Myotonic Dystrophy and Heart Disease. Behavior of Arrhythmic Events and Conduction Disturbances

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Objective
To study the prevalence and natural evolution of arrhythmic events and conduction disturbances in myotonic dystrophy; to correlate the genetic defect with cardiovascular findings; to assess cardiac mortality, frequency, and predictive factors of sudden death; to correlate the severity of the neuromuscular and cardiac involvement; and to define the role of the electrophysiological study (EPS), in myotonic dystrophy.

Methods
Periodic clinical assessment and the following tests were performed in 83 consecutive patients with a mean follow-up of 42±30.63 months: complementary examinations, genetic tests, electrocardiography, echocardiography, and Holter; electrophysiological study was performed in 59 cases.

Results
Atrial tachyarhythmia was observed in 10 (12%) patients, NSVT in 14 (17%), first-degree AVB in 24 (29%), LBBB in 19 (23%), and RBBB in 13 (16%). Symptoms, an increase in the PR interval, QRS enlargement, LVEF < 60%, and age were predictive factors of death. Nine patients died (4 sudden deaths; 2 due to heart failure; 3 due to other causes). Electrophysiological study: H-V interval >70 ms in 34% and > 100 ms in 11% (postprocainamide).

Conclusion
The prevalence of arrhythmic events and conduction disturbances ranged from 50% to 80% after 6 years, and did not correlate with the genetic defect. Atrial flutter was the most common sustained arrhythmia. Cardiac involvement increased as the neuromuscular disease became aggravated, but progression of the cardiac involvement was more rapid than that of the neuromuscular disease. Overall mortality was low (11%) and sudden death occurred in half of the cases. The EPS identified a group at risk for pacemaker implantation.

Key words
myotonic dystrophy, arrhythmias, cardiac conduction system, mortality

Myotonic dystrophy (MD), also known as Steinert’s disease, is the most common form of muscular dystrophy in adults with an estimated prevalence of 1 to 8,000 individuals. It is a primarily neurologic disease with multisystemic impairment, transmitted through autosomal dominant inheritance, and characterized by myotonia. The molecular mechanism of the disease involves expansion of the CTG trinucleotide located in the chromosome region 19q13.3. Healthy individuals may have 5 to 37 (CTG) repeats. The (CTG) repeats correspond to a permutation, and the patients affected may have from 50 to 8,000 repeats.

Cardiac involvement is one of the major characteristics of the disease’s evolution, mainly in regard to rhythm and conduction disturbances. Heart failure or death is rare, and the importance of cardiac arrhythmias in myotonic dystrophy has been reported in case series in the literature. Electrocardiographic alterations may occur in 37 to 80% of the cases and are frequently found in asymptomatic individuals. The His-Purkinje system seems to be the most frequent site of the lesion.

Only a few longitudinal studies have investigated the natural history of cardiac involvement in myotonic dystrophy. In our study, we focused on essentially arrhythmogenic aspects with the following primary objectives: to study the prevalence and natural evolution of arrhythmic events and intracardiac conduction disturbances; to correlate the genetic defect and clinical, functional, and electrocardiographic cardiovascular evaluation findings with the types of arrhythmias documented; to assess the occurrence of cardiac mortality and sudden death; and to identify the predictive factors for the major risk of the conduction system impairment. Our secondary objectives were as follows: to study the correlation between the severity of neuromuscular impairment and cardiac involvement; and to assess the importance of the electrophysiological study (EPS) for indicating therapeutic procedures.

Methods
From June 1989 to May 2000, 83 consecutive patients diagnosed with the classic form of myotonic dystrophy were referred for cardiovascular evaluation from the neuromuscular dystrophy outpatient clinic and the Human Genome Studies Center. Age ranged from 12 to 61 years (mean=36.77±11.95), and 45 (54.22%) patients were of the male sex, and 38 (45.78%) were of the female sex.

The diagnosis of myotonic dystrophy was based on the familial history, distal or facial muscular impairment (weakness, amyotro-
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According to the criteria of Hinkle 11, and sudden death was assessed. Mortality rate, causes and types of death were also assessed.

