Prognostic Significance of Electrocardiographic Abnormalities in Diphtheritic Myocarditis After Hospital Discharge: A Long-Term Follow-Up Study

Turgay Celik, M.D.,* Nazim Selimov, M.D.,† Afet Vekilova, M.D.,‡
Hurkan Kursaklioglu, M.D.,* Atila Iyisoy, M.D.,* Selim Kilic, M.D.,‡
and Ersoy Isik, M.D.*

From the *Department of Cardiology, Gulhane Military Medical Academy, Etlik, Ankara, Turkey; †Department of Cardiology, Central Army Hospital, Baku, Azerbaijan; and ‡Department of Epidemiology, Gulhane Military Medical Academy, Etlik, Ankara, Turkey

Objective: We aimed to investigate the long-term cardiac mortality and the relationship between cardiac mortality and electrocardiographic abnormalities in patients with diphtheritic myocarditis who survived after hospital discharge.

Materials and Methods: Between 1991 and 1996, 32 patients (all males, mean age 21.00 ± 3.77 years) surviving diphtheritic myocarditis were included in the study and they were followed up for an average of 16.3 months (range 10.3–26.8 months) after hospital discharge. Clinical evaluation, ECG, and echocardiography were performed on admission, daily while in hospital and at the time of discharge. ECG changes were permanent during the follow-up period. The causes of death of the patients during follow-up period were inferred from the death records of the patients and talking to the people witnessing cardiac arrest.

Results: We observed that the patients with left bundle branch block (LBBB) and T wave inversion at hospital discharge had lower survival rates than that of the patients without these ECG changes in the long term. Although univariate Cox regression analysis identified LBBB ($P = 0.001$) and T wave inversion ($P = 0.014$) as the predictors of survival, only LBBB was an independent predictor of survival in multivariate Cox regression analysis. Adjusted hazard ratio was calculated as 13.67 for LBBB ($P = 0.001$; CI = 2.81–66.28).

Conclusion: Diphtheritic myocarditis does not only demonstrate a malignant clinical course during acute phase of the disease, but also during the long-term follow-up period, especially in patients with LBBB and T wave inversion. Besides, T wave inversion and LBBB can help us to predict survival rate of the patients in long term. Moreover, LBBB is an independent predictor of long-term survival in diphtheritic myocarditis.

A.N.E. 2006;11(1):28–33

Diphtheritic myocarditis; long-term prognosis; electrocardiography

Diphtheria is an important public health problem in much of the developing world and has had resurgence in Eastern Europe and the republics of former Soviet Union.¹ *Corynebacterium diphtheria* may cause widespread toxin-mediated damage, in the heart (diphtheritic myocarditis), kidneys, and nervous system (especially cranial and peripheral nerves).²

The diphtheria epidemic in the newly independent states of former Soviet Union reached Azerbaijan in 1991.^{3,4} From 1990 to 1996, 2182 cases of

diphtheria and 286 diphtheria fatalities (case fatality rate: 13.1%) were reported in Azerbaijan, primarily among people 5–39 years of age.⁵

Cardiac damage is still the leading cause of mortality in adults with diphtheria, accounting for at least one-third of all deaths.⁶ The diphtheria epidemics in the Russian Federation and newly independent states of former Soviet Union in the 1990s provided an opportunity to investigate the epidemiology and clinical characteristics of diphtheria.^{7,8}

Address for reprints: Turgay Celik, M.D., GATA Kardiyoloji A.D, 06018 Etlik, Ankara, Turkey. Fax: +90 (312) 3042352; E-mail: benturgay@yahoo.com

©2006, Copyright the Authors
Journal compilation ©2006, Blackwell Publishing, Inc.

Although the patients with diphtheritic myocarditis appear to make full recovery,^{9,10} there have been no data about the long-term cardiac mortality and electrocardiographic predictors of it in the patients with diphtheritic myocarditis who survive.

In the current study, we investigated the long-term cardiac mortality and the relationship between mortality and electrocardiographic abnormalities in the patients with diphtheritic myocarditis who survived after hospital discharge.

MATERIALS AND METHODS

Patients

This study was conducted at Gulhane Military Hospital and the Central Army Hospital, a referral center in Baku city for the soldiers with diphtheria from all the regions of Azerbaijan during 1990s diphtheria epidemics. The study was approved by both the national ethic committees and informed consent was obtained from all the patients included in the study.

