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# Electrocardiographic Findings in the Pediatric Patients of Sickle Cell Disease in Chhattisgarh - A Comparative Study

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***Abstract***
*The sickle cell disease has high prevalence in India. The increased lifespan of sickle patients has facilitated to study its cardiovascular effects. The present study documents the electrocardiogram indices between the sickle cell and non-sickle cell subjects from Chhattisgarh state. The study concludes a significant increase in PR interval, corrected QT interval, left ventricular hypertrophy and biventricular hypertrophy and no difference in heart rate and rhythm, ventricular axis and right ventricular dimensions. These observations can be attributed to increased cardiac output on left ventricular dimensions and effect of microinfarcts on myocardial repolarization.*

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## I. Background

Sickle cell disease resulting from substitution of valine for glutamic acid at the 6th position of beta-globin in haemoglobin, is the most prevalent blood inherited disorder. The consequent immunity from fatal malaria has resulted in high prevalence in Asian and African continents.[1] The ICMR study suggests that 20% of sickle cell disease patients die in the first two years of their life and an additional 30% fail to survive till adulthood[2]. The advances in healthcare for inducing fetal haemoglobin and preventing infectious deaths, have increased life span of sickle cell disease patients, and increased prevalence of cardiovascular morbidity and mortality in these patients. The median age for survival of sickle cell disease patients was 14 years in a 1973 study, that improved to 85% surviving beyond the age of 20 years.[3] While the effect of sickle cell on blood pressure indices in Indian population has been recently studied, the data on effects on electrocardiographic manifestations have not been studied from the Indian subcontinent.[1] This study aims to document electrocardiographic indices in children with sickle cell disease as compared to comparable control subjects presenting to a tertiary medical college hospital in Chhattisgarh.

## II. Materials and Methods

**Study design**
Observational cross sectional case cohort study
**Study duration**
January 2016 to September 2017
**Study subjects**
The participants were recruited from the Paediatric Department of the Pt J N M Medical College and associated Dr B R A M Hospital, Raipur. Controls were healthy age matched patients without any hemoglobinopathy.
**Inclusion criteria**
All sickle cell anaemia patients with SS pattern under the age group 8 to 18 yrs were included in the study.
**Exclusion criteria**
Sickle cell disease with known acquired heart disease and congenital heart disease, anemia due to chronic illnesses, and thalassemia.

**Sample Size**
Sample Size for Unmatched Case-Control Study Assumptions
Two-sided confidence level(1-alpha) = 95
Power(% chance of detecting) = 80
Ratio of Controls to Cases = 1
Hypothetical proportion of controls with exposure = 40

Hypothetical proportion of cases with exposure = 69.39
Least extreme Odds Ratio to be detected (from pilot study) : 3.40
Fleiss Sample Size – Cases 48 & Controls 42
Total sample size: 90
Ten percent dropout or loss of follow up = 9
Total final sample size = 99, rounded off to 100 with 50 cases and 50 control subjects to ease mathematical calculations.
Calculated form http://www.openepi.com/SampleSize/SSCC.htm.

**Sampling**

All the demographic and clinical information was collected in the predesigned and pretested questionnaires. The ECG recorded by trained technicians using appropriate sized recording electrodes with the child lying down on an ECG table after a 5 minutes rest period in a separate quiet room with one of the parents present. Ten leads with 6 chest leads and 4 extremity leads were placed at precise anatomical locations by trained ECG technicians and the electrocardiogram recorded at paper speed of 25mm/s and standardized at 0.1mv/mm. ECG tracings were read and interpreted by a single pediatrician. Randomly selected ECG tracing readings were double checked by an independent cardiologist. Standard measurements of heart rate, QTc, and PR intervals were done. Left ventricular hypertrophy diagnosis was based on Sokolow and Lyon voltage criteria. Right ventricular hypertrophy diagnosis was based on the Allenstein and Mori criteria. The biventricular hypertrophy was based on any 1 of 3 indicating RV hypertrophy, namely, R/S ratio in lead Vs or Vs < 1, or S V5 or Vs >7 mm or right-axis deviation greater than +90°, in presence of left ventricular hypertrophy. Left atrial dilatation diagnosis was based on the criteria described by Marcuz. The ECG findings were recorded as categorical variables into spreadsheets for analysis.

**Statistical Analysis**

The statistical t-test analysis and pie chart graphics was done using RStudio Version 1.2.5019 software (© 2009-2019 RStudio, Inc.). The descriptive data was given as means ± standard deviation (SD). The outcomes of the present study did not show normal distribution and were tested for significance by Chi-squared test.