Mild No No support required (abnormal posture) No support required No support required Alone
Moderate No Support required Support required Support required Alone
Severe No No No No With help

Table I - Criteria adopted for classifying the neuromuscular impairment in myotonic dystrophy

<table>
<thead>
<tr>
<th>Activity degree</th>
<th>Running</th>
<th>Walking</th>
<th>Stair climbing</th>
<th>Standing up</th>
<th>Eating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>No</td>
<td>No support required (abnormal posture)</td>
<td>No support required</td>
<td>No support required</td>
<td>Alone</td>
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<tr>
<td>Moderate</td>
<td>No</td>
<td>Support required</td>
<td>Support required</td>
<td>Support required</td>
<td>Alone</td>
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<tr>
<td>Severe</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Support required</td>
<td>With help</td>
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Values of the occurrences and their percentages. The evolutionary behavior was assessed by using the chi-square test (qualitative parameters) and analysis of variance of the repeated measurements complemented by the Bonferroni test (quantitative parameters). The analyses of correlation were performed by using the Pearson correlation test. The Kaplan-Meier methodology was used to calculate the survival curves, and the differences between them were evaluated by using the log-rank test. The search for predictive factors of worse prognosis occurred initially through univariate analysis (Fisher exact and chi-square tests for qualitative parameters). The parameters with P < 0.1 on univariate analysis were assessed by using the Cox proportional hazards model (multivariate analysis) aiming at identifying independent prognostic factors. In all evaluations, the significance level of 5% was adopted.

Results

All patients underwent at least 1 year of clinical and electrocardiographic follow-up, and, after 6 years, 23 patients had completed the entire study protocol. The follow-up duration ranged from 12 to 124 months (mean = 42.17 ± 30.63). Because of these expressive findings of evolutionary analysis, the 6-year follow-up was established as the pattern for analyzing the variables studied. The electrophysiological study was performed in 59 patients: 20 due to palpitation, syncope, or pain, and 39 for risk assessment. The findings of prevalence and natural evolution at the beginning and end of follow-up are shown in table II.

In the first year, 3 patients became asymptomatic, 2 after reversion of sustained atrial tachyarrhythmia and one after pacemaker implantation.

At the beginning of follow-up, one patient had type I second-degree atrioventricular block (AVB), and 2 patients had advanced intermittent AVB. Of the 24 patients with AVB, one evolved to advanced AVB, and 9 (15.25%) patients who did not have AVB evolved to first-degree AVB. Of the 54 (65.06%) patients with no intraventricular conduction disturbance, 8 (14.81%) had some type of intraventricular disturbance, and of the 29 patients with any type of AVB, 4 (13.79%) had evolved to first-degree AVB. Of the 54 (65.06%) patients with no intraventricular conduction disturbance (IVCD), 8 (14.81%) had some type of intraventricular disturbance, and of the 29 patients with any type of AVB, 4 (13.79%) had evolved to worsening of the intraventricular conduction disturbance.

Of the arrhythmias occurring at the beginning of follow-up, sustained atrial arrhythmia manifested in 4 (4.82%) patients as follows: 3 (3.61%) patients had atrial flutter, and one (1.20%) patient had atrial fibrillation. No case of sustained ventricular tachycardia was documented.

The number of cytosine-thymine-guanine trinucleotide (CTG) repeats referring to the entire case series ranged from 100 to 2,333 (mean, 791.15; standard deviation, 439.92).

The findings referring to the case series subgroup “relatives”, comprising 8 parents and 12 children, are shown in table III.

Fig. 1 - Study design - Sequence of evaluations performed during the study in a schematic form. Annual clinical cardiovascular and neurological assessment and echocardiogram, Holter and echo every 2 years. * The electrophysiological study (EPS) was performed on the occasion of symptoms of low cerebral flow or on deciding about risk evaluation. ACSCU- Artificial Cardiac Stimulation Clinical Unit.
Nine (11%) patients died during follow-up. Sudden death accounted for 44% of the deaths (4 patients: 2 patients with first-degree AVB, LBBB, and definitive pacemaker; one patient with first-degree AVB; and one patient with left bundle-branch conduction disturbance). Two patients died due to congestive heart failure (2 siblings with first-degree AVB, LBBB, definitive pacemaker, and myocardial dysfunction), and 3 others had noncardiac death (one due to melanoma, and 2 due to pneumonia). Table IV shows the univariate analysis of qualitative and quantitative variables in regard to the outcome death.

In regard to multivariate analysis, the LVEF on Doppler echocardiography was the only independent predictive factor of evolution to death (P<0.0001).

For defining the rhythm of death and factors of influence, survival curves were elaborated (fig 2). Curve 1 shows the survival rate of the entire case series, and curve 2 shows the survival rate according to LVEF (≤60% and > 60%).

Fifty-nine patients underwent electrophysiological study, 14 (23.73%) of whom had H-V interval ≤55 ms; 25 patients (42.37%) had H-V between 55 and 70 ms; and 20 patients (33.90%) had H-V > 70 ms.

