Notched T Wave as Evidence of Autonomic Nervous Lability in Duchenne Progressive Muscular Dystrophy

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SUMMARY

We investigated the significance of notched T waves on the ECG in 30 patients with Duchenne progressive muscular dystrophy (DMD) and 50 age-matched controls using noninvasive cardiovascular examinations and measurement of urinary catecholamines. Notched T waves were more frequently observed in patients with DMD than in control subjects (46.7% vs. 20.0%, $p < 0.05$). Moreover, their frequency was age-independent in DMD, whereas they decreased with age in controls. Patients with notched T waves showed significantly increased heart rate, prolonged QTc and augmented excretion of urinary adrenaline compared with patients without them. There were no significant differences in casual BP or incidences of characteristic UCG abnormalities, such as mitral valve prolapse, and ECG abnormalities, such as tall R waves in the right precordial leads, between DMD patients with and without notched T waves. These findings suggest that notched T waves are associated with accelerated sympathetic nervous activity rather than progressive cardiac involvement in DMD. (*Jpn Heart J* 36: 741–750, 1995)

Key words: Progressive muscular dystrophy Notched T wave Sympathetic nervous activity

DUCHENNE progressive muscular dystrophy (DMD) is a severe, sex-linked hereditary disease that commonly involves the myocardium. Its cardiac involvement is manifested as congestive heart failure (CHF) and various types of arrhythmias.^{1–3} In addition to life-threatening arrhythmias, patients with DMD frequently exhibit an unexplained and persistent sinus tachycardia preceeding CHF.^{4–6} Unlike other manifestations of cardiac involvement, which are observed in the late stage of DMD, this type of sinus tachycardia is observed before the

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This study was supported in part by a grant-in-aid of Research of Clinical, Etiological and Pathological Aspects of Muscular Dystrophies from the Ministry of Welfare in Japan (S.M.).

Received for publication May 9, 1995.

Accepted August 28, 1995.

appearance of obvious skeletal muscle involvement.⁶⁾ This implies that respiratory failure has no causal relation to this type of sinus tachycardia. Autonomic nervous lability or dysfunction reported to be associated with DMD^{7,8)} seems to underlie this type of sinus tachycardia. Unexplained notched T waves are sometimes observed in healthy young men who are reported to exhibit augmented sympathetic nervous activity in spite of a benign clinical outcome.⁹⁾ Therefore, the present study was designed to assess the autonomic nervous system and the effect of T wave changes on ECG using noninvasive cardiovascular investigations.

SUBJECTS AND METHODS

Patient group: Oral informed consent was obtained from all the patients with DMD. We studied 30 Japanese boys with DMD, aged 9 to 21 years (mean age; 13.7 ± 5.4 years) who were hospitalized at Chikugo National Hospital. DMD was diagnosed by experienced neurologists based on physical and biochemical examinations. Patients exhibited varying degrees of limitations of daily activity, ranging from walking with a waddling gait without assistance to confinement to bed. All patients were normotensive and none had serious cardiovascular symptoms or evidence of CHF, pulmonary infection, electrolyte imbalance or dehydration. Digitalis, diuretics, sympathomimetic agents and antiarrhythmic drugs were not administered during this cross-sectional study.

Standard 12-lead ECGs were recorded at rest. The mean heart rate (HR) was calculated from the R – R interval of the ECG and HR-corrected QT/interval (QTc) was estimated according to Bazett's formula as follows; $QTc = QT / \sqrt{R - R}$. A notched T wave was defined as a definite incisure between the first and second peak in more than three consecutive positive T waves in more than one precordial lead. The incisure had to be located above the isoelectric line and the second peak of the notched T wave had to be easily distinguished from the U wave and the subsequent P wave. We counted the number of precordial leads showing notched T waves, but we did not measure the amplitude of the notching because the amplitude varied beat by beat.

A two-dimensional UCG was performed using a real-time electronic sector instrument (Toshiba SSH-17A, Tokyo) at 2.5 MHz in the standard parasternal long- and short-axes and apical four-chamber views. M-mode UCGs were recorded on a strip chart and two-dimensional B-mode UCGs were recorded on videotape (Toshiba, VHS, Tokyo). Casual blood pressure (BP) was measured 5 min before ECG and UCG recordings with patients in the supine position. The daily urine output was collected and stored in bottles containing 6 N-HCl (20 ml) to maintain the pH below 3.0 for measurement of catecholamine excretion.

