Fetal Atrioventricular Heart Block
Michael A. DiMaio1* and James D. Faix1

CASE DESCRIPTION

As part of routine prenatal care, the obstetrician of a 25-year-old gravida 1, para 0 woman performed fetal heart-rate monitoring at 22 weeks gestational age. The fetal heart rate was 90 bpm, below the expected range of 120–160 bpm. This finding prompted a subsequent fetal ultrasound and echocardiogram.

The ultrasound exam showed no evidence of hydrops. Cardiac anatomy was normal, with 4 appropriately sized chambers, no valvular defects, and no abnormal communications between the right and left circulations. However, the electrocardiogram demonstrated a 2:1 atrioventricular heart block (1 ventricular beat for every 2 atrial beats). Previously, a first-trimester screen to detect fetal aneuploidy had been performed and the results were normal. Results of serologic testing for hepatitis B, varicella, and rubella viruses were consistent with maternal immunity. Results of syphilis and HIV antibody tests were also negative. The expectant mother had no significant medical history, was taking no medications, and had no history or symptoms of autoimmune disease.

CASE DISCUSSION

Fetal bradycardia is defined as a heart rate <110 bpm. The differential diagnosis of fetal bradycardia includes sinus bradycardia, nonconducted atrial bigeminy, and congenital heart block. Sinus bradycardia is often a result of conditions that cause fetal hypoxia, such as maternal hypotension, umbilical cord prolapse, and placental abruption. Nonconducted atrial bigeminy refers to the presence of electrical signals originating from atrial foci outside the sinus node which are not transmitted to the ventricle. Congenital heart block (CHB)2 refers to complete or incomplete dissociation of atrial and ventricular contractions owing to conduction abnormalities. CHB has an incidence of approximately 1 in 20 000 live births. If fetal bradycardia is detected, ultrasound examination and fetal echocardiogram should be performed to assess for structural heart defects in the fetus, such as transposition of the great vessels or atrial septal defect. Additionally, the ultrasound examination may detect abnormalities of the placenta or umbilical cord. If congenital malformation is excluded, maternal blood should be tested for the presence of autoantibodies, especially those against Ro, which are commonly associated with CHB (1).

The Ro antigen was first described as a target of autoimmunity in 1962 and was identified in patients with systemic lupus erythematosus. It was also found in patients with Sjögren syndrome (SS) and was independently named SS-A by a second group of investigators. Both groups also described an antigen closely associated with Ro/SS-A, which was named La by one group and SS-B by the other. We now know that Ro is actually 2 proteins with different molecular masses, coded by different genes. Ro60 (60 kD) is an RNA-binding protein which acts as a quality checkpoint for misfolded RNA, and Ro52 (52 kD) is a ubiquitin ligase which interacts with many different types of molecules (2). La is a smaller protein (48 kD) which protects RNA from nonspecific enzymatic digestion (3). Antibodies to all 3 have been implicated in CHB (4). A recent study has suggested that the presence of antibodies to La may be more important than previously thought (5). However, it should be noted that only 1%–2% of mothers with antibodies to either Ro or La will have affected pregnancies.

Although antibodies may be transferred at any time during gestation, the susceptibility period for CHB is often reported as 18–24 weeks, and over 80% of cases are detected before 30 weeks of gestation (4). The pathologic spectrum of atrioventricular conduction abnormalities ranges from first-degree heart block (static lengthening of the PR interval beyond 0.2 s) to

1 Department of Pathology, Stanford University Medical Center, Stanford, CA.
* Address correspondence to this author at: Department of Pathology, Stanford University Medical Center, 300 Pasteur Drive, Lane 235 MC 5324, Stanford, CA 94305-5324. Fax 650-725-6902; e-mail madimaio@stanford.edu.
Received July 15, 2013; accepted December 11, 2013.
DOI: 10.1373/clinchem.2013.212035
© 2013 American Association for Clinical Chemistry

2 Nonstandard abbreviations: CHB, congenital heart block; SS, Sjögren syndrome; ANA, antinuclear antibody; IIF, indirect immunofluorescence.

QUESTIONS TO CONSIDER

1. What conditions can cause an abnormally slow fetal heart rate?
2. What conditions can cause congenital heart block?
3. What additional testing should be performed?
third-degree heart block (failure of the sinoatrial node signal to conduct to the ventricles). Of those children with conduction abnormalities born to mothers with Ro/La antibodies, most will have first-degree block. However, progression to second-degree and irreversible third-degree block in the postnatal period is well documented (4). The exact pathologic mechanism of fetal heart block remains unclear. The 2 leading theories involve apoptosis (programmed cell death) and cross-reactivity (6). According to the apoptosis theory, transferred maternal anti-Ro antibodies bind to apoptotic fetal cardiac cells that express the Ro antigen. On binding, a humoral and cellular inflammatory cascade is triggered which leads to proliferation of fibroblasts, with subsequent scarring and dysfunction of cardiac conduction pathways. The cross-reactivity theory proposes that anti-Ro antibodies cross-react with a protein involved in regulation of calcium channels in the cardiac conduction system.

