Observational Study

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Cardiac conduction disturbances and aging in patients with Duchenne muscular dystrophy

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Abstract

The majority of patients with Duchenne muscular dystrophy (DMD) have electrocardiographic abnormalities, but the clinical significance of conduction disturbances remains unclear. This study aimed to evaluate age-dependent cardiac conduction disturbances by electrocardiogram (ECG) to identify risks of complete atrioventricular (AV) block in this patient population.

In total, 47 patients with DMD (age, ≥20 ys) who recorded ECGs at our hospital from July 2015 to June 2016 were included in this study. The PR interval and QRS duration in their previous ECGs were analyzed retrospectively. Associations between ECG findings and left ventricular (LV) systolic function obtained from the latest echocardiography were examined.

The mean age of patients was 27.6±6.0 years, and the mean observation period was 9.8±3.7 years. The PR interval gradually increased with age, but no ECGs showed an abnormally prolonged PR interval. On the other hand, the QRS duration tended to increase progressively with age, and some patients had an abnormally prolonged QRS duration. The QRS duration was not correlated with LV systolic function ($P=0.867$). One patient who developed a complete AV block had a drastically prolonged QRS duration before the onset of the disorder.

The QRS duration tended to increase progressively with age, irrespective of LV systolic function in patients with DMD. Attention should be paid to the QRS duration as an indicator of risk for complete AV block in older patients.

Abbreviations: AV = atrioventricular, DMD = Duchenne muscular dystrophy, ECG = electrocardiogram, LV = left ventricular, LVDd = left ventricular diastolic dimension, LVEF = left ventricular ejection fraction.

Keywords: aging, complete atrioventricular block, Duchenne muscular dystrophy, electrocardiogram, QRS duration

1. Introduction

Duchenne muscular dystrophy (DMD) is a X-linked recessive disorder that occurs at a rate of 1/3500 male births.[1] The genetic locus involved in this abnormality has been identified as the dystrophin gene. Although respiratory failure and cardiomyopathy are major causes of death, a multidisciplinary treatment approach including noninvasive ventilatory support, steroids, and cardiac therapy (eg, angiotensin-converting enzyme inhibitors and β blockers) has lengthened survival in these patients. Most patients with DMD present with abnormal electrocardiogram (ECG) findings, but the clinical significance of conduction disturbances has not been extensively described.

2. Materials and methods

The study protocol was approved by the Institutional Review Board of National Center of Neurology and Psychiatry (approval number: A2016–063, approval date: October 11, 2016).

Participants were 47 patients with DMD (age, ≥20 ys) who recorded ECGs from July 2015 to June 2016 at our hospital. This study was a retrospective observational study.

Previous ECGs of the participants were analyzed retrospectively to examine changes in the PR interval and QRS duration by year. ECGs showing a rhythm other than sinus rhythm were excluded from the analysis. When there were multiple ECGs in 1 year, the latest ECG was used; when no ECG was recorded, data were treated as missing.

The latest echocardiogram examined within six months of ECG recording was analyzed. Participants were classified into 3 groups according to LV function based on LV end-diastolic dimension (LVDd) and LV ejection fraction (LVEF): normal function (LVDd <55 mm and LVEF >55%), mild dysfunction (LVDd <55 mm and LVEF <55%), and severe dysfunction (LVDd >55 mm and LVEF <55%).

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2.1. Statistical analysis

To evaluate the effect of age, trends of the PR interval and QRS duration were estimated using the following local level model. In this model, i and t are indices of patient and age, respectively.

$$log(y_{it}) \sim N(m_t + b_i, \sigma_0^2),$$

$$m_t \sim N(m_{t-1}, \sigma_1^2),$$

$$b_i \sim N(0, \sigma_2^2),$$

where, y_{it} is the PR interval or QRS duration, m_t is its trend, and b_i is the effect of the patient. We estimated the posterior distribution of the parameters using MCMC software WinBUGS ver. 1.4.3.

To evaluate the association between LV systolic function and QRS duration, we compared the 3 groups (normal, mild dysfunction, and severe dysfunction) in terms of QRS duration using the Kruskal–Wallis test, with a significance level of 0.05. The test was performed with R ver. 3.2.1.

Table 1

Baseline clinical characteristics.

