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Title: Electrocardiographic Findings of Leprosy

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Introduction

Leprosy is contagious disease caused by the bacillus Mycobacterium Leprae. The World Health Organization (WHO) reported that in 2015, 174608 new cases were detected in 136 countries worldwide(1). It is continues to have a significant global impact. The absolute mechanism of contagious of leprosy is not completely known. The most common view was that the disease was transmitted by contact between of leprosy and healthy persons. However the idea that leprosy is recently transmitted by respiratory system tract has been increasing. Although leprosy affects the peripheral nerves and skin and it can cause irreversible impairment of nerve function and chronic disability(2). There are also studies showing the effects of leprosy in the cardiac autonomic system(3). The autonomic disorder in leprosy patients can be explained on the basis of neurotrophic action of lepra bacilli that infiltrate the nerve fibres(4). In this study, we tried to examine the reflections of these cardiac and autonomic effects on ECG.

Methods

After the ethical committee approval was obtained, Elazıg Dermatology and Leprosy Hospital records were reviewed retrospectively. A total of 66 people, including, 33 people with leprosy and 33 people without the leprosy disease were included in the study. The demographic features, the risk factors, cardiovascular histories, ECG and ecocardiographic findings of all patients were obtained from the hospital records. The Schiller Cardiovit AT-102 plus was used (10 mm/mV calibration and 25 mm/s velocity) for the standard 12-derivation ECG recordings. The patients ECG recordings were examined by the two expert cardiologists, and in the case of controversy, a third cardiologist make decision. Only lepramatous leprosy patients were included in the study. The ECG recordings were compared in terms of heart rate, PR interval, QT, QTc, JTc and T peak to end (Tp-e) duration. ECG recordings of the groups were compared based on the frequencies of right bundle branch block (RBBB), left bundle branch block (LBBB), left anterior hemiblock (LAH), left posterior hemiblock (LPH), first degree atrioventricular block, unifasiculer block, bifasiculer block, trifascicular block and fragmentated QRS. QTc intervals were calculated using the Bazett formula. QT interval is calculated as the interval from the beginning of the QRS to the end of the T wave. JTc is defined as the corrected JT interval and it is calculated as QTc minus QRS Duration (JTc = QTc - QRS duration). The Tp-e interval is defined as the interval from the peak of T wave to the end of T wave. Fragmentation on ECG defined as: presence of an additional R wave or, presence of a notch in the tip of the S wave or more than one large R'

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wave in two consecutive derivation(5). Those with drug use that could affect ventricular repolarization were excluded from the study.

Statistical Analysis

Statistical analysis was performed via SPSS 15.0 for Windows Evaluation Version statistical package. Continuous variables were presented as mean±standard deviation . Categorical variables were summarized as frequencies. Differences between the two groups according to continuous variables were determined by the independent samples t-test . Categorical variables were compared by, chi-square or Fisher's exact test. A p value of <0.05 was accepted statistically significant.

Results

The mean age of the leprosy group was significantly higher than the non-leprosy group (70.06±13.74 vs 56.66±13.52, p<0.01). Average duration of illness in the leprosy group was 43.57±15.11 years. The proportion of male gender was significantly higher in the group with leprosy(24(%72.7) vs 15(%45.5), p=0.024). Statistically, there are not significant differences between the groups, related to the diabetes mellitus , hypertension, smoking and coronary artery disease(CAD). 11 patients (%33.3) had limb amputation (4 finger and 7 limb amputations). Hand, foot, eye and nose involvement in 2 patients; hand, foot and eye involvement in 18 patients; foot and eye involvement in 4 patients; foot and hand involvement in 4 patients was observed. In 3 patients only eye, in 1 patient only foot and in 1 patient only hand involvement was observed. There was no statistically difference between the groups in terms of heart rate, PR period, JTc duration, and LPH, 1st degree AV block, bifascicular block, trifasciculer block, QRS fragmentation, left and right branch block frequency on ECG (Table 1). In leprosy group, QT (391.30 vs 367.66, p <0.01), QTc (423.57 vs 407.15, p <0.01) and T peak to T end (74.18 vs 66.93, p<0.001) intervals were significantly longer than non leprosy group. The left anterior hemiblock(LAH) was observed more in patients with Leprosy disease (42.4% in 14 patients), than the non-leprosy group (42.4% vs. 12.1%, p < 0.01). In addition, unifasiculer block ratio was significantly high in the leprosy group (39.4% vs. 9.1%, p <0.01). When the leprosy patients were examined according to sex, there was no statistically significant difference between the groups based on ECG findings(Table 2).

