High prevalence of early repolarization in the pediatric relatives of Sudden Arrhythmic Death Syndrome (SADS) victims and in normal controls

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Running title: Pediatric early repolarization

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Word Count:

Abstract

Background & Aims: Elevation of the ECG J-point in the inferior and lateral leads (early repolarization) has been described in survivors of VF arrest and occurs in adult first degree relatives of sudden cardiac death (SCD) probands at a frequency significantly greater than in controls, raising the possibility that this could represent an independent risk factor in the aetiology of SCD. However, data on early repolarization in the pediatric population are lacking. This study aimed to assess the prevalence of early repolarization in pediatric first degree relatives of sudden arrhythmic death (SADS) victims.

Methods: Pediatric relatives (aged <18 years) of SADS probands referred to the Inherited Arrhythmia Clinic at Great Ormond Street Hospital had their initial screening ECG reviewed for evidence of J-point elevation. J-point elevation was defined as QRS-ST slurring or a discrete notch in two or more inferior (II, III, aVF) or lateral (I, aVL, V4, V5, V6) leads with the change beginning >1mV from baseline.

Results: The ECGs of 77 consecutive pediatric first degree relatives of SADS victims from 46 families were reviewed by two assessors. J-point elevation was present in 24 patients (31%) of this patient group compared to the reported prevalence of 5-13% in the published general pediatric population (p=0.02) and in the internal control group 19% (p=0.07). Subgroup analysis according to J-point elevation and ST segment morphologies showed a significantly higher prevalence of intermediate risk type early repolarization in the study group compared to controls (75% vs. 38%; p=0.02).

Conclusions: Infero-lateral J-point elevation occurs in a substantial proportion of pediatric first degree relatives of SADS probands with a similar prevalence to that described in adults. This suggests that early repolarization could be an important inherited trait when evaluating relatives of SADS victims. However, prospective follow up of this group of children is important to establish the

implication of this finding in future risk stratification, given the apparently high prevalence in normal individuals.

Background

Sudden arrhythmic death syndrome (SADS) is the sudden and unexpected death of an individual where no cause can be identified on post-mortem examination. SADS accounts for around 500 deaths per year in the UK and represents 10-20% of sudden deaths in the pediatric population(1) . Previous studies have identified evidence of inherited cardiac conditions, primarily long QT syndrome (LQTS) and Brugada syndrome (BrS), in up to 50% of adult relatives of SADS cases on clinical cardiological assessment(2). More recently, we have shown that comprehensive clinical evaluation of pediatric first-degree relatives of SADS probands results in a diagnostic yield of 14%(3). Furthermore, clinical and genetic screening of children as part of a broader family screening programme identifies evidence of familial cardiac disease in 19-30% of families(3). These results highlight the age related penetrance to many of the conditions identified and the importance of comprehensive screening of pediatric family members in SADS cases, but also raise the possibility of additional, potentially heritable, causes of sudden cardiac death (SCD).

The 'J-point' on an ECG is defined as the junction between QRS complex and the ST-segment(4). Elevation of the J-point on an ECG occurs in 1-5% of the general adult population with a predisposition for males, athletes and people of African descent(5). The prevalence of the early repolarization ECG pattern in children is not well defined, although historically it has been felt to be a common, benign finding (6, 7). The association between J-point abnormalities and SCD was first reported in the context of BrS, with J-point elevation present in the right precordial leads(8). More recently, early repolarization changes in the infero-lateral leads have been shown to exist with greater frequency in adult survivors of idiopathic VF arrests(9, 10). Analysis of adult populations screened in the context of SADS shows an increased prevalence of infero-lateral early repolarization(11), suggesting this may represent an inherited proarrhythmic trait. However, there are no data on the prevalence of early repolarization in the pediatric relatives of SADS victims. The

aim of this study, therefore, was to determine whether the increased frequency of infero-lateral J-point elevation seen in adult SADS relatives is also present in the pediatric population.

