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ORIGINAL ARTICLE

Cardiac autonomic dysfunction in sickle cell anaemia and its correlation with QT parameters

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ABSTRACT

Background: Abnormalities of QT parameters together with cardiac autonomic neuropathy (CAN) confer significant risks of cardiac morbidity and mortality in patients with diabetes mellitus. We questioned whether or not CAN influences occurrence of QT interval prolongation and dispersion in patients with sickle cell anaemia (SCA). **Materials and Methods**: Forty stable adult sickle cell patients with 44 healthy haemoglobin AA controls were studied. Baseline electrocardiograms were obtained and cardiovascular autonomic function tests were performed using standard protocols. **Results**: Mean corrected QT (QTc) in sickle cell patients was significantly higher (P = 0.001) than the mean of controls. Similarly, mean QT dispersion (QTcd) was higher (P = 0.001) in the former than in the latter. Mean QTc in patients with CAN was longer than patients with normal autonomic function (461 ± 26 ms versus 411 ± 23 ms), P = 0.001 (OR of 17.1, CI 3.48–83.71). Similarly, QTcd was higher (P = 0.001) in patients with CAN than those with normal cardiac autonomic function. Positive correlations were found between CAN with QTc and QTcd (r = 0.604, P = 0.001, r = 0.523, P = 0.001, respectively). **Conclusion**: CAN is a risk factor for abnormalities of QT parameters in SCA and both may be harbinger for cardiac death.

Key words: Cardiac arrhythmias, cardiac autonomic neuropathy, sickle cell anaemia, QTc

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INTRODUCTION

Cardiovascular abnormalities have been recognized as a common complication of sickle cell anaemia (SCA);[1] and together with pulmonary disease accounts for many deaths in these patients.[2,3] Common findings in the heart of SCA patients include cardiac enlargement, hyperactive precordium and systolic murmurs are probably due to chronic anaemia the patients often have. In addition, individuals with SCA often experience vaso-occlusive crisis that occasionally may be associated with cardiac arrhythmias, myocardial infarction and sudden cardiac death (SCD).[4]

QT interval on the electrocardiogram (ECG), also called electromechanical time is a known risk factor for polymorphic ventricular arrhythmias in normal population and in patients with cardiovascular disease.[5] The heart rate-corrected QT interval (QTc) has been shown to be a predictor of prognosis in patients with chronic heart failure, diabetes mellitus, chronic renal failure patients on dialysis and in individuals with myocardial infarction.[6,7] Preliminary reports have suggested that QTc prolongation is common in individuals with SCA.[8] Similarly, QT dispersion (QTcd), which is the difference between maximum and minimum QTc interval on the 12 lead ECG, reflects inhomogeneity in ventricular repolarisation.[9] QTcd has also been shown in individuals with cardiovascular diseases to be a risk factor for cardiac arrhythmias and death.[10] Recently, there has been an increasing interest on the implications of cardiac autonomic neuropathy (CAN) in individuals with SCA. The occurrence of CAN in these patients increases their morbidity and mortality profile. Indeed, this has been suggested as one of the possible mechanisms of SCD in patients with SCA.[11] QTc prolongation and QTcd have been demonstrated to be associated with CAN in diabetes and epileptic patients on carbamazepine therapy.[12,13] However, the relationship between CAN and QTc in SCA patients has not been clearly defined. Therefore, this study assessed autonomic function and QT parameters in stable SCA patients.

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MATERIALS AND METHODS

Forty (20 males and 20 females) consecutive adult SCA patients were recruited from the Medical Outpatient

Department of our hospital for the study. Forty-four (21 males and 23 females) healthy haemoglobin AA subjects were selected from willing medical students and members of staff as controls. All the subjects had haemoglobin electrophoresis done to confirm their genotype. Exclusion criteria included previous stroke, diabetes mellitus, heart failure and chronic liver disease. Subjects who smoked cigarette or consumed more than three bottles of alcoholic beverages were also excluded. None of the participants were on medications such as beta blockers, nitrates, tricyclic antidepressants which could affect autonomic function or drugs known to prolong QTc such as halofantrin, risperidol, amiodarone and anti-histamines. Informed consent was obtained from all participants and approval was gotten from the Ethics Review Committee of our hospital.