Baseline characteristics of study participants	
Variable	**Total (n = 47)**
Male sex	47 (100.0)
Age, ys	27.7 ± 6.0
Cardiac indices and laboratory data	
Left ventricular diastolic dimension (mm)	45.7 ± 11.2
Left ventricular ejection fraction (%)	40.9 ± 18.3
Brain natriuretic peptide (pg/mL)	58.0 ± 116.4
Creatine kinase (IU/L)	422 ± 411
Ventilator use	
Non-invasive positive pressure ventilation	43 (91.4)
Invasive positive presure ventilation	2 (4.3)
Medications	
Renin-angiotensin system inhibitors	41 (87.2)
β-blockers	39 (83.0)
Potassium-sparing diuretics	11 (23.4)
Loop diuretics	9 (19.1)
Digitalis	1 (2.1)
Pimobendan	5 (10.6)
Amiodarone	3 (6.4)

Categorical and consecutive data are presented as number (percentage) and mean ± standard deviation, respectively.

3. Results

Table 1 shows baseline clinical characteristics of the study population, which comprised 47 male patients (mean age, 27.6 ± 6.0 ys) who were diagnosed with DMD (33, based on genetic analysis; 14, based on clinical features). LVDd and LVEF were 45.7 ± 11.2 mm and 40.9 ± 18.3%, respectively. BNP levels varied widely depending on cardiac function. Creatine kinase levels were 422 ± 411 IU/L. Forty-three patients used nocturnal or all-day noninvasive positive pressure ventilation, and 2 patients used invasive positive pressure ventilation with tracheotomy. Most patients were administered renin-angiotensin system inhibitors and β-blockers for cardiomyopathy, and 3 patients were administered amiodarone for nonsustained ventricular tachycardia.

In total, 386 previous ECGs of study participants were analyzed by year. The changes in the PR interval and QRS duration according to age are shown in Fig. 1. The PR interval was relatively short in young patients, and increased with age; however, no ECGs showed abnormally prolonged PR intervals. On the other hand, the QRS duration tended to increase progressively with age, and in some patients, the values were abnormally prolonged. ECGs of 12 patients showed QRS durations longer than 120 msec. The QRS morphology showed a right bundle branch block pattern in 5 patients, left bundle branch block pattern in 2 patients, and non-specific intraventricular conduction disturbance in 5 patients.

We evaluated the relationship between QRS duration and LV systolic function in 45 patients whose echocardiography results were examined within six months of the latest ECG recording. Sixteen patients had normal LV function, 19 patients had mild LV dysfunction, and 10 patients had severe LV dysfunction. No significant differences were observed in QRS duration among the 3 groups (104.8 ± 15.9 mm, 104.5 ± 16.5 mm, and 107.2 ± 17.3 mm, respectively; $P = .867$) (Fig. 2).

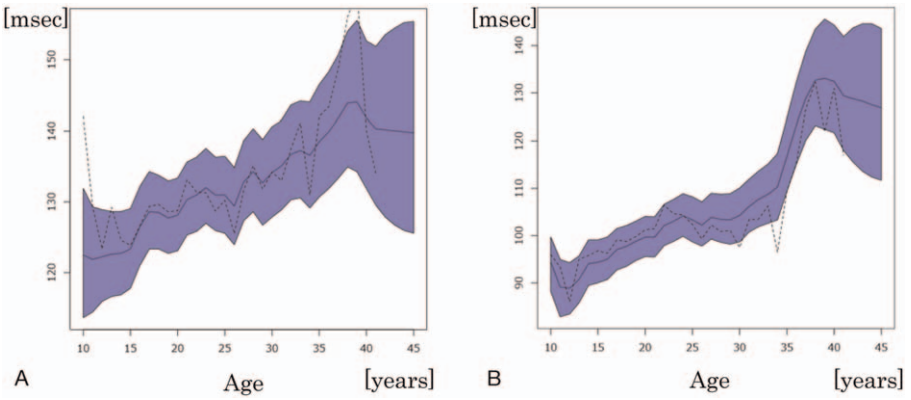

Figure 1. Trends of the PR interval (A) and QRS duration (B). Solid lines represent the estimated trends of the PR interval and QRS duration. Filled areas represent 95 percent confidence intervals for the trends. Dashed lines represent means of the observed PR interval (A) and QRS duration (B) for each age.

