CLINICAL SIGNIFICANCE OF INFEROLATERAL EARLY REPOLARISATION AND LATE POTENTIALS IN CHILDREN WITH BRUGADA SYNDROME

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HIGHLIGHTS:

- Depolarization and repolarization abnormalities are recognized risk factors in adults with Brugada syndrome (BrS), but have not been previously evaluated in children

- Our study shows a high prevalence of late potentials on signal averaged ECG (particularly in those with a higher risk phenotype) and inferolateral early repolarization in children with BrS, but these were not significantly associated with increased arrhythmic risk

- The findings suggest that different risk factors may be important in paediatric BrS compared to adults

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ABSTRACT

Introduction. The clinical utility of inferolateral early repolarisation (ER) and late potentials (LP) in children with Brugada Syndrome (BrS) has not been previously evaluated. The aim of this study was to determine the prevalence of electrocardiographic (ECG) abnormalities in children with BrS, and to investigate their relationship with clinical outcomes.

Methods. 43 patients with BrS and 47 controls aged ≤18 undergoing systematic clinical and ECG evaluation, including signal-averaged ECG (SAECG) and pharmacological provocation testing, between 2003 and 2019 were included.

Results. Four patients with BrS (9%) presented with a spontaneous type 1 Brugada pattern; the remaining 39 (91%) were diagnosed following ajmaline provocation testing. Twelve BrS patients (28%) had late potentials (LP) on SAECG compared to 1 (2%) in controls (p=0.001). LP were more common in 5 patients with a high-risk phenotype (60% vs 24%) but this was not statistically significant. Twelve patients with BrS (28%) had inferolateral early repolarisation (ER) and 2 (5%) had fractionated QRS (f-QRS), but there were no statistically-significant differences with controls in these parameters. A significant arrhythmia (non-sustained ventricular tachycardia or atrial fibrillation) was seen in 4 patients (9%).

Conclusions. This study shows a high prevalence of SAECG abnormalities in children with BrS compared with controls, but this was not significantly associated with a high-risk phenotype.

Keywords: *Brugada syndrome, ajmaline testing, late potentials, inferolateral early repolarisation, fractioned QRS, arrhythmic risk, sudden cardiac death*

INTRODUCTION

Brugada Syndrome (BrS) is an inherited arrhythmia syndrome characterised by a typical electrocardiogram (ECG) pattern (coved ST-segment elevation ≥ 2 mm, followed by a negative T-wave, in the right precordial leads) and associated with an increased risk of sudden cardiac death (SCD) [1,2]. While a history of syncope and the presence of a spontaneous type I BrS ECG pattern have been associated with increased risk of arrhythmic events, risk stratification in children without a spontaneous type I ECG pattern remains problematic [3,4,5]. In particular, there are no data on whether the presence of inferolateral early repolarisation (ER) or fragmented QRS complexes (f-QRS) on the 12-lead ECG, and late potentials (LP) on signal-averaged electrocardiography (SAECG) are associated with an increased risk of ventricular arrhythmia [6,7,8,9] in the paediatric population. The aim of this study was to determine the prevalence of inferolateral ER, f-QRS and LP in children with BrS, and to investigate their clinical utility.

MATERIAL AND METHODS

Patients

Forty-three consecutive patients diagnosed with BrS aged ≤ 18 years and followed up in the Centre for Inherited Cardiovascular Diseases, Great Ormond Street Hospital for Children (GOSH), London, United Kingdom, between August 2003 and February 2019 were included in this study. The diagnosis of BrS was made in the presence of a spontaneous or drug-induced type I BrS ECG pattern [1,10,11]. A further 47 consecutive patients undergoing ajmaline provocation testing due to a family history of BrS (n=19) or SCD (n=33) in whom the test was negative served as a control group.