Adrenaline and noradrenaline concentrations were assayed by high-performance liquid chromatography. The sensitivity of the catecholamine assays was 0.01 ng/ml, and both intra-assay and interassay coefficients of variation were below 7%.

Control group: We randomly selected 50 control subjects from among 81 age-matched schoolboys. Mean age of the selected subjects was 13.2 ± 6.3 years old. They underwent the same evaluations as the patients as part of their annual physical examinations in the elementary and high schools in Fukuoka City. Oral consent was obtained from the school director and the teachers. Organic heart disease was excluded by physical examination and by means of ECG, UCG and chest roentgenograms. We excluded 21 subjects because of the presence of heart murmurs, simple obesity, borderline cardiomegaly, borderline hypertension, or ECG abnormalities such as first to second degree of atrioventricular block ($n = 4$) and right bundle branch block ($n = 3$). Results were analyzed by three independent cardiologists who were unaware of the study protocol.

Data are expressed as the mean value $\pm$ S.D. Differences in the incidence (%) of notched T waves, mitral valve prolapse (MVP) and left ventricular (LV) wall asynergy were analyzed by the chi-square test. Other values were analyzed by the Student's t-test for unpaired samples using a one- or two-tailed comparison as appropriate. A p value below 0.05 was considered statistically significant.

RESULTS

ECG: The characteristic notched T waves were present in 14 (46.7%) of 30 patients with DMD compared with 10 (20%) of 50 control subjects ($p < 0.01$).

Figure 1. Standard ECG of a 9-year-old boy with DMD. Notched T waves were present in leads V_2 (arrows) and V_3 .

Figure 2. ECG of a 10-year-old boy with DMD. A notched T wave was observed in lead V₂ with beat-to-beat variation. Peak R and S points are shown because of the obscure QRS complex in V₁.

Figure 3. ECG of a 19-year-old adolescent with DMD. A notched T wave was present in lead V₁ and was associated with an increased R/S ratio (≈ 3.2).

The number of precordial leads showing notched T waves tended to be greater in DMD patients than in controls (1.8 ± 0.7 vs. 1.2 ± 0.6 , $p = 0.062$). The notched T waves were most commonly observed in the right precordial leads (V₁₋₃) on standard ECGs in both patients with DMD and control subjects. ECGs of representative patients showing typical notched T waves are shown in Figures 1 to 3. Prominent tall R waves in V₁^{10,11)} were observed especially in patients aged 15

years or older (Figure 3).

We analyzed the data for subgroups of < 15 years of age and ≥ 15 years of age. There was no significant difference in the frequency of notched T waves between patients and control subjects < 15 years (60.0% vs. 32.0%, $p = \text{N.S.}$), but the frequency of notched T waves was significantly higher in patients ≥ 15 years compared with control subjects ≥ 15 years (44.7% vs. 8.7%, $p < 0.01$). Therefore, there was an age-dependent decrease in the incidence of notched T waves in control subjects (32.0% vs. 8.7%, $p < 0.05$), while there was no age dependence in the incidence of this T wave change in DMD patients (60.0% vs. 44.7%, $p = \text{N.S.}$).

R/S ratio in V_1 was significantly ($p < 0.01$) lower in DMD patients < 15 years of age (0.4 ± 0.1) than in patients ≥ 15 years (2.4 ± 0.8). The ratio increased with age, suggesting that it was an index of progressive cardiac involvement.^{10,11} There was no significant difference in the R/S ratio between patients with and without notched T waves (2.6 ± 1.1 vs. 2.3 ± 0.6), suggesting that the increased R/S ratio in V_1 in DMD patients was not related to the appearance of notched T waves. Since QTc is reported to show dispersion among precordial leads, it was evaluated in V_1 consistently. This allowed us to analyze the relationship between the T wave notching and the alteration of QTc. The QTc tended to be prolonged in patients and control subjects with notched T waves compared with patients and controls without notched T waves (Table I).