## III. Observation

The data was tabulated for 50 patients of sickle cell disease and 50 healthy controls without any haemoglobinopathy. There were 27 male sickle cell patients (54%), and 23 female sickle cell patients (46%), while in the control group 31 males (62%) and 19 females (38%) respectively (chi-square, p=0.073) [Figure 1]. The age distribution had among sickle cell patients below 13 years , 20 subjects (40%), above 13 years, 30 subjects (60%) while in non sickle cell control group, below 13 years, 22 subjects (44%), and above 13 years, 28 subjects (56%) (chi-square, p=0.099). The electrocardiogram was abnormal in 45 (90%) sickle cell patients as compared to 23 (46%) among non sickle cell controls. In the electrocardiographic study, there was no significant difference between sickle cell patients and non sickle cell subjects for tachycardia (7 vs 3, p=.318 (NS)), for sinus arrhythmia (22 vs 31, p=.109 (NS)), left axis deviation (21 vs 12, p=.060 (NS)), and right ventricular hypertrophy (10 vs 4, p=.094 (NS)) respectively. There was significant difference between the sickle and non sickle subjects for PR interval (22 vs 3, p=.0001 (S)) and QTc interval (10 vs 2, p=.016 (S)), left ventricular hypertrophy (22 vs 9, p=.009 (S)) and biventricular hypertrophy (5 vs 0, p=.033 (S)).

## IV. Discussion

The repeated metamorphosis from non-sickle to sickle shape renders the red blood cells irreversibly sickle shaped and prone to haemolysis and consequent chronic hemolytic anaemia that is responsible for cardiac manifestations of sickle cell disease. The multi-organ damage is accentuated by recurrent ischaemia - reperfusion injury, results in chronic vasculopathy. The chronic anaemia increases the cardiac output along with minimal increase in heart rate, resulting in increased stroke volume and left ventricular dilation.[4] The accentuated wall stress causes eccentric hypertrophy of the left ventricle. The electrocardiographic (ECG) manifestations of the left ventricular and bi-ventricular hypertrophy are increasingly documented.[5] The evidence of myocardial stress is seen in the form of tachycardia and non specific ST-T changes on electrocardiogram.[6]

The electrocardiogram was abnormal in 90% of sickle cell patients as compared to 46% of non sickle controls. The abnormal electrocardiogram amongst sickle cell patients have similarly been noted as high as 72.7% by Akinola [7], 78% by Uzsoy [8], and 73.1% by Dosunmu [5] in their respective studies. The African study documented 96.7% abnormal electrocardiograms in sickle patients as compared to 2% in normal controls [5]. The higher percentage of abnormal electrocardiogram among the normal controls in our study is possibly

because the sinus arrhythmia has been classified as abnormal ecg indice in our study. The sinus arrhythmia is otherwise common in young people.

The heart rate was found to have no significant difference between the sickle cases and the controls in this study (p=0.318). The African study had significantly higher heart rates among the sickle patients, with no effect of hematocrit values observed in their study [5]. The mean heart rates of 77.28±14.61 in sickle cases and 77.19±15.30 in normal controls was documented by Dosunmu [5]. These observations are concordant with findings of the present study. The study by Adegoke[10] found no significant difference in sinus rhythm and left axis deviation as also seen in the present study between the two groups. The distribution of right ventricular hypertrophy was seen comparable between the two groups (p=0.094). The right ventricular hypertrophy was seen in 20% sickle cases in present study as was also seen in previous studies, 28% by Dosunmu [5]. However, the study by Odia [11] had only 2% incidence of right ventricular hypertrophy in ECG of sickle subjects.

There was a significant difference observed in the PR interval (44% vs 6%, p=.0001 (S)) and QTc interval (10 vs 2, p=.016 (S)) between the sickle cell patients and non sickle cell controls. A similarly significantly increased PR interval was observed in various previous studies 23% by Dosunmu [5], 29% by Uzsoy [8], 50% by Klinefelter [12], and 9.1% by Akinola [7]. These studies observed these differences irrespective of the hematocrit levels. No difference in mean PR interval was observed in a study by Odia in 30 Nigerian patients. The significantly prolonged QTc interval was seen in 61.7% Dosunmu [5], 28% Bode Thomas [13], and 11% Holloman[14]. However, no difference was documented in the QTc interval in a study of 30 Nigerian patients by Odia [11], and Sproule [15]. Bode Thomas [13] described changes of myocardial ischaemia can accentuate the arrhythmogenic substrate in sickle cell patients. Odia [11] proposed that the prolonged QTc interval in sickle cell patients can detect increased vulnerability to arrhythmias and sudden cardiac deaths.

