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Progress in the pathogenesis and treatment of cardiac manifestations of neonatal lupus

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Abstract

Purpose of review—To provide new insights into pathogenesis, prevention and management of cardiac manifestations of neonatal lupus (cardiac neonatal lupus) and issues pertinent to all anti-SSA/Ro positive individuals of childbearing age.

Recent findings—Antibody specificity with high risk for cardiac neonatal lupus remains elusive, but high titers of Ro60, Ro52 or Ro52p200 antibodies appear to be required. Varying antibody specificities to the p200 region of Ro52 can induce first-degree block in a rodent model. In consideration of the contribution of macrophages to inflammation and fibrosis in cardiac neonatal lupus, hydroxychloroquine (HCQ) is being considered as preventive therapy. Cord blood biomarkers support the association of fetal reactive inflammatory and fibrotic components with the development and morbidity of cardiac neonatal lupus. Data from U.S. and French registries do not provide evidence that the prompt use of fluorinated steroids in cases of isolated block significantly alters fetal/neonatal morbidity or mortality.

Summary—The search for a high-risk cardiac neonatal lupus antibody profile remains, but high-titer antibodies to Ro60 and R052 are a consistent finding, and this may guide the need for fetal echocardiographic surveillance. The uniform use of fluorinated steroids to prevent progression of cardiac neonatal lupus or reduce mortality does not appear justified. HCQ, based on diminishing an inflammatory component of cardiac neonatal lupus, is under consideration as a potential preventive approach.

Keywords

anti-SSA/Ro antibodies; congenital heart block; neonatal lupus

Introduction

Maternal autoimmunity is a significant environmental factor with the potential to irreversibly influence fetal and neonatal health. Although the relationship between systemic lupus erythematosus (SLE) and Sjogren's syndrome and congenital heart block (CHB) and neonatal skin rashes was described by 1960, the ‘culprit’ antibody reactivity to the SSA/ Ro-SSB/La ribonucleoprotein complex was identified 20 years later [1]. Neonatal lupus was a

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term given to various fetal and neonatal manifestations associated with exposure to maternal anti-SSA/Ro-SSB/La antibodies [2]. With time came the remarkable realization that the mother's clinical disease was not the common denominator but rather this specific set of autoantibodies. In fact, bradycardia in a mid-to-late second trimester fetus is often the first clue to the presence of anti-SSA/Ro-SSB/La antibodies in a completely asymptomatic mother. The recent study from Stockholm County in Sweden reported only one of 20 cardiac neonatal lupus cases is born to a mother previously diagnosed with SLE [3]. The spectrum of cardiac manifestations of neonatal lupus (cardiac neonatal lupus) includes heart block (the most characteristic) and involvement beyond the atrioventricular node, myocarditis, dilated cardiomyopathies, valvular abnormalities and endocardial fibroelastosis. In this review, cardiac neonatal lupus will be used rather than CHB. The disease is rare with few population estimates. The recent Sweden study reported the incidence of anti-SSA/Ro autoantibody-related second- and third-degree block to be 1 : 23,300 [3]. In mothers with the candidate autoantibodies, the disease occurs in 2% of pregnancies [4] and recurs in 18% [5]. The mortality approaches 18%, and most children require lifetime pacing [6]. A major challenge in elucidating the mechanism of antibody injury relates to the fact that the target antigen is intracellular. Thus, accessibility to circulating maternal antibodies can be explained by either a cross-reactive cardiac myocyte surface antigen or cellular processes such as apoptosis that deliver the SSA/Ro or SSB/La antigens to the membrane surface. Surveillance of mothers at risk for cardiac neonatal lupus in an offspring relies on fetal echocardiograms. However, the low penetrance of disease, controversy over treatment of incomplete block if identified at all and irreversibility of complete block call into question the utility of such measurements. This review will cover bench-to-bedside studies from the recently published literature that provide insights into the pathogenesis and management of cardiac neonatal lupus.

