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To Evaluate the Conventional and Advanced Brain MR Imaging in Patients with Sickle Cell Anemia: A Cross Sectional Study

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Abstract

Background: To evaluate the conventional and advanced brain MR imaging in patients with sickle cell anemia.**Material and Methods:**This prospective observational case–control study included 70 SCD (SCA 45, SCT 25) cases having no neurological problem and 60 healthy controls. The control group included Male subjects of the age 10-45, whereas female subjects were 15-50 years old. The SCA and SCT male and female participants were of age group 11-30years, 15-45 years and 14-40 years, 15-55 years respectively.**Results:**The average of all ROIs of different regions in SCD, SCT, and control were taken out. The FA values showed a statistically significant difference between patients with SCD and control subjects in CC genu (0.62 vs 0.68, P = 0.004), splenium (0.61 vs 0.67, P = 0.005), left centrum semiovale (0.43 vs 0.49, P = 0.001), anterior periventricular white matter left side (0.40 vs 0.47, P = 0.008), posterior periventricular white matter left side (0.38 vs 0.49, P = 0.005), pons left (0.43 vs 0.51, P = 0.001), head of caudate nucleus left (0.31vs 0.63, P = 0.001), and lentiform nucleus left (0.32 vs 0.52, P = 0.001). ADC values showed a statistically significant difference between patients with SCD and control subjects in the CC genu (0.93 vs 0.85, P = 0.001), right caudate nucleus (0.86 vs 0.79, P = 0.001), left caudate nucleus (0.87 vs 0.79, P = 0.001), left thalamus (0.85 vs 0.81, P = 0.001),and right and left pons (0.88 vs 0.84, P = 0.014 and 0.88 vs 0.84 P = 0.018).**Conclusion:**Decrease in FA and increase in ADC found in various brain regions without visible signal intensity changes on conventional MRI in patients with SCD are associated with microstructural changes consistent with axonal damage due to vasculopathy.

Keywords: Sickle cell anemia, brain MR imaging.

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Introduction

Sickle cell anemia (SCA) is a hemolyticanemia characterized by abnormally shaped (sickled) red blood cells (RBCs), which are removed from the circulation and destroyed at increased rates, leading to anemia. Of greater clinical importance, the sickled RBCs cause vascular occlusion, which leads to tissue ischemia and infarction. The un- derlying abnormality in the RBC of SCA is the presence of abnormal sickle cell hemoglobin (Hb S), which, when deoxygenated, becomes relatively insoluble and forms aggregates with other hemoglobin molecules within the RBC. These aggregates develop into long chains, which distort the RBC into a sickled shape and impair flow through vessels. In addition, the deformed RBCs tend to adhere to endothelium, worsening vascular occlusion, ischemia, and the likelihood of tissue infarction. For the vast majority of patients with SCA, the vasoocclusive complications of the

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disease are much more clinically troublesome than is the anemia, which is usually well tolerated.[1,2]

Sickle cell disease (SCD) is an autosomal recessive haemoglobinopathy characterized by ongoing haemolytic anaemia, episodes of vaso-occlusion and progressive organ failure. Millions are affected worldwide, and approximately 312.000 neonates with this haematological disorder are born annually.[3] SCD is caused by a single nucleotide substitution in codon 6 of the β-globin gene. This mutation leads to the formation of abnormal haemoglobin, called HbS.[4] When deoxygenated, HbS erythrocytes become sickle or crescent-shaped, rigid and prone to lysis. These sickle cells interact with leukocytes and the vascular endothelium causing occlusion and vas- culopathy, subsequently leading to abroadrangeof acute and chronic complications including cerebrovascular disease.[5,6]

The most common neurological complication in children and adults with SCD is the development of silent cerebral infarcts (SCIs), also referred to as silent strokes.[7-9] In contrast to the clinically overt strokes, SCIs do not lead to apparent focalneurologicalsymptomsand can only be detected with neuroimaging techniques.[10,11]As a consequence, SCIs are identified incidentally or through screening. Although SCIs do not lead to any tangible motor or sensory deficits, they are associated with cognitive morbidity and an increased risk of future strokes.[12-14] SCIs are visible as focal lesions on both computed tomography (CT) scans and magnetic reson- ance imaging (MRI) scans. Detection is however better by MRI due to the greater range of contrast between soft tissues and greater detail in the depiction of intracranial structures.[15]

