Research Article

Asymptomatic Hypocalcaemia and QT Prolongation in Patients with Chronic Liver Disease

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Abstract

Background: Prolonged low levels of calcium in blood is a common finding in patients having long-standing liver disease as breakdown, degradation and digestion of calcium is related to stores of Vitamin D in body. Among these patients long-standing low stores of calcium remains ignored because of absence of any symptoms.

Objective: To assess the frequency of hypocalcaemia and QT prolongation among patients presenting with chronic liver disease in a tertiary care hospital

Methods: It was an observational cross-sectional study. It was carried out in North Medical Ward, Department of Medicine Mayo Hospital Lahore from 15-08-2017 to 15-04-2018. 110 patients fulfilling the selection criteria were enrolled. Blood sample were drawn and examined in the hospital Laboratory for evaluation of calcium levels. If levels were <8.8mg/dL, then hypocalcaemia was labeled. ECG was done to assess QT interval. If QT>460ms, then QT prolongation was labeled. All data was noted on proforma. Data was analyzed using SPSS version 20.

Results: The mean age of patients was 46.45±8.67years. There were 44(40%) males and 66(60%) females. The mean BMI of patients was 22.73±4.25kg/m2. The mean duration of CLD was 7.09±3.42years. The mean calcium level of patients was 7.70±1.48mg/dl. In this study, 73(66.4%) patients had hypocalcaemia while 29(26.4%) patients had prolonged QT. The hypocalcaemia causing QT prolongation was found in 24(21.8%) patients.

Conclusion: As far as current study is concerned low serum calcium levels are reason for remarkable QT prolongation and this is a grave situation. Due to absence of any symptoms or adverse reactions this condition goes on without coming into notice. But as far as its consequences are concerned it can become a reason for ventricular arrhythmias and remarkably can play a role in increased death rate of affected individuals. So we should try our best to identify extraordinary low levels of calcium and QT prolongation, though presenting without symptoms , if successful in doing so low levels of calcium and prolonged QT interval could be corrected at initial stages and this will directly decrease both morbidity and mortality.

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Keywords | Hypocalcaemia, QT prolongation, chronic liver disease, calcium level

Introduction

Chronic liver diseases (CLD), i.e., persistent inflammation of liver and permanent nodular liver texture leading to abnormal liver functions (cirrhosis) due to Hepatitis C Virus has become a major health hazard across the whole world. It has become a large threat to health in Pakistan.[1] Hepatitis C virus has a considerable potential to cause chronic liver disease as compared to Hepatitis B virus. It can become a cause of acute and chronic hepatitis, cirrhosis and chronic carrier state of hepatitis (dormant stage of virus when it is inactive and not harming body but waiting for favourable conditions to activate itself). It can also lead to hepatocellular carcinoma.[2]

Fluid, electrolyte and nutritional status of patients of CLD are determined by many variables which are usually related. Malnutrition, ascites, hypocalcemia and hyponatremia are known poor prognostic factors in CLD, early identification and appropriate management can decrease disease burden and number of deaths by this disease.[3]

Prolonged QT interval on ECG significantly manifests hypocalcemia. This is of significance because QT prolongation is an important cause of sudden cardiac death. One study showed that the hypocalcaemia was seen in 84.8% patients and QT prolongation was found in 37.5% patients. While hypocalcaemia without any significant QTc prolongation was seen in 47.2% patients.[4]

Studies show prevalence of QT prolongation in 23%-60% of CLD patients. QT prolongation was reported to be 60% in one study.[5] Another study by Sulehria et al. showed the incidence of QT prolongation in 24% of cirrhotic patients.[6] One more local study showed that incidence of QT prolongation was 48% in cirrhotic patients.[7]

Aim of this study is to find out the frequency of hypocalcemia and QT prolongation in patients presenting with CLD in a tertiary care hospital. Literature has reported that hypocalcemia is major cause of complication in CLD patients. Variables results have been noticed regarding QT prolongation among CLD patients. QT prolongation leads to cardiac complications in CLD cases. We want to carry out this research to find out the severity of problem in local population. So that preventive measures can be taken and in CLD patients, if calcium level found to be reduced, early interventions can be made to prevent QT prolongation, which results in reduction of cardiac problems in CLD cases.

