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An expanded phenotype of maternal SSA/SSB antibody-associated fetal cardiac disease

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Abstract

Objectives—Conventional manifestations of fetal Sjögren's antibodies (SSA/SSB) associated cardiac disease include atrio-ventricular block (AVB), transient sinus bradycardia, endocardial fibroelastosis (EFE) and dilated cardiomyopathy. We describe other manifestations of cardiac disease.

Methods—We describe three fetuses with unique myocardial and conduction system disease.

Results—One had isolated EFE with subsequent mitral and tricuspid valve chordal avulsion, the second had sinoatrial and infrahisian conduction system disease, and in both, neonatal progression to life threatening disease occurred. The third had sinus node dysfunction and atrial flutter.

Conclusion—These findings expand the clinical phenotype of maternal SSA/SSB antibody associated fetal cardiac disease.

Keywords

Fetus; arrhythmia; AV block; repolarisation abnormalities; magnetocardiography

Introduction

Approximately 1–3% of fetuses exposed to maternal Sjögren's antibodies (SSA/SSB) develop immune-mediated inflammation and fibrosis of the conduction system and/or the myocardium [1,2]. Since its initial description nearly 30 years ago, the cardiac disease phenotype identified by both echocardiography and magnetocardiography now includes atrio-ventricular (AV) conduction disturbances [1°, 2° and 3° AV block (AVB)] with or without patchy echogenicity of the endocardium consistent with endocardial fibroelastosis (EFE), dilated cardiomyopathy, transient sinus bradycardia, ventricular and junctional ectopic tachycardia, repolarisation abnormalities and distinctive patterns of heart rate acceleration [1–5].

As part of our ongoing evaluation of maternal SSA/SSB antibody associated fetal cardiac disease by fetal echocardiography and magnetocardiography, we recently cared for three fetuses that manifested novel electrophysiologic abnormalities in utero with unusual postnatal progression of disease. The findings presented here expand the phenotype of maternal SSA/SSB antibody associated cardiac disease to include previously unreported non-AVB conduction system abnormalities and myocardial disease.

Cases

Case 1

This was the second fetus of an asymptomatic mother with SSA (Sjögren's) antibodies whose previous fetus presented with complete AVB and EFE at 19 weeks of gestation [5]. We evaluated the second fetus at 17 weeks of gestation. The echocardiogram showed a structurally normal heart with 1:1 AV conduction and a normal mechanical PR interval. There were no areas of patchy echogenicity in the endocardium. Both systolic function (ventricular shortening) and diastolic function (AV valve, ductus venosus and pulmonary venous Doppler profiles) were normal. Despite the normal fetal echocardiogram, the mother insisted on prophylactic dexamethasone therapy (4 mg orally per day). At 19 weeks, patchy echogenicity of the AV valves and right ventricle without AV valve insufficiency or cardiac dysfunction was seen [Figure 1(A)]. The Doppler-derived mechanical PR interval was normal, but the magnetocardiogram revealed T-wave alternans (TWA) [Figure 1(B)]. The mother received intravenous immune globulin (IVIg), 1 g/kg. Subsequent fetal echocardiograms showed slow improvement of the patchy echogenicity as gestation progressed. The 1.9 kg female infant was delivered at 35 weeks because of oligohydramnios. She was asymptomatic, had a normal 12-lead electrocardiogram (ECG) without TWA, and only minimal residual patchy echogenicity limited to the mitral and tricuspid valve chordae on an otherwise normal echocardiogram [Figure 1(C)]. Prednisone was given in a tapering dose over the next 4 weeks.

At 7 weeks, after a 3-day history of poor feeding and tachypnea, the infant presented in severe respiratory distress and low cardiac output syndrome. Echocardiography revealed severe mitral insufficiency and moderate tricuspid insufficiency [Figure 1(D)]. At surgery, through a transatrial approach, it was found that a significant portion of the medial aspect of the posterior leaflet of the mitral valve was completely flailed because of avulsion of the chordae from the papillary muscle. The chordal stump of the underlying papillary muscle was still present, but the tissue of the papillary muscle appeared calcified. The posterior leaflet was repaired using two separate chordal replacements consisting of Goretex suture and autologous pericardium. There was also a single area of flail chordae on the anterior leaflet of the mitral valve, which was similarly repaired. Finally, the middle portion of the anterior leaflet of the tricuspid valve was avulsed from the corresponding papillary, and was repaired in the same fashion as the mitral valve. Examination of the excised tissue showed no histological abnormalities and negative direct immunofluorescence staining for IgG, IgM and C3. Now 6 months old, she is being treated with diuretics and ACE inhibitors and is growing along the 5th percentile. Because of surgical intervention, she has developed 1° AVB and incomplete right bundle branch block.