Methods

Patients and controls

One hundred and six consecutive pediatric (aged <18 years) first degree relatives of SADS victims were referred for screening in the Inherited Arrhythmia Clinic at Great Ormond Street Hospital between August 2003 and July 2013. Inclusion criteria for the proband were as previously described: sudden unexpected death aged 1-50 years, no known family history of ICC and no evident cardiac pathology at post-mortem examination; probands with non-pathognomonic histopathological findings such as ventricular hypertrophy and myocardial fibrosis were also included(3). Families in whom the index event in the proband was aborted or resuscitated cardiac arrest were excluded; therefore, none of the probands had pre-mortem cardiac investigations. Only first-degree paediatric relatives were included in the analysis, and children who were diagnosed following screening with any inherited cardiac condition (ICC) were excluded. In addition, if investigation (either clinical or genetic) into the proband or other adult first degree family members revealed a known ICC, these children were also excluded from the study group(3). The resulting study group following exclusions consisted of 77 pediatric patients and is depicted in Figure 1.

The 12-lead ECGs of 84 unrelated individuals who underwent ECG screening for a range of non-cardiac indications including: gastro-oesophageal reflux, prior to the introduction of pharmaceutical agents; migraines; pre-operative hemangiomas; joint swelling and rashes were used to develop an internal control group. These individuals had normal cardiovascular examinations and structurally normal hearts on echocardiography (where undertaken). Individuals with conditions that could

potentially be associated with cardiac malformations such as muscular dystrophies, metabolic storage disorders or genetically proven syndromes were excluded from the control group. In addition, data from a previously published study including 55 normal children were used as an external control group(7).

Clinical Evaluation

Systematic evaluation of the study participants was performed as previously described(3). Briefly, all patients underwent: detailed medical and family history; physical examination; 12-lead ambulatory ECG; signal-averaged ECG and echocardiography. 12-lead ECGs were performed at rest in the supine position. Exercise testing was undertaken in children greater than 120cm who are also able to follow simple instructions (usually older than 7 years, n=35, [45%]). Ajmaline provocation testing was not undertaken routinely but was performed in 15 patients (19%) older than 12 years. Genetic testing was not routinely performed.

Patients underwent clinical follow up on a regular basis until they were transitioned to adult services (usually by the age of 18 years), or to the end of the study period.

ECG Analysis

J-point elevation in the study population was assessed using the initial screening ECG. Previously published criteria for J-point elevation were used (9, 11, 12). Briefly, the presence of slurring or notching of the terminal portion of the QRS complex in at least two inferior (II, III, aVF) or lateral (I, aVL, V4, V5, V6) leads was sufficient to diagnose J-point elevation. ECGs were reviewed by two investigators (AM and JPK) blinded to the patient details, family history and any previously stated

opinions from other professionals in a random order unique to each assessor. Control ECGs were analysed for J-point elevation using identical criteria.

ECGs were considered positive when both assessors agreed criteria for J-point elevation were met. The ECGs in which assessor opinion varied were re-reviewed by the senior author (JPK) for a final decision. The ECGs that met criteria for early repolarization were further categorised into subgroups according to the patterns of J-point elevation and ST segment morphology. Early repolarization patterns were defined as follows: primary electrical disorder; inferior early repolarization >0.2mV; inferior early repolarization 0.1-0.2mV; lateral early repolarization >0.1mV and inferolateral early repolarization(12). These have been previously suggested to reflect a risk continuum, with the lowest risk pattern also being the most prevalent in the general population(12). The ST segment patterns were either ascending/upsloping (>0.1mV elevation 100ms after the J point or >0.1mV elevation throughout the ST segment) or horizontal/descending (<0.1mV elevation at 100ms after the J point), as described previously(13).

Statistics

SPSS for Mac v22 was used for all statistical analyses. Data are presented as n (%) where categorical, mean values (± standard deviation) where normally distributed and median (±interquartile range [IQR]) for non-normally distributed data. Inter-observer reliability was calculated on the study ECGs including a Cohen's kappa co-efficient to analyse consistency of reporting. Following ECG analysis, comparisons were made using the chi-squared or Fisher's exact test for categorical measurements and a Student *t* test for continuous variables. Analysis was repeated with single family members selected at random from the study group to estimate the prevalence of J-point elevation with any familial clustering effect excluded. The internal control group contained no family groups. A statistical significance of 5% (p value <0.05) was considered persuasive evidence for all analyses.

