

## The Prolonged Corrected QT-Interval in Children Presented with Acute Rheumatic Fever

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### ABSTRACT

**Objective:** To determine the frequency of prolonged corrected QT-interval on ECG in children presented with acute rheumatic fever.

**Study Design:** Prospective observational study.

**Place and Duration of Study:** Department of Paediatric Cardiology, National Institute of Cardiovascular Diseases Karachi, Pakistan from Aug 2020 and Feb 2021.

**Methodology:** Children presented with features of acute rheumatic fever and fulfilling the selection criteria were enrolled in the study. After getting consent, their demographic details, clinical features, lab values and echo findings were recorded in pro forma. Their 12-lead ECG was analysed by two paediatric cardiology fellows for rhythm and conduction abnormalities at the time of admission and after getting treatment. Bazette's formula used for calculation of corrected QT-interval, data analysed in SPSS version 21 and presented in tabulated form.

**Results:** A total of 50 patients were included in the study. There were 31(62%) males and 19(38%) females, 37(74%) patients presented with recurrence and 13(26%) for the first time. On 12-lead ECG corrected QT-interval was prolonged in 14(28%) patients and it was significantly correlated with heart rate of the patients with acute rheumatic fever ( $p$ -value 0.027).

**Conclusion:** Prolonged corrected QT-interval is significantly related with acute rheumatic fever and should be evaluated in each patient of acute rheumatic fever.

**Keywords:** Acute Rheumatic fever, Corrected QT-interval, Rheumatic heart disease.

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### INTRODUCTION

Acute rheumatic fever is a major public health problem and it is more common in developing countries<sup>1</sup>. Currently, the annual incidence varies from < 0.5/100 000 in highly developed countries to > 100/100 000 in poor countries.<sup>2</sup> Rheumatic fever (RF) is an autoimmune, multiorgan inflammatory disease that occurs as a sequel of group A  $\beta$ -haemolytic streptococcal infection in genetically susceptible individuals.<sup>3</sup> The patients develop carditis (50–78%), arthritis (35–88%), chorea (2–19%), erythema marginatum (6%) and subcutaneous nodules (1–13%).<sup>4</sup> Approximately, 60% of patients in endemic countries develop chronic rheumatic heart disease, which is a complication of rheumatic fever.<sup>5</sup> The diagnosis of initial episodes of acute rheumatic fever is based on modified Jones criteria which was first proposed by T. Duckett Jones in 1944. It requires two major or one major plus two minor criteria with evidence of group A streptococcal infection. The diagnosis of subsequent

episodes of the disease requires a confirmation of two major criteria or one major and two minor criteria or three minor criteria.<sup>6-7</sup> Acute rheumatic fever is very prevalent in our region and the relationship of prolonged corrected QT-interval on ECG with acute rheumatic fever has not been studied in our population. So, we aimed to study the cost effective and simple tool of diagnosis which may result in timely diagnosis and management of acute rheumatic fever and prevention of complications like heart failure and progression of the disease.

### METHODOLOGY

This study was conducted at the Department of Paeds Cardiology, NICVD Karachi for a period of six months between August 2020 and February 2021, after getting permission from the ethical review board (ERC#33/2019). Total 50 patients, who were fulfilling inclusion criteria according to modified Jones criteria revised in 2015 were enrolled in the study.

**Inclusion Criteria:** Children with features of acute rheumatic fever were included.

**Exclusion Criteria:** Patients were selected by using non-probability, consecutive sampling technique and

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patients having history of using drugs that prolonged QT-interval and having electrolytes abnormalities were excluded.

After getting consent from the parents or guardians, history and examination was done on each patient and investigations including CBC, ESR, CRP, ASOT and throat swab culture sent. Demographic characteristics, clinical, laboratory, electrocardiographic and echocardiographic findings of the patients were evaluated. Standard 12 lead ECG performed in all the enrolled patients to look for heart rate, rhythm, PR-interval, QT-interval and Bazett formula used for calculation of corrected QT-interval. Two dimensional echocardiography performed in all the patients. The diagnosis of acute rheumatic fever was made in accordance with the modified Jones criteria. Benzathine penicillin G was started for secondary prophylaxis with 3 week intervals in all patients. Oral steroids, and non-steroidal anti-inflammatory drugs (NSAIDs) when the steroid was gradually decreased, were given in the presence of moderate-to-severe carditis, whereas NSAIDs was given alone in the situation of mild carditis. Anti-congestive therapy consisting of digoxin, diuretics, or angiotensin-converting enzyme inhibitors was started in patients with evidence of heart failure. Treatment was continued for 4-8 weeks according to the severity of carditis together with clinical and laboratory responses to treatment. All data collected on pro forma and entered in SPSS version 21. Frequency and percentages calculated for categorical variables and Chi -square test used to ascertain the impact of effect modifiers on outcome variables. The *p*-value of ≤ 0.05 taken as criteria for statistical significance.

