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Cardiac Manifestations of Neonatal Lupus: A Review of Autoantibody Associated Congenital Heart Block and its Impact in an Adult Population

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Abstract

Within the last decade the prevalence of adult patients living with congenital heart disease equals that seen in children. This expanding population poses a challenge to clinical cardiologists who will be caring for patients with the clinical manifestations of this condition. Neonatal lupus is a model of passively acquired auto-immunity and is responsible for the majority of clinical cases of congenital heart block. This review will focus on the presentation, pathophysiology, and the long-term follow up of congenital heart block associated with neonatal lupus, as well as discuss important diagnostic tests, familial implications, and pacemaker issues associated with the care of an adult with congenital heart block.

Keywords

neonatal lupus; congenital complete atrioventricular block; autoantibody associated congenital heart block; pacemaker therapy; SSA/Ro; SSB/La

As of the year 2000, at least as many adults with congenital heart disease are living in the United States as are children.[1] Since we are heading into an era where more patients with structural or functional (cardiomyopathic or arrhythmic) congenital heart defects will be over the age of 21 years,[2,3] cases will increasingly present to adult cardiologists.

This review will focus on the presentation, pathophysiology, and the long-term follow up of congenital heart block (CHB) in patients with neonatal lupus, which contrasts to non-autoimmune antibody-associated CHB, such as that associated with structural heart disease (l-transposition of the great vessels, heterotaxia, etc.), or surgically-induced HB. The discussion of CHB in this article will hopefully shed some light on the diagnostic and therapeutic challenges facing cardiologists, and enable them to answer the following clinical questions:

- What tests are important as part of the management of CHB?
- What implications will a diagnosis of CHB have on the patient's family?

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- What pacemaker setting is most appropriate for CHB patients?
- What quality of life can the patient expect post-pacemaker treatment?

BACKGROUND

CHB is a rare illness, affecting 1 in 15,000 to 20,000 live births.[4] In most cases, CHB is characterized pathologically by fibrous tissue that either replaces the atrioventricular node and its surrounding tissue or by an interruption between the atrial myocardium and the atrioventricular node.[5] Although it can occur as an isolated defect or in association with tumors like mesothelioma,[6] and with complex structural heart disease such as heterotaxias and congenitally-corrected l-transposition of the great arteries,[7] the large majority of CHB cases (60–90%) presenting in utero or in the neonatal period are due to maternal antibodies that cross the placenta in neonatal lupus.[8,9] Fetal echocardiography has allowed the prenatal diagnosis of CHB to be made routinely.[10]

PATHOPHYSIOLOGY

Neonatal lupus is a model of passively-acquired auto-immunity, in which tissue injury in the fetus is presumed to be related to the transplacental passage of maternal IgG autoantibodies to SSA/Ro and/or SSB/La intracellular ribonuclear proteins.[11] The mother may have systemic lupus erythematosus or Sjögren's Syndrome, or, as in over a third of the cases, may be asymptomatic herself. [11] Maternal antibodies which begin crossing the placenta as early as 11 weeks of gestation are associated with the development of cardiac abnormalities, rash, and/or various liver and blood cell abnormalities in the newborn (Table 1).[12–17] Skin, liver, and blood cells are regenerative and, as such, the effect of passively-acquired antibodies on these systems disappears with the clearance of the antibodies in the 6th to 8th month of post-natal life.[11] In contrast, the regenerative processes that are responsible for the transient nature of skin, hepatobiliary, and hematologic manifestations do not occur in cardiac tissue, and thus the permanent reversal of third degree CHB has never been observed.[11]

CARDIAC MANIFESTATIONS

Clinical Phenotype

For a long time the only widely recognized cardiac abnormality in neonatal lupus was CHB. However, the development of a Research Registry for Neonatal Lupus,[18] coupled with increasing clinical experience, have helped advance the recognition of other cardiovascular abnormalities in the spectrum of neonatal lupus (Table 2).[19–27]

These abnormalities include diffuse myocardial disease both with and without conduction disturbances, simple structural defects (not causal of the atrioventricular block per se), and several other electrophysiologic anomalies.[19] Fifteen to twenty percent of patients with neonatal lupus present with diffuse myocardial disease before birth, and others may clinically manifest myocardial dysfunction after birth even with adequate pacemaker therapy.[19–23] This diffuse myocardial disease can be in the absence of conduction abnormalities, suggesting that cardiomyopathy may also be a separate manifestation of neonatal lupus. [22] Structural congenital heart disease has been reported in 16–42% of patients with CHB.[24,25] These lesions include persistent ductus arteriosus requiring intervention, atrial and ventricular septal defects, and semilunar and atrioventricular valvular abnormalities. Electrophysiological abnormalities aside from CHB include both transient and persistent sinus node dysfunction, a long ECG QT interval, ventricular and junctional tachycardia, and atrial flutter,[19,26] however a true association of these latter abnormalities with maternal anti-SSA/Ro antibodies has not been uniformly established across different cohorts.

