Congenital Heart Block in Neonatal Lupus: The Clinical Perspective

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INTRODUCTION

Isolated congenital heart block (CHB) in a structurally normal heart is almost invariably associated with the presence of maternal antibodies to the intracellular ribonucleoproteins SSA/Ro and SSB/La (1, 2). This near-universal association suggests that isolated CHB is a passively acquired autoimmune disease, in which maternal autoantibodies cross the placenta and injure the previously normal fetal heart. Other neonatal abnormalities, including cutaneous manifestations, cholestasis and cytopenias, are also associated with anti-SSA/Ro-SSB/La antibodies in the maternal and fetal circulation and are now grouped under the heading of neonatal lupus (NL) syndromes. This term –derived from the resemblance of the neonatal rash to the subacute cutaneous rash of systemic lupus erythematosus (SLE) in adults– is clearly a misnomer, as the newborn does not have a systemic autoimmune disease and the mother may be completely asymptomatic. The noncardiac manifestations of NL are generally transient, resolving at about 6 months of life coincident with the disappearance of maternal autoantibodies from the neonatal circulation. To date, however, complete (3rd degree) heart block is essentially irreversible.

The relative rarity of autoimmune-associated CHB has posed a challenge to clinical and epidemiologic researchers. The establishment in 1994 of the Research Registry for Neonatal Lupus (3), a rare disease registry funded by the U.S. National Institutes of Health, has enabled the acquisition of larger and thus more statistically reliable series, data from which are reported here. Currently, the Registry follows 337 mothers with anti-SSA/Ro and/or -SSB/La antibodies and their children with neonatal lupus syndromes, including 207 with CHB only, 103 with NL rash only, 29 with CHB and rash, 3 with isolated cardiomyopathy (CM), and 7 with hepatic and/or hematologic manifestations.

CLINICAL PRESENTATION

The classic description of neonatal lupus is one of a fetus or newborn discovered to have a slow heart rate due to CHB in the absence of causative structural abnormalities, for which laboratory investigation reveals antibodies to SSA/Ro and/or SSB/La in the maternal serum. Although the mother may have SLE, Sjögren's syndrome (SS) or an undifferentiated autoimmune syndrome (UAS), many mothers are entirely asymptomatic.

Many cases are discovered in utero, most commonly between 18 and 24 wk of gestation. The degree of heart block includes all levels from 1st degree, discovered only incidentally on electrocardiogram (i.e., after birth, although echocardiogram can identify a Doppler equivalent of a prolonged PR interval), through 3rd degree (complete) heart block with ventricular rates below 50 beats per minute (bpm). Mortality (including fetal demise) is ~20%; the highest mortality occurs in prematurely delivered newborns in the first few months of life (3). Approximately two-thirds of all recognized cases receive pacemaker insertion before reaching adulthood (3), and current practice suggests that virtually all patients with complete heart block will have a pacemaker at some point in their lives. Risk factors for needing a pacemaker include very slow heart rates (below 55 bpm), symptoms such as poor exercise tolerance, cardiomegaly, long QRS or QT durations, ectopy, syncope, or structural or functional heart disease (4).

Unfortunately, conduction system disease alone is not the whole story in NL. There is a disturbingly high incidence of late CM leading to low output congestive heart failure, death or transplant, even after successful pacemaker implantation for the associated heart block (3, 5). CM can be seen in the absence of 3rd degree heart block; 3 children of antibody-positive mothers from the Registry series had CM with no apparent block, and CM associated with 1st degree block/prolonged PR interval was seen in another Registry child and in a case reported by Rosenthal *et al*. (6). A minority of cases (23 of 128 currently enrolled in the Registry, or 18%) exhibit congenital structural abnormalities that do not in themselves account for atrioventricular (AV) block, including atrial septal defect and patent ductus arteriosus.

Other organ systems may be involved in the newborn, in the presence or absence of CHB. The characteristic NL rash involves the scalp and face, particularly the periorbital region, and is photosensitive. In some instances the rash is present in other locations and can cover virtually the entire body. The lesions are superficial inflammatory plaques, typically annular or elliptic with erythema and scaling. Hypopigmentation is frequent and may be a prominent feature. The rash typically appears within a few weeks of life (most commonly at 6 wk) lasting to late infancy, and resolves by 6 to 8 months of life, usually with minimal scarring (7). Occasionally, newborns of mothers with anti-SSA/Ro-SSB/La antibodies may present with various cytopenias (1, 3, 8) and/or liver enzyme abnormalities (9-12).

The incidence of neonatal lupus in an offspring of a mother with anti-SSA/Ro antibodies is ~2% (2, 13-15). When an anti-SSA/Ro-positive mother has previously given birth to a child with NL, the risk of CHB in a subsequent pregnancy rises to ~18% (3, 16). In our Registry, of 94 subsequent pregnancies after having a child with CHB, 18 (19%) resulted in CHB and 7 (7%) in a child with NL rash. Importantly, a mother who has given birth to a child with cutaneous manifestations can subsequently give birth to a child with CHB. Of 36 pregnancies subsequent to the birth of a child with NL rash, 9 (25%) resulted in CHB and 14 (39%) in a second child with rash. As previously reported, there is no gender-based difference in the frequency of either CHB or NL rash (3, 7).

