Original Article

Electrocardiographic Changes and Troponin T Levels in Children with Severe Malaria Anemia and Heart Failure

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Abstract

Background: Severe malaria anemia is a major cause of childhood heart failure in malaria endemic countries. The resulting hypoxic-ischemic injuries may cause myocardial damage detectable by electrocardiogram (ECG) and elevated troponin T (cTnT) levels. **Objective:** Evaluate the ECG changes and cTnT levels in children with severe malaria anemia compared with those who had uncomplicated malaria without anemia. **Methods:** Consecutive children with severe malaria anemia were recruited as subjects while controls were age- and gender-matched children with uncomplicated malaria without anemia. ECG findings, cTnT levels, and the proportion of children with elevated cTnT were compared between subjects and controls. **Results:** There were 43 subjects with a mean age of 25.7 ± 22.9 months. Controls were forty children; mean age was 31.2 ± 20.0 months. All the subjects and 10 (25.0%) controls had ECG abnormalities. Five (11.6%) subjects and no control had ST segment changes, $P = 0.06$. Twenty-three percent of subjects compared to 5% of the controls had prolonged QTc, $P = 0.027$. Median cTnT of subjects (131.8 ng/L) was not significantly higher than the 85.9 ng/L of controls, $P = 0.99$. The median cTnT of subjects that died 208.9 ng/L was higher than in survivors 99.6 ng/L, $P = 0.51$. **Conclusion:** Prolonged QTc was more prevalent in children with severe malaria anemia compared to those without anemia, suggesting that children with severe malaria anemia were more prone to arrhythmias. The median cTnT value in the subjects was not significantly lower than that in controls, suggesting that children with severe malaria anemia are not prone to myocardial injury any more than those with uncomplicated malaria without anemia.

Keywords: *Anemia, electrocardiogram, heart failure, malaria, myocardial injury, troponin T*

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Introduction

Heart failure is a common cause of childhood mortality and morbidity, especially in developing countries where it contributes between 5.8% and 15.5% of all pediatric hospital admissions.[1-3] Whereas structural heart diseases such as congenital heart defects and dilated cardiomyopathy are the common causes of childhood heart failure in developed world,[4] infectious etiology predominate in developing countries.[1-3] Severe anemia and bronchopneumonia are the common causes of heart failure in resource-limited countries such as Nigeria.[1-3] Severe anemia is responsible for 28–73.1% of childhood heart failure in Nigeria.[1-3]

Severe malaria anemia is often the most common cause of severe anemia in Nigerian children.[1-3,5] The hypoxia from the severe anemia may cause ischemic myocardial injury; this can be picked up on the electrocardiographic (ECG) evaluation of affected children. Mani *et al*.[6] demonstrated in Indian children with nutritional anemia that significantly more children with nutritional anemia had T wave abnormality, ST

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segment depression, and elevation compared to children without anemia. This is consistent with myocardial ischemia. The ECG changes of T wave abnormality, ST segment depression, and elevation have been documented in patients with malaria, and the ECG changes were noted to subsequently disappear on follow-up.[7] This may suggest that myocardial injury is transient and resolves with resolution of the severe malaria anemia. It has been shown that progressively worsening anemia in children would lead to worsening of the left ventricular dysfunction eventually causing congestive heart failure.[8] In this study, the ECG changes in children with severe malaria anemia would be evaluated.

Myocardial damage can also be detected by elevated levels of troponin T.[9,10] Troponin T is one of a complex of three regulatory proteins involved in muscle contraction. The others are troponin I and C. The troponins are present in skeletal and cardiac muscles. The cardiac-specific troponins are the T and L types.[11] Troponin T level is elevated in the blood following damage to the myocardium and has been used as a reliable cardiac biomarker.[9,10] A good example of the use of troponin T as a biomarker of myocardial insult is in asphyxiated infants. Troponin T is elevated following myocardial injury and it correlates well with severity and outcome of the perinatal asphyxia.[12] It is possible that in severe malaria anemia, in the presence of myocardial injury, troponin T level would also be raised and thus provide additional basis for detecting possible myocardial damage.

In this study, the electrocardiographic changes and troponin T values of children with severe malaria anemia and heart failure requiring blood transfusion are compared to children with uncomplicated malaria without anemia. The troponin T level was evaluated also in children who died in comparison to those who were discharged.