While the Silent Cerebral Infarct Transfusion (SIT) randomized controlled trial showed that chronic red blood cell trans- fusions reduce the risk of recurrent infarction, this benefit was incomplete with some children in the transfusion therapy arm also developing infarctrecurrence.[16]

Material and Methods

This prospective observational case–control study was carried out after taking the approval of the protocol review committee and institutional ethics committee. The study included70 SCD (SCA 45, SCT 25) cases having no neurological problem and 60 healthy controls. The control group included Male subjects of the age 10-45, whereas female subjects were 15-50 years old. The SCA and SCT male and female participants were of age group 11-30years, 15-45 years and 14-40 years, 15-55 years respectively.

Inclusion criteria

- The cases were neurologically asymptomatic cases of SCA or SCT.
- The control group included healthy subjects in the age group 15–50 years.

Exclusion criteria

- Patients with SCD with abnormal neurological examination or a history of stroke. Informed consent was taken from both the case and control groups before the procedure.
- There is no conflict of interest.

Methodology

All brain MR imaging data were acquired from a 1.5‐ T MR Imaging scanner (Signa Excite; GE Healthcare, Milwaukee, WI, USA) using an eight‐ channel phased‐ array head coil and a gradient system with a slew rate of 120 mT/m/s and a maximum gradient amplitude of 33 mT/m. None of the study participants required sedation or general anesthesia to undergo the procedure. After triplaner scans and acquisition of calibration data, axial T1 WI, T2 WI, T2‐ FLAIR, sagittal T1‐ FLAIR, DWI, three‐ dimensional (3D) TOF MRA, and SWI sequences were acquired from each subject. Images from these sequences were used to

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diagnose pre‐ existing lesion in patients, and those who had lesion diagnosed were excluded from comparative DTI study.

DTI data were acquired using echo planer imaging with a data acquisition matrix of 128 × 128, field of view (FOV) of 26 × 24, TR/TE of 10000/99, flip angle 90°, and NEX of 2. Contiguous 3‐ mm‐ thick slices with no interslice gap were acquired in the axial direction covering the whole brain. The protocol comprises 25 diffusion gradient directions with b value of 0 and 1000 s/mm2 The mean acquisition time for DTI was approximately 10 min 30 s and 20 min for DTI data processing.

DTI data were transferred to a commercially available work station Adw 4.4. All images were first visually inspected for apparent artefacts, auto correction was done, and DTI‐ based color map was generated. Quantitative analysis was performed by outlining regions of interest (ROIs) on FA maps with size ranging from 4 pixels (2 × 2) and 40 pixels (8 × 5). Standard square to rectangle symmetric ROIs were used for analysis of FA and ADC according to anatomic shape of the brain area.
The routine images were analyzed and reported initially by a junior radiologist with 3 years of experience, which was followed by a repeat examination and validation by a senior radiologist with 10 years of experience. Quantitative analysis of FA and ADC maps was done by manually drawing ROI on axial images on various brain areas: superior and inferior frontal, parietal, occipital, and temporal white matter areas, anterior and posterior periventricular areas, centrum semiovale, basal ganglia (lentiform nucleus, head of caudate nucleus), thalamus, cerebral peduncles, pons, cerebellar white matter, and corpus callosum (CC).
Superior and inferior frontal white matter ROIs were drawn on the axial slice that was at the level of five slices superior to the superior edge of CC and at the level of inferior edge of rostrum, respectively. Parietal white matter ROIs were also placed at the same slice of superior frontal white matter. The ROIs of occipital white matter, basal ganglia, and thalamus were drawn at the level of inferior edge of splenium. The ROIs of temporal white matter were at the level of inferior edge of frontal lobe. The ROIs of posterior and anterior periventricular areas were drawn at the level of the roof of lateral ventricle. For CC at the level of frontal horn and atrium of lateral ventricle, mid line in genu, and splenium region. The ROIs of the cerebral peduncle and pons were at the level of optic chiasm and superior cerebellar peduncle, respectively. Cerebellar white matter ROIs were drawn at the level of inferior edge of pons.17,18
Statistical Analysis
The data was tabulated as mean ± standard deviation (SD). Results were analyzed using Statistical Package for Social Sciences) version 25.0. A $p<0.05$ was considered statistically significant.