DIAGNOSTIC CONSIDERATIONS

The identification of fetal bradycardia by either auscultation or routine obstetric ultrasound should prompt two immediate responses. The first is to obtain a 2-dimensional and M-mode fetal echocardiographic and Doppler ultrasound to document whether there is an atrial arrhythmia or AV block, and to what degree. Only 2nd or 3rd degree block will be clinically manifest as bradycardia. These studies will also ascertain whether there are any major structural abnormalities of the heart such as AV septal defects, left atrial isomerism or abnormalities of the great arteries, which can themselves cause heart block regardless of the presence of maternal autoantibodies. An associated myocarditis is supported by the finding of decreased contractility in addition to secondary changes such as an increase of cardiac size, pericardial effusions and tricuspid regurgitation.

The second response is to evaluate the mother's serum for the presence of anti-SSA/Ro with or without anti-SSA/La antibodies. The enzyme-linked immunosorbent assay (ELISA) is the most common and probably the most sensitive method for detection of these antibodies. Immunoblot may be performed for evaluation of the fine specificity of the anti-SSA/Ro response, but does not alter the management of an identified case of CHB. In most women with affected children, immunoblot reveals reactivity to either the 52kD or 60kD Ro antigen (although the former is more common), and anti-SSB/La antibodies are also present (17). Therefore, immunoblot may be more useful for deciding on the management of a pregnant woman in whom there is concern regarding the possibility of having an infant with CHB.

THERAPEUTIC OPTIONS

Because CHB is most often identified between 18 and 24 wk of gestation, intrauterine therapy ought to be possible. The clinical approach includes obstetric and rheumatologic management of both the fetus identified with CHB and the fetus with a normal heart rate but at high risk of developing CHB. In either situation, the critical decision is whether any treatment is necessary. Guidelines are not well established and are based empirically on anecdotal evidence. For the fetus identified with CHB, the clinician needs to know if the presence of bradycardia represents an irreversible fibrotic process and if continued autoimmune tissue injury will cause progressive damage. The rationale for treatment of identified heart block is to diminish a generalized inflammatory insult and lower the titer of maternal autoantibodies. Several intrauterine therapeutic regimens have been tried, including dexamethasone (6, 18), which is not metabolized by the placenta and is available to the fetus in an active form, and plasmapheresis (19). Maternal risks of dexamethasone are similar to those of any glucocorticoid and include infection, osteoporosis, osteonecrosis, diabetes, hypertension and preeclampsia. Fetal risks include oligohydramnios, intrauterine growth retardation and adrenal suppression. Recently in the United States, an NIH-funded multicenter double-blind placebo-controlled prospective trial has been initiated to evaluate the efficacy of 4 mg/day of dexamethasone (taken orally by the mother) in the treatment of newly identified 1st, 2nd or 3rd degree block [the PRIDE (PR interval and dexamethasone evaluation) in CHB Trial].

With regard to prophylactic therapy of the high-risk mother (documentation of high titer anti-SSA/Ro-SSB/La antibodies, anti-48kD La and 52kD Ro on immunoblot, and a previous child with NL) there is little support for initiation of either prednisone or dexamethasone. Maternal prednisone (at least in low and moderate doses) early in pregnancy does not prevent the development of CHB (20). This might be anticipated since prednisone given to

the mother is not active in the fetus (21) and levels of anti-SSA/Ro-SSB/La antibodies remain relatively constant during corticosteroid therapy. A recent report by Shinohara *et al*. (22) found CHB in 15 of 61 infants born to 40 mothers with anti-SSA/Ro antibodies who did not receive glucocorticoids, but this unexpectedly high prevalence may be explained by the retrospective nature of the study and potential referral bias. Conversely, CHB did not occur in any of 26 fetuses whose mothers were given steroids prior to the 16th wk of gestation, but given incidence rates of ~2% (2, 13-15), the authors may have needed to follow more than 26 pregnancies to find an infant with complete block. In our group, we have noted that in 5 of 61 pregnancies in which CHB developed, the mothers had been taking prednisone prior to the fetal diagnosis (20).