Materials and Methods

Consecutive children diagnosed with severe malaria anemia, in heart failure, requiring blood transfusion, and presenting to the children's emergency room (CHER) of a teaching hospital in Southern Nigeria were recruited as subjects. The controls consisted of age- and sex-matched children presenting to CHER with fever or history of fever and diagnosed with uncomplicated malaria without anemia. Ethical approval was given by the Ethics and Research Committee of the teaching Hospital.

A convenience sample size of 40 subjects and 43 controls were recruited. The subjects were diagnosed with anemic heart failure if they fulfilled the diagnostic criteria for heart failure[13] and also had severe anemia (packed cell volume [PCV] of <15%). Patients with less severe anemia who also had anemic heart failure were included in the study.

- Significant tachycardia for age (>160 beats/min in infancy, >140/min at 2 years, >120/min at 4 years, and >100/min above 6 years). Where fever was present, 10/min for every 1°C rise in temperature was allowed for)
- Significant tachypnea for age(>60 cycles/min in the newborn, >40 cycles/min <24 months, 30 cycles/min in 2–5 years, >28 cycles/min in 5–10 years, and >25 cycles/min in >10 years)
- Cardiomegaly (displaced apex beat with a central trachea or cardiothoracic ratio >60% in <5 years and >50% in >5 years)
- Tender hepatomegaly of at least 3 cm size below the right costal margin.

The fulfillment of at least three of the four criteria above including the presence of soft tender hepatomegaly was diagnostic of anemic heart failure. The protocol for blood transfusion in the study center was to transfuse when the hematocrit was <15% or when the hematocrit was 15% and above with signs of cardiovascular decompensation (tachycardia, tachypnea, and tender hepatomegaly). The subjects received whole blood. The amount of blood that was transfused was calculated based on the maximum allowable volume of 20 ml/kg for whole blood given over 4 h.

The following information was obtained at admission, the age, sex, and the socioeconomic status using the methods described by Olusanya *et al*.[14] The patient's weight was measured using an appropriate weighing scale. Malaria parasite test was done in subjects and controls using the microscopic method described by the World Health Organization (WHO) and done by a WHO certified microscopist.[15] The PCV and hemoglobin electrophoresis were done for the subjects and controls.

Two milliliters of blood was obtained from the children via an aseptic procedure for the determination of cTnT. The blood was spun, and the plasma was decanted into a plain universal bottle and kept in a freezer at −4°C until it was ready for analysis. The cTnT was measured by the electrochemiluminescence immunoassay method with ChemWell microstrip reader by Awareness Technology, USA. The lower limit of measurement of the assay was 0.00 ng/ml. The troponin T test kit lot number was 20110510, manufactured by Hangzou Eastbiopharm, Hangzhou, China. Levels above 100 ng/L was considered elevated as utilized by the previous authors.[16]

A 12 lead electrocardiogram was performed on both subjects and controls; it was recorded using a portable

electronic electrocardiograph (Schiller AT-1 Model, Switzerland). The analysis was done in the standard manner by one of the authors (WES).[17] QTc was considered prolonged if it was >0.440 s. ST segment changes (elevation or depression) occurred when the ST segment was >2 mm above or below the isoelectric line. A shift of up to 2 mm in the left precordial leads was considered normal.[18] The ECGs were recorded on admission, before transfusion.

Statistical analysis

Data were entered into SPSS version 16.0 (Chicago IL, USA), and analysis was done with this tool. Simple proportions were expressed in percentages while means and standard deviations were computed for continuous variables such as age, weight, PR, and QTc intervals. While difference in the medians of troponin T levels between variables was compared using the median test since the troponin T values were not normally distributed. Differences in proportions were determined using Chi-square or Fisher's exact tests while the comparison of means of variables such as cTnT levels and electrocardiographic intervals between subjects and controls was done with Student's *t*-test. Statistically significant values were set at $P \leq 0.05$.

Results

Characteristics of study population

There were 43 subjects with a mean age of 25.7 ± 22.9 (range; 1–132) months. The controls were forty children with a mean age of 31.2 ± 20.0 (range; 4–120) months. There was no significant difference in the mean age of subjects and control, $P = 0.34$ (confidence interval [CI] = −16.8-5.9). Forty (93.0%) of the subjects were <5 years old while 3 (7.0%) were 5 years and older. Of the forty subjects <5 years, 8 (20.0%) were infants. The males were 19 (44.2%) and females were 24 (55.8%). The male:female ratio was 1:1.3. Their mean weight was 11.7 ± 4.3 (range; 4.1–29.0) kg, and 31 (72.1%) of the subjects were in the low socioeconomic class. The detail of the distribution of the subjects is shown in Table 1.

