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Original article

Historical assessment of diphtheritic myocarditis from a hospital in northeastern Thailand

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Background: Although there have been many descriptive studies of diphtheria from resource limited countries, descriptions of the natural history of diphtheritic myocarditis in patients from these countries are scarce.
Objective: To present the natural history of diphtheritic myocarditis from a hospital in northeastern Thailand.
Methods: The clinical features of 38 patients with diphtheria admitted to the Khon Kaen University Hospital in northeastern Thailand between 1983 and 1996 were reviewed.
Results: Of the 38 cases of diphtheria, 10 progressed to diphtheritic myocarditis (26%). Electrocardiographic findings of the 10 patients with myocarditis were myocardial and conduction abnormalities. The presence of a clinically severe (toxic) type ($P < 0.001$) or a swollen neck (bull neck) ($P = 0.001$) was a predictor of the occurrence of myocarditis. Five (50%) of the 10 patients with myocarditis had conduction abnormalities (third-degree atrioventricular block 3, left bundle branch block 1, and right bundle branch block 1). Four patients with severe symptomatic bradyarrhythmia (third-degree atrioventricular block 3, and left bundle branch block 1) received ventricular pacing, and 3 patients died after this pacing. Echocardiographic abnormalities of left ventricular dilatation and myocardial hypertrophy were found in all 5 patients with conduction abnormalities. All 6 of 7 survivors of diphtheritic myocarditis had normal 12-lead electrocardiographic results at 1-month follow-up. A patient who was the survivor of third-degree AV block had an electrocardiographic finding of flat T waves, and with a complete echocardiographic normalization of left ventricular dilatation and myocardial hypertrophy.
Conclusion: The present study confirms that increasing diphtheria immunization coverage in the population remains the most important strategy for the control of diphtheria. In resource limited countries, clinical findings, electrocardiography, and sometimes where available, echocardiography are helpful in assessing the severity of diphtheritic myocarditis, decision making of acute management, and predicting fatal outcome.

Keywords: Diphtheritic myocarditis, echocardiography, electrocardiography, fatal outcome, myocarditis, pacemaker

Although diphtheria has been under control in the developed world as a result of the success of routine immunization with diphtheria vaccine, the disease still occurs in many developing countries [1]. The causative microorganism of diphtheria is *Corynebacterium diphtheriae* [2]. It has been well documented over 100 years ago that infection with toxigenic *C. diphtheriae* produces the formation of an inflammatory pseudomembrane, and that its toxin, which is absorbed into the circulation, causes multiple organ damage, particularly in the heart (myocarditis), nervous system, and kidney [2, 3]. Cardiac involvement usually occurs by the end of the second week of infection in about 10%–25% of patients and is the main cause of death from this disease [4].

Patients with diphtheritic myocarditis appear pale, restless, and weak. Physical examination may reveal an abnormal pulse rate, either rapid or slow, dyspnea, congestive heart failure or sometimes cardiogenic shock, and an abnormal electrocardiogram (ECG) including myocardial or conduction system involvement [5, 6]. An ECG finding of a severe conduction defect such as third-degree atrioventricular (AV) block or bundle branch block, is usually associated with a fatal prognosis [5, 6]. Recently, there have been a few reports of echocardiographic abnormalities in patients

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with diphtheritic myocarditis, but these data are limited [7]. Although there have been many descriptive studies of diphtheria in resource limited countries including Thailand, data on clinical outcomes of myocarditis in patients with diphtheria are scarce [3, 4, 6, 8-11]. The ability to predict from available clinical parameters whether diphtheritic myocarditis will develop would help in clinical assessment and management. The authors therefore reviewed and analyzed clinical findings of patients with diphtheria who presented to the Khon Kaen University (Srinagarind) Hospital in northeastern Thailand.

Materials and methods

Patients

Thailand is a southeastern Asia country with a land area of 513,115 square kilometers and is divided into 4 regions; central, northern, northeastern, and southern. Khon Kaen University (KKU) Hospital is located in the central area of northeastern Thailand, and is close to the Lao People's Democratic Republic (neighboring Thailand). The distance between the KKU Hospital and the Lao PDR capital city (Vientiane) is only 261 kilometers; about a 4-hour drive. The population of the northeastern Thailand was approximately 17 million in 1985. In this study, we retrospectively included the clinical and electrocardiographic assessments of 38 consecutive patients with cases of diphtheria who presented to the Khon Kaen University (Srinagarind) Hospital, a 1100-bed hospital in northeastern Thailand, between January 1983 and December 1996. On admission to hospital the parents or legal guardians of patients had provided written informed consent for diagnosis and treatment. This retrospective study, including the review and publication of the cases, was approved by the Khon Kaen University Human Research Ethics Committee with the approving number of HE500511.