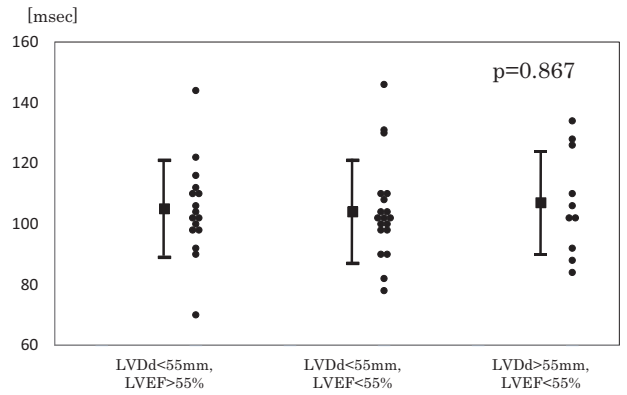

Figure 2. The distribution of QRS duration by groups according to LV systolic function. There was no statistically significant difference among the three groups.

One patient developed a complete AV block at age 28 (Fig. 3), requiring implantation of a permanent pacemaker. He had a deletion of exon 17 in the dystrophin gene. His ECGs during the previous 13 years showed that, although the PR interval did not exceed the normal limit, the QRS duration increased drastically before the onset of a complete AV block (Fig. 4). Moreover, his 12-lead ECG recorded 2 months before the onset of the disorder showed a right bundle branch block pattern (Fig. 5). His echocardiography showed normal LV systolic function (LVDd 41 mm, LVEF 56%).

4. Discussion

In the current study, we found that both the PR interval and QRS duration tended to increase with age, and whereas the PR interval was not abnormally prolonged, the QRS duration was abnormally prolonged in some patients. There was no correlation between the QRS duration and LV systolic function in patients with DMD.

4.1. ECG changes with age

Most patients with DMD have abnormal electrocardiographic tracings such as tall R waves and increased R/S amplitude in lead V1, Q waves in the left precordial leads, right axis deviation, or complete right bundle branch block.[2] Sinus tachycardia, shortened PR intervals, prolonged QTc intervals, and premature atrial and ventricular contractions were also reported.[3,4] These patients with LVEF<35% have a significant higher burden of ventricular tachycardia.[5] However, the clinical significance of conduction disturbances in patients with DMD remains unclear. In the current study, we found that the PR interval was not prolonged in all cases. A short PR interval has been considered a specific finding associated with DMD, and according to Perloff, this likely reflects atriofascicular bypass tracts or accelerated

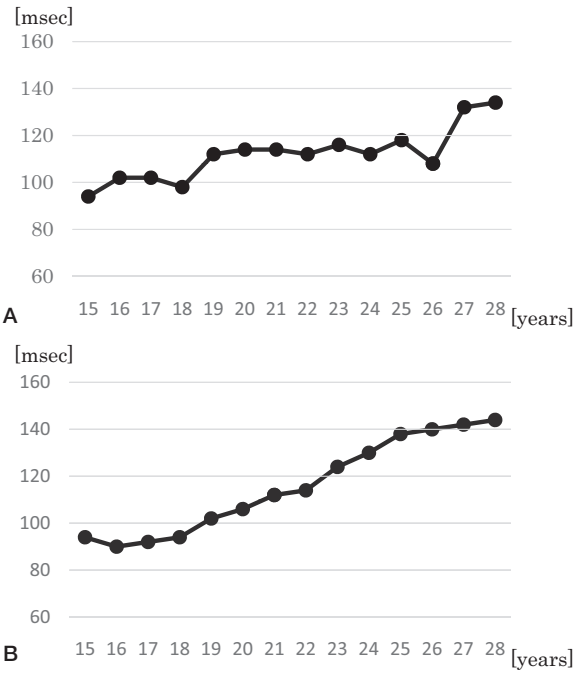

Figure 4. Changes in the PR interval (A) and QRS duration (B) with age in the patient who developed a complete AV block.

conduction within the AV node.[6] Given that atrial tachyarrhythmia is not common in patients with DMD, a short PR interval does not appear to be of clinical significance. On the other hand, the QRS duration tended to increase progressively with age. Nomura et al[7] examined histologically the cardiac conduction system in patients with DMD, and reported that only Purkinje fibers showed significant degeneration. Bies et al[8] suggested that dystrophin was localized to the membrane surface of normal human Purkinje fibers, and that defective dystrophin expression might contribute to cardiac conduction disturbances in patients with DMD.