Table 1: Characteristics of study subjects and controls

Characteristic	Subjects	Control	*P*
Mean age (months)	25.7±22.8	31.2±20.0	0.25
Mean weight (kg)	11.7±4.3	13.2±5.5	0.17
Gender			
Male	19	18	1.00
Females	24	22	
Socioeconomic class			
High	1	4	
Middle	11	14	0.17
Low	31	22	

The mean age, gender, and social status between the subjects and controls were comparable [Table 1].

Laboratory investigations

There were 37 (86.0%) subjects with AA genotype while 3 (7.0%), 2 (4.7%), and 1 (2.3%) had SS, AS, and AC, respectively. All the controls had AA genotype. The mean PCV of the subjects was 13.6 ± 4.0 (range; 7–21%). The mean PCV of the control was 33.9 ± 2.7 (range; 30–38%), it was significantly higher than that of the subjects, $P \leq 0.0001$ (CI = −21.8–−18.8). Of the subjects, 20 (46.5%) had a PCV of < 15% while 23 (53.5%) had PCV ≥15%.

The median cTnT of the subjects 131.8 (range; 0.0–4028.0) ng/L was not significantly higher than that of the control 85.9 (range; 0.0–952.0) ng/L, $P = 0.92$. There were 21 (48.8%) subjects who had elevated troponin T compared to 17 (42.5%) controls. The difference was not statistically significant, $P = 0.66$.

The electrocardiographic findings

All the subjects 43 (100%) had sinus tachycardia while 10 (25.0%) controls had sinus tachycardia. One subject each had atrial rhythm and electrical alternans while 2 (4.7%) subjects each had right bundle branch block and left ventricular hypertrophy. Five (11.6%) subjects and none of the controls had ST segment changes in at least two leads, $P = 0.06$. Of the five subjects with ST segment changes, none had sickle cell disease [Figure 1 depicts ST segment depression in one of the subjects]. Ten (23.3%) subjects and two (5.0%) controls had prolonged QTc, $P = 0.027$. The distribution of the other ECG findings among the subjects and controls are shown in Table 2.

Relationship between electrocardiogram changes and troponin T levels

Table 3 shows that the median cTnT values in subjects with or without ST segment changes and the values in subjects with or without prolonged QTc were not

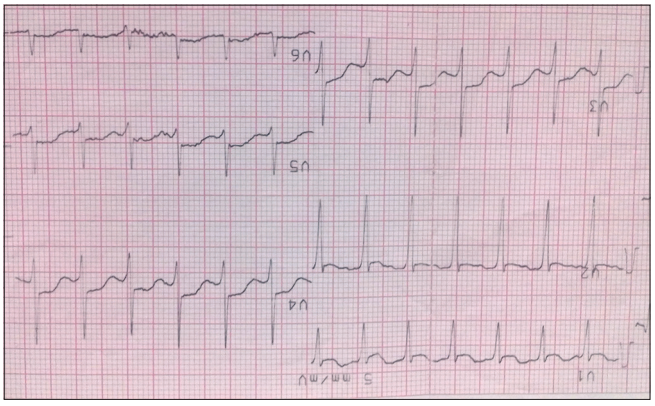

Figure 1: An electrocardiographic tracing depicting ST segment depression in one of the subjects

Table 2: The mean values of electrocardiographic parameters of the subjects and control

Characteristics	Subjects	Control	*P*
P wave (°)	33.56±56.63	30.33±56.24	0.80
PR interval (s)	0.108±0.027	0.110±0.024	0.72
QRS interval (s)	0.070±0.010	0.069±0.010	0.65
QRS axis (°)	47.64±24.00	47.1±24.17	0.92
QTc (s)	0.434±0.082	0.419±0.018	0.26
T axis (°)	39.23±16.12	45.5±28.07	0.21

Table 3: The median troponin (cTnT) values of subjects by ST segment changes, QTc duration, and outcome

Categories of subjects	Median cTnT (ng/dl)	Range (ng/dl)	*P*
ST segment changes			
With ST segment changes	83.1	0.0-1555.0	0.96
Without ST segment changes	94.8	0.0-4028.0	
QTc duration			
Prolonged QTc	167.4	4.9-4028.0	0.79
Normal QTc duration	83.1	0.0-3739.0	
Outcome			
Died	208.9	73.6-289.9	0.51
Discharged	99.6	0.0-4028.0	

statistically significantly different, $P = 0.96$ and $P = 0.79$, respectively.

