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Clinical and Laboratory Correlates of QTc Duration in Adult and Pediatric Sickle Cell Disease

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Abstract

Background: Sickle cell disease, a common genetic disorder in African Americans, manifests an increased risk of sudden death, the basis of which is incompletely understood. Prolongation of heart rate–corrected QT (QTc) interval on the electrocardiogram, a standard clinical measure of cardiac repolarization, may contribute to sudden death by predisposing to *torsades de pointes* ventricular tachycardia.

Methods: We established a cohort study of 293 adult and 121 pediatric sickle cell disease patients drawn from the same geographic region as the Jackson Heart Study (JHS) cohort, in which significant correlates of QT duration have been characterized and quantitatively modeled. Herein, we establish clinical and laboratory correlates of QTc duration in our cohort using stepwise multivariate linear regression analysis. We then compared our adult sickle cell disease data to effect-size predictions from the published JHS statistical model of QT interval duration.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

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Results: In adult sickle cell disease, gender, diuretic use, QRS duration, serum ALT levels, anion gap, and diastolic blood pressure show positive correlation; hemoglobin levels show inverse correlation; in pediatric sickle cell disease, age, hemoglobin levels, and serum bicarbonate and creatinine levels show inverse correlation. The mean QTc in our adult sickle cell disease cohort is 7.8 milliseconds longer than in the JHS cohort, even though the JHS statistical model predicts that the mean QTc in our cohort should be > 11 milliseconds shorter than in the much older JHS cohort, a differential of > 18 milliseconds.

Conclusion: Sickle cell disease patients have substantial QTc prolongation relative to their age, driven by factors some overlapping, in adult and pediatric sickle cell disease, and distinct from those that have been defined in the general African American community.

Keywords

QRS; QT; QTc; Repolarization; Sickle

Introduction

Sickle cell disease is a common genetic disorder in African Americans. Despite many advances in the management, sickle cell disease patients continue to have a reduced life expectancy with a median survival of about 40 years, similar to that in historical registry studies. [1] One contributor to early mortality in sickle cell disease is an increased risk of sudden death, the basis of which is not well understood. [1,2] A better understanding of the factors responsible for sudden death in sickle cell disease is urgently needed, [2] to improve long-term outcomes for these patients.

Heart rate–corrected QT (QTc) interval on the electrocardiogram (ECG) is a standard clinical marker for assessing duration of cardiac repolarization. QTc prolongation is a risk factor for sudden death in the general population, and an independent predictor of sudden death in sickle cell disease. [1–3] An abnormal degree of QTc interval prolongation may contribute to sudden cardiac death, by predisposing to a potentially fatal form of ventricular tachycardia known as *torsades de pointes*. [4,5] Several pioneering studies, of adult and/or pediatric patients with sickle cell disease, have reported an increased risk of QTc prolongation [3,6–10] Among these studies, several possible clinical and laboratory correlates of QTc duration have been identified, including inpatient status, hemoglobin or hematocrit levels, aspartate aminotransferase (AST) levels, pulmonary hypertension, echocardiographic tricuspid regurgitation jet velocity, and sickle hemoglobin genotype. However, a full understanding of the factors affecting QTc interval in sickle cell disease has been hampered by differences in study designs (cross-sectional, casecontrol, retrospective), sample sizes (from 73 to 224), age groups (pediatric and/or adult), clinical contexts (outpatient, hospitalized), varying exclusion criteria, and multiple studies lacking a control or reference population comparison. Therefore, the magnitude of, clinical implications of, and factors affecting, QTc prolongation in sickle cell disease remain uncertain. In other contexts, addressing such factors affecting QTc can have important clinical implications; for example, it has been reported that drug-induced QT prolongation can be a leading cause of new drug rejection by the FDA, and that QT prolongation of 5–10 ms has led to removal of drugs from the market, [11,12] and current FDA guidance for drug studies states that a QTc

effect of 5 ms is “the QTc threshold of regulatory concern. ”[31] Improved understanding of QTc prolongation in sickle cell disease could likewise have important clinical implications, for decreasing the early mortality in these patients.

We have established a cohort study of 414 African American patients with sickle cell disease, including 293 adult patients and 121 pediatric patients 11–17 years old, followed in the adult, pediatric, and transition Sickle Cell Clinics at the University of Mississippi Medical Center (UMMC) in Jackson, Mississippi; this cohort was developed to investigate interactions between common genetic variants and other clinical and laboratory QTc-prolonging factors in adult and pediatric sickle cell disease patients.

Comparison with published normative means of groups within epidemiological studies can be valuable in evaluating sickle cell disease cohort data. For example, comparison of blood pressure data in sickle cell disease patients (predominantly African American) in the Cooperative Study of Sickle Cell Disease cohort with the normative group mean blood pressure values, of age- and gender-stratified groups of African Americans within the National Health and Nutrition Examination Survey I and II studies, allowed the clinical definition of “relative hypertension ” in sickle cell disease. [13] Our sickle cell disease cohort is drawn from the same community and geographic region as the Jackson Heart Study (JHS), a study of cardiovascular risk factors in a large community-based cohort of adult African Americans in Mississippi. [14,15] In the JHS, significant independent correlates of QT interval duration have been characterized and quantitatively modeled. [15] Therefore, the JHS represents a valuable epidemiological comparison group, with an established statistical QT model, with which to evaluate QTc duration in our sickle cell disease cohort.

Herein, we establish the baseline clinical and laboratory correlates of QTc duration in our sickle cell disease cohort, both in univariate analysis and stepwise multivariate linear regression models. In addition to the QTc interval, we also evaluate its two subcomponents: QRS duration and the JTc interval. [16–18] We compare our data to published JHS data, within the framework of approximate effect-size predictions from the JHS statistical model of QT duration, [15] to provide insights into QTc prolongation in sickle cell disease adults with the general adult African American community.