We recommend that the fetuses of all women with anti-SSA/Ro antibodies be evaluated by serial echocardiography (23), but especially those of women with high-titer antibodies that recognize the 52kD component on SDS-immunoblot and have associated anti-SSB/La antibodies. A recent major advance in echocardiography has made possible the in utero detection of 1st degree block. The development of a new non-invasive Doppler technique to measure the mechanical PR interval in the absence of an electrocardiogram may allow earlier diagnosis and treatment possibilities. Normative data have been published (24), and the technique validated in two cases (25, 26). To explore related immune CM, a new Doppler index of fetal cardiac function, the Tei myocardial performance index, has been established in utero (27). A U.S.-based multicenter NIH-funded trial is currently underway to assess the frequency of 1st degree block in mothers with anti-SSA/Ro antibodies, and whether it is a marker for more advanced block (PRIDE in CHB, discussed above). Echocardiograms are done weekly from 16 to 26 wk and every other week until 32 wk; all echocardiographers are trained to perform the novel measurement of the mechanical PR interval. The rationale is to evaluate the fetal heart with the most sensitive tools during the period of presumed vulnerability.

From a purely supportive and mechanistic point of view, fetuses with very slow heart rates and hydrops have been treated with sympathomimetics via the maternal circulation (28), or even digoxin or fetal pacing (29), as well as early delivery. In the absence of controlled studies (which may never be feasible given the rarity of CHB), plasmapheresis, digoxin, diuretics and/or fetal pacing should be considered highly experimental and only reserved for those cases where the fetus is in a life-threatening situation with hydrops and deteriorating cardiac function.

After birth, treatment of the symptomatic infant often involves pacemaker therapy, and supportive treatment for low output or congestive heart failure. Despite the presence of intact antibody against SSA/Ro and SSB/La in breast milk, breastfeeding appears to confer no risk in the child's disease when compared with formula, although caution should prompt cessation of breastfeeding in a case of worsening CM or rash (30).

All neonates (both healthy infants and those with CHB) whose mothers have anti-SSA/Ro or -SSB/La antibodies should be protected from excessive exposure to the sun, since they may develop skin lesions up to 6 months of age while the maternal antibodies persist. Treatment is generally conservative, and in many cases no intervention is required. Topical corticosteroids, preferably non-fluorinated, may be used. High-potency topical corticosteroids can produce systemic effects. Since the lesions are transient and generally benign, systemic therapies such as antimalarials are not recommended in young children, in whom the thera-peutic dose approaches the toxic dose (7). In most cases the other, rarer manifestations of neonatal lupus, such liver enzyme abnormalities and cytopenias, are self-limited (8-11).

Mothers who have had children with NL need to be aware of several important points to guide future management. If the mother has no signs or symptoms of a rheumatic disease, she should be reassured that she does not have SLE. Approximately half of these mothers do go on to develop rheumatologic symptoms; however, severe life-threatening SLE is rare. Of 157 Registry mothers evaluated, 52 (33%) were asymptomatic, 28 (18%) had UAS, 29 (18%) had SLE, 31 (20%) had SS, 11 (7%) had SLE/SS, and 1 (< 1%) had rheumatoid arthritis(RA)/SS at the time NL was identified (prior to or at birth). Mean follow-up was 7.5 yr. Twenty-one (40%) of the 52 initially asymptomatic mothers developed symptoms of a rheumatic disease: 3 (6%) developed UAS, 9 (18%) SS and 9 (18%) SLE. Of the 28 mothers initially categorized as having UAS, 3 (11%) developed SLE and 4 (14%) SS. Four (13%) of 31 mothers with SS progressed to SLE. Notably, the majority of patients with SLE at the time of the affected pregnancy have not experienced disease progression.

A longitudinal study comparing 94 children of anti-SSA/Ro-SSB/La-positive mothers (including 49 born with NL and 45 unaffected siblings) with age- and ethnicity-matched controls whose mothers were antibody-negative, found that joint stiffness was the single rheumatologic symptom reported significantly more often in the children of antibody-positive mothers than in the control group (31). Six (12%) of the 49 children born with NL developed a definable autoimmune disease (2 juvenile RA, 1 Hashimoto's thyroiditis, 1 psoriasis/iritis, 1 psoriasis/Type I diabetes, and

1 congenital hyothyroidism/nephrotic syndrome) by age 13 yr, compared with none of the unaffected siblings and none of the controls. The mothers of these 6 children all had autoimmune disease themselves (however, it must be pointed out that of the 55 antibody-positive mothers studied, only 6 remained asymptomatic through follow-up). While the small sample size precludes definitive determinations of risk, children who have had NL and whose mothers have an autoimmune disease should be closely followed with regard to autoimmune symptoms in childhood.

CONCLUSIONS

Approximately 2% of all mothers with anti-SSA/Ro antibodies have a baby with CHB, independent of whether the mother has a rheumatic disease or is totally asymptomatic. Mothers who have given birth to a child with NL, be it CHB or rash, face a nearly 20% risk that their next child will have CHB. All women with SLE, SS, RA or only the history of a positive ANA who are planning a pregnancy should be screened for anti-SSA/Ro and -SSB/La antibodies by ELISA. If these antibodies are present, prophylactic therapy is not indicated but serial echocardiographic analysis (preferably with assessment of the mechanical PR interval) is suggested. Treatment of CHB identified in utero is not established but guidelines are provided (see author's discussion of Management of SLE During Pregnancy, in this volume).

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