impairment in adults when compared to controls. SCA is associated with a higher proportion of mood abnormalities.

**Keywords:** Neuropsychiatric impairment; Sickle cell anemia; Cognitive impairment.

## 1. INTRODUCTION

Sickle cell anemia is a common genetic condition due to a disorder of hemoglobin [1, 2] that is inherited in an autosomal recessive mode of inheritance [3, 4]. Each year approximately 200,000 infants are born with sickle cell anemia (SCA) in Africa [1]. The frequency of sickle cell trait in Nigeria ranges between 15% and 30%. The prevalence of sickle cell anemia is approximately 20 per 1000 births, indicating that approximately 150,000 children are born annually in Nigeria with sickle cell anemia [1]. Nigeria has the largest concentration of patients with sickle cell anemia in the world [5].

There are no clear data on survival of patients with sickle cell anemia on the African continent [1]. However, a recent study in Ilorin Nigeria showed that the mean age of adult SCA patient was $23.0 \pm 6.6$ years in contrast with the mean age of $40.0 \pm 16.9$ years of the general healthy population [3]. Many SCA patients now survive beyond the fourth decade with optimal management [3]. This increasing age of survival has proportionally increased the risk of developing cognitive impairment [6, 7].

Central nervous system complications are widespread among patients with sickle cell disease (SCD). Among these complications are overt stroke or silent cerebral infarction, and impairment in cognitive function. Moreover, these are among the most devastating long-term complications of the disease [6, 8]. Brain damage can be present in SCD patients without any clinical evidence of stroke [8]. However, silent cerebral infarction, defined as an ischemic change in brain tissue in the absence of any clinical history of stroke, is observed by magnetic resonance imaging (MRI) in approximately 17% of the patients with SCA [9, 10]. Furthermore, children with haemoglobin SS (HbSS) and normal MRI findings have been noted to have cognitive deficits and a decline in academic performances [11].

The proposed pathophysiologic mechanism of cognitive impairment in sickle cell disease includes the following: recurrent micro-infarction of the central nervous system, hypoxic damage to the brain secondary to chronic anemia, hypoxic damage exacerbated by acute events, and chronic nutritional deficiency associated with increased metabolic demands [12]. Other causes include overt stroke and silent cerebral infarcts and neuronal loss [6, 8].

The pattern of cognitive impairment includes tests of arithmetic performance, vocabulary, visual motor speed, coordination [13], executive functioning [6], verbal intelligence quotient (IQ), psychomotor speed, and attention [14]. The reported predictors of poorer neurocognitive function include low hemoglobin, age of the patient, and brain hippocampal volume [14, 15].

Further psychological complications identified in both children and adults with SCD included increased perception of pain, poor coping ability; impaired quality of life sequel to difficulties with daily functioning; and anxiety and depression [16]. Pain and the society's attitude toward patients with SCA aggravate their mood dysfunction. High rates of anxiety and depression have also been found in children with SCD [17-19]. The factors that are highlighted as possible causes of depression and anxiety in patients living with sickle cell disease include the chronicity of their health challenges; unpredictable nature of sickle cell crises; frequent recurrent painful episodes; repeated medical problems such as anemia, leg ulcers, kidney failure, central nervous

system complications, poor growth, physical structural abnormalities, and reduced life expectancy; and social prejudice and stereotyping [4]. The Pain in Sickle Cell Epidemology Study (PiSCES) project observed that 27.6% of the patients with SCD had depression while 6.5% had anxiety disorder, and these subjects had poorer functioning on all aspects of health-related quality of life [10]. Other studies provided a prevalence rate of depression ranging from 18% to 44% [20-22]. A study conducted by Ogunfowora *et al*. [23] observed that patients with SCA have a higher prevalence of depression compared to those with malaria.

The recommended interventional modalities for the psychological problems include patient education, cognitive behavioral therapy, and special educational provision to help improve the quality of life of SCD patients [16]. A nonrandomized study suggests the use of hydroxyurea therapy to improve cognitive functioning in patients with SCD [18].

Studies on neurocognitive and mood assessment in adolescents and adult Nigerians and indeed Africans with sickle cell anemia are generally scant, hence the need for this multidisciplinary study among sickle cell disease patients in this region. This study, therefore, aimed at determining the prevalence, pattern, and predictors of cognitive and mood impairment among sickle cell anemia patients without overt stroke.