The patients with dilated cardiomyopathy and/or depressed left ventricular systolic functions (left ventricular ejection fraction <55%), ECG changes not persisting after hospital discharge, and age <15 years were excluded from the study. Because all the patients with complete atrioventricular (AV) block (7 patients) did not survive, they were excluded from the study. Between 1991 and 1996, 32 patients with diphtheritic myocarditis (32 males, mean age 21.00 ± 3.77 years) surviving were included in the study and they were followed up for an average of 16.3 months (range 10.3–26.8 months) after hospital discharge. The severity of myocarditis was evaluated using clinical criteria like general condition, arterial pressures, heart sounds, extent of tachycardia and character of arrhythmia, and degree of heart failure.

Study Protocol

Clinical evaluation, ECG recordings, and transthoracic echocardiography (TTE) were performed on admission to hospital, daily while in hospital, and at the time of discharge. ECG changes evaluated for long-term prognosis in the study group were permanent during the follow-up period. Empirical treatment was commenced without waiting for laboratory results confirming diphtheria. Benzylpenicillin (100,000 IU/kg four

times a day for 14 days, intravenously), diphtheria antitoxin (daily doses of 40,000–120,000 IU, intramuscular), and prednisolone (1 mg/kg per day, intravenously) were used in the treatment. After hospital discharge, control visits were performed every 6 months. All the patients were reevaluated by physical examination, ECG, and TTE in control visits. Also, survival status of the patients was controlled by calling them every month. The cause of death of the patients during follow-up period was inferred from the death records of the patients and talking to the people witnessing cardiac arrest. TTE was performed using ESAOTE 2.5 MHz probe (ESAOTE, Genova, Italy) at the left lateral position.

Classification and Definitions

Diphtheria was defined as an exudative inflammation of the upper respiratory tract (with or without pseudomembranes) and a positive throat culture for a toxin-producing strain of *C. diphtheria*. There is no uniformly accepted clinical classification of diphtheria. The severity of acute diphtheria was classified by three features as stated in Russian classification of diphtheria: presence or absence of pseudomembranes, anatomical distribution of pseudomembranes, and toxicity.¹¹ The clinical form was localized if there was nonmembranous pharyngotonsillitis or pseudomembranes on tonsils only; or as extensive if the pseudomembranes extended to fauces, uvulae, palate, pharynx, or lower respiratory tract. The disease was classified as toxic if there was marked lymphadenopathy or subcutaneous edema of the neck ("bull neck"). Neuropathy was defined as a new onset of sensory or motor defects in cranial or peripheral nerves detected on physical examination.¹¹

Classification of an ECG as abnormal was based on the criteria for (diphtheritic) myocarditis.¹² Arrhythmias, abnormal Q waves, and repolarization abnormalities were accepted as myocardial abnormalities. Specific criteria included ST-segment elevation of 1 mm, at least two consecutive chest leads or one limb lead, ST-segment depression >1 mm, T wave inversion (except V₁ and aVR), isoelectric T waves, right and left atrial and ventricular hypertrophy, and QTc interval >0.39 seconds. The following abnormalities were defined as conduction abnormalities: AV block, bundle branch block (BBB), and hemiblock. ECG abnormalities were regarded as diphtheria related if there was a change

from abnormal to normal findings, or the reverse, or if there was no other explanation (underlying cardiovascular disease or medication) for a persistent abnormality.

The North American Society of Pacing and Electrophysiology (NASPE) defined sudden cardiac deaths (SCDs) as those that were either a witnessed cardiac arrest within an hour of the onset of acute symptoms, or an unexpected, unwitnessed death in a patient known to be well in the last 24 hours.¹³

Statistical Analysis

Results are expressed as the mean ± SD and percents. The relationship between independent (ECG variables) and dependent variables (survival status) was analyzed using Cox regression model in univariate analysis. We investigated the effects of different ECG variables on survival by calculating hazard ratios (HR) in univariate analysis for all the variables. Variables for which the unadjusted P value < 0.20 in univariate Cox regression analysis were identified as potential risk markers and included in the full model. We reduced the model by using backward elimination method. Survival curves were generated by the Kaplan–Meier method and log-rank tests were used to assess differences in survival. Survival was calculated from the time of hospital discharge to censor or end point. The study end point was cardiac death. A probability value of <0.05 was considered significant. Statistical analyses were performed by using SPSS 11.5 Statistical Package Program for Windows (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Seventy patients with diphtheritic myocarditis were referred to the cardiology clinics. Twenty-eight patients died in the hospital stay with a mortality rate of 40%. Of these, 10 patients had left bundle branch block (LBBB); 6 patients, T wave inversion; 3 patients, ST changes especially in the precordial leads; 7 patients, complete AV block; and 2 patients, intraventricular conduction delay (IVCD). Moreover, 10 patients were excluded from the current study. Of these, 7 patients had depressed left ventricular function with a left ventricular ejection fraction (LVEF) <55% and 3 patients had transient ECG changes not persisting after hospital discharge. Among the patients with

