Eclampsia and abnormal QTc

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Summary

Background: Abnormalities of calcium and magnesium metabolism are known risk factors for QT interval prolongation and have been reported in eclampsia.

Objective: To determine if eclampsia is associated with QT abnormalities

Methods: In a prospective study, the QT interval corrected for heart rate (QTc), serum calcium, magnesium and potassium were compared among 30 intrapartum eclamptics and 30 age, parity and gestational age-matched women with uncomplicated pregnancy

Results: Primigravidae made up 93.3% of patients. Mean age was 19.5± 4.2 years Blood pressure was significantly higher among patients than controls (163.0 ± 34.7mmHg versus 120.4 ± 18.6mmHg systolic, p<0.05) and (104.7 ± 15.2mmHg versus 79.6 ± 10.7mmHg, p<0.05). Heart rate ranged from 76 to 163 beats per minute (bpm) and 65 to 112bpm among patients and controls respectively. The corresponding QTc were 390-572 and 390-460 respectively. Compared to the controls, patients had significantly higher mean heart rate (121.1 ± 24.9bpm versus 89.3 ±12.9bpm, p<0.05) and higher QTc (470.4 ± 42.4 versus 436.3 ±17.7; p<0.05) . Compared to the controls, the eclamptics also had higher frequency of sinus tachycardia (90% versus, 13.3%) Odd Radio (OR) =29.57; 95% Confidence Interval (CI) = 5,87-174.08, p=0.00), abnormal QTc (46.7% versus 6.6%, OR = 9.2; 95% CI =1.61-68.48, p=0.01) and T-axis deviation (26.6% versus 3.3%, OR=10.55, 95% CI=1.2-244.3, p=0.03)

Serum calcium level was significantly lower among patients than controls (2.0± 0.4mmol/L versus 2.3 ±0.2mmol/L, p<0.05). The eclamptics had higher frequency of hypocalcaemia than the controls (40% versus 6.6%; OR = 14, 95% CI = 1.58 - 316.9, p=0.01). Serum magnesium, potassium, urea and creatinine levels were similar between the two groups.

Conclusion: Eclampsia is associated with abnormal QTc that may be related to maternal hypocalcaemia. Correction of electrolyte abnormalities and cautions about agents that have potential for QT prolongation are vital in the care of eclamptics.

Keywords: *Eclampsia, Abnormal QTc, Hypocalcaemia.*

Résumé

Introduction: Les anormalités du métabolisme du calcium et magnessium sont des facteurs de risqué connus pour la prolongation intervalle QT et ont été rapportée en éclampsie.

Objectif: Déterminer si l'éclampsie est associée vec des anormalités QT.

Methodes: D'après une étude en perspective, l'intervalle QT, corrigé pour la pulsation du Coeur (Otc) sérum calcium, magnésium et potassium ont été comparé parmi 30 éclamptiques intrapartum et âgé de 30, parité et groupe d'âge des femmes gestationelle avec grossess sans complications.

Résultats: Primigravidae composé de 93,3% de patients, Age moyen était 19,5±4,2 ans. Tension arterielle était remarquablement élevée parmi des patients plus que chez des contrôle (163,0±37,7mmHG contre 120,4±18,6mmHg systolique, P<0,05) et (104,7±15.2mmHg contre 79,6±10,7mmHg, P<0,05). Pulsation du (Coeur varie de 76 à 163 par minute (bpm) et 65 à ½ bpm parmi des patients et des contrôles respectivement. Les QTc correspondant étaient 390 - 572 et 390 - 460 respectivement. Par rapport à des controls, des patients avaientt la pulsation du Coeur moyenne remarquablement élevée (121,1 ± 24,9 bpm contre 89,3 ± 12,9bpm, P<0.05) et QTS plus élevé (470,4 ± 42,4, contre 436,3 ± 17,7, P <0,05) par rapport aux contrôles, l'éclamptique aussi avait la fréquence plus élévéede la tachycardie simusale (90% contre 13,3; proportion bizarre (ou) = 29,57,95% intervalle de confiance (CI) = 5,87 -174,08, P=0.00) QTc anormal (46,7% contre 6,6%,OU=10,55, 95%CI = 1,2-244,3, P=0,03).