Clinical and electrocardiographic evaluation

All patients underwent detailed clinical evaluation, including family history, assessment of symptoms (including syncope, presyncope, palpitation and chest pain), echocardiography, resting 12-lead ECG and SAECG, and ambulatory Holter monitoring. Separate resting 12-lead ECGs were performed with the right ventricular leads (V1 and V2) in the standard and high parasternal positions - second intercostal space [high-lead ECG (HLECG)] [12,13]. The QT interval was corrected for heart rate using Bazett's formula [14]. Data on genetic testing and electrophysiological study (EPS) were also collected, where available.

The SAECG was considered to be positive for LP if ≥ 2 vectors were abnormal: filtered QRS duration ≥ 114 ms, duration of terminal QRS < 40 μV (low- amplitude signal duration) ≥ 38 ms and root-mean-square voltage of terminal 40 ms ≤ 20 μV [15]. Early repolarisation was defined as J-point elevation of at least 0.1 mV in the presence of QRS slurring or notching, in the inferior and/or lateral leads [16]. A f-QRS was defined as the presence of multiple spikes within the QRS (≥ 4 spikes in 1 or ≥ 8 spikes in all of the leads V1, V2 and V3) [17].

Pharmacological provocation testing

Pharmacological provocation testing was performed using ajmaline, with the exception of one patient who underwent flecainide provocation testing at the time of electrophysiological study (EPS) for investigation of palpitation. The test was considered positive in the presence of J-point elevation of ≥ 2 mm with coved ST elevation in one or more right precordial leads (high parasternal or standard V1-V2) [18,19].

Assessment of arrhythmia and risk stratification

Data on the presence of arrhythmia were obtained from ambulatory Holter monitoring and implantable loop recorder or ICD interrogation, where available. Atrial fibrillation (AF), other atrial arrhythmias (including atrial flutter and focal atrial tachycardia), non-sustained ventricular tachycardia (NSVT) and sustained ventricular tachycardia (VT) or fibrillation (VF) were considered significant arrhythmias [20,21]. EPS was considered positive if any sustained ventricular arrhythmia (VF, polymorphic VT or monomorphic VT lasting more than 30 seconds) was inducible [22,23].

Children with BrS were considered *a priori* to be in high-risk group for SCD if they presented with aborted cardiac arrest; spontaneous type 1 ECG Brugada pattern, with or without a history of syncope; or inducible VT/VF during EPS [24,25].

Patients were followed up to the end of the study period (February 2019) or transition to adult services at 18 years of age.

Statistical analysis

All statistical analyses were performed using Stata/IC 15.1. Values were expressed as mean and standard deviation (SD) or 95% confidence interval (95%CI) for normally-distributed data or median and interquartile range (IQR) for skewed data. The Chi-square test (with Fisher exact test or Mantel-Haenszel correction when indicated) was used for comparison of categorical variables and linear regression for continuous variables. Means were compared between two groups using Student´s t-test. Differences were considered statistically significant when the p-value was < 0.05.

RESULTS

Baseline and clinical characteristics

Table 1 shows baseline clinical features of the study cohort. Mean age at diagnosis or time of pharmacological provocation was 12.2±4.4 years in patients with BrS, compared to 15.7±2.4 years in controls (p<0.001). All patients had a structurally normal heart on echocardiography. Median follow-up time was 2.0 years (IQR 1.0-5.3).

Four patients (9%) had a spontaneous type 1 BrS pattern; the remainder were diagnosed on pharmacological provocation. Fifteen patients (35%) had undergone a cardiac intervention: primary prevention ICD implantation (n=3), implantable loop recorder (n=7) or EPS (n=7).

Analysis of ECG features and arrhythmic events

Twelve patients with BrS (28%) had LP on SAECG, compared to 1 (2%) in controls (p=0.001). Inferolateral ER was present in 12 (28%) patients and 13 controls (28%; p=0.979), and 2 (5%) were found to have a f-QRS complex, compared to 0 controls (p=0.225). Mean corrected QT interval (QTc) was 413 ms in patients with BrS and 406 ms in controls (p=0.100). Four patients (9%) had a significant arrhythmia [2 (5%) had NSVT and 2 (5%) had AF] compared to none in the control group (p=0.048).