Diagnostic criteria

Diagnosis of diphtheria was based on a clinical syndrome that consisted of upper respiratory tract illness with sore throat, fever, and a typical diphtheritic adherent membrane or a pseudomembrane of the tonsils, pharynx, or nose and/or with a positive result for a toxin-producing strain of *C. diphtheriae* on culture of a throat, and/or nasal swab (22 cases).

Because *C. diphtheriae toxin* can produce localized inflammation (pseudomembrane) and generalized symptoms (toxicity), this study, according to the WHO manual, classified the clinical severity of diphtheria according to the extent of localized inflammation (pseudomembrane) and generalized symptoms (toxicity) [12]. Therefore, the clinical severity of this disease was classified as tonsillar type (mild form or localized type) if there was a pseudomembrane on the tonsils only, or as the combined type (moderate form or extensive type) if the pseudomembrane extended beyond the tonsils to the fauces, uvula, palate, pharynx, or lower respiratory tract, and as severe (toxic) type if there was cervical lymphadenopathy, subcutaneous edema, swelling of the neck (bull neck), or distant organ involvement (adapted from [12]). A patient with acute pharyngitis or tonsillitis without a membrane, but with a positive culture result for toxigenic *C. diphtheriae* was considered a carrier [12], and was not included in this study.

Diphtheritic myocarditis was defined as existing in a patient with diphtheria, who had no history of previous heart disease, if they had either clinical signs of congestive heart failure, or electrocardiographic abnormality, or both. An electrocardiographic abnormality was classified into two categories, namely myocardial and conduction system involvement. Myocardial abnormalities were defined as arrhythmias such as premature atrial contractions, premature ventricular contractions, or abnormal Q waves, and repolarization abnormalities such as ST-T segment elevation >1 mm in at least two chest leads or one limb lead, ST-T segment depression >1 mm, and abnormal T-wave or a prolonged QTc interval. The QTc interval was calculated by dividing the measured QT interval by the square root of the R-R interval, where the R-R interval is the time between two successive R waves on the ECG. QTc interval >0.45 ms was considered to be prolonged. Conduction abnormalities were defined as AV block, bundle branch block, and hemiblock [13].

Echocardiographic abnormalities were defined as a reduction of left ventricular systolic function, left ventricular dilatation, or myocardial hypertrophy. The left ventricular systolic function was assessed according to fractional shortening (FS). FS was defined as a proportion of differences of values in dimensions between the left ventricular internal dimension at end-diastole (LVIDd) and left ventricular internal dimension at end-systole (LVIDs) divided by LVIDd. The definition of FS is as follows: ((LVIDd–LVIDs)/ LVIDd) × 100 (percent). A fractional shortening of

less than 25% was considered as a reduction of left ventricular systolic function. Left ventricular dilatation was defined as a LVIDd of more than two standard deviations from the mean of normal reference value. Myocardial hypertrophy was defined as left ventricular posterior wall thickness of more than two standard deviations above the mean of normal reference value [14, 15].

Neuropathy was defined as new onset of sensory or motor defects in cranial or peripheral nerves detected on physical examination.

A diphtheria immunization program in Thailand was recommended to provide diphtheria-tetanus toxoid with pertussis (DPT) vaccine at ages 2, 4, 6, and 18 months, 4–6 years, and a dose of tetanus and diphtheria (Td) toxoids at age 12–16 years [11]. Diphtheria immunization history of each child was classified into 1 of 3 immunization-history groups: complete, incomplete, or no immunization. Patients were considered to have complete immunization if they had received complete diphtheria immunization up to date for age. Patients were considered to have incomplete immunization if they had received diphtheria immunization, but were not up to date for age.

