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Relationship of QTc Interval Prolongation with Acute Ischemic Stroke

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ABSTRACT

Introduction: Many electrocardiographic (ECG) changes have been observed after strokes. We analyzed the QTc interval prolongation following stroke. **Aim:** The study aimed to assess if the prolongation in QTc interval is related to the occurrence of acute ischemic stroke. **Methods:** This cross-sectional study was conducted from July to December 2018. We included 100 consecutive patients with first-ever ischemic stroke who were admitted to our emergency department, who were age-matched and gender-matched with a control group of 100 non-stroke patients that visited our outpatients department for diseases other than cerebrovascular or cardiovascular ones. A single 12-lead resting ECG examination was done in all patients at the time of their emergency department admission. **Results:** No significant difference between the two groups regarding the age distribution and mean age was found. 56.5% of the sample were males but the difference was not significant between both gender groups. The main presenting symptoms of stroke cases were right-sided weakness (47%), left-sided weakness (36%), and right-sided weakness and aphasia (10%). 34% of the cases had prolonged QTc interval while none of the controls had a prolonged interval (p-value<0.001). No significant difference was observed among stroke patients concerning gender (p-value=0.584). **Conclusion:** Our findings support many previous studies on the brain-heart interaction during acute ischemic strokes and reinforce previous conclusions that assessment of the QTc interval might aid to stratify morbidity and mortality risks in patients with acute ischemic stroke. To accomplish the acute stroke effects on QTc interval prolongation, we need further larger size analytic studies.

Keywords: stroke, QTc interval, ECG, ischemia.

1. INTRODUCTION

The cardiovascular (CVS) complications are extremely common following stroke and represent a major form of morbidity and mortality to those patients (1-5). The relationship between heart and brain in the setting of acute stroke has been subjecting to debate for decades, in which several studies pointed out the relationship between acute cerebrovascular events and electrocardiographic (ECG) changes (2, 6-10). There are several ECG changes following acute stroke; prolonged QTc interval represents one of the commonest changes among them. Specifically, the occurrence of ECG repolarization changes (e.g., prolongated QTc interval) has been detected up to 90% of unselected acute stroke patients; such changes may impose a management and diagnostic dilemma, both to physicians and neurologists. Another point to highlight is that these ECG changes might be responsible for sudden death in stroke patients (7, 11). Dysautonomia and a sudden surge in the sympathetic nervous system output are thought to be responsible for these ECG changes. The frontal lobe, insular cortex, amygdala, and the stellate ganglia control the autonomic nervous system and therefore, modulate the cardiac conduction system and the heart rate thereafter. When the cardiac QTc interval prolongs, the myocardium becomes unstable and ventricular ectopic beats ensue, sometimes very frequently. The latter event can rapidly and unexpectedly degenerate into polymorphic ventricular tachycardia or even ventricular fibrillation, and finally sudden death (1,12).

2. AIM

The study aimed to analyze whether ischemic stroke imposes any prolongation in the cardiac QTc interval or not during the early acute phase of cerebral ischemia.

3. METHODS

This observational cross-sectional study was conducted at the neurology department of the Shorsh general teaching hospital, Sulaymaniyah, Iraq from July 1 to December 31, 2018. We included 100 consecutive patients with first-ever ischemic stroke who were admitted to our emergency department. We had an age-matched and gender-matched control group of 100 consecutive non-stroke patients that visited our outpatients' department for diseases other than cerebrovascular or cardiovascular ones.

We have excluded patients who had sustained a previous stroke (ischemic or hemorrhagic), traumatic brain injury, structural heart disease (such as dysrhythmia, coronary heart disease), organ failure (renal or hepatic), medications which affect the QTc interval (such as antiarrhythmic drugs), electrolytes and acid-base imbalances, and age below 18 years.

All patients underwent routine blood tests; complete blood counts, erythrocyte sedimentation rate, blood sugar, liver function, urea and electrolytes, thyroid function, and serum lipid profile. An urgent non-contrast CT brain scanning was done on admission to the emergency department in all patients.

A single 12-lead resting ECG examination was done in all patients at the time of their emergency department admission. The QT interval was measured manually by a single person from the onset of the QRS complex to the point at which the T-wave ends. It was measured for 3 to 5 consecutive waves and averaged (12). Lead II was chosen for this purpose as most normal reference ranges based upon measurements from this limb lead (13). The corrected value (QTc) was then calculated using Bazett's formula (14).

Automated ECG machines were not used to calculate the QT and QTc intervals, as the accuracy of these automated tools is limited (15). A QTc interval of >44 ms in men and >46 ms in women is regarded as prolonged and abnormal (12).

The collected data were organized, tabulated and statistically analyzed using Statistical Package for Social Sciences (SPSS) version 23.0 by an independent statistician. A comparison of variables was performed by Student's t-test and Levene's test for equality of variance. We calculated the P-value and a 95% confidence interval (95% CI). Significance levels were set at a P-value of less than 0.05 in all cases.