In 2 patients (5%), HLECG unmasked a type 1 Brugada pattern; a further 2 (5%) developed a type 2 pattern or non-specific J-point elevation, and thirty-nine (90%) were normal. Seven patients (16%) underwent an EPS, of which 1 was positive. Eleven patients (26%) underwent genetic testing, with a likely pathogenic/pathogenic variant in SCN5A identified in 5 (45% of those tested).

Clinical significance of ECG abnormalities and risk stratification

Five patients (12%) were classified in the high-risk group. Their characteristics are described in **Table 2**. Three high-risk patients (60%) had LP on SAECG compared to 9 low-risk individuals (24%), p=0.061. One high-risk patient (20%) had ERP in contrast with 11 patients (29%) with lower risk, p=0.675. No high-risk patient had fQRS, whereas this was seen in 2 low-risk patients (5%), p=0.599. **Figure 1** shows illustrative examples of ECG patterns identified in children with BrS.

Four of the high-risk patients (80%) had a pathogenic SCN5A variant compared to 1 low risk patient (3%), p<0.001.

DISCUSSION

Inferolateral ER, LP and fQRS are recognised risk factors in adults with BrS but their clinical significance has not been investigated in children with BrS. This study reports a high prevalence of LP and inferolateral early repolarisation in children with BrS, but neither these nor fQRS appear to be associated with a high-risk phenotype in this population, although there was a non-significant trend towards higher risk in patients with LP.

Diagnosis of Brugada Syndrome in Children

The diagnosis of BrS is based on the presence of a type I Brugada ECG pattern with clinical symptoms or family history of BrS or SCD [26]. The genetic basis of BrS remains poorly understood, but variants in the cardiac sodium channel gene (*SCN5A*) account for approximately 20% of cases [27]. In children, *SCN5A* pathogenic/likely pathogenic variants are associated with a higher prevalence of sinus node dysfunction, cardiac conduction disease and a worse

prognosis [28]. The findings in the present study that *SCN5A* variants were more common in those patients identified *a priori* as being higher risk is in keeping with this, although these results should be interpreted with caution due to the small numbers.

Utility of resting and Signal-Averaged ECG and clinical implications

Pharmacological provocation with ajmaline can be used as a diagnostic tool to unmask latent BrS, but, in children, should be performed in an expert setting with an experienced team, due to the risk of life-threatening arrhythmic complications [29]. Importantly, a negative ajmaline test in young children may need to be repeated, due to the age-related penetrance of the response in up to 25% of cases [19,30]. The availability of additional, non-invasive, investigations would be very useful in the routine assessment of children at risk of BrS, particularly in those in whom an ajmaline test has not been performed. Our study suggests that the presence of LP and inferolateral ERP may be useful as additional diagnostic adjuncts in the routine assessment of children being screened for BrS, to identify those individuals who may benefit from lifestyle advice, including the need to avoid drugs that can precipitate ventricular arrhythmias in BrS and the management of fever.

Risk stratification in Paediatric Brugada Syndrome

Recent studies have shown that the combination of depolarization and repolarization abnormalities (f-QRS, inferolateral ERP and QT prolongation), along with a history of VF and syncopal episodes, are important predictors of VF and SCD in adults with BrS [31,32]. However, there have been no systematic studies assessing the utility of these ECG parameters in children with BrS. In the present study, we have shown that LP are more frequently observed in high-risk children with BrS, although this difference was not statistically significant. This is likely to be related to the small number of patients and low event rates, but it is also possible that different

risk factors are important in the paediatric population and further, larger studies to investigate potential risk factors in childhood BrS are required.