Methods

We performed a cross-sectional study of pediatric and adult sickle cell disease patients, in steady state, followed in the adult, pediatric, and transition Sickle Cell Clinics at the UMMC; all adult patients signed informed consent, and all pediatric patients had a parent/guardian sign informed consent with patient signed assent if indicated; the protocol was approved by the Institutional Review Board at UMMC. Adult patients were defined as age ≥ 18 years, and pediatric patients defined as age < 18 years, on the day of the study ECG and laboratory measurements; we recruited down to age 11 years old. Patients with the HbSS, HbSC, and HbS/β-thalassemia (HbS/β; both HbS/β^{0} and HbS/ β^{+}) genotypes of sickle cell disease were included. Exclusion criteria included patients with acute illness or vasoocclusive crisis requiring hospitalization within the prior 2 weeks; patients with bundle branch block, pacemaker, or arrhythmia; and patients unable to give consent. Patients on

defined QT-altering medications were excluded, based on the approach done in the JHS. [15] Categorical prolonged-QTc was defined as >440 ms for pediatric patients, and >450 ms and >460 ms in adult men and women, respectively. [8,18–20,32,33]

Laboratory and ECG Measurements

Each participant underwent a supine, clinical 12-lead ECG, done at standard paper speed of 25 mm/s, using the Bazett correction to calculate QTc, [15,18] during a regular clinic visit, at which all other clinical data collection, and laboratory studies, were done (all adult patients attended a morning clinic; pediatric patients had morning or afternoon clinics). Laboratory values utilized for analyses were those routinely measured at Sickle Cell Clinic visits, with the exceptions of magnesium and phosphorous, which were measured due to their known association with QTc duration. The QT interval measurements were performed manually with calipers in blinded fashion by 2 independent cardiologists (1 adult and 1 pediatric, after cross-training for respective age groups); we determined the percentage difference between the 2 measurements, and if <10%, the average was used as the study value, but if ≥10%, a third cardiac electrophysiologist performed these measurements in a blinded fashion, and then the closest 2 measurements were averaged (after assuring that they had < 10% difference); JTc was calculated based on the formula: JTc = QTc – QRS.

Statistical Analysis

The Shapiro-Wilk test was used to test if the observations deviated from a normal distribution. QTc for the adult cohort followed a normal distribution ($P = .3396$); QTc for the pediatric cohort deviated significantly from a normal distribution ($P = .0006$); QTc for the combined (adult + pediatric) cohort followed a normal distribution ($P = .01127$).

Descriptive Statistics

Subjects were grouped into adult (age ≥ 18 years) and pediatric (age < 18 years). Each age group was grouped as male and female. Basic descriptive statistics for subject data were expressed as a combined (adult + pediatric) data baseline table, and separate adult data baseline and pediatric data baseline tables. Continuous variables were presented as mean and standard deviation; categorical variables were presented as frequency and percentage.

Univariate Analysis

Pearson's correlation coefficients (r) and Spearman's rank correlation coefficient (ρ) were calculated to assess the link and the degree of relationship between variables. We computed and examined the correlations between each factor in the baseline tables and displayed them in correlation matrices. Significant coefficients were marked according to the specified p-value significance level in plot matrices. Univariate regression analyses were performed to identify association between QTc and associated factors. To explore the relationship of each clinical factor individually with QTc interval, the linear regression model included QTc as dependent variable (Y), and each clinical factor (along with age and sex, as done in the JHS [15]) as independent factors (X).

Multivariate Analysis

Multiple linear regression analyses were performed to identify baseline demographic and clinical characteristics associated with QTc. We preselected variables with $P < .15$ from the univariate regression analyses and included them in the multiple linear stepwise regression analyses. We compared several methods of multivariate linear regression analysis, including traditional stepwise methods, [15] both forward and backward, and also a machine learning method (LASSO).

The forward stepwise linear regression model started by adding each preselected variable ($P < .15$ in univariate analysis) one by one until there were no remaining variables. The backward stepwise method involved starting with all preselected variables and then removing the least significant variable remaining, one by one. For both stepwise methods, we considered the t statistic for the coefficients of each variable, and Akaike information criterion (AIC) values and R-squared (R^2) for the models. The variance inflation factor (VIF) was used to evaluate the presence of multicollinearity. Models were tested for colinearity issues and residual plots were evaluated with no serious problems detected (VIF < 5).

We used four different diagnostic graphs to evaluate each model's residuals. And we consider R^2, p-values of F test, AIC, standard error of the model, Durbin Watson Test, and Residual Normality Test to select our best models. Then the model (R^2 = xxx, P = xxx) was selected as the best-fitting model for the adult or pediatric group. We calculated the partial R^2 for each variable in our best model; the variable with higher partial R^2 explains more of the QTc variance in the model; partial R^2 has a positive relationship with the variable's importance.

All statistical analyses were performed using R version 3.5.2.

Results

Baseline characteristics of our overall cohort are presented (Table 1), as are a comparison of these characteristics in male and female participants within the adult and pediatric subcohorts (Table 2). Overall, 71.5% were genotype HbSS, 19.6% genotype HbSC, and 8.7% genotype HbS/β; overall, the mean hemoglobin level was 9.40 g/dL, including 9.42 g/dL for adults and 9.34 g/dL for pediatric. Overall, 21% of our sickle cell disease cohort met the definition of categorical prolonged-QTc, including 15.7% of adults and 33.9% of pediatric patients. Based on evaluation of reported clinical diagnoses, were no apparent cases of a personal or family history of hereditary long-QT syndrome, a relatively rare disorder, [33] in our cohort.