4. RESULTS

One hundred patients with stroke were included in the study beside another group of one hundred individuals who were enrolled as a control group (with no stroke). Eighteen percent of the whole sample aged less than 50 years and 15.5% were older than 80 years. Table 1 shows no significant difference between the two groups regarding the age distribution (p-value=0.20) as well as the mean age (p-value=0.98). It is evident in the table that 56.5% of the sample were males but the difference was not statistically significant between the groups (p-value= 0.669). The majority (92.5%) of the sample were Kurds while the rest were Arabs. More than half (54%) of the stroke cases had neither hypertension nor diabetes, compared with

Age <50	13	(13.0)	23	(23.0)	36	(18.0)	
50-59	24	(24.0)	20	(20.0)	44	(22.0)	
60-69	0	(0.3)	0	(0.2)	1	(0.3)	
70-79	19	(19.0)	18	(18.0)	37	(18.5)	
≥80	13	(13.0)	18	(18.0)	31	(15.5)	0.207*
Mean (±SD)	64.1	(±13.3)	64.1	(±16.0)			0.981**
Gender							
Male	58	(58.0)	55	(55.0)	113	(56.5)	
Female	42	(42.0)	45	(45.0)	87	(43.5)	0.669*
Ethnicity							
Kurds	91	(91.0)	94	(94.0)	185	(92.5)	
Arabs	9	(9.0)	6	(6.0)	15	(7.5)	0.421*
Total	100	(100.0)	100	(100.0)	200	(100.0)	

Table 1. Socio-demographic characteristics of the two groups. *P-value, **By t-test for two independent samples. - Age in years. - SD, standard deviation

	Cases (n=100)		Controls (n=100)		Total		
	No.	(%)	No.	(%)	No.	(%)	P-value
Diseases							
None	54	(54.0)	57	(57.0)	111	(55.5)	
Hypertension	28	(28.0)	30	(30.0)	58	(29.0)	
Hypertension and diabetes	15	(15.0)	8	(8.0)	23	(11.5)	
Diabetes	3	(3.0)	5	(5.0)	8	(4.0)	0.428*
Smoking							
None	86	(86.0)	73	(73.0)	159	(79.5)	
Yes	11	(11.0)	16	(16.0)	27	(13.5)	
Ex-smoker	3	(3.0)	11	(11.0)	14	(7.0)	0.038
Chief complaint							
Right side weakness	47	(47.0)	0	(0.0)	47	(23.5)	
Left side weakness	36	(36.0)	0	(0.0)	36	(18.0)	
Right side weakness and diplopia	1	(1.0)	0	(0.0)	1	(0.5)	
Right-sided weakness and aphasia	10	(10.0)	0	(0.0)	10	(5.0)	
Coma	1	(1.0)	0	(0.0)	1	(0.5)	
Double vision with the feeling of rotation	3	(3.0)	0	(0.0)	3	(1.5)	
Feeling of rotation	2	(2.0)	0	(0.0)	2	(1.0)	
Headache	0	(0.0)	50	(50.0)	50	(25.0)	
Low back pain	0	(0.0)	21	(21.0)	21	(10.5)	
Shoulder pain	0	(0.0)	2	(2.0)	2	(1.0)	
Hand paresthesia	0	(0.0)	8	(8.0)	8	(4.0)	
Upper limb pain	0	(0.0)	4	(4.0)	4	(2.0)	
Benign positional peripheral vertigo	0	(0.0)	6	(6.0)	6	(3.0)	
Neck pain	0	(0.0)	9	(9.0)	9	(4.5)	<0.001*
Total	100	(100.0)	100	(100.0)	200	(100.0)	

Table 2. Clinical presentations of the two groups.*By Fisher's exact test, - No., number; %, percent

57% of the control group (p-value=0.428). The main presenting symptoms of stroke cases were right-sided weakness (47%), left-sided weakness (36%), and right-sided weakness and aphasia (10%) (Table 2). Thirty-four percent of the cases had a prolonged QTc interval while none of the controls had a prolonged interval (p-value<0.001) (Table 3). No significant difference was observed among stroke patients with respect to gender (p-value=0.584). No statistically significant association between QTc interval prolongation and the presenting symptoms was found (p-value=0.85) (table 4). As shown in figure 1, there was no statistically significant association between right-sided weakness as well as left-sided weakness with the QTc interval (p-value=0.390).