Limitations

The main limitation of the study is the small number of patients, although these are similar to previously published paediatric cohorts [30,33]. In addition, the study is limited by its retrospective methodology and the possibility that some of the control individuals may have had false negative ajmaline tests. Furthermore, patients in the control group were older than those in the BrS group, which may have affected the findings. Finally, the follow-up time was too short to allow us to investigate the relationship between LP and other ECG features and arrhythmic events, and future longer-term studies are required to assess this.

CONCLUSIONS

This study shows a high prevalence of SAECG abnormalities in children with BrS but this was not significantly associated with increased arrhythmic risk. Future and larger studies are required to investigate the role of non-invasive ECG parameters in risk stratification in childhood BrS.

FIGURE LEGEND

Figure 1: Illustrative examples of ECG abnormalities in children with BrS

A. **Inferolateral early repolarisation** in a 15-year-old girl with a family history of BrS in a first-degree relative and type I Brugada ECG pattern on ajmaline provocation testing, not considered *a priori* to be in a high-risk group – The red arrows show early repolarisation in the inferior and lateral leads.
B. **Late potentials on signal-averaged ECG** in a 14-year-old boy with a family history of sudden cardiac death in a first-degree relative and a type I Brugada ECG pattern on ajmaline provocation testing, not considered *a priori* to be in a high-risk group.
C. **Fractionated QRS complexes** in the same patient as panel B – shown in V1, V2, the inferior limb leads and aVL.

TABLES

***Table 1**. Comparison of cases and controls*

	Patients with BrS (n=43)	Controls without BrS (n=47)	P value
Age (yo) at diagnosis, mean (SD)	12.2 (4.4)	15.7 (2.4)	0.000
Males, No. (%)	15 (35%)	22 (47%)	0.288
Family history of Brugada Syndrome, No. (%)	29 (67%)	19 (40%)	0.012
Family history of SCD, No. (%)	23 (53%)	33 (70%)	0.129
Symptoms that could be attributed to arrhythmias, No. (%)	13 (30%)	7 (15%)	0.127
Presented arrhythmias on records, No. (%)	4 (9%)	0 (0%)	0.048
History of syncope episodes, No. (%)	3 (7%)	4 (9%)	0.786
LP on SAECG, No. (%)	12 (28%)	1 (2%)	0.001
Inferolateral ERP, No. (%)	12 (28%)	13 (28%)	0.979
Fragmented QRS complex, No. (%)	2 (5%)	0 (0%)	0.225
Corrected QT interval, ms (95%CI)	413 (407-419)	406 (400-412)	0.100

BrS = Brugada Syndrome. IQR = Interquartile Range. SCD: sudden cardiac death. LP: late potentials. SAECG: signal-averaged ECG. ERP: early repolarisation pattern.

***Table 2**. Description of high-risk patients*

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**
Sex	Female	Female	Male	Male	Male
Diagnosis	Spontaneous type 1 BrS ECG	Spontaneous type 1 BrS ECG	Positive Ajmaline challenge	Spontaneous type 1 BrS ECG	Type 1 BrS ECG + Positive Ajmaline challenge
Age at diagnosis (y)	1	1	14	1	8
Family history (BrS / SCD)	BrS	BrS	BrS	No	No
ICD	No	No	Yes	Yes	Yes
Other interventions	Loop recorder implantation	Loop recorder implantation	Loop recorder implantation. EPS (inducible VT)	No	EPS
Significant arrhythmias	No	Atrial fibrillation	NSVT	No	NSVT
Events	No	No	No	Syncope	No
ECG features	LP on SAECG	LP on SAECG	LP on SAECG	ERP	No
Genetics	SCN5A likely pathogenic variant	SCN5A likely pathogenic variant	SCN5A likely pathogenic variant	SCN5A likely pathogenic variant	No genetically tested

BrS = Brugada Syndrome. SCD: sudden cardiac death. ICD: Implantable cardioverter defibrillator. EPS: Electrophysiology study. NSVT: Nonsustained ventricular tachycardia. LP: late potentials. SAECG: signal-averaged ECG. ERP: early repolarisation pattern.

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