A baseline ECG was taken in supine standard position which was used to determine the observed QT interval (QTo). The QT interval was corrected (QTc) for the heart rate using the Bazett's formula.[14] Prolonged QTc was defined as QTc ≥ 444 ms and 432 ms in females and males, respectively.[15] The Cardiovascular autonomic function tests were performed in the morning in a quiet room after an initial 15 rest. Subjects were trained initially to perform the manoeuvre correctly and protocol used for the autonomic test is as stated in previous published works.[16-18] A standard test sequence was followed: Valsalva manoeuvre, deep breathing test, a lying to-standing and sustained handgrip test. A period of 5 minutes rest was given after each test. The ratio of longest R-R interval on ECG shortly after the Valsalva manoeuvre to the shortest R-R interval immediately after the strain period was calculated and expressed as the Valsalva ratio. Value of 1.4 or below was considered abnormal. The deep breathing test involved paced breathing at a rate of six deep breaths per minute. The difference in R-R interval on the ECG tracing during expiration (longest) and in inspiration (shortest) was calculated ($RR_{expiration}$–$RR_{inspiration}$). Value less than 1.2 was considered abnormal. The 30:15 ratio was the heart rate (HR) response from lying-to-standing position and was expressed as the ratio between the 30th and 15th R-R interval. Ratio less than 1.04 depicts impairment in the reflex function. CAN was defined as occurrence of three or more CAR tests.[19] The ECG tracings were read manually by one of the investigators blinded to clinical status of the subjects. Blood pressure sympathetic reflex test was evaluated using systolic blood pressure (SBP) and diastolic blood pressure (DBP) responses to change in posture from supine position to erect posture for minimum of 3 minutes. Drop in SBP (20 mmHg) and DBP below 10 mmHg was considered as abnormal responses. The third sympathetic blood pressure reflex test involved sustained isotonic handgrip at about 30% of normal maximum strength using the dominant hand. Abnormal value was a drop in DBP below 15 mmHg.

Data analysis

The data obtained were analysed using the Statistical Package for Social Sciences (SPSS) computer soft ware version 14. Simple frequency distribution table was constructed. Mean was used as summary index, while the standard deviation was used as an index of variation. Student *t*-test was used to assess for difference between means of continuous variables. Chi square was used to test association between discrete variables. *P* value of 0.05 or less was taken as statistically significant.

RESULTS

Baseline characteristics of the study group are presented in Table 1. The mean age of sickle cell patients (25.1 ± 6.0 years) studied was similar ($P > 0.05$) to that of the controls (26.3 ± 5.1). However, the mean haemoglobin concentration of the patients was significantly ($P = 0.001$) lower than that of the controls' haemoglobin level. Similarly, the anthropometric parameters (weight, height and body mass index) were reduced ($P = 0.002$, 0.0001 and 0.03, respectively) in the patients when compared with the controls. The mean heart rate of the patients at rest was 84 ± 12 beats/minutes which was higher ($P = 0.003$) than that of the controls (76 ± 11). Although, SBP and DBP were normal in the two groups, both were significantly higher ($P = 0.04$ and 0.001, respectively) in patient than control group.

Mean QTc which was 457 ± 33 ms in sickle cell patients was significantly higher ($P = 0.001$) than the mean QTc of the controls (399 ± 24 ms). Similarly, mean QTcd was higher ($P = 0.0010$) in the former (78 ± 15 ms) than in the latter (46 ± 12 ms). 57.5% of the patients against 15.9% of controls had prolongation of QTc ($P = 0.0001$).

CAN was present in 21 (53%) sickle cell patients compared with four (9%) controls who had autonomic dysfunction ($P = 0.0001$). Mean QTc in patients with CAN

Table 1: Baseline characteristics of the study group

Characteristics	SCA patients (*n*=40) Mean (SD)	Controls (*n*=44) Mean (SD)	*P* value
Age (years)	25.1 (6.0)	26.3 (5.1)	>0.05
Haemoglobin (gm/dl)	8.4 (2.4)	13.1 (0.9)	0.001*
Weight (Kg)	51.6 (11.1)	62.4 (12.5)	0.002*
Height (M)	1.6 (0.1)	1.7 (0.1)	0.0001*
Body mass index (Kg/m^2)	19.1 (3.2)	21.8 (4.2)	0.03*
Heart rate (beats/min)	84 (12)	76 (11)	0.003*
Systolic BP (mmHg)	123 (11)	116 (14)	0.04*
Diastolic BP (mmHg)	79 (8)	68 (11)	0.001*
QTc (ms)	457 (33)	399 (24)	0.001*
Prolongation (number, %)	23 (57.5)	7 (15.9)	0.0001*
QTcd	78 (15)	46 (12)	0.001*

BP – Blood pressure; QTc – Corrected QT interval; QTd – QT Dispersion; *statistically significant

was longer than patients with normal autonomic function (461 ± 26 ms versus 411 ± 23 ms), *P* = 0.001 (OR of 17.1, CI 3.48-83.71). Similarly, QTcd was higher in patients with CAN (96 ± 26 ms) than those with normal cardiac autonomic function (57 ± 25 ms), *P* = 0.001 (OR of 10.2, CI 3.22-43.52). Strong correlations were found between CAN with QTc and QTcd (r = 0.604, *P* = 0.001, r = 0.523, *P* = 0.001, respectively).