## 2. METHODS

This case-control study was conducted at the hematology outpatient and daycare clinics of a tertiary hospital. The subjects included consenting sickle cell anemia patients with hemoglobin HbSS diagnosed using the acetate electrophoresis method. The patients with symptoms, signs, and laboratory evidence of meningitis, stroke, seizure disorder, or traumatic brain injury were excluded. The patients were assessed at their steady state: "defined as the period when the patients with SCA is free of infection, pain, or other disease process" [24]. The steady state is determined by a careful history and physical examination. We interviewed forty-one (41) patients were matched for age, gender, and educational status with an equal number of controls selected from their siblings and other healthy consenting persons in the hospital environment. This sample size is consistent with similar local studies assessing cognitive function in sickle cell disease patients in similar settings [19]. All the consenting subjects had their demographic information such as age, gender, and educational status recorded using a structured questionnaire. Other relevant details recorded were drug and alcohol use, past medical history, and a history of traumatic brain injury. A general physical and neurological examination was conducted on all subjects by a neurologist.

Cognitive function was assessed in both groups using the community screening interview For dementia (CSID), Saint Louis University Mental Status examination (SLUMS), Mini Mental State Examination (MMSE), and the Trail Making Test A (TMTA), while Mood (anxiety and depression) was evaluated using the Hospital Anxiety and Depression Scale (HADS). The CSID, SLUMS, and TMTA were administered by clinicians, while the HADS was self-administered. The steady-state packed cell volume (PCV) level of the patients was obtained from their outpatient medical records.

To determine the presence of cognitive impairment based on the total SLUMS score, we considered their educational attainment based on previously established cutoff points. For subjects with less than tertiary education, a score of 24 and below was considered impaired; whereas, for subjects with tertiary education, a score below 27 was considered impaired [25, 26]. For the MMSE, which has been established as a very useful cognitive screening instrument particularly in elderly and hospitalized patient, a score of 23 or less was indicative of cognitive impairment. They were further classified into normal cognition, mild impairment, moderate impairment, and severe impairment based on their MMSE scores of 25-30, 20-25, 10-20, and 0-10, respectively [27], with each lower score indicating a need for greater supervision. MMSE is an instrument that has been proven to be effective in the screening of cognitive impairment in a general outpatient clinic setting [28]. MMSE has a sensitivity of 66% and a specificity of 99% in dictating cognitive decline [29].

To establish the cutoff points for the impairment of cognitive function among the subjects based on their total CSID score, the performance score of pretested randomly selected persons in the study environment was obtained. The pretested population was made up of both genders with age ranging from 18 years to 75 years. The average total CSID score from this population was 61.2 (SD = 8.1), and two times the standard deviation (2 SD) of the total CSID score for the population was 16.2. The cognitive impairment score less than 2 SD based on the performance on CSID was fixed at total CSID less than 61.2 minus 2XSD (i.e., any score $<45$).

The TMTA is an instrument that principally assesses attention, concentration, visual scanning, psychomotor speed, and sequencing. The cognitive performance of patients is determined by the time taken by the patient to complete the task of making the trail by connecting the numbers ranging from 1 to 25. The previous cutoff points were established for cognitive impairment a time score greater than 78 s [2, 30, 31].

The presence of depression or anxiety was assessed using the self-administered HADS questionnaire. Based on the scores of patients, they can be categorized into normal, borderline, or abnormal if the total score is either 0-7, 8-10, and 11-21, respectively [32].

### 2.1. Ethics

Informed oral or written consent was obtained from all the subjects recruited in the study, after the study was carefully explained to them. Participation in the study was voluntary. Ethical approval for this study was obtained from the Ethical Committee of the University Teaching hospital. The study was conducted based on the ethical guidelines of this committee.

### 2.2. Data Analysis

The data collected was analyzed using STATA software version 14. Chi-square analysis (Yates correction/Fisher's Exact Test when the expected cell count was less than 5) was used to determine the differences in the categorical variables between the patients in the case and control groups. Unadjusted (univariate) linear regression analysis was performed to determine the predictors of cognitive function using the SLUM, TMTA, and CSID scores. The variables with 95% confidence interval excluding the null value of 0 or $p < 0.05$ were used to model an adjusted (multivariate) linear regression analysis.

