Prolongation of QT Interval in ECG: A Hidden Complication of Cirrhotic Liver Disease

Ajeet Kumar[1], Syeda Urooj Riaz[2], Rajesh[3], Syed Hussain Mehdi Kazmi[4], Rajesh Kumar[5], Muhammad Ishaq Ghauri[6]

Abstract

Objective: To determine frequency of QT interval prolongation in ECG of patients with decompensated liver cirrhosis in a tertiary care hospital of Karachi, Pakistan.

Methods: A total of 60 patients with cirrhosis were included in this study. Clinical examination to see the presence of ascites, liver span and encephalopathy, and related investigation such as liver function tests, serum albumin, prothrombin time and ultrasound abdomen for portal vein size was done and they were labelled as suffering from cirrhotic liver disease. Two 12 lead ECG was done >5 minutes apart, when found same and QT interval calculated.

Results: The average age of the patients came out to be 45.37 ± 6.59 years. There were 36 (60%) were male and 24 (40%) female. Frequency of QT prolongation in patients with decompensate liver cirrhosis was observed in 12 (20%) cases.

Conclusion: This study demonstrates that cirrhotic cardiomyopathy is a common occurrence. The frequency of QT prolongation was 20% in patients with cirrhosis.This study demonstrates the direct relationship of cirrhotic cardiomyopathy with the severity of liver disease. Therefore patients with cirrhosis should be investigated for prolonged QTc and the proper diagnosis and treatment.

Keywords: Cirrhosis, Cardiomyopathy, Prolonged QTc, Complication of Chronic Liver Disease, Chronic Liver Disease, Viral Hepatitis.

IRB: Approved by Ethical Review and Research Committee of Jinnah Medical and Dental College. Dated: 10th June 2017.

Citation: Kumar A, Riaz SU, Rajesh, Kazmi SHM, Kumar R, Ghauri MA. Prolongation of QT interval in ECG: a hidden complication in cirrhotic liver disease [Online]. Annals ASH KM&DC 2019;.

(ASH & KMDC 24(1):20;2019)

Introduction

Cirrhosis is a very common ailment in Pakistan[1], mostly caused by viral hepatitis B and C[2]. Its prevalence is still very high despite measures to control the viral infections. Many complications can occur as a result of cirrhosis, out of which ascites, portal hypertension and varies are well-known. Many new complications are being recognized which include hepato-pulmonary and sleep-apnea syndromes[3]. The effects of cirrhosis on cardiovascular and circulatory system are not well studied[4].

A prolongation of QT interval has been shownto represent the most common electrocardiographic finding in patients with cirrhosis[5,6]. Accordingly, altered ventricular repolarization is considered as part of the definition of cardiomyopathy[7]. Although cirrhotic cardiomyopathy may be silent in most patients but may result in failure when cirrhotic patients under go stress such as infections, therapeutic paracentesis, transjugular intrahepatic protosystematic shunt (TIPS) and liver transplantation. QT interval prolongation is a simple and easily determined marker of cirrhotic cardiomyopathy[8]. After myocardial infarction and even in healthy individuals a prolonged QT interval is associated with a higher risk of sudden death and cardiac mortality in

[1,2,4,5,6] Department of Medicine,
Jinnah Medical and Dental College, Karachi.
[3] Department of Medicine,
Sir Syed College of Medical and Health Sciences, Karachi.

Correspondence: Dr. Syeda Urooj Riaz,
Department of Medicine,
Jinnah Medical and Dental College
Email: urooj_sr@hotmail.com
Date of Submission: 12th January 2019
Date of Acceptance: 10th April 2019

patients with inherited and acquired forms of long-QT syndrome[6-7].

In a study conducted in Civil Hospital Lyari reported that of 78 confirmed patients of cirrhosis, the mean SD of QT interval was 0.438 0.015 sec. The mean QT value was significantly more in patients with cirrhosis as compared to normal (p= 0.006). The prolongation of QT was reported in 19.2% of patients with cirrhosis[9].

The aim of the study is to determine frequency of QT prolongation in patients with liver cirrhosis, and to identify the magnitude of this problem so that in future patients with cirrhosis should be investigated for prolonged QTc and the proper diagnosis and treatment can reduce the morbidity and mortality associated with this problem.

Patients and Methods

This was a cross-sectional study conducted in the medical wards of Jinnah Medical College Hospital, Karachi. The duration of the study was six months from 15th September 2016 to 15th march 2017.