Table 1. Electrocardiographic Changes of the Patients with Diphtheritic Myocarditis

ECG Changes	Patients (n = 32)	
	No.	Percent
ST-segment changes	23	71.9
T wave inversion	11	34.4
QTc interval prolongation	9	28.1
Ventricular extrasystole	10	31.3
Second-degree atrioventricular block	13	40.6
Left anterior fascicular block	9	28.1
Left posterior fascicular block	2	6.3
Right bundle branch block	12	37.5
Left bundle branch block	11	34.4

low LVEF, 4 patients had LBBB; 2 patients, IVCD; and 1 patient, Mobitz type-II AV block. A total of 32 patients with diphtheritic myocarditis eligible for the study were followed up for an average of 16.3 months. All the patients were male whose mean ages were 21.00 ± 3.77 years. The average in-hospital stay of the patients was 16.25 ± 4.25 days (range 10–25 days). Permanent electrocardiographic changes (>6 months) that suggested diphtheritic heart damage are represented in Table 1. The most frequently encountered ECG abnormality was ST segment changes (23 patients, 71.9%). LBBB and right bundle branch block (RBBB) were detected in 11 (34.4%) and 12 (37.5%) patients, respectively. T wave inversion was observed in 11 (34.4%) patients. Second-degree AV block was observed in 13 patients. All of them had Mobitz type-I AV block and they were asymptomatic during in-hospital stay. The duration of second degree AV block in these patients was confined to in-hospital follow-up period. Ten patients had ventricular extrasystoles in-hospital stay. Ventricular extrasystoles were not frequent (<10 ventricular extrasystoles per hour) and complex. The average follow-up duration from the onset of hospital discharge to last control visit was 16.3 months. Twelve patients died at the end of 26 months. The survival rates of the patients according to ECG changes are listed in Table 2. We observed that the patients with LBBB and T wave inversion at hospital discharge had lower survival rates than that of the patients without these ECG changes in the long term as shown in Figures 1 and 2, respectively. As shown in Figure 1, all patients with LBBB died at the end of 24 months.

Table 2. The Survival of the Patients According to Their Electrocardiographic Findings (%)

	Presence of LBBB (n = 11)	Presence of T Wave Inversion (n = 11)
6 months	100.0	100.0
12 months	81.8	90.9
18 months	12.0	36.4
24 months	0.0	36.4

LBBB = Left bundle branch block.

Effects of variables on survival were analyzed by using univariate and multivariate Cox regression analyses. In univariate analysis, nine variables were analyzed as the predictors of survival. As shown in Table 3, univariate analysis identified LBBB ($P = 0.001$) and T wave inversion ($P = 0.014$) as the predictors of survival in our study population. When multivariate analyses were done using two variables in backward elimination analysis in

Figure 1. The survival graphic of the patients with diphtheritic myocarditis according to presence of left bundle branch block (log-rank = 20.61, df = 1, $P < 0.001$). LBBB = Left bundle branch block. **Figure 2.** The survival graphic of the patients with diphtheritic myocarditis according to presence of T wave inversion (log-rank = 7.12, df = 1, $P = 0.007$).

Cox regression model, statistical significance of T wave inversion disappeared. Only the presence of LBBB continued to be a statistically significant predictor of survival in the model. Adjusted hazard ratio was calculated as 13.67 for LBBB ($P = 0.001$; CI=2.81–66.28).

DISCUSSION

Current study reveals that the presence of LBBB in patients with diphtheritic myocarditis who survive is an independent risk factor for cardiac death in the long term. Also, patients with diphtheritic myocarditis in whom T wave inversion is observed have lower survival rates than that of the patients without these ECG changes in the long-term follow-up period.