## 3. RESULTS

We evaluated the cognitive function in 41 patients with SCA without overt stroke and an equal number of controls. The demographic characteristics of the study population are as represented in Table 1. There were more female patients in the case group (66%) than in the control group (35%). Similarly, more male patients were in the control group (65%) than in the case group

**Table 1: Socio-demographic characteristics of the study population, by study group.**

| Variable | SCA patients (*N* = 41) *n* (%) | Controls (*N* = 41) *n* (%) | Total (*N* = 82) | *p*-value of difference |
|---|---|---|---|---|
| **Age category (years)** | | | | |
| 10-19 | 8 (19.5) | 7 (17.1) | 15 (18.3) | 0.431 |
| 20-29 | 24 (58.5) | 29 (70.7) | 53 (64.6) | |
| ≥30 | 9 (22.0) | 5 (12.2) | 14 (17.1) | |
| **Gender** | | | | |
| Female | 27 (65.8) | 14 (34.8) | 41 (50.0) | 0.004 |
| Male | 14 (34.2) | 27 (65.2) | 41 (50.0) | |
| **Educational status** | | | | |
| Primary | 1 (2.44) | 3 (7.3) | 4 (4.9) | 0.456 |
| Secondary | 17 (41.5) | 13 (31.7) | 30 (36.6) | |
| Tertiary | 23 (56.1) | 25 (61.0) | 48 (58.5) | |

SCA: Sickle Cell Anaemia.

**Table 2: Prevalence of cognitive impairment using the SLUM, TMTA, MMSE, and CSID methods, by study group.**

| Cognitive function assessment | Case (*N* = 41) | Control (*N* = 41) | Total (*N* = 82) | *p*-value of difference |
|---|---|---|---|---|
| **SLUM assessment using prim or sec education (*n* = 34)** | | | | |
| Primary or secondary education with SLUM score <24 | 7 (38.9) | 1 (6.3) | 8 (23.5) | 0.043 |
| Primary or secondary education with SLUM score ≥24 | 11 (61.1) | 15 (93.7) | 26 (76.5) | |
| **SLUM assessment using tertiary education (*n* = 48)** | | | | |
| Tertiary education with SLUM score <27 | 13 (56.5) | 13 (52.0) | 26 (54.2) | 0.753 |
| Tertiary education with SLUM score ≥27 | 10 (43.5) | 12 (48.0) | 22 (45.8) | |
| **SLUM assessment for all patients** | | | | |
| Impaired cognitive function | 20 (48.8) | 14 (34.1) | 34 (41.5) | 0.179 |
| Unimpaired cognitive function | 21 (51.2) | 27 (65.9) | 48 (58.5) | |
| **TMTA assessment (*n* = 82)** | | | | |
| >78 s (impaired cognitive function) | 4 (9.8) | 1 (2.4) | 5 (6.1) | 0.359 |
| ≤78 s (normal cognitive function) | 37 (90.2) | 40 (97.6) | 77 (93.9) | |
| **MMSE assessment (*n* = 82)** | | | | |
| <24 (impaired cognitive function) | 3 (7.3) | 0 (0) | 3 (3.7) | 0.241 |
| ≥24 (normal cognitive function) | 38 (92.7) | 41 (100) | 79 (96.3) | |
| **CSID** | | | | |
| <45(impaired cognitive function) | 2 (4.9) | 0 (0.0) | 2 (2.4) | 0.494 |
| ≥45(normal cognitive function) | 39 (95.1) | 41 (100) | 80 (97.6) | |

SLUM: Saint Louis University Mental State Examination; TMTA: Trail Making Test A; MMSE: Mini-mental State Examination; CSID: Community Screening Instrument for Dementia; SCA: Sickle Cell Anaemia.