Study procedures

On admission to the KKU Hospital, a detailed history was obtained for each patient including age, sex, duration between onset of symptoms and presentation at a hospital, immunization history, the presenting complaints, site of patch, clinical presentation, its chronological development, treatment received, and other pertinent clinical features.

Throat and/or nasal swabs for *C. diphtheriae*, complete blood count, urine examination, blood samples for creatinine and electrolyte analysis, chest X-ray examination, and ECG were performed for each patient at admission. Echocardiography was performed when a patient was admitted to the intensive care unit. Patients with diphtheritic myocarditis were reassessed by twelve-lead electrocardiograms every day after documentation of a diagnosis of acute diphtheritic myocarditis. All ECG recordings were interpreted by pediatric cardiologists.

Patients with severe (or toxic) type were treated with penicillin G sodium (100,000 units/kg/day) intravenously for 14 days. Patients with tonsillar type or combined type received intramuscular benzyl penicillin (50,000 units/kg/day for 5 days), followed by oral penicillin V (50 mg/kg/day for 5 days). Close contacts of the patient were administered either penicillin or erythromycin orally for 7 days.

Patients with severe (toxic) type received 80,000–100,000 IU of equine diphtheria antitoxin (DAT) intramuscularly. Patients with combined type received 40,000–60,000 IU of DAT and patients with tonsillar type received 15,000–25,000 IU of DAT.

Tracheostomy was performed if there was laryngeal airway obstruction by a pseudomembrane. Either pulmonary edema or congestive heart failure was treated with furosemide (1 mg/kg/dose, as required), and cardiogenic shock was treated with inotropic infusions (dopamine, 10 micrograms/kg/min or dobutamine, 10 micrograms/kg/min).

Patients with severe symptomatic bradyarrhythmia or congestive heart failure were taken to the intensive care unit and received hemodynamic monitoring and support. Patients who developed a severe symptomatic bradyarrhythmia (ventricular rate less than 50 beats per minutes) including third degree AV block or left bundle branch block were provided with ventricular pacing until sinus rhythm was restored or the patients died. Temporary pacemaker wires were inserted via the femoral vein with use of a sterile technique and the position was checked by fluoroscopy. The pacemaker was set to pace at a rate of 100 beats/min.

The echocardiographic studies were performed with an Irex System 3 machine (IREX Medical Systems; Ramsey, NJ, USA) in 4 patients and with a Hewlett-Packard Sonos 1000 machine (Hewlett-Packard, Andover, MA, USA) in one patient. A standardized M-mode with two-dimensional echocardiographic examination was performed with standard views [15]. All echocardiographic images were recorded on half-inch videotapes for reviewing and analysis and were reviewed by one author (M.P.).

Before hospital discharge, all surviving patients received diphtheria toxoid. Each diphtheria survivor was reevaluated by twelve-lead ECG at 1 month after the attack of diphtheria. The patient who was a survivor of complete heart block also had a repeat echocardiographic study at a 1-month follow-up. Repeat ECG and echocardiographic studies were done at 2-month follow-ups if abnormalities persisted.

Statistical analysis

The data were analyzed with Stata, version 10 (Stata Corp, College Station, TX, USA). Continuous

data were expressed as the median and were compared using a Mann–Whitney test. Categorical data were compared using either a Chi-square test or Fisher's exact test where appropriate.

Results

In this study we included 38 patients with clinical presentations of respiratory tract diphtheria during the 14 years from 1983 to 1996. Thirty-seven (97%) patients were admitted during 1983 to 1988 and the last case (in patient 10, see **Table 1**) came from the Lao People's Democratic Republic (neighboring Thailand) in 1996. KKU Hospital records between 1997 and December 2012 did not reveal any more cases of diphtheria (**Figure 1**).

Initial clinical features

The patients had a mean age of 6.97 ± 3.50 years (median 6.0; range 3 to 16 years). Twenty-two (58%) patients were boys. Two patients (ages 3 and 6 years) were siblings and lived in the same house. All these patients typically presented with low grade fever, sore throat, and pseudomembrane. Among these 38 patients, 22 (58%) were classified as tonsillar type, 11 (29%) had combined type, and 5 (13%) had severe (toxic) type (**Table 1**). Thirty-five patients received DAT and the interval from onset of symptoms to DAT administration was 4.50 ± 1.38 (median 5.0, range; 2–7) days. Ten (26%) patients had diphtheritic myocarditis. Five patients (patients 1, 2, 6, 9, and 10) had clinically severe cardiac involvement with cardiomegaly and were admitted to the intensive care unit. Four patients (patients 1, 2, 6, and 10) had severe conduction disturbances with severe symptomatic bradyarrhythmia (third-degree AV block 3, and left bundle branch block 1) received pacemakers. Three (8%) patients had severe upper airway obstruction requiring tracheotomy, and five (13%) patients had diphtheritic neuropathy (**Table 1**).