Sample size is calculated with the know prevalence of prolonged QT interval in 19.2% cases of post infection liver cirrhosis[9], with 95% Confidence interval and marginal error is 10%. The sample size is 60 for this study. Sampling technique was non-probability consecutive sampling.

The inclusion Criteria was patients of cirrhosis of age between 20 years and 60 years, of either sex.The exclusion criteria patients with valvular heart disease, patients of cirrhosis having co-morbidity like hypertension or chronic kidney disease, ischemic ease or malignancy, thyroid disease and diabetes and patients on drug causing QT prolongation (e.g. beta blockers, calcium channel blocker, anti-arrhythmic drug and cardiac glycosides)

This study was conducted in the medical wards of Jinnah Medical College Hospital, Karachi. Patients fulfilling the inclusion criteria were enrolled in the study after informed consent. History was taken from patients regarding age, sex and duration of cirrhosis. Clinical examination to see the presence of ascites, liver span and encephalopathy, and related investigation such as liver function tests, serum albumin, prothrombin time and ultrasound was done. Two 12 lead ECG was done >5 minutes apart if both were same and QT interval calculated. corrected QT (QTc) values was calculated for all patients by the formula: QTC = QT/R-R[10] .Two reading was taken and mean value of QTc>0.44 second was taken as prolonged[10]. The data was recorded on predesigned proforma by the researcher and in order to control the bias. This study was approved from ethical review committee of the hospital.

Data was entered and analyzed by SPSS version 20. Descriptive statistics was used. Quantitative variables such as age, duration of disease and QT interval were presented as mean and standard deviation. Frequency and percentage were calculated for sex and QT prolongation. Stratification was done regard to age, sex and duration of disease to see the effects of these variables on outcome through chi-square test and $p \leq 0.05$ was considered as significant.

Results

A total of 60 patients with liver cirrhosis were included in this study. Most of the cases were 41 to 50 years of age. The average age of the patients was 45.37 ± 6.59 years (95% CI: 43.66 to 47.07) similarly average duration of disease and QTc interval were also presented in Table 1.

Out of 60 patients 36 (60%) were male and 24 (40%) female. Frequency of QT prolongation in patients with decompensate liver cirrhosis was observed in 12 (20%) cases.

QT prolongation in patients was 23.7% (9/38) in 41 to 50 years of age and 25% (2/8) in 51 to 60 years of age but significant difference was not observed among age groups (p=38) as shown in Table 2. QT prolongation in patients was 16.7% (6/36) in male and 25% (6/24) in female. Insignificant difference was observed (p=0.429) as presented in table 2. Similarly duration of disease did not effect in QT prolongation in patients (p=0.79) as shown in Table 2.

Discussion

Cirrhotic cardiomyopathy is diagnosed infrequently because of unawareness regarding association. It has quite many features including prolongation of QTc, decreased myocardial contraction force, increased HR and diastolic dysfunction[11].

Several electrophysiological mechanisms like reduced beta- adrenoceptor density, postreceptor signal defects, abnormal excitation-contraction coupling have been suggested as the cause of molecular abnormalities for the conductance and impaired cardiac contractility[12]. Beta-receptor density and sensitivity is reduced in cirrhosis, along with altered G protein and calcium channel functions[13]. This results in both impaired chronotropic responses and electromechanical uncoupling; the coupling between the cardiac output and arterial compliance is an important factor affecting the left ventricular stress and work done by it[14]. The increased interval correlates with a higher incidence of sudden cardiac death. The pathogenesis of increased QT interval is unclear. The structural changes in cardiomyocyte membrane with increased cholesterol content with resultant membrane fluidity compromises the calcium and potassium pumps. In cirrhotics increased plasma levels of estrogens has also been implicated for the increased incidence of QT interval prolongation. This interval is increased in 30 to 60% of patients and level of increase relates to degree of hepatic dysfunction[15]. On the other hand, a too compliant arterial system will hamper prompt and timely delivery of blood to different parts of the body and also delay flow in important vascular beds. These effects will be more prominent in the patients with excessive cardiac output, stroke volume and vascular beds of varying vascular resistance as in cirrhotic cardiomyopathy[16]. Prolongation of QTc duration and increased Heart rate can be used as a non-invasive and rapid diagnostic marker of cirrhotic cardiomyopathy as was proved in the study conducted in 2007[9]. Prolongation of QTc interval has been shown to be useful for assessment of severity of chronic liver disease[17].