Case 2

A primigravida with known SSA/SSB antibodies was sent to us for fetal echocardiography at 20 weeks after fetal bradycardia was detected during a routine obstetrical visit. By echocardiography, the fetal heart rate was 95 bpm, with a 1:1 AV relationship and normal mechanical PR interval. By fetal magneto-cardiogram (fMCG), the QRS complex (QRS) duration was prolonged (77 ms, normal <50 ms) and approximately 5% of the recorded rhythm was junctional ectopic tachycardia (JET) at rates of 180–190 bpm. The mother was given dexamethasone 4 mg orally per day.

Results of serial echocardiograms and fMCG are summarised in Table I. On subsequent examinations, AV conduction remained normal, the QRS duration gradually increased (94 ms at 32 weeks) and the JET first slowed (at 24 weeks) and then disappeared (by 28 weeks).

A 3.1-kg male infant was delivered electively by C-section at 37 weeks. Figure 2 shows the progression of electrocardiographic changes between birth and 4 months of age. The infant received prednisone after birth for 1 month; the dose was then tapered over the next 3 weeks. The 12-lead ECG on Day 1 of life showed low left atrial rhythm, normal PR interval, left bundle branch block with QRS duration 100 ms and left anterior hemiblock). Because of the widespread conduction system disease, the infant was given IVIg (2 g/kg). The sinus mechanism had returned on a follow-up ECG performed at 19 days of life. At 2 months of age, the 12-lead ECG showed progressive QRS prolongation, return of the low left atrial rhythm and rare episodes of 2° AV block. At 4 months of age, the QRS duration increased to 150 ms, and by Holter monitoring, there was loss of atrial activity, and slowing of the ventricular escape rate to 74 bpm and TWA. The infant was immediately referred for dual chamber pacing.

He is now 6 months of age with significant sinus node dysfunction: bradycardia, a blunted heart rate response with agitation or activity, predominant junctional rhythm with slow or absent atrial activity and abrupt sinus arrest. He is dependent on the rate response function of his pacemaker for heart rate augmentation. Most recently, pauses in the ventricular rhythm have been observed during pacemaker follow-up evaluations. By echocardiography, his systolic function is normal, and he has no EFE. Because of the unusual and progressive conduction system disease, we tested this infant for a mutation in the transcription factor gene NKX2.5. This gene has a critical role in diverse cardiac developmental processes including the development of the conduction system [6,7]. No mutation was found in the coding and immediate flanking region of the gene, analysed by PCR amplified DNA sequencing.

Case 3

We evaluated a 32-year-old asymptomatic secunda-gravida whose fetus presented with bradycardia at 23 weeks of gestation. We diagnosed 3° AV block with atrial bradycardia (atrial rate 100, ventricular rate 52 bpm), mild cardiomegaly but normal systolic function, a small (5 mm) pericardial effusion and extensive EFE. Elevated SSA antibody titers confirmed a presumptive diagnosis of isoimmune disease. The fMCG revealed 3° AV block, normal QRS duration, abnormal repolarisation and a QTc interval of 461 ms (Table II). The mother received oral dexamethasone (4 mg/day) and one dose of IVIg (1 g/kg). Because of the poor prognosis associated with a ventricular rate of <55 bpm [8] and the known chronotropic effects of transplacental terbutaline of the fetal heartrate (FHR) [9], the mother also received oral terbutaline (5 mg every 6 h). One week later, the effusion had resolved, and a second fMCG revealed increased atrial and ventricular rates, normal repolarisation with no change in the QTc interval. The EFE did not progress on serial echocardiograms.

