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Sex-specific clinical course of young patients with Brugada syndrome

Short Title: Sex-specific clinical course of young BrS patients

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1 **Introduction**

2 Brugada syndrome (BrS) is an inherited arrhythmia that causes sudden death due
3 to ventricular arrhythmias. Despite its autosomal-dominant inheritance, the prevalence of
4 Brugada-type ST elevation is male-dominant in adults,¹ suggesting specific modifiers
5 may promote the BrS phenotype in males or protect females. Paediatric BrS shows no
6 significant sex differences and a higher risk of lethal arrhythmic events (LAEs);²
7 however, age-dependent changes in clinical findings around puberty remain unclear.
8 Therefore, we aimed to clarify the sex differences in the number of diagnoses and LAEs
9 by age and in ECG findings before and after puberty and identify risk factors for LAEs in
10 young patients with BrS.

12 **Methods**

13 This cohort study included patients with inherited arrhythmias referred for
14 genetic testing to Kyoto University and Shiga University of Medical Science from
15 hospitals across Japan between 1996 and 2020. Among patients with clinically suspected
16 BrS, we analysed probands aged ≤ 20 years identified as having probable or definite BrS,
17 using a Shanghai scoring system score of ≥ 3.5 to minimise false positives (Figure 1A).³

18 The primary outcome was LAE, including sudden cardiac death (SCD), aborted
19 SCD, documented sustained ventricular tachycardia or ventricular fibrillation, or
20 appropriate implantable cardioverter-defibrillator shocks. We examined the impact of
21 puberty on LAE incidence or electrocardiogram (ECG) findings in patients with BrS,
22 stratified by sex.

23 Puberty was defined as beginning at 11 years of age, based on the mean age at
24 which Tanner stage 2 is attained among Japanese (10.8 and 10.0 years for males and

1 females, respectively).⁴ Pre- and post-puberty were defined as 0–10 years and 11–20
 2 years, respectively. ECG findings were considered abnormal if they were not within the
 3 previously reported 98th percentile.⁵

4 Genetic testing was performed as described previously.⁶ The complementary
 5 DNA sequences of *SCN5A* were based on the GenBank reference sequence
 6 NM_198056.3. A genetic variant was considered causal when it was categorised as
 7 pathogenic or likely pathogenic based on the American College of Medical Genetics and
 8 Genomics and Association for Molecular Pathology guidelines.

9 Fisher's exact test and Mann–Whitney U-test were used for categorical and
 10 continuous variables, respectively. Univariate logistic regression analysis was used to
 11 explore factors associated with LAEs. Statistical analysis was conducted only for
 12 probands, and calculations were performed using JMP Pro (version 16.1.0; SAS, Cary,
 13 NC, USA) and R (version 4.3.1; R Foundation for Statistical Computing, Vienna,
 14 Austria) software.

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16 **Results**

17 Of the 68 young patients with BrS, this study analysed 57 probands: 42 males and 15
 18 females. These patients underwent detailed examinations based on symptoms (44%),
 19 school heart screenings (33%), or regular visits for other diseases (23%). Baseline
 20 symptoms included 12, 11, and two cases of LAEs, syncope, and palpitations,
 21 respectively. The median age at diagnosis was 8.0 [4.5–14.0] years. Females were
 22 diagnosed at a younger age than males (6.0 [2.0–8.0] years vs. 11.0 [5.75–15.25] years, p
 23 < 0.01). Family histories of BrS and SCD were observed in four (7%) and 14 (25%)
 24 patients, respectively. Pathogenic or likely pathogenic *SCN5A* variants were detected in

1 46% of the patients. Spontaneous type 1 ECG patterns were observed in 93% of the
 2 patients. During the mean follow-up of 5.3 ± 5.9 years, 13 patients (23%) experienced 17
 3 LAEs, with an overall annual LAE rate of 5.6%/year. The sex-specific LAE rates were
 4 5.7%/year and 5.4%/year for males and females, respectively.

5 The proportion of females among newly diagnosed patients decreased from 42%
 6 in pre-puberty to 0% in post-puberty (Figure 1B). Notably, no female patient experienced
 7 LAEs after puberty (Figure 1C), and there was no significant difference in clinical
 8 characteristics between the pre- and post-puberty diagnosed age groups, except for the
 9 difference in sex distribution (Figure 1D).

10 Consecutive ECG findings were analysed in 13 patients with multiple ECGs
 11 taken before and after puberty. Notably, Brugada-type ST elevations attenuated after
 12 puberty in five of the nine female patients (56%) (Figure 1E); however, no male patient
 13 (0 of 4) showed any attenuation in their ECGs. Among the five female patients who
 14 exhibited ECG attenuation, two had LAEs before puberty; however, none developed
 15 LAEs after puberty. These two patients began quinidine therapy (17 and 32 mg/kg/day)
 16 after LAEs, but the medication did not affect their Brugada-type ST elevations.