**RESULTS**

A total of 50 patients were included in the study. There were 31(62%) male and 19(38%) female patients, 37(74%) were known cases of rheumatic heart disease and presented with recurrence while 13(26%) presented for the first time (Table 1).

On echocardiography, Mitral regurgitation (MR) was present in all patients 50(100%), most of the patients had severe MR 31(62%), moderate 16(32%) and mild MR in only 3(6%) patients. Mitral stenosis (MS) was present in 12(24%) patients, among them 7(14%) have severe MS, moderate MS in 2(4%) and mild MS in 3(6%) patients. Aortic regurgitation (AR) was present in 22(44%) patients, majority of them have mild AR 12(24%) patients, moderate 9 (18%) and severe AR in 1(2%) patients. Aortic stenosis was

present in 3(6%) patients and among them 2 patients (4%) have moderate AS and 1(2%) has mild AS.

On 12 lead ECG, most of the patients have tachycardia 25(50%), sinus rhythm was present in 46 patients (92%) and 4 patients have atrial fibrillation. PR-interval and corrected QT-interval were prolonged in 20(40%) and 14(28%) patients respectively. PR-interval was prolonged in 13(26%) cases with normal corrected QT-interval and in 7(14%) cases with prolonged corrected QT-interval. Corrected QT-interval was prolonged in 7(14%) patients with normal PR interval and in 7(14%) patients with prolonged PR interval. All the patients having prolonged QT-interval (16%) also had prolonged corrected QT-Interval, while corrected QT-interval was prolonged in 6(12%) patients with normal QT-interval as well, statistically significant with *p*-value 0.018. Corrected QT-interval was prolonged in 10(20%) patients with tachycardia, in 3(6%) patients with normal heart rate and in 1(2%) patients with bradycardia with *p*-value 0.027(Table 2).

**Table 1: Demographic Details of the patients**

Characteristics	Total	Corrected-QT Interval		P-value
		Normal	Prolonged	
Total (n)	50	36 (72%)	14 (28%)	-
<b>Gender</b>				
Male	62% (31)	61.1% (22)	64.3% (9)	0.836
Female	38% (19)	38.9% (14)	35.7% (5)	
Age (years)	12.68 ± 1.94	12.75 ± 2.02	12.5 ± 1.79	0.687
9 to 12 years	42% (21)	38.9% (14)	50% (7)	0.475
13 to 15 years	58% (29)	61.1% (22)	50% (7)	
<b>Socioeconomic status</b>				
Low	88% (44)	88.9% (32)	85.7% (12)	0.756
Middle	12% (6)	11.1% (4)	14.3% (2)	
<b>Knowledge of the disease</b>				
Low	86% (43)	86.1% (31)	85.7% (12)	0.151
Good	8% (4)	11.1% (4)	0% (0)	
Very Good	6% (3)	2.8% (1)	14.3% (2)	
<b>Known case of RHD</b>				
First presentation	26% (13)	25% (9)	28.6% (4)	0.796
Recurrence	74% (37)	75% (27)	71.4% (10)	

**DISCUSSION**

Acute rheumatic fever (ARF) is an inflammatory disease which is caused by group A β-haemolytic Streptococcus infection and is still an important reason for mortality and morbidity in low in-come countries.<sup>8-9</sup> A 2005 systematic review concluded that there were approximately 471,000 cases of ARF each year (336,000 in children aged 5-14 years), 15.6-19.6 million prevalent cases of RHD and approximately 350,000 annual deaths as a result of ARF or RHD; almost all

deaths occurred in low-income and middle-income countries.<sup>10-11</sup>. Our study also showed prevalence of most cases in the low socioeconomic class. Because of low education and poor knowledge of the disease, many of these cases present late in the course of the disease and compliance of these patients to secondary prophylaxis not good. In our study most cases were known patients of rheumatic heart disease and presented in severe conditions, they were not compliant to routine follow up and penicillin prophylaxis.