Basic Science of Cardiac Lesions

The signature lesion of auto-antibody associated CHB is fibrosis but the precise mechanism of tissue injury remains an area of intense investigation. The challenge in linking autoantibodies to CHB is explaining how extracellular maternal antibodies react with the intracellular SSA/Ro and SSB/La antigens, which are most abundant in fetal heart tissue between 18 and 24 weeks.[28] Apoptosis induces translocation of these normally intracellular antigens to the cell surface where they would then be exposed to circulating antibodies.[29] An alternative hypothesis is that maternal anti-Ro and anti-La autoantibodies bind to L-type calcium channels on fetal cardiomyocytes and inhibit inward calcium influx, ultimately leading to calcium dysregulation, calcium overload, and subsequent apoptosis.[30–32] The generation of antibody bound apoptotic cardiocytes (essentially an immune complex) activates macrophages with the subsequent secretion of proinflammatory (tumor necrosis factor alpha) and profibrotic factors.[33,34] Whatever the trigger for apopotosis, the opsonization of apoptotic cardiomyocytes via toll-like receptors on macrophages is crucial to the inflammatory cascade initiating the replacement of healthy atrioventricular nodal and myocardial tissue by fibrosis.[33]

It is important to note that this model may not fully explain the pathogenesis of CHB in neonatal lupus. Only 2% of neonates born to mothers with the candidate antibodies have CHB, and the risk of recurrence is only 17–18%.[24,35] There is also no consistent link of the usually high antibody titers to the development of CHB. [11] Additionally, despite the presence of identical antibodies in the maternal circulation, heart block is not observed in the mother.[24] In fact, most mothers are clinically asymptomatic and are only recognized to have anti-Ro and anti-La autoantibodies after the diagnosis of CHB is made in the fetus. [19,24] Although anti-Ro and anti-La antibodies are necessary, their presence alone does not cause CHB. The evolution of CHB from fibrosis likely requires a window of vulnerability, an environmental exposure, and a genetic predisposition. The importance of environmental factors is highlighted by the presence of discordant identical twins.[36] Future research in genetics and biomarkers associated with early cardiac injury will hopefully fill in the gaps of our understanding of CHB in neonatal lupus.

CLINICAL IMPACT

The clinical impact of autoantibody associated CHB is significant. The overall mortality rate for complete CHB is 4% to 29%.[5] There is a 15% mortality rate before 3 months of age, [11] and a 14% mortality rate from cardiac complications (Adam-Stokes attacks, cardiac failure, sudden death) of CHB, which may develop at any age.[37] Generally, CHB patients with structural heart disease have a higher mortality than those without structural heart disease.[5] The outcome of clinically-manifested diffuse myocardial disease associated with maternal autoantibodies in the absence of intervention is very poor, with a greater than 80% rate of fetal demise or need for cardiac transplantation.[20–23] Even beyond the newborn period, the rare development of late cardiomyopathy may reach 10%.[11]

The fetally-acquired disease of cardiac manifestations of neonatal lupus may, in fact, be confined to the conduction system and thus not associated at all with other systemic manifestations, and the consequences may solely be related to the HB itself, perhaps indistinguishable from a structural abnormality. We have often read that anti-Ro associated CHF might carry a worse prognosis than that of a structural etiology, but in the absence of a concomitant myocardial injury, we never understood why this should be so.

LONG-TERM FOLLOW UP AND ADULT ISSUES

Although CHB is associated with significant morbidity and mortality, there is an 80% cumulative survival rate at 3 years. [11] As these children move into adulthood, careful consideration of the congenital lesion will be needed to recognize the management and therapeutic challenges associated with this disease.

