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QTc Interval Prolongation and Stroke: Any Differences between Ischemic and Hemorrhagic Strokes?

QTc Aralığı Uzaması ve İnme: İskemik ve Hemorajik İnme Arasındaki Farklar

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ABSTRACT

Purpose: Strokes results in a multitude of electrocardiographic (ECG) changes, and a prolongation of the QTc interval is a well-observed one. We analyzed QTc interval prolongation among males and females who presented with acute stroke.

Material and Methods: This observational study was conducted at the department of neurology of the Sulaimaniya general teaching hospital, from August 2012 to May 2013, and involved 100 consecutive patients who presented with acute stroke; 50 had ischemic stroke and the rest (n=50) had hypertensive intracerebral hemorrhage. All patients underwent resting 12-lead ECG within half an hour of A&E admission. The QTc interval was calculated and analyzed. A comparison among males and females in both stroke types was done.

Results: The ischemic group had 25 males and 25 females; 25 patients (25%; 13 males and 12 females) demonstrated QTc interval prolongation. Thirty two males and 18 females constituted the hemorrhagic group; QTc interval prolongation was observed in 18 males and 8 females (n=26; 26%). There was no statistically significant difference in the QTc interval prolongation among males of the ischemic stroke versus hemorrhagic group (P-value<0.73), females of the ischemic versus hemorrhagic group (P-value<0.32), and males and females within the ischemic stroke (P-value<0.40). However, a significant difference was noted between males and females within the hemorrhagic group (P-value<0.09; 95% CI, 481.85 to 530.82).

Conclusion: Only males and females with hypertensive intracerebral hemorrhage demonstrated a statistically significant difference in QTc prolongation in favor of females. Whether this observation is clinically significant or not, it needs further analytic studies.

Key Words: stroke; QTc interval prolongation; ECG

ÖZET

Amaç: İnmeler genellikle çok sayıda elektrokardiyografi (EKG) değişiklikleri ve QTc aralığının uzaması ile karakterizedir. Çalışmamızda akut inme ile başvuran kadın ve erkek hastaların QTc aralığını analiz ettik.

Materyal ve Metod: Bu gözlemsel çalışmada Ağustos 2012"den Mayıs 2013'e, Süleymaniye genel eğitim hastanesinin nöroloji bölümünde akut inme ile başvuran 100 hasta dahil edildi; 50 iskemik inme ve 50 intraserebral hipertansif kanamalı. Tüm hastalara A&E kabulünü müteakip yarım saat içirisinde dinlenme durumunda EKG yapıldı. QTc aralığı hesaplanıp analiz edildi. Her iki inme tipinde de kadınlar ve erkekler arasında bir karşılaştırma yapıldı.

Bulgular: İskemik grubunda 25 erkek ve 25 kadın vardı, 25 hastada (% 25, 13 erkek ve 12 kadın) QTc aralığı uzaması saptandı. Otuz iki erkek ve 18 kadın hemorajik grubu oluşturdu; QTc aralığı uzaması 18 erkek ve 8 kadında gözlendi (n = 26;% 26). QTc aralığı uzaması açısından hemorajik grup erkekler iskemik inmesi olan erkekler ile karşılaştırıldığında

(P-değeri <0.73). iskemik ve hemorajik gruplara ait kadınlar kendi aralarında karşılaştırıldığında (P-değeri <0.32) ve iskemik inmeli kadın ve erkekler arasında karşılaştırıldığında (p değeri <0.40) istatistiksel olarak anlamlı bir fark gözlenmesken hemorajik grup içerisinde kadın ve erkek arasında önemli farklılık gözlendi (% 95 CI, 481,85-530,82 P-değeri <0.09).

Sonuç: Hipertansif intraserebral kanamalı kadın ve erkekler karşılaştırıldığında QTc uzamasının istatistiksel olarak kadınlarda daha uzun olduğu gözlendi.Bu bulgunun klinik olarak önemli olup olmadığı daha üst düzeyde analitik çalışmayı gerektirmektedir.