Results

Demographics

The study population consisted of 77 subjects from 46 families; the control population contained 84 patients not from clustered family groups. The baseline characteristics of both study groups are shown in Table 1. Both populations were well matched for age and gender. The study population were predominantly of white Caucasian ethnicity, other ethnicity subgroups did not make up a large enough number to consider this as a variable for further analysis. The study group consisted of first-degree relatives of SADS victims, as previously described. The index cases (SADS victims) were aged between one and 46 years at the time of death (median 25 ± [12.5-32.5]). The circumstances surrounding the death of the index case were known in 26 of 46 families (57%) and are shown in Figure 2; the group labelled unknown represent individuals where the event was not witnessed or the exact circumstances were unclear.

Prevalence of J-point elevation

There was good inter- and intra-observer reliability for the reporting of early repolarization, with 93% total agreement (p=<0.0001). The inter-observer kappa value was 0.82, trending towards complete agreement between both assessors. Within six sets of data there was observer disagreement, the opinion of the senior author was considered the final decision on all ECGs. J-point elevation criteria were met in either inferior, lateral or both set of leads in 24 patients (31%; Table 1). Using a single relative randomly sampled from each family, J-point elevation was present in 13 patients from 46 families (28%).

There was a trend towards a higher prevalence of infero-lateral J-point elevation in the study group (n=24, [31%]) compared with internal controls (n= 16, [19%]) although this did not reach the predefined significance level (p=0.07). However, the prevalence of early repolarization was significantly higher than in the published pediatric controls where early repolarization is reported in 13% (7) (p=0.02). J-point elevation occurred more frequently in the inferior leads than lateral or infero-lateral in both study and control groups (Table 1).

Table 2 shows the clinical and electrocardiographic features of pediatric SADS relatives with, and without, J-point elevation. There was a trend towards a higher prevalence of J-point elevation in the infero-lateral leads in females and also towards a shorter QRS duration, but neither were interpreted as significant (p=0.1 and p=0.09, respectively).

Morphology of early repolarization

There were no ECGs from either the study or internal control groups meeting early repolarization criteria for a primary electrical disorder. In both study and control groups, inferior early repolarization 0.1-0.2mV was the most common pattern although this was more prevalent in the study cohort (n=18 [75%] vs n=6 [38%]; p=0.02). There was a difference in the overall distribution of early repolarization pattern subtypes (p=0.04), with the control group showing a more even spread across lower risk types (Table 3). Figure 3 shows examples of lateral (Figure 3A) and inferior (Figure 3B) early repolarization patterns identified in pediatric first-degree relatives of SADS victims.

Table 4 shows the ST segment pattern in all patients found to have early repolarization. The prevalence of horizontal/descending ST segment morphology in the study population was significantly greater than in the internal controls where the two subtypes of ST change were more evenly distributed (p=0.04).

Clinical outcomes

Median follow-up time was 5.02 years (IQR 3.17-6.54 years). There were no deaths or sustained ventricular arrhythmias during follow up. One patient with horizontal/descending early repolarization had an episode of non-sustained ventricular tachycardia associated with palpitation.

Discussion

This study, the first to report infero-lateral early repolarization changes in an exclusively pediatric population, shows a high prevalence of J-point elevation amongst first degree pediatric relatives of SADS victims, in keeping with recent adult studies (11). Furthermore, subgroup analysis of early repolarization morphology revealed a significantly higher prevalence of intermediate and high risk subtypes compared to controls. The results suggest that J-point elevation may be an inherited pro-arrhythmic trait, although infero-lateral early repolarization was also present at a high frequency in controls, highlighting the problem of age-related changes in the resting ECG.

