Prevalence of inherited cardiac conditions in paediatric first-degree relatives of patients with idiopathic ventricular fibrillation

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ABSTRACT

Aims

Idiopathic ventricular fibrillation (IVF) is diagnosed in out-of-hospital VF survivors after comprehensive investigations have excluded structural heart disease or inherited channelopathies. Current guidelines recommend clinical screening of first-degree relatives of IVF survivors, but this approach has not been validated in children. This study aimed to assess the yield of clinical cardiac screening in child first-degree relatives of IVF victims.

Methods

A retrospective observational study was conducted of all consecutive paediatric first-degree relatives of IVF patients referred to our centre between December 2007 and April 2020. Patients underwent systematic evaluation, including medical and family history; 12-lead resting, signal-averaged and ambulatory electrocardiogram (ECG); echocardiogram; exercise testing; cardiac magnetic resonance imaging; and ajmaline provocation testing.

Results

60 child first-degree relatives of 32 IVF survivors were included [median follow-up time of 55 months (IQR 27.0 – 87.0 months); 30 (50%) females]. 8 patients (13.3%) from 6 families (18.8%) received a cardiac diagnosis: long QT syndrome (n=4); Brugada syndrome (n=3); and dilated cardiomyopathy (n=1). There were no deaths during follow-up.

Conclusion

This study demonstrates a high yield of clinical screening for inherited cardiac disease in child first-degree relatives of IVF survivors. These findings highlight the variable expression of inherited cardiac conditions and the importance of comprehensive clinical evaluation in paediatric relatives, even when extensive investigations in the proband have not identified a

clear aetiology. Moreover, our results support the validity of the investigations proposed by current guidelines in family relatives of IVF survivors.

Keywords

Idiopathic Ventricular Fibrillation

Paediatric population

First-degree relative

Sudden cardiac death

Inherited cardiac condition

Family screening

DECLARATIONS

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Conflicts of interest/Competing interests

The authors have no conflicts of interest to declare.

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Code availability

Not applicable

INTRODUCTION

Idiopathic ventricular fibrillation (IVF) is diagnosed in survivors of an out-of-hospital cardiac arrest (OOHCA) with documented ventricular fibrillation (VF) after cardiac, respiratory, metabolic and toxicological causes have been excluded through comprehensive clinical investigations [1][2]. It accounts for 1.2% of OOHCA survivors presenting with a shockable rhythm [3]. Although, by definition, there is no identifiable aetiology in the proband, evaluation with a resting electrocardiogram (ECG), exercise test and echocardiogram is recommended as a class I indication in all first-degree relatives of IVF victims, given the incomplete penetrance and variable expression of inherited cardiac conditions (ICC), with ongoing follow up recommended in young relatives due to the possibility of age-related penetrance [4][5]. Additional investigations (ambulatory ECG monitoring, cardiac MRI and pharmacological provocation testing) are recommended as a class IIa indication [2]. A low diagnostic yield of this approach has recently been reported in adult relatives of IVF survivors [6], but its clinical utility in paediatric relatives has not been investigated. This study aimed to investigate the yield of clinical cardiac screening in child first-degree relatives of IVF victims.

METHODS

Data collection

A retrospective observational study was conducted of all consecutive paediatric (aged ≤18 years) first-degree relatives of IVF victims referred to the Centre for Inherited Cardiovascular Diseases at Great Ormond Street Hospital between December 2007 and April 2020. A diagnosis of IVF was made in the proband at their referral hospital after clinical investigations had excluded a cardiac, respiratory, metabolic and toxicological diagnosis, in particular structural heart disease and inherited arrhythmia syndromes. The

activity at the time of OOHCA was categorised as (a) rest; (b) sleep; (c) exercise; (d) emotional stress; or (e) unknown (supplementary Fig. 1).

Clinical evaluation

Patients underwent systematic evaluation, including personal and family medical history; physical examination; resting 12-lead ECGs, including ECGs with the anterior leads in the standard and high parasternal positions (HL ECG) [2], lying and standing ECGs [7]; signal averaged ECG (SAECG) [8]; two-dimensional, colour and Doppler echocardiography; and ambulatory ECG monitoring. Exercise testing; cardiac magnetic resonance imaging (MRI); and ajmaline provocation testing were also performed in patients old enough to undergo these investigations. Genetic testing was not routinely performed in the paediatric relatives. Fig. 1 shows the screening algorithm for first-degree paediatric relatives of IVF victims. Clinical data were collected at baseline and during follow-up until patients were transitioned to adult services at 18 years of age, or until the end of the study period. The diagnostic work-up of the first-degree relatives of patients with IVF is depicted in Fig. 2.
Standard diagnostic criteria were applied for specific cardiac diagnoses, as previously described [9][10][11][12][13][14][15].