Updates On Antibody Specificities And Pathogenicity

To date, two nonmutually exclusive hypotheses have been advanced to explain the molecular mechanism(s) by which anti-SSA/Ro-SSB/La antibodies to normally sequestered intracellular antigens initiate injury in the fetal heart. The first posits that the intracellular target antigens translocate to the surface of cardiomyocytes undergoing apoptosis during physiological remodeling and are bound by circulating maternal autoantibodies. The formation of pathogenic antibody-apoptotic cell immune complexes promotes proinflammatory and profibrotic responses [7–9]. The second hypothesis is based on molecular mimicry whereby antibodies cross-react with L-type calcium channels and cause dysregulation of calcium homeostasis [10–12]. Although several studies have attempted to identify specific epitopes within the SSA/Ro and SSB/La antigens that associate with cardiac neonatal lupus, most of these studies report epitopes common to the anti-SSA/Ro-SSB/La response regardless of fetal outcome. Importantly, different antibody subsets are identified depending on the immunoassay employed. Indeed, the sensitivity of peptide or recombinant protein ELISAs for anti-Ro60 antibodies is low and may result in false negatives [13,14].

Over the last decade, there has been a major focus on the antibody response against the p200 epitope, spanning Ro52 amino acids (aa) 200–239, as a candidate biomarker conferring an increased maternal risk for the development of cardiac neonatal lupus in an offspring

[15,16]. The high prevalence of the p200 response in women giving birth to a child with cardiac neonatal lupus has been confirmed by several groups. However, there have been inconsistencies regarding its utility in high-risk assessment relative to the pregnancy exposure [17]. Consensus has not been reached as to whether this antibody response is also similarly observed in anti-SSA/Ro-exposed healthy children when all other maternal antibody reactivities to components of the SSA/Ro-SSB/La complex are equivalent. To overcome a limitation of most previous studies that prevalence and titer of maternal antibodies have not been measured during the time of fetal exposure, Reed et al. [18] evaluated umbilical cord blood and maternal serum during affected and unaffected pregnancies for reactivity to p200, full length Ro52, Ro60 and SSB/La. The frequencies of p200, Ro52, Ro60 and SSB/La autoantibodies were not significantly different between cardiac neonatal lupus and anti-SSA/Ro-exposed unaffected children. However, neonatal anti-Ro52 and Ro60 titers were highest in cardiac neonatal lupus neonates and their unaffected siblings compared to unaffected neonates without a cardiac neonatal lupus sibling. Although both maternal anti-Ro52 and p200 autoantibodies were less than 50% specific for cardiac neonatal lupus, anti-p200 was the least likely of the SSA/Ro autoantibodies to be false positive in mothers who have never had a cardiac neonatal lupus-affected child. Titers of anti-Ro52 and p200 did not differ during a cardiac neonatal lupus or unaffected pregnancy from the same mother. Thus, the utility of anti-p200 antibodies as a biomarker over standard commercial ELISAs (which report out positivity to SSA/Ro not specifically Ro52 or Ro60) to guide the level of fetal surveillance was not established.

Tonello et al. [19] reported on an Italian cohort of anti-SSA/Ro exposed pregnancies in 81 mothers (cardiac neonatal lupus in 16). As in Reed's article, testing was done during the pregnancies. The prevalence of anti-p200 antibodies was significantly higher in those mothers whose offspring developed cardiac neonatal lupus (advanced block) compared to those whose children were unaffected ($P = 0.03$). Likewise, combinations of anti-p200 with anti-Ro52 and anti-Ro60 antibodies were significantly more frequent in the women with fetuses developing cardiac neonatal lupus than in the controls. Women whose children had cardiac neonatal lupus had significantly higher mean anti-Ro52, anti-Ro60 and anti-p200 levels than the women whose children were unaffected ($P = 0.003$, $P = 0.0001$ and $P = 0.04$, respectively). However, a shortcoming emphasized in a dialogue reviewing this study was the fact that the investigators included mothers with low titer reactivities who would have been expected to be of lower risk [20].

