

## Duchenne Muscular Dystrophy: Electrocardiographic Analysis of 131 Patients

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### Abstract

**Background:** Cardiac involvement is known to occur in patients with Duchenne muscular dystrophy (DMD). The electrocardiogram (ECG) shows some typical changes in DMD, which makes it a useful test for the diagnosis of cardiac lesion in this disease.

**Objective:** To evaluate the electrocardiographic changes in patients with DMD and to correlate these changes with the age of the population studied.

**Methods:** ECG of 131 patients diagnosed with DMD were examined. Several electrocardiographic variables were analyzed, and the patients were divided into two groups - one with and one without changes, for each variable studied. The correlation between the two groups and the age of the patients was analyzed. Garson's criteria were used to establish the electrocardiographic parameters of normality.

**Results:** ECG was abnormal in 78.6% of the patients. All showed normal sinus rhythm. The following percentages were found for the main variables studied: short PR interval = 18.3%; abnormal R waves in  $V_1$  = 29.7%; abnormal Q waves in  $V_6$  = 21.3%; abnormal ventricular repolarization = 54.9%; abnormal QS waves in inferior and/or upper lateral wall = 37.4%; conduction disturbances in right bundle branch = 55.7%; prolonged  $QT_c$  interval = 35.8%, and wide QRS = 23.6%. Unpaired t test was used to establish the correlation between age and the electrocardiographic variables studied in the two groups. Statistically significant differences were found only for the abnormal repolarization variable.

**Conclusion:** Electrocardiographic abnormalities are common in DMD, revealing early cardiac involvement. Only the abnormal ventricular repolarization variable was more frequent, however at a lower age range ( $p < 0.05$ ). (Arq Bras Cardiol 2010;94(5):583-586)

**Key words:** Muscular dystrophy, Duchenne; electrocardiography; heart block.

### Introduction

Duchenne muscular dystrophy (DMD) is the most frequent neuromuscular disease, with an X-linked recessive genetic inheritance pattern. It affects practically only male children. The gene responsible for DMD was isolated in 1986, and the protein that it produces - dystrophin, was also identified its absence results in muscular changes<sup>1,2</sup>.

It is the most common form of progressive muscular dystrophy, with an incidence of approximately one in 3,500 live births<sup>3,4</sup>.

The manifestations start approximately in the third to fifth year of life, and are characterized by progressive loss of muscle strength and elevation of serum creatine kinase enzyme (CK); the outcome is quite variable<sup>5</sup>.

Most of these children die before the age of 20 years, usually of respiratory infection that rapidly progresses to respiratory failure. However, in approximately 10% of the cases, death is known to result from cardiac causes, especially ventricular dysfunction. That is why prompt identification of cardiac lesions is important, and this requires careful cardiac investigation<sup>6</sup>. Cardiac involvement is concomitant with skeletal muscle involvement, and for this reason patients diagnosed recently and those diagnosed later in the course of the disease may show the same electrocardiographic pattern<sup>5,7</sup>.

Typical ECG shows increased R-wave amplitude in right precordial leads, as well as increased Q-wave depth in left precordial leads and limb leads. T-wave inversion may also be found in precordial leads, especially in the right ones. The electrocardiographic changes are believed to reflect a selective damage of the posterobasal area of the left ventricle, with lateral extension, resulting in an abnormal cardiac contraction that is first observed in the posterior free wall behind the mitral valve<sup>8,9</sup>.

These electrocardiographic changes are typical. However, according to reports of the literature, their prevalence is

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pretty variable because they have not been studied in light of the criteria of electrocardiographic normality for children as described by Garson Jr.<sup>10</sup>. Application of these criteria, as was done in the present study, may lead to less mistaken diagnoses and provide more reliable information.

## Methods

The electrocardiographic recordings of 131 patients with DMD were analyzed in the period between February 2004 and March 2009. The patients had been referred from the neuromuscular disease outpatient service of Paulista School of Medicine, Federal University of São Paulo, and all diagnoses had been made by means of muscle biopsy and blood biochemistry. The Institutional Research Ethics Committee approved the study protocol according to the principles of the Declaration of Helsinki.

