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Passively Acquired Anti-SSA/Ro Antibodies Are Required for Congenital Heart Block Following Ovodonation but Maternal Genes Are Not

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Abstract

Anti-SSA/Ro antibodies are necessary but not sufficient to provoke autoimmune-associated congenital heart block (CHB). Genetic factors are likely contributory. Accordingly, HLA-related candidates and single-nucleotide polymorphisms in the promoter region of tumor necrosis factor α and codon 10 in transforming growth factor β1 (TGFβ1) were evaluated in a unique family: the surrogate mother (anti-SSA/Ro positive), the biologic father, and the CHB-affected child (product of ovodonation). There was an HLA mismatch between the affected child and the surrogate mother. However, both the biologic and the surrogate mothers shared DQ2 and the profibrosing leucine polymorphism at codon 10 of TGFβ. In conclusion, we observed that CHB can develop in a genetically unrelated child exposed in utero to anti-SSA/Ro antibodies. Testing for anti-SSA/Ro antibodies might be considered in women undergoing artificial fertilization. It is possible that there is no direct association of maternal genes beyond a contributory role in generating the autoantibody.

Autoimmune-associated congenital heart block (CHB) is the clinical end point following a pathologic cascade of immunologic/fibrotic events that occur in 2% of fetuses exposed to maternal anti-SSA/Ro and/or anti-SSB/La antibodies (1). Accumulating evidence supports the necessity of maternal autoantibodies for the development of CHB (for review, see ref. 2). However, the low penetrance of disease suggests that other factors, such as maternal and fetal genetics, may be contributory. It is well established that the maternal genes HLA–DRB1*02 and *03 are strongly associated with the presence of SSA/Ro and SSB/La

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Brucato had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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antibodies, regardless of whether the mother has Sjögren's syndrome, has systemic lupus erythematosus, or is asymptomatic (3,4).

Susceptibility genes may involve a broad spectrum of candidates ranging from effector pathways involving antigen presentation (e.g., HLA) to effector pathways controlling both cellular inflammation and fibrosis. Previous studies have demonstrated that the A polymorphism at the −308 promoter (tumor necrosis factor 2 [TNF2]) of the TNFα gene and the leucine polymorphism at codon 10 of the transforming growth factor β (TGFβ) gene (possibly conferring increased inflammation and scarring potential, respectively) occur more frequently in children with CHB than in their unaffected siblings (5). With regard to HLA, Siren et al reported an increased frequency of class I HLA–Cw3 in children with CHB compared with their mothers and healthy subjects from the general population (6). The HLA alleles that were enriched in the mothers were DRB1*03, DQB1*02, DQA1*05, and HLA–Cw7 (7), a finding corroborated by Colombo and colleagues (8). The available data suggest that genetic effects at the HLA complex may be operating at both maternal and fetal levels.

The current study was initiated to identify whether genes of the HLA complex and other candidate genes, of maternal or fetal origin, are associated with clinical disease in the fetus, or whether solely HLA alleles predispose to autoantibody secretion, a required but not sufficient factor for disease development. The availability of a unique family in which CHB developed in a fetus conceived by in vitro fertilization of a donor egg that was implanted in an unrelated woman with anti-SSA/Ro antibodies provided insight into these issues.

CASE REPORT

The surrogate mother (patient), a 36-year-old asymptomatic Italian white woman, underwent ovodonation due to infertility (gravida 0). The biologic mother was healthy and without any known autoimmune disease. The oocyte was fertilized by the surrogate mother's husband (the biologic father). Following successful implantation, the surrogate mother received folic acid and progestins for 3 months.

Assessments during the pregnancy included normal results of obstetric ultrasonography at weeks 8, 10, and 16. At 23 weeks, an echocardiogram revealed complete atrioventricular block in the fetus, with a ventricular rate of 52 beats per minute and an atrial rate of 130–140 beats per minute. The fetus showed no signs of an associated cardiomyopathy, and ventricular function was normal. However, mild left ventricle dilatation and tricuspid regurgitation were noted. There were no anatomic abnormalities.

The surrogate mother was subsequently evaluated and found to have antinuclear antibodies (1:640 titer) and antibodies reactive with SSA/Ro and SSB/La. Tests for anti–double-stranded DNA antibodies, rheumatoid factor, and antithyroid antibodies all had negative results. An extensive rheumatologic evaluation revealed only a history of photosensitivity.