Anahtar Kelimeler: İnme; QTc aralık uzaması; EKG

INTRODUCTION

A multitude of ECG changes[1-4] have been observed in patients who presented with acute strokes, both ischemic and hemorrhagic. In particular, repolarization changes, such as prolongation in the QTc interval, have been noticed in as much as 90% of unselected stroke victims[2] these may well result in a management and diagnostic dilemma, both to physicians and neurologists. Another concern is that these cardiac electrophysiological changes might be responsible for sudden death in stroke sufferers[5,6.]

MATERIAL and METHODS

This observational study was conducted at the neurology department of the Sulaimaniya general teaching hospital, Iraq, from August 2012 to May 2013. A total of 100 consecutive patients who had developed their stroke and who were admitted to our A&E were included in the study. A total of 50 patients who had been diagnosed with acute completed ischemic strokes[7] and 50 hypertensive intracerbral hemorrhagic strokes[8] constituted the target studied groups. Patients were excluded from the study if they have been already diagnosed with ischemic or structural heart disease; have pre-existing cardiac dysrhythmia or conduction defects; and/or have been receiving a medication (or medications) which could influence the cardiac conduction system.

All patients (n=100) underwent routine blood tests, including complete blood counts, erythrocyte sedimentation rate, liver function, urea and electrolyte, lipid profile, thyroid function, and prothrombin and activated thromboplastin times. An urgent non-contrast CT brain scanning was done at the time of A&E admission in all patients; a repeat CT scan (n=16) or brain MRI (n=7) was done after 24-48 hours if the initial CT scan was unremarkable in patients who bear a clinical diagnosis of ischemic stroke. A transthoracic eachocardiographic assessment was carried out within 2-3 days of hospital admission. All patients were examined by neurologists and neurology trainees.

A single 12-lead resting ECG examination was done within 30 minutes of A&E 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 beats and averaged[9]. Lead II was chosen for this purpose as most normal reference ranges are based upon measurements from this limb lead[10]. The corrected value (QTc) was then calculated using the Bazett formula[11]. Automated ECG machines were not used to calculate the QT and QTc intervals, as the accuracy of these automated tools has been shown to be limited[12]. A QTc interval of >44 ms in men and >46 ms in women was considered prolonged and abnormal[9].

The collected data were organized, tabulated, and statistically analyzed using Statistical Package for Social Sciences (SPSS) version 17 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 95% confidence interval (95% CI). Significance levels were set at P-value of less than 0.05 in all cases.

RESULTS

Tables 1 and 2 display the various patients' characteristics while table 3 demonstrates the patients' QTc prolongation with respect to their stroke pattern and gender. Tables 4 to 7 show the comparison among patients (males and males; ischemic and hemorrhagic strokes) who demonstrated prolonged QTc interval.

Table 1. Patients' characteristics and vascular risk factors. All patients (n=100) were included in this table, regardless of their age, gender, or their QTc interval.

Variable	Ischemic stroke (n=50)	Hemorrhagic stroke (n=50)	Total number of patients (%)
Hypertension	**31**	**48**	**79 (79%)**
Diabetes mellitus	**12**	**6**	**19 (19%)**
Hyperlipidemia	**44**	**18**	**62 (62%)**
Cigarette smoking Smokers Ex-smokers Non-smokers	 **15** **3** **41**	 **5** **1** **35**	 **20 (20%)** **4 (4%)** **76 (76%)**
Previous stroke	**12**	**3**	**15 (15%)**
Alcohol drinking	**1**	**4**	**4 (4%)**

-None of the patients had coagulopathy, bleeding tendency, head trauma, valvular heart disease, cardiac dysrhythmia, or cardiac conduction defects.

Table 2. Characteristics of patients (n=51) who demonstrated prolonged QTc interval, regardless of their stroke pattern.

Variable	Number (%)
Age groups' distribution (n=51)	
20-29	1 (1.9%)
30-39	1 (1.9%)
40-49	8 (15.6%)
50-59	12 (23.5%)
60-69	14 (27.4%)
70-79	8 (15.6%)
80-90	5 (9.8%)
99-100	2 (3.9%)
Gender	
Males	31 (62%)
Females	20 (38%)
Hypertension	41 (80.3)
Diabetes	36 (70.5%)
Hyperlipidemia	39 (76.4%)
Smoking	
Smokers	12 (23.5%)
Ex-smokers	2 (3.9%)
Non-smokers	37 (72.5%)
Previous Stroke	6 (11.7%)
Alcohol Drinking	3 (5.8%)

Table 3. Patients' total number, gender, and their QTc interval prolongation with respect to their stroke pattern.