In this study average age of the patients was 45.37 ± 6.59 years. Out of 60 patients 36 (60%) were male and 24 (40%) female. In Shaikh et al[18] study mean age was 46.2 years 55.41% were male and 44.59% were female.

In present study frequency of QT prolongation in patients with decompensate liver cirrhosis was observed in 12 (20%) cases. The electrophysiological abnormalities included prolonged repolarization, which manifests itself in the form of prolonged QT interval[19].

Table 1. Descriptive Stastics

		Variables		
Statistics		Age (Years)	Duration of Disease treatment (Months)	QTc Interval
Mean		45.37	9.20	.40
95% Confidence Interval for Mean	Lower Bound	43.66	7.88	.386
	Upper Bound	47.07	10.52	.415
Median		46	8.00	.42
Std. Deviation		6.59	5.09	.055
Inter quartile Range		8	6	.09

N=60

Table 2. Frequency of QT Prolongation in Patients with Decompensate Cirrhosis with respect to Age Groups, Gender & Duration of disease treatment. N=60

Age Groups (Years)	QT Prolongation Yes n (%)	No n (%)	Total	Chi Square
31 to 40	1 (7.1)	13 (92.9)	14	1.78
41 to 50	9 (23.7)	29 (76.3)	38	
51 to 60	2 (25)	6 (75)	8	
Male	6 (16.7)	30 (83.3)	36	0.625
Female	6 (25)	18 (75)	24	
≤6 months	4 (19)	17 (81)	21	0.45
7 to 12 months	5 (17.9)	23 (82.1)	28	
>12 months	3 (27.3)	8 (72.7)	11	

In this study 20% of the patients had prolonged QTc interval. This finding is very much identical with prior study done on electrophysiological abnormalities by Zuberi et al in 2006[9] and Shaikh et al[19] in 2011. That study showed QTc interval prolongation in 19.2% and 21.62% of cirrhotic patients. However Wong [in 2009] disputes such values and reports QTc interval abnormalities at a staggering 45% in cirrhotic subjects and further elaborates that QT prolongation is present in only 5% of the general population which is a significant finding. This means that the patients who have QT interval prolongation are much more susceptible to polymorphic ventricular tachyarrhythmias than normal controls[9].

Bernardi M et al observed that frequency of cirrhotic cardiomyopathy increased from 25% in child-Pugh class A to 51% in class B and up to 60% in child-Pugh class C associated with prolong QT-

intervel[20]. Yildiz R also observed a proportional increase in the frequency of cirrhotic cardiomyopathy according to the severity of cirrhosis of liver with increase in pro-BNP[21]. There are number of components of this disorder which include three phenomena: electrophysiological changes, echo cardiographic abnormalities and the fluctuation of levels of Natriuretic peptides[21].

QT prolongation in patients was 23.7% (9/38) in 41 to 50 years of age and 25% (2/8) in 51 to 60 years of age but significant difference was not observed among age groups (p=38) in this study. QT prolongation in patients was 16.7% (6/36) in male and 25% (6/24) in female.

Several authors have demonstrated a prolonged QT interval, especially in patients with alcoholic cirrhosis and Child-Pugh class C[22,23,24]. Genovesi et al[22] studied QT interval length in 48 male cirrhosis patients and identified an increased QTc in all 3 Child-Pugh classification groups (A: 425 ± 24 milliseconds; B: 452 ± 30 milliseconds; C: 465 ± 24 milliseconds). In Mozoset al[25] study with 38 cirrhosis patients (50% male), QTc values were considerably longer (A: 462 ± 25 milliseconds, B: 493 ± 62 milliseconds, and C: 520 ± 45 milliseconds). The most obvious reason for the differences is purely methodological: Genovesi et al[19] used only lead V5 for their QT/QTc analyses, whereas we used all 12 leads and chose the longest QT/QTc intervals from those leads as our principal measures. The differences may also reflect some other factors associated with QT interval prolongation: the inclusion of female patients, inflammation, malnutrition, hyperglycemia, and low testosterone[24].

In the study by Bernardi[10] the prevalence of QT interval prolongation did not differ between patients affected by alcohol-related cirrhosis and those with the post-viral disease. However, only 7% of patients were affected by alcoholic cirrhosis and 12% had cirrhosis of mixed aetiology. In a study by Bal[25] a prolonged QTc was seen more commonly in patients with alcoholic cirrhosis (60%) as compared to non-alcoholic cirrhosis (35%) and alcoholic cirrhosis was one of the independent predictors of QT interval prolongation.

