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Developmental Aspects of Long QT Syndrome Type 3 and Brugada Syndrome on the Basis of a Single *SCN5A* Mutation in Childhood

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OBJECTIVES The aim was to investigate at what age electrocardiographic characteristics of long QT syndrome type 3 (LQT3) and Brugada syndrome (BS), based on a single *SNC5A* mutation, appear.

BACKGROUND The QT interval (QT) in LQT3 is prolonged during bradycardia. It is not clear yet if this is obvious in young children with a relative fast heart rate (HR).

METHODS Thirty-six children with an *SNC5A* gene mutation (1795insD) and 46 non-carrier siblings were investigated. In different age groups, HR, QT, QT_c, and ST-segment elevation on a 12-lead electrocardiogram (ECG), and HR, QT, QT_c, and ΔQT after the longest pause in a Holter (recording) were evaluated.

RESULTS In all age groups, HR at rest tended to be lower in carriers than in non-carriers, and QT was longer in carriers than in non-carriers. The Brugada phenotype was found >5 years. Gender specific differences were not identified. The QT at lower HR and ΔQT were longer in carriers than in non-carriers. A QT_c of ≥0.44 s at the lowest HR (sensitivity 100%; specificity 88.4%) and ΔQT ≥60 ms (sensitivity 100%; specificity 82.6%) were good predictors for having LQT3.

CONCLUSIONS We conclude that electrocardiographic characteristics of LQT3 and BS show age-dependent penetrance. A QT prolongation and conduction disease were present from birth onwards, whereas ST-segment elevation only developed >5 years. Good tools for clinical diagnosis of LQT3 in this family are QT_c at the lowest HR and ΔQT after a pause in a Holter, even at very young age. (J Am Coll Cardiol 2005;46:331–7) © 2005 by the American College of Cardiology Foundation

The QT interval (QT) in congenital long QT syndrome type 3 (LQT3) is disproportionally prolonged during bradycardia (1). Mutations in the cardiac sodium channel gene *SCN5A* are responsible for LQT3 (2), Brugada syndrome (BS) (3), and isolated cardiac conduction disease (4–6). We recently described a large eight-generation family with >200 adults characterized by premature nocturnal sudden death, LQT3, and BS (7). The underlying genetic defect was a mutation in *SCN5A* (TGA insertion at position 5537 leading to the insertion of aspartic acid (1795insD) within the C-terminal domain) (6,7).

In LQT3, symptoms generally occur after puberty (8,9), and in BS, the electrophysiological phenotype is most prevalent in the third decade. In both syndromes, male subjects seem to be at increased risk (10,11). In our family, we followed children, some shortly after birth, to investigate several clinical parameters in relation to age, gender, and genotype. The aim of the study was to establish the age of onset of the electrocardiogram (ECG) patterns of LQT3 and BS.

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METHODS

Patients. We included all but four (refusal of genetic evaluation) children (age <16 years) from this family, who were genetically proven to be carrier or non-carrier of the 1795insD *SCN5A* mutation. All parents and children ≥12 years provided written informed consent for clinical and genetic evaluation. Data were collected between 1965 and 2002 and in different age groups (0 to 1, 1 to 3, 3 to 5, 5 to 8, 8 to 12, and 12 to 16 years). Since the genetic analysis (year 2000), the children could be divided into carriers and non-carriers.

Monitoring parameters. The children were evaluated by history, ECG (12-lead), Holter recording (Holter), ergometry, and signal-averaged electrocardiogram (SAECG).

In the ECG (supine position), heart rate (HR [beats/min]), PQ interval (PQ [ms]), QRS width (ms), occurrence of right bundle branch block (RBBB) (rSR′ ≥90 at <4 years; ≥100 at >4 years), J waves (rounded second wave of QRS interval), ST-segment elevation (≥1 mm in V_1, V_2, or V_E [under xiphoid bone]; measured 40 ms after the J-point), QT, and QT_c (ms; lead II; Bazett [12]) were evaluated.

In the Holter, mean, lowest, and highest HR, QT at different HR, QT_c at the lowest HR, ΔQT (QT after the longest pause minus the QT of the preceding QRS interval;

Abbreviations and Acronyms

AP = action potential
BS = Brugada syndrome
ECG = electrocardiogram
HR = heart rate
I_{to} = transient outward current
LQT3 = long QT syndrome type 3
SAECG = signal-averaged electrocardiogram

a pause was defined as an R-R that was >50% longer than the preceding R-R; Fig. 1), longest R-R, AV conduction, and rhythm disturbances were analyzed. All parameters in ECG and Holter before pacemaker implantation were evaluated at least every three years.

During ergometry (>8 years; bicycle test), HR at rest, exercise, and recovery, and QT at different HR were measured (13).

In SAECG (>5 years; 40 Hz), QRS interval width (ms), D40 (ms; time in which the voltage <40 μV at end of QRS interval), V40 (μV; root mean square voltage for terminal 40 ms of QRS interval), and late potentials (LP) were measured (14).