The surrogate mother was treated with dexamethasone (4 mg intramuscularly, twice daily at 24 weeks), and salbutamol (12 mg daily). The dosage of dexamethasone was then reduced at 25 weeks to 4 mg orally daily, and treatment was continued throughout the remainder of the pregnancy. However, there was no effect on the fetal ventricular rate.

At 37 weeks, a male child (2,810 gm) was delivered by caesarean section. Two days after his birth, a pacemaker was inserted in the child, whose ventricular rate was 50 beats per minute. Dexamethasone was discontinued and replaced by tapering doses of prednisone. The child was breastfed. In the months after birth, clinical and echocardiographic signs of severe dilated cardiomyopathy developed in the child. Given the severity of disease, the child received a heart transplant at the age of 17 months.

Results of the analysis of candidate genes in the family members are shown in Table 1. The child with CHB had HLA–DQB1*0206, DRB1*0713, and Cw*0416, and the biologic father had DQB1*0306, DRB1*0413, and Cw*0416. Based on the genetic evaluation of the biologic father and the child with CHB, the biologic mother shared DQB1*02. The child carried the TGFβ polymorphism at Leu^{10} (also conferred by the egg donor) but did not have the TNFα −308A polymorphism, the TNF2 allele.

DISCUSSION

The rarity of CHB suggests that its pathogenesis represents a complex interplay between immunologic, genetic, and environmental factors. The necessity for fetal exposure to maternal autoantibodies reactive with SSA/Ro is strongly supported by this unique case in which isolated heart block developed in the implanted conceptus of an unrelated egg donor.

Maternal genes may promote cardiac disease via 2 mechanisms, maternal and fetal. Such promotion by maternal means suggests that these genes would be expected to facilitate generation of the requisite autoantibodies. Support for this possibility is the presence of DR3 in the surrogate mother (7,8). Fetal inheritance of maternal genes that confer some permissive factor in the cascade to cardiac scarring cannot be unambiguously assigned in this situation, because both DQ2 as well as the profibrosing TGFβ allele were shared between the surrogate and biologic mothers. Furthermore, the contribution of placental genes per se (i.e., maternal decidua basalis) is also confounded by this sharing. Moreover, it is notable that HLA and the candidate polymorphisms in TGFβ and TNFα that are overrepresented in the biologic mothers of children with CHB (7,9,10) were present in the surrogate mother. This finding may simply represent the common genes associated with generation of the putative antibodies described above, but it is nevertheless provocative. As in other polygenetic disorders, associated alleles may be common in the population, and thus the ovum donor may have to carry these susceptibility alleles. These alleles may be important in conferring host fetal injury induced by maternal anti-SSA/Ro antibodies. Further studies are needed to evaluate the maternal genetic risk factors that could influence the placenta and subsequently the fetal environment. In addition, paternal factors may confer protection.

Testing for anti-Ro/SSA antibodies might be considered in women undergoing artificial fertilization. Despite the rarity of CHB, even in mothers with these autoantibodies, knowledge based on the results of such testing might be helpful for women contemplating undergoing artificial fertilization in order to weigh the risks and benefits. Although it is unknown from this case report whether maternal genes per se contribute to a fetal genetic susceptibility component, maternal genes do appear to contribute to the required autoantibody response.

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Table 1

Polymorphism of candidate genes for CHB, including HLA, TNFα (rs1800629; TNFα −308A TNF2 allele, proinflammatory), and TGFβ1 (rs1982073; T allele, profibrosing, which encodes leucine at codon 10)*

	DQB1	DRB1	Cw	TNFα	TGFβ
Surrogate mother	0203	0311	0701	0102	T/C
Biologic father	0306	0413	0416	0101	C/C
CHB-affected child (product of ovodonation)	0206	0713	0416	0101	T/C

*Primers for amplification of tumor necrosis factor α (TNFα; jTNF2) and transforming growth factor β1 (TGFβ1; codon 10) polymorphisms were used as previously described (5,11). Reaction conditions and genotyping methods of low-resolution HLA have been previously described (12).

CHB = congenital heart block.