Maternal Antiphospholipid Syndrome Presenting as Neonatal Lupus with Congenital Complete Heart Block in the Fetus

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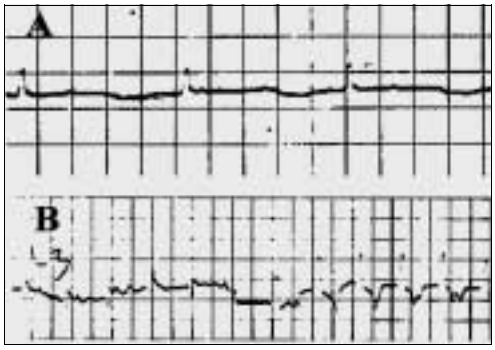
Congenital heart block is a rare condition that has been associated with the presence of maternal antiphospholipid antibodies [1]. CHB occurs in 1:22 000 of liveborn infants, and appears in 3.6% of newborns to mothers with known systemic lupus erythematosus. It is currently considered an example of passively acquired autoimmunity, whereby maternal immune abnormalities lead to the production of autoantibodies crossing the placenta and presumably affecting an otherwise normally developing fetus. In CHB, abnormal maternal immunization is thought to stimulate autoantibody production against SSA/Ro and SSB/La antigens. Antibodies to SSA/Ro ribonucleoproteins in maternal sera have been demonstrated almost universally when CHB develops in an offspring [1]. The SSB/La antigen-antibody system is also strongly associated with the development of CHB [1]. These maternal antibodies are transferred via the placenta to the fetus and are believed to transmit irreversible immunological injury to the developing fetal heart tissue, thus causing third-degree atrioventricular block. Although there is no unique antibody profile specific for CHB, women with a high or low risk of having a child with CHB can be identified. High levels of anti-SSA/Ro and anti-SSB/La are associated with a significantly increased risk of having CHB. Female infants

CHB =congenital heart block

appear to have an increased risk of CHB. The risk of having a subsequent child with congenital heart block ranges between 12 and 16% [2]. CHB is a serious condition with 60% of children requiring pacemakers, and 15–22% dying [1]. Pregnancies at risk are difficult to identify, since 66% of the mothers are asymptomatic at delivery.

CHB and other neonatal abnormalities affecting the skin, liver, and blood elements are grouped together under the title "neonatal lupus syndromes." Neonatal lupus was so termed because cutaneous lesions of the neonate resembled those seen in SLE. CHB is irreversible and is most commonly detected during the second trimester. In contrast, the non-cardiac manifestations of neonatal lupus are transient, resolving during the first 6 months of life, coincident with the disappearance of maternal autoantibodies from the maternal circulation [1]. Owing to the presence of antiphospholipid antibodies with recurrent arterial and/or venous thrombosis and thrombocytopenia, it is referred to as antiphospholipid syndrome [3]. Approximately 50% of these patients are considered to have primary APS and 50% secondary APS. Secondary APS seems to be clinically indistinguishable from primary APS except for an association with SLE. Recurrent fetal loss in non-SLE patients represents the most frequent clinical presentation of primary APS in young women [3,4]. The frequency of pregnancy loss in aPL-positive women without a previous history of miscarriage, thrombosis or thrombocytopenia is minimal. Most patients with incidental aPL who are otherwise healthy have uneventful pregnancies. Therefore, the predictive aPL value for pregnancy complications in the general population is very low. The presence of clinical manifestations of APS, and especially a previous history of recurrent miscarriages, make the finding of aPL very significant [3]. At the present time, however, the exact clinical criteria that are sufficient to indicate screening or examination for aPL in pregnant women are still unclear. Conversely, it is not entirely clear how CHB in the fetus in the presence of aPL allows us to better diagnose the mother's condition.

We report the case of a newborn who presented with a congenital complete atrioventricular block in the presence of aPL and discuss the above questions in this context.



Electrocardiogram of newborn at birth **[A]** and after pacemaker insertion **[B].**

Patient Description

A healthy 32 year old, 30 week gravida woman was sent to the emergency room by a community medical center nurse because of fetal bradycardia detected on Doppler ultrasound. Her obstetric history was significant because of two consecutive spontaneous abortions in the first trimester. The fetal bradycardia was confirmed in the hospital and an emergency cesarean section was performed. A premature female baby was born weighing 1,200 g with an Apgar score of 5/6 and severe bradycardia of 40 beats/minute. Immediate resuscitation including repeated intratracheal adrenalin and intravenous adrenalin was given but failed to raise the heart rate above 60 beats/min, despite normal oxygen saturation. The infant was transferred to the neonatal intensive care unit and was mechanically ventilated and treated by intratracheal surfactant for respiratory distress syndrome. Electrocardiography showed complete atrioventricular block [Figure A]. Another attempt to raise the heart rate with intravenous isoprel was also unsuccessful.

Laboratory evaluation of the maternal serum showed the presence of lupus anticoagulant with prolonged activated partial thromboplastin time 40.7 sec (normal 25–37), PTT 40.2 sec (normal 24–34), and PTT phospholipid serum 41.7 sec (normal 27–35) in the presence of anti-cardiolipin immunoglobulin M 15 u/ml (normal 0–10) and absence of anti-cardiolipin IgG. It revealed positive anti-nuclear antibodies of 0.656 (n = 0–0.155), and autoantibodies to SSA/Ro, borderline autoantibodies to SSB/La and absence of autoantibodies to double stranded-DNA, SM, RNP and SCL-70.