Discussion

Today, leprosy continues to be a significant health problem. Despite the advances in its diagnosis and treatment, the fact that 174608 new cases were reported in 2015(1). It shows that how much this disease continues to be an actual threat. Due to the variation of its immunopathology, it has wide clinical results (6). Although primary involvement happens in the skin and peripheral nervous system, the cardiac system is also affected by this disease, and the follow-up of the cardiac system requires special attention. In this study, we showed that the leprosy disease is an important cause of QT, QTc and Tp-e intervals prolongation. In addition to the findings of other studies conducted before, we showed that in the disease leprosy, most of the involvement occurs in the left anterior branch. The fact that left anterior hemiblock (LAH) is detected in 42.4% of leprosy patients is quite remarkable.

So, what causes to the QT and QTc interval prolongation and the high rates of LAH? Such cardiac effects of the leprosy have been evaluated in earlier studies, and it was showed that the disease leprosy causes cardiac amyloidosis (7) and that it affects the cardiac autonomous system (5-10). So, is it possible that the only cause of the high frequency of LAH and the prolongation of QT and QTc in leprosy could be due to these reasons? In some studies conducted before, it has been shown that the QT and QTc intervals were not prolonged in amyloidosis(11, 12) and in echocardiographic examinations of our patients, we did not follow the appearance compatible with amyloidosis. In this case, we think that the reason of QT, QTc and Tp-e interval prolongation is mostly the involvement of the autonomous nervous system. In leprosy patients, the parasympathetic system involvement occurs before the sympathetic system involvement and parasympathetic system involvement is more severe. The severity of the neuropathy is directly correlated with the duration of the disease (13). These disorders that develop in the autonomous system are explained by the neutrophilic effects of the leprosy bacilli that infiltrate the sympathetic and parasympathetic fibers. The autonomous and intrinsic cardiac involvement affect ventricular repolarization and prolong the QTc and Tp-e intervals (14, 15). It is now well known that QT and QTc prolongation cause life-threatening arrhythmias and it has also started to be realized that LAH is important as well regarding cardiac comorbidities. In studies conducted before, LAH has been founded that it is associated with increased cardiac death in patients with suspicion of coronary artery disease and increased mortality in-hospital and during the 6 months follow up in patients with acute coronary syndrome (16,17). Hence, in leprosy patients, besides QT and QTc prolongation, LAH that occurs at high rates is also an important ECG finding that should be considered and it is highly important to monitor the QT and QTc intervals on ECG to predict arrhythmic events in these patients. On the other hand, recent

studies showed that prolongation of the interval Tp-e is a marker of ventricular arrhythmias, increased risk of mortality in congenital long QT syndromes, hypertrophic cardiomyopathy(HCMP) and also in patients with myocardial infarction who undergoing primary PCI(18-21). Prolongation of Tp-e interval indicates a period of potential vulnerability to reentrant ventricular arrhythmias(22). Therefore, it is clinically important that we have shown that Tp-e interval is prolonged in leprosy patients, and it shows us that we should be careful about cardiac complications, especially arrhythmic events.

In this study, we could not find a statistically significant difference between the groups in terms of CAD, but contrary to our work, it has also been shown that the frequency of coronary artery disease is higher in leprosy patients at old ages and it shown that some deaths among leprosy patients were due to cardiac causes(23). Also Yajima M. et al study's results suggest that, paralytic arterial changes in leprosy patients may promote the ischemic cardiac disease and coronary sclerosis(24). But we think, further research is needed to make a definite decision in this regard.

The other important point is, why the involvement occurs in the left anterior branch most commonly in the leprosy disease. Is it the most sensitive conduction area to the effects of leprosy on autonomous functions is the left anterior branch, or is it that leprosy's intrinsic cardiac involvement occurs most in this area? Does this ECG finding show the area where the leprosy disease is most effective in the heart? To our knowledge, these questions do not have complete answers. Unfortunately, our study cannot provide a complete explanation to these questions because it does not include histopathological evaluation. There is a need for further studies on this subject, and our study could provide guidance for the research of this subject.