**Table 3: Cognitive task with significantly better performance in controls compared to SCA patients using SLUM and CSID.**

| Variable | (*N*) | Mean (SD) | Significant level (*p* value) |
|---|---|---|---|
| **SLUM (Naming)** | | | |
| SCA | 41 | 2.46(0.78) | 0.016 |
| Control | 41 | 2.83(0.54) | |
| Total | 82 | | |
| **SLUM (Repetition)** | | | |
| SCA | 41 | 3.68(1.30) | 0.015 |
| Control | 41 | 4.29(0.90) | |
| Total | 82 | | |
| **SLUM (Recall of short story)** | | | |
| SCA | 41 | 5.80(2.27) | 0.003 |
| Control | 41 | 7.17(1.79) | |
| Total | 82 | | |
| **CSID (Language expression)** | | | |
| SCA | 41 | 14.22(4.23) | 0.001 |
| Control | 41 | 21.22(5.72) | |
| **Total** | **82** | | |

**Table 4: Predictors of cognitive impairment using the MMSE score among patients with cognitive impairment.**

| Variable | Cognitive impairment | |
|---|---|---|
| | **Unadjusted coefficient (95% CI), *p*-value** | **Adjusted coefficient (95% CI), *p*-value** |
| Systolic blood pressure | −0.14 (−0.24; −0.04), 0.009 | −0.17 (−0.44; 0.11). 0.205 |
| Diastolic blood pressure | −0.10 (−0.22; 0.02), 0.109 | *Not included in the final model |
| Hemoglobin | −0.29 (−0.93; 0.35), 0.339 | *Not included in the final model |
| Sodium | −0.01 (−0.10; 0.08), 0.806 | *Not included in the final model |
| Potassium | 1.00 (−2.35; 4.39), 0.528 | *Not included in the final model |
| Chloride | 0.01 (−0.09; 0.11), 0.767 | *Not included in the final model |
| Urea | −1.00 (−2.27; −0.53), 0.004 | −0.97 (−2.03; 0.08), 0.068 |
| Creatinine | −0.09 (−0.18; −0.01), 0.041 | −0.01 (−0.11; 0.09), 0.864 |
| Bicarbonate | 0.14 (−1.61; 1.89), 0.863 | *Not included in the final model |

*Variable was not significant in the unadjusted (univariate) linear regression model.

(34%). These differences were statistically significant at $p = 0.004$. However, there were no statistically significant differences between the age categories ($p = 0.431$) and the educational status ($p = 0.456$) of the patients in the case and control groups. The youngest patient was 14 years old; whereas, the oldest patient was 41 years. The mean age of the SCA subjects and the controls was 25.05(±5.69) and 23.95(±5.78), respectively; $p = 0.389$.

All screening instruments found a higher prevalence of cognitive impairment among sickle cell anemia patients. The respective prevalence of cognitive impairment among SCA subjects and controls using the different instruments are shown in Table 2. There were no statistically significant differences in cognitive function between the patients in the case and control groups using SLUM ($p = 0.179$), TMTA ($p = 0.359$), MMSE ($p = 0.241$), and CSID (0.494) scores. However, when specific cognitive task using SLUM and CSID was compared in both groups, the controls performed better in naming, repetition, recall, and language fluency. This is presented in Table 3.

In the unadjusted linear regression analysis (Table 4), the systolic blood pressure (SPB) of patients was inversely and significantly correlated with their MMSE scores (Spearman's correlation coefficient = −0.14 (95% CI = −0.24; −0.04), $p = 0.009$). On the other hand, there was a direct linear correlation between the creatinine levels of the patients and their MMSE scores (Spearman's correlation coefficient = −0.14 (95% CI = −0.24; −0.04), $p = 0.009$). Having adjusted for SBP (Spearman's correlation coefficient = −0.17 (95% CI = −0.44; 0.11), $p = 0.205$) and creatinine levels (Spearman's correlation coefficient = −0.01 (95% CI = −0.11; 0.09), $p = 0.864$) in the multivariate model, none of these two variables was significantly correlated with the

**Table 5: Predictors of cognitive impairment using the SLUM score among patients with cognitive impairment.**

| Variable | Cognitive impairment | |
|---|---|---|
| | **Unadjusted coefficient (95% CI), *p*-value** | ***Adjusted coefficient (95% CI), *p*-value** |
| Systolic blood pressure | −0.05 (−0.19; 0.09), 0.491 | - |
| Diastolic blood pressure | 0.01 (−0.15; 0.18), 0.888 | - |
| Hemoglobin | −0.79 (−1.81; 0.22), 0.111 | - |
| Sodium | −0.02 (−0.10; 0.05), 0.542 | - |
| Potassium | 0.63 (−2.10; 3.37), 0.627 | - |
| Chloride | −0.01 (−0.09; 0.07), 0.854 | - |
| Urea | −0.66 (−1.53; 0.20), 0.124 | - |
| Creatinine | −0.05 (−0.13; 0.03), 0.180 | - |
| Bicarbonate | 0.03 (−1.38; 1.44), 0.968 | - |

*Adjusted (multivariate) linear regression was not performed because no variable was significant in the unadjusted (univariate) regression analysis.