The H-V interval at baseline was measured in all patients who underwent electrophysiological study. However, under pharmacological stress (postprocainamide), the H-V interval was measured in 46 patients, and the mean values of that interval were 74.37±13.16 (for patients with H-V < 100 ms) and 112±6.16 (for patients with H-V > 100 ms). Procainamide could not be used in 13 patients because of hypotension or marked bradycardia.

Because of these findings associated with the clinical manifestations and functional clinical behavior, pacemakers were implanted in 15 patients. The characteristics of these 15 patients compared with those of the 44 patients who underwent electrophysiological study, and for whom no artificial stimulation was indicated, are shown in table V.

The electrophysiological study was also very important for assessing tachyarrhythmias and for establishing the clinical correlations. No relevant induced tachyarrhythmias occurred. Sustained ventricular tachycardia was induced in 5 patients, 3 of whom had rapid and poorly tolerated tachycardia, one had monomorphic tachycardia, and one had branch-to-branch tachyarrhythmia.

Concomitant analysis of the findings of the H-V interval and induction of tachyarrhythmias on the electrophysiological study al-
lowed the establishment of therapeutic management in 19 (32.20%) patients. Pacemaker implantation was indicated in 15 patients, and the implantable cardioverter-defibrillator (ICD) was indicated in 4.

The findings of the electrophysiological study in regard to the occurrence of symptoms had totally distinct implications in defining the therapy. Patients undergoing pacemaker implantation (bradyarrhythmias) more often had symptoms (P=0.0142) with a relative risk of 2.234 (0.986 – 5.061) and odds ratio = 5.833 (1.485 – 22.91). On the other hand, symptomatic patients undergoing ICD implantation (tachyarrhythmias) showed no difference as compared with the asymptomatic patients (P=0.3246).

No correlation (Pearson correlation analysis) was observed between the results of the genetic study (number of CTG repeats) and the variables of the arrhythmic events and conduction disturbances: PR interval (R=0.2406), QRS duration (R=0.2699), occurrence of atrial (R=0.0003) and ventricular (R=0.0011) tachyarrhythmias, and measurement of the H-V interval (R=0.2349).

Discussion

Of the presentations of myotonic dystrophy, the classic form is the most prevalent and is associated with CTG expansion in the chromosome region 19q13.3. It was the first single-locus disease recognized with the anticipation phenomenon, the genetic phenomenon of increase in disease severity and earlier disease beginning in successive generations.

The findings in this study reliably confirm the concept proposed by Church that, in myotonic dystrophy, the heart is sooner or later impaired.

In this study, which assessed cardiac involvement through the behavior of arrhythmic events and conduction disturbances, the consecutive inclusion of 83 cases of the classic form of myotonic dystrophy essentially followed neurological and genetic criteria.

The clinical evaluation of our patients showed that, at the beginning of the study, only 22% of the patients had cardiovascular symptoms (10% palpitations, 6% presyncope or syncope, and 6% precordial pain). After a 6-year follow-up, 56% were symptomatic (17% palpitations, 13% presyncope or syncope, and 26% precordial pain), which is a significant evolutionary difference (P < 0.0005). This represents a contribution to the literature, which so far had reported no natural evolution of those manifestations.

At the beginning of the study, 99% of the patients were in FC I heart failure, and none of them had complaints or a physical examination characteristic of cardiac decompensation. With evolution, however, heart failure was responsible for 2 deaths.

Some studies have shown rates of cardiac impairment expressed as electrocardiographic abnormalities ranging from 37 to 80%, involving short case series. The overall prevalence of conduction disturbances in our study was 50% in the initial assessment and the greatest prevalences were as follows: sinus bradycardia, 20% of the cases; first-degree AVB, 29%; isolated or associated ASRBBB, 23%; LBBB, 16%; left bundle-branch conduction disturbance (LBBCD), 9%, more prevalent than RBBB, 1%. The latter finding is not in accordance with the data in the literature that indicate a greater prevalence of RBBB. The discordances may result from differences in the profile of the population, the follow-up duration,
and the well-known cardiac abnormalities studied, although not all studies specified such factors. 13,14,16,17,18,22. In regard to LBBB, the findings are surprising because that disturbance is usually associated with the systemic diseases that impair the cardiovascular system and with the presence of left ventricular dysfunction, which was not observed in our case series at the beginning of follow-up. However, of the patients who died during follow-up, 6 (66.7%) had LBBB or left bundle-branch conduction disturbances.