Some variables showed significant ($P < .05$) male-female sex differences within the adult and pediatric cohorts. Within the adult sickle cell disease cohort, there were significant male-female differences in heart rate, QTc interval, QRS duration, JTc interval, systolic blood pressure, history of deep-vein thrombosis and/or pulmonary embolism (DVT/PE), hydroxyurea use, and hemoglobin level and mean corpuscular volume (MCV), absolute reticulocyte count, and serum levels of bicarbonate, creatinine, lactate dehydrogenase

(LDH), total bilirubin, globulin, potassium, AST, and alanine aminotransferase (ALT) (Table 2). The mean QT intervals are nearly identical between male and female adult sickle cell disease patients, although the mean QTc interval in females is longer by 15.03 ms ($P < .0001$), associated with their higher heart rate. The longer QTc in females does not fully reflect their more prolonged repolarization, given that mean QRS duration is shorter in females by 6.16 ms ($P < .0001$), but mean JTc interval (a more direct measure of repolarization duration) is thereby longer in females by 21.19 ms ($P < 0001$).

Univariate Analyses

In univariate analysis, multiple factors showed significant association with QTc duration in adult and pediatric sickle cell disease patients (Tables 3A and 3B); these tables show factors displaying significance to $P < .15$, since this cutoff was used for inputs into multivariate linear regression models. Univariate analysis found that 25 clinical, laboratory, and ECG variables display significance to $P < .05$ in the adult cohort and 8 clinical, laboratory, and ECG variables display significance to $P < .05$ in the pediatric cohort.

Multivariate Analyses

We next performed multivariate linear regression analysis, including forward stepwise, backward stepwise, and LASSO machine learning. We chose the backward stepwise models to proceed with further analyses, since percent variance explained (R^2) was the highest with this model (Supplemental Table 1, available online). In backward stepwise analysis of the adult cohort (Table 4), the following 7 factors, with their corresponding percent variation explained (partial R^2), showed significant, independent association with QTc duration: female sex (8.0%), diuretic use (6.6%), hemoglobin level (5.1%), anion gap (4.0%), ALT level (3.2%), QRS duration (3.1%), and diastolic blood pressure (1.7%), for a total of 31.9% of variation explained. The hemoglobin association was negative, indicating QTc prolongation with greater degrees of anemia. Because the diuretic effect is determined by only 6 adult patients taking diuretics, we repeated the analysis with these 6 patients excluded, and there is approximately a 1 ms difference in QTc interval (432 ms vs 431 ms with diuretics excluded); and diastolic blood pressure falls out of significance, while chloride levels reach significance, when diuretics are excluded from the analysis (XY and JFM, unpublished observation). In backward stepwise analysis of the pediatric cohort (Table 4), the following 4 factors, with their corresponding percent variation explained (partial R^2), showed significant, independent association with QTc duration: serum creatinine level (10.8%), serum bicarbonate (9.4%), age (8.9%), and hemoglobin level (7.1%), for a total of 36.2% of variation explained (we note that the optimal pediatric model, with optimal AIC and SE, includes hemoglobin, even though $P = .0729$); all 4 of the pediatric associations had negative values.

Comparison with the JHS Cohort

To better understand QTc data of our adult sickle cell disease cohort within the broader context of QTc regulation in the general adult African American community, we compared our data to the JHS data. [15] Because our combined (pediatric + adult) data, our adult data, and the JHS data each fits a normal distribution, we were able to compare the mean ± SD for statistical significance ($P < .05$). The mean QTc in our combined sickle cell disease cohort

(431.8 ms) is longer, by 7.5 ms ($P < .0001$), than the mean QTc in the JHS cohort (424.3 ms). The mean QTc of our adult sickle cell disease cohort (432.1 ms) is longer than the mean QTc in the JHS cohort by 7.8 ms ($P < .001$). There were 3 individuals, or 1.024% of our adult cohort, with a QTc > 500 ms, which is the level at which the risk of *torsades de pointes* ventricular tachycardia is generally thought to increase and is not significantly different from the JHS cohort having 0.44% with QTc > 500 ms ($P = .152$); in our pediatric cohort there were no patients with QTc > 500 ms, which gives an overall of 0.7% with QTc > 500 ms for our combined adult + pediatric cohort.

We compared our adult sickle cell disease cohort data to 9 of the 10 independent, significant covariates associated with QT interval duration in the multivariate regression model of QT in the JHS (Table 3 within Ref. [15]; we did not collect data on the 10th covariate, Sokolow-Lyon voltage correlate of left ventricular mass). There are significant differences in these factors between adult sickle cell disease patients and the general African American community (Table 5), with our adult cohort displaying shorter R-R interval (0.795 s vs 0.956 s in JHS); younger age (31.08 years vs 54.14 years in JHS); closer to equal numbers of males and females (51.0% female vs 63.5% female in JHS); shorter QRS duration (90.05 ms vs 91.89 ms in JHS); less systemic hypertension (22.18% vs 60.33% in JHS); leaner body mass (body mass index of 26.02 kg/m ^{2} vs 31.64 kg/m ^{2} in JHS); less coronary heart disease (2.05% vs 5.57% in JHS); and less diuretic use (2.0% vs 20.5% in JHS), all of which would predict that the QT interval our adult sickle cell disease cohort should be substantially shorter than in the community-based JHS; only lower potassium levels (4.12 mmol/L vs 4.27 mmol/L in JHS) would predict a QT duration longer in our adult cohort, by 0.77 ms, than in the JHS. In sum total, the JHS model predicts that the QT interval in our adult sickle cell disease cohort should be shorter, by 44.52 ms, compared with the mean QT interval in the JHS (combined male + female) cohort (413.17 ms); however, the actual mean QT interval in our adult cohort (386.5 ms) is 17.8 ms higher than that predicted (368.7 ms) by the JHS model.