Fetal/infant mortality of maternal autoantibody-induced CHB approaches 30%, with death occurring predominantly in utero or within the first few months of life. Studies of effective treatment have been controversial and have shown mixed results. The majority of treatments proposed in the literature have focused on steroid drugs, such as the fluorinated compounds dexamethasone and betamethasone, which are not metabolized by the placenta and are transferred to the fetus in active forms. One study showed no difference in reversibility between steroid-treated and -untreated cases of third-degree heart block, although a subset of fetuses diagnosed with second-degree heart block improved to first-degree heart block at birth (4). Moreover, steroid therapy showed improved outcomes with regard to cardiac-related pleural and pericardial effusions. Another study showed that dexamethasone treatment of fetuses with congenital heart block in the absence of structural heart disease resulted in 90% infant survival at 1 year, compared to 46% survival in those not treated. In fetuses treated with a combination of dexamethasone and β-adrenergic agents, infant survival at 1 year was 95% (7). Other proposed therapies have included hydroxychloroquine, intravenous gammaglobulin, and plasmapheresis. A recent review of the literature concluded that, although there is not enough definitive evidence to recommend any specific treatment, intravenous gammaglobulin may be the best choice (8).

Laboratory testing for maternal autoantibodies with antinuclear antibody (ANA) screening assays during routine pregnancy is not recommended. Although many studies have shown increased rates of spontaneous abortion, stillbirth, and preeclampsia in mothers with a positive ANA screening result, a study of over 400 obstetric patients in whom ANA screening was performed did not demonstrate any difference in fetal outcome (9). Therefore, the American Congress of Obstetricians and Gynecologists guidelines for prenatal care do not include recommendations for performing a screening ANA. Instead, fetal heart rate monitoring performed at prenatal visits may serve a screening role for CHB, with any abnormality prompting additional work-up. Still, an expectant mother with an autoimmune rheumatic disease or previous CHB and increased concentrations of anti-Ro and/or anti-La antibodies should have close fetal echocardiographic surveillance beginning in the second trimester.

It is important to note that ANA testing using indirect immunofluorescence (IIF) may be unreliable for the detection of anti-Ro and anti-La antibodies. Many cell lines used as a substrate for ANA testing by IIF can lack sufficient quantities of the Ro and La proteins, and there is also evidence that both antigens may relocate from the nucleus to the cytoplasm. Lack of standardization of IIF materials and the requirement for experienced laboratory staff to interpret IIF assays further contribute to testing inaccuracy. The American College of Rheumatology has issued guidelines recommending that IIF remain the gold standard for ANA testing because the use of immunoassays employing solid phases with multiple antigens may be less sensitive (10). However, the relative sensitivities of the 2 approaches may depend on the specific assays used. Indeed, some commercially available IIF substrates may fail to detect anti-Ro unless special modifications of the cultured cells are made (11). Still, in some cases of CHB, autoantibodies may not be detected due to very low maternal titers.

CASE FOLLOW-UP

Because congenital heart block was highly suspected, maternal serum was screened for ANA by ELISA immunoassay (Bio-Rad ANA) and was strongly positive, with a relative index of 10.171 (reference interval, <1). Confirmatory indirect immunofluorescence was negative. Given the discordant results, specific immunoassays for both anti-Ro and anti-La were performed and resulted in concentrations of 145 and 80 U/mL, respectively (reference interval, <20 U/mL). At 23 weeks gestation, the expectant mother was treated with 2 mg of dexamethasone twice daily to prevent progression. She underwent weekly fetal echocardiograms thereafter, and the exam at 26 weeks identified third-degree atrioventricular block. Due to concern for sudden death of the fetus and hydrops, a caesarean section delivery was scheduled and performed at 31 weeks gestation. One week before delivery, she received a 2-day course of betamethasone to enhance fetal lung maturity.
On delivery, the female neonate weighed 1.7 kg, and her heart rate was approximately 45 bpm. At 2 h of life, a dual-chamber pacemaker was surgically implanted. The immediate postoperative course was unremarkable, and her heart rate was set at 140 bpm. The infant had no skin rash and no thrombocytopenia that would be suggestive of neonatal lupus. Specific immunoassays for anti-Ro and anti-La were performed on neonatal serum and were 100 U/mL and 63 U/mL, respectively (reference interval, 20 U/mL). Echocardiogram and electrocardiogram demonstrated normal cardiac anatomy with no significant valvular regurgitation, and normal function of the pacemaker. Aside from persistent third-degree heart block, the infant’s hospital course was significant only for minor feeding difficulties, and she was discharged to home at age 52 days with her surgically implanted pacemaker. Of note, the mother was not advised against breastfeeding her child. Though anti-Ro and anti-La are detected in breast milk, there is no proven association of congenital heart block with breastfeeding.

QUESTIONS TO STIMULATE DISCUSSION

1. During a routine prenatal visit, an expectant mother with no significant medical history is found to be carrying a fetus with an abnormally low heart rate. What is the differential diagnosis and what additional testing should be performed?
2. What is the suspected mechanism of congenital heart block resulting from anti-Ro antibodies?
3. What laboratory methods are available for screening for antinuclear antibodies, and what are the advantages and disadvantages of these methods?

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures or Potential Conflicts of Interest: No authors declared any potential conflicts of interest.

References


POINTS TO REMEMBER

- Congenital heart block is a rare disorder, usually associated with maternal transfer of antinuclear antibodies, especially those against Ro.
- Treatment is controversial with variable effect. Corticosteroids may help target the inflammation associated with development of autoantibody-associated CHB as well as improve fetal lung maturity before premature caesarean delivery.
- Prenatal screening for maternal antinuclear antibodies should not be performed routinely in most pregnancies. Furthermore, generalized ANA screening assay is not indicated, whereas targeted tests for anti-Ro should be performed in these situations.
- ELISA or multiplex immunoassays are more sensitive for detection of anti-Ro antibodies than routine indirect immunofluorescence for antinuclear antibodies. If positive, confirmatory indirect immunofluorescence should be performed by experienced laboratory staff to determine autoantibody titer and pattern.