Niveau du sésum calcium était remarquablement en baisse chez des patients plus que chez des contrôles (2,0±0.4mmol/L contre 2,3 ±0,2mmol/L:P<0,05). L'éclamptique avait une fréquence plus élévée d'hypocalcemic plus que chez des contrôles (40% contrôl 6,6% OU +14,95% CI = 1,58-3169,P =0,01). Sérum magnesium potassium. urée et niveau créatine était pareil entre les deux groupes.

Conclusion: Eclampsie est liée avec QTc anormal qui pourrait etre en rapport avec l'hypocalcémie maternelle. La correction d'anormalité electrolyte et prudence en matière des agents qui ont un potentiel pour la prolongation QT sont majeurs dans la prise en charge des éclamptiques.

Introduction

Eclampsia is a syndrome characterized by generalized convulsion, elevated blood pressure and proteinuria

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with or without oedema occurring after 20 weeks of gestation. Its occurrence varies from 1 in 100 to 1 in 1700 in developing countries where it is also an important cause of maternal mortality[1,2]. Its pathogenesis is still incompletely understood. Abnormalities of calcium and magnesium metabolism, particularly, hypocalcaemia probably play important roles in the pathogenesis of pregnancy induced hypertension and eclampsia[3,4]. Thus, calcium supplementation has been found useful in the prevention of pre-eclampsia[5], while treatment and prevention of eclampsia with magnesium sulphate has been established[6-8]. QT interval represents the total time from the onset of ventricular depolarisation to the completion of repolarisation. Prolonged QT interval is a disorder of cardiac repolarisation caused by alteration in the transmembrane cation contents. This reduces net ventricular repolarising current, thereby amplifying the intrinsic spatial dispersion of repolarisation, a prime step for development of re-entry phenomenon. The net results are QT interval prolongation, abnormal T-waves, generation of early after-potential and development of arrhythmias[9,10].

Hypocalcaemia, a reported occurrence in eclampsia[3,4] is an independent risk factor for QT prolongation[11]. Some drugs including chlorpromazine, an antipsychotic/anticonvulsant agent and quinolones used in treating infection in eclampsia have also been shown to prolong QT[12,13]. The main significance of QT interval prolongation is the development of *torsade de pointes*, a potentially lethal ventricular polymorphic tachyarrhythmia that may cause sudden cardiac death[9,10]. Cardiac arrest and heart failure have been recently reported in about 0.1% of patients with eclampsia[6].

In spite of the presence of the potential risk factors for QT prolongation in eclampsia, information on QT in this condition is lacking. In addition to its therapeutic implications, such information may provide insight into some of the causes of high mortality in eclampsia. We therefore determined the QT among eclamptic patients.

Methodology

Thirty consecutive patients with intra-partum eclampsia admitted into the labour ward of Usman Danfodiyo University Teaching Hospital, Sokoto, Nigeria between August 2001 and July 2002 served as the subjects. Information about age, tribe, parity, gestational age, history of diabetes and medications used prior to admission were obtained. Blood pressure was measured using standard mercury shygmomanometre (Accosson), size 150cm length and 35cm breadth. Three readings were taken after about 15 minutes of rest. The average of the last two readings was taken as the blood pressure. Systolic blood pressure $\geq$ 140mmHg and/or diastolic blood pressure $\geq$90mmHg were required to make a diagnosis of systemic hypertension[14]. Clinical evaluation was carried out to exclude structural or primary heart disease. The diagnosis of intra-partum eclampsia was based on the presence of generalised convulsions, systemic hypertension, proteinuria of at least 2+ by dipstix and established labour

with or without oedema.