On the other hand, both QT parameters were similar in controls with and without CAN (*P* > 0.05) as shown in Table 2.

DISCUSSION

It is well known that SCD in its homozygous form (HbSS) confers risk of sudden unexpected death (SUD). This study evaluated some of the factors that have been linked with SUD in sickle cell patients. Our results show that the mean QTc and QTcd were higher in sickle cell patients than in the controls. These findings are similar to reports by previous studies which evaluated QT parameters in sickle cell patients.[8,9,20] Twenty-three (57.5%) individuals with SCA and seven (15.9%) controls had QTc prolongation. The prevalence in our study is higher than the report by Liem *et al.,*[8] which showed that 38% of children and young adults in Chicago with SCA had QTc prolongation. Unlike our study, Liem *et al.,* used the same cut-off value for both males and females which may misclassify some of their male patients.[8] Lengthening of QTc and increased QTcd had been associated with risk of ventricular tachyarrhythmias, cardiac arrest and sudden death.[21] This is due to prolongation and inhomogeneity of ventricular repolarisation which is a harbinger for arrhythmias. Similarly, some studies have associated QTc prolongation and QTcd to pulmonary hypertension and chronic transfusion which are common in SCA.[9,22,23]

On the autonomic function assessment, 23/40 (53%) sickle cell patients had autonomic dysfunction while only 4/44 (9%) controls had CAN. This shows that CAN occurs in SCA and is suspected to be a risk for SUD in this group of patients. This is similar to report by Romero-Mestre *et al.,* who found the prevalence of autonomic dysfunction in SCA patients to be 58.3%.[11] Functions of the parasympathetic arm of the cardiovascular autonomic system appeared to be more impaired than those of the sympathetic arm. The involvement of autonomic dysfunction as a possible cause of SUD has been reported in many diseases and this may also imply in SCA.[17,24]

Table 2: Cardiac autonomic function and QT parameters in SCA and Controls

Subjects	CAN present	CAN absent	*P* value	OR, CI
Sickle cell anaemia				
Number (%)	21 (53)	19 (47)		
QTc Mean(SD)	461 (26)	411 (26)	0.001*	17.1, 3.48-83.7
QTcd Mean(SD)	96 (26)	57 (25)	0.001*	10.2, 3.22-43.5
Controls				
Number (%)	4 (9)	40 (91)		
QTc Mean (SD)	408 (22)	392 (22)	>0.05	
QTcd Mean (SD)	46 (16)	45 (15)	>0.05	

CAN – Cardiac autonomic neuropathy; QTc – Corrected QT interval; QTd – QT Dispersion; SD – Standard deviation; OR – Odd ratio; CI – Confidence interval; *statistically significant

Significantly, when mean QTc and QTcd of our patients with CAN were compared with those without CAN, both parameters were increased in the former than the latter. Strong correlations were found between QTc and QTcd with CAN (r = 0.604, *P* = 0.001, r = 0.523, *P* = 0.001, respectively). To the best of our knowledge, there are no studies that evaluated the relationship between cardiac autonomic dysfunction and QT parameters in SCA in our environment. However, some workers have shown direct linear relationship between the extent of CAN and QTc interval in patients with epilepsy and type 2 diabetes mellitus.[25-27] In a study involving type 2 diabetic patients by Kumhar *et al.,* and Kahn *et al.,* strong correlations were found between QT parameters and cardiac autonomic dysfunction.[12,26,27] Incidentally, one of the patients studied by Kahn *et al.,* who had both cardiac autonomic dysfunction and prolonged QTc died unexpectedly. Furthermore, our findings have significant clinical implications because the presence of chronic anaemia (hypoxia) in the presence of CAN favouring unopposed sympathetic activation with abnormalities of ventricular repolarisation predisposes to ventricular electrical instability and increased risk of cardiac arrhythmias.

Sickle cell patients commonly experience crises which may be life threatening and in some instances cause SUD. However, our study was carried out in "steady state" when they were free of crises. Nevertheless, subclinical vaso-occlusion has been reported in SCA in "steady state" which is associated with varying degree of damage to microcirculation in different organs including nervous tissues and the heart.[28] This may explain why CAN and abnormalities of QT parameters occur simultaneously in this group of patients. In addition, Post mortem studies in patients with SCA had demonstrated abundant foci of old and new degeneration in the sinus node, atrioventricular node and Bundle His, with foci of fibrosis and fibromuscular dysplasia leading to narrowing of many small coronary arteries.[29] These abnormalities are suggestive of electrical instability of the heart as one of the terminal events in some individuals with SCA.

In conclusion, QTc prolongation and increased QTcd are common findings on electrocardiogram in sickle cell patients. Cardiac autonomic dysfunction is a risk factor for abnormalities of QT parameters in our SCA patients and both may be harbinger for cardiac arrhythmias and SCD.

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