The patients underwent clinical examination and 12-lead ECG in a Dixtal EP3™ (Brazil) device, at a recording speed of 25 mm/s, and calibration standardized at 1.0 mV/cm.

By means of a magnifier, the ECG recordings were analyzed by two cardiologists with more than 20 years of experience in electrocardiography. Data were inserted in an Excel worksheet. The following electrocardiographic parameters were analyzed: PR interval; R wave in V<sub>1</sub>; Q wave in V<sub>6</sub>; ventricular repolarization; presence of QS waves in inferior and upper lateral walls; branch blocks; conduction disturbances in the right bundle branch; ST segment; corrected QT interval; and duration of the QRS complex. Abnormal ventricular repolarization was defined as the finding of inverted or flattened T waves in two or more contiguous leads. Garson's criteria<sup>10</sup> were used as the normal electrocardiographic parameters for each age group.

For each electrocardiographic parameter studied, the patients were divided into two groups (with or without changes), so as to evaluate a possible relationship between the prevalence of these changes in each parameter and age.

## Statistical analysis

Continuous variables were expressed as mean and standard deviation. Categorical variables were expressed as percentage. Unpaired t test was used to evaluate the possible correlations with the different ages; p values < 0.05 were considered for rejection of the null hypothesis. The Figure 1 typical electrocardiogram of a patient with DMD.

## Results

All 131 patients were males with a mean age of 9.4 years ± 3.4 years.

The main electrocardiographic changes found in the study population are shown in Table 1. Mean age, standard deviation and confidence interval of the groups in relation to the normal and abnormal parameters are shown in Table 2.

## Discussion

DMD is a condition characterized by changes in the skeletal muscles and an unknown degree of cardiac involvement.

**Table 1 - Electrocardiographic changes in DMD, considering the normal pattern according to Garson's criteria**

Changes	n	%
Short PR interval	24	18.3
Sinus tachycardia	3	2.2
Abnormal R in V <sub>1</sub>	39	29.7
Abnormal Q in V <sub>6</sub>	28	21.3
Abnormal ventricular repolarization	72	54.9
Abnormal QS in inferior and/or upper lateral walls	49	37.4
Right bundle branch block	10	7.6
Conduction disturbance in right bundle branch	73	55.7
ST-segment elevation	8	6.1
Prolonged QT <sub>c</sub>	47	35.8
Wide QRS	31	23.6
Typical ECG: abnormal R in V <sub>1</sub> and Q in V <sub>6</sub>	9	6.8
Normal ECG	28	21.3

ECG - electrocardiogram.

**Table 2 - Mean age (years) in relation to the normal and abnormal electrocardiographic parameters**

Change	Mean age ± SD (CI)		p
	No	Yes	
Short PR interval	9.5 ± 3.3 (8.9-10.1)	8.4 ± 2.0 (7.5-9.2)	NS
Abnormal R in V1	9.1 ± 3.0 (8.4-9.7)	9.2 ± 3.2 (8.7-10.8)	NS
Abnormal Q in V6	9.4 ± 3.0 (8.8-10.0)	9.0 ± 3.5 (7.6-10.4)	NS
Abnormal ventricular repolarization	10.1 ± 2.8 (9.3-10.8)	8.4 ± 3.1 (7.7-9.2)	*
QS in inferior and/or upper lateral walls	9.2 ± 2.9 (8.6-9.9)	9.2 ± 3.3 (8.3-10.2)	NS
Right bundle branch block	9.1 ± 3.0 (8.5-9.6)	11.4 ± 3.8 (8.6-14.1)	NS
Conduction disturbances in right bundle branch	9.0 ± 2.8 (8.2-9.7)	9.5 ± 3.2 (8.7-10.2)	NS
ST-segment elevation	9.1 ± 3.0 (8.6-9.7)	10.8 ± 3.1 (8.2-13.4)	NS
Prolonged QTc	9.4 ± 2.9 (8.7-10.0)	9.1 ± 3.4 (8.1-10.1)	NS
Wide QRS	8.9 ± 3.1 (8.3-9.5)	10.4 ± 2.7 (9.4-11.4)	NS
Typical ECG: abnormal R in V1 and Q in V6	9.4 ± 3.1 (8.8-9.9)	8.2 ± 2.8 (6.0-10.4)	NS
Normal ECG	9.0 ± 3.2 (8.4-9.7)	10.2 ± 2.6 (9.1-11.2)	NS