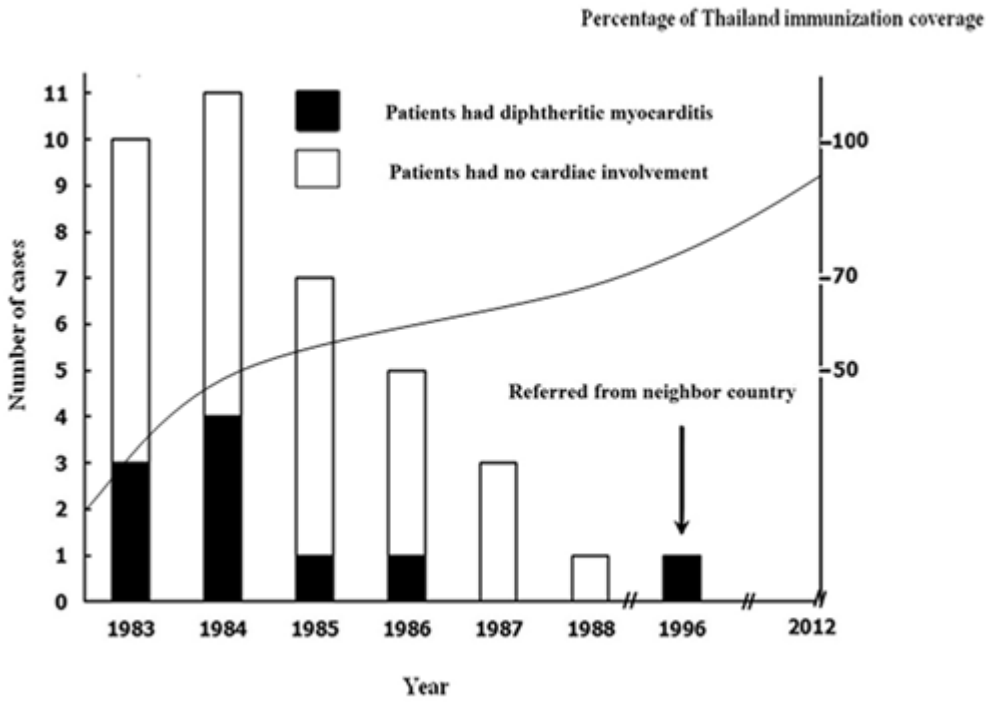

Figure 1. Annual distribution of patients with diphtheria admitted to Khon Kaen University Hospital during 1983–1996.

Table 1. Features of 38 patients with diphtheria who were admitted to the Khon Kaen University Hospital in northeastern Thailand