**Table 6: Predictors of cognitive impairment using the TMTA score among patients with cognitive impairment.**

| Variable | Cognitive impairment | |
|---|---|---|
| | **Unadjusted coefficient (95% CI), *p*-value** | ***Adjusted coefficient (95% CI), *p*-value** |
| Systolic blood pressure | 0.51 (−0.32; 1.35), 0.222 | - |
| Diastolic blood pressure | 0.42 (−0.56; 1.41), 0.392 | - |
| Hemoglobin | 0.78 (−6.39; 7.94), 0.814 | - |
| Sodium | −0.06 (−0.41; 0.29), 0.729 | - |
| Potassium | 0.99 (−1.21; 2.84), 0.125 | - |
| Chloride | −0.31 (−0.63; 0.12), 0.061 | - |
| Urea | 0.55 (−1.59; 2.68), 0.210 | - |
| Creatinine | −0.16 (−0.53; 0.21), 0.378 | - |
| Bicarbonate | 0.47 (−2.80; 1.90), 0.255 | - |

*Adjusted (multivariate) linear regression was not performed because no variable was significant in the unadjusted (univariate) regression analysis.

**Table 7: Predictors of cognitive impairment using the CSID score among patients with cognitive impairment.**

| Variable | Cognitive impairment | |
|---|---|---|
| | **Unadjusted coefficient (95% CI), *p*-value** | ***Adjusted coefficient (95% CI), *p*-value** |
| Systolic blood pressure | −0.19 (−0.35; −0.02), 0.031 | - |
| Diastolic blood pressure | −0.07 (−0.27; 0.14), 0.521 | - |
| Hemoglobin | −0.07 (−1.34; 1.19), 0.899 | - |
| Sodium | −0.01 (−0.12; 0.211), 0.941 | - |
| Potassium | 0.38 (−1.67; 2.21), 0.228 | - |
| Chloride | −0.02 (−0.15; 0.10), 0.685 | - |
| Urea | −0.11 (−1.46; 0.25), 0.101 | - |
| Creatinine | −0.08 (−0.20; 0.05), 0.210 | - |
| Bicarbonate | 0.10 (−2.08; 2.29), 0.921 | - |

MMSE scores. No variable was significantly correlated with the SLUM scores in Table 5 (nonsignificant 95% confidence interval and *p*-values); hence, there was no need for an adjusted model.

Table 6 showed that an adjusted regression analysis was not performed because no variable was significantly correlated with the TMTA scores (nonsignificant 95% confidence interval and *p*-values) in the unadjusted model.

**Figure 1: Prevalence of anxiety among SCA patients and controls using HADS.**

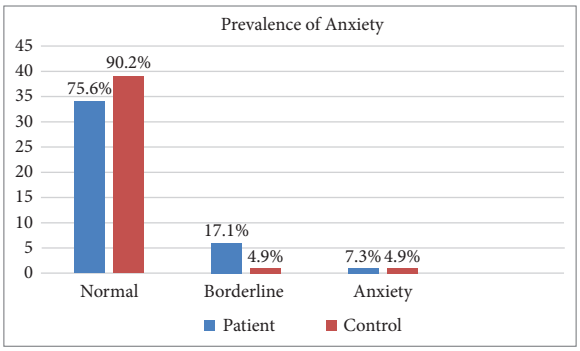
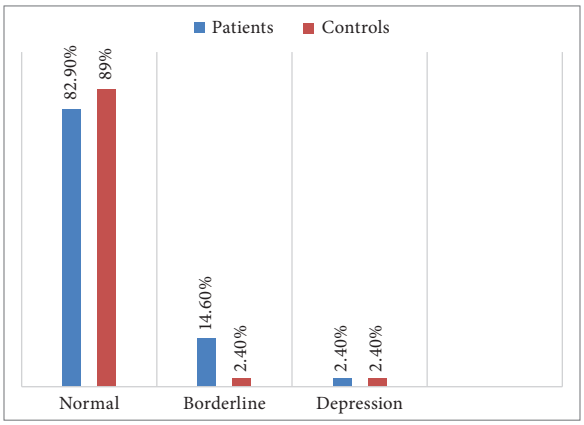