\*p < 0.05; NS - non-significant; SD - standard deviation; CI - confidence interval.

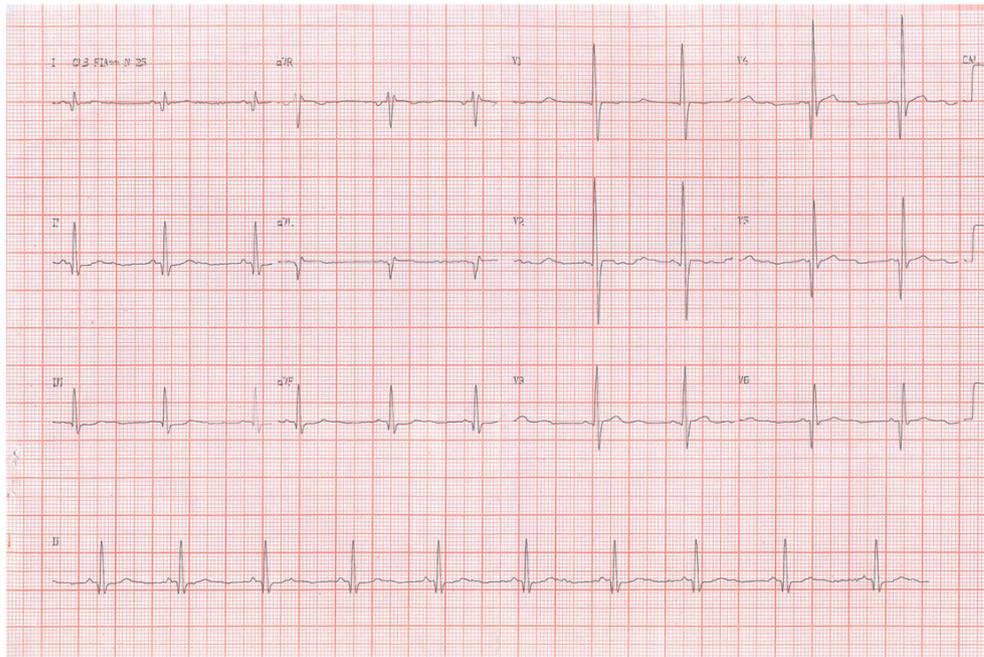


Figure 1 - Typical electrocardiogram of a patient with DMD (prominent R wave in  $V_1$  and deep Q wave in  $V_6$ ; abnormal R in  $V_1$  + Q in  $V_6$  pattern).

However, the clinical manifestations of heart failure are modest or unapparent, and the symptoms appear later in a phase in which respiratory failure predominates. This, sometimes, makes it hard to establish the cause of dyspnea - whether it results from respiratory muscle failure or from heart failure itself<sup>11</sup>.

ECG may contribute to the diagnosis, because abnormalities are described in up to 93.3% of the cases in the literature<sup>7,12</sup>. It is a low-cost non-invasive method with excellent reproducibility, in addition to being widely used in all health care services. It can provide important information, since some of the characteristic changes of DMD are clearly expressed in the electrocardiographic recording.

Nevertheless, the analysis of abnormal features in the ECG of children is frequently mistaken by patterns considered normal, thus making the diagnosis of some electrocardiographic abnormalities particularly difficult. For this reason, Garson's criteria<sup>10</sup> were used in this study in order to correct these distortions.