Patient number	Age/Sex (years)	Diphtheria immunization	Interval from onset of symptoms to DAT administration (days)	Clinical severity/ pseudomembrane extent	12-lead electrocardiography (day after onset of this illness)	Other manifestations (day after onset of this illness)	Procedures	Outcome
1*	3/M	no	6	severe/ T, F, U, Pa, Ph.	T-wave inversion, prolonged QTc interval, third-degree AV block (6)	bull neck (3), palatal paralysis (9), ophthalmoplegia (30), peripheral neuropathy (49).	temporary pacemaker (6-16)	survived
2	3/F	no	5	severe/ T, F, U, Ph, L.	ST-T segment depression, QTc prolonged (5), ST-T segment depression, PR prolonged, severe bradycardia with LBBB (6)	bull neck (3), palatal paralysis (5), thrombocytopenia (6)	tracheostomy (5-6), temporary pacemaker (6)	died of cardiogenic shock (6)
3	4/M	Incomplete	6	combined / T, F, Ph.	sinus bradycardia, QTc prolonged, RBBB (10)			survived
4	5/M	Incomplete	5	combined/ T, F, Ph.	sinus tachycardia, QTc prolonged (12)			survived
5	4/M	Incomplete	6	combined/ T, F, Ph.	sinus tachycardia, QTc prolonged, PVC (11)			survived
6	6/F	no	5	severe/ T, F, U, Ph.	ST-T segment depression, QTc prolonged, AV dissociation, ventricular extrasystole (5), third-degree AV block (6)	bull-neck (3), airway obstruction (6), palatal paralysis (6)	tracheostomy (5-6), temporary pacemaker (6)	died of cardiogenic shock (6)
7	7/M	Incomplete	7	combined/ T, F, Ph.	sinus tachycardia, PVC (12)			survived
8	12/M	Incomplete	5	combined/ T, F, Ph.	sinus tachycardia, QTc prolonged (10)			survived
9	15/F	no	5	severe/ T, F, U, Ph, L.	T-wave inversion (5), PR prolonged, QTc prolonged (8),	bull neck (4), palatal paralysis (7)		survived
10	8/F	no	7	severe/ T, F, Pa, Ph, L, N.	ST-T segment elevation, third-degree AV block (7), frequent multi-focal PVCs (8), ventricular tachycardia (9), ventricular fibrillation (10)	bull-neck (4), airway obstruction (6), thrombocytopenia (8), palatal paralysis (8), nephritis and acute renal failure (10)	tracheostomy (6-10), temporary pacemaker (7-10)	died of ventricular fibrillation (10)
11	3/M	no	3	combined/ T, F, U.	normal		none	survived
12	4/F	Incomplete	4	tonsillar/ T.	normal		none	survived
13	3/F	Incomplete	4	tonsillar / T.	normal		none	survived
14	4/F	no	5	combined/ T, Ph.	normal		none	survived
15	4/M	Incomplete	5	tonsillar / T.	normal		none	survived
16	4/M	Incomplete	4	tonsillar / T.	normal		none	survived
17	4/M	no	3	combined/ T, F, U.	normal		none	survived
18	5/F	Incomplete	2	tonsillar / T.	normal		none	survived
19	5/M	Incomplete	2	tonsillar / T.	normal		none	survived
20	5/F	Incomplete	4	tonsillar / T.	normal		none	survived
21	5/M	Incomplete	5	tonsillar / T.	normal		none	survived
22	5/M	no	6	combined/ T, Ph.	normal		none	survived
23	5/F	Incomplete	3	tonsillar / T.	normal		none	survived
24*	6/F	Incomplete	7	tonsillar / T	normal		none	survived
25	6/M	Incomplete	4	tonsillar / T.	normal		none	survived

Table 1. (Continue) Features of 38 patients with diphtheria who were admitted to the Khon Kaen University Hospital in northeastern Thailand

Patient number	Age/Sex (years)	Diphtheria immunization	Interval from onset of symptoms to DAT administration (days)	Clinical severity/ pseudomembrane extent	12-lead electrocardiography (day after onset of this illness)	Other manifestations (day after onset of this illness)	Procedures	Outcome
26	7/F	Incomplete	6	tonsillar / T.	normal		none	survived
27	8/M	Incomplete	5	combined/ T, F, N Ph.	normal		none	survived
28	9/F	Incomplete	3	tonsillar / T.	normal		none	survived
29	9/M	Incomplete	4	tonsillar / T.	normal		none	survived
30	9/M	Incomplete	4	tonsillar / T.	normal		none	survived
31	10/M	Incomplete	4	tonsillar / T	normal		none	survived
32	7/M	complete	2	tonsillar / T.	normal		none	survived
33	9/M	complete	3	tonsillar / T.	normal		none	survived
34	10/M	no	5	combined/ T, Ph, N.	normal		none	survived
35	10/F	unknown	DAT-not available	tonsillar / T	normal		none	survived
36	11/F	unknown	DAT-not available	tonsillar / T	normal		none	survived
37	15/F	unknown	5	tonsillar / T	normal		none	survived
38	16/M	unknown	DAT-not available	tonsillar / T.	normal		none	survived

M = male, F = female, DAT = diphtheria antitoxin, T = tonsils, F = fauces, U = uvula, Pa = palate, Ph = pharynx, L = larynx, N = nasal, AV = atrioventricular, LBBB = left bundle branch block, RBBB = right bundle branch block, PVC = premature ventricular contraction, *Two patients were siblings, † One patient had thalassemia as an underlying disease.