A standard 12-led electrocardiogram (ECG) was recorded during the intrapartum period using automated ECG machine (EKG 2000, Bionet Co. Ltd). Lead placements were as recommended by the American Heart Association[15]. ECG paper speed was set at 25mm per second while calibration was set at 10mm per mV. About 5 cycles were recorded per ECG lead. In order to prevent observer's error, the same investigating Cardiologist verified all measurements manually. The leads with the most distinct Q and T waves were utilised for manual measurements. QT interval was considered as the total time from the beginning of Q wave to the end of T wave. It was corrected for heart rate using Bazett's formula: QTc=QT/Ö RR. QTc > 460 was considered prolonged. T-axis outside 0°-90° was considered as T-axis deviation.

About 10mls of blood was withdrawn for the determination of serum calcium, magnesium and glucose using Banguski, Xyledye Blue calorimetric and glucose oxidase tests respectively. Serum potassium, urea and creatinine were also determined. Serum calcium < 2.2mmol/L, serum magnesium < 0.8mmol/L and serum potassium < 3.5mmol/L constituted hypocalcaemia, hypomagnesium and hypokalaemia respectively.

Patients on admission prior to hospitalisation were excluded from the study. This is because records of such medications were usually not available to determine whether they could potentially prolong QT interval. Patients on medication that could cause QT prolongation (chlorpromazine, quinine, halofantrine, artemeter and quinolones) prior to ECG recording as well as those with diabetes mellitus and structural heart disease were also excluded.

Age, parity, tribe and gestational age-matched healthy individuals with normal pregnancy in established labour served as control.

Statistical analysis

Data entry and analysis were done using Epi-Info software. Values are presented as mean ± SD. Continuous variables were compared using Student's t-test

Table 1 Baseline clinical and personal data of patients and controls

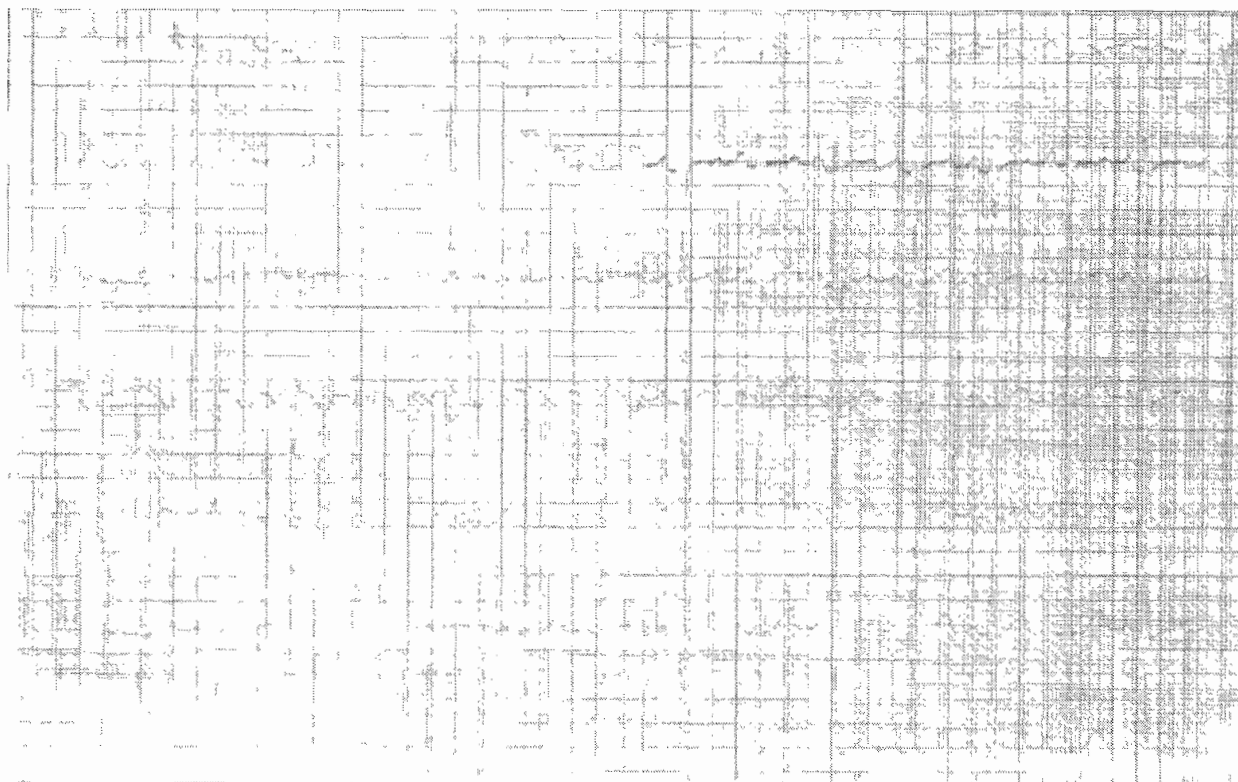| Characteristics		Patients N = 30	Controls N = 30
Tribes (N (%)	Hausa/Fulani	24(80.0)	25(83.3)
	Ibo	1(3.3)	2(6.7)
	Yoruba	2(6.7)	1(3.3)
	Others	3(10.0)	2(6.7)
Parity N (%)	Primigravida	28(93.3)	30(100.0)
	Multigravida	2(6.7)	0(0)
Gestational age>38 weeks N(%)		30(100.0)	30(100.0)
Age (years)		19.5±4.2	20.2±2.7
*Systolic blood pressure (mmHg)		163.0±24.7	124.8±18.1
*Diastolic blood pressure (mmHg)		104.7±15.02	79.6±10.7