We next applied heart rate correction to the group mean QT interval of our adult sickle cell disease cohort, to give a predicted mean QTc interval (413.28 ms), which is shorter, by 18.82 ms, than the actual mean QTc interval of our adult sickle cell disease cohort (432.1 ms). The predicted mean QTc interval of our adult cohort (413.28 ms) is shorter, by 11.02 ms, than the mean QTc interval of the JHS cohort (424.3 ms), even though, as noted above, the actual mean QTc interval of our adult cohort (432.1 ms) is 7.8 ms higher than the mean QTc of the much older, more female-weighted, and more overweight/obese JHS cohort.

Comparison Using Fridericia Correction

As noted above, our study utilized the Bazett correction for heart rate, given that this correction was utilized in the JHS, [15,18] and by the clinical ECG machines in our institution. However, the Fridericia correction (QTc^F) is an alternative correction method and has been used for comparison purposes in JHS analyses. [18] We applied the QTc^F to the actual, and the JHS model-predicted, mean QT intervals of our adult sickle cell disease cohort, and to the JHS cohort. The JHS model-predicted QTc^F interval in our adult cohort (398.11 ms) is shorter, by 21.35 ms, than the mean QTc^F interval in the JHS cohort (419.46 ms). However, the actual mean QTc^F interval in our adult cohort (417.55) is 19.44 ms higher than that

predicted (398.11 ms) by the JHS model and is only 1.91 ms shorter than the mean QTc^F of the JHS cohort, indicating “relative ” QTc prolongation in adult sickle cell disease when using the QTc^F.

Discussion

Herein, we present baseline clinical and laboratory characteristics of our prospectively recruited, cross-sectional sickle cell disease cohort. This study is the largest reported to date on prolongation of QTc in sickle cell disease, and our patients were in as close to a baseline state as is possible for sickle cell disease patients who attend our outpatient clinics on a regular basis.

We establish that patients with sickle cell disease, at baseline clinical status, have QTc interval prolongation, compared with the general African American community as represented by the JHS cohort. This is true even though our adult cohort is much younger than the adult JHS cohort and has multiple other features (leaner, less hypertension, less diuretic use, less coronary heart disease, and shorter QRS durations), which would predict shorter QTc intervals compared with the JHS cohort (Table 5), based on the JHS quantitative QT statistical model.[15] This demonstrates that there are factors, distinct from those regulating QT interval duration in the general African American population, responsible for QTc interval prolongation in sickle cell disease. The QTc analyses presented herein, by univariate analysis and multivariate linear regression modeling, provide evidence for a number of these factors in sickle cell disease (Table 4): ALT levels, hemoglobin levels, anion gap, and diastolic blood pressure in adult sickle cell disease; and creatinine levels, bicarbonate levels, and hemoglobin levels in pediatric sickle cell disease. Future investigations will further characterize the QTc interval–associated factors described herein, to attempt to better understand the mechanisms by which they affect repolarization. We will also investigate their interaction with genetic variants known to modify QT interval duration in the African American population.

The 15.7% of our 293 sickle cell disease adults (11.8% of males, 19.5% of females) meeting the definition of categorical prolonged-QTc is similar to the 15% on initial screening, but lower than the 37.9% at the end of follow-up, in the retrospective study of 140 sickle cell disease adults of Upadhya et al.,[3] although that study utilized a longer definition for categorical prolonged-QTc in adult females (>470 ms) than utilized for our adult females (>460 ms). The 15.7% categorical prolonged-QTc in our adult cohort is also lower than the 39% of males, and 27% of females, in the retrospective study of 224 sickle cell disease adults by Indik et al.,[9] although that study utilized a shorter definition (>440 ms) for categorical prolonged-QTc in adult males than utilized for our adult males (>450 ms), and 58% of their ECGs were obtained on inpatients. In the study of Indik et al., QTc duration was associated with hemoglobin and AST levels in univariate analysis, but not multivariate analysis [9]; in our adult cohort both hemoglobin and AST levels were significant in univariate analysis, and hemoglobin level remained significant in multivariate analysis.

The 33.9% of our 121 pediatric sickle cell disease patients (11–17 years old) meeting the definition of categorical prolonged-QTc is similar to the 38% reported for 76 sickle cell

disease children and young adults (10–24 years old) in the cross-sectional study of Liem et al., [8] in which categorical prolonged-QTc was associated, in univariate analysis, with multiple episodes of acute chest syndrome and with higher mean LDH and AST levels; however, in our pediatric cohort the association of QTc duration with acute chest syndrome and LDH levels was not significant in univariate analysis. Multivariate linear regression in our pediatric cohort showed age, creatinine, bicarbonate, and hemoglobin to be significant and negatively correlated with QTc duration. A case-control study from Nigeria showed a negative correlation with hematocrit level in 62 pediatric sickle cell disease patients compared to 40 age- and gender-matched controls. [10] The mechanism for the negative correlation of serum creatinine with QTc in our pediatric cohort is un-known; we speculate that it may be related to lower muscle mass, and/or glomerular hyperfiltration, known to occur in sickle cell disease patients from a young age. [21,22]

As noted above, we used the Bazett formula, which has been widely used in clinical electrocardiography, for heart rate correction in calculating QTc. Different heart rate adjustment methods for the QT interval, such as Fridericia, Framingham, Hodges, and others, have been proposed, but in general, it is often unclear whether any given method is optimal for any given patient or clinical context, and the Bazett correction continues to be recommended in hereditary long-QT syndrome and other contexts. [5,20,23–25] Herein, even if using the Fridericia correction for heart rate, where the adult sickle cell disease cohort has nearly the same mean QTc^F as the JHS cohort (<2 ms difference), the JHS model predicts that the mean QTc^F should be >21 ms shorter in our adult cohort. Therefore, just as adults with sickle cell disease have “relative ” hypertension compared with the general African American population, [13] our adult sickle cell disease cohort has “relative ” QTc prolongation, compared with the general African American population, when using the Fridericia correction.