Results

Conventional MRI findings

The conventional MRI of the control subjects was normal. 2 patients with SCA showed T2 and T2‐ FLAIR hyperintensity in deep white matter, which did not show restriction on DWI. The first patient was a 40‐ year‐ old female having T2‐ FLAIR linear hyperintensity in deep white matter of left frontal lobe. Another patient was an 19‐ year‐ old female with SCA having small T2‐ FLAIR hyperintensity in deep white matter of right frontal lobe. MRA did not reveal any stenosis or occlusion. SWI images were unremarkable.
All DTI images were inspected visually for echo‐ planer imaging‐ related susceptibility artifacts and geometric distortion, after EPI distortion correction, color, and grey map were

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generated. In all 30 ROIs with 60 variables, that is, FA and ADC values for each region, were analyzed and compared with the corresponding contra- lateral area of same patient and with comparable area of controls. The average of all ROIs of different regions in SCD, SCT, and control were taken out. The FA values showed a statistically significant difference between patients with SCD and control subjects in CC genu (0.62 vs 0.68, P = 0.004), splenium (0.61 vs 0.67, P = 0.005), left centrum semiovale (0.43 vs 0.49, P = 0.001), anterior periventricular white matter left side (0.40 vs 0.47, P = 0.008), posterior periventricular white matter left side (0.38 vs 0.49, P = 0.005), pons left (0.43 vs 0.51, P = 0.001), head of caudate nucleus left (0.31vs 0.63, P = 0.001), and lentiform nucleus left (0.32 vs 0.52, P = 0.001). The remaining areas with decreased FA values are given in [Table 1].

Table 1: FA value comparison in SCD, SCT, and control.

Region of measurements	SCD	SCT	Control	P
Centrum semiovale (right)	0.45±0.073	0.43±0.08	0.48±0.05	0.004
Centrum semiovale (left)	0.43±0.07	0.45±0.08	0.49±0.05	0.001
Corpus callosum genu	0.62±0.04	0.63±0.05	0.68±0.06	0.004
Corpus callosum splenium	0.61±0.05	0.65±0.06	0.67±0.06	0.005
Anterior periventricular (right)	0.39±0.06	0.41±0.06	0.46±1.54	0.003
Anterior periventricular (left)	0.40±0.06	0.45±0.06	0.47±0.05	0.008
Posterior periventricular (right)	0.39±0.06	0.40±0.06	0.50±0.07	0.001
Posterior periventricular (left)	0.38±0.06	0.40±0.06	0.49±0.06	0.005
Superior frontal white matter (right)	0.38±0.11	0.39±0.07	0.51±0.07	0.001
Superior frontal white matter (left)	0.36±0.09	0.39±0.06	0.50±0.05	0.001
Parietal white matter (right)	0.42±0.09	0.45±0.09	0.49±0.05	0.001
Parietal white matter (left)	0.42±0.08	0.43±0.07	0.49±0.06	0.001
Occipital white matter (right)	0.60±1.26	0.44±0.07	0.47±0.09	0.76
Occipital white matter (left)	0.41±0.10	0.43±0.46	0.49±0.07	0.001
Thalamus (right)	0.54±1.26	0.39±0.12	0.49±O.09	0.89
Thalamus (left)	0.36±0.08	0.40±0.11	0.49±0.08	0.001
Lentiform nucleus (right)	0.32±0.11	0.32±0.13	0.51±0.06	0.005
Lentiform nucleus (left)	0.32±0.11	0.32±0.14	0.52±0.05	0.001
Temporal white matter (right)	0.40±0.11	0.41±0.10	0.49±0.06	0.003
Temporal white matter (left)	0.45±0.09	0.4386±0.08	0.50±0.07	0.001
Head of caudate nucleus (right)	0.30±0.11	0.33±0.15	0.63±0.10	0.003
Head of caudate nucleus (left)	0.31±0.10	0.33±0.14	0.63±0.11	0.001
Cerebral peduncle (right)	0.50±0.10	0.52±0.08	0.54±0.07	0.012
Cerebral peduncle (left)	0.50±0.13	0.50±0.09	0.55±0.07	0.004
Inf. frontal white matter (right)	0.34±0.07	0.37±0.06	0.46±0.05	0.001
Inf. frontal white matter (left)	0.35±0.08	0.37±0.10	0.46±0.06	0.003
Pons (right)	0.45±0.07	0.45±0.04	0.50±0.06	0.001
Pons (left)	0.43±0.037	0.44±0.07	0.51±0.10	0.001
Cerebellar white matter (right)	0.49±0.10	0.50±0.15	0.49±0.04	0.49
Cerebellar white matter (left)	0.48±0.10	0.49±0.14	0.48±0.06	0.98

