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Fetal Arrhythmias Associated with Cardiac Rhabdomyomas

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Abstract

Background—Primary heart tumors in fetuses are rare and mainly represent rhabdomyomas. The tumors have a variable expression and can be associated with arrhythmias, including both wide and narrow QRS tachycardia. Although multiple Doppler techniques exist to assess fetal heart rhythm, it can be difficult to record precise electrophysiological pathologies in fetal life.

Objective—Investigations defining precise electrophysiological diagnosis were performed using fetal magnetocardiography (fMCG).

Methods—In addition to routine fetal echocardiography, fMCG was used to investigate electrophysiologic rhythm patterns in a series of 10 fetuses with cardiac rhabdomyomas.

Results—The mean gestational age of the fetuses was 28.6 weeks (SD $\pm$ 4.7 weeks). The multiple rhabdomyomas were mainly located in the right and left ventricles as well as around the AV groove. Arrhythmias or conduction abnormalities were diagnosed in all 10 patients, although only six of them were referred due to that indication. Remarkably, 80% (8/10) had associated Wolff-Parkinson-White pre-excitation. In addition, we found prominent p waves in four fetuses.

Conclusion—In fetuses with rhabdomyomas, a disease where rhythm pathology is common, precise electrophysiological diagnosis can now be made by fMCG. fMCG is complimentary to echocardiography for rhythm assessment, and can detect conduction abnormalities that are not possible to diagnose prenatally with M-mode or pulsed Doppler ultrasound. Risk factor assessment using fMCG can support pregnancy management and post-natal treatment and follow-up.

Keywords

rhabdomyomas; fetus; infants; arrhythmia; WPW pre-excitation

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Conflict of interest: none

Introduction

Primary heart tumors in children are rare. The incidence has been reported to range between 0.08 and 0.2% (1, 2); however, the true incidence of cardiac tumors in prenatal life is difficult to estimate as these tumors often regress over time. In addition, atrial tumors can be small and may be difficult to recognize, and not all pregnancies are screened with ultrasound. The majority of the cardiac tumors in fetal life are rhabdomyomas. These cardiac tumors are highly associated with tuberous sclerosis complex, which has a prevalence of about 1: 8.000 in newborns (3).

DeVore and colleagues, using echocardiography, were the first to report on rhabdomyomas in *utero* (4). Most rhabdomyomas are located in the fetal ventricular septum (5), but they have been present in all cardiac chambers. Cardiac findings associated with rhabdomyomas are related to the size and position of the tumor and vary widely. The tumors can be clinically silent or cause hemodynamically significant obstructions, heart failure, cerebral embolization, arrhythmias, and sudden cardiac death. Symptoms can be due to a variety of anatomic prerequisites including displacement, mobility, space occupation, coronary infiltration, and flow obstruction.

Post natal electrocardiograms can show a variety of conduction defects, including tachycardia (ventricular, atrial ectopic, and supraventricular) and bradycardia, prolonged PR interval, non-specific ST changes, Wolff–Parkinson-White (WPW) pre-excitation and aberrant atrial and intraventricular conduction (6–10). Surgical resection of cardiac tumors is necessary primarily if they induce severe hemodynamically relevant obstructions. Ablation can be necessary in case of life-threatening rhythm disorders (11).

Prenatally, cardiac tumors are associated with several arrhythmias (12, 13). As it has not been possible to measure precise electrophysiological pathologies using direct methods in fetal life, the mechanisms of the arrhythmias are often inferred on the basis of mechanical echo/Doppler measurements. However, severe arrhythmias can induce fetal hydrops (14, 15), fetal or neonatal death (16) and can cause interruption of the pregnancy (17).

This retrospective case series presents data from fetal magnetocardiography recordings. Fetal magnetocardiography is the magnetic analogue of the fetal ECG, but provides improved signal quality due to its favorable signal transmission properties through tissue. Thus, this is the first report to describe the precise electrophysiology of these subjects. We also summarize the known literature.

Patients and Methods

Patients

The fMCG records of pregnant women referred to the Biomagnetism Laboratories at the Department of Medical Physics, University of Wisconsin-Madison from 2002 to 2013 were retrieved from our database.