Limitations

This study has several limitations. We evaluated QT and QTc interval duration, given that these are the standard ECG measures of repolarization used in clinical medicine. However, there are other aspects of repolarization, such as QT dispersion, Tp-e interval and Tp-e/QTc ratio, and other measures that also provides insight into repolarization defects in sickle cell disease. [5,26,27] We evaluated the QTc interval at a single point in time, as close to a baseline condition for sickle cell patients as possible, and longitudinal assessment will be valuable. [28,29] The retrospective analysis by Upadhya et al. [3] noted above, with a mean follow-up of 9 years, indicated that mortality in sickle cell disease is associated with increase in QTc interval duration with time; it is un-known whether any of this mortality was associated with *torsades de pointes* ventricular tachycardia.[3] We plan to do prospective follow-up of our sickle cell cohort to include evaluation of the relationship between QTc interval duration and mortality. The basis of the large difference in diuretic effect size of 44.7 ms with diuretic use in our adult cohort (Table 4), compared with an effect size of 2.3 ms with diuretic use in the JHS cohort (Table 5; and Table 3 within Ref.[15]), requires further analysis, and replication in other studies; however, even with this large difference, the effect results in only < 1% (0.43 ms of 44.52 ms) of the predicted QT difference between the JHS and our adult sickle cell disease cohort (Table 5). Furthermore, we recognize that the JHS did not

evaluate as broad a range of clinical and laboratory variables for inclusion into their QT statistical model—such as hemoglobin, ALT, or anion gap—as did we; however, we feel that given the JHS is a community-based cohort, where the degrees of anemia, and comorbidities such as iron overload with hepatic dysfunction, would not be near the degree present in our adult sickle cell disease cohort, these factors would not likely have a major influence on the comparison of QT/QTc between our two cohorts, although it would be of interest to ascertain the effects of the nonoverlapping factors from our statistical model (Table 4) on the JHS model. Lastly, even with improved characterization of QTc prolongation in sickle cell disease, the clinical significance of this remains uncertain. Although both clinical studies and autopsy studies demonstrate the importance of sudden death and ventricular arrhythmias in sickle cell disease mortality,[2] there remains very limited specific information on *torsades de pointes* ventricular tachycardia in sickle cell disease.[30]

Conclusion

Our study demonstrates that sickle cell disease is associated with substantial QTc prolongation present even in young patients and has further defined significant clinical and laboratory correlates, some overlapping and some distinct, in adult and pediatric sickle cell disease, and distinct from those that have been defined in the general African American community. Our sickle cell disease cohort, which also includes DNA samples and is developing an echocardiographic dataset, provides a resource for further investigation of the relationship between clinical, laboratory, imaging, and genetic factors and QTc prolongation in sickle cell disease patients. This will promote better standing, and improved management, of factors contributing to sudden cardiac death and premature mortality in sickle cell disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline Characteristics of Combined Sickle Cell Disease Cohort.

Characteristic (*n* = 414)	Mean (SD) *or n* (%)
Age (years)	26.24 (11.51)
Gender—female	203 (49.0)
—male	211 (51.0)
Genotype SS	296 (71.5)
Genotype SC	81 (19.6)
Genotype S/β-thalassemia	36 (8.7)
Heart rate (bpm)	76.75 (13.39)
QT (ms)	382.19 (30.94)
QTc (ms)	431.79 (25.86)
QRS (ms)	89.01 (9.70)
JTc (ms)	342.78 (26.65)
Prolonged-QTc	87 (21.0)
QTc > 500 ms (%)	3 (0.7)
BMI (kg/m^2)	24.91 (6.83)
Systolic blood pressure (mm Hg)	118.30 (13.75)
Diastolic blood pressure (mm Hg)	69.42 (10.15)
Pulmonary hypertension	17 (4.1)
Acute chest syndrome	74 (17.9)
Stroke/TIA/abnormal-TCD	94 (22.7)
DVT/PE	53 (12.8)
Avascular necrosis	98 (23.7)
Leg/ankle ulcers	5 (1.2)
Sickle retinopathy	96 (23.2)
Hydroxyurea use	235 (56.8)
Diuretic use	6 (1.4)
Opioid medication use (nonmethadone)	330 (79.7)
Chronic RBC transfusions	73 (17.6)
Transfusional iron overload	151 (36.5)
Chelation (Exjade, Jadenu, Desferal)	96 (23.2)
Ferritin (ng/mL)	15,972,458
Ferritin >1000 ng/mL	149 (37.2)
WBC (×1000/μL)	10.98 (4.20)
Platelets (×1000/μL)	367.30 (159.01)
Abs. Reticulocyte count (×1000/μL)	256,186 (121,963)
Hemoglobin (g/dL)	9.40 (1.94)
MCV (fL)	86.65 (12.23)
Potassium (mmol/L)	4.15 (0.44)
Magnesium (mg/dL)	1.94 (0.18)
Calcium (mg/dL)	9.27 (0.40)

