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Mortality in myotonic dystrophy patients in the area of prophylactic pacing devices

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ABSTRACT

Objectives: Our study purports to determine whether implantation of a prophylactic pacemaker in MD patients with HV interval ≥70 ms lowers the risk of sudden death, which may be essentially due to complete atrioventricular block.
Background: Sudden death occurs more frequently in patients with myotonic dystrophy (MD) than in the control population.
Methods: From 1994 to 2008, 100 consecutive patients were enrolled, 49 of whom were implanted.
Results: During an average follow-up of 74±39 months, 10 deaths occurred. Nine were due to respiratory failure. Only one sudden death occurred, whereas 46% of patients were considered at risk of sudden death according to the criteria of Groh et al. [5]. The incidence rate of sudden death was only 0.2 per 100 patient-years. One patient developed a paroxysmal syncopal sustained ventricular tachycardia.
Conclusions: The prophylactic implantation of PM in MD patients who are identified as being at risk of sudden death according to Groh's criteria reduced the incidence rate of sudden death. The one sudden death in an implanted MD patient suggests the likelihood that pacemaker implantation did not totally forestall this event. Ventricular arrhythmias may be involved in the sudden deaths in MD patients, in which case the implantation of an implantable cardiac defibrillator could be indicated.

1. Introduction

Myotonic dystrophy (MD1), the most frequent adult form of muscular dystrophy, is a hereditary autosomal dominant disease with variable penetrance that occurs in 1 to 10 persons out of 100,000 [1]. It is caused by a mutation on the long arm of chromosome 19 in the form of an unstable expansion of cytosine–thymine–guanine (CTG) repeats in the untranslated region of the gene for myotonin protein kinase [2,3]. MD1 leads to multiple systemic complications, essentially related to muscular weakness, respiratory failure, cardiac arrhythmias and cardiac conduction disturbances. In the MD population, the age of death is lower than in the general population [4,5], and the frequency of sudden death is higher [3–11]. The 2002 study by Lazarus et al. [12] demonstrated that a pacemaker (PM) should be implanted in patients with MD if their His-ventricle (HV) interval is ≥70 ms, even if they are asymptomatic, in order to protect them from the clinical consequences of profound bradycardia and to facilitate the diagnosis and management of frequent paroxysmal tachyarrhythmias. Recently Groh et al. [5] identified several electrocardiographic abnormalities linked to sudden death in MD patients. In our study we put forward the hypothesis that the prophylactic implantation of a PM decreases the mortality, especially when due to sudden cardiac death, in MD patients.

2. Patients and methods

2.1. Patients

Between 1994 and 2008 all consecutive patients with genetically confirmed MD1 treated by our university institution's multidisciplinary team for the care of patients with neuromuscular diseases underwent cardiovascular evaluation on their first visit and were subsequently monitored until the last clinical observation or death. The infantile form of MD was excluded of this study.

Initial clinical evaluation consisted of a physical examination and a Brooke score. The presence of sleep apnea syndrome was evaluated by standard polysomnographic studies. Cardiological evaluation comprised a 12-lead rest electrocardiogram (ECG), a 24-hour ambulatory ECG, transthoracic echocardiography, right and left ventricular radionuclide angiograms, and electrophysiologic (EP) testing after obtaining the patient's written, informed consent. The EP testing was performed using standard techniques with 2 quadripolar catheters introduced in the femoral vein and worked up into the high right atrium, the bundle of His region and then the right ventricle. Several variables were measured during this EP study: AH interval (ms), HV interval (ms), atrioventricular Wenckebach point (beats/min) during atrial stimulation at increasing rate, sinus node recovery time (ms). If normal atrioventricular conduction parameters were found, all these measurements were repeated after infusion of 1 mg of atropine. The criterion for PM implantation was an HV interval ≥70 ms, whether the patient was

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symptomatic or not [12]. This led us to split our population into two groups: implanted MD patients (PM group) and non-implanted MD patients (non-PM group). The patients at risk of sudden death were defined according to the criteria of Groh et al. [5]: non sinus rhythm, a PR interval of 240 ms or more, QRS duration of 120 ms or more, or second-degree or third-degree atrioventricular block (AVB).

2.2. Algorithm specifications

The implanted PMs were dual-chamber PM (ELA Medical and SORIN units), either Chorus RM, Talent II DR, or Symphony DR. A specific diagnostic algorithm was downloaded in Chorus RM and Talent II DR to the random-access memory of the PM, making it possible to diagnose bradycardia and tachycardia. Symphony DR was programmed in AAI Safe R mode (pause allowed ≤3 s). Bradycardia events could be ventricular pauses or sinus bradycardia (pauses ≥3 s). The diagnosis of tachycardia, based on ventricular rate analysis, was made when a beat-to-beat heart rate acceleration ≥25% at the onset of tachycardia occurred, followed by a heart rate ≥150/min for more than five consecutive cycles. With each event the time and date were recorded, along with marker chains, all retrievable by PM interrogation. Each marker chain included atrial and ventricular events preceding and following the diagnostic cycle, so as to be able to clarify the nature of the event.

2.3. Patient follow-up

Patients of the PM group were seen bi-annually in the implantation center. Each visit involved an interrogation about existing symptoms, a physical examination, a 12-lead rest ECG and a complete PM interrogation including retrieval of the algorithm data diagnostic.

Patients of the non-PM group were monitored once a year by clinical examination and ECG. A 24-hour ambulatory ECG was performed if syncope, dizziness or palpitations were reported. The EP study was not repeated during the follow-up period.

In case of death the date and primary cause of death were obtained from medical records if the death occurred in hospital, whereas it was recorded by interviewing the general practitioner or the family in the case of death at home. No post-mortem analysis of PM or autopsy was carried out.