UCG: There were no significant differences in left atrial and right ventricular (RV) dimensions, as measured by M-mode UCG, or in parameters of LV function, such as the diastolic descending rate of the anterior mitral leaflet and isovolumetric contraction and relaxation times between DMD patients with and without notched T waves (Table II). The LV ejection fraction was not estimated because local LV wall asynergy was observed in some patients. Wall and valvular motion abnormalities such as MVP and local LV asynergy in DMD patients^{12,13} detected by B-mode real-time UCG tended to be concentrated in the patients ≥ 15 years. There was no difference in the incidence of these motion abnormali-

Table I. HR and QTc in DMD Patients and Controls According to the Presence or Absence of Notched T Waves

Notched T wave	DMD patients (13.7 $\pm$ 5.4 y.o., n = 30)		Control subjects (13.2 $\pm$ 6.3 y.o., n = 50)	
	present (46.7%)	absent (53.3%)	present (20.0%)	absent (80.0%)
HR	93 $\pm$ 11	87 $\pm$ 10	81 $\pm$ 13*	74 $\pm$ 13**
QTc	422 $\pm$ 28	409 $\pm$ 23	412 $\pm$ 20	402 $\pm$ 22*

HR = heart rate; QTc = HR-corrected QT interval on ECG; * $p < 0.05$ and ** $p < 0.01$ vs. patients with DMD showing notched T waves.

Table II. UCG Parameters, BP and Urinary Catecholamine Levels in DMD Patients with and without Notched T Waves

	Notched T wave	
	Present (n = 16)	Absent (n = 14)
UCG		
LAD (cm)	1.88 ± 0.61	2.19 ± 0.54
RVD (cm)	1.13 ± 0.31	1.35 ± 0.18
DDR (mm/sec)	88.5 ± 19.9	97.2 ± 24.4
ICT (msec)	41.6 ± 10.4	35.1 ± 12.0
IRT (msec)	58.4 ± 12.1	49.3 ± 12.6
LVPW asynergy (%)	7 (43.8%)	6 (42.9%)
MVP (%)	6 (37.5%)	4 (28.9%)
BP		
SBP (mmHg)	99.1 ± 5.3	102.0 ± 8.3
DBP (mmHg)	62.0 ± 4.4	62.2 ± 7.4
Urinary CA		
Ad (μg/day)	12.10 ± 7.43	8.47 ± 3.01*
NAd (μg/day)	52.5 ± 31.4	48.8 ± 22.9

Ad = adrenaline; CA = catecholamine; DBP = diastolic blood pressure; DDR = diastolic descending rate; ICT = isovolumetric contraction time; IRT = isovolumetric relaxation time; LAD = left atrial dimension; LVPW = left ventricular posterior wall; MVP = mitral valve prolapse; NAd = noradrenaline, RVD = right ventricular dimension; SBP = systolic blood pressure; * $p < 0.05$ vs. patients with DMD showing notched T waves.

ties between patients with and without notched T waves (Table II).

HR, BP, urinary catecholamines: HR as estimated by the recorded ECG tended to be greater in patients with DMD with notched T waves than in patients with normal T waves ($p = 0.06$, one-tailed analysis). In the control group, HR was significantly higher in subjects with notched T waves than in subjects without notched T waves (Table I). There were no significant differences in systolic and diastolic BP between patients with and without notched T waves. The daily urinary excretion of adrenaline, but not noradrenaline, was significantly ($p = 0.032$, one-tailed analysis) higher in patients with notched T waves than in patients without notched T waves (Table II).

DISCUSSION

Cardiac involvement in DMD has been well documented but usually observed in the late stage of this slowly progressive disease.¹⁻³⁾ In the present study, notched T waves were more frequently observed in DMD patients than in control subjects. These T wave changes were not related to the casual BP, UCG abnormalities, or patient age. These T wave changes tended rather to be associated with increased HR, prolonged QTc and elevated urinary adrenaline excretion, suggesting an accelerated sympathetic nervous activity in the genesis of these T wave changes. This autonomic nervous aspect is consistent with previous reports.^{6,7)}