Characteristic (*n* = 414)	Mean (SD) *or n* (%)
Phosphorous (mg/dL)	3.99 (0.84)
Chloride (mmol/L)	104.27 (3.08)
Bicarbonate (mmol/L)	24.13 (2.54)
Anion gap (mmol/L)	12.12 (2.17)
Glucose (mg/dL)	100.01 (29.69)
Albumin (g/dL)	4.41 (0.37)
Total protein (g/dL)	7.80 (0.63)
Globulin (g/dL)	3.38 (0.54)
LDH (U/L)	604.11 (437.65)
Total bilirubin (mg/dL)	2.68 (2.20)
AST (U/L)	39.37 (22.41)
ALT (U/L)	25.65 (16.72)
ALP (U/L)	113.91 (63.83)
Creatinine (mg/dL)	0.79 (1.03)
CKD	17 (4.1)
CKD not on hemodialysis	13 (3.14)
ESRD on hemodialysis	4 (0.97)

Baseline clinical and laboratory characteristics of combined adult and pediatric sickle cell disease cohort.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; bpm = beats per minute; CKD = chronic kidney disease; DBP = diastolic blood pressure; DVT/PE = deep-vein thrombosis and/or pulmonary embolism; ECG = electrocardiogram; ESRD on HD = end-stage renal disease on hemodialysis; fL = femtoliter; g/dL = grams per deciliter; kg/m^2 = kilograms per square meter; LDH = lactate dehydrogenase; MCV = mean corpuscular volume; med. = medication; ms = millisecond; mV = millivolt; μL = microliter; NA = not applicable; ND = not done; RBC = red blood cell; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; TCD = transcranial doppler; U/L = units per liter; WBC = white blood cells.

Table 2

Clinical and Laboratory Characteristics—Males/Females—Adult and Pediatric Sickle Cell Disease Cohorts.

Characteristic	Adult (*n* = 293) Mean (SD) or *n* (%)		*P* value	Pediatric (*n* = 121) Mean (SD) or *n* (%)		*P* value
	Male (*n* = 144)	Female (*n* = 149)		Male (*n* = 67)	Female (*n* = 54)	
Age (years)	30.62 (9.73)	31.53 (10.81)	0.639	14.63 (1.67)	14.36 (1.71)	.377
Genotype SS	106 (73.6)	100 (67.1)	0.276	49 (73.1)	41 (75.9)	.888
Genotype SC	26 (18.1)	32 (21.5)	0.556	14 (20.9)	9 (16.7)	.722
Genotype S/β-thalassemia	11 (7.6)	17 (11.4)	0.369	4 (6.0)	4 (7.4)	1
Heart rate (bpm)	72.87 (12.49)	78.11 (13.84)	<0.0001	78.39 (12.78)	81.31 (12.91)	.194
QT (ms)	386.87 (31.32)	386.43 (33.20)	0.947	372.93 (23.16)	369.53 (26.11)	.363
QTc (ms)	424.43 (26.76)	439.46 (24.79)	<0.0001	427.51 (26.96)	435.57 (17.50)	.115
QRS (ms)	93.18 (9.33)	87.02 (9.45)	<0.0001	88.46 (8.84)	84.09 (8.24)	.014
JTc (ms)	331.25 (25.87)	352.44 (24.44)	<0.0001	339.05 (27.99)	351.48 (19.10)	.008
Prolonged-QTc	17 (11.8)	29 (19.5)	0.101	21 (31.3)	20 (37.0)	.642
QTc > 500 ms	2 (1.4)	1 (0.7)	0.617	0 (0)	0 (0)	NA
BMI (kg/m^2)	24.45 (6.23)	27.52 (6.85)	<0.0001	21.52 (6.19)	23.07 (6.47)	.106
Systolic blood pressure (mm Hg)	120.91 (14.77)	117.06 (14.86)	0.006	118.31 (10.39)	114.77 (10.04)	.120
Diastolic blood pressure (mm Hg)	71.23 (9.92)	72.54 (8.44)	0.246	63.61 (10.48)	63.26 (9.16)	.981
Pulmonary hypertension	5 (3.5)	10 (6.7)	0.321	1 (1.5)	1 (1.9)	1
Acute chest syndrome	29 (20.1)	27 (18.1)	0.771	10 (14.9)	8 (14.8)	1
Stroke/TIA/abnormal-TCD	36 (25.0)	32 (21.5)	0.565	15 (22.4)	11 (20.4)	.963
DVT/PE	18 (12.5)	34 (22.8)	0.031	0 (0.0)	1 (1.9)	.446
Avascular necrosis	42 (29.2)	41 (27.5)	0.854	10 (14.9)	5 (9.3)	.508
Leg/ankle ulcers	4 (2.8)	1 (0.7)	0.208	0 (0)	0 (0)	NA
Sickle retinopathy	41 (28.5)	39 (26.2)	0.756	8 (11.9)	8 (14.8)	.846
Hydroxyurea use	93 (64.6)	69 (46.3)	0.002	38 (56.7)	35 (64.8)	.473
Diuretic use	3 (2.1)	3 (2.0)	1.000	0 (0)	0 (0)	NA
Opioid med. use (nonmethadone)	120 (83.3)	132 (88.6)	0.259	36 (53.7)	42 (77.8)	.011
Chronic RBC transfusions	28 (19.4)	22 (14.8)	0.363	12 (17.9)	11 (20.4)	.913
Transfusional iron overload	60 (41.7)	64 (43.0)	0.917	15 (22.4)	12 (22.2)	1