We should point out that this variability regarding the prevalence of electrocardiographic changes results from the fact that the criteria of normality for children vary immensely from one author to another. Garson's criteria<sup>10</sup> include the so-called limits of normal; they are encompassing and widely accepted in the literature, since they describe "normal" patterns, quantifying all electrocardiographic findings according to the age range.

Of the 131 cases, 103 (78.3%) showed some type of electrocardiographic change; in only 28 patients the electrocardiogram was absolutely normal. No differences were found between the groups of normal and abnormal findings in relation to age, except for the ventricular repolarization

variable, as has been already explained. These findings are relevant and show that the cardiac involvement is very common and is not dependent on the patient's age.

Takami et al's study<sup>7</sup> analyzed electrocardiographic changes in young patients with DMD and, likewise, did not find statistically significant differences when the groups were divided by age.

The classical description of prominent R waves in right precordial leads with deep Q waves in left precordial leads that express the electrically inactive zone in the posterolateral wall is common and usually described as an electrocardiographic change typical of DMD. In our study population, this pattern was found in only nine patients (6.8%).

This electrocardiographic pattern is practically a trademark of the disease, and results mainly from myocyte degeneration with consequent fibrosis and fat deposition. The fibers in this area of the heart (posterolateral wall) suffer greater functional stress, thus leading to the abnormality described, which is expressed as a deep Q wave in  $V_6$  and marked R wave in  $V_1$ . Several patients present with *pectus excavatum*, which leads to a rightward rotation of the heart. However, this abnormality occurs only in the case of patients in advanced stages of the disease, when they face great difficulty to walk and, therefore, to attend outpatient visits, but this was not observed in any of the patients in the present study.

T wave abnormalities resulting from different types of myocardial aggression were found in 72 patients (54.9%). These unspecific findings reveal that some degree of lesion is already present in the cardiac muscle, even in earlier phases of the muscular disease.

Abnormal QS waves in inferior and/or upper lateral walls were also frequent, like in other studies, and were present in

49 cases (37.4%)<sup>7,13</sup>. The real meaning of these changes remains unknown. However, the electrically inactive area described in the posterior wall is probably not restricted to this region.

Right bundle branch block was present in 10 patients (7.6%), and conduction disturbances in the right bundle branch were highly prevalent (55.7%). However, we cannot state that there is a time correlation between this disturbance and the bundle branch block properly installed, and no statistically greater presence of blocks is observed in the older population.

Likewise, for the other electrocardiographic changes, abnormal ventricular repolarization excluded, no differences were observed as regards age. Interestingly, for the abnormal ventricular repolarization variable, the group with abnormality had a lower mean age than the group without abnormality (8.4 years versus 10.1 years;  $p < 0.05$ ). Considering that DMD is a progressive process, the electrocardiographic changes were expected to be more prevalent among the higher age ranges; however, this did not occur with any of the other variables studied. A possible explanation for this phenomenon is that the more severely ill patients are subject to a more intense selective elimination and, thus, do not survive for the making of subsequent analyses.

In 31 patients (23.6%), there was wide QRS complex, some with right bundle branch block, but no left bundle branch block. Short PR interval was found in 24 patients (18.3%), a percentage lower than that found in other studies<sup>7,13</sup>. ST-segment elevation was found in eight patients (6.1%), and prolonged QT<sub>c</sub> interval in 47 (35.8%), figures quite higher than those described by other authors, that ranged from zero to 1.4%<sup>5,7</sup>. This finding may be clinically important, because sudden death cases have been described in patients with DMD in a long-term follow-up study<sup>14</sup>. The true cause of these abnormalities is unknown. However, the global and diffuse cardiac involvement, not only of the contractile component but also of the conduction of the electrical stimulus is probably

decisive to determine these ECG changes.

Several arrhythmias are found in DMD. Nonetheless, analysis of rest 12-lead ECG is not very adequate to detect this type of condition. In some studies using ambulatory ECG monitoring (Holter monitoring), persistent sinus tachycardia was the type of arrhythmia most commonly found<sup>14,15</sup>. Although ECG is a “photograph” of just a few instants, it is not a totally inadequate method for the detection of this arrhythmia, which was present in 2.2% of the patients in our study. This percentage is quite lower than those described in other studies, that ranged from 17.4% to 26%<sup>7,15</sup>. The pathogenesis of this arrhythmia remains unknown; however, fibrous and/or fat infiltration of the sinus node are believed to be involved.