Notched T waves, which are also called bifid T waves, dome-and-dart T waves and late-phased dart T waves, are often observed in patients with congenital heart disease,¹⁴⁾ cerebrovascular accident,^{15,16)} alcoholism,^{17,18)} ischemic heart disease,¹⁹⁾ and even in healthy young individuals.^{9,19,20)} Therefore, this type of T wave change appears to involve heterogeneous mechanisms. Delayed repolarization somewhere in the ventricles is believed to be partly responsible for the appearance of notched T waves. Ishikawa and Ohnuma²⁰⁾ have suggested that physiological hypertrophy in the RV outflow tract causes a local repolarization delay in adolescents, leading to the appearance of notched T waves in right precordial leads. Awa et al¹⁴⁾ reported that the amplitude of the T wave notching was closely correlated with the shunt ratio in patients with atrial septal defect, which is a representative congenital heart disease associated with RV overload. Watanabe et al¹⁹⁾ suggested that right precordial notched T waves in children were related to delayed repolarization in the predominant RV and that left precordial notched T waves in the elderly were related to delayed repolarization in the hypertrophic or ischemic LV. On the other hand, Atterhög⁹⁾ reported that healthy young men with primary T wave aberrations (flattening or notching) showed signs of increased sympathetic tone, such as increases in HR and diastolic BP. Such T wave aberrations were found to be benign in a 5-year follow-up study when they were isolated ECG findings. It is possible that increased sympathetic tone contributes to the appearance of notched T waves in patients with cerebrovascular accidents^{15,16)} or alcoholism in the absence of organic heart disease.^{17,18)} Increased sympathetic tone *per se* causes various T wave aberrations^{9,21)} and influences the QT interval.^{22,23)} These findings suggest that the local delay in ventricular repolarization based on the local hypertrophy or increased sympathetic tone leads to this characteristic T wave change.

In the present study, notched T waves were seen in the same precordial leads (i.e., V₁₋₃) in DMD patients and control subjects. RV overload resulting from thoracic deformity and impaired respiratory function is frequently associated with DMD. The similarity between precordial leads showing notched T waves in DMD patients and control subjects implies that RV overload associated with DMD is responsible for the high incidence of right precordial notched T waves in DMD patients compared with RV-predominant normal adolescents. However, the R/S ratio in lead V₁ was not correlated with the incidence of notched T waves in patients with DMD. In UCG, there were no significant differences in the RV dimension and the incidences of wall and valvular motion abnormalities between patients with and without notched T waves. Moreover, the incidence of notched T waves decreased with age in controls, but showed no age-related change in patients with DMD. These findings suggest that the reported age-dependent progressive RV overload associated with DMD is not re-

sponsible for the high incidence of right precordial notched T waves in patients with DMD. The first reason why the patients with DMD in this study had no obvious signs of RV overload is the age distribution, which is somewhat skewed toward younger age (i.e., ranging from 9 to 21 years with a mean age of 13.7 ± 5.4 years). The second reason is the exclusion of serious cardiovascular and respiratory complications associated with DMD. In this light, this study included bias in the selection of patients.

Unexplained sinus tachycardia is reported to be frequent in patients with DMD.^{6,7)} In the present study, HR tended to be increased and QTc tended to be prolonged in both patients and controls with notched T waves. Sympathetic discharge tends to prolong the QTc, although depending in part on the laterality of the accelerated sympathetic influence.^{22,23)} Urinary excretion of adrenaline, but not noradrenaline, was greater in patients with than without notched T waves in the present study. These findings support the conclusion that an increase in sympathetic tone may have contributed to the high incidence of notched T waves in patients with DMD. There was no difference in systolic and diastolic BP between patients with and without notched T waves. Although this finding may have been influenced in part by the exclusion of hypertensive patients, it is more likely that this finding is a result of possible vasomotor dysregulation associated with DMD.⁸⁾

Previous ECG studies in patients with DMD did not examine the significance of notched T waves,^{5,6,10,11)} possibly because notched T waves are so labile that they are easily transformed into nonspecific T wave aberrations.⁹⁾ Frequency domain analysis of heart rate variability has been used in a number of clinical settings. In a preliminary study using power spectral analysis of heart rate variability, Yotsukura et al²⁴⁾ observed an increased LF/HF ratio in patients with DMD over a 9-year follow-up period, even in the absence of CHF. Other studies have also suggested that unexplained sinus tachycardia seen on the standard ECG of patients with DMD is related to autonomic, and not to cardiac, dysfunction.^{6,7)} The present results are consistent with the results of the above-cited studies and provide support for the hypothesis that the sympathetic neurovascular system is involved in the development or sustenance of DMD,⁸⁾ although long-term follow-up study is essential to verify this hypothesis.

Our conclusions are limited by the cross-sectional nature of the patient study in comparison with the retrospective nature of the control study. However, in association with several lines of reported supportive evidence,^{6-8,24)} the accelerated but labile sympathetic tones are highly likely in the fundamental pathophysiological feature of DMD, irrespective of age, disease progression, and accompanying complications.

ACKNOWLEDGEMENTS

We thank Drs. Masahiro Imoto, Masamichi Tamura and Takayoshi Yamane for evaluating the data in a blind manner. We also thank Ms. Reiko Masaki for her excellent technical assistance with the UCG recordings.

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