Statistics

Normally distributed data are presented as mean values (± standard deviation) and non-normally distributed variables as a median [± interquartile range (IQR)]. Categorical variables are presented as number (*n)* and percentages (%). Fisher's exact test was used to compare categorical variables. A *P*-value <0.05 was considered to be statistically significant. Statistical analysis was performed using R Studio software version 1.2.1335 [16].

RESULTS

Clinical characteristics of probands

Sixty paediatric first-degree relatives of 32 probands with IVF were included in this study. Table 1 shows the baseline characteristics of the probands. The circumstances surrounding proband's OOHCA were recorded in 26 of 32 families (81.3%). Three probands (9.4%) did not undergo ICD implantation. One declined after careful counselling and died suddenly 6 years later. Another died due to severe hypoxic brain injury secondary to the OOHCA 11 days after the event while still an inpatient. The third proband was a 17-month-old girl who had undergone an arterial switch repair of transposition of the great arteries in the neonatal period, and subsequently presented with OOHCA. Coronary angiography did not demonstrate any coronary obstruction and no cause was identified for her cardiac arrest, which was therefore attributed to IVF. She did not undergo ICD implantation in view of her young age. Genetic analysis was performed in 15 probands (46.9%), 10 were not tested (31.3%) and data were not available in 7 (21.9%). No pathogenic/likely pathogenic (P/LP) variants were identified. One proband (6.6% of those tested) was heterozygous for a variant in the *SCN5A* gene [p.Ser1103Tyr (NM_198056.2:c.3308C>A)] present at a high count in controls (2134/277388 alleles, including 92 homozygotes in the gnomAD database, accessed 19/10/2020). This variant was considered unlikely to be the primary cause of his presentation, but could not be ruled out completely as a secondary contributor. Two further probands (13.3% of those tested) were found to carry variants of unknown significance in *VCL, PKP2* and *KCNJ5* genes although there were no available data regarding the exact variants identified.

Clinical characteristics and prevalence of inherited cardiac conditions in paediatric first-degree relatives of IVF victims

Table 2 shows the demographic characteristics of the paediatric first-degree relatives of individuals with IVF. A diagnosis of an ICC was made on screening in 8 individuals (13.3%) from 6 families (18.8%), at a median age of 10.0 years [IQR 8.3 – 11.5 years] (Fig. 3). The median time from initial screening to diagnosis was 17 months [IQR 9.0 – 42.3 months]. The clinical characteristics of the affected patients are detailed in Table 3. Four patients (50.0%) had an additional family history of sudden cardiac death in more distant relatives (patients 2, 3 and 7 in a second-degree relative and patient 8 in a third-degree relative).

Three individuals (5.0%), including 2 siblings, received a diagnosis of Brugada syndrome (BrS) after developing a type 1 Brugada ECG pattern on Ajmaline provocation testing. Another patient (1.7%) was diagnosed with dilated cardiomyopathy (DCM) on two-dimensional echocardiogram (patient 4) (Fig. 4A-B) [14][15]. Additionally, four individuals (including two siblings) were diagnosed with suspected long QT syndrome (LQTS) (6.9%). The diagnosis in patient 5 was suspected on the basis of a resting 12-lead ECG showing a corrected QT (QTc) of 450 ms with paradoxical QTc prolongation on standing to 550 msec and the development of broad-based and notched T-waves throughout. His brother (patient 6) received a LQTS diagnosis after his 12-lead ECG showed a QTc interval of 490 ms with broad-based T-waves. Additionally, despite initial QTc shortening during exercise, his QTc at four minutes of recovery was 480ms (Fig. 4C). Patient 7 had a QTc of 460ms with flat T-waves inferolaterally on her resting 12-lead ECG and paradoxical QT prolongation and bifid T-waves inferolaterally on exercise testing. Patient 8 was diagnosed with LQTS following the finding of borderline QTc prolongation on serial resting 12-lead ECGs (QTc of 470ms) with flat T-waves anterolaterally, and paradoxical QTc prolongation with T-wave inversion

on her standing ECG. There was no correlation between diagnosis with an ICC and gender, ethnicity or symptoms (Table 4).