SCA: sickle cell anemia, SCT: sickle cell trait

ADC values showed a statistically significant difference between patients with SCD and control subjects in the CC genu (0.93 vs 0.85, P = 0.001), right caudate nucleus (0.86 vs 0.79, P = 0.001), left caudate nucleus (0.87 vs 0.79, P = 0.001), left thalamus (0.85 vs 0.81, P =

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0.001),and right and left pons (0.88 vs 0.84, P = 0.014 and 0.88 vs 0.84 P = 0.018). The remaining areas with increased ADC values are mentioned in [Table 2].

Two patients with SCA with silent infarct, when compared to without infarct ones, have lower FA in right (0.33 vs 0.38) and left (0.34 vs 0.36) along with high ADC value in right (0.85 vs 0.79) and left (0.84vs 0.82) superior frontal region.

Table 2: Comparison of ADC values in SCD, SCT, and control

Region of measurements	SCD	SCT	Control	P
Centrum semiovale (right)	0.89±0.07	0.43±0.08	0.48±0.05	0.004
Centrum semiovale (left)	0.84±0.04	0.45±0.08	0.49±0.05	0.001
Corpus callosum genu	0.84±0.05	0.63±0.034	0.68±0.06	0.004
Corpus callosum splenium	0.93±0.07	0.65±0.06	0.67±0.06	0.005
Anterior periventricular (right)	0.39±0.06	0.41±0.06	0.46±1.54	0.002
Anterior periventricular (left)	0.40±0.06	0.45±0.06	0.47±0.05	0.008
Posterior periventricular (right)	0.38±0.06	0.40±0.06	0.50±0.07	0.001
Posterior periventricular (left)	0.38±0.06	0.40±0.06	0.49±0.06	0.005
Superior frontal white matter (right)	0.38±0.11	0.39±0.07	0.51±0.07	0.001
Superior frontal white matter (left)	0.36±0.09	0.39±0.06	0.50±0.05	0.001
Parietal white matter (right)	0.42±0.09	0.45±0.09	0.49±0.05	0.001
Parietal white matter (left)	0.42±0.08	0.43±0.07	0.49±0.06	0.001
Occipital white matter (right)	0.60±1.26	0.44±0.07	0.47±0.08	0.76
Occipital white matter (left)	0.41±0.10	0.43±0.46	0.49±0.07	0.001
Thalamus (right)	0.54±1.26	0.39±0.12	0.49±O.09	0.89
Thalamus (left)	0.36±0.08	0.40±0.11	0.49±0.09	0.001
Lentiform nucleus (right)	0.32±0.11	0.32±0.13	0.51±0.06	0.005
Lentiform nucleus (left)	0.32±0.11	0.32±0.14	0.52±0.05	0.001
Temporal white matter (right)	0.40±0.11	0.41±0.10	0.49±0.06	0.003
Temporal white matter (left)	0.45±0.09	0.45±0.08	0.50±0.07	0.001
Head of caudate nucleus (right)	0.30±0.11	0.33±0.15	0.63±0.10	0.003
Head of caudate nucleus (left)	0.31±0.10	0.33±0.14	0.63±0.11	0.001
Cerebral peduncle (right)	0.50±0.10	0.52±0.08	0.54±0.07	0.012
Cerebral peduncle (left)	0.50±0.13	0.50±0.09	0.55±0.07	0.004
Inf. frontal white matter (right)	0.35±0.06	0.37±0.06	0.46±0.05	0.001
Inf. frontal white matter (left)	0.35±0.08	0.37±0.10	0.46±0.06	0.003
Pons (right)	0.45±0.07	0.45±0.04	0.50±0.06	0.001
Pons (left)	0.43±0.05	0.44±0.07	0.51±0.10	0.001
Cerebellar white matter (right)	0.49±0.10	0.50±0.15	0.48±0.04	0.49
Cerebellar white matter (left)	0.48±0.10	0.49±0.14	0.48±0.06	0.98