Prolongation of the QT-interval (>0.44s) is seen even with mild increments in portal pressure in subjects with cirrhosis and in noncirrhotic patients with portal hypertension, whereas a further increase has been described after TIPS insertion. Both delayed repolarization of cardiomyocytes due to K+ channel abnormalities and sympathoadrenergic hyperactivity may contribute to QT-interval prolongation. The QT-interval dispersion has been associated with the severity of liver dysfunction. It also varies from daytime to nighttime, probably reflecting diurnal variations in autonomic tone, circulatory status, and respiratory and oxygen demand. The QT-interval corrects itself in only 50% of subjects after a liver transplant. A recalculation of QT intervals based on heart rate and other liver-related parameters are now indicated to better dissect out the contribution of changes in QT-interval to heart-related morbidity and mortality in subjects with cirrhosis. According to some authors, QT-interval prolongation might be an important sign helpful to identify patients with cirrhosis at risk of cirrhotic cardiomyopathy.

Conclusion

This study demonstrates that cirrhotic cardiomyopathy is a common occurrence. The frequency of QT prolongation was 20% in patients with cirrhosis. There is a direct relationship of cirrhotic cardiomyopathy with the severity of liver disease. So that in future patients with cirrhosis should be investigated for prolonged QTc and the proper diagnosis and treatment can reduce the morbidity and mortality associated with this problem.

Although a fair amount of knowledge has been gained from the recent surge in the disease and subsequent investigations, further studies are needed. For instance, additional studies regarding management of complications of chronic liver disease are required. Research should continue in finding ways to decrease occurrence of disease and early detection. Hopefully, timely sharing of accurate information will help control the spread and magnitude of future occurrences.

By this study we know that we usually do not take into account cardiac complication of cirrhotic liver disease.

Acknowledgment

We are grateful to the department of Medicine JMCH for prompt collection of cases and management.