Additional cardiac abnormalities

One patient (1.7%) was found to have a bicuspid aortic valve and moderate aortic stenosis. This child had a family history of an OOHCA secondary to IVF in his father who also had a bicuspid aortic valve, as did his own paternal grandmother. Two further individuals (3.3%) were found to have a dysplastic mitral valve with mild prolapse and mild regurgitation on their first screening echocardiogram. In addition, 2 patients (3.3%) had late potentials on their SAECGs with no other electrocardiographic or imaging abnormalities.

Clinical outcomes

Five out of the 8 patients who received a diagnosis of a suspected ICC (62.5%) were commenced on medication: the 4 patients with suspected LQTS were started on a beta-blocker and the patient with DCM on a beta-blocker and an angiotensin-converting enzyme inhibitor. Additionally, one patient with LQTS (patient 7) underwent insertion of an implantable loop recorder (ILR) after presenting with syncope and presyncope. To date, these symptoms have not correlated with any arrhythmia. Genetic testing on an inherited arrhythmia gene panel was performed during the follow-up period in the aforementioned individual and no P/LP variants were detected. There were no deaths during follow-up.

DISCUSSION

This study is, to our knowledge, the first to comprehensively evaluate the yield of potentially inherited cardiac conditions in child first-degree relatives of IVF survivors, and shows a relatively high yield of cardiac disease.

Detailed cardiological evaluation determines an underlying heritable cardiac disorder in up to 50% of adult and child family members of sudden arrhythmic death syndrome (SADS) victims [9][17][18], defined as a sudden unexpected death where comprehensive post-mortem and toxicology investigations fail to identify a cause and non-cardiac aetiologies have been excluded [19]. The aetiology of OOHCA caused by VF would be expected to be similar to that of SADS victims, and, indeed, exhaustive cardiac monitoring follow-up and comprehensive diagnostic investigations have been shown to diminish the number of VF survivors with an undiagnosed aetiology, with an underlying condition detected in up to 30% of patients with an initial diagnosis of IVF [3][20]. However, in a substantial proportion of probands, an underlying aetiology remains unknown, resulting in a diagnosis of IVF. Despite this, clinical cardiological screening of first-degree relatives of an IVF victim is recommended, even when extensive investigations in the proband have not yielded a diagnosis, but this approach has not been systematically evaluated in a paediatric population.

The present study shows that an underlying cardiac condition is present in over 18% of first-degree paediatric relatives of IVF survivors, including an ICC of relevance to IVF in over 13%. This finding could be explained by incomplete penetrance and variable expression of inherited cardiac conditions [5]. In particular, dynamic phenotypic expression in cardiac ion channel diseases resulting in ECG abnormalities being intermittent, or even absent, could explain the presence of false negative tests results in probands [21]. It is also possible that the findings in the paediatric relatives could represent *de novo* ICCs, although this seems unlikely given that, in at least two families, two siblings were similarly affected. In addition,

the fact that not all probands underwent extensive clinical investigations to completely exclude a known cardiac aetiology could have led to a lack definitive diagnosis in the proband. We did not assess for early repolarization (ER) in this study, as this can be a normal finding in children, but we have previously shown a high prevalence of ER in childhood relatives of sudden arrhythmic death victims [22].

Our findings contrast with previous reports of adult first-degree relatives of IVF survivors. In one study, no abnormalities were detected on clinical screening, although persistent early repolarisation was documented in 20% of the 72 first-degree relatives of 33 IVF victims [23]. More recently, Mellor *et al.* evaluated 201 first-degree adult relatives of 96 IVF victims and found evidence of an inherited arrhythmia syndrome in 5 individuals (3%) from 4 families (4%) [6]. These differences could be explained by the natural history and age-related penetrance of ICCs. The fact that the mean age of the first-degree relatives in the aforementioned study [23] was 36±13 years whereas in the present study was 6.5±4.4 years might have had an impact on the different yield of cardiac diagnosis. In keeping with the findings in our study, sodium channel blocker provocation led to a diagnosis of BrS in asymptomatic relatives of 3 separate IVF probands [6], highlighting the complex nature of the inheritance of BrS. Together, these findings emphasize the importance of systematic assessment of first-degree relatives of IVF victims and support the validity of current international guidelines [2] in both adult and child first-degree relatives of IVF survivors.
It has been previously shown that screening of first-degree relatives of unexplained sudden cardiac death victims can lead to the correct diagnosis in the proband [24][25]. As the probands were managed in other centres, it was beyond the scope of this study to investigate whether the same applies in the context of IVF, but our data suggest that this may be the

case. Further long-term prospective follow-up studies are needed to demonstrate this inference.