Diphtheritic Myocarditis and Mortality

Diphtheria was once one of the most feared diseases to affect children and adolescents, causing death due to acute laryngeal obstruction,

Table 3. Effects of Various ECG Variables on the Survival in Univariate and Multivariate Cox Regression Analyses

	Unadjusted HR	95% CI	P	Adjusted HR ^a	95% CI	P
LBBB	15.25	3.27–71.18	0.001	13.67	2.81–66.28	0.001
T wave inversion	4.57	1.36–15.36	0.014	3.60	0.89–14.55	0.072
ST changes	1.07	0.29–3.98	0.915			
QTc prolongation	1.23	0.37–4.08	0.740			
Ventricular extrasystole	2.28	0.49–10.42	0.288			
Second-degree AV block	2.61	0.78–8.66	0.218			
LAFB	1.08	0.32–3.61	0.901			
LPFB	2.65	0.58–12.21	0.211			
RBBB	1.54	0.50–4.80	0.453			

LBBB = left bundle branch block; AV = atrioventricular; LAFB = left anterior fascicular block; LPFB = left posterior fascicular block; RBBB = right bundle branch block.

^aAdjusted for T wave inversion and left bundle branch block.

myocarditis, or respiratory paralysis.² Diphtheritic myocarditis occurs in 10–20% of patients who initially present with oropharyngitis. Overall, diphtheritic myocarditis has an associated mortality rate of 60%, and it accounts for the majority of deaths related to diphtheria.² The principle manifestations of diphtheritic myocarditis are dilated cardiomyopathy and different types of dysrhythmia and conduction disturbances.¹⁴

Diphtheria toxin inhibits elongation factor-2 activity in protein synthesis and causes DNA fragmentation and cytolysis.¹⁵ The myocardium shows hyaline degeneration and necrosis associated with active inflammation in the interstitial spaces. Conduction tissue is also affected.¹⁶ Fifty percent of the patients with diphtheritic myocarditis develop severe conduction abnormalities usually associated with fatal outcomes. The high incidence of cardiac rhythm and conductive disturbances in diphtheria is explained by the response of cardiac muscle and conduction to diphtheria toxin and its effects on extra and intracardiac, nervous, endocrine, and vegetative systems as well.¹⁷

Diphtheritic Myocarditis and LBBB

LBBB usually appears in patients with underlying heart disease. It is associated with significantly reduced long-term survival with 10-year survival rates as low as 50% probably reflecting the severity of underlying cardiac disease.¹⁸ It was reported that among patients with coronary artery disease, the presence of LBBB correlated with more extensive disease, more severe left ventricular dysfunction, and reduced survival rates.¹⁹ In another clinical study, the long-term outcome of patients with BBB who have no clinical evidence of cardiac dis-

ease was investigated.²⁰ It was found that isolated LBBB was associated with an increased risk of developing overt cardiovascular disease and cardiac mortality in that study.²⁰ Also, Rabkin et al. showed that the 5-year incidence of sudden death as the first manifestation of heart disease was 10 times greater than in men with LBBB who had no clinical evidence of ischemic or valvular heart disease than in those without it.²¹ The patients with LBBB might have fibrosis and cellular hypertrophy representing optimal conditions for the development of life-threatening ventricular arrhythmias. Margera et al. found that especially the presence of LBBB had an ominous prognostic significance independent of echocardiographic and hemodynamic indexes of right and left ventricular function.¹² Also the same authors showed that LBBB was correlated to the most severe left ventricular damage. But the patients with diphtheritic myocarditis were not included in that study. However, our study consisted of the patients with diphtheritic myocarditis without signs of dilated cardiomyopathy and their LVEF values were greater than 55%. Our study has demonstrated that the presence of LBBB is an independent risk factor for long-term mortality in patients with diphtheritic myocarditis. We speculate that LBBB might increase the risk of malignant reentrant arrhythmias including ventricular tachycardia in patients suffering from diphtheritic myocarditis in the long term.

Diphtheritic Myocarditis and Other ECG Changes

Diphtheria-related ECG changes such as ST changes, T wave inversion, and arrhythmias occur between days 3 and 47 (median 11 days) from the

onset of the disease, and usually remain for several weeks.^{17,22,23} The patients with diphtheritic myocarditis who survive were reported to make full recovery in some studies.^{9,10} However, up to now there has been no available data about the effects of ECG variables related to diphtheritic myocarditis on long-term prognosis and mortality. On the contrary to above-mentioned studies, we do not consider that the patients with diphtheritic myocarditis make a full recovery. These patients have an increased risk of death even after an uneventful course during in-hospital stay.

CONCLUSION

In conclusion, diphtheritic myocarditis does not demonstrate only a malignant clinical course during acute phase of disease, but also during the long-term follow-up period especially in patients who have LBBB and T wave inversion. Clearly, patients with these ECG abnormalities have poor survival although they have normal left ventricular systolic function. In addition, these ECG changes including T wave inversion and LBBB can help us to predict survival rates of the patients in long term. Furthermore, LBBB is an independent predictor of long-term survival in patients with diphtheritic myocarditis. Because of the high risk of cardiac mortality, the patients with LBBB and T wave inversion after hospital discharge should be closely followed both in short and long terms.