Clearly, there is a need to better predict women at the greatest risk for the development of cardiac neonatal lupus in an offspring. To advance the field beyond what is already known, it would be important to enroll at the very least only women with high-titer antibodies during the pregnancy under study. However, it may be that even identifying the highest risk autoantibody profile is not sufficient and efforts to define fetal factors need greater emphasis.

Just as the clinical utility of identifying epitope specificity of the anti-Ro52 response has continued to be evaluated, likewise the pathogenicity of this response continues to be studied. The question persists: whether there is one single specific antibody profile underlying most cases of autoimmune-associated cardiac neonatal lupus, or whether there

may be several antibody specificities and cross-targets involved. To this end, Hoxha et al. [21*] have exploited a rodent model to define further the reactivity profile of anti-p200 antibodies. In brief, despite low-to-absent reactivity toward rat p200 and different binding profiles toward mutated rat peptides indicating recognition of different epitopes within Ro52p200, immunoglobulin (Ig)G purified from two mothers of children with cardiac neonatal lupus (advanced block) induced abnormalities in rat cardiac conduction. However, the abnormalities were restricted to prolongation of the PR interval and not second- or third-degree block. These findings support the hypothesis that several antibody specificities and cross-targets may exist and contribute to cardiac neonatal lupus in anti-Ro52 antibody-positive pregnancies. Thus, it is likely that there is not one single cardiac neonatal lupus inducing antibody specificity, but rather several different specificities that may act in an additive fashion to induce substantial damage in the fetal heart and lead to complete atrioventricular block. Unfortunately, as in prior studies using animal models, the cardiac phenotype remains mild. One explanation may be that levels of IgG crossing the placenta in rodents are insufficient to lead to full-blown inflammation and fibrosis of the murine fetal atrioventricular node. This consideration notwithstanding, even in humans it should be pointed out that placental transport at the 18–24-week vulnerable period is far less efficient than months later at term. Alternatively, essential fetal susceptibility factors may be absent in the mouse and rat strains studied thus far. In support of this possibility, it has been reported that fetal major histocompatibility complex modulates the penetrance of first-degree block in a rat model of cardiac neonatal lupus [22], and genetic variants modulating fetal cardiac function and/or inflammatory responses in the presence of maternal antibodies may amplify disease susceptibility and phenotype severity. At this time, a robust animal model that fulfills Koch's postulates and demonstrates advanced block with appropriate histologic correlates has not yet been developed.

Driven by the histologic features of cardiac neonatal lupus as demonstrated in autopsies of fetal hearts dying with the disease [23], Clancy et al. [24*] have focused on an in-vitro model to recapitulate the underpinnings of the inflammatory infiltrate and subsequent fibrosis. On the basis of consistent demonstration of fibrosis of the atrioventricular node surrounded by macrophages and multi-nucleated giant cells, this group addressed macrophage signaling stimulated by ssRNA associated with the Ro60 protein and investigated the impact of antagonizing innate cell drivers such as toll-like receptor (TLR)7/8. Epigenetic modifications that affect transcription factors nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) and signal transducer and activator of transcription 1 were chosen to assess the phenotype of macrophages in which TLR7/8 was ligated following treatment with either anti-Ro60/Ro60/hY3 RNA immune complexes or transfection with hY3. On the basis of microarray, tumor necrosis factor alpha (TNF-α) and interleukin 6 were among the most highly upregulated genes in both stimulated conditions. This upregulation was inhibited by preincubation with hydroxychloroquine (HCQ), a drug which inhibits TLR ligation and is currently being studied to reduce the recurrence rate of cardiac neonatal lupus. In contrast, the resultant gene expression profile observed following stimulation with TNF-α or interferon alpha (IFN-α) (neither signal through TLR) was not inhibited by HCQ. Ligation of TLR7/8 resulted in increased histone methylation, a requirement for binding of NF-κB at certain promoters that was significantly decreased by

HCQ. HCQ may act more as a preventive measure in downregulating the initial production of IFN-α or TNF-α and may not directly affect the resultant autacoid stimulation reflected in TNF-α- and IFN-α-responsive genes. The potential benefit of antimalarials in the prevention of heart block in an anti-SSA/Ro antibody exposed offspring [25,26] may include, in part, a mechanism targeting TLR-dependent epigenetic modification.