The left ventricular and biventricular hypertrophy were found to be significantly more prevalent among sickle cell patients in the present study. The left ventricular hypertrophy was the commonest ECG abnormality observed in 75% sickle patients in studies by Dosunmu [5], 70% in Ng [16], 63.8% in Akinola [7]. The outcomes of the present study coincide with the increasing prevalence of left ventricular hypertrophy with age as witnessed in Dosunmu [5], Lester [17], and Gerry [18] studies. [Figure-2] The biventricular hypertrophy was also observed to be significantly more in sickle cell patients in the present study. The biventricular hypertrophy was similarly found high in study by Dosunmu, 13.7% [5], Oguanobi, 11.7% [9], and Aluko, 17.9% [19]. However, Adegoke [10] found no significant difference in incidences of biventricular hypertrophy in the two groups. Galdwin [4] postulated that chronic anaemias cause augmentation in left ventricular dimensions as an effect of increased cardiac output and minimally increased heart rate. The degree of dilatation has been proposed to correlate with degree of anaemia [17]. In the present study there was an increase noted in left ventricular dimensions with increasing age [Figure 2].

## V. Conclusion

The study concludes that the electrocardiogram indices that are influenced by increased cardiac output and repolarization disarray including the left ventricular hypertrophy and biventricular, and PR and QTc intervals vary significantly between the pediatric sickle patients from non sickle subjects. The difference in heart rates and rhythm are not different between the two subjects. The electrocardiogram can therefore prove a non expensive widely available modality to portend cardiac outcome in sickle cell patients.