*$p<0.05$

Fig. 1.   *A 22 year old eclamptic with abnormal QTc (QTc = 500)*

while discrete variables were compared using chi-square test with Yate's correction. Fisher – Exact test was applied where appropriate. A p-value <0.05 was considered statistically significant.

Results

The baseline personal and clinical data of the study group controls are shown in Table 1. 80% of the patients belonged to the Hausa and Fulani tribes of Nigeria. The primigravidae made up 93.3% of patients.

The biochemical parameters of patients and controls are compared in Table 2. The mean serum potassium, urea and creatinine were similar between the two groups. Serum calcium levels was significantly lower among patients than controls (2.0 ± 0.4mmol/L, range 1.8-2.6mmol/L) versus (2.3 ± 0.2mmol/L, range 2.1-2.8mmol/L) (t=3.5

df=58 p<0.05). The eclamptics had higher frequency of hypocalcaemia than the controls (40% versus 6.6%; OR =14, 95% CI = 1.58-316.68, p=0.01). The mean serum magnesium level did not suffer significantly among patients and controls (0.9 ± 0.2mmol/L, range: 0.7 – 1.7mmol/L) versus (0.85 ± 0.3mmol/L, range 0.5–1.8mmol/L ($t = 0.8$ df = 58, p>0.05).

The ECG parameters of patients and controls are shown in Table 3. Heart rate ranged from 76 to 163 beats per minute (bpm) and 65 to 112 bpm among patients and controls respectively. The corrected QT interval (QTc)

Table 3   **Comparison of the ECG parameters of patients and controls**

Parameters	Patients N = 30	Controls N = 30
*Heart rate (beat/min)	121.1 ± 24.9	89.3 ±12.9
*RR interval (ms)	13.1 ± 2.9	17.6 ± 3.3
QT interval (ms)	336.7 ± 44.5	351.4 ± 26.9
*QTc	470.4 ± 42.4	436.3 ±18.7
*Abnormal QTc N(%)	14(46.7)	2 (6.7)
*Sinus tachycardia N(%)	27 (90.0)	7 (23.)
*T-wave axis deviation N (%)	8 (26.7)	1 (3.3)
Left atrial enlargement N(%)	5 (16.7)	0
Left axis deviation N (%)	2 (6.6)	0
Left ventricular hypertrophy N (%)	1 (3.3)	0
Premature ventricular contraction N(%)	1 (3.3)	0

*p <0.05.