Characteristic	Adult (*n* = 293) Mean (SD) or *n* (%)		*P* value	Pediatric (*n* = 121) Mean (SD) or *n* (%)		*P* value
	Male (*n* = 144)	Female (*n* = 149)		Male (*n* = 67)	Female (*n* = 54)	
Chelation (Exjade, Jadenu, Desferal)	34 (23.6)	41 (27.5)	0.527	12 (17.9)	9 (16.7)	1
Ferritin (ng/mL)	1847 (2776)	1962 (2697)	0.637	853 (1337)	799 (1284)	.993
Ferritin > 1000 ng/mL	52 (37.4)	69 (46.9)	0.131	17 (27.0)	11 (21.2)	.612
WBC (×1000/μL)	11.13 (4.10)	11.21 (4.62)	0.647	10.44 (3.80)	10.62 (3.69)	.837
Platelets (×1000/μL)	349.42 (150.00)	371.37 (157.79)	0.168	397.78 (179.31)	365.93 (157.02)	.210
Abs. reticulocyte count (×1000/μL)	266,225 (115,981)	237,473 (132,855)	0.031	275,208 (122,671)	258,637 (99,121)	.601
Hemoglobin (g/dL)	9.81 (2.21)	9.05 (1.68)	0.007	9.52 (2.11)	9.11 (1.38)	.494
MCV (fL)	88.79 (10.85)	85.43 (13.41)	0.026	83.48 (11.17)	88.26 (12.56)	0.038
Potassium (mmol/L)	4.23 (0.50)	4.01 (0.41)	<0.0001	4.33 (0.37)	4.12 (0.31)	<.001
Magnesium (mg/dL)	1.96 (0.20)	1.96 (0.19)	0.792	1.90 (0.16)	1.89 (0.14)	.606
Calcium (mg/dL)	9.19 (0.40)	9.19 (0.37)	0.849	9.47 (0.37)	11.08 (11.90)	.656
Phosphorous (mg/dL)	3.65 (0.85)	3.71 (0.57)	0.169	4.84 (0.60)	4.60 (0.63)	.035
Chloride (mmol/L)	103.34 (3.37)	104.05 (2.61)	0.068	105.14 (2.85)	106.28 (2.60)	.030
Bicarbonate (mmol/L)	24.53 (2.55)	23.51 (2.83)	<0.001	24.89 (2.10)	23.83 (1.61)	.003
Anion gap (mmol/L)	12.13 (2.38)	12.55 (1.91)	0.019	11.55 (2.09)	11.62 (2.14)	.981
Glucose (mg/dL)	101.35 (15.77)	102.79 (45.56)	0.130	92.95 (10.34)	96.01 (16.71)	.050
Albumin (g/dL)	4.37 (0.35)	4.29 (0.38)	0.117	4.67 (0.27)	4.55 (0.29)	.049
Total protein (g/dL)	7.59 (0.61)	7.71 (0.58)	0.104	8.21 (0.61)	8.10 (0.52)	.430
Globulin (g/dL)	3.22 (0.57)	3.42 (0.52)	0.001	3.54 (0.54)	3.54 (0.40)	.577
LDH (U/L)	450.50 (238.20)	401.00 (259.20)	0.006	1120.65 (558.13)	971.20 (363.68)	.340
Total bilirubin (mg/dL)	3.03 (2.25)	2.22 (1.90)	<0.001	3.17 (2.84)	2.45 (1.64)	.240
AST (U/L)	37.35 (18.29)	35.71 (26.90)	0.008	51.45 (18.86)	40.21 (17.55)	.001
ALT (U/L)	25.95 (16.67)	22.88 (16.27)	0.028	30.94 (17.56)	26.13 (15.80)	.060
ALP (U/L)	95.63 (50.97)	96.05 (48.72)	0.446	175.12 (75.84)	134.40 (64.30)	.002
Creatinine (mg/dL)	1.13 (1.60)	0.70 (0.54)	<0.0001	0.51 (0.17)	0.45 (0.12)	.074
CKD	10 (6.9)	7 (4.7)	0.567	0 (0)	0 (0)	NA
ESRD on hemodialysis	4 (40.0)	0 (0.0)	0.103	NA	NA	NA

Comparison of baseline clinical and laboratory characteristics in males and females, within the adult and pediatric sickle cell disease cohorts.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; bpm = beats per minute; CKD = chronic kidney disease; DBP = diastolic blood pressure; DVT/PE = deep-vein thrombosis and/or pulmonary embolism; ECG = electrocardiogram; ESRD on HD = end-stage renal disease on hemodialysis; g/dL = grams per deciliter; kg/m^2 = kilograms per square meter; LDH = lactate dehydrogenase; MCV = mean corpuscular volume; med. = medication; ms = millisecond; mV = millivolt; μL = microliter; NA = not applicable; ND = not done; RBC = red blood cell; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; TCD = transcranial doppler; U/L = units per liter; WBC = white blood cells.

Table 3A

Univariate Analysis of QTc Associations—Adults (n = 293).

