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Original Article

Physiology Section

QTc Changes in Non-pregnant Females with Severe iron Deficiency Anaemia

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ABSTRACT

Background: A prolonged QT interval is a biomarker for ventricular tachyarrhythmias and a risk factor for sudden death. It is associated with a faulty storage of excess iron in the myocardium, which is described in several hereditary and acquired conditions. However, we do not have enough evidence on the fact that iron deficiency can affect the QT interval. We hypothesized that iron plays an important role in the generation and the propagation of electrical impulses at the level of the myocardial membrane and that it alters the QT interval; so we recorded the QT interval in severely anaemic, non-pregnant females and compared it with that in age and sex matched controls.

Methods: 30 non-pregnant females with severe iron deficiency anaemia, Haemoglobin- <6gm% and low serum ferritin levels were subjected to the ECG test. The QTc of each subject was calculated by using Bazzet's formula and this was compared with that of an equal number of sex and age matched controls.

Results: A significantly shortened QTc was observed in severe iron deficiency anaemia (SIDA) (390±23ms) as compared to that in the controls (419±19ms) (P>0.001). There was a significant positive correlation between the serum ferritin levels and the QTc interval.

Conclusion: A shortened QTc was observed in the SIDA group because of the sympathetic over activity which was secondary to the hyper dynamic circulation.

Key Words: QTc interval, Severe iron deficiency anaemia, Non-pregnant females

INTRODUCTION

The QT interval represents the electrical depolarization and repolarization of the left and right ventricles. A prolonged QT interval is a biomarker for ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death. The modern computer based ECG machines can easily calculate the corrected QT, but this correction may not aid in the detection of patients who are at an increased risk of arrhythmia. The standard clinical correction can be done by using Bazzet's formula.

An abnormal prolonged QT interval could be due to the Long QT syndrome, adverse drug reactions, hypothyroidism and myocardial injury and it is also associated with a faulty storage of excess iron as has been described in several hereditary and acquired conditions [1-4]. In the heart, iron is deposited predominantly in the myocardial cells, rather than in the interstitium [5,6]. This leads to an impaired generation and propagation of electrical impulses at the level of the myocardial membrane [6-9]. It has been suggested that excessive intra-cellular iron interferes with the electric function of the heart, either by generating large amounts of free radicals or by causing selective dysfunction of the Na^+ channels [6,8,10]. The aberrant function of the Na^+ and the K^+ channels contributes to the aetiology of the prolonged QT syndrome, ventricular tachyarrythmias and atrial fibrillation [7,11-14]. Iron also has a role in the production of the rectifying currents. However, we do not have enough evidence on the fact that iron deficiency can cause impairment of the generation and the propagation of the electrical impulses and that it can affect the QT Interval. Some studies have shown an increased QTc in anaemic patients. We hypothesized that iron plays an important role in the generation and the propagation of electrical impulses at the level of the myocardial membrane and that it alters the QT interval; so we recorded the QT interval in severely anaemic, non-pregnant females and compared it with that in age and sex matched controls.

METHODS

This cross sectional case control study was conducted in the Department of Physiology and Medicine in our medical institution. After taking the approval of the ethical committee, 60 individuals were selected for the study and they were categorized into two groups. Group 1 included 30 non-pregnant females with severe iron deficiency anaemia (SIDA) (Hb<6gm%). Group 2 included 30 age and sex matched controls. The sample size was calculated on the basis of the prevalence of the admitted patients in our hospital. After taking the informed consent of the patients, their histories were noted. Their physical examinations were done. Their vitals were recorded. During the general physical examination, the following signs were looked for: pale tongue, pale conjunctiva, koilonychia, pedal oedema and ascites. This was followed by a cardiovascular examination in which the heart sounds, cardiac murmurs, raised JVP, hepatosplenomegaly, basal crepitation and any other cardiac abnormalities were looked for. This was followed by routine respiratory, central nervous and abdominal system examinations. Except for pale tongue, pale conjunctiva and koilonychia, no other of the above said abnormalities were found. Particular care was taken to exclude the intrinsic cardio vascular diseases. A complete haemogram was done by using an autoanalyzer and by doing peripheral smears. The serum ferritin levels were estimated. About 3 ml of the patients blood samples were collected by a clean venipuncture. The blood was allowed to clot. The serum was separated and it was stored at –20^{0}C. The ferritin levels were