17 Univariate analysis of the probands revealed that fragmented QRS complexes
 18 (odds ratio [OR]: 19.1, 95% confidence interval [CI]: 1.90–192) and previous LAEs (OR:
 19 14.7, 95% CI: 1.37–158) were significantly associated with LAEs (Figure 1F). In
 20 contrast, family histories and *SCN5A* variants were not significantly associated with
 21 LAEs. However, probands with pathogenic or likely pathogenic *SCN5A* variants had
 22 significantly more S-waves in lead I, J-waves in inferolateral leads, and prolongation of
 23 PR and QRS intervals (Figure 1G).

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1 Discussion

2 This study demonstrated that the number of new diagnoses and the incidence of LAEs
3 decreased in female patients with BrS after puberty, with approximately half of the
4 females showing attenuation of Brugada-type ST elevations. Testosterone has been
5 considered to contribute primarily to the male predominance in BrS;⁷ however, these
6 results suggest that increased levels of estradiol may have a protective effect against BrS,
7 consistent with previous studies.^{8–10}

8 Fragmented QRS complexes and previous LAEs have been reported as risk
9 factors in adult patients.¹ We confirmed that fragmented QRS complexes can also apply
10 to young patients. Fragmented QRS complexes indicate the heterogeneity of ventricular
11 tissues that contribute to arrhythmic substrates. We also demonstrated that *SCN5A*
12 variants were associated with conduction delay and repolarisation abnormalities, but not
13 with LAEs. However, whether *SCN5A* variants are a risk factor for LAEs in adult and
14 young patients with BrS remains controversial, and further studies are needed for risk
15 stratification in young patients. Consequently, these limitations should be considered
16 when interpreting our results: (i) referral bias, (ii) small sample size, and (iii) racial
17 differences. This study focuses on Japanese patients and therefore cannot be generalized
18 to other populations/ethnicities.

19 In conclusion, approximately half of the young female patients with BrS exhibited
20 attenuated Brugada-type ST elevation and showed no LAEs after puberty. Therefore, this
21 study provides critical insights for developing risk stratification specific to young patients
22 with BrS.

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4

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1 **Figure legends**

2 Figure 1

3 (A) Study flowchart. (B) The number of patients with BrS stratified by age at diagnosis:
 4 21 males (0–10y), 21 males (11–20y), 15 females (0–10y), 0 females (11–20y). (C)
 5 Incidence of all LAEs stratified by age: 6 males (0–10y), 6 males (11–20y), 5 females (0–
 6 10y), 0 females (11–20y). (D) Comparison of clinical characteristics of probands with
 7 BrS stratified by age at diagnosis between pre-puberty (0–10 years) and post-puberty
 8 (11–20 years). Family histories were considered positive if first- or second-degree
 9 relatives were diagnosed with definite BrS or if these relatives experienced SCD at an age
 10 < 45 years. (E) Attenuation of Brugada-type ST elevations after puberty. Vertical dotted
 11 lines indicate the transition between pre- and post-puberty periods. (F) Risk factors for
 12 LAEs in univariate logistic analysis. ECG findings were evaluated using the initial ECGs.
 13 Fragmented QRS complexes were defined as abnormal fragmentation within the QRS
 14 complex with ≥ 4 spikes in V1 or ≥ 8 spikes in leads V1–V3. An aVR sign was defined
 15 as $R \geq 0.3$ mV or $R/q \geq 0.75$ in the aVR lead. A large S-wave in lead I was defined as an
 16 amplitude ≥ 0.1 mV or a duration ≥ 40 ms. J-waves were defined as an elevation of the J-
 17 point by at least 0.1 mV in at least two inferior (II, III, and aVF) and/or lateral (I, aVL,
 18 and V4–V6) leads. Late potentials on the signal-averaged ECG were defined as positive
 19 when two of the following three criteria were met: filtered QRS duration > 114 ms, root
 20 mean square voltage of the terminal 40 ms in the filtered QRS < 20 μ V, and duration of
 21 low amplitude signals < 40 μ V in the terminal filtered QRS > 38 ms. Two independent
 22 cardiac electrophysiologists (T.I. and T.M.), who were blinded to the patients and clinical
 23 presentation, evaluated all ECGs. (G) Comparison of ECG findings based on the *SCN5A*
 24 variant status: 26 patients had pathogenic or likely pathogenic *SCN5A* variants

1 (*SCN5A*⁺), and 30 were *SCN5A*[−]. Sinus node dysfunction was defined as sinus
2 bradycardia without complete atrioventricular block below the 98th percentile for age.⁵
3 Prolongation of PR, QRS, and QT intervals (above the 98th percentiles for age) were
4 evaluated in lead II.⁵ QT intervals were corrected for heart rate using the Bazett's
5 formula. BrS, Brugada syndrome; CI, confidence interval; ECG, electrocardiogram; FH,
6 family history; HR, heart rate; LAE, lethal arrhythmic event; No, number; OR, odds ratio;
7 Pt, patient; SCD, sudden cardiac death; Spont, spontaneous.
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