Anti-Ro–Associated Sinus Bradycardia in Newborns

To the Editor:

In the study by Mazel et al., the authors reported that passive transfer of human anti-Ro/SSA and anti-La/SSB autoantibodies into naive pregnant mice induced bradycardia and first-degree AV block in pups, suggesting a possible sinoatrial node involvement. We have observed similar findings in humans.

In the last 4 years, we prospectively followed 21 pregnancies in anti-Ro/SSA–positive mothers, performing ECGs in the newborns in the first days after birth. In 3 cases (14.3%), a significant transient sinus bradycardia was observed (heart rate less than third centile for age). Case 1 was a female newborn, spontaneously delivered at 39 weeks of gestation, weight 2670 g, Apgar score at 1 and 5 minutes of 9/10, and a heart rate of 90 bpm 2 days after birth. Case 2 was a female newborn, spontaneously delivered at 41 weeks of gestation, weight 3200 g, Apgar score at 1 and 5 minutes of 9/10, and a heart rate of 70 bpm 2 days after birth. Case 3 was a male newborn, delivered by cesarean section at 38 weeks of gestation because of fetal growth retardation, weight 2340 g, Apgar score at 1 and 5 minutes of 9/10, and a heart rate of 90 bpm 2 days after birth. In the 3 cases, prenatal ultrasound fetal heart rate was normal; no perinatal complications (in particular, no metabolic or thermal problems) were observed, and possible causes of bradycardia in newborns were excluded, e.g., electrolyte abnormalities and drug interferences. In all cases, bradycardia disappeared within 10 days after birth, with no sequelae. Two mothers had systemic lupus erythematosus, and 1 had an undifferentiated connective tissue disease.

Anti-Ro/SSA antibodies may react with 2 different antigenic components of different molecular weights: 52 and 60 kDa. Many observations suggest a prevalent role of anti-Ro/SSA directed against the 52-kDa component in the pathogenesis of congenital AV block. Notably, all the mothers of our 3 cases were anti-Ro/SSA positive, with a fine specificity directed against the 60-kDa component of the Ro antigen in immunoblot. Our observations indicate that sinus bradycardia and sinus node dysfunction occur not only in experimental animals passively transfused with anti-Ro/SSA antibodies but potentially are also detectable in human newborns. In this regard, a possible prevalent role of antibodies directed against the 60-kDa component of the Ro complex is also suggested. It is tempting to speculate that IgG from anti-Ro/SSA–positive mothers could affect calcium channels and/or other physiologic mechanisms responsible for the automaticity or action potential genesis at the sinus node.4

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Response

It has been nearly 2 decades since the observation was made that congenital complete heart block (CHB) is associated with maternal autoantibodies to SSA/Ro ribonucleoproteins and, more recently, with SSB/La (Reference 2, review). A major consequence of these findings was to draw the attention of the rheumatology community to this fascinating problem of passively acquired autoimmunity. Through continued efforts of 2 newfound colleagues, the rheumatologist and cardiologist, there have been many important advances in this orphan disease. The target antigens and their genes are now well characterized, arrhythmogenic potential of the cognate autoantibodies has been identified, and animal models are being developed for study. Indeed, study in this disease exemplifies bench-to-bedside research.

We are delighted to learn that our bench model of CHB has a human correlate. Our findings that direct administration of antibodies from mothers whose children have CHB to pregnant mice resulted in significant sinus bradycardia and first-degree AV block in the pups focused the clinician’s attention not only on the AV node but also on sinoatrial (SA) node conduction abnormalities. Accordingly, Dr Brucato’s findings are of great interest and suggest that the spectrum of conduction abnormalities associated with maternal autoantibodies extend beyond the AV node. Although there is work to be done to define the true prevalence of sinus bradycardia in neonates of mothers with anti-SSA/Ro antibodies and to provide assurances that neonates of mothers with other autoantibodies are not similarly affected, the link to the animal model is promising. It remains a research challenge to identify the molecular mechanism by which a maternal antibody in the neonatal circulation affects the SA node. It is conceivable that maternal antibodies account for many fetal sinus bradycardias.

Our previous finding demonstrating inhibition of Ca current in the human fetal ventricular myocyte by autoantibodies suggests that SA node Ca current and/or other pacemaker currents might also be affected and could contribute to the underlying mechanism of sinus bradycardia. This hypothesis is supported by our passive murine model, recently published. Taken together, Dr Brucato’s findings and our data raise an important clinical question, that is, should we include maternal anti-SSA/Ro and SSB/La antibodies in the workup of unexplained fetal sinus bradycardia?

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_Circulation_. 2000;102:e88-e89
doi: 10.1161/01.CIR.102.11.e88
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/102/11/e88

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