estimated by ELISA in batches of ten each, along with normal and abnormal controls. The ECG was recorded after giving 5 minutes of rest to the patients to allay their anxieties. The ECG was recorded by using a CARDIART 108T, J8A 14901 machine, all the 12 leads. The QT interval was corrected for the heart rate by using Bazzet's formula. The standard clinical correction is done by using Bazett's formula, which is named after the physiologist Henry Cuthbert Bazett for calculating the heart rate-corrected QT interval QTc. Bazett's formula is as follows: $QTcB=^{QT}/_{\sqrt{RR}}$ where QTc is the QT interval which is corrected for the heart rate, and RR is the interval from the onset of one QRS complex to the onset of the next QRS complex, which is measured in seconds, which is often derived from the heart rate (HR) as 60/HR (here QT is measured in milliseconds). However, this nonlinear formula over-corrects at high heart rates and under-corrects at low heart rates.

STATISTICAL ANALYSIS

All the data were entered and analyzed by using Statistical Package for Social Sciences (SPSS), version 16. The data were presented as mean ±SD. The independent t-test was used to analyze the difference between the variables in the control group and in the patients with severe iron deficiency anaemia. The difference between the groups was considered as statistically significant at a probability value of <0.05. The correlation between serum ferritin and QTc was analyzed by using Pearson's formula.

RESULTS

The demographic data on the severe iron deficiency anaemia cases and the healthy controls has been summarized in [Table/Fig-1]. The mean age of the SIDA group was 28.10±5.10 years (range 20-40), while the mean range of the control group was 28.17±5.02 years, which was statistically not significant. The serum ferritin level was significantly lower in the SIDA group (p>0.0001). There was a significant difference in the QTI in the two groups. The QTI in the SIDA group was 310±37 ms against 350±27ms in the control group (p<0.0001). The QTc was also shortened in the SIDA group as compared to that in the control group (390±23ms 419±19ms respectively with statistical significance (p<0.001).

DISCUSSION

In the present study, we observed a shortened QT interval and a shortened QTc in the SIDA patients as compared to those in the age and sex matched controls. There was a positive correlation between serum ferritin and QTc.

Our study had several limitations. The sample size was small. Relatively low number of the included subjects was due to the study design, which was set up to limit the influence of several co variables and the less number of the admitted SIDA patients in our hospital. Measuring the serum iron and the total iron binding globulin (TIBG) was necessary, which we did not do, as serum iron is an indicator of the extra-cellular iron and as TIBG is another indicator of the total iron stores. We did not perform echocardiography to assess the ventricular function of the heart, which could have been a confounding factor in assessing the QT interval. We measured the QT interval manually by using a magnifying lens, which cannot be as accurate as that which is measured by computerized measurements. We did not measure the serum electrolytes like Na^+, K^+ and Ca^+ which could affect the QT interval. An additional limitation was that not all the medications which could affect the QTc were included in our methodology.

	Group 1 SIDA N=30	Group 2 Controls N=30	T value	P value
Age (yrs)	28.10±5.10	28.17±5.02	0.051	0.960
Hb (gm%)	3.71±1.12	13.24±0.70	39.337	0.000*
MCV(µ3)	71.80±6.8	87.30±5.5	9.840	0.000*
Ferritin (ng/ml)	14.06±1.83	30.35±3.05	25.020	0.000*
SBP (mmHg)	112.47±7.08	113.10±6.82	0.353	0.725
DBP (mmHg)	66.80±6.13	76.13±5.063	6.424	0.000*
HR (bpm)	95.80±13.59	84.39±9.472	-3.777	0.000*
QTInterval(ms)	310±37	350±27	4.397	0.000*
QTcB (ms)	390±23	419±19	3.944	0.000*

[Table/Fig-1]: Demographic variables among SIDA and controls.
*P<0.05; SIDA: severe iron deficiency anemia; Hb: Hemoglobin; MCV:mean corpuscular volume;SBP:systolic blood pressure;DBP:diastolic blood pressure: QTcB:Bezzet's correction.