In our study, one patient was diagnosed with suspected LQTS on the basis of a prolonged QTc on his resting 12-lead ECG and a paradoxical QTc prolongation on standing. The response of the QT interval to the brief tachycardia induced by standing has been proven to aid in the diagnosis of LQTS [7], although there are conflicting data on its utility in the paediatric population [26]. However, in the patient reported here, the paradoxical QTc prolongation on standing was considered sufficiently diagnostic in the context of a diagnosis of LQTS in his brother and IVF in their mother.

Of note, a diagnosis of ICC was significantly more common in relatives of female probands. Although this finding should be interpreted with caution given the small numbers, it is possible that this may reflect underdiagnosis in the female probands; this in keeping with substantial recent data showing underdiagnosis of cardiovascular disease and under-representation of women in clinical trials [27][28].

LIMITATIONS

This study is limited by missing clinical data in the probands, as the vast majority of these were investigated in other centres, meaning that a systematic comparison of ECG features between probands in whom an ICC was subsequently identified in a first-degree relative and those who did not was not possible. Owing to the age range of this paediatric population, not all individuals underwent complete and systematic comprehensive investigations, including pharmacological challenge, cardiac MRI and exercise testing. This raises the possibility of

additional undiagnosed individuals and highlights the importance of ongoing clinical screening in this cohort. In addition, genetic testing was performed in only one child in our cohort and there are no data on genetic testing in the probands, which may also have resulted in an underestimate of ICC in this cohort.

CONCLUSION

This study demonstrates a relatively high yield of ICCs on clinical screening of child first-degree relatives of IVF survivors, even when diagnostic tests in the proband have not identified a clear aetiology. These findings are in contrast with recent data on adult fisrt-degree relatives of IVF probands and emphasize the variable expression and incomplete and age-related penetrance of inherited cardiac conditions and the importance of the implantation of standardised comprehensive clinical screening in paediatric relatives of IVF victims. In addition, our results support the validity of the initial investigations proposed by current guidelines in family relatives of IVF victims. Further studies with longer-term follow up are warranted to confirm these findings.

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Table 1 Baseline characteristics of probands with IVF

Baseline information	**Probands (*n* = 32)**
Female, *n* (%)	13 (40.6)
Age at IVF, mean (± SD)	31.56 (±12.9)
Ethnicity	
Caucasian, n (%)	21 (65.6)
Asian, n (%)	2 (6.3)
Black African/Caribbean, n (%)	2 (6.3)
Mixed Caucasian and Asian, n (%)	1 (3.1)
Mixed Caucasian and Black African, n (%)	1 (3.1)
Other/not known, n (%)	5 (15.6)
Symptoms	
Absent, n (%)	19 (59.4)
Syncope, *n* (%)	4 (12.5)
Palpitations	2 (6.3)
Breathlessness, *n* (%)	2 (6.3)
Unknown, *n* (%)	6 (18.8)
Implantation of an ICD, *n* (%)	29 (90.6)

ICD: implantable cardioverter-defibrillator; IVF: idiopathic ventricular fibrillation; SD: standard deviation.

Table 2 Baseline characteristics of paediatric first-degree relatives of individuals with IVF

Baseline information	**Paediatric patients (*n* = 60)**
Female, *n* (%)	30 (50.0)
Age at screening, mean (± SD)	6.5 (±4.4)
Ethnicity	
Caucasian, *n* (%)	32 (53.3)
Asian, *n* (%)	4 (6.7)
Black African/Caribbean, n (%)	6 (10.0)
Mixed Caucasian and Asian, n (%)	2 (3.3)
Mixed Caucasian and Black African, n (%)	1 (1.7)
Other/not known, n (%)	15 (25.0)
Symptoms	
Absent, *n* (%)	49 (81.7)
Palpitations, *n* (%)	3 (5.0)
Syncope, *n* (%)	3 (5.0)
Chest pain, *n* (%)	5 (8.3)
Family history of IVF in first-degree relatives	
Father, *n* (%)	29 (58.3)
Mother, *n* (%)	21 (35.0)
Sibling, *n* (%)	10 (16.7)
Family history of SCD in second-degree relatives, *n* (%)	7 (11.7)
Family history of SCD in third-degree relatives, *n* (%)	8 (13.3)
Median follow-up, months [IQR]	55 [27.0 – 87.0]

IQR: interquartile range; SCD: sudden cardiac death; SD: standard deviation.