4.2. Relationship between QRS duration and LV systolic function

ECG abnormalities have been reported to have no correlation with the presence or absence of cardiomyopathy.[9,10] We also found that the QRS duration and LV systolic function were not correlated with each other, suggesting that predicting cardiac function based on ECG findings is difficult, and vice versa.

4.3. Risk for complete AV block

One of the 47 patients developed complete AV block. Three cases of complete AV block have previously been reported in patients with DMD diagnosed by gene analysis,[11–13] with the ages at

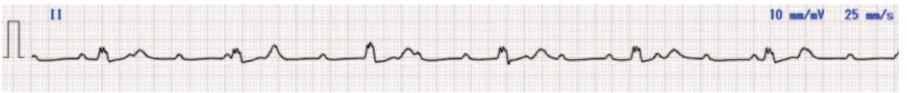

Figure 3. ECG of the 28-year-old patient who developed a complete AV block with a ventricular escape rhythm of 39 beats/min.

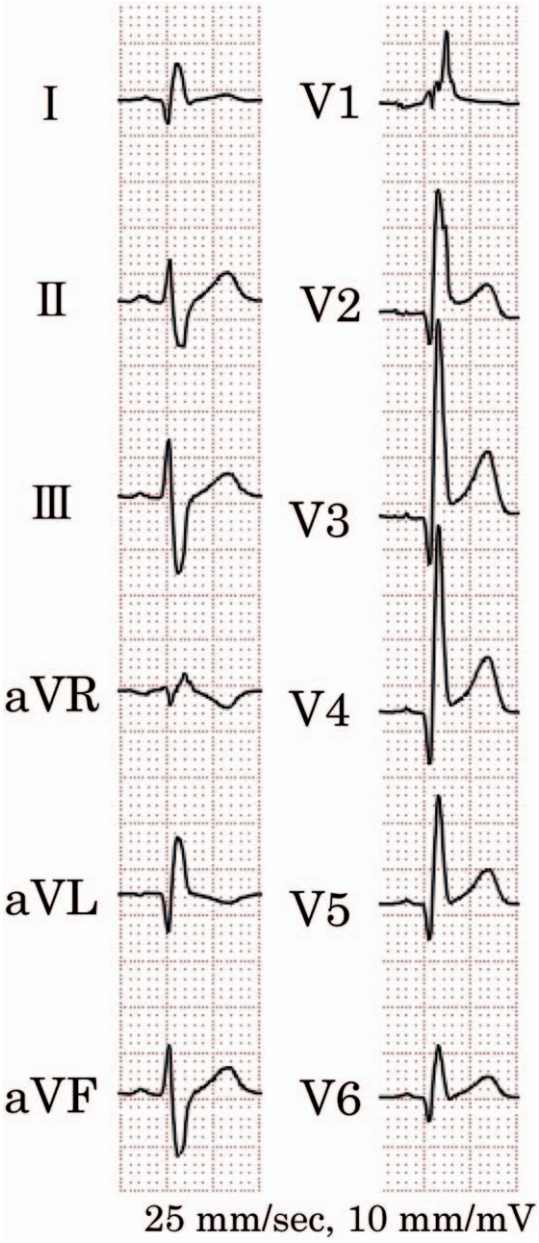

Figure 5. 12-lead ECG recorded 2 months before the onset of a complete AV block.

onset being 30, 33, and 40 years. Two reports described that the ECGs before the onset of the disorder showed complete right branch block.[11,13] Complete AV blocks are rarely associated with DMD, but given that the age of onset is relatively high, improved survival among patients with DMD might be attributable to the development of complete AV block in older patients. Further studies are necessary with regard to the indication for prophylactic pacemaker implantation.

The current study has some limitations. This study did not include a control group for statistical analysis of the ECG parameters. In our study population, progression to complete AV block was observed only in one case. Further studies with a larger patient population, including a control group, will be needed.

In conclusion, the QRS duration tended to increase progressively with age, irrespective of LV systolic function in patients with DMD. Attention should be paid to the QRS duration as it may serve as an indicator of risk for complete AV block in older patients.

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