Laboratory evaluation of the newborn's serum showed positive ANA of 0.48 and SSA. There was absence of DS DNA, SSB, RNP, SCL-70 and anti-cardiolipin IgG.

At the age of 4 days she underwent a pacemaker insertion and closure of pulmonary ductus arteriosus. The heart rate was set to 120 beats/min [Figure B] and there were no postoperative complications. Following further treatment for her prematurity, the infant was discharged in stable condition weighing 2,100 g at the age of 30 days.

Comment

Based on the last consensus classification criteria for APS, the mother's condition in our case is compatible with APS, although at the time of pregnancy the criteria were not fully met. She had had two previous unexplained miscarriages less than 10 weeks apart, and had high titer of SSA/Ro. If the present pregnancy had not been diagnosed and treated, it could have ended in fetal death due to CHB.

APS is related to all forms of fetal complications including intrauterine growth retardation and low birth weight [5]. The present case of a low birth weight female newborn with ANA and

SLE= systemic lupus erythematosus
APS = antiphospholipid syndrome
aPL = antiphospholipid antibodies

PTT = partial thromboplastin time

ANA = anti-nuclear antibodies

SSA/Ro antibodies is typical in its clinical presentation, with a more severe form of CHB that required a pacemaker insertion.

Recurrent pregnancy loss is one of the main features of APS [8], and the risk of a subsequent child with CHB is 18% [1]. While the predictive value of aPL for pregnancy complications is very low in the general population [4], assay for SSA (anti-Ro) and SSB (anti-La) antibodies should be performed in the sera of pregnant women with APS (as defined by the presence of aPL and the clinical criteria), or when CHB is detected in a fetus of an asymptomatic pregnant woman. The presence of clinical manifestations of APS, and especially a history of recurrent miscarriages, makes the finding of aPL very significant [3]. Women with APS are at high risk for subsequent pregnancy loss if untreated. Fetal loss, which is the most characteristic obstetric feature of APS and may lead to death in about 20% of cases, was prevented in this case due to the early detection of fetal CHB. However, it is unclear precisely which clinical criteria are sufficient to indicate screening or examination for aPL in a pregnant woman. It is recommended that all women with either SLE or APS be closely monitored during pregnancy, as also suggested by others [4]. A complete autoantibody profile, including anti-DNA, anti-SSA/Ro, anti SSB/La, and aPL (anti-cardioplipin IgG and IgM and lupus anticoagulant) should be available before or at least in early pregnancy [4]. This, in turn, will lead to the appropriate medical approach to both the fetus and the mother and will prevent unnecessary complications that may culminate in fetal death. It has, in fact, been suggested that all mothers with anti SSA/Ro and/or SSB/La should have serial fetal echocardiography performed by an experienced pediatric cardiologist and focusing on gestational weeks 16–24 [1].

This case indicates that asymptomatic SLE should always be suspected in infants born with CHB. We propose broadening the screening for early detection even when the mother does not fulfill the full obstetric criteria for APS. The obstetrician should be aware of APS as a risk factor for two main reasons. The first is to prevent premature birth of an uncompromised fetus by considering a trial treatment during pregnancy and avoiding unnecessary cesarean section. When persistent bradycardia is not a sign of fetal distress, it can be the initial sign for a diagnosis of prenatal complete atrioventricular heart block. Echocardiography, which is used to assess fetal hemodynamic status, may detect signs of fetal deterioration. Treatment strategies are debatable and may include prophylactic therapy for high risk pregnant women and a combination of intrauterine plasmapheresis with plasma exchange or with corticosteroids. Hydrops fetalis and a further drop in the ventricular heart rate warrant urgent cesarean section and pacemaker management of the newborn. Second, identification of autoimmune disease in the pregnant woman will lead to better follow-up and treatment of her own disease. The management protocol may include: planning of conception when disease is inactive; frequent follow-up visits by an internist-obstetrician team; use of sequential ultrasonographic, Doppler and fetal echocardiographic examinations; serial evaluations of maternal immunological condition; and low dose aspirin beginning 1 month before attempting conception and throughout pregnancy.

The presence of ANA in the sera of both the mother and newborn is not entirely clear. Anti-nuclear antibodies are not part of aPL [4], and their presence in sera is therefore not part of APS. While the criteria for SLE in the mother were not present, it is possible that SLE may develop in the future. The literature support that some, but not all, mothers with CHB newborns may develop SLE [1]. Different series revealed that 48–100% of asymptomatic mothers will develop rheumatic disease [1], although a more recent study showed that only 14% of asymptomatic mothers developed rheumatic disease [1]. From these studies it can be concluded that asymptomatic mothers do not invariably become ill, and that the specificity of anti-SSA/Ro SSB/La antibodies is highly stable for years, independent of the maternal clinical status. Since the newborn's condition is considered to be neonatal lupus syndrome, it can be argued that the presence of ANA suggests that the mother's condition is more than APS. Neonatal lupus syndrome is a passively acquired autoimmunity, where maternal autoantibodies cross the placenta and result in fetal tissue damage [1]. The disparity of disease between mother and child, particularly in cardiac disease, underscores the misleading nature of the term "neonatal lupus."

This case illustrates that neonatal lupus syndrome presenting with CHB is a misnomer since it appears without any SLE in the mother. We propose "neonatal APS" as a more suitable term.

In conclusion, we suggest that CHB in the context of APS should be termed neonatal APS, and that screening pregnant women should be broadened to include women who have aPL with some clinical characteristics of APS.

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