Variable	Ischemic stroke		Hemorrhage stroke	
	Total Number	Prolonged QTc*	Total Number	Prolonged QTc*
Male	25	13	32	18
Female	25	12	18	8
Total	50	25	50	26

*Defined as a corrected QT interval of >44 ms in males and 46 ms in females.

Table 4. Comparison between males and females within the ischemic stroke group (n=25) who had prolonged QTc interval.*

Gender	Number	SMD	P-value	95% Confidence Interval	
				Lower	Upper
Male	13	32.198	0.40	452.566	491.480
Female	12	19.8		475.602	500.764
Total	25	27.676			

-SMD, standardized mean difference.
*Defined as a corrected QT interval of >44 ms in males and 46 ms in females.

Table 5. Comparison between males and females within the hemorrhagic stroke group who had prolonged QTc interval (n=26).*

Gender	Number	SMD	P-value	95% Confidence Interval	
				Lower	Upper
Male	18	31.31	0.09	461.752	492.893
Female	8	29.29		481.850	530.825
Total	26	33.066			

-SMD, standardized mean difference.
*Defined as a corrected QT interval of >44 ms in males and 46 ms in females.

Table 6. Comparison between males of the ischemic stroke group (n=13) versus those of the hemorrhagic group (n=18) who had prolonged QTc interval.*

Variable	Number	SMD	P-value	95% Confidence Interval	
				Lower	Upper
Acute ischemic stroke	13	32.198	0.73	452.57	491.480
Acute hemorrhagic stroke	18	19.80		461.752	492.893
Total	31	27.68		463.633	486.567

-SMD, standardized mean difference.
*Defined as a corrected QT interval of >44 ms in males and 46 ms in females.

Table 7. Comparison between females of the ischemic stroke group (n=12) versus those of the hemorrhagic group (n=8) who had prolonged QTc interval.*

Variable	Number	SMD	P-value	95% Confidence Interval	
				Lower	Upper
Acute ischemic stroke	12	19.80	0.32	475.602	500.764
Acute hemorrhagic stroke	8	29.29		481.850	530.825
Total	20	25.027		483.732	507.158

-SMD, standardized mean difference.
*Defined as a corrected QT interval of >44 ms in males and 46 ms in females.

Out of the total 100 patients (both ischemic and hemorrhagic strokes), 51 (51%) showed a QTc interval prolongation. The ischemic stroke group had 50 males and 50 females while males (n=32) outnumbered females (n=18) in the hemorrhagic stroke group. Twenty five patients (50%) within the ischemic stroke group had QTc prolongation (13 males and 12 females) while 26 (52%) patients within the hemorrhagic stroke patients (18 males and 8 females) demonstrated QTc prolongation.

Of the 51 patients with QTc prolongation, 34 (66%; i.e, two thirds) were between the ages of 50 to 79 years and 31 (62%) were males and 20 (38%) were females; 41 (80.3%) were hypertensive, 39 (76.4%) were hyperlipidemic, and 36 (70.5%) were diabetic. A prior history of stroke was found in 6 (11.7%) patients.

A direct comparison between males and females of the ischemic groups, males of the ischemic versus hemorrhagic group, and females of the ischemic versus the hemorrhagic group had revealed no statistically significant difference in terms of their QTc prolongation; P-value<0.40, P-value<0.73, P-value<0.32, respectively. However, there was a statistically significant difference between both genders within the hemorrhagic stroke group (P-value<0.09; 95% CI, 481.85 to 530.82) in favor of females.

DISCUSSION

Several investigators have documented a variety of ECG changes in patients with acute ischemic or hemorrhagic strokes[1-4]. These range from non-specific ST-T changes to sudden cardiac death[13].

Many patients with stroke have one or more vascular risk factors that predispose them to coronary artery disease, as well. The presence of these ECG changes in the acute stroke setting may create a diagnostic and management dilemma, not only to cardiologist but also to neurologists. It is critical to distinguish that these ECG abnormalities are the cause behind developing stroke, are caused by stroke per se, or are totally unrelated to stroke[14,15].