Conflict of Interest

Authors have no conflict of interests and no grant/funding from any organisation

References

1. Ahmad K. Pakistan: a cirrhotic state? Lancet. 2004 Nov 20-26;364(9448):1843-44. PMID:15565744 DOI:10.1016/S0140-6736(04)17458-8
2. Walsh K, Alexander GJ. Update on chronic viral hepatitis.Postgrad Med J. 2001 Aug;77(910):498-505. PMID:11470928 PMCID:PMC1742112
3. Ogata T, Nomura M, Nakaya Y, Ito S. Evaluation of episodes of sleep apnea in patients with liver cirrhosis.J Med Invest. 2006 Feb;53(1-2):159-66. PMID:16538010
4. Nordin C, Kohli A, Beca S, Zaharia V, Grant T, Leider J, et al. Importance of hepatitis C co-infection in the development of QT prolongation in HIV-infected patients. J Electrocardiol. 2006 Apr;39(2):199-205. Epub 2005 Nov 28. PMID:16580420 DOI:10.1016/j.jelectrocard.2005.09.001
5. Henrikesen JH, Fuglsang S, Bendtsen F, Christensen E, Møller S. Dyssynchronous electrical and mechanical systole in patients with cirrhosis. J Hepatol. 2002 Apr; 36(4): 513-520. PMID:11943423
6. Ytting H, Henriksen JH, Fuglsang S, Bendtsen F, Moller S. Prolonged QTc interval in mild portal hypertensive cirrhosis. J Hepatol. 2005Oct; 43(4): 637-644.PMID:16083986DOI:10.1016/j.jhep.2005.04.015
7. Zambruni A, Trevisani F, Caraceni P, Bernardi M. Cardiac electrophysiological abnormalities in patients with cirrhosis. J Hepatol. 2006 May; 44(5): 994-1002.Epub 2006 Jan 24. PMID:16510203 DOI:10.1016/j.jhep.2005.10.034
8. Ma Z, Lee SS. Cirrhotic cardiomyopathy; getting to the heart of matter. Hepatol. 1996; 24: 451-459.DOI: 10.1002/hep.510240226.
9. Zuberi BF, Ahmed S, Faisal N, Afsar S, Memon AR, Baloch I, et al. Comparison of heart rate and QTc duration in patients of cirrhosis of liver with non-cirrhotic controls. J Coll PhysiciansSurg Pak. 2007; 17(2): 69-71.
10. Charbit B, Samain E, Merckx P, Funck-Brentano C. QT interval measurement: evaluation of automatic QTc measurement and new simple method to calculate and interpret corrected QT interval. Anesthesiology. 2006 Feb; 104(2): 255-260 PMID:16436843
11. Moller S, Henriksen JH. Cirrhotic cardiomyopathy: a pathophysiological review of circulatory dysfunction in liver disease. Heart. 2002 Jan; 87(1): 9-11.PMCID: PMC1766971
12. Fisch C. Evolution of the clinical electrocardiogram. Journal of the American College of Cardiology. 1989 Nov 1;14(5):1127-1138.
13. Liu H, Song D, Lee SS. Cirrhotic cardiomyopathy. GastroenterolClin Biol. 2002; 26: 842-847.
14. Henriksen JH, Bendtsen F, Hansen EF, Moller S. Acute non-selective beta-adrenergic blockade reduces prolonged frequency-adjusted Q-T interval (QTc) in patients with cirrhosis. J Hepatol. 2004 Feb; 40(2): 239-246. DOI: https://doi.org/10.1016/j.jhep.2003.10.026
15. Sawant P, Vashishtha C, Nasa M. Management of Cardiopulmonary Complications of Cirrhosis.Int J Hepatol. 2011; 2011: 280:56-59.Published online 2011 Jul 19. doi: 10.4061/2011/280569
16. Moller S, Henriksen JH. Cardiopulmonary complications in chronic liver disease. World J Gastroenterol. 2006 Jan; 12(4): 526-538. Published online 2006 Jan 28. doi: 10.3748/wjg.v12.i4.526
17. Arikan C, Kilic M, Tumgor G, Levent E, Yuksekkaya HA, Yagci RV et al. Impact of liver transplantation on rate-corrected QT interval and myocardial function in children with chronic liver disease. Pediatr Transplant. 2009 May; 13(3):300-306. doi: 10.1111/j.1399-3046.2008.00909.x.Epub 2008 Jun 4. PMID: 18537904
18. Shaikh S, Abro M, Qazi I, YousfaniA.Frequency of cirrhotic cardiomyopathy in patients with cirrhosis of liver: A tertiary care hospital experience. Pak J Med Sci. 2011 Sep; 27(4): 744-748.
19. Genovesi S, PrataPizzala DM, Pozzi M, Ratti L, Milanese M, Pieruzz F, et al. QT interval prolongation and decreased heart rate variability in cirrhotic patients: relevance of hepatic venous pressure gradient and serum calcium. ClinSci (Lond). 2009 May 14;116(12):851-859. doi: 10.1042/CS20080325.
20. Bernardi M, Caladra S, Colantoni A, Trvisani F, Raimondo ML, Sica G, et al. Q-T interval prolongation in cirrhosis: prevalence relationship with severity, and etiology of the disease and possible pathogenetic factors. Hepatol. 1998 Jan; 27(1): 28-34. PMID:9425913 DOI:10.1002/hep.510270106
21. Yildiz R, Yildirim B, Karincaoglu M, Harputluoglu M, Hilmioglu F. Brain natriuretic peptide and severity of disease in non-alcoholic cirrhotic patients. J Gastroenterol Hepatol. 2005 Jul; 20(7): 1115-1120.DOI: 10.1111/j.1440-1746.2005.03906.x
22. Genovesi S, PrataPizzala M, Pozzi M, Ratti L, Milanese M, PieruzziF,et al. QT interval prolongation and decreased heart rate variability in cirrhotic patients: relevance of hepatic venous pressure gradient and serum calcium. ClinSci(Lond) 2009 May; 116(12): 851-855. doi: 10.1042/CS20080325.
23. Vrtovec B, Meden-Vrtovec H, Jensterle M, Radovancevic B. Testosterone-related shortening of QTc interval in women with polycystic ovary syndrome. J Endocrinol Invest. 2008; 31: 653-655. https://doi.org/10.1007/BF03345619
24. Bal JS and Thuluvath, P.J. Prolongation of QTc interval: relationship with etiology and severity of liver disease, mortality and liver transplantation. Liver Int. 2003 Aug; 23(4): 243-248. PMID: 12895263
25. Mozos I, ChiulanC, Gorun C, Costea S. Serum uric acid in stroke. Annals of West University of Timi?oara. Ser Chem. 2007; 16: 227-230