		Hemoglobin	Ferritin	QTcB
Hemoglobin	Pearson Correlation	1	0.960**	0.472**
	P value		0.000	0.000
Ferritin	Pearson Correlation	0.960**	1	0.458**
	P value	0.000		0.000
QTcB	Pearson Correlation	0.472**	0.458**	1
	P value	0.000	0.000	

[Table/Fig-2]: Bivariate correlation among Hemoglobin, ferritin and QTcB
**Correlation is significant at the 0.01 level (2-tailed). QTcB: Bezzet's correction.

In the initial description of the formula for the QT interval which was corrected for the heart rate, Bazzet noted that women had a longer corrected QT interval than men [15]. Although these observations have been reproduced several times, the mechanism of this gender difference in the QT interval is unclear [16-20]. The gender differences appear at puberty and decrease but do not disappear later in life [4]. Because of the gender differences in the QT interval, men were excluded from this study. In vitro studies have reached discrepant conclusions, but the weight of evidence does not support an acute physiologic effect of oestrogens or androgens on the action potential duration [21,22]. Some studies have reported a prolonged QT interval in pregnant females. That was the reason why pregnant females were excluded from this study. In our study, we observed a significant reduction in the QT interval and in QTc as compared to those in healthy individuals. There was a significant correlation between Haemoglobin and Ferritin and QTc. Many investigators have found a significant correlation between serum ferritin and QTc. Wu et al., independently showed that the serum iron levels affected the dispersion of QT in patients who were treated with peritoneal dialysis [23]. However, the studies on the dialyzed subjects are frequently hampered by abrupt changes in the electrolyte levels and varying degrees of cardiomyopathy [24]. These co-morbidities influence the action potentials through the heart, possibly obscuring the effect of the iron metabolism abnormalities [7,25]. We tried to limit the effect of several co-variables by eliminating the subjects with pre-existing arrhythmias and those who were taking medications which were known to affect the depolarization of the heart. One report suggested that by lowering the ferritin levels, some cardic arrhythmias could be

reversed [26]. To substantiate this finding, we did not observe any ectopics in patients with low ferritin levels. The experimental data suggested that the propagation of the action potential through the membrane of the myocardial muscle was primarily affected by elevated serum iron and ferritin levels by the reduction of the currents which passed through the Na^+ channels as a whole [8,9]. These channels are critical for depolarization, whereas the prolongation of QT is predominantly dependent on the K^+ rectifier current [11-14,25]. Excessive iron deposition in the heart resulted in the alteration of the outward K^+ current, but the inward rectifier current was unchanged [6]. This data suggested that the observed prolongation of QT (which correlated with increased serum ferritin levels) was an intracellular phenomenon. Recently, new data have emerged which have suggested that in the epithelial cells, there is a concurrent uptake of Na^+ and iron, the latter being sequestrated as ferritin [27]. This process affects the inward K^+ current as well. It is possible that this ferritin dependent K^+ current is involved in the pathology. It is possible that very low levels of ferritin might affect the ferritin dependent K^+ current, both the outward and the inward rectifier current and that it may affect the QT interval. But we observed a rather shortened QTc in the SIDA subjects. Possibly the ferritin levels were not low enough to cause dysfunction of the ferritin dependent K^+ current. A shortened QTc is caused by increased sympathetic activity which is secondary to the hyperdynamic circulation. The sympathetic activity shortens the QTc by shortening the phase of repolarization.

The focus of our study was to check whether SIDA prolonged the QTc in females, which made them more prone to develop cardiac arrhythmias. Studies have shown that it is not because of changes in the oestrogen or progesterone levels [21,22]. We observed that even SIDA could not prolong the QTc; in fact, it shortened it. So, this study excluded the possibility of SIDA being one of the cause for a prolonged QT interval. It also forms a platform for further studies to elucidate other mechanisms by which the QTc can be prolonged.

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