Beyr and coworkers published a landmark paper in the year 1944 describing several ECG changes in patients with acute subarachnoid hemorrhage[16]. This had opened the way to our understanding of stroke-induced ECG changes. According to Khechinashvili and Asplund[2]. ECG changes in the form of ischemic ST-T changes and/or QTc interval prolongation were found in more than 90% of unselected patients with ischemic stroke and intracerebral hemorrhage, but their prevalence was much lower after exclusion of patients with preexisting structural heart disease. On the other hand, Golan and Livneh[5] concluded that such ECG abnormalities were present in approximately 30% of acute stroke sufferers.

Prolongation in the QTc interval have been found in 45% of patients with acute stroke (ischemic and hemorrhagic) while disturbances in cardiac rate and rhythm (such as polymorphic ventricular tachycardia are present in 25% of

cases[1,17]. According to Suffer and coworkers[18] these abnormalities are evanescent and their frequency and severity are highest during the first 24 hours of stroke; this explains the importance of continuous cardiac monitoring in acute stroke patients.

Fifty one percent of our patients demonstrated a QTc interval prolongation, a figure that approximates those of Goldstein[1] and Connor[17] In addition, the number of our patients who had QTc interval prolongation was somewhat equal (50% of ischemic stroke versus 52% of hemorrhagic strokes). According to Akbar and colleagues[13] repolarization changes and especially prolongation of the QTc interval are the commonest ECG changes, irrespective of the stroke type (ischemic or hemorrhagic; 63.6% versus 68.5%) and this also correlates well with our findings as well as the results of Khechinashvili and Wong (76% versus 71%)[2,19].

Dysautonomia and a surge in the sympathetic nervous system output are thought to be responsible for these ECG abnormalities and changes. The frontal lobe, insular cortex, amygdala, and the stellate ganglia play a central role in controlling the autonomic nervous system and therefore, influencing the cardiac conduction system and heart rate[13]. When the QTc interval prolongs, the myocardium becomes unstable and ventricular ectopic beats develop frequently. The latter can readily degenerate into polymorphic ventricular tachycardia or even ventricular fibrillation[2,20].

Khechinashvili and Asplund[2] concluded that the presence of QTc interval prolongation in acute stroke (ischemic and hemorrhagic) usually represents pre-existing coronary artery disease rather than a direct consequence of the stroke itself on the heart. On the other hand, Soliman and colleagues[21] found that QTc interval prolongation is associated with a significantly increased risk of incident stroke independent of traditional stroke risk factors. In addition, Maebuchi and coworkers[22] had linked QTc interval prolongation to the future development of cardiovascular disease in the general population.

In our study, there was a statistically significant difference between males and females (in favor of females) who had developed hypertensive intracerebral hemorrhage and QTc interval prolongation. Direct head-to head gender comparison (after correction for age and vascular risk factors) between ischemic versus hemorrhagic stroke revealed no significant difference, however. The latter also applies to both genders within the ischemic stroke.

The pertinent literature[1-4] does not mention which gender is more likely to demonstrate this ECG abnormality (to avoid pitfalls, these studies had adjusted their variables and findings for age, race, and gender) but it does mention that QTc prolongation is more common in hemorrhagic strokes (78%) than in ischemic ones (51%)[23]. Our results and findings need further analytic studies to clarify the association between QTc prolongation and stroke with respect to gender and its future implications.

CONCLUSION:

Only males and females who had hypertensive hemorrhagic stroke demonstrated a statistically significant QTc prolongation in favor of females. Whether this observation is “clinically” significant or not, it needs further analytic studies to define the role of QTc interval prolongation in stroke in terms of gender preference.

Limitations of the study:

1. The number of cases was relatively small.
2. There was no “healthy” group as well as no locally or nationally published articles which target the same topic so that we might compare the results with.
3. The size and location of the stroke and their relationship with the QTc interval prolongation were not assessed.

4. Only a single ECG examination was done, at the time of A&E admission. No 24-hour cardiac Holter monitoring was done.

Therefore, the findings might well have been different if the aforementioned factors were addressed.

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