Table 3 Characteristics of the paediatric first-degree relatives in whom an inherited cardiac condition was identified

Patient Gender	Dx	Age at Dx	Diagnosis made by	Sympt	Genetic testing	Relation to P - OOHCA circumstances	P's age at IVF	P Alive	Additional FHx of SCD
1 F	BrS	8y	Ajmaline Test	N	NP	Mother - Rest	36y	N	N
2 F*	BrS	10y	Ajmaline Test	N	NP	Mother - Sleeping	37y	Y	Y
3 M*	BrS	9y	Ajmaline Test	N	NP	Mother - Sleeping	37y	Y	Y
4 F	DCM	3y	Echo	N	NP	Mother - Rest	29y	Y	Y
5 M*	LQTS	9y	ECG	N	NP	Mother - Emotion	34y	Y	N
6 M*	LQTS	10y	ECG, ET	N	NP	Mother - Emotion	34y	Y	N
7 F	LQTS	12y	ECG, ET	S	Negative	Father – Unkown	33y	Y	N
8 F	LQTS	18y	ECG	N	NP	Sister - Rest	7y	Y	Y

* Siblings.

BrS: Brugada syndrome; FHx: family history; DCM: dilated cardiomyopathy; Dx: diagnosis; ECG: electrocardiogram; Echo: echocardiography; ET: exercise test; F: female; LQTS: long QT syndrome; M: male; N: No; NP: not performed; OOHCA: out-of-hospital cardiac arrest; P: proband; S: syncope; SCD: sudden cardiac death; Sympt: symptoms; Y: yes; y: years.

Table 4 Characteristics of the paediatric first-degree relatives of IVF victims with an inherited cardiac diagnosis compared with those with no diagnosis

Baseline information	**IC Diagnosis (*n* = 8),** *n* (%)	**No IC Diagnosis (*n*=52),** *n* (%)	***P*-value**
Sex (Male/Female)	4 (50.0)	26 (50.0)	0.707
Caucasian ethnicity	5 (62.5)	27 (51.9)	0.707
Symptoms	1 (12.5)	10 (19.2)	>0.999
Abnormal resting ECG	5 (62.5)	0 (0.0)	<0.001
Abnormal standing ECG	3 (37.5)	0 (0.0)	0.009
Abnormal SAECG	0 (0.0)	2 (3.9)	>0.999
Abnormal echo	1 (12.5)	3 (5.8)	0.445
Abnormal ET	3 (37.5)	0 (0.0)	0.012
Positive ajmaline C	3 (37.5)	0 (0.0)	0.006
Female proband	5 (62.5)	20 (38.5)	0.018

C: challenge; Dx: diagnosis; ECG: electrocardiogram; Echo: echocardiography; ET: exercise test; IC: inherited cardiac diagnosis; SAECG: signal averaged ECG.

Fig. 1 Diagnostic algorithm for paediatric first-degree relatives of IVF victims

*dependent on age.

ECG: electrocardiogram; HL: high-lead ECG; IVF: idiopathic ventricular fibrillation; MRI: magnetic resonance imaging; SAECG: signal-averaged ECG.

Fig. 2 Investigations performed in first-degree relatives of individuals with IVF

ECG: electrocardiogram; HL: high precordial lead; IVF: idiopathic ventricular fibrillation; MRI: magnetic resonance imaging; SAEG: signal averaged ECG.

Fig. 3 Pie chart showing the diagnosis identified in paediatric first-degree relatives of patients with IVF

Brugada S: Brugada syndrome; DCM: dilated cardiomyopathy; IVF: idiopathic ventricular fibrillation; LQTS: long QT syndrome.

Fig. 4 Clinical investigations of the paediatric first-degree relatives in whom an inherited cardiac condition was identified

a*. Apical four-chamber echocardiography view showing dilated left ventricle in a patient with DCM. **b*.** Reduced left ventricular fractional shortening using M-Mode echocardiography from parasternal long-axis view. **c†.** 12-lead ECG exercise test showing a QTc at 4th minute of recovery of 480ms.

* Patient 4 (DCM diagnosis)
† Patient 5 (LQTS diagnosis)

QTc: corrected QT interval; DCM: dilated cardiomyopathy; LQTS: long QT syndrome.