Reversal of fetal heart block in antibody-positive mother after hydroxychloroquine and dexamethasone

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Case Report

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Abstract

Maternal autoantibody related complete heart block in the fetus is considered irreversible. During prenatal care for a 25 year old nulliparous Hispanic woman with newly diagnosed nephrotic range proteinuria and positive anti-nuclear antigen antibody, complete fetal heart block with a ventricular rate of 60 beats per minute was detected on a fetal echocardiogram at 28 weeks gestation. A small pericardial effusion and ascites were noted consistent with fetal hydrops. Dexamethasone and hydroxychloroquine were initiated. Fetal rhythm improved to Mobitz type 1 second-degree heart block, with a ventricular rate of 91 beats per minute. The fetus was born prematurely at 34 weeks gestation with second-degree heart block which improved to first-degree heart block prior to hospital discharge. First-degree heart block persisted at 2 years of age with a P-R interval of 185 milliseconds. Transplacental treatment with dexamethasone and hydroxychloroquine were associated with sustained reversal of complete heart block to sinus rhythm.

Case Report

A 25 year old nulliparous Hispanic woman with no prior medical history presented with nephrotic-range proteinuria (24-hour urine collection with 5,460 mg of protein) at 27 weeks gestation with antinuclear antigen-positive > 1:2,560 in speckled pattern and negative double stranded DNA antibody. At that time, the fetal heart rate, as measured with fetal Doppler, was 150 beats per minute (bpm). At 28 weeks gestation, the fetal heart rate was 60 bpm, and she was admitted to labor and delivery. Complete heart block (CHB) with a ventricular rate of 60 bpm was diagnosed on fetal echocardiography. Maternal medications included prenatal vitamins and iron. There was no family history of congenital heart disease or autoimmune disorders. Laboratories sent on admission revealed both SSA and SSB antibodies > 8.0 units/ml. A small pericardial effusion and ascites were noted on admission, consistent with fetal hydrops. Atrioventricular dissociation with an atrial rate of 148–158 bpm and a ventricular rate of 58–60 bpm was demonstrated (Fig. 1). There was mild to moderate tricuspid and mitral valve insufficiency and mildly diminished right ventricular systolic function. There was no ultrasonographic evidence of endocardial fibroelastosis. By Doppler imaging, a large atrial reversal wave was intermittently noted in the umbilical vein, ductus venosus, and inferior vena cava due to atrial contraction against a closed atrioventricular valve (Fig. 2). The Huhta cardiovascular profile score was 8 (minus 2 for hydrops and cardiomegaly). After discussion of the risks and benefits with the mother, with input from maternal-fetal medicine, neonatology, and pediatric cardiology, dexamethasone 4 mg daily was initiated to treat the fetal heart block. Fetal heart rhythm was monitored daily by the maternal-fetal medicine physicians, and weekly by the fetal cardiologists. Rheumatology and nephrology consults established a working diagnosis of undifferentiated connective tissue disease. Per their recommendations, at 29 weeks gestation 200 mg hydroxychloroquine daily was initiated and dexamethasone was increased to 4 mg twice daily after one week given proteinuria and decreased complement levels. The day after initiation of hydroxychloroquine, fetal echo revealed improvement to Mobitz 1 second-degree heart block (Wenckebach) with a ventricular rate of 91 beats per minute (Fig. 3). Atrioventricular valve insufficiency and biventricular systolic function were improved, and ascites resolved. Pericardial effusion was still

present. Over the next month, there was resolution of atrioventricular valve insufficiency and no further evidence of fetal hydrops, Cardiomegaly and the small pericardial effusion remained stable.

At 34 weeks gestation, the patient presented in preterm labor and progressed to spontaneously delivery of a 1650 gram female infant. Apgar scores were 3, 4, and 8 at 1, 5, and 10 minutes respectively. Physical examination demonstrated an alert and active newborn in no acute distress, with an irregular heart rate. Twelve lead electrocardiogram (ECG) showed second-degree heart block Mobitz type 1 with an average ventricular rate of 100 bpm (Fig. 4a). ECG prior to neonatal hospital discharge at 9 days of age revealed first-degree heart block with a P-R interval of 174 milliseconds. Initial echocardiogram demonstrated normal biventricular systolic function, mildly dilated right atrium and ventricle, and mild tricuspid regurgitation. Subsequent ECG during outpatient follow-up at 2 years of age demonstrated first-degree heart block with a P-R interval of 185 milliseconds (Fig. 4b). Follow-up echocardiogram at 3 months of age demonstration resolution of tricuspid regurgitation and normal sized right sided structures.

Discussion

Autoimmune disorders such as systemic lupus erythematosus (SLE) and Sjogren's syndrome affect many women of childbearing years and are associated with fetal cardiomyopathy, fetal heart block, growth restriction, preeclampsia, preterm birth, and stillbirth. The majority of infants born with high-grade antibody-mediated heart block eventually require a pacemaker (3), which has lifelong implications affecting quality of life and healthcare costs. To our knowledge, this is the first case demonstrating sustained reversal of fetal complete heart block temporally associated with initiation of maternal dexamethasone and hydroxychloroquine. Our case is unusual in terms of time onset, 28 weeks gestation. Typically heart block occurs at 18 to 24 weeks gestation, however, fetal heart block diagnosed later in gestation has been previously reported. (4–9)