Study Limitations

Although this study has presented these findings, it has some limitations such as being a single center study, the low number of patients, the lack of histopathological results, and the lack of long-term follow-up of patients with QT prolongation and those that developed LAH. Furthermore, the statistical significance of the age difference between the groups may have affected on the results.

Conclusion

As a result, leprosy is a multisystem disease with significant cardiac effects. Leprosy has a significant effect on QT, QTc and Tp-e intervals. Prolongation of the QT, QTc and Tp-e intervals are indicator of the leprosy's effect on the cardiac autonomic system. The ratio of the left anterior hemiblock is also quite high and that may be a marker of the area where leprosy is most effective on the heart. However, further research is needed in this regard.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Table 1. Baseline Characteristics and ECG Findings of the Patients With and Without Leprosy

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Variables	Leprosy (+) (n=33)	Leprosy (-) (n=33)	P value
Age(years), mean (SD)	70.06±13.74	56.66±13.52	**<0.01***
Gender (male), n (%)	24(%72.7)	15(%45.5)	**0.024***
Diabetes Mellitus, n (%)	3(%9.1)	2(%6.1)	1
Hypertension, n (%)	15(%45.5)	8(%24.2)	0.071
CAD, n (%)	4(%12.1)	2(%6.1)	0.672
Smoking, n(%)	8(%24.24)	11(33.33)	0.415
Heart Rate (bpm)	71.95±17.72	75.18±11.10	0.300
PR (ms)	162.00±28.89	154.12±23.07	0.225
QT (ms)	391.30±38.80	367.66±24.20	**<0.01***
QTc (ms)	423.57±25.49	407.15±19.96	**<0.01***
LAH, n (%)	14 (%42.4)	4(%12.1)	**<0.01***
LPH, n (%)	1(%3.0)	2(%6.1)	1
First degree block, n (%)	6(%18.2)	2(%6.1)	0.258
Unifascicular block, n (%)	13(%39.4)	3(%9.1)	**<0.01***
Bifascicular block, n (%)	3(%9.1)	4(%12.1)	1
Trifasciculer block, n (%)	0(%0)	0(%0)	
LBBB, n (%)	2(%6.1)	0(%0)	0.492
RBBB, n (%)	4(%12.1)	3(%9.1)	1
QRS Fragmentation, n(%)	5(%15.15)	2(%6.06)	0.477
JTc (ms)	314.36±32.33	313.87±22.34	0.94
T peak to T end interval(ms)	74.18±11.03	66.93±8.72	**<0.01***

Independent Samples T-Test, chi-square Test, Fisher'sExact Test (Continues variables are reported mean±SD or median, Categorical variables are reported n%). *p<0.05 statistically significant.
Abbreviations: CAD, Coronary artery disease; LAH, Left anterior hemiblock; LPH, Left posterior hemiblock; LBBB, Left bundle branch block; RBBB, Right bundle branch block.

Table 2. ECG findings according to sex in patients with leprosy

	(n=24)	(n=9)	
Heart Rate (bpm)	69.25±13.09	79.22±13.35	0.300
PR (ms)	159.16±31.42	169.55±20.33	0.062
QT (ms)	397.70±42.22	374.22±21.15	0.123
QTc (ms)	421.87±25.62	428.11±26.09	0,540
LAH, n (%)	11(%45.83)	3(%33.33)	0.698
LPH, n (%)	1(%4.16)	0(%0)	1
First degree block, n (%)	4(%16.66)	2(%22.22)	1
Unifascicular block, n (%)	10(%41.66)	3(%33.33)	1
Bifascicular block, n (%)	3(%12.50)	0(%)	0.545
Trifasciculer block, n (%)	0(%0)	0(%0)	
LBBB, n (%)	2(%8.33)	0(%0)	1
RBBB, n (%)	4(%16.66)	0(%0)	0.555
QRS Fragmentation, n(%)	4(%16.66)	1(%11.11)	1
JTc (ms)	308.25±31.95	330.66±28.89	0.076
T peak to end interval(ms)	75.00±10.32	72.00±13.15	0.495

Independent Samples T-Test, chi-square Test, Fisher'sExact Test (Continues variables are reported mean±SD or median, Categorical variables are reported n%). *p<0.05 statistically significant.
Abbreviations: LAH, Left anterior hemiblock; LPH, Left posterior hemiblock; LBBB, Left bundle branch block; RBBB, Right bundle branch block.