Discussion

Brain injury in SCD is diffuse and insidious, and conventional neuroimaging often underestimates the extent of injury. In this study, we compared FA and ADC values in different areas of brain in SCA (homozygous) and SCT (heterozygous) with normal control subjects. We had 70 SCD (SCA 45, SCT 25) cases having no neurological problem and 60 healthy controls. Two cases of SCA having SCI were excluded from DTI study. In these two cases, DTI values were taken separately. Due to age- related alterations in white matter

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micro structure in DTIstudies, we have included controls in the same age range as that of cases in this study.

Conventional MRI findings

2 cases of SCA (4.44%) showed T2‑ FLAIR hyperintensity, suggestive of SCI. Both patients had T2‑ FLAIR hyperintensity in deep white matter. The deep white matter is perfused by arterioles and is more liable to inadequate perfusion and subsequent infarction. Small‑ vessel disease in SCD is due to the formation of intravascular masses of dense or less flexible sickled erythrocytes in peripheral arterioles and post capillary venules. FLAIR sequence is one of the most reliable conventional MRI acquisition techniques for assessing the presence of SCI.[19-21]

Previous studies have defined stenosis as obvious narrowing or focal signal dropout in a major artery and occlusion as signal loss from the distal portion of a major artery.[22,23] In our study on MRA, no evidence of any stenosis or occlusion was observed.

Intracranial hemorrhage is a know complication of SCD. Bleeding may be parenchymal, subarachnoid, or intraventricular. None of our patients had intracranial and micro‑ hemorrhages in SWI images. This may be possible as all our cases were asymptomatic.[24,25]

In this study, a wide range of bilateral changes in FA and ADC values were observed in patients with SCD compared with healthy control subjects. Using an ROI‑ based analytic approach, the results of this study indicate significantly reduced FA values, increased ADC values, or both for patients with SCD clustered in different areas of brain, CC, frontal white matter, centrum semiovale, periventricular areas, and head of the caudate nucleus, thalamus, cerebral peduncle, and pons. Bilaterally decreased FA and increased ADC values were the findings in patients with SCD compared with healthy control subjects in almost all brain areas measured even if the difference was without statistical significance and ADC values was observed in SCD between the right and the left sides of the brain in certain areas such as temporo‑ occipital white matter, periventricular, central semiovale, and thalamic region. These asymmetries can be explained by the fact that there are microstructural changes secondary to vascular involvement in different severities between the two hemispheres. Two patients of SCD with silent ischemia had significantly lower FA values and higher ADC values in various brain areas. This finding suggests that this subgroup of patients with SCD has more severe microstructural changes than patients with SCD without silent infarct.[26-28]

Reduction in FA and an increase in ADC values were noticed in patients with SCD as compared with SCT as the severity of disease is more in homozygous cases. Myelination, axonal water, and packing of axonal fibers all affect the ADC in the brain tissue. The loss of myelinated axons may cause loosing of anatomic barriers to water diffusion and may result in increased ADC values. Reduced FA can be caused by reduced axons per cross‑ sectional area, reduced axonal calibre and density, or decreased myelin.[29] In our study, the FA changes are attributable to axonal damage in the brain tissue that is exposed to chronic ischemia. The increase in ADC values may represent increased extracellular water content secondary to gliosis and to micro and macroscopic cystic changes in the brain. These findings are consistent with the results reported in chronic ischemia. Decreased FA, increased ADC, or both were not only in CC, basal ganglia, or lobar white matter areas but also in cerebral peduncle and pons, suggesting patients with SCD have global brain involvement.

Conclusion

We conclude that decrease in FA and increase in ADC found in various brain regions without visible signal intensity changes on conventional MRI in patients with SCD are associated with microstructural changes consistent with axonal damage due to vasculopathy.

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