Outcome

Of the 43 subjects, 3 (7.0%) died while forty were discharged home. The mean duration of admission of the subjects was 5.5 ± 4.6 (range; 2–28 days). The mean duration of admission of the subjects with PCV <15% was 6.2 ± 5.9 (2–28 days) was longer than the value in subjects with ≥15% being 4.8 ± 2.2 (range; 3–9 days), $P = 0.30$ (CI = −4.1–1.3). The difference in median cTnT of the subjects that died and those that were discharged was not statistically significant, $P = 0.51$ [Table 3]. Of the three patients who died, one each had electrical alternans and atrial rhythm while the third patient had left ventricular hypertrophy. The one with electrical alternans had cardiac tamponade. All three had in addition, ST segment changes.

Discussion

This study demonstrated that although more subjects than controls had ST segment changes, suggesting myocardial injury, the difference was not statistically significant. This is similar to findings in the previous studies on anemia in both children and adults where the differences in ST segment changes in subjects with anemia and the controls without anemia were however significant.[19,20] The ST segment changes are reported to be transient in earlier reports,[19,20] it is not clear if that is the case in this study since there were no longitudinal ECG follow-up evaluations. Although all three deaths had ST segment changes, how much the possible myocardial ischemia may have contributed to death could not be ascertained since the autopsy was not done. It is possible that other metabolic abnormalities associated with severe malaria anemia such as metabolic acidosis, and hypoglycemia may have contributed to death in these cases. It is also possible that other factors other than myocardial ischemia, such as electrolyte derangement not evaluated in this study may have contributed to the ST segment changes seen in this study. This is borne out of the finding of lower cTnT levels in children with ST segment changes compared to those without ST segment changes.

There were significantly more subjects with prolonged QTc than were in controls. Prolonged QTc increases the likelihood of developing arrhythmias which could sometimes be fatal, causing sudden death.[16] Prolong QTc have similarly been reported among Nigerian children with anemia.[21] In that study, the prevalence of children with prolonged QTc was 8.8% which is lower than the 23.3% obtained in the present study. The difference could be due to the fact that children in this study had more severe anemia compared to those in the earlier study. This finding in the present study of almost a quarter of the subjects having prolonged QTc may suggest susceptibility to fatal forms of arrhythmias in children with severe malaria anemia. However, some of these fatal forms of arrhythmias such as atrial and ventricular fibrillations were not recorded in this study. It is possible that the single ECG evaluations done in this study could have missed the occurrence of arrhythmias as they may be transient.[7] This may not have been the case if continuous ECG monitoring was done. The absence of fatal forms of arrhythmia is however consistent with a study on children and adults with severe forms of malaria, where ECG rhythm abnormality that can cause death was not seen on continuous ECG monitoring.[22] Prolonged QTc has been demonstrated in children with sickle cell anemia, in this study, though none of the subjects with sickle cell anemia had prolonged QTc. This may have been due to the relatively smaller sample size in this study. It is possible that other factors such as anti-malaria like quinine which some of the patients had in this study may have contributed to the finding.

In this study, the median level of cTnT in subjects (131.8 ng/L) was not statistically significantly higher than in controls (85.9 ng/L). This finding is similar to the work by Ehrhardt *et al*.,[23] who found no significant difference in the mean levels of troponin T in African children with both severe and uncomplicated *Plasmodium*

falciparum malaria. This finding may suggest that children with severe malaria anemia are not particularly more susceptible to myocardial injury compared to those with uncomplicated malaria without anemia.

Although the median cTnT of subjects who died was twofold higher than the value in those who survived, the difference was not statistically significant. This may have been due to the very wide range of values in the subjects (0.0–4028 ng/L) coupled with the small sample size of the study. However, the clinical significance of the twofold higher median value of cTnT in subject that died compared to those that survived may suggest that myocardial injury could have contributed to mortality in this study. It is possible that besides severe malaria anemia, the twofold higher median cTnT level in the subjects that died may have been caused by other factors such as underlying heart diseases in the subjects, acid-base, and electrolyte disturbances. However, possible underlying heart disease was not excluded from this study as echocardiogram was not done for the subjects.

There is a limitation to the interpretation of our results. Other factors such as electrolyte levels, blood glucose, and pH that affect ECG were not determined in this study. It is possible that abnormalities in these parameters may have caused some of the ECG changes seen.

Conclusion

Significantly more subjects than controls had prolonged QTc suggesting that children with severe malaria anemia were prone to developing arrhythmias. The median cTnT level in subjects was not significantly different from that in controls, suggesting that severe malaria anemia may not have caused myocardial injury. However, the twofold higher median cTnT level in subjects that died compared to survivors may suggest that myocardial injury possibly from other causes may have contributed to death.