Methods

It was an analytical cross-sectional study. Due to convenience and constraints of time and resources, a very small sample of 110 patients having age 18-60 years of either gender reporting to OPD with CLD for at least 1 year were selected by non-probability purposive sampling after taking verbal informed consent according to Helsinki declaration. Diabetic patients (BSR>186mg/dl)and patients with IHD, history of MI, stroke within past 3 months (on medical record), patients with diagnosed liver malignancy, taking calcium supplementation and patients with cardiac arrhythmias were excluded. Population characteristics (name, age, gender, BMI, duration of CLD) were also noted. Then blood sample was taken by 3cc disposable syringe using aseptic technique. Samples were stored in vials and sent to laboratory of hospital and levels of calcium were examined. If levels were <8.8mg/dL, then hypocalcaemia was labeled (as per operational definition).

A 12-lead ECG was done of each patient and a QT interval adjusted by heart rate (corrected QT interval, QTc) was determined by using Bazett's formula.

Data analysis were carried out by SPSS version 20. Mean and SD was calculated for quantitative variables like age, BMI and duration of CLD and calcium level of patients (mg/dl). Frequency and percentage was calculated for qualitative variables like gender, hypocalcemia and QT prolongation. Data was stratified for age, gender, BMI and duration of CLD. Post-stratification, chi-square test was applied for association. P-value < 0.05 was taken as significant.

Results

There were 44(40%) males and 66(60%) females with mean age of 46.45±8.67years.The mean BMI, mean duration of CLD and mean calcium level of patients was 22.73±4.25kg/m^2, 7.09±3.42 years, 7.70±1.48 mg/dl respectively. Out of 110 patients, 73(66.4%) patients had hypocalcemia while 37(33.6 %) had normal calcium level. There were 29(26.4%)

patients had prolonged QT while 81(73.6%) had normal QT interval. Data were stratified for age of patients. In patients aged ⩽ 40years, 19 (67.9%) had hypocalcemia while in patients aged 41-60years, 54 (65.9%) had hypocalcemia. The difference was insignificant (p>0.05). Data were stratified for gender of patients. In male patients, 30(68.2%) had hypocalcemia while in female patients, 43 (65.2%) had hypocalcemia. The difference was insignificant (p>0.05). Data were stratified for BMI of patients. In underweight patients, 17 (70.8%) had hypocalcemia, in normal weight patients, 30 (62.5%) had hypocalcemia and in overweight or obese patients, 26 (68.4%) had hypocalcemia. The difference was insignificant (p>0.05). Data were stratified for dura-tion of CLD. In patients having CLD from 2-8years, 51 (68.0%) had hypocalcemia while in patients having CLD from 9-15years, 22 (62.9%) had hypocalcemia. The difference was insignificant (p>0.05).

Data were stratified for age of patients. In patients aged 40 years, 11 (39.3%) had prolonged QT while in patients aged 41-60years, 18 (22.0%)had prolonged QT. The difference was insignificant (p>0.05). Data were stratified for gender of patients. In male patients, 12(27.3%) had prolonged QT while in female patients, 17(25.8%) had prolonged QT. The difference was insignificant (p>0.05).Data were stratified for BMI of patients. In underweight patients, 8(33.3%) had prolonged QT, in normal weight patients, 18(37.5%) had prolonged QT and in overweight or obese patients, 3 (7.9%)had prolonged QT. The difference was insignificant (p>0.05). Data were stratified for duration of CLD. In patients having CLD from 2-8years, 17 (22.7%) had prolonged QT while in patients having CLD from 9-15years, 12(34.3%) had prolonged QT. The difference was insignificant (p>0.05).

Table 1: *Basic Demographics*

Age (Years)		**46.45± 8.67**
Gender	*Male*	44 (40.0%)
	Female	66 (60.0%)
BMI (kg/m²)		22.73± 4.25
Duration of CLD (Years)		7.09 ± 3.42
Calcium level of patients (mg/dl)		7.70 ± 1.48
Hypocalcaemia	*Yes*	73 (66.36%)
	No	37 (33.64%)
Prolonged QT interval	*Yes*	29 (26.36%)
	No	81 (73.64%)