	Cases (n=100)		Controls (n=100)		Total		
QT	No.	(%)	No.	(%)	No.	(%)	P-value
Normal	66	(66.0)	100	(100.0)	166	(83.0)	
Prolonged	34	(34.0)	0	(0.0)	34	(17.0)	<0.001
Total	100	(100.0)	100	(100.0)	200	(100.0)	

Table 3. Prolongation of the QTc interval in the two study groups. - QT, QT interval; QTc, corrected QT interval, - No., number; %, percent

	QTc interval				Total		
	Normal		Prolonged				
Symptoms	No.	(%)	No.	(%)	No.	(%)	P-value
Right-sided weakness	30	(63.8)	17	(36.2)	47	(100.0)	
Left-sided weakness	25	(69.4)	11	(30.6)	36	(100.0)	
Right-sided weakness and diplopia	1	(100.0)	0	(0.0)	1	(100.0)	
Right-sided weakness and aphasia	7	(70.0)	3	(30.0)	10	(100.0)	
Coma	1	(100.0)	0	(0.0)	1	(100.0)	
Double vision with the feeling of rotation	1	(33.3)	2	(66.6)	3	(100.0)	
Feeling of rotation	1	(50.0)	1	(50.0)	2	(100.0)	0.853*
Total	1	(50.0)	1	(50.0)	2	(100.0)	

Table 4. Prolongation of QTc interval by symptoms among stroke cases (n=100). - No., number; %, percent

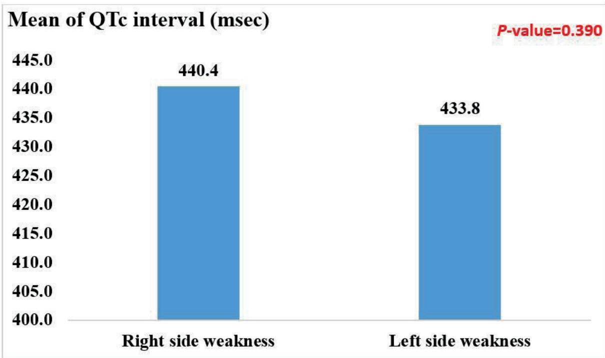

Figure. 1. Means of QTc interval by the laterality of the weakness.

5. DISCUSSION

The autonomic and ECG changes following an acute stroke in patients without the underlying cardiac disease are common, well-thought-out because of the dysautonomic activity or disturbed autonomic regulation of the cardiovascular system (CVS). In addition to those complications, the sequelae are tremendously also common in subsequent strokes, which represent a major cause of mortality and morbidity (1-5). QTc prolongation is a good predictor of mortality (16). For that reason, the ECG is regarded as a quick, available and affordable marker for follow-up and identification of stroke patients who are at risk for QTc prolongation and prevention of subsequent events. The QT interval is reliant on the heart rate, and that is the greater the rate the shorter the QT and vice versa. Thus, using heart-rate corrected QT (QTc) instead of the uncorrected QT is necessary (17).

The presented study shows that 34% of the acute ischemic stroke cases demonstrated a prolonged QTc interval, while none of the controls had a prolonged one (p=value<0.001). To date, there has been no specific reason for the commonly observed association between cerebrovascular events and QTc interval prolongation (18). However, one hypothesis is that acute cerebral lesions induce a quickly increasing intracranial pressure, which sequentially causes abnormally elevated levels of plasma catecholamines (19,20). This catecholamine rise may have a myocardial effect (21), such as QTc prolongation.

Several studies suggested that there were no statistically significant changes in the QTc interval of patients with right-sided weakness and that of the left-sided weakness (11,15,22); these findings are consistent with the present study. Our previous study did a direct head-to-head gender comparison for both ischemic and hemorrhagic strokes concluded that there was no statistically significant difference between males and females (23); those findings are also consistent with our findings here.

It should be noted that the QT interval can be modulated by several factors, such as the circadian rhythm, meals, smoking, physical activities, serum electrolyte, and medications (24-26). Furthermore, there is a reasonable ethnic variability in the QTc interval (27,28). However, bias because of the above reason is seeming to be slight in the present study because most of the cases and controls were Kurds. At present, there is an essential need for further studies to evaluate the role of QTc as a predictive factor for long-term prognosis following acute stroke. Interventions and prevention strategies in patients at high risk could improve outcomes and reduces mortality in those patients.

The likely limitations of the study should be highlighted. Our study encompassed a relatively small number of patients from a solitary center and the majority of the patients and controls were of Kurdish ethnicity; the findings would have been different if the number of cases was larger and that those other ethnicities were enrolled. Besides, the study does not reflect the practice of stroke in the whole of Iraq. The current study is an observational one; an analytic study is required to assess the clinical significance of our findings.

6. CONCLUSION

Our discoveries support the prior studies on the brain-heart interaction during acute ischemic stroke. Our results reinforce previous findings that assessment of QT interval might aid to stratify morbidity and mortality risks in patients with acute ischemic stroke. To accomplish the acute stroke effects on QT interval prolongation we need further larger size studies.

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- **Patients consent statement**: The Hospital and Kutdistan Board for Medical Specializations' committee approved the study. Signed informed consent were obtained from all patients or via their next of kin/caregiver.
- **Authors contribution**: OSMA, ASS, and ANS gave a substantial contribution to the conception and design of the work. OSMA and ANS contributed to acquisition, analysis, and interpretation of data. OSMA, ASS, and ANS drafted the article. OSMA, ASS, and ANS had a role in critically revising the article for important intellectual content and gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- **Conflict of interest**: None declared.
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