Cellular mechanism of J-point elevation

J-point elevation occurs due to a difference in the action potential current between the ventricular epicardial and endocardial layers. Initial rapid repolarization is dependent on deactivation of sodium channels and activation of voltage-gated potassium channels (I_{to}). Where there is prominence of I_{to} channels in the epicardial layers compared to the endocardial layers a net voltage gradient is created which manifests on the surface ECG as J-point elevation (14). Adult case control studies suggest an overall increase in cardiac mortality, with a particularly increased risk associated with inferior changes (15). Recent retrospective studies have reported an association between early

repolarization and VF (9, 12, 15), challenging the traditional thought that J-point elevation is a benign finding. Prospective studies have also demonstrated an increased risk of arrhythmia related death in adults with early repolarization (16). To date, however, there have been no studies evaluating the importance of early repolarization in children.

Early repolarization pattern in the pediatric population

The high frequency of infero-lateral J-point elevation in both the internal and external control groups is in keeping with previous reports of a higher prevalence of early repolarization in pediatric populations compared with adults(15). This suggests that there is a change in the terminal portion of the QRS complex which occurs during the transition from child- to adult-hood. It has been shown that high testorsterone levels and low visceral fat appear to be associated with expression of the Brugada phenotype, and may account for the clinically observed male predominance in BrS(17). The mean age in the present study was 7.3 ±4.2 years, and most patients were seen prior to the onset of puberty. It is possible, therefore, that similar hormonal influences may explain the apparent age-related changes in the ECG phenotype in this study. Furthermore, whilst in adult cohorts the prevalence of early repolarization is greatest in males, the opposite was observed in this study, and one could speculate that hormonal influences may play a role in this. Prospective studies are required to address the question of whether pubertal changes in females are also associated with a reduction in the presence of early repolarization in the normal population.

Early repolarization as a marker of sudden cardiac death

The frequency of J-point elevation in SADS relatives is similar between pediatric and adult populations, raising the possibility that early repolarization represents an underlying inherited arrhythmic disorder. Comprehensive, systematic and ongoing evaluation throughout childhood is

important in the context of SADS to help uncover familial diagnoses(3). In BrS, a spontaneous type 1 ECG pattern has been associated with a substantially higher risk of malignant ventricular arrhythmias (18), and patients with BrS and infero-lateral J-point elevation appear to have a worse overall outcome (19). Early repolarization has also been associated with malignant arrhythmias and subsequently been shown as an inheritable trait in adults (20). The results of the present study show that early repolarization is seen more frequently in children overall and specifically more frequently in pediatric relatives of SADS victims. Early repolarization is an additional finding to be identified in the process of screening for ICC, however, prospective studies are needed to clarify whether early repolarization in children from SADS families confers a long term risk of malignant arrhythmias. Age, activity and ethnicity have been shown to affect the prevalence of early repolarization changes (21), and further work is needed to decipher pathological from benign early repolarization and establish whether these rules can be applied to a pediatric population, where a proportion of patients appear to "outgrow" their ECG abnormalities.

The most commonly observed pattern of early repolarization in pediatric relatives of SADS victims in this study was 0.1-0.2mV J-point elevation inferiorly only, which, although not thought to represent the most highly malignant subtype of early repolarization, has been reported as an intermediate risk group (12), and is significantly different from the control population. Further prospective and larger multicentre studies are required to investigate the clinical significance of this finding. There are currently no specific recommendations on the management of asymptomatic children with early repolarization. The findings of the present study suggest that discussions with families need to focus on the importance regular follow up to monitor ECG development throughout childhood, but the prognostic value of early repolarization in this context remain unknown.

Limitations

The prevalence of J-point elevation within the internal control group described is greater than that seen in other pediatric data (6, 7). This may be explained by the fact that our internal controls were patients under review for (non-cardiac) medical conditions, and this may therefore result in an overestimation of the prevalence of early repolarization in the control group. In addition, pre-mortem ECGs were not available for the index cases and, due to the retrospective nature of the study and the fact that adult relatives are not followed up in our pediatric institution, it was not possible to compare the ECG findings from the study group to the SADS index case or other relatives. Long term prospective follow up data are still needed to assess the persistence of ECG changes in children, assess how these changes correlate between family members and draw further conclusions on the risk profile of early repolarization in children.