At 28 weeks, the fetus developed atrial flutter and severe oligohydramnios (amniotic fluid level 2, normal 10–12). The mother was hospitalised, given IV hydration and a second dose of IVIg. Twelve hours later, the fetus was still in atrial flutter, but the amniotic fluid had increased. The mother was then given digoxin, 0.5 mg IV every 8 h, and shortly thereafter, the fetal rhythm converted back to 3° AV block. Digoxin (0.25 mg orally every 12 h) was continued until delivery. A third fMCG at 32 weeks showed a normal QTc, no T-wave abnormalities and 3° AVB.

At 34 weeks, the fetal ventricular rate fell to 50 bpm, but increased to 56 after the dose of transplacental terbutaline was increased. A 2.6-kg female infant was delivered at 38 weeks. She received a dose of IVIg and was treated with hydrocortisone for 2 months after birth. An epicardial dual chamber pacemaker was placed at 1 day of age because of severe bradycardia

(heart rate 48 bpm). The infant has normal ventricular function and dimensions, and only mild residual EFE. Atrial flutter has not recurred.

Discussion

The pathogenesis of the variable expression of immune-mediated fetal cardiac disease, including the findings of progressive sinus node and infrahisian conduction system abnormalities, atrial flutter, and a life threatening syndrome of late-onset myocardial damage in the face of normal ventricular function and AV conduction, is unknown. It is likely that the selective expression of both sodium and calcium ion channels is altered in disease, and which is predominantly affected determines the clinical manifestations of disease. Evidence for an acquired channelopathy in either or both calcium and action potential sodium channels is the following. First, SSA antibodies inhibit the L- and T-type calcium currents and down regulate L-type currents in the fetal rabbit heart [10]. Second, perfusion of hearts by Langendorff technique with anti-52-kD SSA antibodies from mothers whose children developed AV block alters the sodium channel action potentials. In addition, sinus node dysfunction and progressive intraventricular conduction delay is observed before the development of AV conduction defects [11]. Such findings have not been observed in the human fetus until the current report. Finally, the presentation and progression of disease in Fetus 2 is reminiscent of Lev-Lenegre disease, an SCN5A mutation in the cardiac sodium channel gene causing clinically progressive conduction system disease [12].

In utero treatment of AV block with fluorinated steroids has been reported to attenuate both myocardial and conduction system sequelae, though not in a consistent fashion [1,3–5]. The mechanism is unknown, but dexamethasone is known to stabilise sodium channels and has modulated conduction system disease associated with a single mutation in the SCN5A coding region [13]. If dexamethasone is given for maternal SSA/SSB antibody associated fetal cardiac disease when inflammation has not progressed to fibrosis, normal conduction or ventricular function may be restored. We speculate that disease in Fetuses 1 and 2 may have been modulated by early in utero treatment: noteworthy is the postnatal progression to junctional rhythm in Fetus 2 and chordal avulsion in Fetus 1 after anti-inflammatory treatment ceased. The postnatal progression of disease and the known persistence of circulating IgG antibodies for 2–3 months in the neonate may justify postnatal treatment with steroids.

Chordal disruption resulting in flail mitral valve leaflets has been previously reported, but not in association with maternal SSA/SSB antibodies. In addition, previously reported patients presented much earlier than our patient, with clear evidence of in utero chordal rupture [14]. It is possible that fetal/neonatal chordal rupture may be a manifestation of unrecognised SSA/SSB mediated myocardial disease; we suggest that maternal SSA/SSB antibody titers be evaluated in the mothers of affected infants.

The spectrum of maternal SSA/SSB antibody-associated fetal cardiac disease may have previously been underappreciated in part because of the limitations of Doppler and 2-D echocardiography, which can only discern gross changes in the mechanical AV relationship and myocardial function. The next goal will be detecting the earliest and most subtle electrophysiological signs of disease by magnetocardiography to further direct treatments that modulate disease.

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Figure 1.

Case 1: Echocardiograms. (A) Four chamber view of the fetal heart at 26 weeks showing patchy and diffuse patchy echogenicity in the endocardium (arrows): two spots in the LA, along the chordae of the mitral and tricuspid valves, in the RV endocardium, and at the apex of the LV. (B) Rhythm strip obtained during magnetocardiography showing different T-wave morphologies consistent with T-wave alternans. (C) Echocardiogram at 1 day of age, showing normal dimensions and almost complete resolution of the patchy endocardial echogenicity. (D) At 3 months of age, the anterior leaflet of the mitral valve is flail, there is severe mitral insufficiency and left atrial enlargement.

