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RESEARCH LETTER

In Children and Adolescents From Brugada Syndrome–Families, Only *SCN5A* Mutation Carriers Develop a Type-1 ECG Pattern Induced By Fever

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Brugada syndrome (BrS) is a rare inherited condition in which ventricular arrhythmias may cause syncope, aborted cardiac arrest, or sudden cardiac death. Although BrS is associated with mutations in the *SCN5A* gene, most adult patients are *SCN5A*-mutation negative.[1] Fever can unmask the diagnostic Brugada type-1 pattern on the ECG[2] and precede arrhythmic symptoms, especially in children.[3] All children considered at risk for BrS, based on a family history of BrS or a BrS genotype are currently advised to record an ECG during fever (≥38.5°C/101.3°Fahrenheit) for diagnosis and risk stratification. This is stressful and time consuming for both patients and parents. We hypothesized that a type-1 fever-ECG and symptoms only occur in children with a familial *SCN5A* mutation.

One hundred eleven pediatric patients aged <19 years were eligible because they had ≥1 fever-ECG recorded and were at-risk for BrS, by having a BrS genotype, a first-degree family member with BrS, or a first-degree family member with a BrS genotype. After exclusion of probands, carriers of overlap syndrome mutations or multiple *SCN5A* variants, and those with structural cardiac abnormalities, 97 children were included. Fever-ECGs and nonfever-ECGs recorded during outpatient visits closest to the date of the fever-ECGs were analyzed for a type-1 pattern by a blinded expert (A.A.M.W.) and patient characteristics were collected. Patients with ≥1 type-1 fever-ECG during follow-up were compared with those without. Categorical variables were compared using a χ^2 test or Fisher exact test, and Bonferroni correction for multiple comparisons was applied where appropriate. Continuous variables were compared using a Wilcoxon rank-sum test for not-normal distributions. The study was approved by the Institutional Review Board. Informed consent was waived because the study used retrospective data from regular care.

A total of 309 ECGs from 97 patients were analyzed (193 fever-ECGs and 116 nonfever-ECGs). A type-1 pattern was seen on 22 (11.4%) fever-ECGs from 14 different patients and on none of the nonfever-ECGs. The median age at first episode of a fever-induced type-1 was 7.1 (2.8–10.6) years. In 7 patients the type-1 pattern was not apparent on the first recorded fever-ECG, but on a subsequent fever-ECG recorded after a median of 0.7 (0.1–4.9) years. A positive family history for sudden cardiac death, sex, first-degree family member with phenotypic BrS, median age at first presentation, and follow-up duration were similar in the 2 groups (Table). All patients with ≥1 type-1 fever-ECG were carriers of a (likely) pathogenic *SCN5A* variant (13 [2.3%]) or had a 50% likelihood of being a carrier (1 [7.1%]). This genetic background differed significantly from the group without type-1 fever-ECG ($P<0.001$), where 31 patients (37.3%) were carriers of a (likely) pathogenic *SCN5A* variant and 38 (45.8%) were from a genotype-elusive family (Table). In the child with ≥1 type-1 fever-ECG and a 50% likelihood of being a carrier, no genetic diagnostic testing had been performed. His father was diagnosed with BrS after an

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Table. Baseline Characteristics

	F-type-1$_{pos}$ (n=14)	F-type-1$_{neg}$ (n=83)	Complete Cohort (n=97)	*P* Value
Sex, No. of males (%)	11 (78.6)	43 (51.8)	54 (55.7)	0.08
Median age at first presentation in years (IQR)	4.4 [1.3-6.3]	3.7 [0.8-6.9]	4.0 [0.9-6.8]	0.86
Median follow-up duration in months (IQR)	39 [12-95]	25 [4-41]	27 [4-43]	0.14
First-degree family member with BrS phenotype, n (%)	12 (85.7)	66 (79.5)	78 (80.4)	0.74
Family history of sudden cardiac death, n (%)	5 (35.7)	23 (27.7)	28 (28.9)	0.54
Genotype				
(Likely) pathogenic *SCN5A* variant, n (%)	13 (92.9)	31 (37.3)	44 (45.4)	<0.01
First-degree family member with (likely) pathogenic *SCN5A* variant, n (%)	1 (7.1)	6 (7.2)	7 (7.2)	
Unknown, n (%)	—	1 (1.2)	1 (1.0)	
First-degree family member variant of unknown significance, n (%)	—	7 (8.4)	7 (7.2)	
Genotype elusive, n (%)	—	38 (45.8)	38 (39.2)	

BrS indicates Brugada syndrome; F-type-1pos, ≥1 type-1 fever-ECG; F-type-1neg, without type-1 fever-ECG; and IQR, interquartile range.

aborted cardiac arrest at age 31 and was found to carry a *SCN5A* variant of unknown significance/likely pathogenic variant.

In this cohort only 1 child had an episode of ventricular arrhythmia, namely nonsustained ventricular tachycardia during fever. He had ≥1 type-1 fever-ECG and carried a *SCN5A* mutation. No patients in this cohort were symptomatic.

We show that, with the exception of 1 child who had not yet been tested for the familial variant, only pediatric patients from BrS-families with a *SCN5A* mutation developed a type-1 ECG during fever. The occurrence of symptoms in this population was low. The molecular and cellular mechanisms underlying the fever-dependent manifestations of BrS are complex. Fever may augment dysfunction of the mutated sodium cardiac channels, which could lead to an increased susceptibility to develop a type-1 ECG and arrhythmias.[4] The group without type-1 fever-ECG was genetically heterogeneous. According to our study results, a BrS-phenotype without a *SCN5A*-mutation seems to be absent or concealed during childhood and fever. This apparent difference in genetic background in children with BrS compared with adults is in agreement with recent large cohort studies, in which the proportion of *SCN5A* mutation carriers in young patients appears to be higher compared with adults (62% to 77% versus 23% to 27%).[3,5]

This study describes a relatively large cohort of pediatric patients from BrS families with numerous fever- and nonfever-ECGs. Limitations are the heterogeneous cohort and retrospective study design, which are inevitable in studying this disease. Sensitivity analyses including only those patients with a first-degree family member with a clear BrS phenotype did not change our results.

We conclude that, if future cohort studies support our findings, recording of fever-ECGs may not be mandatory in pediatric patients from BrS families without a *SCN5A*-mutation because their risk for a fever-induced Brugada type-1 ECG and arrhythmic events is low. A drug challenge, preferably after puberty, can finally make or reject a diagnosis of BrS in these children.

ARTICLE INFORMATION

The data will be made available to other researchers for the purpose of reproducing the results upon reasonable request.

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Disclosures

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