Informed consent was obtained from each participant and the University of Wisconsin Institutional Review Board reviewed and approved the fMCG protocol.

The study included 10 subjects diagnosed with fetal cardiac rhabdomyomas. The patients were referred from several Midwest fetal programs due to the underlying cardiac diagnosis, with or without associated clinical arrhythmias. The mean gestational age at time of the first measurement was 28.6 weeks ($SD \pm 4.7$ weeks). The fMCG data ($n=12$ studies) were evaluated. One fetus was measured on three separate occasions.

Methods

Review of the literature—‘Pubmed’ search, including keywords “rhabdomyoma” and “fetal arrhythmia”, was done. All studies in English written language were included in the literature analysis.

Measurements

A 37-channel monoaxial (Magnes, 4D Neuroimaging, Inc, San Diego, Calif, USA) or a 21-channel (Tristan Technologies, USA) vector superconducting quantum interference device (SQUID) was used to record the fMCG tracings. Recordings about 10 minutes in duration were obtained in a magnetically shielded room. The SQUID was placed directly above and in direct contact with the mother’s abdomen. A SonoSite M-Turbo (Bothwell, Wash., USA) portable ultrasound scanner equipped with a 60-mm broadband (2–5 MHz) curved array transducer was first used to locate the position of the fetal heart prior to positioning the SQUID. Spatial filtering was used to remove maternal interference (18). All fMCG recordings were reviewed by at least 2 pediatric cardiologists.

Results

Review of the literature

The ‘pubmed’ search identified 30 English written publications. 24 were available as original publications and six as abstracts. Nine studies reported 10 rhabdomyoma cases, 3 studies included less than 10 subjects, and a total of 18 were single case reports.

A total of 213 fetuses with fetal rhabdomyomas were reported in the literature. The locations of the tumors are shown in Table 1. In 78 (37%) of subjects arrhythmias presented prenatally, but arrhythmias were often not classified.

Fetal measurements

10 fetuses were included in our study with a mean gestational age of 28.6 weeks ($SD \pm 4.7$ weeks). All fetuses had multiple cardiac rhabdomyomas. These tumors were mainly located in the right and left ventricles (Table 2). In some cases atrial extension was found and the AV groove was affected. No patients were on anti arrhythmic agents at the time of their procedure.

Arrhythmias or conduction abnormalities were diagnosed in all 10 patients, although only six of them were referred for that indication. Referral diagnosis and fMCG diagnosis for fetal study patients are shown in Table 2. The referring diagnosis was supraventricular tachycardia (SVT) in three fetuses. All three had fetal WPW pre-excitation. It is remarkable that in our patient series of rhabdomyomas, 80% (8/10) of the fetuses had associated WPW pre-excitation. 50% of these (4 of 8) had intermittent WPW pre-excitation on fMCG. The mean PR interval was shorter in fetuses with WPW pre-excitation (52 ms $SD \pm 23$ ms), compared to those without WPW pre-excitation (88 ms ($SD \pm 6$ ms)). In fetuses with WPW pattern the QRS durations were generally in the high normal range which is narrower than is seen with postnatal WPW pattern. Indeed the duration from the beginning of the P-wave to the end of QRS complex was 121 ms or less in three fetuses. This may suggest that the insertion of the accessory connection is more proximal and close to the normal conduction pathways than is typically seen in WPW.

In addition, we found prominent P wave amplitude and duration in four fetuses when compared to gestation-match normative data (19).

Postnatal ECGs were available in eight neonates. Six of them had fetal WPW pre-excitation, three of them were intermittent. In 50% of the subjects (3 of 6), fetal WPW pre-excitation was confirmed in postnatal life.

In addition to these electrophysiological findings, the evolution of conduction abnormalities can be demonstrated in subject eight. (Figure 1) This fetus was measured three separate times during pregnancy (24, 33 and 36 week gestation). Initially, only prominent p-waves were seen, but over time this fetus developed premature atrial contractions and WPW pre-excitation. The conduction abnormalities can also be confirmed by postnatal ECG (Figure 1).