Late Diagnostic Challenges

For an adult cardiologist examining a patient with HB, a myriad of other conditions are considered before the diagnosis of CHB comes to mind. These causes include, but are not limited to, myocardial ischemia or infarction, infectious origins such as viral or lyme carditis, infiltrative myocardial diseases such as sarcoidosis or hemochromatosis, and idiopathic fibrosis and calcification of the electrical conduction system known as Lenegre-Lev Syndrome.[38] When all these causes are exhausted one can consider CHB.

Incomplete heart blocks as the initial cardiac presentation in neonatal lupus can progress to complete heart block at any age despite the absence of circulating antibodies.[11] Autoantibodies may initiate fibroblast proliferation but they are not required for the progression of fibroblast proliferation and scarring. This suggests that there are a small percentage of individuals who have grown into adults with an undiagnosed CHB. To diagnose CHB in these individuals, one must prove the existence of maternal autoantibodies. Recently, a case-report in 2010 by Navaravong et al reported on a 43-year-old man with asymptomatic bradycardia found to exhibit a late presentation of complete CHB (CCHB) with an unknown etiology. [2] In this case, the patient was asymptomatic with a normal heart structure and function. His ECG and exercise test findings were compatible with atrioventricular nodal block. His Lyme titers were negative and other acquired causes were ruled out, convincing the authors that the patient was exhibiting a late presentation of CCHB. Neonatal lupus was not fully considered and the patient's mother was not tested for autoantibodies to SSA/Ro and SSB/La in this case. Strictly speaking, one cannot diagnose autoimmune antibody-associated CHB beyond the newborn period without demonstrating maternal anti-Ro or anti-La antibodies.[39]

It is important for clinicians to recall that neonatal lupus (aka autoantibody-associated CHB) is responsible for the majority of isolated CHB cases. This condition is the result of transient passage of maternal auto-antibodies which disappear by the 6th to 8th month of post-natal life. While the patient may no longer possess these antibodies, the mother would. Routine testing for anti-Ro and anti-La antibodies in the mother of any patient presenting with evidence of CHB can yield insight to disease manifestation, therapeutic options, prognosis, and familial implications.[40]

Knowledge of maternal antibody status can guide familial counseling. If the patient's mother is antibody positive, it is important for the patient to know that he or she cannot pass antibody-associated-CHB on to his/her children. While children are protected, siblings are not. The overall rate of recurrence of a second child with cardiac manifestations of neonatal lupus is 17.4%,[24] suggesting that siblings of the affected patient should receive a cardiac evaluation to determine their risk. Overall, the cardiac manifestations of neonatal lupus are the result of an auto-immune phenomenon in the mother. As such, once the mother is identified as antibody positive, the entire family, both the patient's children and siblings, are at increased risk for the future development of some form of systemic or organ specific rheumatologic disease.[41,42]

Therapeutic Challenges

Knowledge of maternal antibody status will also guide therapeutic approaches in the adult patient with CHB. The variability in the clinical presentation of CHB is a challenge for pediatric cardiologists, especially in regard to pacing therapy. Controversies exist over whom to pace and when. Some clinicians argue that all patients over 15 years of age, whether asymptomatic or not, should have a pacemaker implanted,[43] whereas others routinely implant epicardial electrodes and subclavicular pacemakers within the first month in all infants with complete CHB.[44,45] There is a higher complication rate when using pacemakers in neonates which includes central venous obstruction, tricuspid valve abnormalities, abandoned leads, multiple invasive procedures, and infection.

Once the decision is made to pace, recent research has brought some consensus to the best type of pacing. Conventional right ventricular (RV) apical pacing may result in desynchronization of ventricular electrical activation and is associated with deleterious left ventricular (LV) modeling, LV dilatation, and LV asymmetrical hypertrophy.[46–48] Children with CHB and chronic RV pacing were found to have significant reductions in maximal (measured by VO2 max) and submaximal (measured by anaerobic threshold) exercise capacity, accompanied by choronotropic insufficiency.[49] Additionally, traditional RV pacing in children with CHB has been shown to precipitate immediate cardiomyopathy and acute heart failure in a select group of patients—namely in patients of mothers with connective tissue disease.[2,23,50,51]

Deleterious effects of chronic RV pacing in children can be avoided by bi-ventricular pacing or the increasingly favored LV pacing approach. Improved ejection fractions were observed in patients with CHB when pacing was relocated from the right to the LV epicardium.[52,53] Recently, preliminary results from a multicenter study showed chronic LV pacing in children with CHB results in better LV function as compared to chronic RV pacing.[54] These results emphasize the importance of LV pacing or a bi-ventricular approach to pacing patients with CHB.