Once a fetus develops complete heart block, it is generally considered. Surveillance and therapy are directed at preventing progression of disease and the development of cardiomyopathy. Serial echocardiograms and obstetric sonograms beginning at 16 weeks gestation are recommended in anti-Ro/SSA antibody-positive women for detection of atrioventricular block (11). However, most cases of congenital heart block are identified when the fetus presents with bradycardia and examination reveals the presence of second or third-degree block. In addition, only one-third of these women have a pre-existing diagnosis of autoimmune disease (12). Unrecognized autoimmune disease may result in delayed diagnosis of heart block until hydrops and cardiomyopathy have developed,increasing the risk of fetal demise (2–4, 6, 12–14). Vigilance and early treatment of antibody-mediated cardiomyopathy and heart block in the fetus are imperative to prevent life-threatening and lifelong adverse consequences. Furthermore, there is a higher case fatality rate in minorities with autoimmune disease compared to Caucasians (2). Access to healthcare, delays in diagnosis, and implicit bias of healthcare providers all likely contribute to this inequity. Multicenter studies including racial and ethnic diversity are required to identify life-saving and cost-effective primary and secondary prevention of fetal autoimmune cardiac disease

The efficacy of maternal steroid therapy on fetuses with immune-mediated complete heart block remains a controversial topic, with inconclusive large systematic reviews and multinational trials (6, 15). Although dexamethasone is not FDA approved for treatment of complete heart block in the fetus, it is utilized by most experts for this indication (4, 10). Other proposed therapies include plasmapheresis and intravenous gamma globulin, they are expensive and not always reimbursed by insurance (16). However, a recent retrospective multicenter trial, demonstrated that routine transplacental fetal treatment with dexamethasone, beta agonists for bradycardia below 50 to 55 beats/minute, and the addition of IVIG for extensive endocardial fibroelastosis or incomplete AV block was associated with significantly lower rates of perinatal mortality compared with previously reported outcomes in predominantly untreated patient cohorts with advanced atrioventricular block (4–9). The authors noted that previous studies included seronegative mothers of fetuses with AV block, which likely represents another disease process not responsive to steroids. Flouronated corticosteroids cross the placenta and are believed to mitigate the inflammatory cascade, which can harm the conduction system and myocardium in a susceptible fetus, caused by high titer anti-Ro antibodies (4, 17). Recently, the role of macrophage Toll-like receptor signaling in maternal anti-Ro mediated congenital heart block has attracted interest. Observational and case-control studies from multiple registries have shown a lower prevalence of fetal heart block in pregnant women receiving hydroxychloroquine, an orally administered Toll-like receptor antagonist (18, 19). Aggregate data from a multinational database from England, France, and the United States has also shown a protective effect against cardiac disease in subsequent pregnancies, by treating high-risk mothers with hydroxychloroquine (20). Recently, a prospective trial testing prophylactic use of hydroxychloroquine in mothers with previous pregnancies complicated by heart block demonstrated a reduction in recurrence of congenital heart block, suggesting a role for hydroxychloroquine in secondary prevention of fetal cardiac disease in antiSSA/Ro exposed pregnancies (21). Hydroxychloroquine is protective against Lupus flares during pregnancy (1), however, efficacy for reversal of fetal heart block and cardiomyopathy has not been proven. Rare cases of reversal of first and second degree heart block were reported in the PRIDE study (17) but no reversal of third degree heart block was noted. Hydroxychloroquine has a gradual onset of action.(22) thus in our case it is more likely that dexamethasone was responsible for the initial reversal of complete heart block. We speculate the sustained and continued improvement was due to hydrocycholorquine. The role of hydroxychloroquine in sustained improvement of the autoimmune cardiomyopathy deserves further investigation. .

We present a case of complete heart block diagnosed *in utero* in a woman with no history of autoimmune disease prior to pregnancy. Reversal of complete heart block, resolution of hydrops, and improved cardiac function in the fetus were temporally associated with the initiation of dexamethasone and subsequent hydroxychloroquine in the mother and persisted for the remainder of the pregnancy. Furthermore, the second-degree heart block present at birth improved to first-degree heart block by 9 days of age. One to one atrioventricular conduction has persisted for 2 years. We are optimistic that pacemaker placement will never be indicated. To our knowledge, this is the first case demonstrating sustained reversal of fetal complete heart block, which in our case was associated with maternal use of dexamethasone and

perhaps hydroxychloroquine. Prospective studies are needed to further evaluate the role of dexamethasone and hydroxychloroquine in fetuses with antibody-mediated fetal cardiac disease.

Declarations

STATEMENTS AND DECLARATIONS:

The authors have no relevant financial or non-financial interests to disclose.

Consent to Publish:

Parents signed informed consent regarding publishing their data.

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Figures

Figure 1

Mitral-aortic inflow-outflow Doppler (a) and M-mode across the right atrium and left ventricle (b) showing atrioventricular dissociation with an atrial rate of 148-158 bpm and a ventricular rate of 58-60 bpm on presentation.

Figure 2

Large atrial reversal waves (arrows) on umbilical venous (a) and inferior vena cava (b) Doppler.

Figure 3

Mitral-aortic inflow-outflow Doppler demonstrating Mobitz 1 second-degree heart block with variable atrioventricular conduction after therapy with dexamethasone and hydroxychloroquine.

Figure 4

Twelve lead ECG at birth (a) with second-degree heart block Mobitz type 1 with an average ventricular rate of 100 bpm. Repeat ECG at two years of age (b) with first-degree heart block.