Discussion

fMCG identified arrhythmias and conduction defects in fetuses with cardiac rhabdomyomas, even in the absence of clinical symptoms. As associated arrhythmias in this population can be severe, precise electrophysiological diagnosis is essential. Precise diagnosis can improve obstetrical surveillance for development of tachycardia and impact the type of first-line anti arrhythmic agent chosen, should fetal tachycardia develop.

The almost universal presence of WPW and conduction abnormalities in the fetal rhabdomyoma population presents a dilemma in the selection of antiarrhythmic agents for management of SVT. The safety of digoxin – a drug known postnatally to enhance conduction over an accessory AV connection leading to adverse events – has not been assessed with fetal tachycardia, but reports of fetal mortality in the non-hydropic fetus during treatment with digoxin are rare. Yet recently, Strasburger reviewed three recent publications suggesting that Sotalol is safe and effective for the non-hydropic fetus with SVT and should be the first line treatment of choice. Likewise, flecainide or amiodarone have better conversions rates in the hydropic fetus. Given this body of knowledge, we recommend that Sotalol rather than digoxin be considered for first-line treatment of SVT in the non-hydropic fetus with rhabdomyoma. Finally, comprehensive neonatal electrophysiological evaluation and management should be anticipated because tachyarrhythmia is a well known complication, with or without prominent P waves or WPW pre-excitation in utero.

Rhabdomyomas *in infants* show a wide spectrum of clinical symptoms. Miyake and colleagues reported a series of 106 rhabdomyoma cases (20). Hemodynamic changes were reported in 17% of the children, whereas significant arrhythmias were found in 16 % of the patients. These arrhythmias include ventricular tachycardia (6%), WPW pre-excitation (WPW) with sustained SVT (2%) and WPW with no SVT (8%) and non-WPW sustained supraventricular tachycardia in 5% of the patients. Low-grade arrhythmia was found in 12%, and various other arrhythmias were found in 28% of the patients.

In our series by fMCG, fetal rhabdomyomas were most often located in the right and left ventricles, however, identified rhythm abnormalities—WPW, giant P-waves, atrial ectopic tachycardia—were mostly atrial or AV reentrant, rather than ventricular, in origin. This suggests that tumors may be present in the atria even though they are not visible with ultrasound. Atrial tumors may be much smaller than ventricular tumors, yet may have a larger effect on rhythm, because of the atrial capacitance and greater automaticity of intrinsic atrial cells, as well as the established routes for macro-reentry. We did not observe ventricular tachycardia or premature ventricular contractions. Similar findings are reported in the literature in infants and children (Table 1).

WPW pre-excitation was present in 80 % of the fetuses. The prevalence of WPW pre-excitation implies that the tumors affect the AV groove and effectively form an accessory connection. The observation of SVT implies that accessory connections associated with tumors can conduct retrograde as well as antegrade, and therefore are clinically significant. The number of WPW cases in this study might be higher than those reported in children, but postnatal WPW ECG pattern was also found in 50% of the prenatal diagnosed WPW pre-excitation patterns. Strasburger and colleagues have reported that WPW pre-excitation is more common in fetal life, and in infants pre-excitation is known to regress over the first year (21).

None of the fetal conduction abnormalities were diagnosed with routine clinical echocardiographic examinations. In particular, mechanical PR shortening, a potential indicator of WPW pre-excitation, was not observed by echocardiography. We speculate that the mechanical PR interval is substantially lengthened as the result of either atrial mechanical alteration related to prolonged P wave duration, and/or abnormal and eccentric ventricular mechanical activation leading to prolonged isovolemic contraction time. Our data corroborate that fetal echocardiography cannot detect pre-excitation using mechanical PR intervals in fetal rhabdomyomas. Indeed, in case four, a suspected PR prolongation was reported at referral. This has been commonly assumed, but until now has not been systematically investigated.