To provide clues to the pathogenesis of cardiac neonatal lupus with translational implications for management, several candidate biomarkers in cases at risk for disease were evaluated [27*]. The biomarkers were chosen based on their potential roles in inflammation, fibrosis and cardiac dysfunction: C-reactive protein (CRP), NT-pro-B-type natriuretic peptide (NT-proBNP), troponin I, matrix metalloproteinase (MMP)-2, urokinase plasminogen activator (uPA), urokinase plasminogen activator receptor (uPAR), plasminogen and vitamin D. On the basis of evaluation of 139 samples from the umbilical cord and 135 maternal samples, cord CRP, NT-proBNP, MMP-2, uPA, uPAR and plasminogen levels were higher in cardiac neonatal lupus-affected fetuses than in unaffected cases, independent of maternal rheumatic disease or medications taken during pregnancy. Maternal CRP and cord troponin I levels did not differ between the groups. Cord and maternal vitamin D levels were not significantly associated with cardiac neonatal lupus, but average maternal vitamin D level during pregnancy was positively associated with longer time to postnatal pacemaker placement. These data support the association of fetal reactive inflammatory and fibrotic components with development and morbidity of cardiac neonatal lupus independent of maternal risk factors. The authors suggest that following CRP and NT-proBNP levels after birth can potentially monitor severity and progression of cardiac neonatal lupus. MMP-2 and the uPA/uPAR/plasminogen cascade provide therapeutic targets to decrease fibrosis. Although decreased vitamin D did not associate with increased risk, given the positive influence on postnatal outcomes, maternal levels should be optimized.

Approach To Treatment

Given the fetal bioavailability of fluorinated steroids and the presumed inflammatory response contributing to cardiac injury, these drugs have been considered in both the treatment and prevention of cardiac neonatal lupus. Although not uniformly effective, these drugs have been associated with reversal of first- and second-degree heart block [6,28–31]. As third-degree heart block has never been permanently reversed with any treatment, the utility of instituting fluorinated steroids with known side effects [30,32,33] has been questioned. Published data are limited and discordant regarding the efficacy of fluorinated steroids in reducing the mortality of cardiac neonatal lupus [28,34,35], which poses a therapeutic dilemma when isolated third-degree block is identified.

Leveraging data from a large registry of cardiac neonatal lupus cases, the efficacy of fluorinated steroids with regard to progression, mortality and need for pacemaker implantation was addressed [36**]. In this retrospective study restricted to anti-SSA/Ro-exposed cases presenting with isolated advanced heart block in utero who received either fluorinated steroids within 1 week of detection ($N = 71$) or no treatment ($N = 85$), the following outcomes were evaluated: development of endocardial fibroelastosis, dilated cardiomyopathy and/or hydrops fetalis; mortality; and pacemaker implantation. In Cox

proportional hazards regression analyses, fluorinated steroids did not significantly prevent the development of disease beyond the atrioventricular node [adjusted hazard ratio = 0.90; 95% confidence interval (CI): 0.43–1.85; $P = 0.77$], reduce mortality (hazard ratio = 1.63; 95% CI: 0.43–6.14; $P = 0.47$) or forestall/prevent pacemaker implantation (hazard ratio = 0.87; 95% CI: 0.57–1.33; $P = 0.53$).

In aggregate, these data do not provide evidence that prompt fluorinated steroid use significantly alters fetal/neonatal morbidity or mortality. Variables that differed between treated and untreated groups included year of birth, which did not associate with extranodal disease, and HCQ use, which was so infrequent that it precluded meaningful analysis. Multivariable analyses revealed no identifiable maternal or fetal risk factor for progression of disease beyond the atrioventricular node. Consistent with previous reports, extranodal disease was significantly associated with mortality [6,28,37,38].