REFERENCES

- Expanded Programme on Immunization (EPI). Update: Diphtheria epidemic in the newly independent states of the former USSR, January 1995–March 1996. *Wkly Epidemiol Rec* 1996;71:245–250.
- White NJ, Hien TT. Diphtheria. In Cook GC, (ed.): *Manson's Tropical Diseases*, 20th Edition. London, Saunders, 1996, 931–935.
- Hardy IR, Dittmann S, Sutter RW. Current situation and control strategies for resurgence of diphtheria in newly independent states of the former Soviet Union. *Lancet* 1996;347:1739–1744.
- Vitek CR, Wharton M. Diphtheria in the former Soviet Union: Reemergence of a pandemic disease. *Emerg Infect Dis* 1998;4:539–550.
- Vitek CR, Velibekov AS. Epidemic diphtheria in the 1990s: Azerbaijan. *J Infect Dis* 2000;181(Suppl. 1):S73–S79.
- Rakhmanova AG, Lumio J, Groundstroem K, et al. Diphtheria outbreak in St. Petersburg: Clinical characteristics of 1860 adult patients. *Scand J Infect Dis* 1996;28:37–40.
- Galazka AM, Robertson SE, Oblapenko GP. Resurgence of diphtheria. *Eur J Epidemiol* 1995;11:95–105.
- Eskola J, Lumio J, Vuopio-Varkila J. Resurgent diphtheria—are we safe? *Br Med Bull* 1998;54:635–645.
- Bethell DB, Dung NM, Loan HT, et al. Prognostic value of electrocardiographic monitoring of patients with severe diphtheria. *Clin Infect Dis* 1995;20:1259–1265.
- Kneen R, Pham NG, Solomon T, et al. Penicillin vs. erythromycin in the treatment of diphtheria. *Clin Infect Dis* 1998;27:845–850.
- Turjanov MH, Beljaeva NM, Tzaregorodsev AD. Diphtheria. *Medicina (Mosc)* 1996;254.
- Morgera T, Di Lenarda A, Dreas L, et al. Electrocardiography of myocarditis revisited: Clinical and prognostic significance of electrocardiographic changes. *Am Heart J* 1992;124:455–467.
- Kim SG, Fogoros RN, Furman S, et al. Standardized reporting of ICD patient outcome: The report of a North American Society of Pacing and Electrophysiology Policy Conference, February 9–10, 1993. *Pacing Clin Electrophysiol* 1993;16:1358–1362.
- Dung NM, Kneen R, Kiem N, et al. Treatment of severe diphtheritic myocarditis by temporary insertion of a cardiac pacemaker. *Clin Infect Dis* 2002;35:1425–1429.
- Collier RJ. Understanding the mode of action of diphtheria toxin: A perspective on progress during the 20th century. *Toxicon* 2001;39:1793–1803.
- Hadfield TL, McEvoy P, Polotsky Y, et al. The pathology of diphtheria. *J Infect Dis* 2000;181(Suppl. 1):S116–S120.
- Loukoushkina EF, Bobko PV, Kolbasova EV, et al. The clinical picture and diagnosis of diphtheritic carditis in children. *Eur J Pediatr* 1998;157:528–533.
- Mirvis DM, Goldberger AL. Electrocardiography. In Braunwald E, Zipes DP, Libby P (eds.): *Heart Disease*, 6th Edition. Pennsylvania, WB Saunders Company, 2001, pp. 103–104.
- Newby KH, Pisano E, Krucoff MW, et al. Incidence and clinical relevance of the occurrence of bundle branch block in patients with thrombolytic therapy. *Circulation* 1996;94:2424–2428.
- Fahy GJ, Pinski SL, Miller DP, et al. Natural history of isolated bundle branch block. *Am J Cardiol* 1996;77:1185–1190.
- Rabkin SW, Mathewson FA, Tate RB. Natural history of left bundle-branch block. *Br Heart J* 1980;43:164–169.
- Salih MA, Suliman GI, Hassan HS. Complications of diphtheria seen during the 1978 outbreak in Khartoum. *Ann Trop Paediatr* 1981;1:97–101.
- Lumio JT, Groundstroem KWE, Melnick OB, et al. Electrocardiographic abnormalities in patients with diphtheria. *Am J Med* 2004;116:78–83.