The evolutionary electrocardiographic findings showed a significant progression (P<0.0001) of the PR interval and QRS duration after 6 years of follow-up, corresponding to a mean increment of 0.1 ms and 0.03 ms, respectively, every 3 years. The PR interval behavior was not assessed on the electrophysiologic study for identifying the site of impairment of the conduction system; however, the electrocardiographic characteristics (IVCD or bundle-branch block with enlargement of the QRS in 24 of 35 patients with first-degree AVB and considerable temporal variations) suggested that a nodal atrioventricular impairment did not occur, revealing a worse prognosis.

Yet on the electrocardiogram, the presence of an inactive electric area (pathologic Q waves) was observed in 33% of the cases, which had inactive electric areas in some ventricular site with predominance of the septal and lateral regions. These alterations may be attributed to the disarray in myocardial fibers (alteration in the sequence of activation) and to impairment in the perivascular musculature. These electrical findings, in the absence of clinical evidence of coronary heart disease, suggest focal myocardial lesion 9,16,26-29. In addition, the evolutionary results of some patients have shown the following: a reduction in pseudonecrosis, probably due to worsening of the conduction disturbances that may mask these aspects on the electrocardiogram9,18; and an increase in the number of inactive areas that suggest the existence of myocardial disease progression, although in a very insidious form as compared with the evolution of the conduction system impairment.

No episode of paroxysmal sustained ventricular tachycardia occurred or was identified on 24-hour Holter. However, ventricular arrhythmia (more than 200 ventricular extrasystoles per hour or NSVT) was present in 17% of our patients in the initial evaluation, and in only 3% after 6 years of follow-up. Atrial tachycardia was present in 12% of the patients (5% sustained, of which 75% were atrial flutter and 25% were atrial fibrillation). After reversion of arrhythmia, all our patients with sustained atrial tachycardia were maintained on antiarrhythmic medication and without anti-coagulation, because no patient remained in atrial fibrillation.

In addition to intra-atrial and intraventricular conduction disturbances, the modification in refractoriness and disarray of the muscle fibers may participate in the arrhythmogenic substrate of those arrhythmias 9,13,19,22,26,30,31. The abnormalities documented on the electrocardiogram and on Holter, which were transient at the beginning but established throughout the follow-up, represented instability in stimulus conduction or generation, or both.

Colleran et al 32 reported that the prevalence of atrial tachyarhythmias, mainly atrial fibrillation, is greater in patients with the severe form of the disease. Our results are in accordance with that statement when they show lower rates in a group of patients, of whom 93% had the mild form of the disease on the first assessment. They also agree when they demonstrate the induction of atrial tachyarhythmia in 20% (12/59) of the patients undergoing electrophysiologic study. Nine of those 12 patients were on a follow-up longer than 3 years, and, of them, 55% evolved to more severe forms of the neuromuscular disease.

Unlike that which happens with the skeletal muscle, myocardial impairment is rarely identified in myotonic dystrophy. Few cases of ventricular failure have been reported. However, mild abnormalities in systolic and diastolic function have been documented on echocardiography 9,29,33. Similarly to those findings, we observed that, in 95% of the cases, LVEF was > 60%, and, in only one, it was < 50% (LVEF=47%). In a 3-year follow-up, 4 of 6 patients who had a reduction in LVEF (< 60%) died (2 sudden deaths and 2 deaths due to heart failure).

In the period between the first and last assessment, 19% of the cases had an insidious worsening in their neuromuscular disease, 56% of whom also had worsening in their conduction disturbances or arrhythmic events, or both. The low prevalence of cardiovascular symptoms at the beginning of the disease is due to the rare myocardial impairment in this phase. However, with the progression and worsening in the neuromuscular disease, subclinical myocardial dysfunction may occur 9,29,33.

In our case series, the presence of the anticipation phenomenon in regard to the neuromuscular disease was once again demonstrated. In 8 parent-child pairs, the size of the genetic defect is at least 2.4 times greater in the children than that in parents. Our results showed that, for the first time, the anticipation phenomenon was also present in the conduction system impairment, because in 5 of the 8 parent-child pairs (62%) the alterations related to the conduction system were much more severe than those present in the parents. The age of appearance of the alterations related to cardiac conduction occurred at least 20 years before in 80% of the children when compared with the age of appearance in parents (P<0.0001).

We believe that in the classic form, the earlier (second decade of life) the manifestations of neuromuscular disease occur, even when only myotonia, the greater the degree of impairment of the His-Purkinje system in young adults, who usually have the greater numbers of repeats. On the other hand, when symptom onset of the neuromuscular disease occurs late (third and fourth decades), the manifestations of the cardiac conduction disturbances should correlate with the time of evolution and the degree of phenotypic variation of the disease.