With regard to the efficacy of steroids to prevent the development of cardiac neonatal lupus, the Research Team for Surveillance of Autoantibody-Exposed Fetuses and Treatment of Neonatal Lupus Erythematosus, the Research Program of the Japan Ministry of Health, Labor and Welfare, performed a national survey on pregnancy of 635 mothers positive for anti-SSA/Ro antibodies. Cardiac neonatal lupus (advanced block) was detected in 16. In multivariate analysis, the use of corticosteroids before conception [odds ratio (OR): 4.28, $P = 0.04$] and high titer of anti-SSA/Ro antibodies (OR: 3.58, $P = 0.02$) were independent and significant risk factors for the development of cardiac neonatal lupus [39]. The use of corticosteroids (equivalent doses of prednisolone, at ≥ 10 mg/day) after conception before 16 weeks of gestation was an independent protective factor against the development of cardiac neonatal lupus (OR: 0.16, $P = 0.03$). However, the use of continuous corticosteroids both before and after conception had no effect on the development of cardiac neonatal lupus. The difficulty in interpreting these results is that different preparations of steroids were used, making it challenging to sort out the effect of fluorinated steroids in particular. Moreover, there was only a small number of cases in which CHB developed ($N = 16$). Not unexpectedly, high titer of anti-SSA/Ro antibodies was an independent risk factor for cardiac neonatal lupus.

Levesque et al. [40**] reported the results of a large retrospective French registry of 214 cases with cardiac neonatal lupus (advanced block). The use of fluorinated steroids was neither associated with survival nor with regression of second-degree CHB. The authors also leveraged this registry to address factors associated with mortality which in this cohort approached 16%. In agreement with previous publications [6,28], hydrops (hazard ratio = 12.4; 95% CI: 4.7–32.7; $P < 0.001$) and prematurity (hazard ratio = 17.1; 95% CI: 2.8–103.1; $P = 0.002$) were associated with fetal/neonatal mortality. During a median follow-up of 7 years (birth to 36 years), 148 of 187 children born alive (79.1%) had a pacemaker, 35 (18.8%) had dilated cardiomyopathy (DCM) and 22 (11.8%) died. In multivariate analysis, factors associated with child death were in utero DCM (hazard ratio = 6.37; 95% CI: 1.25–32.44; $P = 0.0157$), postnatal DCM (hazard ratio = 227.58; 95% CI: 24.33–2128.46; $P < 0.0001$) and pacemaker implantation (hazard ratio = 0.11; 95% CI: 0.02–0.51; $P = 0.0035$).

Conclusion

The search for a unique antibody profile that will predict the development of cardiac neonatal lupus remains elusive, but high titers of Ro60, Ro52 or Ro52p200 antibodies appear to be required. Varying antibody specificities to the p200 region of Ro52 can induce first-degree block in a rodent model. A robust animal model of cardiac neonatal lupus has yet to be developed. In consideration of the contribution of macrophages to the inflammation and fibrosis in cardiac neonatal lupus, HCQ is being considered as preventive therapy. Cord blood biomarkers support the association of fetal reactive inflammatory and fibrotic components with the development and morbidity of cardiac neonatal lupus. Data from two large registries do not support the use of fluorinated steroids in cases of isolated third-degree block as a means of preventing progressive injury.

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protective against child death and fluorinated steroids do not associate with a better outcome than not using fluorinated steroids. [PubMed: 26284740]

Key Points

- There is not one singular epitope of Ro52p200 that is specific for the development of first-degree heart block in a murine model.
- Targeting downstream transcription factors and epigenetic modifications following Toll-like receptor 7/8 ligation in macrophages may be the mechanism of action of HCQ and provide rationale for its role in prevention of disease.
- On the basis of data from two large registries, treatment of advanced block with fluorinated steroids does not prevent further injury.