Statistical analysis. Data are expressed as mean ± SD. A two-tailed Student *t* test for unpaired samples (with equal or unequal variances, determined with F-ratio testing) or Fisher exact test was performed. A $p < 0.05$ was considered statistically significant. Sensitivity and specificity of QT_c and ΔQT were calculated with the 2 × 2 method for determining predictive values of a diagnostic test.

RESULTS

Patient characteristics/history. Mean age at first visit was 7.1 ± 5.0 for carriers (n = 36; 21 boys and 15 girls) and 5.9 ± 2.1 years for non-carriers (n = 46; 24 boys and 22 girls). None of the carriers had complaints; they only came to our attention because of identification of the disorder in one of the parents. Total follow-up period for carriers and non-carriers was 9.6 ± 9.3 years versus 10.8 ± 7.2 years. Follow-up period until pacemaker implantation (n = 30; 5 AAI, 14 VVI, 11 DDI) for carriers was 3.6 ± 5.9 years. During follow-up, no sudden death occurred.

ECG. In all age groups, HR at rest tended to be lower in carriers than in non-carriers, but was within the normal range for age (Table 1) (15). The PQ was not different between carriers and non-carriers (data not shown). The QRS width was mostly longer in carriers (Table 1). We found no signs of RBBB or J waves in either group. The QT was longer in carriers in every age group (Fig. 2A). Similar results were found for QT_c; QT_c in carriers increased with age (0.39 ± 0.02 s at 0 to 1 year vs. 0.49 ± 0.06 s at 12 to 16 years; $p < 0.001$). An ST-segment elevation ≥1 mm occurred more often in carriers >5 years (5 to 8 years: $p = 0.09$; 8 to 12 and 12 to 16 years: $p < 0.05$; Table 1; Figs. 2B and 3). The ST-segment elevation was ≥2 mm in 0%, 20%, 50%, and 80% of the children <5, 5 to 8, 8 to 12, and 12 to 16 years, respectively. There were no differences between male and female carriers in the aforementioned parameters, including QT_c (boys, 0.44 ± 0.06 s vs. girls 0.44 ± 0.04 s; other data not shown) and ST-segment elevation.

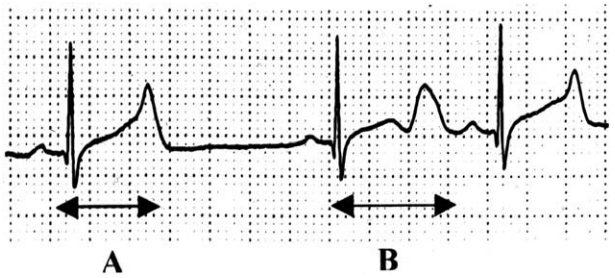

Figure 1. ΔQT = QT interval after the longest pause in a Holter recording minus QT of the preceding QRS interval (**B** − **A**).

Table 1. Electrocardiographic Parameters

	Carriers	Non-Carriers
HR (beats/min)		
Age (yrs)		
0–1	144 ± 23 (7)	172 ± 25 (6)*
1–3	117 ± 28 (4)	127 ± 23 (10)
3–5	88 ± 9 (5)	102 ± 20 (12)
5–8	82 ± 13 (6)	90 ± 13 (13)
8–12	74 ± 19 (5)	82 ± 15 (18)
12–16	69 ± 14 (9)	79 ± 12 (13)
QRS width (ms)		
Age (yrs)		
0–1	49 ± 11	45 ± 8
1–3	73 ± 16	57 ± 13*
3–5	76 ± 11	55 ± 13*
5–8	82 ± 20	64 ± 11*
8–12	72 ± 11	66 ± 11
12–16	89 ± 19	73 ± 13*
% w/ST-segment elevation		
Age (yrs)		
0–1	14	0
1–3	0	10
3–5	40	42
5–8	83	38
8–12	100	44*
12–16	88	31*

Mean ± SD (n). *$p < 0.05$.
Carriers = with *SNC5A* gene mutation (1795insD); HR = heart rate; Non-Carriers = without *SNC5A* (1795insD).

Holter. Above one year, mean and lowest HR in the Holter were mostly lower in carriers (Table 2). Highest HR did not differ between the two groups (data not shown). Similarly >1 year QT at HR <110 to 120 beats/min were longer in carriers (Fig. 4). The QT after the longest pause and ΔQT were longer in carriers (Table 2); QT_c at the lowest HR for the whole group was longer in carriers than in non-carriers (0.47 ± 0.09 s vs. 0.36 ± 0.03 s; $p = 0.0000$). The differences in QT increase with age. Mean, lowest, and highest values of QT_c at the lowest HR and of ΔQT in both groups are shown in Figure 5. A QT_c of ≥0.44 at the lowest HR (sensitivity 100%; specificity 88.4%) and a ΔQT ≥60 ms (sensitivity 100%; specificity 82.6%) were good predictors for having LQT3. All carriers