**Table -II: ECG changes in Acute Rheumatic Fever**

Characteristics	Total	Corrected-QT Interval		p-Value
		Normal	Prolonged	
Total (N)	50	36 (72%)	14(28%)	-
<b>Heart rate</b>				
Normal	48%(24)	58.3%(21)	21.4%(3)	0.027*
Tachycardia	50%(25)	41.7%(15)	71.4%(10)	
Bradycardia	2%(1)	0%(0)	7.1%(1)	
<b>Rhythm</b>				
Rhythm sinus	92%(46)	94.4% (34)	85.7%(12)	0.307
Arrhythmia	8%(4)	5.6% (2)	14.3%(2)	
<b>PR interval</b>				
Normal	60%(30)	63.9%(23)	50%(7)	0.368
Prolonged	40%(20)	36.1%(13)	50%(7)	
<b>RR interval</b>				
Normal	92%(46)	94.4%(34)	85.7%(12)	0.307
Abnormal	8%(4)	5.6%(2)	14.3%(2)	
<b>QT interval</b>				
Normal	84%(42)	91.7%(33)	64.3%(9)	0.018*
Prolonged	16%(8)	8.3%(3)	35.7%(5)	
<b>ECG changes after anti-inflammatory treatment</b>				
HR improved	34%(17)	41.7%(15)	14.3%(2)	0.203
Rhythm normalized	8%(4)	5.6%(2)	14.3%(2)	
PR interval normalized	24%(12)	25%(9)	21.4%(3)	
QT normal	10% (5)	5.6%(2)	21.4%(3)	
cQT normal	24%(12)	22.2%(8)	28.6%(4)	

Acute rheumatic fever may present as joint pain, carditis, chorea, erythema marginatum and subcutaneous nodules in children.<sup>12</sup> Patients may have a history of fever and in cases of progressive heart disease, it may present as murmur of mitral regurgitation or heart failure in severe cases.<sup>13</sup> In our study, most of the patients presented with features of carditis and mitral regurgitation were the major finding on echocardiography. This correlates with other studies in which the most common presentation was also cardities followed by arthritis.<sup>14</sup>

It is also evident that carditis is the most common presentation of ARF and also has important consequences in the course of the disease.<sup>15</sup> Various

rhythm and conduction abnormalities have been reported in the literature. More recently, attention has been directed toward the QT-interval in rheumatic fever. The duration of electrical systole as measured by the Q-T interval is known to be prolonged in a variety of pathologic states. In certain instances, a definite lengthening of the Q-T interval has been seen in rheumatic carditis. The prolongation of the Q-T interval in the electrocardiogram of patients suffering from valvular disease or rheumatic carditis was noticed by Berliner (1931) and by Drawer, Hafkesbring, and Ashman (1937). It has been shown that there is a correlation between acute phase reactants and prolonged QT interval. Karacan et al. found a significant correlation between prolonged corrected QT interval and patients without carditis.<sup>16</sup>

Rhythm disorders are less common than conduction disorders in patients with ARF and prolonged corrected QT-intervals are more common than expected.<sup>17-18</sup> First degree of AV block is the most common conduction abnormality in patients with ARF. Sokolow et al., reported conduction abnormalities detected by ECG in 88(60%) of 147 cases. Of these, 83(94.3%) were reported as first degree AV block, 3(3.4%) with complete AV block and 2(2.3%) with intraventricular block.<sup>19</sup> In Zalstein's study, among 65 patients diagnosed with ARF, 72.3% of the patients diagnosed with first degree AV block, the second and third degree blocks were 1.5% and 4.6% of all cases, respectively.<sup>17-20</sup> In our study, incidence of first degree AV block (prolonged PR-interval 40%,20 cases) was lower than the previous reports in the literature. Although the vast majority of rhythm and conduction abnormalities detected during the course of ARF are self-limited and respond well to anti-inflammatory treatment, our study results were not compatible with this. PR-interval normalized in only 12 patients, QT-interval normalized in 10% and corrected QT interval normalized in 24% cases after treatment, so further studies are needed with both control and cohort groups of patients with acute rheumatic fever with larger sample size involving cardiac and general pediatric centres to see the effect of disease activity and anti-inflammatory treatment on prolonged corrected QT-interval and other conduction abnormalities with long term follow up.

We suggest a routine ECG evaluation in all the patients with Acute Rheumatic Fever and calculation of prolonged corrected QT-interval in every case.

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**Authors' Contribution**

Following authors have made substantial contributions to the manuscript as under:

MAA: & R: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

FUR: & ASS: Data acquisition, data analysis, approval of the final version to be published.

VK: & NP: Critical review, concept, drafting the manuscript, approval of the final version to be published.

Authors agree 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.

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