**Figure 2: Prevalence of depression among SCA patients and controls using HADS.**




In Table 7, only SPB was inversely and significantly correlated with the CSID scores (Spearman's correlation coefficient = −0.19 (95% CI = −0.35; −0.02), $p = 0.031$) in the unadjusted regression model. Hence, no multivariate regression analysis was conducted.

Using HADS, the prevalence of anxiety was 7.3% and 4.9% among the SCA patients and the controls, respectively. More SCA patients had borderline anxiety (17.1%) when compared to controls (4.9%). Moreover, this is represented in Figure 1. There was a slightly higher number of SCA patients with borderline depression of 14.6% compared to 2.4% among controls. Both SCA patients and controls had 2.4% prevalence of depression as shown in Figure 2.

## 4. DISCUSSION

This case-control study was aimed at establishing the possibility of SCA being a major risk factor for cognitive impairment in adolescent and adult Nigerians. Different from previous studies that mainly involved children, we enrolled patients aged between 14 and 41 years, with the mean age of the SCA patients in this study being 25.05 (±5.78). Although the sample size was smaller than that in similar studies, we observed using different neuropsychological instruments that, when compared with controls, patients with SCA did not have statistically significant worse global cognitive performance. The findings in this study were not in good agreement with the reports from previous studies that had observed statistically worse cognitive performance among children with SCA [11, 33]. Day *et al.* [8] observed from a review of studies comparing cognitive function among SCA patients and control that there was a significantly poorer performance in SCA patients in up to 71% of the papers reviewed. The findings of no significant difference in global cognitive performance between our SCA and controls despite the fact that there was statistically significant difference in the age of the SCA group and control is in good agreement with previous conclusion from a review. Moreover, it observed that the age of controls among younger people has little effect on their performance [8].

In addition, our study observed a negative correlation between systolic the blood pressure of SCA and a direct correlation between their serum creatinine levels with their MMSE scores. Other parameters both clinical and biochemical had no significant predictive values with their cognitive performance on the screening instruments used in this study.

Compared to the findings from the PiSCES [10] and other studies [20-22] which found a prevalence of depression among SCA patients to be 27.7% and 18-44%, respectively, we found depression in only 2.4% of our SCA patients. Moreover, the depression observed was similar to that observed among controls. However, more patients had borderline depression, which was 14.6% compared to 2.4% among controls. Similarly, the rate of occurrence of anxiety among SCA patients (7.3%) was just slightly more than that observed among controls (4.9%). A significantly higher proportion of SCA patients (17.1%) compared to controls (4.9%) had borderline anxiety. Using a questionnaire with stratification into only normal or depression/anxiety may obtain a slightly higher prevalence of depression and anxiety in our SCA patients. An increased sample size screened for cognitive impairment may obtain a much more significant difference in the prevalence of cognitive impairment between SCA patients and control. The other likely cause of a lower prevalence of mood disorder among our SCA patients may be due to the effective counseling session offered to patients in the daycare clinic and support obtained in the sickle cell club.

## *5.* CONCLUSION

Sickle cell anemia was associated with cognitive impairment in adults with sickle cell anemia in the absence of obvert stroke. However, this was not statistically significant when compared to gender and educationally matched controls. On the HADS, SCA patient had a higher percentage of patients with mood disorder compared to controls.

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**Author Contributions**
**Williams, Uduak. E.** – Conception of the study, Literature search, Organization of the study, Data collection, Writing of first draft, and Manuscript preparation; **Marcus Inyama** – Conception of the study, Organization of Study, Data Collection, Manuscript preparation; **Soter Ameh** – Data analysis, writing of initial draft and Manuscript preparation; **Sidney Kelechi Oparah** – Conceptualization of the Study, Organization of the Study and Manuscript preparation; **Henry Okpa** – Data analysis, writing of the initial draft and Manuscript preparation.

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**Conflict of Interest**
None.

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