Characteristics	Estimate	SE	*P* value
JTc	0.955	0.022	<.0001
Heart rate	0.609	0.108	<.0001
Gender	15.029	3.012	<.0001
Diuretic use	49.565	10.315	<.0001
WBC	1.534	0.333	<.0001
QRS (*per* ms)	0.681	0.155	<.0001
Ferritin (*per* ng/mL)	0.002	0.001	<.0001
ALT	0.384	0.090	<.0001
Hemoglobin	2.887	0.759	<.0002
Creatinine	4.654	1.280	<.0004
Chloride	−1.779	0.493	<.0004
Anion gap	2.446	0.690	<.0005
Globulin	9.255	2.720	<.0008
ALP	0.100	0.030	<.0010
AST	0.216	0.065	<.0011
Total bilirubin	1.875	0.740	<.0118
ESRD on hemodialysis	52.239	18.229	<.0133
Age	0.3724	0.1512	<.0145
Genotype SS	7.704	3.256	<.0187
Stroke/TIA/abnormal-TCD	8.160	3.541	<.0220
Chelation (Exjade, Jadenu, Desferal)	7.820	3.405	<.0224
Albumin	−9.771	4.328	<.0248
Phosphorous	4.670	2.088	<.0261
Abs. reticulocyte count	0.000	0.000	<.0301
Chronic RBC transfusions	8.860	4.073	<.0305
Pulmonary hypertension	12.964	6.780	<.0569
Chronic kidney disease	11.943	6.494	<.0670
BMI	0.402	0.231	<.0831
Calcium	−6.814	4.006	<.0901
Genotype SC	−6.070	3.761	<.1077
Platelets	0.016	0.010	<.1149
Hydroxyurea use	4.699	3.062	<.1260
Diastolic blood pressure	0.259	0.170	<.1300
Genotype S/β-thalassemia	−7.638	5.092	<.1348

Univariate analysis of associations between clinical and laboratory characteristics and QTc in the adult sickle cell disease cohort, ranked in descending order of significance, down to $P < .15$; the effect size estimate is per unit for continuous variables, and per presence for categorical variables.

Units and Abbreviations: same as in Table 2.

Table 3B

Univariate Analysis of QTc Associations—Pediatric (n = 121).

Characteristic	Estimate	SE	*P* value
JTc	0.905	0.035	<.0001
Age	−5.938	1.154	<.0001
Creatinine	−54.347	14.089	<.0002
Hemoglobin	−3.882	1.033	<.0003
Bicarbonate	−3.305	1.050	<.0022
Heart rate	0.383	0.152	<.0130
WBC	1.267	0.510	<.0144
Total bilirubin	1.620	0.823	<.0516
Genotype S/β-thalassemia	−14.659	7.662	<.0582
Gender	8.065	4.248	<.0601
Platelets	0.021	0.011	<.0659
QRS duration	0.376	0.230	<.1049
LDH	0.006	0.004	<.1321

Univariate analysis of associations between clinical and laboratory characteristics and QTc in the pediatric sickle cell disease cohort, ranked in descending order of significance, down to $P < .15$; the effect size estimate is per unit for continuous variables, and per presence for categorical variables.

Units and Abbreviations: same as in Table S2.

Table 4

Stepwise Backward Multivariate Linear Regression of QTc Associations.

Group characteristics	Change in QTc			
	(ms)	SE	Partial R^2	*P* value
Adult (*n* = 293)				
Female sex	16.881	3.069	0.080	<.0001
Diuretic use	44.743	9.565	0.068	<.0001
QRS (*per* ms)	0.553	0.149	0.031	.0002
ALT (*per* U/L)	0.298	0.084	0.032	.0005
Hemoglobin (*per* g/dL)	−2.266	0.727	0.051	.002
Anion gap (*per* mmol/L)	1.988	0.668	0.040	.003
Diastolic blood pressure (*per* mm Hg)	0.331	0.160	0.017	.039
Pediatric (*n* = 121)				
Age (*per* year)	−3.005	1.252	0.089	.0181
Creatinine (*per* mg/dL)	−35.344	15.377	0.108	.0235
Bicarbonate (*per* mmol/L)	−2.642	1.064	0.094	.0146
Hemoglobin (*per* g/dL)	−2.112	1.166	0.071	.0729

Univariate analysis of associations between clinical and laboratory characteristics and QTc in the pediatric sickle cell disease cohorts, ranked in descending order of significance, down to $P < .15$; the effect size estimate is per unit for continuous variables, and per presence for categorical variables.

Abbreviations: same as in Table S2.

Table 5

Application of Effect Sizes of Covariates Known to Independently Affect QT Duration in the JHS Model.

Covariate from JHS model	QT change in JHS model (ms)	JHS mean (Ref. [15])	Adult Sickle mean (present study)	*P* value	Predicted QT difference (ms) (JHS – Sickle)
R-R interval (*per* 10 ms)	1.4	956 ms	795 ms	<.001	22.54
Female sex	14.8	63.5%	51.0%	<.001	1.85
QRS (*per* ms)	0.42	91.89 ms	90.05 ms	.002	0.77
Age (*per* year)	0.26	54.14 years	31.08 years	<.001	6.0
Potassium, serum (*per* mmol/L)	−5.1	4.27 mmol/L	4.12 mmol/L	<.001	−0.77
Hypertension	3.0	60.33%	22.18%	<.001	1.14
BMI (*per* kg/m^2)	2.2	31.64 kg/m^2	26.02 kg/m^2	<.001	12.39
Coronary heart disease	4.7	5.57%	2.05%	<.05	0.17
Diuretic use	2.3	20.5%	2.0%	<.001	0.43
Sokolow-Lyon voltage (*per* mV)	1.0	NA	ND	–	–
Total predicted QT difference between JHS and adult sickle cell disease (JHS – Sickle): 44.52 ms					

QT effect size predictions for each independent covariate from the JHS model (Table 3 in Ref. [15]), applied to the corresponding covariates in our adult sickle cell disease (Sickle) data (n = 293), to predict effect size on the QT interval in our adult Sickle cohort—defined as difference in QT between the two cohorts (JHS minus Sickle) for each covariate (mean values for JHS covariates adapted, combining men and women, from in Ref. [15]). P-value for difference of means between JHS and adult Sickle cohorts.

BMI = body mass index; bpm = beats per minute; JHS = Jackson Heart Study; kg/m^2 = kilograms per square meter; mmol/L = millimoles per liter; ms = millisecond; mV = millivolt; NA = not applicable; ND = not done; Sickle = sickle cell disease.