Diphtheritic myocarditis

Ten (26%) patients had myocarditis. Patients with clinically severe (toxic) type ($P < 0.001$), clinical presentation of neck swelling (bull neck) ($P = 0.001$), neuropathy ($P = 0.001$), or laryngeal obstruction ($P < 0.015$) were associated with the development of myocarditis (**Table 2**). All 10 patients with myocarditis had abnormal findings on 12-lead electrocardiography and myocardial abnormalities were found in all 10 patients (prolonged QTc interval 7, premature ventricular contraction 4, ST-T segment depression 2, T-wave inversion 2, ST-T segment elevation 1). Four patients had sinus tachycardia. Ischemic findings like those seen in patients with an acute myocardial infarction including ST-T segment depression (patients 2 and 6) and ST-T segment elevation (patient 10) were found in 3 fatal cases (patients 2, 6, and 10) (**Table 1** and **Figure 2**). Five (50 %) of the 10 patients with myocarditis had conduction abnormalities (third-degree AV block 3, left bundle branch block 1, and right bundle branch block 1). All 5 patients with conduction abnormalities also had ECG findings of myocardial abnormalities. Four patients with severe conduction abnormalities (third-degree AV block 3, and left bundle branch block 1) had severe symptomatic bradyarrhythmia and had received ventricular pacemakers (**Table 1**).

Table 2. Clinical characteristics of patients with and without myocarditis

Characteristics	Myocarditis (n = 10)	No myocarditis (n = 28)	*P*
Age (years) median; range (mean ± SD)	5; 3–15 (6.70 ± 4.00)	6; 3–16 (7.07 ± 3.38)	0.526
Sex: Male	6 (60)	16 (57)	>0.999
Rural residence	10 (100)	25 (89)	0.552
Diphtheria immunization			0.277
no	5 (50)	5 (18)	
incomplete	5 (50)	17 (61)	
complete	0 (0)	2 (7)	
unknown	0 (0)	4 (14)	
Clinical severity			<0.001
tonsillar	0 (0)	22 (79)	
combined	5 (50)	6 (21)	
severe	5 (50)	0 (0)	
Laryngeal obstruction (%)	3 (30)	0 (0)	0.014
Bull neck (%)	5 (50)	0 (0)	0.001
Thrombocytopenia (%)	2 (20)	0 (0)	0.064
Acute renal failure (%)	1 (10)	0 (0)	0.263
Neuropathy (%)	5 (50)	0 (0)	0.001
Fatal cases (%)	3 (30)	0 (0)	0.014

Data are numbers (%) of patients, unless otherwise indicated, *P* = probability value

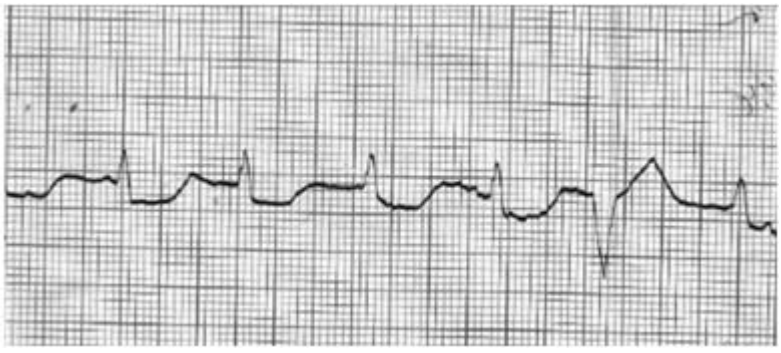

Figure 2. An electrocardiogram (lead 2) of patient number 6 (see **Table 1**) was recorded on the 5th day after onset of illness. There are ventricular extrasystole, ST-T segment depression, prolonged QTc interval and atrioventricular (AV) dissociation. On the following day (6th day after onset of illness), this patient had an electrocardiographic change to third-degree AV block.

Echocardiographic results

Echocardiography was performed in all 5 patients with diphtheritic myocarditis and conduction abnormalities. Echocardiographic abnormalities were found in all 5 patients (see previous definition). Left ventricular dilatation and myocardial hypertrophy were found in all 5 patients studied. Reduction of left ventricular systolic function was found in all 3 patients who died (**Figure 3**).