Conclusions

This study shows a high prevalence of J-point elevation in the pediatric relatives of SADS probands, in keeping with recent adult studies. This suggests that J-point elevation may represent a familial inherited trait, even in children and adolescents. There is a greater prevalence of early repolarization and ST segment subtypes in higher risk categories in children, however, caution must be executed to avoid overestimating the risk in the normal pediatric population, where these changes are frequent and change during later childhood and puberty can be expected.

Acknowledgments

With thanks to C.C McCorquodale for her advice and expertise in statistical analysis.

Disclosures

None

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Tables

Table 1. Demographics of SADS relatives compared with controls screened for J-point elevation

	Controls n=84 (%)	*Study cohort n=77 (%)*	*Significance*
Sex			p=0.9
Male	40 (48)	36 (47)	
Female	44 (52)	41 (53)	
Age (years)	7.2 ± 5.1	7.3 ± 4.2	p=0.9
Ethnicity			N/C
Caucasian	28 (33)	48 (62)	
Asian	13 (16)	9 (12)	
Black African/Caribbean	7 (8)	1 (1)	
Other/Not Known	36 (43)	19 (25)	
Presence of J-point elevation			
Any leads	16 (19)	24 (31)	p=0.07
Inferior II, III aVF	11 (13)	16 (21)	
Lateral I, aVL, V4-6	5 (6)	5 (6)	
Infero-lateral	2 (2)	3 (4)	

Table 2. Clinical and ECG features of SADS relatives

	Whole cohort n=77	*Positive J-point elevation n=24 (%)*	*Negative J-point elevation n=53 (%)*	*Significance*
Sex				p=0.1
Male	36 (47)	8 (33)	28 (53)	
Female	41 (53)	16 (67)	25 (47)	
Age (years)	7.3 ± 4.2	7.1 ± 3.6	7.3 ± 4.5	p=0.8
ECG (ms)				
PR interval	141 ± 23	146 ± 21	139 ± 23	p=0.2
QRS duration	55 ± 14	51 ± 13	57 ± 14	p=0.09
QTc interval	392 ± 27	395 ± 28	391 ± 26	p=0.6

Table 3. Pattern of early repolarization identified

	Positive study group n=24	*Positive internal control group n=16*	*Significance*
Pattern of early repolarization			p=0.04
Primary electrical disorder	0	0	-
Inferior >0.2mV	0	2	p=0.15
Inferior 0.1-0.2mV	18	6	p=0.02
Lateral 0.1mV	4	3	p=1
Inferolateral	2	5	p=0.09

Table 4. ST segment pattern in early repolarisation

	Positive study group n=24 (%)	*Positive internal control group n=16 (%)*	*Significance*
Horizontal/Descending	18 (75)	7 (44)	p=0.04
Ascending/Upsloping	6 (25)	9 (56)	

Figure legends:

Figure 1: Study sample exclusion flow chart

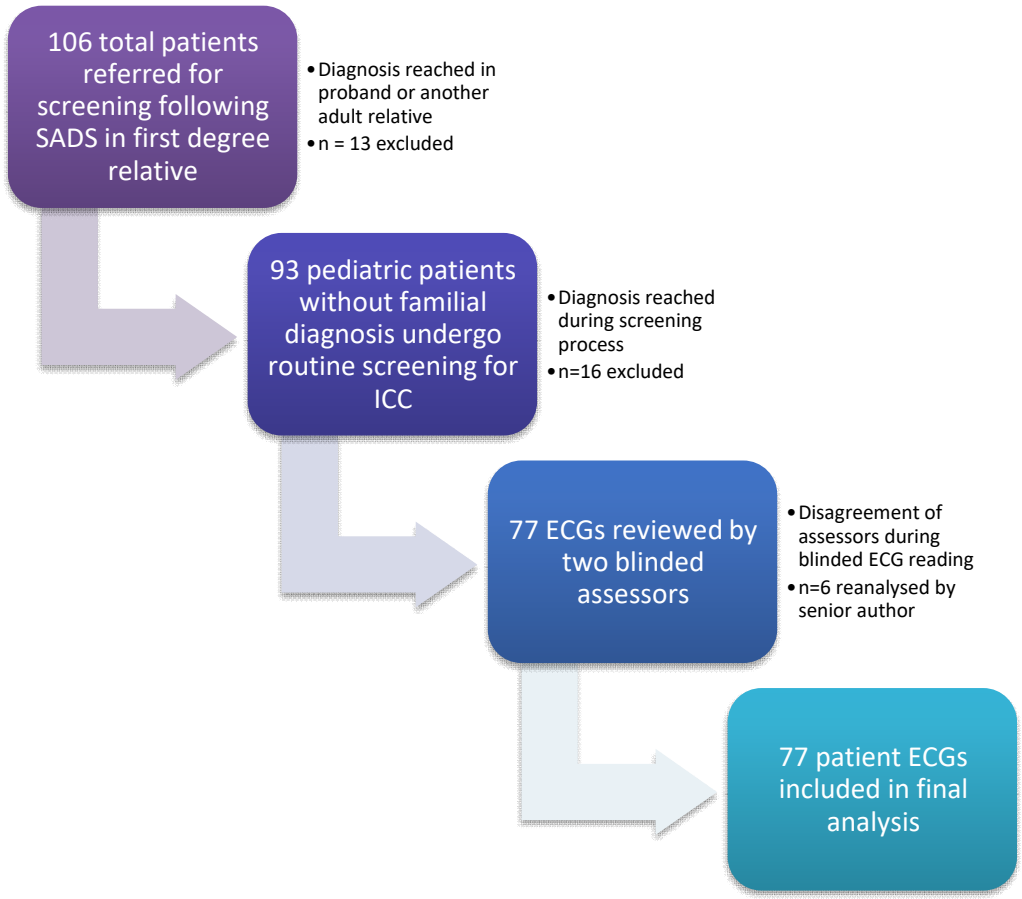

Figure 2: Circumstances of index cases's death

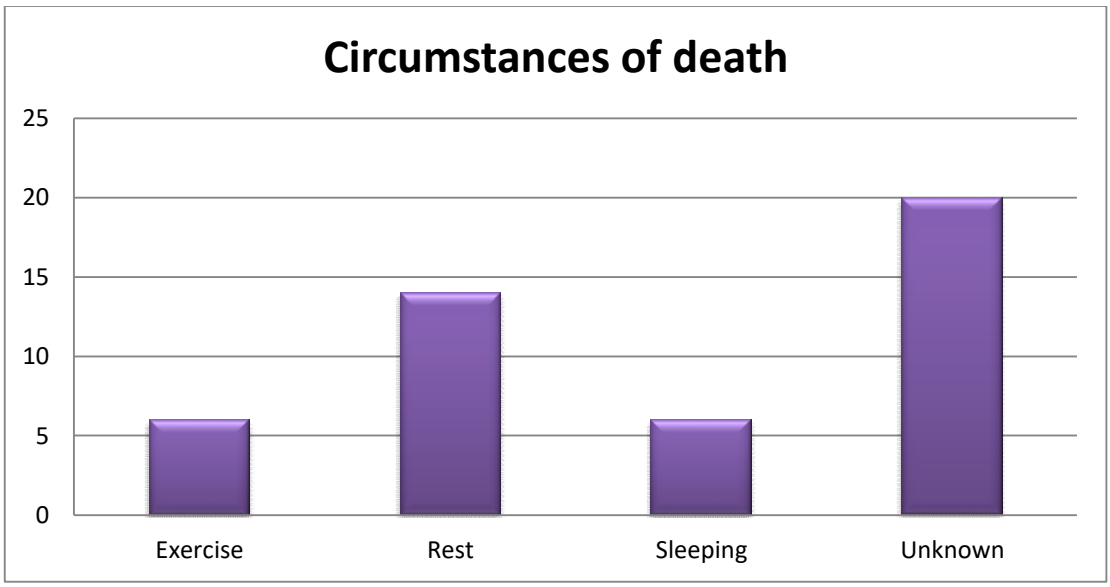

Figure 3: Example ECGs demonstrating early repolarization laterally (**3A**) and inferiorly (**3B**)