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Conflicts of interest

There are no conflicts of interest.

References

1. Lagunju IA, Omokhodion SI. Childhood heart failure in Ibadan. West Afr J Med 2003;22:42-5.
2. Sadoh WE, Akinsete AM. Epidemiology of childhood heart failure in Benin City. Niger J Cardiol 2006;3:12-5.
3. Anah MU, Antia-Obong OE, Odigwe CO, Ansa VO. Heart failure among paediatric emergencies in Calabar, South Eastern Nigeria. Mary Slessor J Med 2004;4:58-62.
4. Hsu DT, Pearson GD. Heart failure in children: Part I: History, etiology, and pathophysiology. Circ Heart Fail 2009;2:63-70.
5. Okafor HU, Nwaiwu O. Anemia of persistent malarial parasitemia in Nigerian children. J Trop Pediatr 2001;47:271-5.
6. Mani A, Singh T, Calton R, Chacko B, Cherian B. Cardiovascular response in anemia. Indian J Pediatr 2005;72:297-300.
7. Franzen D, Curtius JM, Heitz W, Höpp HW, Diehl V, Hilger HH. Cardiac involvement during and after malaria. Clin Investig 1992;70:670-3.
8. Puri VK, Pathak V, Mehrotra A, Saxena PN. Systolic time intervals in anemic children with or without congestive heart failure. Indian J Pediatr 1984;51:407-11.
9. Sadoh WE, Eregie CO. Cardiac troponin T as a marker of myocardial injury in a group of asphyxiated African neonates. Paediatr Int Child Health 2012;32:43-6.
10. Bhayana V, Henderson AR. Biochemical markers of myocardial damage. Clin Biochem 1995;28:1-29.
11. Crook MA. Cardiovascular disease. In: Clinical Chemistry and Metabolic Syndrome. 7th ed. London, United Kingdom: Edward Arnold Publisher Ltd.; 2006. p. 325-6.
12. Szymankiewicz M, Matuszczak-Wleklak M, Vidyasagar D, Gadzinowski J. Retrospective diagnosis of hypoxic myocardial injury in premature newborns. J Perinat Med 2006;34:220-5.
13. Omokhodion SI. Childhood heart failure. In: Omokhodion SI, Osinusi K, editors. Pediatric Cardiology and Respiratology. WACP Update Series. Lagos, Nigeria: West African College of Physicians; 1996. p. 72-82.
14. Olusanya O, Okpere E, Ezimokhai M. The importance of socioeconomic class in voluntary fertility control in a developing country. West Afr J Med 1985;4:205-12.
15. World Health Organization. Basic Malaria Microscopy. Part I Learner' Guide. 2nd ed. Geneva: World Health Organization; 2010. p. 21-36.
16. Eisenberg MA, Green-Hopkins I, Alexander ME, Chiang VW. Cardiac troponin T as a screening test for myocarditis in children. Pediatr Emerg Care 2012;28:1173-8.
17. Park MK, Guntheroth WG, editors. Basic measurements. In: How to Read Pediatric ECGs. St. Louis, MO: Mosby Year Book; 1992. p. 10-32.
18. Park MK, Guntheroth WG, editors. Basic measurements. In: How to Read Pediatric ECGs. St. Louis, MO: Mosby Year Book; 1992. p. 42-5.
19. Stanojevic M, Stankov S. Electrocardiographic changes in patients with chronic anemia. Srp Arh Celok Lek 1998;126:461-6.
20. Weiskopf RB, Viele MK, Feiner J, Kelley S, Lieberman J, Noorani M, *et al.* Human cardiovascular and metabolic response to acute, severe isovolemic anemia. JAMA 1998;279:217-21.
21. Bode-Thomas F, Ogunkunle OO, Omotoso AB. The QT interval in Nigerian children, with sickle cell anemia. Trop Cardiol 2003;29:9-11.
22. Bethell DB, Phuong PT, Phuong CX, Nosten F, Waller D, Davis TM, *et al.* Electrocardiographic monitoring in severe falciparum malaria. Trans R Soc Trop Med Hyg 1996;90:266-9.
23. Ehrhardt S, Wichmann D, Hemmer CJ, Burchard GD, Brattig NW. Circulating concentrations of cardiac proteins in complicated and uncomplicated *Plasmodium falciparum* malaria. Trop Med Int Health 2004;9:1099-103.