In sum, electrocardiographic changes are common in patients with DMD, and were found in 103 (78.3%) of the 131 patients evaluated in the present study. The ECG changes most frequently found included abnormal ventricular repolarization, abnormal QS waves in inferior and/or upper lateral walls, and conduction disturbances in the right bundle branch. All data presented unequivocally corroborate ECG as a useful tool in the cardiac assessment of this severe disease.

#### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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#### Study Association

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## References

1. Kunkel LM. Analysis of deletions in DNA from patients with Becker and Duchenne muscular dystrophy. *Nature*. 1986; 322:73-7.
2. Mônico AP, Neve RL, Colleti-Feener C, Bertelson CJ, Kurnit DM, Kunkel LM. Isolation of candidate cDNA for portions of the Duchenne muscular dystrophy gene. *Nature*. 1986; 323: 646-50.
3. Van Essen AJ, Kneppers ALJ, Van der Hout AH, Scheffer H, Ginjaar IB, Ten Kate LP, et al. The clinical and molecular genetic approach to Duchenne muscular dystrophy: an updated protocol. *J Med Genet*. 1997;34:805-12.
4. Mockton G, Hoskin V, Warren S. Prevalence and incidence of muscular dystrophy in Alberta, Canada. *Clin Genet*. 1982; 21:19-24.
5. Thrush PT, Allen HD, Viollet L, Mendell JR. Re-examination of the electrocardiogram in boys with Duchenne muscular dystrophy and correlation with its dilated cardiomyopathy. *Am J Cardiol*. 2009;103: 262-5.
6. Gilroy J, Cahalan JL, Berman R, Newman M. Cardiac and pulmonary complications in Duchenne's progressive muscular dystrophy. *Circulation*. 1963;27:484-93.
7. Takami Y, Takeshima Y, Awano H, Okizuka Y, Yagi M, Matsuo M. High incidence of electrocardiogram abnormalities in young patients with Duchenne muscular dystrophy. *Pediatr Neurol*. 2008;39: 399-403.
8. Sanyal SK, Johnson WW, Thapar MK, Pitner SE. An ultrastructural basis for electrocardiographic alterations associated with Duchenne's progressive muscular dystrophy. *Circulation*. 1978; 57:1122-9.
9. Frankel KA, Rosser RJ. The pathology of the heart in progressive muscular dystrophy: epimycocardial fibrosis. *Human Pathol*. 1976;7: 375-86.
10. Garson Jr A. The electrocardiogram in infants and children: a systematic approach. Philadelphia: Lea & Feibiger; 1983.
11. Sultan A, Fayaz M. Prevalence of cardiomyopathy in Duchenne and Becker's muscular dystrophy. *J Ayub Med Coll Abbottabad*. 2008;20(2):7-13.
12. Gulati S, Saxena A, Kumar V, Kalra V. Duchenne muscular dystrophy: prevalence and patterns of cardiac involvement. *Indian J Pediatr*. 2005; 72(5):389-93.
13. Sluka C. The electrocardiogram in Duchenne progressive muscular dystrophy. *Circulation*. 1968;38:933-40.
14. Corrado G, Lissoni A, Beretta S, Terenghi L, Tadeo G, Foglia-Manzillo G, et al. Prognostic value of electrocardiograms, ventricular late potentials, ventricular arrhythmias, and left ventricular systolic dysfunction in patients with Duchenne muscular dystrophy. *Am J Cardiol*. 2002;89:838-41.
15. Kirchmann C, Kececioglu D, Korinthenberg R, Dittich S. Echocardiographic and electrocardiographic findings of cardiomyopathy in Duchenne and Becker-Kiener muscular dystrophies. *Pediatr Cardiol*. 2005;26:66-72.