2.4. Statistical analysis

Data are reported as the mean value ± SD. Baseline characteristics in patients of the PM and non-PM groups were compared with univariate analysis using Fisher exact and chi-square tests for qualitative parameters, and with the Student *t* test for quantitative parameters. A p value <0.05 was considered significant. The Kaplan–Meier methodology was used to calculate the survival curves, and the logrank-test was used to evaluate the differences between them.

3. Results

3.1. Patients

One hundred consecutive patients (59 men and 41 women) with myotonic dystrophy were included. Mean age at inclusion was 40 ± 13.8 years old. Their mean baseline characteristics are summarized in Table 1. None of them had a PM at the first assessment. Seventeen of them had experienced syncope or presyncope. Left ventricular radionuclide function was normal (≥50%) in 83 patients but altered in 17 patients (only 3 of whom were under 40%). Right ventricular radionuclide function was normal (≥45%) in 52 patients and altered in 48 patients. Sleep apnea syndrome was diagnosed with standard polysomnographic studies in 51 patients. Nocturnal treatment of this sleep apnea syndrome by non-invasive positive-pressure ventilation was followed regularly by 70.6% (n = 36) of them. (The others either refused the treatment or failed to follow it regularly). No patient was under permanent mechanical respirator at the time of recruitment.

Table 1
Baseline mean characteristics of MD patient population.

	Total population, n = 100	PM group, n = 49	Non-PM group, n = 51	p value
Age (years)	40 ± 13.8	40.7 ± 12.8	39.4 ± 14.7	NS
Women (n)	41	21	20	NS
Brooke score	4 ± 2	4 ± 2	4 ± 3	NS
Sleep apnoea syndrome (n)	51	28	23	NS
Syncope or presyncope (n)	17	12	5	NS
Normal ECG (n)	50	16	34	0.0009
Spontaneous AFib or AFl (n)	5	4	1	NS
Spontaneous NSVT (n)	1	0	1	NS
LV end-diastolic diameter (mm)	47 ± 5	47 ± 6	46 ± 4	NS
Radionuclide LVEF (%)	59 ± 10	57 ± 10	60 ± 11	NS
Radionuclide LVEF <50% (n)	17	7	10	NS
Radionuclide RVEF (%)	44 ± 10	42 ± 10	45 ± 10	NS
CTG repeat length (kb)	2.65 ± 1.58	2.85 ± 1.72	2.46 ± 1.42	NS

Data are expressed as mean values ± SD, or number (%).
AFib = atrial fibrillation; AFl = atrial flutter; NSVT = non-sustained ventricular tachycardia; LV = left ventricle; LVEF = left ventricular ejection fraction; RVEF = right ventricular ejection fraction; CTG = cytosine–thymine–guanine; kb = kilobases; NS = not significant (p>0.05).

3.2. First ECG parameters

Fifty patients had normal conduction intervals on their surface ECG. The other 50 patients had one or more conduction disturbances: 25 of them with a first-degree AVB, 1 with a second-degree AVB (Mobitz 1), 13 with a left anterior block, 9 with right bundle-branch block and 13 with left bundle-branch block. Two patients had a sinus deficiency on the resting ECG, confirmed by a 24-hour ambulatory ECG. No paroxysmal complete AVB was recorded during the baseline 24-hour ambulatory ECG records. Spontaneous arrhythmia was documented in 6 patients: paroxysmal atrial fibrillation or atrial flutter in 5 cases and non-sustained ventricular arrhythmia in 1 case.

3.3. Electrophysiologic testing

All of the patients underwent an EP study. HV interval was ≥70 ms in 49 cases (49%). Wenckebach point was 162 ± 37 beats/min. Sinus node function was normal in all patients. All of the 49 patients with an HV interval ≥70 ms were implanted with a prophylactic dual-chamber PM.

3.4. PM group

There was no significant difference between implanted and non-implanted patients for the following parameters: age, gender, existence of syncope, Brooke score, presence of sleep apnea syndrome, regularly followed nocturnal treatment of this sleep apnea syndrome, median CTG repeat length, left ventricle end-diastolic diameter, left and right ventricular radionuclide functions (Table 1).

ECG was normal in 16/49 PM patients (32.7%) as compared to 34/51 (66.7%) non-implanted patients (p = 0.0009). There was no significant difference between the two groups concerning the presence of spontaneous arrhythmia at the beginning of the follow-up.

3.5. Patients at high risk of sudden death

46 patients (46%) had one or more criteria of sudden death at the time of the clinical evaluation (i.e. severe rhythm as opposed to sinus abnormalities on the ECG performed at study entry, a PR interval of 240 ms or more, QRS duration of 120 ms or more, or second-degree or third-degree AVB), 32 of them were implanted of PM. 65.3% patients (n = 32) of the PM group, as compared to 27.5% (n = 14) of the non-PM group (p = 0.0001), met Groh's criteria of sudden death risk [5].

3.6. Follow-up

Mean duration of follow-up was 74 ± 39 months (12 to 146 months) which represented 617 patient-years. 80/100 patients were monitored for more than 3 years. There was no significant difference in duration of follow-up between patients of the PM group and those of the non-PM group. One patient in the non-PM group was implanted with a PM during the follow-up for symptomatic paroxysmal complete AVB 52 months after the initial evaluation.

Death occurred in 10 cases. The mean age at death was 55 years old. The cumulative survival rate was 99%, 93.9% and 85% at 1, 5 and 10 years respectively (Fig. 1). There were 5 deaths in the PM group (10.2%) and 5 cases in the non-PM group (9.8%) (Fig. 1). There was no significant