Fatal cases

Despite ventricular pacing, three (patients 2, 6, and 10) of the 4 patients with ECG findings of severe conduction abnormalities died. ECG findings of ischemic changes similar to those seen in patients with an acute myocardial infarction including ST-T segment depression (patients 2 and 6) and ST-T segment elevation (patient 10) were also found in 3 fatal cases (patients 2, 6, and 10). One (patient 2) of these patients died 12 hours after ventricular pacing started, another (patient 6) at 20 hours, and another (patient 10) at 80 hours. The duration from onset of the illness to the manifestations of diphtheritic myocarditis was 5, 6, and 7 days and the duration from the onset of the illness to death was 6, 6, and 10 days respectively. The cause of death was cardiogenic shock in 2 and ventricular fibrillation in 1 (**Table 1**).

Follow-up study

Of the 35 diphtheria survivors, 23 (61%) patients came for a follow-up visit at 1 month after discharge (7 patients were survivors of diphtheritic myocarditis).

All 16 patients who did not have diphtheritic myocarditis and 6 of 7 survivors of diphtheritic myocarditis had normal 12-lead electrocardiographic results at 1-month follow-up. Only a patient who was the survivor of third-degree AV block had electrocardiographic finding of flat T waves and occasional ventricular extrasystoles. A repeat echocardiographic study of this patient showed normal left ventricular systolic function with complete normalization of left ventricular dilatation and myocardial hypertrophy. This patient also slowly developed muscular weakness, hypotonia, and hyporeflexia of proximal muscles of 4 extremities evident on day 49 after onset of diphtheria. The motor disturbance became better on day 60th after onset of disease. Also repeat ECG and echocardiographic follow-up studies at this time revealed normal findings (**Table 1**).

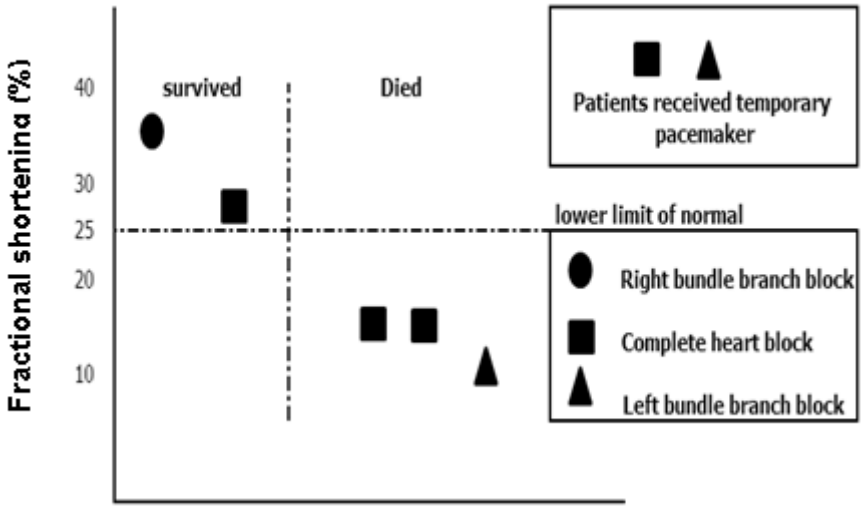

Figure 3. Scatter plot comparing echocardiographic data of fractional shortening of the 5 patients with severe diphtheritic myocarditis who had conduction system abnormalities (third-degree AV block or complete heart block 3, left bundle branch block 1, and right bundle branch block 1).