In four subjects giant p-waves were found. Two subjects had additional macroscopic atrial tumors. Atrial tumors in the other two fetuses were not noted, but could not be entirely excluded. Giant p-waves have also been reported by Li and colleagues (19) in fetuses with AV block and other forms of bradycardia. In that study, the presence of large P wave amplitude often preceded echocardiographic changes of atrial hypertrophy. However the observation of giant p-waves has to be interpreted carefully. A combination of fMCG and echocardiography will be far more useful than either modality alone.

Finally, our study has also shown a series of multiple measurements in different gestational ages of the same fetus. In this fetus (Figure 1a, 1b and 1c), we didn't see the WPW pre-excitation at 23 weeks gestation, but it was presented later on. Therefore, we could show the evolution of a WPW pre-excitation by fMCG. FMCG is an additional tool to register the development (or regression) of conduction abnormalities.

Limitations

The referral bias of this study precludes any comparison of frequency of arrhythmias with other prior studies in infants and children. Similarly, larger and more malignant-appearing tumors may have prompted referral, in which case, greater conduction abnormality might be suspected.

Conclusions

We have shown that precise electrophysiological diagnosis can be made in utero by using fMCG and this procedure should be considered in fetuses with rhabdomyomas when it is available, in order to characterize the extent of accompanying fetal arrhythmias, predict prognosis, and assess potential need for antiarrhythmic pre- or postnatal treatment. Overall, rhabdomyomas tend to regress spontaneously. Conservative prenatal management is therefore advised.

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List of abbreviations

RA	right atrium
RV	right ventricle
LA	left atrium
LV	left ventricle
IVS	interventricular septum
IAS	interarterial septum
LVOT	left ventricular outflow tract
RVOT	right ventricular outflow tract
PAC	premature atrial contraction
PVC	premature ventricular contraction
WPW	Wolff-Parkinson-White Syndrome
SVT	supraventricular tachycardia
SVES	supraventricular extrasystolies
VES	ventricular extrasystolies
GA	gestational age

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Subject 8: GA (weeks) at time of measurement	Referring diagnosis	Different diagnosis by fMCG	Additional diagnosis by fMCG
23 4/7	no arrhythmia		prominent p waves
32 6/7	no arrhythmia	isolated PAC's	WPW
35 5/7	PAC		WPW, bundle branch block cannot be excluded

PAC = premature atrial contraction; WPW = Wolff-Parkinson-White pre-excitation

Figure 1.

Evolution of fetal WPW pre-excitation (subject no. 8)

- Development of conduction abnormalities
- Evolution of conduction abnormalities (23 4/7, 32 6/7 and 35 5/7 week gestation). The first tracing exhibit more artifact because of the early gestational age.
- Postnatal ECG of the same patient

Table 1

Review of the literature

Author	Year	10 Cardiac Rhabdomyomas	Fetal diagnosis	Location of Tumor	Fetal arrhythmias	Types of Fetal Arrhythmias
Miyake (20)	2011	106	42	nn	17	nn
Atalay(3)	2010		3	RA,RV, LV	1	PAC
Yinon (22)	2010	33	33	LV, RV, IVS, RA, intra-arterial septum	2	SVT
Deguelldre (23)	2010	73	20	LA, RA, LV, RV, IAS, IVS	nn	WPW, SVT
Mariano (24)	2009		3	LA, LV, RV, IVS	nn	nn
Isaacs (25)	2009	26	26	nn	13	unclassified
Kamil (26)	2008	19	19	nn	8	unclassified
De Wilde (27)	2007		1	nn	1	pre-excitation, bundle brunch block, compete heart block
Kagan (28)	2004		1	LV wall	1	bradycardia
Isaacs (6)	2004	57	57	RV, LV, IVS, multiple sites	9	
Akalin (29)	2004		no	LV myocardium, lateral wall, IVS, LVOT	0	postnatal PACs, PVCs
Emmel(30)	2004		1	intracardiac	1	SVT
Yen(31)	2003		no	nn	1	postnatal SVT
Pipitone (11)	2002		9	IVS	3	SVES, paroxysmal SVT
Geipel (32)	2001	12	10	LA, RA, LV, RV and IVS	3	SVT
Choi (33)	2000		1	LV,RV,IVS	1	bradyarrhythmia
Mas (34)	2000		1	RA, RV, LV	1	persistent tachycardia
Sallee (35)	1999	11	6	RA,LA, LV, RV, septum	2	irregular heart rate
Beghetti (36)	1997	44	nn	LV,RV, IVS,LVOT,RVOT,LA,RA, SVC, IVC	2	SVT, fetal tachycardia, bradycardia
Wu (37)	1997		1	RV inlet portion	1	SVT
Chaban (38)	1996		1	IVS,LV, RV, atrial septum	1	bradycardia
Coates (39)	1994			IVS	nn	SVT, atrial flutter, AV-block, fetal death
Scurry (40)	1992		no	nn	1	postnatal SVT
Brand (41)	1992		1	LV	1	fetal tachycardia
Ian (42)	1991		1	LV, RV	1	bradycardia
Kim (43)	1989		1	LV	1	SVT