**Figure 1** - ECG parameters between Sickle and Non Sickle Subjects

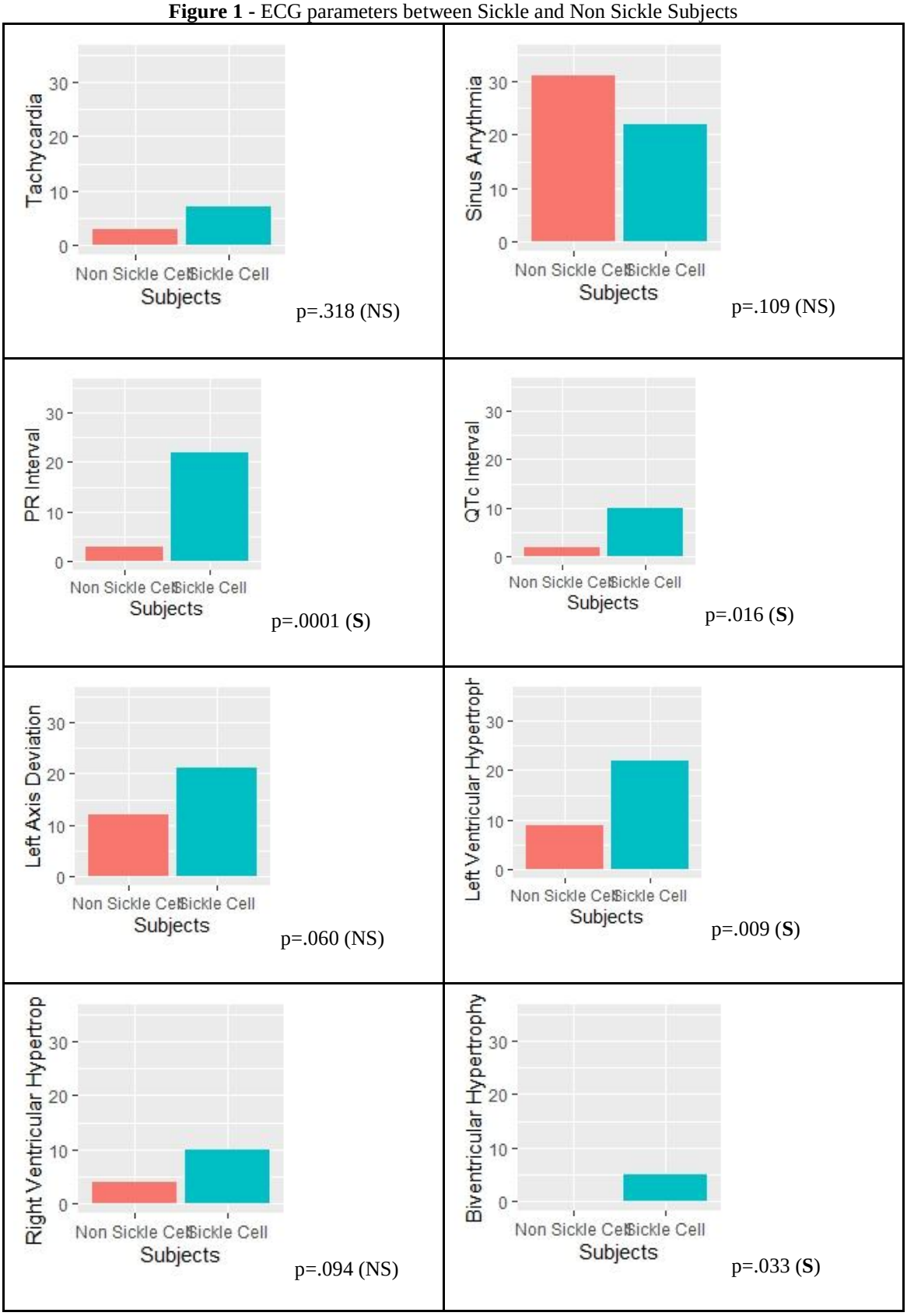
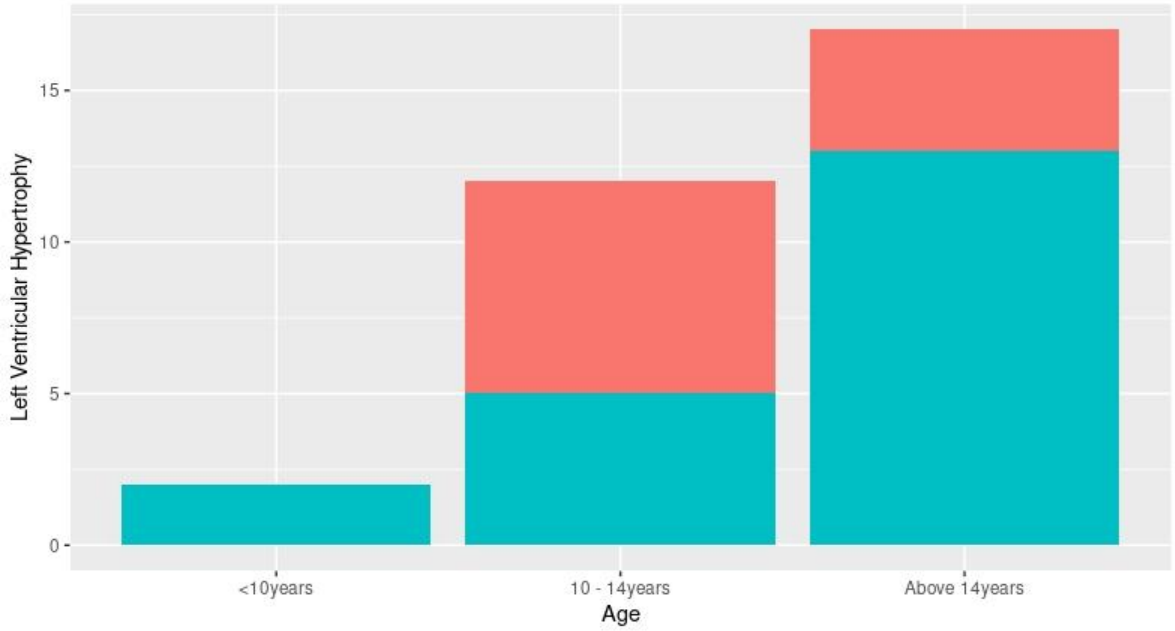


**Table 1**

| ECG Parameter | Sickle Patients n=50 | Non Sickle Subjects n=50 | *Exact Significance 2-tailed* (Significance) |
|---|---|---|---|
| **Sinus Tachycardia** | 7 (14) | 3 (6) | .318 (NS) |
| **Sinus Arrhythmia** | 22 (44) | 31 (62) | .109 (NS) |
| **PR Interval** | 22 (44) | 3 (6) | .0001 (**S**) |
| **QTc Interval** | 10 (20) | 2 (4) | .016 (**S**) |
| **Left Axis Deviation** | 21 (42) | 12 (24) | .060 (NS) |
| **Left Ventricular Hypertrophy** | 22 (44) | 9 (18) | .009 (**S**) |
| **Right Ventricular Hypertrophy** | 10 (20) | 4( 8) | .094 (NS) |
| **Biventricular Hypertrophy** | 5 (10) | 0 (0) | .033 (**S**) |

**Figure 2 -** Increasing Prevalence of Left Ventricular Hypertrophy with Age

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