In our case series, no correlation was observed between the number of CTG repetitions and any conduction disturbance or arrhythmic event, such as the following: PR interval at the beginning of the study (Pearson’s R=0.2406); increase in the value of the PR interval after a 6-year follow-up (Pearson’s R=0.1972); duration of the QRS complex (Pearson’s R=0.2699); and an increase in QRS duration after a 6-year follow-up (Pearson’s R=0.02018). No correlation was observed between the number of CTG repeats and symptoms, LVEF on echocardiogram, and the presence of atrial (Pearson’s R=0.00032) or ventricular (Pearson’s R=0.00107) arrhythmias.

This study showed a correlation between neuromuscular disease and conduction system impairment. All patients with a greater degree of dystrophy (moderate or severe) also had more advanced conduction disturbances and more expressive arrhythmic events, both in the initial phase and in more advanced phases of the disease. However, most patients with mild impairment of the
neuromuscular disease showed a clinical spectrum ranging from normal cardiovascular assessment to high risk of sudden death, both for conduction disturbances (18%) and arrhythmic events (6%). Twenty-one (25.3%) patients with mild impairment of the neuromuscular disease had, on follow-up, an important conduction system impairment, and, in 56% of those who had progression of the neuromuscular disease, concomitant worsening of the cardiac impairment (conduction system or LVEF, or both) was observed.

Total mortality was 11%. Cardiac death occurred in 6%, 2 siblings with first-degree AVB associated with LBBB, left ventricular dysfunction, and definitive pacemaker. Their cause of death was heart failure. Four sudden deaths occurred as follows: one patient had antecedent anteroseptal fibrosis and probable arrhythmic death; 2 patients had LBBB associated with first-degree AVB, 1 with a baseline H-V interval of 100 ms, and another with a pacemaker; one asymptomatic patient had a normal electrocardiogram. This association of sudden death and the presence of areas of fibrosis and conduction disturbances shows the importance of the known physiopathological mechanism of fatal arrhythmia probably implicated in these cases.

Univariate analysis of the factors related to prognosis revealed the following predictive factors of cardiac death: age (P=0.0029); presence of symptoms (P=0.0027); measurement of the PR interval (P=0.0191); duration of the QRS complex (P=0.0741); and left ventricular ejection fraction on echocardiography (P=0.0001). Multivariate analysis through the Cox proportional hazards model showed that left ventricular ejection fraction was the only independent predictive factor of evolution to death.

Some studies aimed at identifying predictive risk factors by using electrophysiological study and correlating the results of the measurements of the H-V interval with the electrocardiographic findings of patients with myotonic dystrophy. 34-36

Our patients underwent electrophysiological study for symptom clarification (34%) or for risk assessment (66%). The H-V interval was increased in more than 50% of the cases and was the finding responsible for the therapeutic indication of the bradycardias (pacemaker implantation) in 15%. Of those, 73% had first-degree AVB associated with LBBB or LBBCD, and these findings were statistically different (P<0.0001) in regard to the group with no indication for pacemaker implantation. Therefore, a group at risk for third-degree AVB and sudden death was identified for the first time in the literature.

Induction of clinically important ventricular tachyarrhythmias on the electrophysiological study defined some cases whose pathophysiologic mechanism was clarified and the therapy defined: implantable cardioverter-defibrillator (ICD), ablation of the arrhythmogenic focus, and use of antiarrhythmic agents. Of the symptomatic patients with induced SVT, one was of the fascicular type (ablation) and 2 were rapid and poorly tolerated SVT (ICD implantation).

In conclusion, in patients with the classic form of myotonic dystrophy, the prevalence of arrhythmic events or conduction disturbances was 50% and worsened after a 6-year follow-up (80%), and a significant occurrence of first-degree AVB and intraventricular block was observed. Atrial flutter was the most frequent sustained arrhythmia. Cardiac impairment increased with the severity of the neuromuscular impairment, but the cardiac disease worsened more rapidly than the neuromuscular disease. Total and cardiac mortality were low (11% and 7%, respectively), sudden death accounted for half of it. The predictive factors for cardiac mortality were clinical manifestations, age, PR interval, QRS duration, and LVEF, the latter being the only independent predictive factor of prognosis. The electrophysiological study defined the therapy for bradyarrhythmias and identified the group at risk for pacemaker implantation.

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References