Figure 2.

Case 2: Postnatal electrocardiograms. Low left atrial rhythm, left axis deviation and left bundle branch block with 1:1 AV conduction and normal PR interval at 1 day of age. QRS duration is 100 ms. At 19 days of age, after IVIg. Occasional sinus beats are noted (arrows), the QTc has increased (489) ms and TWA is noted in the rhythm strip. At 2 months of age, the QRS duration had increased to 118 ms, and the left atrial rhythm returned. By 4 months of age, the QRS duration has increased to 150 ms, the rhythm is junctional, and the rate has fallen to 74 bpm. Beat-to-beat changes in QRS morphology are seen in lead V4.

Table 1

Fetal magnetocardiogram, electrocardiogram and echocardiogram results (Fetus 2).

Gestational age and exam	Rx	FHR (bpm)	QRS duration (ms)	P-wave	PR interval (ms)	QTc (ms)	Rate or % JET	Repolarisation abnormalities	AV block?
Echo 20 weeks	None	95	–	–	150	–	190 bpm	–	No
fMCG 20 weeks	None	94–99	77	Concord	96	507	5–50%	TWD, TWA	No
Echo 24 weeks	Dex	90–101	–	–	150	–	0	–	No
fMCG 24 weeks	Dex	90–103	73	Concord	87	387	5–50%	T-wave flat	No
Echo 28 weeks	Dex	95–100	–	–	154	–	0	0	No
Echo 32 weeks	Dex	95–100	–	–	167	–	0	0	No
fMCG 32 weeks	Dex	96–103	94	Concord	108	407	0	TWD, TWA, ST-depression prominent U-wave	No
Echo 35 weeks	Dex	100–110	–	–	180	–	0	0	No
Postnatal ECG and Holter	HC	90	100	Low left atrial	108	387	0	0	Two episodes type 1 2° AVB
Post IVIG	Dex + IVIG	110	114	Sinus	92	489	0	0	–
2 months	HC	104	118	Low left atrial	88	478	0	0	PVCs, four episodes type 1 2° AVB
4 months	None	74	150	None	–	470	0	0	Junctional rhythm

Echo, echocardiogram; FmCG, fetal magnetocardiogram; ECG, electrocardiogram; AVB, atrio-ventricular block; concord, concordant; Dex, dexamethasone; HC, hydrocortisone; IVIG, intravenous immune globulin; JET, junctional ectopic tachycardia; PVCs, premature ventricular contractions; ms, milliseconds; TWA, t-wave alternans; TWD, t-wave discordance.

Table II

Fetal magnetocardiogram, electrocardiogram and echocardiogram results (Fetus 3).

Gestational age and exam	Rx	Atrial rates (bpm)	Ventricular rates (bpm)	QTc (ms)	Repolarisation abnormalities	Rhythm
23 weeks echo	None	100	52	–	–	3°AVB
23 weeks fMCG	None	115	52	461	TWA	3°AVB
24 weeks echo	Dex, Terb (1), IVIG (1)	110	60	–	–	3°AVB
26 weeks fMCG	Dex, Terb (1)	112	61	471	None	3°AVB
28 weeks echo	Dex, Terb (1)	436	60	–	–	3°AVB; atrial flutter
28.3 weeks echo	Dex, Terb (1), IVIG (2) digoxin	110	61	–	–	3°AVB
32 weeks fMCG	Dex, Terb (1), digoxin	100	57	426	None	3°AVB
34 weeks echo	Dex, Terb (1), digoxin	105	50	–	–	3°AVB
34.3 weeks echo	Dex, Terb (2), digoxin	110	56	–	–	3°AVB
Postnatal ECG	None	98	50	406	None	3°AVB, left atrial rhythm

fMCG, fetal magnetocardiogram; ECG, electrocardiogram; echo, echocardiogram; AVB, atrio-ventricular block; Dex, dexamethasone; IVIG, intravenous immune globulin; bpm, beats per minute; ms, milliseconds; QTc, corrected QT interval; Rx, treatment; Terb, terbutaline; (1), initial dose; (2), second or increased dose; TWA, T-wave alternans.