Table 2: *Comparison of Strata of Age, Gender, BMI, Duration with Hypocalcemia*

		Hypocalcemia		P-Value
		Yes	No	
Age (years)	⩽40	19 (26.0%)	9 (24.3%)	0.85
	41-60	54 (74.0%)	28 (75.7%)	
Gender	Male	30 (41.1%)	14 (37.8%)	0.74
	Female	43 (58.9%)	23 (62.2%)	
BMI (kg/m²)	Underweight	17 (23.3%)	7 (18.9%)	0.05
	Normal	30 (41.1%)	8 (21.6%)	
	Overweight & obese	26 (35.6%)	22 (59.5%)	
Duration	2-8	51 (69.9%)	24 (64.9%)	0.59
	9-15	22 (30.1%)	13 (35.1%)	

Table 3: *Comparison of Strata of Age, Gender, BMI, duration with Prolonged QT*

		Prolonged QT		P-Value
		Yes	No	
Age (years)	⩽40	11 (37.9%)	17 (21.0%)	0.072
	41-60	18 (62.1%)	64 (79.0%)	
Gender	Male	12 (41.4%)	32 (39.5%)	0.86
	Female	17 (58.6%)	49 (60.5%)	
BMI (kg/m²)	Underweight	8 (27.6%)	16 (19.8%)	0.006*
	Normal	18 (62.1%)	30 (37.0%)	
	Overweight & obese	3 (10.3%)	35 (43.2%)	
Duration	2-8 years	17 (58.6%)	58 (71.6%)	0.20
	9-15 years	12 (41.4%)	23 (28.4%)	

*P-value < 0.05 will be considered as significant.

Discussion

Frequency of End stage liver is highest in Pakistan due to liver failure and so is the death rate.[8]

In our study, the mean calcium level of patients was 7.70±1.48mg/dl. In this study, 73(66.4%) patients had hypocalcemia and 29(26.4%) patients had prolonged QT. A significant manifestation of hypocalcaemia is prolongation of the QT interval on the ECG. This is of significance because QT prolongation is an important cause of sudden cardiac death. One study showed that the hypocalcaemia was seen in 84.8% patients and QT prolongation was found in 37.5% patients. While hypocalcaemia without any significant QT prolongation was seen in 47.2% patients.[4]

Studies show prevalence of QT prolongation in 23%-60% of CLD patients. QT prolongation was reported to be 60% in one study.[5] Another study by Sulehria et al. showed the incidence of QT prolongation in 24%

of cirrhotic patients.[6] One more local study showed that incidence of QT prolongation was 48% in cirrhotic patients.[7]

Study of Bashir A et al,found that frequency of QT prolongation was 4.5% in Child PughGrade A, 23.2% in Child Pugh Grade B, and 32.0% in Child Pugh Grade C. This study found out association of Child Pugh Scoring system with QT prolongation and statistically significant ($p< 0.05$)[9] relation was found to be present. The results presented by M Aliet al. in which they showed the frequency of QT prolongation to be 48%,[10] is comparable with our study as the current study findings revealed the frequency of QT prolongation to be 26.4%.

In a study Bernardi et al, reported prolonged QT in 46.2% patients of CLD.[5] Birda CL et al., reported prolonged QT in 5.4 % of CLD patients.[11] Liu Pet al demonstrated a QT prolongation frequency of 10.07% in their study.[12] Kumar A et al determined the frequency of QT prolongation to be 20 % in their study population.[13]

Hypercalcemia that is present in progressive stages of CLD without progression to cancer is not common and is the process is difficult to understand. [14]

In our study, the mean age of patients was 46.45± 8.67years. Data were stratified for age of patients. In patients aged 40years, 19 (67.9%) had hypocalcemia while in patients aged 41-60years, 54 (65.9%) had hypocalcemia. The difference was insignificant ($p> 0.05$). In patients aged 40years, 11(39.3%) had prolonged QT while in patients aged 41-60years, 18 (22.0%) had prolonged QT. The difference was not significant ($p>0.05$).

In our study, there were 44(40%) males and 66(60%) females. Data were stratified for gender of patients. In male patients, 30 (68.2%) had hypocalcemia while in female patients, 43 (65.2%) had hypocalcemia. The difference was not significant ($p>0.05$). In male patients, 12(27.3%) had prolonged QT while in female patients, 17(25.8%) had prolonged QT. The difference was insignificant ($p>0.05$).