Table 2   **Comparison of the biochemical parameters of patients and controls**

Parameters	Patients N = 30	Controls N = 30
*Serum clcium (mml/L)	2.0 ± 0.04	2.3 ± 0.2
Serum magnesium (mmol/L)	0.9 ± 0.2	0.9 ± 0.3
Serum potassium (mmol/L	4.2 0.7	4.4 ± 0.7
Serum urea (mmol/L)	4.6 ± 1.6	4.0 ± 1.1
Serum creatinine (mg%)	1.0 ± 0.1	0.9 ± 01
*Hypocalcaemia N (%)	12(40)	2 (6.7)
Hypomagnesaemia N (%)	2(6.7)	2(6.7)

*p <0.05.

values were 390-572 among the patients and 390 – 460 among the controls. Only 5 (16.7%) patients had QTc greater than 500. Compared to the controls, patients had significantly higher mean heart rate (121.1 ± 24.9 bpm versus 89.3 ± 12.9bpm) (t-6.2, p<0.05), higher frequency of sinus tachycardia (OR = 29.57, 95% CI = 5.87 – 174.08, p=0.00) and significantly higher QTc (470.4 ± 42.4 versus 436.3 ± 17.7; t=4.1; p<0.05). The frequency of abnormal QTc was higher among the study group than controls (46.7% versus 6.6%, OR = 9.19, 95% CI =1.60–68.48, p=0.01). T-axis deviation (-18 to 110) was present in 8 (26.6%) eclamptics and 1 (3.3%) woman with healthy pregnancy (OR = 10.55, 95% CI = 1.17–241.26, p=0.03.

An ECG tracing illustrating an eclamptic patient with abnormal QTc is shown in Figure 1.

Discussion

This study shows that eclampsia is associated with hypocalcaemia, abnormal QTc and T-axis deviation. Serum magnesium did not differ significantly among patients and controls. A relationship between low maternal serum calcium and pregnnancy-related hypertension and eclampsia has been widely demonstrated[3,4]. A high level of maternal parathyroid hormone has been suggested as the pathogenetic basis of hypocalcaemia in eclampsia[3]. Most of our patients, like in the previous reports from Nigeria[16], were young primigravidae. The dominance of Hausa and Fulani tribes in the current report was due to the predominance of these tribes in Northwestern Nigeria where this study was carried out. Early marriage and child bearing are also frequent among these tribes.

The current report is to our knowledge the first on QT in eclampsia. Hypocalcaemia is a known cause of QT interval prolongation[11] and may play important roles in the genesis of abnormal QTc in eclampsia[3,4]. Eclamptic patients as shown in this report were more likely to have hypocalcaemia than women with normal pregnancy. Hormonal changes may be a contributing factor to abnormal QT in eclampsia. Clinical and experimental studies have shown that female gender is associated with higher risk of QT interval prolongation than men. This has been attributed to a probable sex steroid-related specific regulation of ionic channels (calcium, potassium) such that estrogen facilities QT interval response to agents or conditions that prolong QT interval[17]. Thus, the high estrogen level during pregnancy may therefore increase QT sensitivity to hypocalcaemia.

Alteration of trans-membrane cation contents is the major mechanism underlying the disorder of cardiac repolarisation. The net results of this disorder include reduced net ventricular repolarising current, amplified intrinsic spatial dispersion of repolarisation and development of QT interval prolongation and T-wave abnormality[9,10]. The main significance of QT interval prolongation is however the development of arrhythmias. This largely accounts for the negative outcome of diseases associated with QT interval prolongation. Though an associa-

tion between abnormal QTc and mortality has been identified in patients with cardiac disease, its significance in patients without cardiac disease is unclear[18].

Agents and conditions that prolong QT interval without increasing the transmural dispersion of repolarisation or early depolarisation-induced extrasystole do not cause arrhythmia. Sertindole, an antipsychotic agent, for example has low arrhythmia potential despite QT interval prolongation because its has no significant effect on ventricular dispersion of repolarisation[19]. Furthermore, QT interval prolongation less than 500 is unlikely to induce arrhythmias[18]. A few of our patients had T-axis deviation. This is an independent predictor of cardiovascular event, though more in men than women[20].

In conclusion, eclampsia is associated with prolonged ventricular repolarisation evidenced by abnormal QTc measured on the surface ECG. This may be related to maternal hypocalcaemia. Correction of electrolyte abnormalities and cautious use of agents that prolong QT interval are advocated in eclampsia.

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