Author	Year	10 Cardiac Rhabdomyomas	Fetal diagnosis	Location of Tumor	Fetal arrhythmias	Types of Fetal Arrhythmias
Hamner (44)	1989			RA, RV	1	SVT with subsequent heart block during labor
Alkalay (45)	1987		no	IVS, LVOT, ventricular myocardium	1	persistent irregular heart beat
Hoadley (13)	1986		1	LV apex, IVS, RVOT	1	occasional short run of tachycardia, irregular heart beat
Bimbaum (12)	1985		1	LV apex, RV apex	1	SVT, PAC

nn= not known, RA= right atrium, RV= right ventricle, LV=left ventricle, IVS= interventricular septum, LVS= left ventricle, LVOT=left ventricular outflow tract, RVOT= right ventricular outflow tract

PAC=premature atrial contraction, PVC = premature ventricular contraction, WPW= Wolff-Parkinson-White Syndrome, SVT= supraventricular tachycardia, SVES= supraventricular extrasystoles, VES= ventricular extrasystoles

Table 2
Pre- and postnatal electrophysiological findings and tumor locations in all fetuses

No	GA (weeks) at measurement	Location of multiple tumors	Referred diagnosis	Different diagnosis by fMCG	Additional diagnosis by fMCG	P (ms)	PR (ms)	QRS (ms)	QT (ms)	QTc (ms)	RR (ms)	Postnatal ECG finding
1	33	right and left ventricle	SVT	sinus tachycardia	atrial ectopic tachycardia with WPW	38	63	58	280	469	357	WPW
2	26 2/7	right atrium, right ventricular apex	sinus bradycardia	single ectopy	intermittent WPW, prominent p-waves, short PR interval, change in QRS morphology	40	67	52	349	493	503	?
3	34 3/7	right ventricle, tricuspid valve	normal	intermittent T-wave inversion, ST depression, QRST wave discordance		61	104	60	252	382	434	no WPW
4	20 5/7	left ventricle	first degree AV block		intermittent WPW (none/intermittent), ST-elevation	48/48	96/94	52/58	265/298	46/470	405/401	no WPW
5	30	left ventricle	no arrhythmia		giant p wave, no pre- excitation	42	100	48	240	361	442	no WPW
6	34 5/7	antero-lateral papillary muscle of mitral valve, left ventricle, IVS	SVT		WPW	83	96	104	217	332	425	?
7	30 2/7	LV apex, lateral mitral valve, right atrium	tachycardia		giant p waves, normal QRS, none/ intermittent WPW	48/61	81/84	61/67	292/323	447/492	426/430	no WPW
8	23 4/7	septal wall left ventricle	no arrhythmia		giant p waves, WPW	38	92	48	205	320	413	WPW
9	30	right and left ventricle	no arrhythmia		WPW	29	35	81	338	515	430	WPW
10	26 2/7	RVOT, mitral valve, left ventricular wall	SVT		blocked and conducted PAC, intermittent WPW	45	68	71	306	453	457	no WPW

GA= gestational age, LV= left ventricle, IVS= interventricular septum, RVOT= right ventricular outflow tract, SVT= supraventricular tachycardia, PAC= premature atrial contractions, ? missing data