In another study, the mean BMI of patients was 22.73±4.25kg/m^2. Data were stratified for BMI of patients. In underweight patients, 17(70.8%) had hypocalcemia, in normal weight patients, 30 (62.5%) had hypocalcemia and in overweight or obese patients, 26(68.4%) had hypocalcemia. The difference was insignificant ($p>0.05$). Data were stratified for BMI of patients. In underweight patients, 8 (33.3%) had prolonged QT, in normal weight patients, 18(37.5%) had prolonged QT and in overweight or obese patients, 3 (7.9%) had prolonged QT. The difference was not significant ($p>0.05$).

In another study, the mean duration of CLD was 7.09±3.42years. Data were stratified for duration of CLD. In patients having CLD from 2-8years, 51 (68.0%) had hypocalcemia while in patients having CLD from 9-15years, 22 (62.9%) had hypocalcemia. The difference was of no significant ($p>0.05$). In patients having CLD from 2-8years, 17 (22.7%) had prolonged QT while in patients having CLD from 9-15years, 12(34.3%) had prolonged QT. The difference was not significant ($p>0.05$).

Conclusion

In the present research we concluded that low serum levels of calcium occurring without any warning signs are responsible for remarkable increase in QT interval and is a morbid but ignored consequence in patients affected by long-standing liver disease. This can become a cause for ventricular arrhythmias and can play a role in increased death rate in these individuals. So an attempt should be done to identify noteworthy low levels of and prolonged QT ,though having no adverse events, with the aim of taking actions to correct the hypocalcemia and QT prolongation to lessen gravity of disease and death rates in these patient associated with these consequences.

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References

1. Bosan A, Qureshi H, Bile KM, Ahmad I, Hafiz R. A review of hepatitis viral infections in Pakistan. J Pak Med Assoc. 2010;60(12):1045-1058.
2. Ali M, Idrees M, Ali L, Hussain A, Rehman IU, Saleem S, et al. Hepatitis B virus in Pakistan: a systematic review of prevalence, risk factors, awareness status and genotypes. Virology journal. 2011; 8(1): 102.
3. Lalama MA, Saloum Y. Nutrition, fluid, and electro-

lytes in chronic liver disease. Clinical Liver Disease. 2016;7(1):18-20.

4. Alia I, Ahmed W, Sajjad U. Incidence of asymptomatic hypocalcaemia and QT prolongation in patients with chronic liver disease. J Cardiovasc Dis. 2014; 12(1):5-8.
5. Țieranu E, Donoiu I, Istrătoaie O, Găman AE, Țieranu LM, Gheonea DI, et al. Q-T Interval Prolongation in Patients with Liver Cirrhosis. Curr Health Sci J. 2018;44(3):274-279.
6. Sulehria SB, Ghafoor A, Rauf M, Zafar M. Frequency of QTC Prolongation in Chronic Liver Disease. PJMHS Online. 2013;7:986-88.
7. Ali M, Shahzad A, Adil IK, Alam S, Noor H, Imran A, et al. Frequency of Corrected QT Interval in Patients With Cirrhosis. J Rawal Med Coll. 2016;20(2):79-81.
8. Memon MS, Zaki M. Burden of chronic liver disease and liver transplantation in Sindh. JLUMHS. 2013; 12(1): 01.
9. Bhatti AB, Ali F, Satti SA. Prolonged QTc Interval Is an Electrophysiological Hallmark of Cirrhotic Cardiomyopathy. Open Journal of Internal Medicine. 2014;4(1):33.
10. Ali MJJoRMC. Frequency of Corrected QT Interval in Patients With Cirrhosis. 2016;20(2):79-91.
11. Birda CL, Kumar S, Bhalla A, Sharma N, Kumari S. Prevalence and prognostic significance of prolonged QTc interval in emergency medical patients: A prospective observational study. Int J Crit Illn Inj Sci. 2018;8(1):28-35.
12. Liu P, Han D, Sun X, Tan H, Wang Z, Liu C, et al. Prevalence and risk factors of acquired long QT syndrome in hospitalized patients with chronic kidney disease. 2019;67(2):289-294.
13. Kumar A, Riaz SU, Kazmi SHM, Kumar R, Ghauri MIJAoASH, Medical K, et al. Prolongation of QT Interval in ECG: A Hidden Complication of Cirrhotic Liver Disease. 2019;24(1).
14. Kuchay MS, Mishra SK, Farooqui KJ, Bansal B, Wasir JS, Mithal A. Hypercalcemia of advanced chronic liver disease: a forgotten clinical entity! Clinical Cases in Mineral and Bone Metabolism 2016;13(1):15.