These findings are important to adult cardiologists deciding how to pace patients with CHB. In a recent case report, a 38-year-old man with autoantibody associated CHB diagnosed at birth was conventionally treated with RV pacing for his first pacemaker implantation and experienced acute heart failure immediately following implantation.[3] In this case the pediatric cardiologist's experience and approach to pacing was not considered. Since traditional RV pacing in patients with CHB and antibody positive mothers have been shown to precipitate cardiomyopathy and acute heart failure, and given the literature on deleterious effects of RV pacing in CHB, LV pacing or bi-ventricular pacing may be a good initial strategy in adult patients presenting with CHB.[3]

Since CHB is usually detected at birth, it is rare to find an adult patient with CHB who has not already been diagnosed and treated by a pediatric cardiologist. The majority of cases presenting to an adult cardiologist may be the surviving newborns who are more likely to be chronically paced. Greater than 65% of surviving newborns require pacemakers.[11] In chronically- paced patients, traditional implant sites may adversely contribute to myocardial dysfunction and result in less than optimal conditions for pacemaker placement. In addition, the multiple surgeries associated with pacemaker re-implantation can eventually disrupt the usually expected venous and epicardial approaches to lead placement. In each of these clinical situations, pacemaker device therapy may dramatically differ from most of the published information available in the field of adult cardiology. As such, a firm understanding of congenital heart lesions and associated therapeutics should be emphasized among adult cardiologists.

Quality of Life

In general, the prognosis following pacemaker implantation in patients with CHB is excellent,[55,56] although development of heart failure may occur over the long-term.[23] In a 25-year follow-up study of adults with CHB, overall the patients tended to lead normal and productive lives,[55] and there appears to be no contraindication regarding pregnancy to term. Implanting a pacemaker in an adult for any reason substantially improved physical, mental, and health-related quality of life measures.[57,58]

CONCLUSION

As of the year 2000, at least as many adults with congenital heart disease are living in the United States as children.[1] The boundaries between pediatric and adult cardiology are growing weaker. A firm understanding of congenital abnormalities, including CHB related to lupus, will be needed to recognize and prevent the complications of congenital disease presenting in adult life to adult cardiologists. With increased clinical follow-up of patients in the Research Registry for Neonatal Lupus and with educational efforts directed at familiarizing adult cardiologists with congenital conditions, we can improve patient well being and institute management and therapeutic protocols targeted at adult patients with congenitally-diseased hearts. Both pediatric and adult cardiologists must work together to transition adolescents and young adults with congenital cardiac problems, preferably through specialized programs of adult congenital heart disease.

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Table 1

Non- Cardiac Clinical Manifestations of Neonatal Lupus

Skin
Annular erythematous plaques, often with central clearing and occasional scaling
Hepatobiliary
Neonatal cholestasis
Liver failure occurring at birth or *in utero*,
Phenotypic of neonatal iron storage disease or neonatal hemochromatosis
Transient conjugated hyperbilirubinemia occurring in the first few weeks of life
Transient transaminase elevations occurring in the first few months of life
Hematologic
Transient thrombocytopenia is most common
Neutropenia, anemia (Occasional case reports)

Data from refs 12–17

Table 2

Cardiac Clinical Manifestations of Neonatal Lupus and associated mortality rates

Cardiac Defect	Mortality Rate
Electrophysiologic	
Children with isolated CHB	6–8%
Infants with isolated CHB	4–8%
Adults with isolated CHB who were previously asymptomatic	5%
1° AV Block	
2° AV Block	
Complete AV Block	
Atrial and Ventricular Ectopic Beats	
Atrial Flutter	
Ventricular and Junctional Ectopic Tachycardia	
Sinus Node Dysfunction	
Long QT interval	
Myocardial/Functional	80%
Myocarditis	
Cardiomyopathy	
Can develop before birth, after infancy, or in adults	
Can occur with or without conduction abnormalities	
Endocardial Fibroelastosis	
Pericarditis/pericardial effusion	
Structural	
Infants with CHB and structural disease	29%
Children with CHB and structural disease	10%
AV valve dysplasia, stenosis, regurgitation	
Semilunar valve dysplasia, stenosis, regurgitation	
Patent ductus arteriosus	
Atrial septal defects	
Ventricular septal defects	

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