Discussion

This study revealed that 26% of the patients with diphtheria had acute diphtheritic myocarditis. The presence of a clinically severe (toxic) type, bull neck, laryngeal obstruction, thrombocytopenia, neuropathy, or acute renal failure in a patient with diphtheria was associated with the development of myocarditis, which was the primary cause of a fatal outcome. This finding has confirmed previous reports that severe inflammation and systemic involvement by the action of diphtheria toxin is associated with the development of myocarditis [4, 5]. All 10 patients with myocarditis had abnormal ECG findings of myocardial abnormalities, whereas half of these patients had conduction defects including third-degree AV block, and left and right bundle branch block. Four patients with severe conduction abnormalities (third-degree AV block 3, and left bundle branch block 1) had severe symptomatic bradyarrhythmia and had received ventricular pacemakers. Despite ventricular pacing, 3 of the 4 patients with ECG findings of severe conduction abnormalities died. In addition to the ECG findings of severe conduction disturbances, ischemic changes including ST-T segment depression or elevation resembling those seen in patients with an acute myocardial infarction were also associated with fatal outcomes. Moreover, echocardiographic abnormalities were found in all 5 patients with conduction abnormalities who had severe diphtheritic myocarditis. An echocardiographic finding of left ventricular systolic dysfunction was found in all 3 fatal cases in contrast with a survivor of third-degree AV block who had a normal left ventricular systolic function. These findings confirm that cardiac involvement of severe diphtheria is characterized by severe impairment of the myocardium and the conduction system [5, 7].

C. diphtheriae is the causative pathogen of diphtheria [2]. After invasion by a bacteriophage, the pathogen can produce an exotoxin that inhibits the intracellular elongation factor 2 and protein synthesis [2]. The toxin causes local tissue damage and, when absorbed into the circulation causes multiple organ damage, particularly in the heart (myocarditis), nervous system, and kidney [2]. Cardiac damage includes edema, congestion, infiltration by mononuclear cells, and fatty changes within muscle fibers and the conduction system. The toxin may reduce the excitation threshold of the damaged myocardium [5].

We report a patient with third-degree AV block for whom the use of pacemaker was successful, possibly because of specific major damage of the toxin to the conduction system with adequate myocardial contractile function. Interestingly, the survivor of third-degree AV block had underlying thalassemia, which had produced excess iron in many tissues including myocardium. It has been recognized that *C. diphtheriae* grown in a medium low in iron yield more toxin than those grown in media containing higher concentrations of iron [16]. It might be that the survivor from third-degree AV block with thalassemia had a protective benefit from excess iron.

All of the patients with severe bradyarrhythmias presented with early myocarditis, in less than a week, in contrast to the end of the second week as expected from classical descriptions. This finding supports the previous observations that the patients with more severe diphtheritic myocarditis have the earlier onset of carditis symptoms [4].

The findings of the present study are consistent with previously reported findings that severe conduction defects, including third-degree AV block and bundle branch block are associated with poor outcomes [4]. There have been few reports of the survival of patients with third-degree AV block who receive ventricular pacing [17]. Moreover, the present study found that the survivor of third-degree AV block had normal left ventricular systolic function in contrast to left ventricular systolic dysfunction that was found in all 3 fatal cases. Left ventricular systolic dysfunction in patients with severe conduction defects was found to be one of the important determinants of fatal outcomes in these patients.

In Thailand, the introduction and widespread use of DPT vaccine resulted in a rapid decline in diphtheria incidence during 1983–1996, falling to 2 cases per 100,000 population by 1981 to 1 case per 100,000 by 1987. Despite high vaccination coverage of infants and children (>90%) in Thailand, the last patient came from a neighboring country, Lao PDR where immunization coverage has been lower than 60% throughout the 1990s [11]. Now, the epidemiology of diphtheria in the vaccine era has changed, unvaccinated adolescents and adults now are most likely to be affected during outbreaks [8-10].

This historical report has a number of limitations. First, this study is a report of a relatively small number of patients from a single center. Although routine immunization and economic development of Thailand

have greatly decreased, but not eliminated diphtheria cases, KKU Hospital records between 1997 and December 2012 did not reveal any more cases of diphtheria. Second, this study reports clinical studies conducted in the early period of the echocardiographic era and measurement of diastolic function had not been performed.

Conclusion

The present study confirms that diphtheria immunization coverage of the population remains the most important strategy for the control of diphtheria [2, 11]. This study supports the previous findings that the majority of fatal outcomes among patients with diphtheria are associated with myocarditis. Electrocardiographic abnormalities of severe conduction defects including third-degree AV block or left bundle branch block, and of severe myocardial involvement including ST-T segment depression or ST-T segment elevation in patients with diphtheritic myocarditis are markers of severe myocarditis and fatal outcome. In resource limited countries, clinical findings, electrocardiography, and where available, echocardiography are helpful in assessing the severity of diphtheritic myocarditis, decision making for acute management, and predicting fatal outcome.

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